MENINGIOMA: FROM BASIC RESEARCH TO CLINICAL TRANSLATIONAL STUDY

EDITED BY: Hailiang Tang and Allen Ho
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MENINGIOMA: FROM BASIC RESEARCH TO CLINICAL TRANSLATIONAL STUDY

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Table of Contents

07 ***Editorial: Meningioma: From Basic Research to Clinical Translational Study***
Allen Ho and Hailiang Tang

11 ***Factors Related to the Post-operative Recurrence of Atypical Meningiomas***
Wu Ye, Tang Ding-Zhong, Yang Xiao-Sheng, Zhan Ren-Ya and Li Yi

18 ***Sylvian Fissure Meningiomas: Case Report and Literature Review***
Chengwei Cai, Zhoule Zhu, Xinxia Guo, Xiaoming Guo, Hongjie Jiang, Zhe Zheng, Jianmin Zhang, Anwen Shao and Junming Zhu

26 ***Differentially Expressed MicroRNAs in Radioresistant and Radiosensitive Atypical Meningioma: A Clinical Study in Chinese Patients***
Xiaokang Zhang, Guobin Zhang, Huawei Huang, Haoyi Li, Song Lin and Yonggang Wang

34 ***A Retrospective Interventional Cohort Study to Assess the Safety and Efficacy of Sandostatin LAR for Treatment of Recurrent and/or Refractory Meningiomas***
Maya Hrachova, Emely Nhi T. Nguyen, Beverly D. Fu, Manisha J. Dandekar, Xiao-Tang Kong, Gilbert Cadena, Frank P. K. Hsu, John Billimek, Thomas H. Taylor and Daniela A. Bota

45 ***Accurate Preoperative Distinction of Intracranial Hemangiopericytoma From Meningioma Using a Multihabitat and Multisequence-Based Radiomics Diagnostic Technique***
Jingwei Wei, Lianwang Li, Yuqi Han, Dongsheng Gu, Qian Chen, Junmei Wang, Runting Li, Jiong Zhan, Jie Tian and Dabiao Zhou

56 ***Anterior Clinoidal Meningiomas: Meningeal Anatomical Considerations and Surgical Implications***
Tao Xu, Yong Yan, Alexander I. Evins, Zhenyu Gong, Lei Jiang, Huaiyu Sun, Li Cai, Hongxiang Wang, Weiqing Li, Yicheng Lu, Ming Zhang and Juxiang Chen

68 ***Clinial Features, Individualized Treatment and Long-Term Surgical Outcomes of Skull Base Meningiomas With Extracranial Extensions***
Houjie Liu, Haipeng Qian, Xueji Li, Fuxing Zuo, Xiaoli Meng, Shaoyan Liu and Jinghai Wan

83 ***High Copy-Number Variation Burdens in Cranial Meningiomas From Patients With Diverse Clinical Phenotypes Characterized by Hot Genomic Structure Changes***
Junpeng Ma, Yaqiang Hong, Wei Chen, Da Li, Kaibing Tian, Ke Wang, Yang Yang, Yuan Zhang, Yujia Chen, Lairong Song, Liangpeng Chen, Liwei Zhang, Jiang Du, Junting Zhang, Zhen Wu, Dake Zhang and Liang Wang

97 ***An Overview of Managements in Meningiomas***
Lianhua Zhao, Wei Zhao, Yanwei Hou, Cuixia Wen, Jing Wang, Pei Wu and Zaiyu Guo

109 ***Corrigendum: An Overview of Managements in Meningiomas***
Lianhua Zhao, Wei Zhao, Yanwei Hou, Cuixia Wen, Jing Wang, Pei Wu and Zaiyu Guo

111 ***The Preferred Locations of Meningioma According to Different Biological Characteristics Based on Voxel-Wise Analysis***
Chongran Sun, Zhangqi Dou, Jiawei Wu, Biao Jiang, Yasaman Iranmanesh, Xiaobo Yu, Jianru Li, Hang Zhou, Chen Zhong, Yucong Peng, Jianfeng Zhuang, Qian Yu, Xinyan Wu, Feng Yan, Qi Xie and Gao Chen

123 ***Next-Generation Sequencing Analysis of ctDNA for the Detection of Glioma and Metastatic Brain Tumors in Adults***
Jianfeng Liang, Wanni Zhao, Changyu Lu, Danni Liu, Ping Li, Xun Ye, Yuanli Zhao, Jing Zhang and Dong Yang

133 ***MicroRNA-221/222 Inhibits the Radiation-Induced Invasiveness and Promotes the Radiosensitivity of Malignant Meningioma Cells***
Qing Zhang, Lai-Rong Song, Xu-Lei Huo, Liang Wang, Guo-Bin Zhang, Shu-Yu Hao, Hai-Wei Jia, Chui-Lin Kong, Wang Jia, Zhen Wu, Bai-Nan Xu, Gui-Jun Jia and Jun-Ting Zhang

151 ***WHO Grade I Meningioma Recurrence: Identifying High Risk Patients Using Histopathological Features and the MIB-1 Index***
Alexander F. Haddad, Jacob S. Young, Ishan Kanungo, Sweta Sudhir, Jia-Shu Chen, David R. Raleigh, Stephen T. Magill, Michael W. McDermott and Manish K. Aghi

161 ***Multi-Omics Analysis in Initiation and Progression of Meningiomas: From Pathogenesis to Diagnosis***
Jiachen Liu, Congcong Xia and Gaiqing Wang

170 ***Corrigendum: Multi-Omics Analysis in Initiation and Progression of Meningiomas: From Pathogenesis to Diagnosis***
Jiachen Liu, Congcong Xia and Gaiqing Wang

171 ***Clinical Significance of Somatostatin Receptor (SSTR) 2 in Meningioma***
Wei Wu, Yunxiang Zhou, Yali Wang, Lihong Liu, Jianyao Lou, Yongchuan Deng, Peng Zhao and Anwen Shao

183 ***A Novel Scoring System Based on Preoperative Routine Blood Test in Predicting Prognosis of Atypical Meningioma***
Xiaoyong Chen, Guojun Wang, Jianhe Zhang, Gaoqi Zhang, Yuanxiang Lin, Zhangya Lin, Jianjun Gu, Dezhi Kang and Chenyu Ding

196 ***Is DNA Methylation a Ray of Sunshine in Predicting Meningioma Prognosis?***
Lu Shen, Danfeng Lin, Lu Cheng, Sheng Tu, Haijian Wu, Weilin Xu, Yuanbo Pan, Xiaochen Wang, Jianmin Zhang and Anwen Shao

209 ***Molecular Mechanism and Approach in Progression of Meningioma***
Zhiwei Shao, Lihong Liu, Yanghao Zheng, Sheng Tu, Yuanbo Pan, Sheng Yan, Qichun Wei, Anwen Shao and Jianmin Zhang

220 ***High Tumor Mitochondrial DNA Content Correlates With an Improved Patient's Outcome in WHO Grade III Meningioma***
Lingyang Hua, Tareq A. Juratli, Hongda Zhu, Jiaojiao Deng, Daijun Wang, Shuchen Sun, Qing Xie, Hiroaki Wakimoto and Ye Gong

230 *A Quantified Risk-Scoring System for the Recurrence of Meningiomas: Results From a Retrospective Study of 392 Patients*
Zhangzhang Zhu, Chengde Wang, Jiadong Xu, Chunyong Wang, Lei Xia, Qun Li, Jianglong Lu, Lin Cai, Weiming Zheng and Zhipeng Su

238 *Outcome of Tumor-Associated Proptosis in Patients With Spheno-Orbital Meningioma: Single-Center Experience and Systematic Review of the Literature*
Matthias Schneider, Anna-Laura Potthoff, Valeri Borger, Alexis Hadjiathanasiou, Niklas Schäfer, Ági Güresir, Hartmut Vatter, Ulrich Herrlinger, Erdem Güresir and Patrick Schuss

246 *Small Cerebellopontine Angle Meningioma—Surgical Experience of 162 Patients and Literature Review*
Jiyuan Bu, Pengjie Pan, Hui Yao, Weiyi Gong, Yuan Liu, Zhengquan Yu, Zhong Wang, Jiang Wu and Gang Chen

254 *Resection of Olfactory Groove Meningiomas Through Unilateral vs. Bilateral Approaches: A Systematic Review and Meta-Analysis*
Austin Y. Feng, Sandy Wong, Sabir Saluja, Michael C. Jin, Anthony Thai, Arjun V. Pendharkar, Allen L. Ho, Prasad Reddy and Allen D. Efron

267 *Meningioma: A Review of Clinicopathological and Molecular Aspects*
Kristin Huntoon, Angus Martin Shaw Toland and Sonika Dahiya

281 *The Current State of Radiomics for Meningiomas: Promises and Challenges*
Hao Gu, Xu Zhang, Paolo di Russo, Xiaochun Zhao and Tao Xu

293 *Long Non-Coding RNA MEG3 Modifies Cell-Cycle, Migration, Invasion, and Proliferation Through AKAP12 by Sponging miR-29c in Meningioma Cells*
Chenyu Ding, Xuehan Yi, Jiaheng Xu, Zhenhua Huang, Xingyao Bu, Desheng Wang, Hongliang Ge, Gaoqi Zhang, Jianjun Gu, Dezhi Kang and Xiyue Wu

302 *Gene Expression Signatures Identify Biologically Homogenous Subgroups of Grade 2 Meningiomas*
Zsolt Zador, Alexander P. Landry, Ashirbani Saha and Michael D. Cusimano

311 *Prognostic Model That Predicts Benefits of Adjuvant Radiotherapy in Patients With High Grade Meningioma*
Daijun Wang, Shuchen Sun, Lingyang Hua, Jiaojiao Deng, Shihai Luan, Haixia Cheng, Qing Xie, Hiroaki Wakimoto, Hongda Zhu and Ye Gong

320 *Review of Atypical and Anaplastic Meningiomas: Classification, Molecular Biology, and Management*
Taylor Anne Wilson, Lei Huang, Dinesh Ramanathan, Miguel Lopez-Gonzalez, Promod Pillai, Kenneth De Los Reyes, Muhammad Kumal and Warren Boling

337 *Prognostic Significance of Preoperative Neutrophil-to-Lymphocyte Ratio in Patients With Meningiomas*
Yuki Kuranari, Ryota Tamura, Noboru Tsuda, Kenzo Kosugi, Yukina Morimoto, Kazunari Yoshida and Masahiro Toda

346 ***Prophylactic AEDs Treatment for Patients With Supratentorial Meningioma Does Not Reduce the Rate of Perioperative Seizures: A Retrospective Single-Center Cohort Study***
Ming Yang, Yong-Ran Cheng, Meng-Yun Zhou, Ming-Wei Wang, Lan Ye, Zu-Cai Xu, Zhan-Hui Feng and Xun-Tai Ma

354 ***Meningiomas in Premenopausal Women: Role of the Hormone Related Conditions***
Francesco Maiuri, Giuseppe Mariniello, Teresa Somma, Elia Guadagno, Sergio Corvino, Serena Pagano, Valentina Orlando and Marialaura Del Basso De Caro

362 ***Malignant Progression Contributes to the Failure of Combination Therapy for Atypical Meningiomas***
Qing Zhang, Zheng Wen, Ming Ni, Da Li, Ke Wang, Gui-Jun Jia, Zhen Wu, Li-Wei Zhang, Wang Jia, Liang Wang and Jun-Ting Zhang

372 ***Effectiveness of Postoperative Adjuvant Radiotherapy in Atypical Meningioma Patients After Gross Total Resection: A Meta-Analysis Study***
Lingzhe He, Buyi Zhang, Jianmin Zhang, Zhige Guo, Feina Shi and Qiang Zeng

380 ***Clear Cell Meningioma in the Central Nervous System: Analysis of Surveillance, Epidemiology, and End Results Database***
Yubo Wang, Xiaowei Qin, Mingyang Liu, Xinrui Liu, Ying Yu, Gang Zhao and Ying Xu

386 ***Postoperative Long-Term Independence Among the Elderly With Meningiomas: Function Evolution, Determinant Identification, and Prediction Model Development***
Haoyi Li, Huawei Huang, Xiaokang Zhang, Yonggang Wang, Xiaohui Ren, Yong Cui, Dali Sui, Song Lin, Zhongli Jiang and Guobin Zhang

397 ***Progesterone Receptor Expression in Meningiomas: Pathological and Prognostic Implications***
Francesco Maiuri, Giuseppe Mariniello, Oreste de Divitiis, Felice Esposito, Elia Guadagno, Giuseppe Teodonno, Marcello Barbato and Marialaura Del Basso De Caro

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EDITORIAL
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Editorial: Meningioma: From Basic Research to Clinical Translational Study

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Editorial for the Research Topic

Meningioma: From Basic Research to Clinical Translational Study

Meningioma is thought to originate from arachnoidal cells in the central nervous system (CNS) and accounts for approximately 30% of all brain tumors (1). Most meningiomas are low grade benign brain tumors (such as fibroblastic meningioma and meningothelial meningioma), which belong to the World Health Organization (WHO) grade I and have a good prognosis after surgery. About 20% of meningiomas are high grade malignant brain tumors and belong to the WHO grade II (such as atypical meningioma) or WHO grade III (such as anaplastic meningioma) (2). Malignant meningiomas, sometimes may evolve from benign meningiomas, are more aggressive. They have an increased risk of recurrence after surgery and significant mortality rates. Currently, surgical resection combined with adjuvant radiotherapy is the main treatment strategy for malignant meningiomas, and no effective targeted chemotherapies have been developed (3–5).

Thus, in this Research Topic (https://www.frontiersin.org/research-topics/12083/meningioma-from-basic-research-to-clinical-translational-study), we collected more than 60 manuscripts discussing meningioma issues involving from basic research to clinical translational study, intend to deeply state those unresolved problems in meningioma. For example, its recurrence factors, how to improve the prognosis for malignant meningioma patients, what about the targeted chemotherapy for refractory meningioma?

CLINICAL ASPECTS OF MENINGIOMA

Meningiomas are diverse in intracranial locations and pathology, which are classified into three WHO grades and 15 histological subtypes. Sometimes meningiomas presented preferred intracranial locations, which may reflect potential biological features. In this meningioma issue collection, Sun et al. analyzed the preferred locations of meningioma according to different biological characteristics. Malignant meningiomas, compared to benign meningiomas, are more aggressive and have higher risk of recurrence after surgery. Clinical prognosis of meningioma patient is closely related to the WHO grades: patients with benign meningiomas have 5-year survival rates of 92%; however, the 5-year survival rates decrease to 78% in atypical meningiomas, and drop to 47% in anaplastic meningiomas. Currently, effective treatment for malignant meningiomas is still difficult (6). Here, we reviewed several manuscripts discussing meningioma treatment.

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Surgical resection of anterior clinoidal meningiomas remains challenge because of its complicated relationships with surrounding tissues (internal carotid arteries and optic nerves). Xu et al. found that the meningeal structures around the anterior clinoid process may guide and determine the origin and extension of anterior clinoidal meningiomas.

Matthias Schneider et al. analyzed 32 patients with sphenoorbital meningiomas underwent surgical treatment to evaluate the recovery of tumor-associated proptosis. They found that the exophthalmos index could provide a comparable standard in the evaluation.

Currently, consensus is limited regarding the optimal transcranial approaches for surgical resection of olfactory groove meningioma. Feng et al. used meta-analysis to review operative and peri-operative outcomes of unilateral compared with bilateral approaches for such kind of meningioma.

Skull base meningiomas with extracranial extensions are rarely reported. Liu et al. described the clinical features, surgical management and clinical outcomes of these meningiomas and investigated risk factors associated with progression free survival (PFS).

Bu et al. introduced their surgical experience of 162 patients with small cerebellopontine angle meningioma, and showed that surgical treatment should be the first choice for these meningiomas.

Sylvian fissure meningiomas are relatively rare and have different characteristics compared with typical meningiomas. Cai et al. reported such kind of meningioma in their paper.

Wang et al. discussed clear cell meningioma (CCM), a very rare subtype of meningioma. They concluded that CCM patients have a favorable survival rate. Patients diagnosed at 21-60 years old and patients with spinal CCMs have a better prognosis.

Yang et al. in their paper, proved that prophylactic antiepileptic drugs (AEDs) treatment for 186 patients with supratentorial meningioma from their center, does not reduce the rate of perioperative seizures.

Interestingly, Li et al. showed that elderly meningioma patients might present significantly polarization trend in maintaining long-term independence after surgery.

Intracranial hemangiopericytoma and meningioma are both meningeal neoplasms, but they have extremely different malignancy and outcomes. Because of their similar radiological characteristics, they are difficult to distinguish before surgery, leading to a high rate of misdiagnosis. Wei et al. showed that the proposed Meningioma Diagnostic Tool could assist in preoperative diagnosis to distinguish hemangiopericytoma from meningioma.

ADJUVANT RADIOTHERAPY FOR MENINGIOMA

Currently, surgical resection combined with adjuvant radiotherapy is still the main treatment options for malignant meningiomas, for instance anaplastic meningioma. And so far, no effective targeted chemotherapies have been implemented. However, adjuvant radiotherapy is controversy in some circumstances, for example, in the cases of atypical meningiomas.

For atypical meningiomas, the combination of gross total resection (GTR) and adjuvant radiotherapy is still a controversial therapeutic strategy to improve prognosis. Zhang et al. analyzed the factors influencing the prognosis on atypical meningiomas patients treated with GTR and adjuvant radiotherapy in their paper.

He et al. performed a meta-analysis study of effectiveness of postoperative adjuvant radiotherapy in atypical meningioma patients after gross total resection (GTR), and showed that postoperative adjuvant radiotherapy could improve the 5-year local control rate and 5-year PFS (progression free survival).

Wang et al. in their study created a new "prognostic score" that allows personalized recommendations for post-operative adjuvant radiotherapy in patients with high grade meningioma.

RISK FACTORS FOR RECURRENCE IN MENINGIOMA

Here, we also reviewed some manuscripts focusing on meningioma recurrence, discussing the risk factors. For instance, Zhu et al. retrospectively studied 392 meningioma patients after surgery to identify the independent risk factors of recurrence, and constructed a scoring system for the prediction of the risk of postoperative recurrence.

Alexander Fadi Haddad et al. proved that subtotal resection (STR), posterior fossa location, nuclear atypia, and elevated MIB-1 index are prognostic factors for WHO grade I meningioma recurrence. Moreover, MIB-1 index >4.5% is prognostic for recurrence in patients with gross total resection (GTR).

Zhang et al. discussed malignant progression in atypical meningiomas, and they showed that malignant progression was significantly correlated with an increased incidence of recurrence in gross total resection (GTR) plus early EBRT (external beam radiotherapy)-treated intracranial atypical meningiomas.

Wu Ye et al. investigated the relationship between clinicopathological characteristics of atypical meningiomas (AM) and its post-operative recurrence.

Neutrophil-to-lymphocyte ratio (NLR) has been reported as a prognostic factor for several solid tumors. However, the prognostic value of NLR in meningiomas is lack. Yuki Kuranari et al. reported that NLR may be a cost-effective and novel preoperatively usable biomarker in patients with meningiomas. Besides, Chen et al. also confirmed the correlation and clinical significance of preoperative fibrinogen and neutrophil-lymphocyte ratio (F-NLR) scoring system with 3-year PFS (progression-free survival) of patients with atypical meningioma.

UPDATED REVIEWS OF MENINGIOMA

Several reviews in this meningioma issue, discussing advanced management of meningioma from current therapy strategies, novel therapeutic approaches, and future directions, are worth reading. For instance, Taylor Anne Wilson et al. reviewed the update on management of atypical and anaplastic meningiomas, and discussed the risk factors, classification, and molecular

biology of meningiomas as well. Besides, Zhao et al. systematically introduced the current treatment progress of meningioma in their review paper entitled with "An overview of managements in meningiomas". Moreover, Kristin Huntoon et al. reviewed clinicopathological and molecular aspects in meningioma. While there are currently no good adjuvant chemotherapeutic agents available, recent advances in the genomic and epigenomic landscape of meningiomas are being explored for potential targeted therapy for meningioma (7, 8). Shao et al. reviewed advances in chromosomal variations and molecular mechanisms involved in the progression of meningioma, and highlighted the association with malignant biological behavior including cell proliferation, angiogenesis, increased invasiveness, and inhibition of apoptosis.

BASIC RESEARCHES ON MENINGIOMA

In this meningioma topic collection, we also recruited several manuscripts focused on meningioma basic studies from aspects of receptors, sex hormones, and meningioma cells level. Those researches are thought to be promisingly paving ways for future targeted therapies for meningiomas.

Despite high recurrence rate of atypical and malignant subtypes, there is no approved drug investigated for meningioma. Maya Hrachova et al. evaluated efficacy and safety of Sandostatin LAR (octreotide, a kind of somatostatin analogs) in patients with progressive, and/or recurrent meningioma, and identified subset of patients who were more likely to benefit from this treatment. Wu et al. also discussed the clinical significances of somatostatin receptor (SSTR)-2 in meningioma, a G-protein-coupled receptor and can be activated by somatostatin or its synthetic analogs.

Female sex hormones may influence meningioma development. Francesco Maiuri et al. proved that the biological behavior of meningiomas and their pathological findings, including progesterone receptor (PR) expression, are not correlated with the different hormone related conditions in premenopausal female patients. Contraceptives and fertilization therapies should be avoided in patients with meningiomas.

Accumulating evidence indicated that long non-coding RNA maternally expressed gene 3 (MEG3) participated in the progression of meningioma. However, the potential mechanisms of MEG3 need further investigation. Ding et al. showed that MEG3 mediated the aggressive behaviors of meningioma cells *via* miR-29c/AKAP12 axis, supporting that MEG3 served as a promising biomarker for the diagnosis and treatment of human meningioma. Zhang et al. also studied the effect of microRNA-221/222 radiosensitivity in meningiomas in their paper.

OTHER ASPECTS OF MENINGIOMA RESEARCH

Currently, multiple methods have been applied for meningioma research, including genomics, proteomics, epigenetics, radiomics, multi-omics, etc. These techniques will help in deeply explore those aggressive meningiomas.

Ma et al. performed genome-wide genotyping for cranial meningiomas in 383 Chinese patients and identified 9,821 copy number variations, showing patients with diverse clinical features had distinct tumor copy number variations profiles.

The DNA methylation-based meningioma classification published in 2017 (9) used DNA copy number analysis, mutation profiling, and RNA sequencing to distinguish six clinically relevant methylation classes, which contributed to a better prediction of meningioma recurrence and prognosis. Shen et al. summarized the key findings of recent studies on the methylation status and genetic mutations of meningioma and discussed the current deficits of WHO grading.

Studies have shown mitochondrial genome (mtDNA) content varies in many malignancies. However, its distribution and prognostic values in high-grade meningioma remain largely unknown. In the retrospective study, Hua et al. assessed a putative correlation between the mtDNA content and clinical characteristics. They found that high mtDNA content was associated with better outcome in WHO grade III meningioma.

Gu et al. reviewed the latest advancements of radiomics and its applications in the prediction of the pathological grade, pathological subtype, recurrence possibility, and differential diagnosis of meningiomas.

Growing evidence demonstrated the potential of multi-omics study (including genomics, transcriptomics, epigenomics, proteomics) for meningiomas diagnosis and mechanistic links to underlying therapeutic targets. In the review paper, Liu et al. provided a timely and necessary study of such scientific basis for further treatment of meningiomas.

CONCLUSIONS

In conclusion, as discussed above, all of the recent developments are creating new prospects for effective molecularly driven diagnosis, classification and therapy of meningiomas (9–11). However, there is still a long way to go in the study of meningioma from many aspects. There are still many problems, including its cell origin (12), to be solved for this very complicated brain tumor. Here, we had just discussed a very little knowledge on meningioma in this meningioma topic collection. However, with continued research on the mechanisms of meningioma pathogenesis, the screening and development of new drug targets are forthcoming.

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Factors Related to the Post-operative Recurrence of Atypical Meningiomas

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Aim: This study aimed to investigate the relationship between clinicopathological characteristics of atypical meningiomas (AM) and its post-operative recurrence.

Materials and Methods: The clinicopathological characteristics and findings from follow up were retrospectively reviewed and compared between AM and benign meningioma (BM) patients. Univariate and multivariate analyses were employed to identify the factors related to the post-operative recurrence of AM.

Results: More BM patients were females and received complete resection; the recurrence rate was significantly lower in BM patients as compared to AM patients. The progesterone receptor (PR), E-cadherin protein (E-Ca) and β-catenin positive rates and Ki67 labeling index were significantly different between two groups. Univariate analysis showed the age, tumor size, tumor invasiveness, E-Ca expression, and extent of resection were related to the post-operative recurrence of AM. However, multivariate analysis showed only the extent of resection and tumor invasiveness were the independent factors associated with the post-operative recurrence of AM.

Conclusions: The extent of resection and tumor invasiveness are related to the post-operative recurrence of AM. To improve the surgical procedures to maximize the tumor resection is important to improve the prognosis of AM patients.

Keywords: atypical meningiomas, prognosis, recurrence, clinicopathological characteristics, predictive factors, extent of resection, tumor invasiveness

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INTRODUCTION

Meningiomas, a tumor of meningothelial cell origin, are the second most common intracranial tumor and account for about 24–30% of intracranial tumors (1–3). According to the World Health Organization classification system, meningiomas are classified into grade I (typical), grade II (atypical), and grade III (anaplastic) tumors. Most meningiomas are benign (grade I), and atypical meningiomas (AM) account for about 5–7% of meningiomas.

Surgery is a major treatment for meningiomas. The benign meningiomas have a relatively low risk of recurrence (∼10%) after complete resection, but AM and anaplastic meningiomas are characteristically more aggressive in nature and associated with higher recurrence risks (29–52% and 50–94%, respectively) (4). Benign meningiomas (BM) seem to be related to estrogen levels and are more common in women, but AM and anaplastic meningiomas are more common

among men and also seem to have a greater predilection for the cerebral convexities. Some studies have investigated the prognostic factors of AM. Zaher et al. reported that age (<50 years) and total surgical excision were independent prognostic factors for survival and radiotherapy could reduce the post-operative recurrence (5). There is evidence showing that age, male gender, extent of surgical resection, and higher MIB-1 (a commonly used monoclonal antibody that detects the Ki-67 antigen) labeling index influence the prognosis of AM patients, and postoperative radiotherapy fails to provide long-term tumor control (6, 7). In a Korea study, results showed the overall survival was not related to the patient age, gender, tumor location, Ki-67 (a cellular marker for proliferation), Simpson grade, and treatment (8). In patients with skull base AM, the age of disease onset and MIB-1 index were found to be independent prognostic factors of clinical outcome, and adjuvant radiotherapy was recommended to reduce recurrence regardless of the extent of surgical resection (9). Ros-Sanjuan et al. found the extent of excision was the only predictor of post-operative recurrence (10), but Streckert et al. found the brain invasion was also found to be associated with the post-operative recurrence (11). These differences might be ascribed to the age, race, sample size, tumor location, dose of radiotherapy, and other factors. Currently, little is known about the factors related to the post-operative recurrence in AM patients in China mainland.

In the present study, we retrospectively investigated 30 patients diagnosed with AM in two clinical centers, and the clinicopathological characteristics and findings from follow up were collected and compared between AM patients and benign meningioma (BM) patients as controls. Furthermore, the relationships of these factors with post-operative recurrence were explored in AM patients, aiming to provide evidence on the clinical management of AM.

MATERIALS AND METHODS

Patients

A total of 1,068 patients were diagnosed with meningioma according to the 2007 WHO classification in the Department of Neurosurgery of two hospitals (The First Affiliated Hospital of Medical School of Zhejiang University and Tongde Hospital of Zhejiang Province). Among these patients, 37 were diagnosed with AM (3.4%), of whom 30 had complete medical record and received follow up. All these patients were initially diagnosed with AM and did not received surgery or radiotherapy before study. The pathological diagnosis of AM was confirmed by two experienced pathologists (12). In addition, 30 patients diagnosed with BM (WHO grade I) and having complete clinical record were included as controls: they were pathologically diagnosed with BM in the same period; they had no severe heart, liver, and liver disease; there was no metastasis; the age ranged from 18 to 80 years. This was a retrospective study and approved by the Institutional Review Board of two hospitals.

Data Collection

The clinicopathological characteristics were collected by reviewing the medical record: age, gender, surgical findings, imaging findings, presence of and time to post-operative recurrence, managements after recurrence, and survival status. The maximal tumor diameter (cm) was determined on MRI or CT.

Immunohistochemistry

The surgically collected tissues were embedded in paraffin, and 4-μm sections were obtained, followed by immunohistochemistry with two-step Envision method. The surrounding normal brain tissues were used as a positive control, and phosphate buffered solution (PBS) was used instead of primary antibody in the negative control. Following proteins were detected by immunohistochemistry: progesterone receptor (PR), Ki-67, E-cadherin protein (E-Ca) and β-catenin, and following antibodies were used: mouse anti-human PR, mouse anti-human Ki-67 (Long-Island Diagnostic Reagent Co., Ltd), mouse anti-human E-Ca, mouse anti-human β-catenin, and anti-mouse secondary antibodies (DAKO company). In the immunohistochemistry, 3,3'-diaminobenzidine (DAB), hematoxylin and 0.1% hydrochloric acid (HCL) were used, and mounting was done with neutral gum. After immunohistochemistry, sections were observed under a light microscope (OLYMPUS, Japan).

Pathological Assessment

Normally, E-Ca is expressed on the cell membrane, and loss of E-Ca expression on the cell membrane is abnormal. Normally, β-catenin is expressed on the cell membrane and in the cytoplasm, and nuclear expression of β-catenin is abnormal. Cells with yellowish-brown nucleus were regarded positive after immunohistochemistry for PR. Cells with yellow or brown nucleus were regarded positive after immunohistochemistry for Ki67.

Two experienced pathologists scored the pathological findings according to the semi-quantitative immunoreactive scoring (IRS) method: (1) staining intensity (×400): no staining, 0; light yellow, 1, yellowish-brown, 2; brown, 3; (2) counting of positive cells: five fields were randomly selected at ×200, and a total of 200 tumor cells were counted in each field. The proportion of positive cells was determined as follows: <5%, 0; 5–25%, 1; 26–50%, 2; 51–75%, 3; >75%, 4. The final score was the product of above two scores and classified as – (0), – (1–2), ++ (3–6) and + + + (>6). Positive staining refers to +, ++, and + + +, and negative staining refers to –. Ki67 labeling index (Ki67LI) was calculated as follow: number of positive cells / total cells ×100%.

Determination of Edema Index

The edema index (EI) was defined as the edema/tumor volume ratio as previously reported (13): $(V_{edema}-V_{tumor})/V_{tumor}$. The maximal length, width and height of the tumor or edema were measured and the tumor volume was calculated as follow: V = (length × width × height)/2. The peritumoral brain edema was scored as follow: 0, EI = 0 (no peritumoral brain edema); 1, 0<EI≤1 (mild peritumoral brain edema); 2, 1<EI≤2 (intermediate peritumoral brain edema); 3, EI>2 (severe peritumoral brain edema).

Assessment of Tumor Invasiveness

The tumor invasiveness was mainly assessed macroscopically and microscopically.

Brain Invasion

Invasion of the tumor into the brain parenchyma was deemed present when any of the following criteria were met after we performed a standard sampling protocol: (1) the brain–tumor interface was observable and showed invasion of tumor into the brain on hematoxylin-eosin (HE) staining; (2) a sample of tumor was available containing brain tissues within it that displayed reactive astrocytosis or neuronal degeneration; or (3) reactive astrocytes within the tumor were revealed using standard glial fibrillary acidic protein (GFAP) immunostaining.

Dural Invasion

(1) the basal dura mater was invaded by tumor cells on HE staining; (2) tumor cells invaded the dura mater and cause damage; (3) tumor cells invaded the sagittal sinus or contralateral falx cerebri; (4) The area of thickening dura mater close to the tumor was one or more times that of the tumor.

Skull Invasion

(1) The tumor invasion caused local skull deformation or defect; (2) The tumor was adherent to the skull after penetrating the dura mater, and pathological examination showed tumor cell infiltration or tumor nest formation in the bone.

Multiple-Site Invasion

The tumor cells invaded two or more tissues.

Determination of Extent of Resection

The extent of resection was determined according to the Simpson Grading scale: grade I, macroscopically complete tumor resection with removal of affected dura and underlying bone; grade II, macroscopically complete tumor resection with coagulation of affected dura only; grade III, macroscopically complete tumor resection without removal of affected dura or underlying bone; grade IV, subtotal tumor resection; grade V, decompression with or without biopsy (14).

Statistical Analysis

Statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Quantitative data are expressed as mean ± standard deviation (SD) and compared with *t*-test; categorical data were compared with Chi square test. Univariate analysis was done with Kaplan-Meier method to evaluate the relationship of clinicopathological factors (gender, age, tumor diameter, tumor location, peritumoral edema, tumor invasiveness, Ki-67 LI, E-ca positive rate, β-catenin positive rate, PR positive rate, extent of surgical resection, and post-operative radiotherapy) with post-operative recurrence. The independent factors related to the post-operative recurrence of AM were determined by using the multivariate Cox regression analysis. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics of Patients in the AM Group and BM Group

In the AM group, there were 19 females and 11 males, and the mean age was 58.6 ± 16.6 years (range: 20–81 years); 46.7% (14/30) of patients were younger than 60 years. In the BM group, there were 26 females and 4 males, and the mean age was 53.6 ± 14.6 years (range: 5–74 years); 63.3% of patients were younger

TABLE 1 | Clinicopathological characteristics of AM patients and BM patients.

Variables		AM ($n = 30$)	BM ($n = 30$)	*P*
Gender				
	M	11 (36.7)	4 (13.3)	*$P < 0.05$
	F	19 (63.3)	26 (86.7)	
Age (years)				
	Mean	58.6 (20–81)	53.6 (5–74)	$P > 0.05$
	≤60	14 (46.7)	19 (63.3)	
	>60	16 (53.3)	11 (36.7)	
Location				
	Skull base	7	11	$P > 0.05$
	convexity	17	13	
	parasagittal	6	6	
Tumor diameter (cm)				
	Range	5.4 (1.5–10)	4.2 (1.1–11)	*$P < 0.05$
	≤5	14 (46.7)	23 (76.0.7)	
	>5	16 (53.3)	7 (23.3)	
Peritumoral edema				
	Mild (0, 1)	16 (53.3)	13 (43.3)	$P > 0.05$
	Severe (2, 3)	14 (46.7)	17 (56.7)	
Extent of surgical resection				
	Total	18	26	*$P < 0.05$
	Subtotal	12	4	
Radiotherapy	Yes	7	3	$P > 0.05$
	No	23	27	
Recurrence	Yes	12	2	*$P < 0.05$
	No	18	28	
Death	Yes	2	0	$P > 0.05$
	No	28	30	
Invasiveness	Meninges	30 (100%)	25 (83.3%)	**$P < 0.01$
	Brain	12 (40%)	2 (6.7%)	
	Skull	11 (36.7%)	2 (6.7%)	
	Multiple	17 (56.7%)	4 (13.3%)	
β-catenin	Positive	13	27	$X^2 = 14.70$, *$P < 0.01$
	Negative	17	3	
PR	Positive	14	24	$X^2 = 7.18$, *$P < 0.01$
	Negative	16	6	
E-Ca	Positive	13	26	$X^2 = 12.38$, *$P < 0.01$
	Negative	17	4	
Ki67	Positive	13	1	$X^2 = 13.42$, *$P < 0.01$
	Negative	17	29	

AM, atypical meningioma; BM, benign meningioma; E-ca, E-cadherin protein; F, female; M, male; PR, progesterone receptor.

*$P < 0.05$, **$P < 0.01$: AM group vs BM group.*

than 60 years (**Table 1**). Significant difference was observed in the gender between AM group and BM group, but there was no marked difference in the age. The skull base, convexity, and parasagittal meningiomas were found in 7, 17, and 6 patients, respectively, in the AM group, and 11, 13, and 6 patients, respectively, in the BM group, showing no pronounced difference between two groups in the tumor localization. The mean tumor diameter was 5.4 ± 1.7 cm (range: 1.5–10 cm) in the AM group and 4.4 ± 2.0 cm (range: 1.1–11 cm), there was marked difference in the tumor size between them, and more patients in the AM group had the tumor larger than 5 cm in the diameter.

In addition, mild and severe peritumor edemas were noted in 16 and 14 patients, respectively, in the AM group and 13 and 17 patients, respectively, in the BM group, showing no significant difference. Simpson grade I and II were defined as total resection, and Simpson grade III, IV, and V as sub-total resection. As shown in the **Table 1**, the percentage of patients receiving total resection was 86.7% in the BM group (26/30), which was significantly higher than in the AM group (60.0%; 18/30; $P < 0.05$).

In the AM group, seven patients received post-operative radiotherapy, of whom five underwent gamma knife surgery and two received whole brain radiotherapy. In the BM group, three patients received post-operative radiotherapy (all with gamma knife surgery). Patients in both groups did not receive post-operative chemotherapy. There was no marked difference in the proportion of patients receiving post-operative radiotherapy although it in the AM group was slightly higher than in the BM group ($P > 0.05$).

Findings From Follow Up

In the AM group, 30 patients received complete follow up for a median of 34 months (range: 3–69 months), 12 developed recurrence and two died. In the BM group, 30 patients received complete follow up for a median of 32.5 months (range: 18–80 months), two developed recurrence and none died. The recurrence rate in the AM group (40%; 12/30) was significantly higher than in the BM group (6.7%; 2/30) ($P < 0.05$).

Immunohistochemical Findings

Fourteen and twenty-four patients were positive to PR in the AM group and BM group, respectively, showing marked difference between them ($P < 0.01$). Positive E-Ca expression was found in 13 and 26 patients in the AM group and BM group, respectively, showing dramatic difference ($P < 0.01$). 13 and 27 patients were positive to β-catenin in the AM group and BM group, respectively, showing marked difference ($P < 0.01$). The Ki67 LI was 8 ± 4.32% in the AM group and 2.83 ± 1.77% in the BM group, and significant difference was noted in the Ki67 LI between them. Moreover, Ki67 LI ≥8% was found 13 patients in the AM group, but only one patient in the BM group ($P < 0.01$).

Univariate Analysis of Factors Related to the Post-Operative Recurrence

Results showed age, tumor size, tumor invasiveness, and extent of resection were positively related to the post-operative recurrence. The slightly increased recurrence rate in the patients receiving post-operative radiotherapy seemed to be associated with the use of sub-total resection in these patients. In addition, the recurrence rate was also significantly different between patients with triple invasion and remaining patients (**Table 2**).

In addition, E-Ca expression was negatively related to the recurrence rate in the AM group. Although more patients with Ki67 LI ≥8% or being negative to β-catenin had higher recurrence rate, no statistical significance was observed. There

TABLE 2 | Univariate analysis of clinicopathological factors with post-operative recurrence in AM patients.

Variables	*n*	Recurrence (%)	Mean	Median (range)	*P*
Age (years)			58.6	65 (20–81)	*$P = 0.01$
0-60	14	2 (14.3)			
>60	16	10 (62.5)			
Gender					$P = 0.06$
M	11	2 (18.1)			
F	19	10 (52.6)			
Location					$P > 0.05$
Convexity	17	6 (35.3)			
Parasagittal	6	2 (33.3)			
Skull base	7	4 (57.1)			
Maximal diameter (cm)			5.4	5.2 (1.5–10.0)	*$P = 0.01$
0–5.0	14	2 (14.3)			
>5.0	16	10 (62.5)			
Peritumoral edema					0.28
Mild	16	6(37.5)			
Severe	14	6 (42.8)			
Tumor invasiveness					*$P = 0.02$
Single or double invasion	24	7 (25.9)			
Triple invasion	6	5 (83.3)			
Extent of resection					*$P = 0.00$
Total	18	2 (11.1)			
Subtotal	12	10 (83.3)			
Radiotherapy					$P > 0.05$
Yes	7	3 (42.9)			
No	23	9 (39.1)			
Ki67			8.0%	7.0% (3–25%)	$P = 0.12$
<8%	17	5 (29.4)			
≥8%	13	7 (53.8)			
E-ca					*$P = 0.02$
Negative	17	10 (58.8)			
Positive	13	2 (15.4)			
β-catenin					$P = 0.20$
Negative	17	8 (60.0)			
Positive	13	4 (20.0)			
PR					$P = 0.28$
Negative	16	6 (37.5)			
Positive	14	6 (42.9)			

AM, atypical meningioma; E-ca, E-cadherin protein; F, female; M, male; PR, progesterone receptor.
$P < 0.05$: among subgroups.

TABLE 3 | Multivariate analysis of factors related to the post-operative recurrence in AM patients.

Variables	B	SE	Wald	df	sig	Exp(B)
Age	0.354	0.322	1.205	1	0.272	1.425
Gender	0.219	4.368	0.003	1	0.960	1.245
Location	1.007	1.093	0.849	1	0.357	2.739
Maximal diameter	−2.295	1.332	2.972	1	0.085	0.101
Peritumoral edema	2.392	2.105	1.291	1	0.256	10.934
Tumor invasiveness	−5.759	2.868	4.032	1	0.045	0.003
Extent of resection	7.605	3.492	4.742	1	0.029	2008.067
Radiotherapy	11.480	7.868	2.129	1	0.145	96717.926
Ki67	0.034	0.233	0.022	1	0.882	1.035
E-ca	5.934	3.894	2.323	1	0.128	377.752
β-catenin	2.228	2.283	0.953	1	0.329	9.286
PR	−0.583	1.926	0.092	1	0.762	0.558

AM, atypical meningioma; E-ca, E-cadherin protein; PR, progesterone receptor.

was no significant relationship between PR and post-operative recurrence in the AM group (**Table 2**).

Multivariate Analysis of Factors Related to the Post-Operative Recurrence

Multivariate analysis showed the extent of resection ($P = 0.029 < 0.05$) and tumor invasiveness ($P = 0.045 < 0.05$) were closely related to the post-operative recurrence of AM (**Table 3**).

DISCUSSION

Meningiomas are slow-growing, well-circumscribed tumors arising from the arachnoid cap cells of the dura mater. Most meningiomas are benign, which corresponds to the WHO grade I, and AM (WHO grade II) are reported in 5–7% of all cases (3, 4). In the present study, we first compared some clinical characteristics between AM and BM patients. The incidence of meningiomas rises with age and they are most common in sixth and seventh decade of life. In addition, it has been reported that there is a marker female predilection with the female to male ratio of 3:2 to 2:1 (3–5). However, there is evidence showing that BM is more common in women, which seems to be linked to the estrogen levels, and AM and anaplastic meningiomas are more common in males, which might be ascribed to the higher proliferation indices in male meningioma patients (15). In the present study, the female to male ratio was 1.7: 1 in the AM group, and 6.5: 1 in BM group, which were consistent with the above findings and suggested the female predominance in BM. In addition, about 53.3% of AM patients and about 36.7% of BM patients were older than 60 years. This was inconsistent with previously reported, which might be ascribed to the small sample size. Moreover, there was no marked difference in the age between two groups. The distribution of tumor location and the EI were similar between two groups, but AM was significantly larger than BM in our study, and significantly more BM patients received total resection as compared to AM patients (86.7 vs. 60%). These may be related to the more aggressive nature of AM (15). Although more AM patients received post-operative radiotherapy, significant difference was not observed between them.

Surgery remains a mainstay of treatment of meningiomas. The microsurgical removal is a preferred treatment for meningiomas when feasible and with acceptable clinical risk. After surgery (especially complete resection of the tumor), BM patients usually have a favorable prognosis, but AM patients often have the risk for post-operative recurrence despite gross-total resection with removal of involved dura and bone and even after substantial time from the initial surgery, which significantly affects the post-operative survival. The prognosis (such as survival time and recurrence) is closely related to the histological grade of meningiomas and the surgical methods. In a large-scale study, according to the histological grade, the estimated 5 years survival was only 70% in patients with benign tumors, 75% for AM and 55% for patients with anaplastic tumors (16); in another population-based studies, the reported 5-year survival rate was near 90% (17). Berrino et al. reported, the 5 years recurrence rate was 3% in BM, 38% in AM and 78% in anaplastic meningiomas after complete resection (18). In the study of Ostrom et al., the 5-year recurrence rate was about 50% for grade II tumors and 90% for grade III tumors (19). Our results also showed significant difference in the recurrence rate between AM group and BM group (40 vs. 6.7%). In the present study, the overall recurrence rate was 40% within a median of 34 months; 60% of AM patients received complete resection and the recurrence rate was 11.1% in patients receiving complete resection. Currently, the recurrence rate varies among available studies, which might be partially related to the definition of recurrence, surgical methods and therapeutic strategies (3).

Studies have investigated the predictors of post-operative recurrence of meningiomas. The extent of resection, tumor pathological features, tumor location and size, tumor invasion, peritumoral edema, age, and gender have been found to be associated with the post-operative recurrence of meningiomas (20). However, little is known about the factors related to the post-operative recurrence of AM in Chinese population. In the present study, we investigated the relationships of some clinicopathological characteristics of AM with the post-operative recurrence. The univariate analysis showed age, tumor size, tumor invasiveness, and extent of resection were positively related to the post-operative recurrence. In addition, the recurrence rate was also significantly related to the triple invasion (suggesting the tumor invasiveness). For the pathological parameters, E-Ca, Ki67, and β-catenin expressions were also found to be related to the post-operative recurrence. PR expression had no relationship with the post-operative recurrence, which may partially explain female predominance of BM, but not AM. Further multivariate analysis showed only the extent of resection and tumor invasiveness were closely related to the post-operative recurrence of AM. In a more recent study, Ros-Sanjuan et al. showed total resection was the only significant factor associated with recurrence (10). However, even though complete tumor resection is the goal, surgery should be tailored to each patient according to the risks and surgical morbidity (21). In a study involving 76 patients, Kim et al. also found

the brain and/or bone involvement predicted an increased risk of treatment failure despite combination therapy (22). Mantle et al. found the cancer cells invaded the brain by advancing along vessels that bridge the gap between the cancer surface and the cortex, and thus they proposed that these cancer cells were the most frequent source of recurrences after "complete" resection (23).

Currently, the use of radiotherapy in meningiomas patients is still controversial. Generally, the decision to use adjuvant radiotherapy is based on the extent of resection and the histologic tumor characteristics, and it is also added in AM and BM patients. Radiotherapy has been used as the primary treatment for non-resectable tumors for decades. In addition, it may serve as a post-operative adjuvant therapy or in case of recurrence for previously resected meningiomas. In a more recent study, results showed radiotherapy was more often applied after incomplete resection, but postoperative radiotherapy did not improve the progression-free survival (PFS) (24). Of note, there are no convincing findings from randomized controlled clinical trials supporting the use of radiotherapy in meningiomas patients. The role for adjuvant radiotherapy in AM is much more controversial compared to that for anaplastic meningiomas. In the present study, the proportion of patients receiving post-operative radiotherapy was comparable between AM patients and BM patients, and radiotherapy was not related to the post-operative recurrence. Our findings were consistent with previous findings although there is benefit from the use of adjuvant radiotherapy, even after complete resection, in AM patients (25). This might be related to the study design of available studies (most retrospective or observational studies). In our study, seven AM patients received post-operative radiotherapy and three developed post-operative recurrence (42.9%), but nine patients had recurrence among 23 patients without post-operative radiotherapy (39.1%). This paradoxical finding might be explained as that patients receiving post-operative radiotherapy usually had incomplete resection. In addition, the small sample size may also be another reason.

There were still limitations in this study. There were only 30 AM patients recruited, and the duration of follow up was relatively short. In addition, only the recurrence was assessed in our study. The retrospective design in this study also limits the expansion of findings in clinical practice. Thus, more randomized, controlled prospective studies are needed to confirm our findings. In addition, in recent years, genetic mutations have been identified as a factor related to the prognosis of meningiomas and they may also be used to guide the treatment of meningiomas (26). It is necessary to investigate the relationship between genetic markers and post-operative recurrence of AM.

Taken together, BM has a higher prevalence in females, and AM patients have a higher post-operative recurrence rate. Among clinicopathological characteristics, the extent of resection and tumor invasiveness are the independent risk factors of post-operative recurrence in AM patients. Thus, to tailor the surgical procedures and maximize the surgical resection will improve the post-operative prognosis of AM patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of The First Affiliated Hospital of Medical School of Zhejiang University and Tongde Hospital of Zhejiang Province. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LY and ZR-Y conceived the study design. WY and TD-Z were responsible for patient recruitment. WY, TD-Z, and YX-S organized database and were responsible for statistical calculations. WY, ZR-Y, and LY drafted the article. All authors discussed the results, revised the draft, and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Sylvian Fissure Meningiomas: Case Report and Literature Review

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Meningiomas are primary intracranial tumors derived from arachnoid cap cells or meningothelial cells and usually display dural attachment. However, a small proportion of meningiomas that arise from the Sylvian fissure do not manifest dural attachment. Sylvian fissure meningiomas are relatively rare and have differential characteristics as compared with typical meningiomas. Herein, we reported a special case of atypical meningioma in the Sylvian fissure, that showed non-enhancement after contract management. The patient was a 30-year-old woman with a 2-year history of seizures. Preoperative computerized tomography and magnetic resonance imaging scans showed a calcific, non-enhancing lesion in the right insula lobe. The lesion was excised surgically for seizure control. Intraoperatively, the tumor was observed to be closely adhered to the middle cerebral artery (MCA), resulting in mild arterial damage. A case of Sylvian fissure meningioma was ultimately diagnosed by histopathological examination of the resected specimens. Sylvian fissure meningiomas are closely associated with the MCA and exhibit unusual imaging characteristics. Preoperative misdiagnosis may have serious adverse consequences and may result in incorrect surgery. To improve awareness of Sylvian fissure meningiomas on the differential diagnosis of Sylvian fissure lesions among clinicians, we present this report and briefly summarize previously reported cases to describe the clinical, pathological, radiological, and surgical features.

Keywords: meningiomas, Sylvian fissure, case report, atypical, neurosurgery

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INTRODUCTION

Generally, meningiomas originate from the dura mater; however, some cases originate from the Sylvian fissure and show non-dural attachment. These cases can be easily missed preoperatively or may be misdiagnosed. Atypical meningioma is a distinct meningioma subtype and accounts for a small proportion of meningiomas with poor prognosis (1). At present, 38 cases of Sylvian fissure meningiomas have been reported (2–32), and four cases presented an atypical type (19, 22, 25, 30), but none were non-enhanced lesions (30). In this report, we describe a patient who presented with an intracranial mass in the right insula lobe, which was clinically diagnosed as a low-grade glioma based on the results of preoperative neuroimaging, with a subsequent revised diagnosis of meningioma confirmed by postoperative histopathology. In contrast with previous reported cases, our case presented characteristic non-enhancement of the meningioma lesion on contrast-enhanced magnetic resonance imaging (MRI), which is unique. In addition, we have reviewed the relevant literature and summarized the major findings herein to improve the awareness of Sylvian fissure meningiomas among clinicians for the differential diagnosis of Sylvian fissure lesions.

CASE PRESENTATION

The patient was a 30-year-old homemaker with a 2-year history of seizures before admission. She had previously been treated with a routine antiepileptic (sodium valproate; 1,000 mg per day) for 3 months; however, the drug was weaned off because of its side effect (weight gain). Subsequently, she was prescribed lamotrigine (200 mg per day) and topiramate (75 mg per day) for seizure control, but continued to have occasional seizures, once or twice a month. She had no other neurological deficit or past medical history, and results of systemic examinations were normal. She had no family history of hereditary diseases. Electroencephalography performed after admission detected epileptiform activity in the right cerebral hemisphere. Computerized tomography (CT) demonstrated a calcific lesion in the right Sylvian fissure and posterior part of the insula (**Figure 1A**). An MRI scan revealed a lesion in the right insular lobe without any dural attachment, which was primarily hypointense on both T1- and T2-weighted MRI (**Figures 1B,C**). Additionally, the lesion appeared hypointense on susceptibility-weighted imaging (**Figure 1D**), with no obvious enhancement despite administration of gadolinium contrast (**Figures 1E, F**). The results of all preoperative laboratory tests were within normal ranges. Preoperatively, low-grade glioma, including oligodendroglioma, and diffuse astrocytoma, was suspected.

With this provisional diagnosis, the patient was referred for surgical management and underwent a right temporal craniotomy for gross total resection of the tumor and for seizure control. Upon opening the dura and separating the Sylvian fissure, a gray-white lesion (diameter, about 25*20 mm) was observed. It had a relatively elastic consistency and the mass partially invading the brain parenchyma of the insula, was

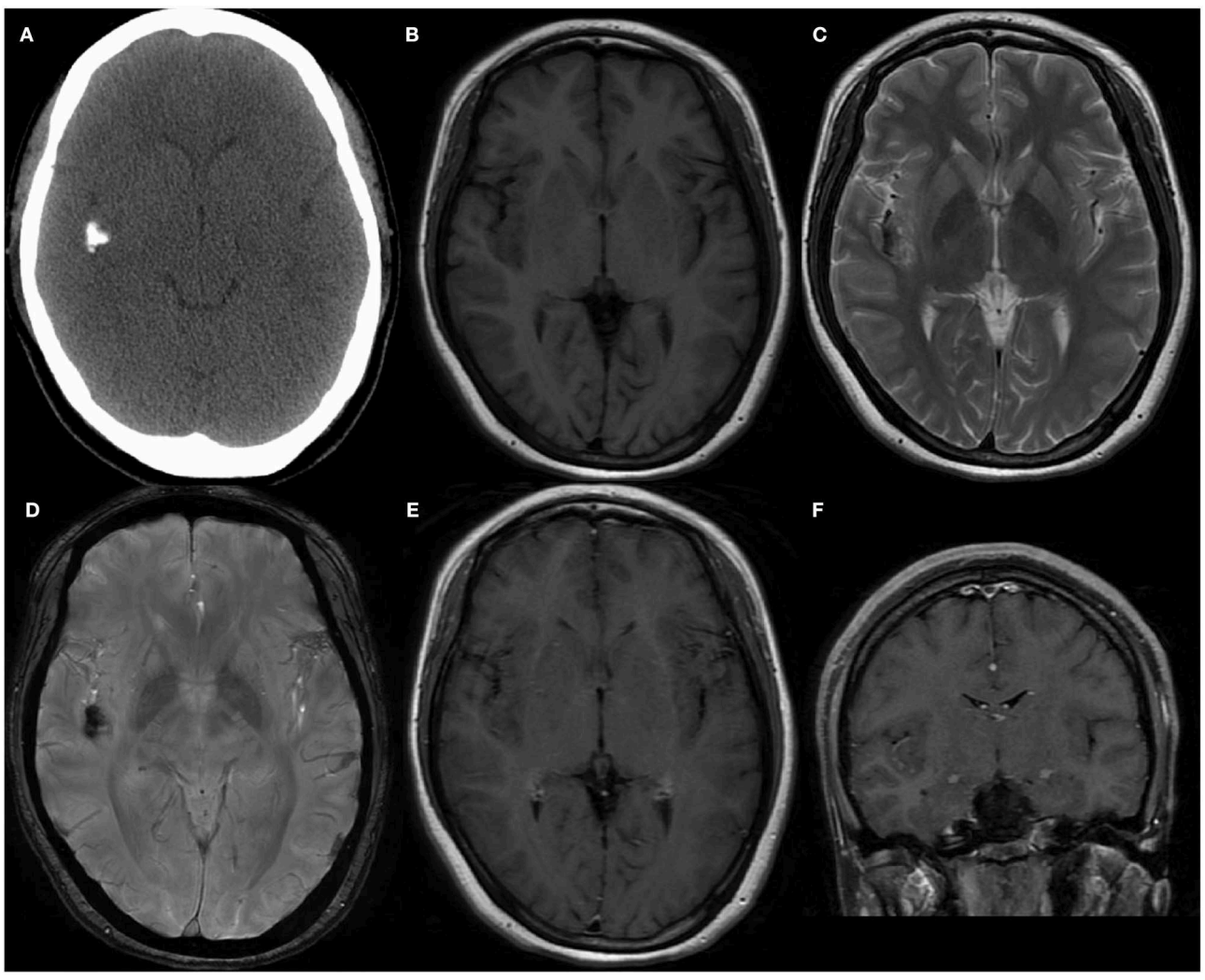


FIGURE 1 | (A) The Computed tomography demonstrated the calcification in right Sylvian fissure and posterior part of insula. **(B,C)** MRI scans revealed a lesion without dural attachment located in right insular lobe which was mainly hypointense on both T1-weighted and T2-weighted. **(D)** Lesion showed hypointense on susceptibility weighted imaging. Enhanced MRI showed no obvious enhancement after gadolinium administration in axial **(E)** and coronal **(F)** position.

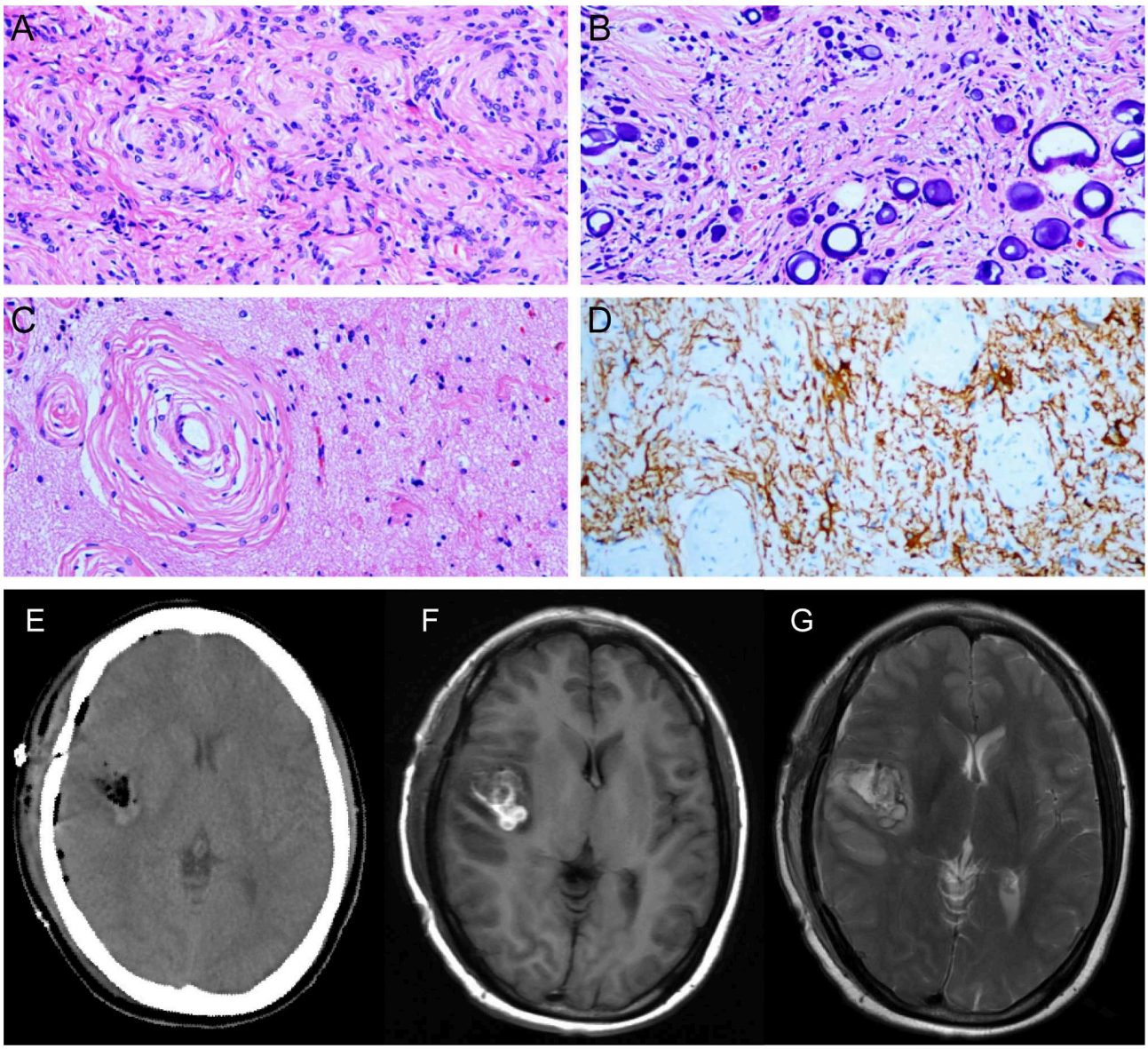


FIGURE 2 | (A) The tumor tissue arranged in swirl structure to form the meningeal corpuscle. **(B)** Psammoma bodies. **(C)** The meningeal corpuscles invade normal brain tissue. **(D)** GFAP staining show brain tissue (+) and meningeal corpuscles (-). Postoperative CT **(E)** and MRI **(F,G)** showed tumor gross total resection.

densely adhered to the branches of the medial cerebral artery (MCA), and had partial calcification. Intraoperatively, despite careful micro-dissection, the MCA perforators were mildly damaged. Ultimately, several surgical specimens of the excised tumor were sent for histopathological analysis. Postoperatively, the results of histopathological examinations revealed a World Health Organization (WHO) grade II meningioma of atypical type (**Figures 2A–D**). Immunohistochemical examinations revealed negative immunoreactivity for Ki-67, progesterone receptor, p53, epithelial membrane antigen, and positive immunoreactivity for vimentin, and somatostatin receptor 2.

Postoperatively, the patient regained consciousness with a mild clinical symptom of hemiplegia in her left limbs, which lasted for nearly 2 weeks but improved gradually with rehabilitation therapy. A follow-up gadolinium-enhanced MRI (postoperative 2 weeks) showed complete total excision of the tumor (**Figures 2E–G**). The patient presented no other postoperative neurological deficit or seizure recurrence for approximately a year and a half. An MRI scan will be performed annually to continuously monitor for any evidence of tumor recurrence.

DISCUSSION

Meningiomas are the second most common primary central nervous system tumors (CNST), accounting for

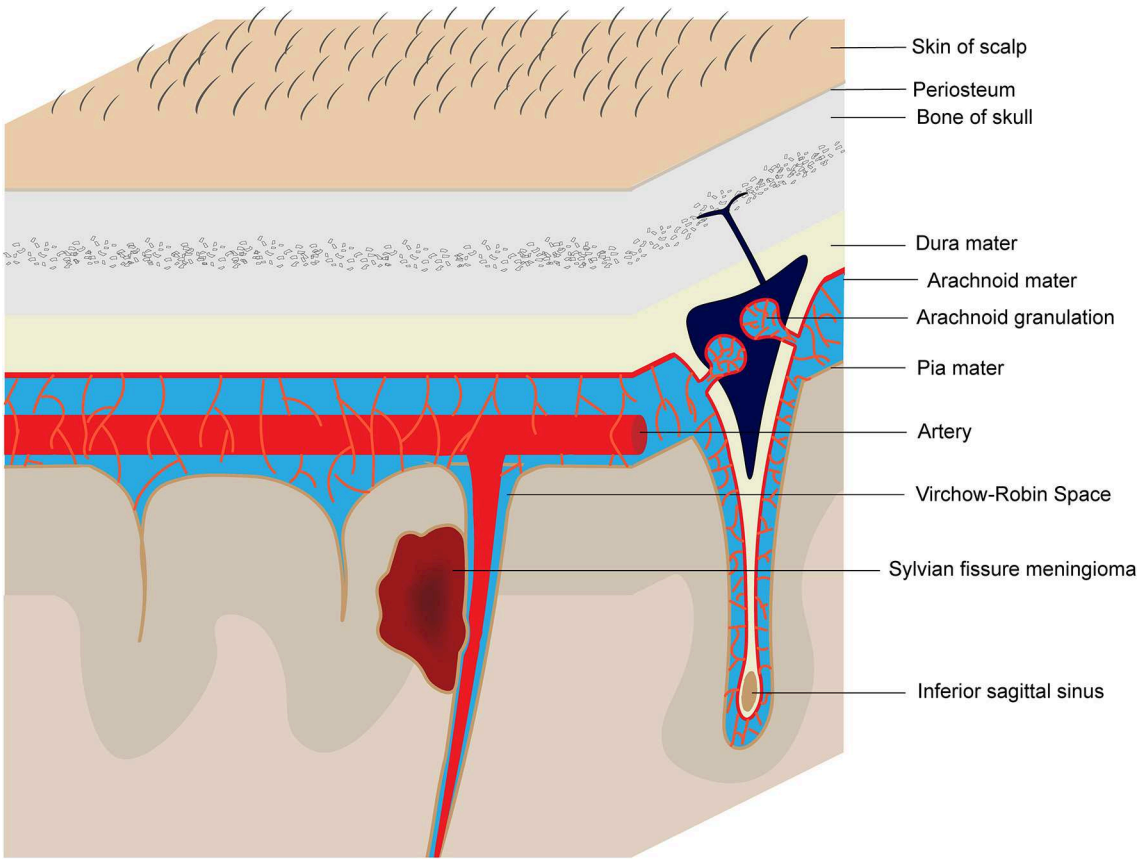


FIGURE 3 | Schematic diagram of the origin of Sylvian fissure meningiomas.

approximately one-third of the primary CNST cases (33, 34). They are postulated to originate from the arachnoid cap and meningothelial cells, which are present in the arachnoid layer of the meninges or Pacchionian granulation, and typically display dural attachment. Occasionally, the arachnoid cap cells can appear in the pia mater of the Sylvian fissure or Virchow-Robin space along the MCA or its branches (23, 31) (**Figure 3**). Our patient presents an additional case of Sylvian fissure meningioma with unusual imaging characteristics and a rare atypical subtype.

The mean onset age of typical meningiomas is about 55 years, and the incidence increases with age, with women having a higher morbidity than men (34). However, the clinical characteristics of Sylvian fissure meningiomas are different. A retrospective analysis of 38 [25 men (65.8%) and 13 female (34.2%)] patients with Sylvian fissure meningiomas reported from 1938 to 2019 (**Table 1**) revealed that the average onset age is about 22.5 ± 17.4 years. Seizure was the major symptom of Sylvian fissure meningiomas (65.8%, 25 patients). Other reported symptoms included headache (39.5%, 15 patients) and hemiparesis (18.4%, 7 patients). Rare instance of initial symptom included visual impairment (2.6%, 1 patient), incidental (2.6%, 1 patient), and dizziness (2.6%, 1 patient). The incidence of seizures in patients with Sylvian fissure meningiomas (65.8%) was reported to be higher than those with common supratentorial meningiomas (29.2%) (35). Generally, seizure frequency depends on tumor location, and the limbic and temporal lobe had the lowest threshold for producing a seizure. Also, hypoxia and metabolic imbalances caused by tumor invasion and extrusion were the potential etiological mechanisms (36).

The majority of common meningiomas are WHO grade I, with approximately 16.9% cases being atypical (WHO grade II) (37). However, the proportion is expected to rise according to the newly recommended WHO 2016 criteria for the classification of atypical meningioma (38). Sylvian fissure meningiomas comprise three types of WHO grades, and previously reported cases were histologically diagnosed as psammomatous (8 cases, 21.1%), transitional (7 cases, 18.4%), meningothelial (7 cases, 18.4%), fibroblastic (7 cases, 18.4%), atypical (4 cases, 10.5%), chordoid (1 case, 2.6%), sclerosing (1 case, 2.6%), lymphoplasmacyte-rich (1 case, 2.6%), and malignant (1 case, 2.6%). The arachnoid cells in all of these cases can manifest divergent differentiation. Presence of brain invasion, which was added to the histological criteria, alone can aid the diagnosis of atypical meningiomas according to the 2016 WHO classification of CNSTs (38). Invasion of the brain parenchyma in our case confirmed a final diagnosis of atypical type meningioma with WHO II grade, which is the fifth case reported till date.

TABLE 1 | Summary of Sylvian fissure meningiomas up to October 31, 2019.

References	Age/Sex	Clinical features	Imaging features	Removal	Histopathology	Follow-up
Cushing et al. (2)	8/M	Epilepsy	N/A	Subtotal	Psammomatous	5y: died
	48/F	Epilepsy	N/A	Subtotal	Psammomatous	1d: died
Barcia-Goyanes et al. (3)	20/F	Epilepsy	N/A	N/A	Psammomatous	N/A
Mori et al. (4)	23/M	Epilepsy	N/A	Subtotal	Transitional	N/A
Saito et al. (5)	31/F	Epilepsy	Hyperdense lesion in CT	Gross total	Psammomatous	N/A
Tsuchida et al. (6)	46/M	Headache	N/A	Gross total	Psammomatous	4y: relapse-free
Awa et al. (7)	16/M	Headache	N/A	Gross total	Meningothelial	2y: relapse-free
Okamoto et al. (9)	27/F	Headache	N/A	Gross total	Fibroblastic	5y: died
	35/F	Headache and visual impaired	Severe edema, hyperdense, and homogeneous lesion in CT	Gross total	Fibroblastic	N/A
Drake et al. (8)	3/F	Headache	N/A	Gross total	Malignant	N/A
Hirao et al. (10)	34/F	Epilepsy	Homogeneous enhancement in CT	Gross total	Fibroblastic	N/A
Silbergeld et al. (11)	4/F	Epilepsy	Homogeneous enhancement in CT	Subtotal, radiation therapy	Meningothelial	N/A
Cho et al. (12)	2/M	Epilepsy and hemiparesis	Severe edema, hyperdense with homogeneous lesion in CT	Gross total	Transitional	2y: relapse-free
Graziani et al. (13)	19/M	Headache and hemiparesis	Moderate edema, calcifications, Hypointense in T1 and T2	Gross total	Psammomatous	N/A
Mori et al. (15)	12/M	Headache	Slight edema, well-enhanced tumor in CT and MRI	Gross total	Transitional	1y: relapse-free
Chiocca et al. (14)	26/F	Epilepsy	Slight edema, hypointense and homogeneous in T1 and T2	Gross total	Fibroblastic	N/A
Matsumoto et al. (16)	62/F	Epilepsy	Hypointense in T1 and T2	Gross total	Psammomatous	N/A
Cooper et al. (17)	4/M	Headache	Severe edema, heterogeneous intensity in T1 and T2	Gross total	Transitional	1y: relapse-free
Mitsuyama et al. (18)	1/M	Epilepsy	Well-enhanced tumor in CT and MRI	Gross total	Fibroblastic	N/A
Kaplan et al. (19)	11/M	Epilepsy	Isointense in T1 and heterogeneous intensity in T2	Gross total	Atypical	N/A
Chang et al. (20)	35/M	Epilepsy	Severe edema, isointense, and homogeneous in T1 and T2	Subtotal, gamma-knife	Transitional	N/A
McIver et al. (21)	23/M	Epilepsy	Heterogeneous intensity in T1 and T2	Subtotal	Chordoid	17m: stable residual tumor
Samson et al. (23)	6/M	Epilepsy	Calcification, edema, heterogeneous enhancement, hypointense on T1 and hyperintense on T2	Gross total	N/A	4y: relapse-free
Cecchi et al. (22)	23/M	Headache and hemiparesis	Moderate edema, heterogeneous intensity in T1 and T2	Subtotal, radiation therapy	Atypical	2y: stable residual tumor
Ma et al. (25)	53/M	Epilepsy	Homogeneous enhancement, edema	Subtotal, gamma-knife	Atypical	2y: stable residual tumor
Chae et al. (24)	69/M	Incidental	Calcification, edema, heterogeneous intensity in T2, heterogenous enhancement	Subtotal	Psammomatous	N/A
Aras et al. (26)	15/M	Epilepsy	Homogeneous enhancement, hypointense on T1 and iso-hypointense on T2, mild edema	1st surgery: subtotal 2nd surgery: gross total	Fibroblastic	3y: relapse-free
	28/M	Epilepsy and hemiparesis	Heterogenous enhancement, hypointense on T1 and heterogeneous intensity on T2, edema	1st surgery: subtotal 2nd surgery: gross total	Meningothelial	5y: relapse-free
Kim et al. (27)	43/M	Epilepsy	Minimal calcification, Isointense in T1 and T2, ring like enhancement, edema	Subtotal	Lymphoplasmacyte-rich	4y: stable residual tumor
Fukushima et al. (28)	10/M	Epilepsy	Heterogeneous enhancement	Subtotal	Sclerosing	1y: stable residual tumor
Donovan et al. (29)	11/M	Epilepsy	Calcification, homogenous enhancement	Gross total	Transitional	10y: relapse-free
	7/M	Epilepsy and headache	Calcification, homogenous enhancement	1st surgery: subtotal 2nd surgery: subtotal	Fibroblastic	2y: stable residual tumor

(Continued)

TABLE 1 | Continued

References	Age/Sex	Clinical features	Imaging features	Removal	Histopathology	Follow-up
	16/F	Epilepsy	Partial calcification, minimal enhancement	Subtotal	Meningothelial	5y: stable residual tumor
Brogna et al. (30)	32/M	Headache and dizziness	Isointense on T1 and T2, homogenous enhancement	Gross total	Atypical	3y: relapse-free
Yamagishi et al. (32)	32/M	Headache	Isointense on T1 and T2, homogenous enhancement	Gross total	Transitional	6m: relapse-free
Amirjamshidi et al. (31)	7/F	Headache and hemiparesis	Calcification, edema, isointense on T1 and T2, vivid enhancement	Gross total	Meningothelial	13y: relapse-free
	5/F	Headache, epilepsy, and hemiparesis	Isointense on T1 and T2, homogenous enhancement	Gross total	Meningothelial	5y: relapse-free
	7/M	Headache, epilepsy, and hemiparesis	Isointense on T1, homogenous enhancement	Gross total	Meningothelial	2y: relapse-free

The main radiological characteristics of meningiomas generally include extra-axial occupation and dura mater attachment (dural tail sign). Contrarily, radiological imaging features of Sylvian fissure meningiomas have differential characteristics, such as intra-axial mass without dural attachment. It is extremely difficult to differentiate Sylvian fissure meningioma from other intracranial masses, such as low-grade glioma, teratoma, metastasis, cavernous hemangioma, tuberculous granuloma, etc. The previously reported 38 cases of Sylvian fissure meningiomas frequently showed hypointense or isointense lesions on T1- and T2-weighted MRI, with homogeneous or heterogeneous enhancement after contrast administration. Some cases also showed calcification or edema on CT and MRI scans, but these features were non-specific. Interestingly, the tumor in our case presented obvious calcification with negligible enhancement on the preoperative contrast-enhanced MRI scan, which significantly complicated the preoperative diagnosis. Meningiomas without enhancement have rarely been reported previously. Kubota et al. (39) and Zhang et al. (40) reported two cases of non-enhancement meningioma, due to the cystic or necrotic changes and distinctive pathological features. We considered that the tumor calcification, as a large number of psammoma bodies are found in pathology, result in non-enhancement in our case.

It is well-acknowledged that the progressive growth and enlargement of typical meningiomas can oppress or enclose the arteries. However, owing to the layer of arachnoid membrane between the blood vessels and tumors, it is relatively easy to intraoperatively discern and separate the meningiomas from the adjacent arteries. Because of the close relationship between the Sylvian fissure meningiomas with the MCA and its branches, blood vessels are more likely to be damaged during resection surgeries. In our case, a branch of the MCA was injured intraoperatively despite careful micro-dissection, and the patient had a mild cerebral infarction postoperatively. Fortunately, the patient recovered without any obvious neurological impairment after an adequate recovery period and remained seizure free for about a year and a half postoperatively. According to the previously reported cases, 22 (57.9%) patients achieved gross total resection in the first attempt and showed favorable outcomes with a relapse-free status (92.3%, 12/13 patients, some patients had no follow-up data) at follow-up even after several years. Of the 15 patients who underwent subtotal resection of tumor, three patients underwent a secondary surgery, and four patients accepted subsequent radiation or gamma-knife therapy. However, the residual tumors in all 15 patients showed no sign of further progression. Patients at risk of serious postoperative complications with gross total excision surgery can be recommended for radiation or gamma-knife therapy (11, 20, 22, 25). Atypical meningiomas are intermediate-grade tumor with a relatively greater risk of recurrence, requiring longitudinal monitoring by sequential radiological imaging. Optionally, radiation therapy can be used if required. The patient was satisfied with the overall treatment course, operation, and intensive nursing; moreover, her seizures are now well under control.

CONCLUSION

Sylvian fissure meningiomas are rare, and a preoperative diagnosis is difficult without adequate knowledge of the case. Due to the special origin, Sylvian fissure meningiomas generally present non-dural attachment and have a close relationship with the MCA (30). Tumor onset usually occurs at a young age and seizures are the most common initial symptom. Sylvian fissure meningiomas have multiple pathological types and effective treatment can ensure a favorable prognosis. However, the tumor should be carefully resected in cases with arterial adherence to avoid collateral artery injuries and postoperative infarction. This study is the fifth report of a rare case of an atypical Sylvian fissure meningioma with unusual presentations on preoperative radiological examination. The case report adds new knowledge to the existing literature and will help to remind clinicians of the rare presentations of atypical meningioma.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the Second Affiliated Hospital of Zhejiang University School of Medicine [Hangzhou].

Written informed consent was obtained from the patient for the publication of this case report.

AUTHOR CONTRIBUTIONS

CC and ZZhu: drafted the manuscript. XinG and XiaG: acquisition of data. HJ, ZZhe, and AS: analysis or interpretation of data. JZhu and JZha: study concept and design.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Differentially Expressed MicroRNAs in Radioresistant and Radiosensitive Atypical Meningioma: A Clinical Study in Chinese Patients

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Background: For atypical meningiomas (AMs), the combination of gross total resection (GTR) and adjuvant radiotherapy (ART) is still a controversial therapeutic strategy to improve prognosis. This study analyzed the factors influencing the prognosis on AM patients treated with GTR + ART by investigating both clinical characteristics and the change in microRNA (miRNA) expression.

Materials and Methods: Adult AM patients who were admitted to the Tiantan hospital from 2008 to 2015 and underwent GTR + ART were included. Patients who suffered recurrence within 3 years after operation were considered radioresistant, while the others were considered radiosensitive. Clinical characterizations were compared between these two groups. The microRNA (miRNA) expression was detected via miRNA microarray in 10 patients, five from the radiosensitive group and from the radioresistant group.

Results: A total of 55 cases were included in this study. No significant difference was found in the clinical characteristics (gender, age, tumor location, tumor size, peritumoral brain edema, and Ki-67 index) between radiosensitive and radioresistant patients. We found seven significantly upregulated miRNAs (miR-4286, miR-4695-5p, miR-6732-5p, miR-6855-5p, miR-7977, miR-6765-3p, miR-6787-5p) and seven significantly downregulated miRNAs (miR-1275, miR-30c-1-3p, miR-4449, miR-4539, miR-4684-3p, miR-6129, miR-6891-5p) in patients resistant to radiotherapy. The differentially expressed miRNAs were enriched mostly in the fatty acid metabolic pathways (hsa00061, hsa01212) and transforming growth factor beta signaling pathway (hsa04350).

Conclusion: For AM patients treated with GTR + ART, the changes in miRNA expression discovered in this study may be a potential predictor of individual sensitivity to adjuvant radiotherapy. Further research is needed regarding the predictive power and mechanism by which these miRNAs influence prognosis.

Keywords: atypical meningioma, radioresistance, radiosensitivity, microRNA, adjuvant radiotherapy

INTRODUCTION

Meningioma, which has an incidence of 6–7 in 100,000 people, has become the most common primary brain tumor, accounting for 36.3% of all primary central nervous system tumors (1). According to the World Health Organization (WHO) criteria, meningioma is currently classified as grade I, II or atypical, and III or anaplastic (2), representing 80, 5–34, and 1–3% (3) of all meningiomas, respectively. Although most meningiomas are benign, the non-benign meningiomas are associated with poor prognosis, including aggressive behavior, and early tumor recurrence or progression (4). As such, for high-grade meningioma, adjuvant radiotherapy (ART) is an important method to control tumor recurrence after surgical resection.

However, due to the controversial results obtained between different studies, whether the ART is beneficial for the treatment of atypical meningioma (AM) patients, especially for those who underwent gross total resection (GTR, Simpson I–II), remains unclear (4–11). Presently, for AM patients, the decision to perform ART after GTR is often based on the experience of the clinician. To our knowledge, the only completed prospective study regarding ART after GTR in AM is European Organization for Research and Treatment of Cancer (EORTC) 22042-26042, which showed that the 3-year progression-free survival (PFS) for AM patients undergoing complete resection (Simpson I–III) followed by treatment with high-dose (60 Gy) radiotherapy is over 70% (12). However, this study provides information regarding the dose and administration of ART but does not address whether ART is necessary after GTR.

During the past two decades, the WHO classification system was significantly revised in 2000 and updated in 2007 and then in 2016 (2). With these changes, the criterions for AM have been "enlarged" (by adding brain invasion as a criterion for the diagnosis of AM), and hence, the incidence of AM has tended to increase throughout time (13). Biological heterogeneity complicates this issue, as certain AM patients may be inherently more insensitive to a given dose of radiation. Failure to control a tumor with a seemingly curative dose would suggest that the tumor is "radioresistant," whereas a "radiosensitive" tumor would be controlled via radiotherapy. When considering radiation toxicity and the lack of consensus among neurosurgeons and meningioma researchers, the decision for ART in AM patients after GTR should be individualized. Thus, predictive strategies to determine the radiosensitivity of AM patients are required to facilitate the future delivery of personalized radiotherapy. MicroRNAs (miRNAs) are a type of small non-coding RNA (containing about 22 nucleotides), which plays a role in RNA silencing and posttranscriptional regulation of gene expression. Moreover, miRNAs are getting increasing attention as potential markers of tumor radiosensitivity and have shown potential in several other malignancies (14–18).

In our institution, after surgical resection, we routinely recommend patients with AM to consult a radiotherapy specialist for further treatment. Interestingly, we found that even for those AM patients who underwent GTR and ART, there were still some differences in prognosis. Therefore, in order to investigate the correlation between radiotherapy sensitivity and miRNA expression, we conducted an extensive miRNA profiling study on tissue samples from postoperative radiotherapy-sensitive and radiotherapy-resistant AM patients who underwent GTR and ART in a single institution and searched for unique miRNA expression signatures that could distinguish radiotherapy-sensitive patients from radiotherapy-resistant patients.

MATERIALS AND METHODS

Ethics Statement

All patients enrolled in the study signed an informed consent form for the current study, and the clinical study was approved by the Medical Ethics Committee of the Capital Medical University.

Patients and Tumor Specimens

Patients diagnosed with AM from 2008 to 2015 were initially identified through the database of our Neurosurgery department at the Beijing Tiantan Hospital. The clinical history of the patients was gathered retrospectively by chart review. Fifty-nine AM patients who underwent gross total resection were identified and selected for further analysis. The operation notes and postoperative magnetic resonance images (MRIs) were reviewed to confirm the extent of the resection. Simpson I (macroscopically complete tumor resection with removal of affected dura and underlying bone)–II (macroscopically complete tumor resection with coagulation of affected dura only) was defined as GTR (19). The pathological reports were reviewed, and all pathological diagnoses were examined and graded independently by two neuropathologists (who were blind to tumor genotypes), according to the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (2). The external-beam radiation was delivered by conventional fractionation up to a total dose of 50–60 Gy. The exclusion criteria included the age $<$18 years old (one case), having other intracranial or systematic malignant tumors before/concurrent (two cases), extracranial tumor location, and loss to follow-up (one case). Therefore, a total of 55 cases were included in this study.

In recent studies, recurrence-free survival in 3 years has been a critical prognostic indicator to estimate the efficiency of radiotherapy for atypical meningioma. Since a prospective study confirmed GTR + ART could make PFS in 3 years $>$70% (12), in this study, patients who suffered tumor recurrence within 3 years (36 months) after GTR + ART were defined as the radioresistant group, while the others were defined as the radiosensitive group. Patient characteristics, including gender, age ($\leq$60 vs. $>$60), tumor location, preoperative tumor size, Ki-67 index, and peritumoral brain edema (PTBE), were compared between these two groups. According to their location, tumors were divided into five categories: convexity (including frontal, temporal, parietal, and occipital), falx/parasagittal, cranial base (e.g., olfactory groove, sphenoid ridge, petroclival region, tuberculum sellae, etc.), lateral ventricle trigone area, and posterior fossa (19). Preoperative MRIs were reviewed to measure tumor size (the longest axis rounded to the nearest millimeter, divided at 4.5 cm) and PTBE. Recurrence-free survival (RFS) was measured

from the date of the surgery to the date of death/last follow-up/progression based on the first radiographic documentation, whichever occurred first.

For every patient, immediately after surgery, tumor samples were fixed with formalin and embedded in paraffin blocks. A random selection was made to obtain 10 tumor samples for further miRNA microarray test, with five samples from the radioresistant group and five from the radiosensitive group.

MicroRNA Microarray

miRNAs were extracted from formalin-fixed and paraffin-embedded tissues using the miRNeasy Mini Kit (QIAGEN) according to the manufacturer's instructions. The concentration and purity of the RNA were measured using the NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific). The quality of the total RNA was accessed using the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). A total of 200 ng of small RNAs were labeled using the FlashTag biotin-HSR RNA labeling kit (Genisphere). First, poly(A) tailing was carried out at 37°C for 15 min in a volume of 15 μl of reaction mixture containing the reaction buffer, $MnCl_2$, ATP, and poly(A) polymerase. Then, the Genisphere biotin complex was ligated at room temperature for 30 min by adding the FlashTag Ligation Mix Biotin and T4 DNA Ligase into the 15-μl reaction mix. The Stop Solution was then added to stop the reaction.

Subsequently, the microRNA cocktails were hybridized and analyzed on microRNAs microarrays version 2 or 3 (Affymetrix). Labeled RNAs were hybridized on GeneChip microarrays, washed, stained, and then scanned using the miRNA-2.0 library for microRNA microarrays version 2 and the miRNA-3.0 library for microRNA microarrays version 3, according to Affymetrix's specifications.

Statistical Analysis

Analyses of clinical data were performed using the SPSS software (release version 21; IBM Corp., Armonk, NY, USA). The tumor size and Ki67 index between groups were compared by independent samples *t*-test. Pearson's chi-square test was used to compare gender, tumor location, and PTBE between groups. Death by the last follow-up was compared using Fisher's exact test. The median RFS of both groups was calculated using the Kaplan–Meier method and compared by log-rank tests. A $p < 0.05$ was regarded as statistically significant.

For microRNA data, the signal intensity was loaded into the Rosetta Resolver System® (Rosetta Biosoftware, USA) for data preprocessing and application of the 75th percentile centering normalization. Simultaneously, the errors of the sample were estimated using the error-weighted approach. Both the fold change and *p*-value for pairwise sample comparisons were calculated to evaluate differentially expressed genes. MiRNAs with a fold change of ≥ 2 or ≤ -2 and a $p < 0.05$ were considered as differentially expressed. Hierarchical clustering was performed using iDEP (20). Significantly upregulated and downregulated miRNAs were selected for pathway analysis using the DNA Intelligent Analysis (DIANA)-miRPath v3.0 software, according to a previously published protocol (21). Briefly, this software is able to link miRNAs to experimentally validated target genes from Tarbase, v7.0, and identify the putative targeted molecular pathways in the Kyoto Encyclopedia of Genes and Genomes (KEGG) (22). The "pathways union" option of the miRPath software was selected, and *p*-values were obtained using Fisher's exact test.

TABLE 1 | Clinical characteristics of the atypical meningioma patients with adjuvant radiotherapy after gross total resection.

Characteristics	Radiosensitive ($n = 43$)	Radioresistant ($n = 12$)	*p*-value
Gender (male/female)	25/18	4/8	0.192
Median age at surgery	52	52	0.673
Tumor location			
Supratentorial (yes/no)	27/16	7/5	0.779
Convexity (%)	15 (34.9%)	3 (25.0%)	0.519
Falx/parasagittal (%)	10 (23.2%)	2 (16.7%)	0.625
Cranial base (%)	8 (18.6%)	3 (25.0%)	0.624
Lateral ventricle trigone area (%)	2 (4.7%)	2 (16.7%)	0.204
Posterior fossa (%)	8 (18.6%)	2 (16.7%)	0.878
Median tumor size (cm)	5.00	5.95	0.265
PTBE (with/without)	11/32	6/6	0.158
Mean Ki 67 index	8.4%	11.5%	0.343
Death by the last follow-up	2	1	0.117
Median RFS (months)	58	28.5	<0.001
Median follow-up (months)	57 (36–127)		

PTBE, peritumoral brain edema; RFS, recurrence-free survival.

RESULTS

Patient Characteristics Analysis

Fifty-five cases of AM were included in this study. For all cases, the last follow-up was in December 2018, with a median follow-up time of 57 months (range, 37–127). A summary of patient characteristics is shown in **Table 1**. A total of 43 patients fulfilled the criteria for the radiosensitive group, and 12 patients were included in the radioresistant group. The radioresistant group consists of 12 cases with a median age of 52 and with most patients younger than 60 years (72%). Similarly, the radiosensitive group consists of 43 cases with a median age of 52 and 83.7% of patients younger than 60 years. Consequently, we failed to find a significant difference regarding age ($p = 0.673$, Fisher's exact test) and gender ($p = 0.192$, Pearson's chi-square test) between the radiosensitive and radioresistant group. There was also no significant difference regarding tumor location, tumor size, and the Ki-67 index between the radiosensitive and radioresistant group. In this study, most tumors were located in the supratentorial area (7 of the radioresistant and 27 of the radiosensitive, $p = 0.779$, Pearson's chi-square test). In the radioresistant group, tumors were most commonly located in the brain convexity and cranial base, respectively, in three patients (25%), followed by falx/parasagittal (16.7%), the lateral ventricle trigone area (16.7%), and the posterior fossa (16.7%). The tumor location of the radioresistant group was not significantly

TABLE 2 | Clinical characteristics of patients whose tumor was detected by microRNA (miRNA) microarray.

Patient ID	Gender	Age	Tumor location	Tumor size (cm)	PTBE	Ki 67 index (%)	Past medical history
C1	Female	33	Convexity	4.5	Yes	1	No
C2	Female	53	Convexity	5.0	Yes	1	Endometrial polyp with resection
C3	Female	54	Posterior fossa	4.8	No	20	Ovarian cyst with resection
C4	Male	18	Cranial base	3.1	Yes	5	No
C5	Female	47	Lateral ventricle trigone area	4.9	No	3	Uterine fibroids
T1	Female	64	Convexity	4.4	Yes	15	Hypertension for 5 years
T2	Female	34	Lateral ventricle trigone area	5.9	No	5	No
T3	Male	24	Posterior fossa	2.7	No	1	No
T4	Female	44	Cranial base	4.1	Yes	30	Chronic superficial gastritis
T5	Male	58	Convexity	6.0	Yes	1	Inguinal hernia with repair
p-value	1.0	0.695	1.0	0.828	1.0	0.526	

C1–C5, radiosensitive group; T2–T5, radioresistant group.

different from the radiosensitive group, which were located in convexity (34.9%), followed by falx/parasagittal (23.2%), the cranial base (18.6%), the posterior fossa (18.6%), and the lateral ventricle trigone area (4.7%). According to the preoperative MRI, median tumor size was 5.95 cm in the radioresistant group and 5.00 cm in the radiosensitive group ($p = 0.265$, independent samples *t*-test). Six patients from the radioresistant group and 11 patients from the radiosensitive group suffered PTBE, but there was no significant difference between these two groups ($p = 0.177$, Pearson's chi-square test). The mean Ki-67 index was 11.5% in the radioresistant group, which was not significantly different ($p = 0.343$, independent samples *t*-test) from that of the radiosensitive group (8.4%). Median RFS differed significantly between the two groups ($p < 0.001$, log-rank test), with 28.5 months in the radioresistant group and 58 months in the radiosensitive group.

MicroRNA Characterization

In this study, tumor samples from 10 patients were selected for miRNA microarray. Five of them suffered tumor recurrence <3 years (36 months) after total resection, which was considered as radioresistant, while the others who did not exhibit tumor recurrence during the follow-up time (>36 months) were considered as radiosensitive. The clinical characteristics of these 10 patients are shown in **Table 2**. Between the radiosensitive and radioresistant group, there was no significant difference in gender, age, tumor location, tumor size, PTBE, and Ki67 index, and no patients suffered severe disease in history. A comparison between the miRNA profiles of the radioresistant and radiosensitive group AM samples revealed 1,466 common miRNAs. We observed 14 significant differentially expressed miRNAs between the radiosensitive and radioresistant cases (**Figure 1A**). Of these, seven were upregulated (miR-4286, miR-4695-5p, miR-6732-5p, miR-6855-5p, miR-7977, miR-6765-3p, miR-6787-5p), while seven were downregulated (miR-1275, miR-30c-1-3p, miR-4449, miR-4539, miR-4684-3p, miR-6129, miR-6891-5p) in the radioresistant cases (**Figure 1B**). Unsupervised hierarchical clustering was performed using iDEP (20). This led to the separation of all the cases into two main clusters, as shown in **Figure 2**. Cluster 1 included five out of six (83.3%) radiosensitive cases, while cluster 2 consisted of the radioresistant cases (four out of four, 100%). The DIANA-miRPath v.3 software (21) was used to explore the biological significance of the 14 miRNAs that were differentially expressed between the radioresistant and radiosensitive group. Three enriched pathways were revealed by this analysis (**Table 3**). According to the KEGG pathway maps, one pathway was the environmental information processing related pathway [transforming growth factor beta (TGF-β) signaling pathway, hsa04350], and the other two were related to metabolic system pathways (fatty acid biosynthesis, hsa00061; fatty acid metabolism, hsa01212).

DISCUSSION

The use of ART for the treatment of AM after GTR has remained controversial. Maybe the single institution and relatively small study scale could be a partial reason for this contradiction. However, recently, two large-scale studies have not managed to reach a consensus. Wang C. et al. showed that ART is not associated with improved overall survival (OS) in patients who underwent GTR [adjusted hazard ratio (HR) = 1.093, $p = 0.737$] (23). However, Rydzewski N.R. et al. demonstrated that GTR in combination with ART was the most critical factor for improved survival (GTR plus ART, HR = 0.47; $p = 0.002$), even though GTR was associated with lower rates of adjuvant radiation usage based on the National Cancer Data Base (NCDB) (7). We speculate that this contradiction in findings could be due to some factors influencing tumor radiosensitivity, which were confounded in the above studies. In order to find interfering factors of the effect of ART after GTR in AM, our study focused on patients who underwent both GTR and ART and aimed to define factors associated with radiosensitivity.

As we all know, in order to make individual treatment decisions, clinicians should weigh and balance multiple factors

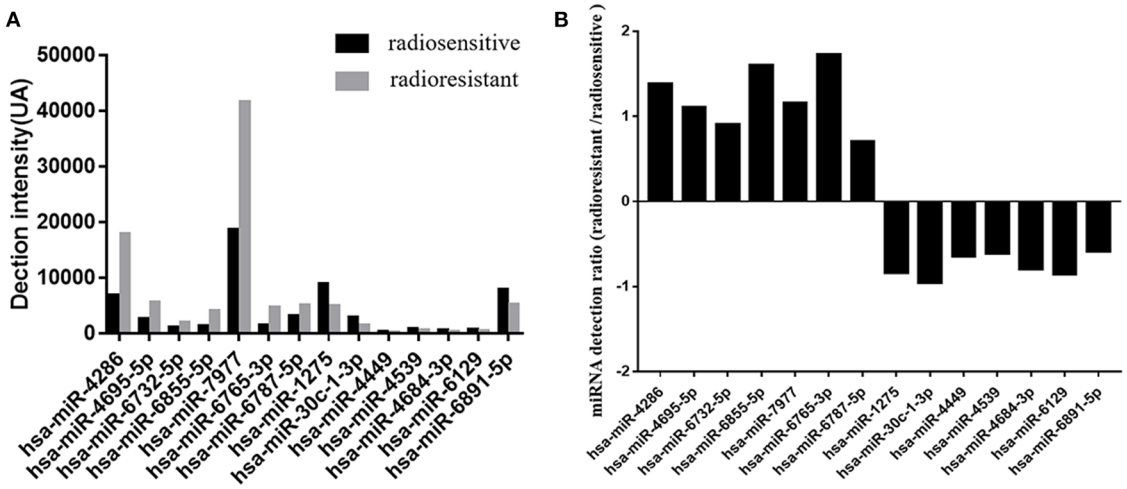


FIGURE 1 | Differential expression microRNAs (miRNAs) in the radiosensitive and radioresistant groups of atypical meningioma with gross total resection plus adjuvant radiotherapy (GTR + ART). **(A)** Detection levels on Affymetrix microarrays of the microRNAs in radioresistant group (*gray*) and radiosensitive group (*black*). Detection intensities correspond to the measured values minus the threshold value. **(B)** The ratios of the measured intensities of microRNAs detected in radioresistant group vs. the intensities in radiosensitive group. The ratios are shown on a $\log_2$ scale.

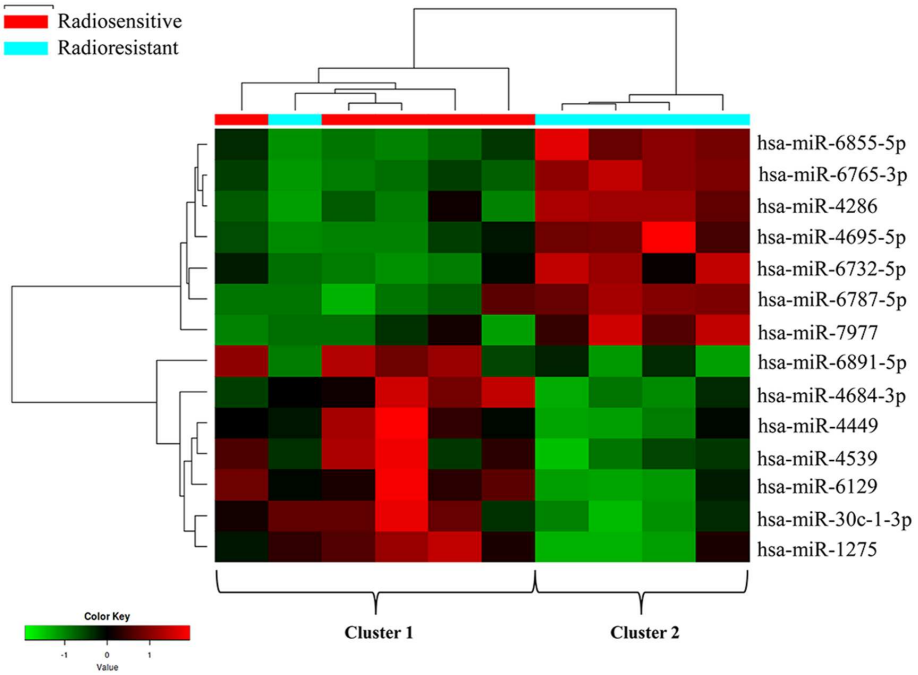


FIGURE 2 | Clustering analysis of the radioresistant and radiosensitive groups using differentially expressed miRNAs. The columns represent the cases, and the lines represent the miRNAs. Red and green indicate high and low expression levels, respectively. Cluster 1: five radiosensitive and one radioresistant; cluster 2: radioresistant.

at different levels. At the clinical level, this study failed to find a significant difference in the characteristics of patients with AM treated with GTR + ART. To explore the factors that exert more influence on these patients, especially to find those factors that contribute to radiosensitivity, we investigated differentially expressed miRNAs. Recent studies have revealed that differences in miRNA expression could influence radiosensitivity in a series of tumors, including, but not limited to, glioblastoma (GBM), breast cancer, lung cancer, melanoma, and cervical cancer (14–18). However, research regarding the role of miRNAs in AM radiosensitivity is scarce. In this study, we found 14 differentially expressed miRNA between radiosensitive and radioresistant AM

TABLE 3 | Results from the DIANA-miRPath v3.0 predictions of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways according to the differential expression microRNAs (miRNAs) between radioresistant and radiosensitive groups.

KEGG pathway maps	Enriched pathway	*p*-value
Metabolism	Fatty acid biosynthesis (hsa00061)	<1 × 10–325
	Fatty acid metabolism (hsa01212)	4.21 × 10–06
Environmental information processing	TGF-beta signaling pathway (hsa04350)	0.040294

patients. We identified seven upregulated miRNAs (miR-4286, miR-4695-5p, miR-6732-5p, miR-6855-5p, miR-7977, miR-6765-3p, miR-6787-5p) and seven downregulated miRNAs (miR-1275, miR-30c-1-3p, miR-4449, miR-4539, miR-4684-3p, miR-6129, miR-6891-5p) in the radioresistant group. According to this pattern of miRNA deregulation, these 10 samples could be divided into two clusters. Notably, the division pattern of these two clusters was nearly coincident with the radiosensitivity division. There was one special patient (subject T4 in **Table 2**) whose miRNA expression pattern was the same to that of the radiosensitive group was considered as radioresistant at clinical level due to the poor radiotherapy effect. Although the tumor located at sphenoid ridge and it is a relatively hard work to design and execute external-beam radiation in this region, the patient still chose to undertake radiotherapy at a local hospital and might experience an unsuccessful radiotherapy, which made the poor prognosis for this patient.

Among the 14 deregulated miRNAs, miR-7977, miR-4286, miR-1275, and miR-30c-1-3p have been previously reported to play a role in tumor malignancy. Horiguchi H. et al. found that miR-7977 was upregulated in acute myeloid leukemia and myelodysplastic syndrome and could reduce the expression of poly(rC) binding protein 1 to interfere with normal hematopoiesis. Moreover, miR-7977 was also reported to regulate the Hippo-YAP pathway, therefore inducing the upregulation of leukemia-supporting stroma growth (24, 25). MiR-4286 is another miRNA that was found to be upregulated in the radioresistant group in our study. In previous studies, its upregulation is also found to be associated with cell proliferation, migration, and invasion via targeting of PTEN and Runx3 (26, 27). As for the downregulated miRNAs identified in our work, miR-1275 was reported to inhibit cell migration and invasion in gastric cancer, while the downregulation of miR-1275 by H3K27me3 could mediate glial induction of GBM cells (28, 29). Furthermore, reduced expression of miR-30c-1-3p was also found in prostate cancer, while overexpression of miR-30c-1-3p was shown to inhibit the progression of prostate cancer (30).

Finally, in order to investigate the molecular pathways affected by the differentially expressed miRNAs between radiosensitive and radioresistant AM, we used the DIANA-miRPath software and found three enriched pathways. The two most significant pathways were fatty acid biosynthesis (hsa00061) and metabolism (hsa01212): fatty acid biosynthesis, biosynthesis, and TGF-β signaling pathways. These pathways have been verified relate to some common chronic disorders such as chronic inflammation, hypertension, and hyperlipidemia (31, 32); however, just as is shown in **Table 2**, these conditions were scarce in patients who undertook miRNA array test. As we all know, fatty acids are the principal constituent of cell membranes and essential components for the energy required for cancer growth. Changes in fatty acid synthesis and metabolism were identified in many different types of tumors and have been considered as a potential therapeutic target in cancer (33). Moreover, several studies have indicated that fatty acid regulation could influence the radiosensitivity of tumors such as prostate cancer and nasopharyngeal carcinoma (34, 35). However, research on fatty acid changes in meningioma is scarce, making it an area worthy of further exploration. The TGF-β signaling pathway is another pathway enriched in this study. There is accumulating evidence to show that the TGF-β signaling pathway is related to meningioma cell proliferation and contributes to the development and/or progression of higher-grade meningiomas (36–38). However, the relationship between the TGF-β signaling pathway and meningioma radiosensitivity remains unclear, thereby requiring further investigation.

The miRNA deregulation pattern discovered in this study could help to define radioresistant AM patients properly; this is important for follow-up treatment. On the one hand, AM patients who are radioresistant and vulnerable to radiation-induced injury could choose observation after GTR. On the other hand, these radioresistant patients are more worth trying radiosensitizer to improve the effect of radiotherapy. The use of miRNA as a kind of treatment method is quite far from clinical practice, but there are still a number of drugs to improve radiosensitivity. For now, several clinical trials about radiosensitizers have been done (39). Among these drugs, RRx-001(NCT02871843) and NVX-108 (NCT02189109) were two novel molecules for glioma. Trial on the first one is still ongoing and that on the latter is completed but no result is published. While waiting for the results of the new drugs, some existing drugs showed potential to improve radiation effect. Valproic acid was reported to improve radiation injury to meningioma stem-like cells *in vitro*, by elevating the G2/M phase of the cell cycle and inducing cell apoptosis (40). Furthermore, hydroxyurea, which could interfere with DNA repair after radiation, has been reported to improve PFS of AM with incomplete resection, which indicates that this drug is a potent radiosensitizer to radioresistant AM (41).

Our study presents some limitations: the inherent limitation of a retrospective analysis, relatively low number of cases due to the rarity of this kind of tumor, the decision to undergo postoperative ART at the discretion of surgeons rather than objective parameters, and the small number of microRNA samples. However, the present study includes a significant follow-up, and all cases are from a single institution, which avoids the "interinstitutional" diagnostic and therapeutic discrepancies.

In summary, we found 14 differently expressed miRNAs in radiotherapy-sensitive and radiotherapy-resistant AM patients. These miRNAs may be used as candidate predictive markers for the benefit of radiotherapy in AM. Should these results be confirmed in future prospective randomized trials, the miRNA

signatures may be used to identify AM patients who may not respond well to adjuvant radiotherapy and may, therefore, benefit from the addition of radiosensitizers or immunotherapy to enhance the radiation response. As such, applying the potential roles of miRNAs in individualized radiotherapy may lead to novel trends in AM therapeutic options.

DATA AVAILABILITY STATEMENT

The datasets (GENERATED) for this study can be found in the [Gene Expression Omnibus (GEO)] (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE144037).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of the Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work. The idea came from the discussion of SL and YW. Material preparation, data collection, and analysis were performed by XZ, GZ, and HL. The first draft of the manuscript was written by HH and XZ and reviewed by GZ and YW. All authors commented on the manuscript and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Retrospective Interventional Cohort Study to Assess the Safety and Efficacy of Sandostatin LAR for Treatment of Recurrent and/or Refractory Meningiomas

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Background: Meningiomas are the most common adult primary intracranial tumors in the United States. Despite high recurrence rate of atypical and malignant subtypes, there is no approved drug indicated specifically for meningioma. Since the majority of meningiomas exhibit high density of somatostatin receptors subtypes, somatostatin analogs have been under close investigation. The aim of this study was to evaluate efficacy and safety of Sandostatin LAR (octreotide) in patients with progressive, and/or recurrent meningioma, and identify subset of patients who were more likely to benefit from this treatment.

Methods: A total of 43 patients ≥ 18 years old were included in the retrospective chart review. The patients underwent treatment with Sandostatin LAR (octreotide) from 01.01.2010 to 06.01.2017 at the University of California, Irvine after confirmation of the diagnosis. Six months progression free survival (PFS6) was defined as a primary endpoint, and the overall survival (OS), safety, and toxicity were identified as secondary endpoints.

Results: The OS for 6 months, 1, and 3 years for all WHO grades was 94.8, 88.1, and 67.0%, respectively. The PFS6 for WHO I, II, III, and all was 89.4, 89, 33.3, and 80% respectively. For patients with no prior surgeries, chemotherapy or radiation, the PFS6 was 88.9, 84.8, and 94.8%, respectively. Interestingly, the PFS6 was 90.5% for skull-based and 80% for 3–6 cm tumors. Patients with tumors in parasagittal location had PFS6 of 83.3% compared to PFS6 of 50.0% for patients with convexity tumors. Evaluation of PFS6 based on the effect of estrogen and progesterone on meningioma identified that ER-PR+ tumors had PFS6 of 87.8% while patients with ER-PR- meningiomas had PFS6 of 62.5%. Median TTP for WHO grade I, II, and III was 3.1, 2.40, and 0.26 years, respectively. Subgroup analysis showed that median TTP was 3.1

years for < 3 cm tumors, 3.22 years for skull-based tumors, 2.37 years for patients with prior surgeries and 3.10 years for patients with no history of chemotherapy. History of radiation had no effect on median TTP. Sandostatin LAR (octreotide) was well-tolerated.

Conclusions: This is one of the largest retrospective analysis of meningioma patients treated with Sandostatin LAR (octreotide) suggesting that this treatment has minimal to no adverse events and could prolong overall survival, and progression free survival especially for patients with ER-PR+ tumors who underwent surgeries for small skull-based tumors.

Keywords: recurrent progressive meningioma, Somatostatin LAR, octreotide, skull based meningioma, meningioma size, meningioma surgery

INTRODUCTION

For Meningiomas are dural-based tumors that arise from an arachnoid layer or meningothelial cells. They are the most common primary adult CNS tumors, and account for 36.8% of all primary brain tumors (1). Most meningiomas are histologically classified as World Health Organization (WHO) grade I tumors (benign, 81.3%) with an indolent course. WHO grade II (atypical, 16.9%) and WHO grade III (anaplastic, 1.7%) tumors classified as high-grade tumors and known to be more aggressive with increased risk of recurrence (2).

If indicated based on tumor size or tumor progression, patients with WHO grade I meningiomas undergo complete surgical resection (3). Approximately 5% of completely resected benign meningiomas, 30% of partially resected benign meningiomas and 40% of atypical meningiomas recur within 5 years after surgery (4). Despite surgical resection and radiation therapy that is the standard of care for WHO grade II and III meningiomas, patients have higher recurrence risk of 29–52 and 50–94%, respectively (5). Depending on tumor location, invasion of surrounding structures, age, and medical comorbidities of the patient, surgical intervention is not always possible. Chemotherapy or biologics are then considered as an alternate treatment option. There is no FDA approved drug indicated specifically for meningioma, and patients with atypical, anaplastic, recurrent, or invasive meningiomas are often left with limited options.

The National Comprehensive Cancer Network (NCCN) guideline identified three drug classes that showed some benefits for treatment of meningioma in retrospective analysis or small phase II trials: vascular endothelial growth factor (VEGF) signaling pathway inhibitors, alpha-interferons, and somatostatin receptor agonists (6, 7). Since the majority of meningiomas exhibit a high density (70%) of somatostatin receptors subtypes (SSTR1–SSTR5), it is not surprising that somatostatin analogs have been under close investigation as a potential treatment option (8, 9).

Somatostatin is an acyclic tetradecapeptide hormone that is produced in hypothalamus and released into systemic circulation, where it exhibits its exocrine and endocrine inhibitory functions by targeting pituitary, pancreas and gastrointestinal tract (10). It also has been implicated in the induction of apoptosis and inhibition of angiogenesis (11). Since naturally occurring somatostatin has a short half-life, somatostatin analogs were developed to achieve a longer half-life (lanreotide, pasireotide, and octreotide).

Sandostatin LAR (octreotide) is another long acting somatostatin analog approved by the FDA for treatment of acromegaly, severe diarrhea/flashing episodes associated with metastatic carcinoid tumors, and vasoactive intestinal peptide (VIP) secreting tumors (12).

Numerous *in vitro* studies investigated antitumor effect of octreotide acetate. For instance, Arena et al. evaluated a role of SSTR in the control of human meningioma cell proliferation and identified that in four out of six primary cell cultures obtained from fresh meningioma surgical sample, the treatment with somatostatin caused inhibition of DNA synthesis induced by the tumor-promoter phorbol myristate acetate (13). Graillon et al. investigated the signal transduction pathways triggered by octreotide and correlated inhibition to cellular markers using a large set of all histological subtypes of meningioma (14). Study showed that octreotide significantly decreased cell proliferation in 88% of meningiomas but did not induce cell death. It was postulated that it had an effect on the level of phosphorylated p70-S6 kinase implicated in rapamycin (mTOR) pathway.

Given that Sandostatin LAR (octreotide) was shown to significantly decrease cell proliferation in 88% of meningiomas with more prominent inhibition in a group expressing a high level of SSTR2a, one of the most frequently expressed receptors in meningiomas, investigative work was initiated to assess its efficacy for treatment of meningiomas (8, 15).

A prospective pilot study showed that 31% of patients with recurrent meningiomas demonstrated a partial radiographic response and 44% achieved progression free survival (PFS) at 6 months with minimal side effects after undergoing treatments with Sandostatin LAR (octreotide) (16). Even though a phase II study conducted to evaluate the efficacy and safety of Sandostatin LAR (octreotide) did not demonstrate a significant benefit, 2 patients experienced prolonged stability of previously progressive tumors (17). Studies that investigated the effect of Sandostatin LAR (octreotide) in patients with a progressive benign residual or recurrent meningioma of the skull base, showed that somatostatin analog can arrest progression and stabilized disease (14).

Numerous clinical studies highlighted potential benefit of Sandostatin LAR (octreotide) for treatment of meningioma, but due to small sample size, no statistical significance was achieved. Thus, our retrospective interventional cohort study with a bigger sample size provides supporting evidence to consider Sandostatin LAR (octreotide) as a potential candidate for meningioma-based treatment taken into an account its tolerability and safety profile.

MATERIALS AND METHODS

The following study was a retrospective interventional cohort analysis conducted at the University of California Medical Center (UCIMC) between January 2010 and June 2017. The study cohort consisted of patients with recurrent and/or progressive WHO grade I, II, or III meningiomas who received treatment with Sandostatin LAR (octreotide). All information related to patients' demographics, cancer type, response to treatment, therapies previously received, and Karnofsky performance scores (KPS) were collected (18). The primary objective of this study was to determine efficacy of Sandostatin LAR (octreotide) in patients with recurrent and/or progressive meningiomas. Six months PFS6 was defined as a primary endpoint, and OS was a secondary endpoint. Safety and toxicity of Sandostatin LAR (octreotide) were assessed as well (19).

Patients Eligibility

Patients were required to be $\geq$ 18 years old with recurrent and/or progressive meningioma expressing sandostatin receptors confirmed by positive ^{111}Indium (^{111}In)—octreotide positron emission tomography (PET) and/or positive immunohistochemistry analysis. The majority of the patients (38) had positive PET scan while remaining patients (5) were diagnosed based on the pathology results. Histological typing and grading of tumors according to the WHO grading system were done via hematoxin and eosin staining. Immunohistochemical staining were done for estrogen receptor (ER), progesterone receptor (PR), Ki-67 and Sandostatin based on the University of California of Irvine protocol. Patients were determined to be poor candidates for surgical resection, stereotactic radiosurgery, or radiation therapy based on tumor location, increased risk factors for postoperative morbidity and mortality, or individual preference for non-invasive approach, or were shown to have recurrence despite surgical or radiation therapy. Patients who suffered from meningioma recurrence were offered treatment independent of history of prior surgeries, chemotherapy, radiation, or radiosurgery treatments. Patients were excluded if metastatic lesions were found on octreotide PET scan or informed consent was not obtained.

Tumor Variables

Tumor size and location were obtained from the MRI scan and official radiologist's report. The largest diameter was used as an overall surrogate for tumor size. Tumor size was categorized into 3 groups: small (tumor <3.0 cm in diameter), medium (tumor ranging 3–6 cm in diameter) and large (tumor more than 6 cm in diameter). Tumor location was subdivided into 3 groups: skull based (cavernous sinus, cerebellopontine angle, clinoid, clivus, foramen magnum, jugular foramen, middle fossa, olfactory groove, orbital, parasellar, petro-clival, petrous, planum sphenoidale, posterior fossa, skull base, sphenoid wing, and tuberculum sellae), falx/parasagittal/convexity, and mixed.

Treatment Plan

The diagnosis of meningioma was confirmed either via ^{111}In-octreotide PET scan or by immunohistochemical analysis. Imaging study (MRI or CT) was done prior to the first drug administration and was repeated every 2–3 months afterwards for an evaluation of tumor status. Imaging studies were used to define the disease recurrence. Patients received deep intragluteal injections of Sandostatin LAR (octreotide) monthly and were treated until disease progression or intolerability. The dose of Sandostatin LAR (octreotide) was gradually increased from 30 to 40 mg per injection if tolerated. Patients were followed for any adverse reactions to the drug. The treatment was stopped if the patient met any of the following criteria: MRI or CT showed tumor progression, serious adverse events, physician discretion, patient's choice to discontinue treatment, death, or lost to follow up. The institutional review board approved the study, and all patients that participated provided written informed consent.

Statistical Methods

Data was analyzed using the IBM SPSS statistical program package (PAWS statistics v18.0). Data was grouped into categories based on demographics, WHO tumor grades, KPS scores, tumor and treatment characteristics, and analyzed using descriptive statistics. The PFS was calculated from the date of initial treatment with Sandostatin LAR (octreotide) until the date of death or disease progression. Patients who did not experience disease progression were censored. The OS was estimated from the date of initial treatment with Sandostatin LAR (octreotide) to the date of death or last known date to be alive. Subjects that have not died were censored at the last known date to be alive. Survival curves were estimated by generating Kaplan-Meier methods. PFS and OS were compared between WHO tumor grades, tumor, and treatment characteristics. The log rank test was used to compare the survival distributions of the groups. $P < 0.05$ for all analyses was considered significant. A proportional-hazards model was used to delineate the risk of death adjusted for covariates. Best radiographic response was determined based on 2010 the Response Assessment in Neuro-Oncology (RANO) Working Group (20). Results from our treatment group were compared to results from previous published studies using Sandostatin LAR (octreotide) for treatment of meningioma.

Safety and Toxicity

Adverse events were reported by patients and/or providers when abnormal laboratory or physical examination findings were identified requiring intervention. Adverse events were recorded from the first date of Sandostatin LAR (octreotide) administration until death or 12 months follow up. The relationship of the adverse event to Sandostatin LAR (octreotide) was also evaluated. It was considered to be a related event when there was an evidence to suggest the relationship between the drug and the adverse event. An unrelated event was thought to

be an adverse event, possibly caused by an underlying disease or biologically improbable event. Safety results were evaluated via descriptive statistics to identify frequency, type, and severity of adverse events.

Treatment related toxicities were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (21). All patients who received Sandostatin LAR (octreotide) were evaluable for toxicity, and toxicity results were compared to other clinical studies.

RESULTS

Patients Characteristics

A total of 43 patients with recurrent or progressive WHO grade I (75.0%), II (11.4%), and III (13.6%) meningiomas were enrolled in this study, including 5 with atypical and 6 with anaplastic meningiomas (**Table 1**). The majority of patients were females (70.5%) who identified as White (38.6%), Hispanic (25.0%), or Asian (22.7%). Median age was 65 years old. Median KPS score was 80. Median number of Sandostatin LAR (octreotide) injections was 8. Evaluation of prior treatments identified that 75.0% of patients with all tumor grades had surgical resections, 45.4% had radiation therapy while 13.6% underwent chemotherapy. Analysis of prior recurrences identified 12 patients with WHO grade I tumors who had no prior recurrences, 7 patients with one recurrence, 10 patients with two recurrences, and 4 patients with three or more recurrences. All patients with WHO grade II and III meningiomas were noted to have two or more recurrences. The cohort consisted of small (<3.0 cm) and medium (3–6 cm) tumors that were predominantly skull base tumors (23 patients). We identified 25 patients with ER positive (ER+), one patient with ER negative (ER-), 18 patients with PR positive (PR+), and 8 patients with PR negative (PR-) statuses. Subgroup analysis showed 17 patients with ER+PR+, 8 patients with ER-PR- and one patient with ER-PR- statuses.

TABLE 1 | Patient demographic and clinical characteristics ($n = 43$).

Characteristics	All Patients
Median Age (years) (range)	66 (35–90)
Male, No. (%)	13 (29.5)
Female, No. (%)	30(70.5)
Ethnicity/race, no. (%)	
• White	16 (37.2)
• Hispanic	11 (25.6)
• Asian	9 (20.9)
• Other	7 (16.3)
Median number of Sandostatin LAR injections	8 treatments (1–25)
KPS score at baseline, no. (%)	
• 50	1 (2.3)
• 60	2 (4.5)
• 70	9 (20.5)
• 80	15 (34.1)
• 90	13 (29.5)
• 100	3 (7)
• Median	80
WHO tumor grade no. (%)	
• 1	32 (74.4)
• 2	5 (11.6)
• 3	6 (13.9)

	WHO Grade 1	WHO Grade 2	WHO Grade 3	All Grades
Prior treatments no. (%)				
• Resection	24 (55.8)	5 (11.6)	5 (11.6)	34 (79.1)
• Chemotherapy	3 (7.0)	1 (2.3)	3 (7.0)	7 (16.3)
• Radiation therapy	12 (30.0)	2 (4.7)	6 (14.0)	20 (46.5)
Previous recurrences no. (%)				
• 0	11 (25.6)	0 (0)	0 (0)	11 (25.6)
• 1	7 (16.9)	0 (0)	0 (0)	7 (16.9)
• 2	10 (23.3)	3(7.0)	2 (4.7)	15 (34.8)
• 3 <	4 (9.3)	2 (4.7)	4 (9.3)	10 (23.3)
Tumor size no. (%)				
• Small (< 3.0 cm)	17 (39.5)	1 (2.3)	2 (4.7)	20 (46.5)
• Medium (3–6 cm)	14 (32.6)	3 (7.0)	4 (9.3)	21 (51.2)
• Large (> 6 cm)	1 (2.3)	1 (2.3)	0	2 (4.7)
Tumor location no. (%)				
• Skull base	21 (48.8)	1 (2.3)	1(2.3)	23 (53.5)
• Parasagittal	3 (7)	1 (2.3)	2 (4.7)	6 (34.8)
• Convexity/Falx	3 (7)	3 (7)	3 (7)	9 (20.9)
• Mixed	5 (11.6)	0	0	5 (11.6)

Toxicity

Toxicity data is reported for all 43 patients (**Table 2**). In general, therapy with Sandostatin LAR (octreotide) was well-tolerated. No CTCAE grade 4 or 5 adverse events were observed. Sandostatin LAR (octreotide) treatments were discontinued in two patients after they experienced significant adverse events. One patient developed cholelitiasis complicated by pancreatitis identified as grade 3 adverse event. The other patient experienced vomiting that was defined as grade 2 event. The majority of grade 2 adverse events included diarrhea (11.4%), headache (6.8%), nausea (4.5%), and abdominal pain (4.5%). Patients more frequently experienced grade 1 events with diarrhea (27.3%) and headache (27.3%) being most common side effects.

Response and Outcome

Analysis indicated that the median PFS for all tumor grades was 3.0 years (95% CI: 2.20–3.80), PFS6 80.6% (95% CI: 0.68–0.93), PFS12 71.9% (95% CI: 0.58–0.86), and PSF36 46.2% (95% CI: 0.21–0.72) (**Table 3.1**). The median PFS for WHO grade I meningiomas was 3.1 years (95% CI: 2.80–3.40), PFS6 89.8% (95% CI: 0.79–1.00), PFS12 82.0% (95% CI: 0.67–0.97), and PSF36 61.5% (95% CI: 0.25–0.98). The median PFS for WHO grade II meningiomas was 2.4 years (95% CI: 1.40–3.30), PFS6 80.0% (95% CI: 0.45–1.00), PFS12 80.0% (95% CI: 0.45–1.00), and PSF36 30.00% (95% CI: 0.00–0.77). The median PFS for WHO grade III meningiomas was 0.2 years (95% CI: 0.05–0.36), patients in this group did not survive past 6 months. The log rank test had a value of $p < 0.001$ which means that there was a statistically significant difference in PFS between the WHO

TABLE 2 | Treatment related CTCAE adverse events ($n = 43$).

Adverse events	CTCAE Grade 1 No. (%)	CTCAE Grade 2 No. (%)	CTCAE Grade 3 No. (%)	CTCAE Grade 4 No. (%)	CTCAE Grade 5 No. (%)	Total No. (%)
Diarrhea	12 (28)	4 (9.3)	0	0	0	16 (37.2)
Loose stools	5 (11.6)	0	0	0	0	5 (11.6)
Headache	11 (25.6)	3 (7.0)	0	0	0	14 (32.6)
Local pain	6 (14.0)	0	0	0	0	6 (14.0)
Flu like symptoms	3 (7.0)	1 (2.3)	0	0	0	4 (9.3)
Weakness	1 (2.3)	1 (2.3)	0	0	0	2 (4.7)
Palmar redness	1 (2.3)	0	0	0	0	1 (2.3)
Chills	1 (2.3)	0	0	0	0	1 (2.3)
Sweats	1 (2.3)	0	0	0	0	1 (2.3)
Arthralgia	1 (2.3)	0	0	0	0	1 (2.3)
Nausea/vomiting	3 (7.0)	2 (4.7)	0	0	0	5 (11.6)
Abdominal pain	2 (4.7)	2 (4.7)	0	0	0	4 (9.3)
Insomnia	3 (7.0)	1 (2.3)	0	0	0	4 (9.3)
Dizziness	4 (9.3)	0	0	0	0	4 (9.3)
Constipation	9 (20.9)	1 (2.3)	0	0	0	10 (23.3)
Anxiety	0 (0)	1 (2.3)	0	0	0	1 (2.3)
Fatigue	4 (9.3)	0	0	0	0	4 (9.3)
Pancreatitis	0	0	1 (2.3)	0	0	1 (2.3)
Cholelithiasis	0	0	1 (2.3)	0	0	1 (2.3)
Abdominal bloating	1 (2.3)	0	0	0	0	1 (2.3)

TABLE 3.1 | Median progression free survival and progression free survival at 6 months, 1 year, and 3 years ($n = 43$).

PFS	WHO Grade 1 (CI 95%)	WHO Grade 2 (CI 95%)	WHO Grade 3 (CI 95%)	ALL (CI 95%)
6 months	89.4% (0.78–1.00)	80.0% (0.45–1.00)	33.3% (0.00–0.71)	80% (0.67–0.92)
1 year	81.5% (0.67–0.96)	80.0% (0.45–1.00)	–	68.3% (0.53–0.83)
3 years	61.1% (0.25–0.97)	30.0% (0.00–0.77)	–	45.9% (0.20–0.71)
Median PFS				
Median	3.1 years (3.0–4.5)	2.4 years (1.3–3.2)	0.2614 years (0.17–1.0)	2.97 years (1.76–4.53)

(–), undetermined.

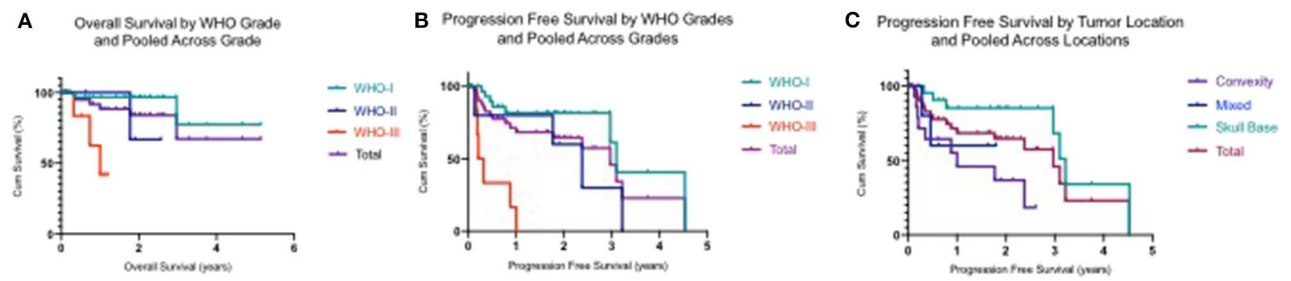


FIGURE 1 | (A) Kaplan–Meier plot demonstrating overall survival by WHO tumor grades and polled across WHO grades. **(B)** Kaplan–Meier plot demonstrating progression free survival by WHO tumor grades and polled across WHO grades. **(C)** Kaplan–Meier plot demonstrating progression free survival by tumor location and polled across locations.

tumor grade groups. Kaplan-Meier curves were generated to analyze the overall PFS and PFS stratified by WHO tumor grade (**Figures 1A,B**). Evaluation based on tumor location showed that PFS6 was 90.5% (CI: 0.79–1.00) for skull base tumors with 83.3% (CI: 0.54–1.00) for parasagittal meningiomas while PFS6 was 50.0% (0.15–0.85) for convexity lesions (**Table 3.2**). Median

TABLE 3.2 | Median progression free survival and progression free survival at 6 months, 1 year, and 3 years based on tumor location and size ($n = 43$).

PFS	Parasagittal (CI 95%)	Convexity (CI 95%)	Skull Base (CI 95%)	Mixed (CI 95%)	Size (< 3 cm) (CI 95%)	Size (3-6 cm) (CI 95%)	Size (>6 cm) (CI 95%)
6 months	83.3% (0.54–1.00)	50.0% (0.15–0.85)	90.5% (0.79–1.00)	60% (0.17–1.00)	73% (0.54–0.92)	80% (0.63–0.98)	100
1 year	62.5% (0.20–1.00)	33.3% (0–0.68)	85.2% (0.70–1.00)	–	66.4% (0.44–0.89)	68.7% (0.48–0.90)	–
3 years	–	–	68.1% (0.36–1.00)	–	44.3% (0.06–0.83)	22.9 (0–0.60)	–
Median PSF	2.38	0.68	3.22 (2.96–4.53)	–	3.10 (0.51–4.53)	2.38 (0.87–3.22)	1.77 (–)

(–), undetermined.

TABLE 3.3 | Median progression free survival and progression free survival based on treatment history at 6 months, 1, and 3 years ($n = 43$).

PFS	Radiation (CI 95%)	Non-radiation (CI 95%)	Surgical (CI 95%)	Non-surgical (CI 95%)	Chemo-therapy (CI 95%)	Non-chemotherapy (CI 95%)
6 months	85.2% (0.70–1.00)	94.7% (0.85–1.00)	74.3% (0.59–0.90)	88.9% (0.68–1.00)	42.9% (0.06–0.80)	84.8% (0.73–0.97)
1 year	85.2% (0.70–1.00)	94.7% (0.85–1.00)	62.7% (0.45–0.80)	–	14.3% (0–0.40)	81.0% (0.67–0.95)
3 years	49.7% (0.07–0.93)	82.9% (0.59–1.00)	37.4% (0.10–0.64)	–	–	57.6% (0.27–0.88)
Median PFS	2.97 (1.76–(–))	2.97 (1.76–(–))	2.37 years (0.87–4.53)	–	0.51 (0.19–1.0)	3.10 (2.37–4.53)

(–), undetermined.

TABLE 4.1 | Median overall survival and overall survival at 6 months, 1, and 3 years ($n = 43$).

OS	WHO Grade 1 (CI 95%)	WHO Grade 2 (CI 95%)	WHO Grade 3 (CI 95%)	ALL (CI 95%)
6 months	96.4% (0.90–1.00)	100%	83.3% (0.54–1.00)	94.8% (0.85–1.00)
1 year	96.4% (0.90–1.00)	100%	41.7% (0.00–0.85)	88.1% (0.77–0.99)
3 years	77.1 (0.43–1.00)	*	*	67.0% (0.36–0.98)
Median OS	–	–	1.0 (0.31–(–))	–

**Final case was censored before this point, (–), undetermined.*

PFS for small tumors was 3.22 years (CI: 2.96–4.53) (**Table 3.2**). Analysis based on the treatment history identified that PFS6 for patients with no history of radiation was 94.7% (CI: 0.85–1.00), no surgeries 88.9% (CI: 0.68–1.00) and no chemotherapy was 84.8% (CI: 0.73–0.97) (**Table 3.3**). Patients with ER-PR+ tumors had PFS6 of 87.8% (CI: 0.72–1.00) while patients with ER-PR- meningiomas had PFS6 of 62.5% (CI: 0.28–0.96).

The median OS for all tumor grades has not been yet reached, thus it could not be reported (**Table 4.1**). There was a low event rate in which half of patients remained alive. The median OS for WHO grade III meningioma was 1.0 (95% CI: 0.45–1.56). The OS for all tumor grades at 6 months was 94.9% (95% CI: 0.88–1.00), 88.4% (95% CI: 0.78–0.99) at 1 year, and 67.2% (95% CI: 0.36–0.99) at 3 years. The OS was also calculated for each WHO tumor grade at 6 months, 1 and 3 years. The OS for I, II, and III at 6 months were 96.6% (95% CI: 0.90–1.00), 100%, and 83.3% (95% CI: 0.54–1.00) respectively. At 1 year, the OS for WHO grade I was 96.6% (95% CI: 0.90–1.00), 100% for WHO grade II and for WHO grade III was 62.5% (95% CI: 0.21–1.00). The OS at 3 years for WHO grade I was 77.2% (95% CI: 0.43–1.00). Kaplan Meier curves were generated to show OS and OS stratified by WHO grade (**Figures 1C,D**). The median OS was achieved for patients with convexity tumors (1.75 years), medium tumor size (2.97 years), and 2.97 years for patients with no prior history of radiation or surgeries (**Tables 4.2** and **4.3**).

DISCUSSION

Currently, there are no FDA approved therapies for management of surgically inaccessible or radiation-refractory recurrent meningiomas. In 2019, the Central Nervous System NCCN guideline recommended somatostatin analogs as valuable therapeutic options for management of progressive or recurrent meningiomas (6). These recommendations were derived from limited studies evaluating various somatostatin analogs (somatostatin, pasireotide, octreotide, and Sandostatin LAR). Our study, on the other hand, is one of the largest reported retrospective analysis of meningioma patients with recurrent and/or progressive disease treated with Sandostatin LAR (octreotide).

Comprehensive review of our study and previously reported data are summarized in **Table 5**. We utilized similar inclusions

TABLE 4.2 | Median overall survival and overall survival at 6 months, 1 year, and 3 years based on tumor location and size ($n = 43$).

OS	Parasagittal (CI 95%)	Convexity (CI 95%)	Skull Base (CI 95%)	Mixed (CI 95%)	Size (< 3 cm) (CI 95%)	Size (3-6 cm) (CI 95%)	Size (>6 cm) (CI 95%)
6 months	100%	87.5% (0.64–1.00)	95% (0.85–1.00)	–	94.4% (0.84–1.00)	94.7% (0.85–1.00)	100%
1 year	80% (0.44–1.00)	65.6% (0.24–1.00)	95% (0.85–1.00)	–	–	82.1% (63.6–100)	–
3 years	–	–	76% (0.42–1.00)	–	–	–	–
Median OS	–	1.75 (–)	–	–	–	2.97 (–)	

(–), undetermined.

TABLE 4.3 | Median overall survival and overall survival based on treatment history at 6 months, 1 year, and 3 years ($n = 43$).

OS	Radiation (CI 95%)	Non-radiation (CI 95%)	Surgical (CI 95%)	Non-surgical (CI 95%)	Chemo-therapy (CI 95%)	Non-chemotherapy (CI 95%)
6 months	95% (0.85–1.00)	94.7% (0.85–1.00)	96.7% (0.90–1.00)	88.9% (0.68–1.00)	100%	93.7% (0.85–1.00)
1 year	83.1% (0.66–1.00)	94.7% (0.85–1.00)	88.1% (0.75–1.00)	88.9% (0.68–1.00)	83.3% (0.54–1.00)	89.6% (0.78–1.00)
3 years	83.1% (0.66–1.00)	41.5% (0–1.00)	82.6% (0.66–0.98)	0	62.5% (0.20–1.00)	67.2% (0.28–1.00)
Median	–	2.97 (1.76–(–))	–	2.97 (0.35–2.97)	–	–

(–), undetermined.

TABLE 5 | Studies of octreotide analogs in refractory recurrent meningiomas.

Author, year of publication	Number of patients and WHO grade of meningioma	Median KPS	PFS6 (%)	Median TTP/PFS (months)	Median OS (months)	Common toxicities
Chamberlain et al. Sandostatin LAR (16)	16 (I, $n = 8$; II, $n = 3$; III, $n = 5$)	80	44	5	7.5	Diarrhea
Johnson et al. Sandostatin LAR (17)	Meningiom a:11 (I, $n = 3$; II, $n = 3$; III, $n = 5$) Hemangiopericytom a: 1	ND	ND	4.25	32.4	Diarrhea, anorexia, nausea, transaminitis
Schulz et al. Sandostatin LAR (14)	13 (I, $n = 8$ localized to skull base that underwent analysis)	ND	ND	24	ND	Well-tolerated, $n = 1$ psychiatric side effects
Simo et al. Octreotide (22)	9 (II, $n = 5$; III, $n = 4$)	80	44.4	4.23	18.7	Diarrhea
Norden et al. Pasireotide LAR (SOM230C) (23)	28 (I, $n = 16$; II/III $n = 18$)	85	32	4.5	Not achieved	Hyperglycemia, hypoglycemia, elevated amylase, elevated lipase, fatigue, hypokalemia
Graillon et al. Everolimus and Octreotide (24)	20 (I, $n = 2$; II, $n = 10$, III $n = 8$)	ND	55	ND	ND	Stomatitis, fatigue, diarrhea
Our study	43 (I, $n = 32$; II, $n = 5$, III $n = 6$)	80	80	35.6	Not achieved	Diarrhea, headache

and exclusions criteria as prior trials. For instance, we included adult patients with recurrent or progressive meningioma diagnosed by PET scan (14, 22) and/or biopsy proven as in Johnson et al. (17). Prior radiotherapy, chemotherapy treatments and/or surgeries were permitted, as it was done in Chamberlain et al. and Johnson et al. (16, 17), in contrast to the study by Simo et al. that included only chemotherapy naïve patients (22). The results of our study were compatible and showed noted improvement from prior investigations. Specifically, PFS6 in our study for all tumor grades was 80.0% while prior studies reported PFS6 in 32.0–44.4% range (14, 16, 17, 22).

The OS for all tumor grades has not been achieved in our study, while other investigations reported OS ranged from 7.5 to 34.2 months. Median KPS status in all studies ranged from 80 to 85. The prospective pilot trial conducted by Chamberlain et al. included 16 patients with low and high grade recurrent meningiomas who received treatment with Sandostatin LAR (octreotide) (16). Analysis indicated PFS6 of 44%, median TTP

TABLE 6 | Targeted therapy for progressive recurrent meningiomas.

Author, year of publication	Inhibitor	Target	N	Tumor Grade	Median KPS	PFS6 (%)	Median TTP/PFS (months)	Common toxicities	Grade 4 or 5 toxicity
Nayak et al. (28)	Bevacizumab	VEGF	15	II, III	ND	43.7	6.5	Fatigue, cerebral hemorrhage	No
Lou et al. (29)	Bevacizumab	VEGF	14	I, II, III	80	85.7	17.9	Thrombocytopenia, proteinuria, craniotomy site cellulitis	Yes
Nunes et al. (30)	Bevacizumab	VEGF	15	NF2	ND	85	15	Hypertension, transaminitis, menorrhagia, irregular menses	No
Alanin et al. (31)	Bevacizumab	VEGF	7	NF2	ND	ND	ND	Intracerebral hemorrhage	Yes
Shih et al. (32)	Bevacizumab+ everolimus	VEGF mTOR	17	I, II, III	ND	69	22	Colitis, chronic thrombotic microangiopathy, proteinuria, nephrotic syndrome	No
Wen et al. (33)	Imatinib	PDGFR	23	I, II, III	80	29.4	2	Anemia, leukopenia, neutropenia, dehydration, dizziness, hypophosphatemia	Yes
Horak et al. (34)	Imatinib	PDGFR	9	I, II, III	ND	66.7	17	ND	ND
Reardon et al. (35)	Imatinib + hydroxyurea	PDGFR	21	I, II, III	ND	61.9	7	Anemia, constipation, edema, fatigue, hypoalbuminemia, hypophosphatemia, rash, neutropenia, thrombocytopenia	Yes

of 5 months and median OS of 7.5 months with minimal toxicity. The phase II study by Johnson et al. evaluated 12 patients with all tumor grades reported median TTP as 4.25 months and median OS as 32.4 months (17). Schulz et al. evaluated 13 patients with WHO tumor grade I meningiomas, and only median TTP was reported as 24 months (14). Simo et al. conducted phase II trial on patients with high-grade meningiomas who received subcutaneous octreotide injections every 28 days and reported PFS6 as 44.4%, median TTP as 4.23 months, and median OS as 18.7 months (22). Norden et al. showed no radiographic response to therapy with pasireotide LAR (SOM230C) on 28 patients with recurrent meningiomas of all tumor grades, PFS6 as 32% and median TTP as 4.5 months, but overall OS was not reached (23). The prospective phase II clinical trial by Graillon et al. evaluated the benefits of combination of everolimus and octreotide in patients with recurrent meningioma who were ineligible for further interventions (24). The PFS at 6 months was 55%, the overall survival rates at 6 and 12 months were 90 and 75%, respectively (24).

Only one prior study by Schulz et al. evaluated PFS based on the tumor location. Schulz et al. evaluated eight patients with skull based WHO grade I tumors and showed PFS was 100% at 48 months with two patients discontinued treatment after 36 months without disease progression (14). Our study included 23 patients with skull-based tumor of which 21 patients had WHO grade 1 meningiomas. The PFS6 for skull-based tumors was 90.5% which is consistent with Schulz et al. No analysis based on tumor grade, location or receptor type were performed in other studies that investigated Sandostatin LAR (16, 17, 22). Our data showed no radiological regression as defined by the RANO criteria (25) which is in agreement with previously published data. Based on *in vitro* studies showing that octreotide significantly decreased cell proliferation but did not induce cell death (13, 14), it is not surprising that prior prospective studies investigating the efficacy of Sandostatin LAR on meningioma showed no evidence of radiological tumor regression (14, 16, 17, 22, 23). It was suggested that even though no radiographical tumor regression was detected, Sandostatin LAR may arrest tumor progression (17). Only recent Phase II clinical trial that evaluated the effectiveness of combination of everolimus and octreotide showed that among the 20 study patients, radiological regression in the tumor volume by >10% was identified in 4 patients (24).

Evaluation based on tumor size and location revealed that the patients with skull-based and small tumors had the longest median PFS of 3.22 and 3.1 years respectively. Interestingly, our cohort showed no difference in the median PFS based on the radiation status while the patients with no history of chemotherapy were noted to have the median PFS of 3.10 years. The patients who underwent surgeries had the median PFS of 2.37 years. Thus, patients with small skull-based tumors with prior surgeries and no history of chemotherapy had the longest median PFS without respect to prior history of radiation.

Evaluation of PFS6 based on the effect of estrogen and progesterone on meningioma was performed. Analysis showed that patients with ER-PR+ tumors had PFS6 of 87.8% (CI: 87.8% (0.72–1.00) while patients with ER-PR- meningiomas had PFS6 of 62.5% (CI:0.28–0.96). These findings are in agreement with previously published data noting that lack of PR expression to be correlated with high tumor grade and tumor recurrence. Pravdenkova et al. showed that expression of the PR alone in meningioma signals a favorable clinical and biological outcome while the lack of receptors correlates with aggressive clinical behavior, progression or recurrence of this tumors (26). Recent retrospective study showed that patients with meningioma with ER+ had a much worse prognosis than those with ER weak or ER- status [Hua]. Since our analysis mainly included patients with ER+ status at least indicates that more than 58% of the cohort had ER+ status (27).

Reported toxicities were consistent across clinical studies with diarrhea, abdominal pain, nausea, vomiting and transaminities being the most common events. Prior studies had <25 patients that resulted in low statistical power.

Our clinical study provides additional evidence to support the rationale for a larger phase study to assess the efficacy of Sandostatin LAR (octreotide). Compared to other therapeutics, Sandostatin LAR (octreotide) had the longer median PFS, PFS6 and safety profile (**Table 6**). There were no observed CTCAE grade 4 or grade 5 adverse events. There was only one CTCAE grade 3 adverse event that identified the patient who was hospitalized with pancreatitis after developing cholelithiasis. Sandostatin LAR (octreotide) was subsequently discontinued in this patient. Erlotinib demonstrated a favorable safety profile compared to all the other drugs, however, median PFS was shorter than for the patients who received Sandostatin LAR (octreotide).

Important to note, that the CNS NCCN guideline classifies somatostatin analog, as a level 2A category for patients with progressive recurrent meningioma while interferon alpha, sunitinib and bevacizumab, and everolimus combination were given 2B category (6). Category 2A evidence is based on lower-level evidence with uniform NCCN consensus that the intervention is appropriate, while category 2B evidence that is also based on lower level of evidence was only granted experts consensus. These recommendations are not surprising, as scientific literature review indicates that somatostatin analogs including Sandostatin LAR (octreotide) are better tolerated therapies with good efficacy as evidenced by longer PSF and PFS6.

Specifically, phase II clinical trial that included 36 patients with high-grade meningioma who received sunitibin showed efficacy of that treatment based on PFS6 of 42%, median PFS of 5.2 months and median OS of 24.6 months (36). However, considerable toxicity was observed with 1 grade 5, 1 grade 4 and 2 grade 3 intratumoral hemorrhages, 1 grade 4 and 1 grade 3 thrombic microangiopathy attributed to known side effect profile of VEGF inhibitors. By comparison all studies on somatostatin analogs including this report indicate well-tolerability and minimal side effects with diarrhea being the most commonly reported side effect.

The phase II clinical study evaluated efficacy of combination of everolimus and bevacizumab in 17 patients with progressive recurrent meningiomas (WHO tumor grade I,II and III) showed that this regiment was well-tolerated, and produced stable diseases in 88% of patients with median PFS as 22 months, PFS as 69% and median OS of 23.8 months (32). No grade 5 or grade 4 toxicities were reported, but four patients (22%) discontinued treatment due to grade 3 toxicities such as proteinurea, colitis and thrombocytopenia. Important to note, that since the sample size was small, additional work in indicated. In comparison, our study is one of largest studies that included 43 patients providing more conclusive results.

The recently published prospective phase II clinal trial that evaluated the efficacy of combination of everolimus and octreotide reported that stomatitis was the most common grade 3 adverse event, seen in 55% of patients, necessitating the discontinuation of both therapeutics in 1 patient and everolimus in another (24).

A retrospective case series evaluated treatment with interferon alpha for patients with high grade meningiomas that showed progression after surgery, radiotherapy, or prior systemic chemotherapy (37). The study revealed the median PFS12 and PFS6 of 17% without radiographical response and moderate toxicity. Unfortunately, given that overall PFS and PFS6 were below benchmark criteria of PFS of 26% for atypical and malignant meningiomas proposed by the Response Assessment in Neuro-Oncology (RANO) Working Group 2014, it appears to be an unlikely candidate for use for treatment of progressive recurrent meningiomas (38).

Thus, based on available clinical data, Sandostatin LAR (octreotide) should be given consideration for managing patients with progressive and/or recurrent meningiomas. Nevertheless, this was a retrospective study with several limitations, imposed by the type of the study. Comparison of Sandostatin LAR (octreotide) to other therapeutics were hindered, as all the studies have different methodologies, size, patient population, or objectives. In addition, our study did not include a control, and prior reported studies were used for comparison. Furthermore, numerous patients were evaluated years after the initial diagnosis with limited number of patients who were diagnosed based on immunohistochemistry results, hindering further stratification based on molecular profile. Despite the stated limitations, our study is one of the largest retrospective studies that provides rationale and supports further investigation of Sandostatin LAR (octreotide) for the treatment of progressive or recurrent meningiomas. Additional prospective, larger scale randomized trials are needed to validate the effectiveness of Sandostatin LAR (octreotide) in meningioma.

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available because of limitations imposed by the patients confidentially and participant privacy. Requests to access the datasets should be directed to Dr. Maya Hrachova, mayahrachova@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of California Irvine Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The following authors have contributed significantly to the experimental design (DB, X-TK, GC, and FH), its implementation (MH, EN, BF, MD, X-TK, GC, FH, and DB), or analysis and interpretation of the data (All authors). All authors were involved in the writing of the manuscript at draft and any revision stages and have read and approved the final version.

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The preliminary analysis has been released as a pre-print at Neuro-Oncology Nguyen et al. (19). Significant changes to the original analysis were made based on re-evaluation of the original data (19).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Accurate Preoperative Distinction of Intracranial Hemangiopericytoma From Meningioma Using a Multihabitat and Multisequence-Based Radiomics Diagnostic Technique

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Background: Intracranial hemangiopericytoma (IHPC) and meningioma are both meningeal neoplasms, but they have extremely different malignancy and outcomes. Because of their similar radiological characteristics, they are difficult to distinguish prior to surgery, leading to a high rate of misdiagnosis.

Methods: We enrolled 292 patients (IHPC, 155; meningiomas, 137) with complete clinic-radiological and histopathological data, from a 10-year database established at Tiantan hospital. Radiomics analysis of tumor and peritumoral edema was performed on multisequence magnetic resonance images, and a fusion radiomics signature was generated using a machine-learning strategy. By combining clinic-radiological data with the fusion radiomics signature, we developed an integrated diagnostic approach that we named the IHPC and Meningioma Diagnostic Tool (HMDT).

Results: The HMDT displayed remarkable diagnostic ability, with areas under the curve (AUCs) of 0.985 and 0.917 in the training and validation cohorts, respectively. The calibration curve showed excellent agreement between the diagnosis predicted by HMDT and the histological outcome, with *p*-values of 0.801 and 0.622 for the training and the validation cohorts, respectively. Cross-validation showed no statistical difference across three divisions of the cohort, with average AUCs of 0.980 and 0.941 for the training and validation cohorts, respectively. Stratification analysis showed consistent performance of the HMDT in distinguishing IHPC from highly misdiagnosed subgroups of grade I meningioma and angiomatous meningioma (AM) with AUCs of 0.913 and 0.914 in the validation cohorts for the two subgroups.

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Conclusions: By integrating clinic-radiological information with radiomics signature, the proposed HMDT could assist in preoperative diagnosis to distinguish IHPC from meningioma, providing the basis for strategic decisions regarding surgery.

Keywords: intracranial hemangiopericytoma, meningioma, diagnosis, magnetic resonance imaging, radiomics

INTRODUCTION

Intracranial hemangiopericytoma (IHPC) and meningioma are both meningeal neoplasms that share similar radiological characteristics (1). However, they have distinct histologic characteristics and biological behaviors (2–4). Unlike the majority of meningiomas, IHPC is malignant (WHO grade II–III) and has a relentless tendency to recur and metastasize (2, 4, 5). After the first relapse, sequential recurrence of IHPC is more frequent and the effectiveness of therapies decreases markedly. Hence, maximal surgical resection is imperative in the initial treatment of IHPC (6, 7). Because IHPC is highly vascularized, there is also a high risk of fatal blood loss during surgery (4).

These differences between IHPC and meningioma mean that accurate preoperative diagnosis is critically important for treatment planning. However, the high degree of overlap in the radiological characteristics has posed a great challenge for preoperative radiological diagnosis (8, 9). This challenge is also evident in the data used in this study, in which 70% of IHPCs were radiologically misdiagnosed as meningiomas and only identified by post-operative pathology analysis.

Although previous studies proved that CT/MRI-based characteristics may contribute to the diagnosis of IHPC, these are qualitative characteristics that are subject to observational bias, resulting in a high level of misdiagnosis of patients with IHPC (8, 10, 11). Imaging texture-based studies have shown that quantitative imaging features from MRI can be effective markers for distinguishing IHPCs and meningiomas (12, 13). However, studies to date lack convincing validation, and due to the small sample size, these models demonstrate only a simple correlation, which has limited clinical utility.

Radiomics, as an emerging medical image processing technique, provides a promising solution to solve this clinical problem. Radiomics can achieve the automatic extraction of high-throughput and high-dimensional imaging features from encrypted big medical imaging data (14, 15). By combining imaging information with preoperative clinical/empirical knowledge, it can identify patterns and subtypes relevant for tumor diagnosis, the evaluation of treatment effects, and prognosis (14, 16–18). Radiomics has been widely applied to predict pathological or genetic phenotypes in intra axil tumors, especially gliomas (19, 20). However, the utility of radiomics in differentiating IHPC and meningioma by multisequence MRI has yet to be established.

In this study, we conducted a retrospective analysis of high-quality data from a 10-year cohort of patients with histopathologically confirmed IHPCs and meningiomas, using multisequence and multihabitat radiomics pipeline to test the ability of radiomics to achieve high accuracy, preoperative diagnosis of IHPC and meningioma in order to assist in presurgery planning for the management and treatment of the two types of tumor.

MATERIALS AND METHODS

Patient Enrollment

Patients were retrospectively enrolled by searching the Picture Archiving and Communications System in our hospital from January 2008 to December 2018. Clinical data were retrieved from the Electronic Medical Record. Patients were randomly split into training ($n = 204$) and validation cohorts ($n = 88$). The study was approved by the institutional review board, and all patient records and information were anonymized and de-identified. The Chinese Clinical Trial Registry identifier of the study was ChiCTR1900022671.

The inclusion criteria were as follows: (1) MR images acquired no more than 1 month before surgery; (2) preoperative standard MR imaging that included T1WI, CE-T1WI, and T2WI sequences; and (3) complete clinical records at initial diagnosis. The exclusion criteria were as follows: (1) history of craniotomy, biopsy, radiotherapy, or chemotherapy; (2) recurring tumors or multiple lesions; and (3) low-quality or unclear MRIs.

The histopathological examination and MR imaging acquisition are provided in **Supplementary Appendix E1**.

Development of HMDT

Preoperative clinical and radiological information may reflect and depict different phenotypes of IHPC and meningioma; thus, we comprehensively integrated correlated clinical, radiological, and radiomics data stream into a machine learning–based model, named IHPC and Meningioma Diagnostic Tool (HMDT), to improve accurate diagnosis of IHPC and meningiomas.

Selection of Preoperative Clinical and Radiological Factors

A total of 14 preoperative clinical/radiological factors were analyzed as potential effective factors as reported in the references (4, 6, 8, 10, 19–24). Univariable and multivariable analyses were used to identify effective factors for the diagnosis and were integrated into a clinical model by logistic regression modeling. Detailed description of radiological factors is shown in **Supplementary Appendix E2**.

Radiomics Analysis

The radiomics analysis process was structured in three phases: radiomic feature extraction, key feature selection, and radiomics signature construction.

Initially, a set of 473 radiomic features were extracted from segmented tumor and peritumoral edema habitats using the Pyradiomics tool (https://pyradiomics.readthedocs.io). These radiomic features fall into four broad categories: shape and size, first-order statistics, textural, and wavelet features. The process of tumor segmentation is described in **Supplementary Appendix E3**. The detailed description of the radiomic feature definition is provided in **Supplementary Appendix E4**.

Feature selection was primarily conducted by assessing feature stability and reproducibility via calculating the concordance correlation coefficient (CCC) and the intraclass correlation coefficient (ICC). Multiclinician, multi-time-point, and perturbation segmentation manners for feature robustness assessment are described in **Supplementary Appendix E5**. We further applied the Mann–Whitney *U*-test to select diagnosis outcome-related radiomic features with a $p < 0.05$.

TABLE 1 | Baseline characteristics in training and validation cohorts.

Characteristics	Training cohort ($n = 204$)			Validation cohort ($n = 88$)			P (inter)
	IHPC ($n = 109$)	Meningioma ($n = 95$)	P (intra)	IHPC ($n = 46$)	Meningioma ($n = 42$)	P (intra)	
Age (median [IQR])	43 (31.51)	50 (39.58)	0.003	42 (28.49)	51 (38.58)	0.015	0.570
Gender							0.359
Male	56 (51.4)	44 (46.3)	0.471	22 (47.8)	16 (38.1)	0.357	
Female	53 (51.0)	51 (53.7)		24 (52.2)	26 (61.9)		
Course of disease (median [IQR])	4 (2.12)	6 (1.24)	0.063	3 (2.12)	4.5 (1.24)	0.177	0.439
Location 1							0.240
Frontal	44 (40.4)	64 (67.4)	<0.001	21 (45.7)	19 (45.2)	0.969	
Posterior	65 (59.6)	31 (32.6)		25 (54.3)	23 (54.8)		
Location 2							0.730
Supra	84 (77.1)	89 (93.7)	0.001	35 (76.1)	41 (97.6)	0.003	
Infra	25 (22.9)	6 (6.3)		11 (23.9)	1 (2.4)		
Location 3							0.732
Left	35 (32.1)	34 (35.8)	0.041	11 (23.9)	23 (54.8)	0.001	
Right	34 (31.2)	41 (43.2)		15 (32.6)	15 (35.7)		
Both	40 (36.7)	20 (21.1)		20 (43.5)	4 (9.5)		
Midline type							0.148
Yes	81 (74.3)	64 (67.4)	0.275	35 (76.1)	20 (47.6)	0.006	
No	28 (25.7)	31 (32.6)		11 (23.9)	22 (52.4)		
Venous sinus invasion							0.801
Yes	49 (45.0)	47 (49.5)	0.519	22 (47.8)	18 (42.9)	0.640	
No	60 (55.0)	48 (50.5)		24 (52.2)	24 (57.1)		
Dural tail sign							0.169
Yes	18 (16.5)	52 (54.7)	<0.001	5 (10.9)	18 (42.9)	0.001	
No	91 (83.5)	43 (45.3)		41 (89.1)	24 (57.1)		
Tumor shape							0.080
Regular	11 (10.1)	9 (9.5)	0.882	5 (10.9)	10 (23.8)	0.107	
Irregular	98 (89.9)	86 (90.5)		41 (89.1)	32 (76.2)		
Enhancement pattern							0.997
Homogeneous	25 (22.9)	19 (20.0)	0.611	10 (21.7)	9 (21.4)	0.972	
Heterogeneous	84 (77.1)	76 (80.0)		36 (78.3)	33 (78.6)		
Tumor margin							0.314
Clear	20 (18.3)	31 (32.6)	0.019	11 (23.9)	16 (38.1)	0.150	
Unclear	89 (81.7)	64 (67.4)		35 (76.1)	26 (61.9)		
Peritumoral edema							0.075
Absent	25 (22.9)	13 (13.7)	0.007	16 (34.8)	11 (26.2)	0.052	
Moderate	60 (63.2)	75 (68.8)		28 (60.9)	22 (52.4)		
Extensive	9 (8.3)	22 (23.2)		2 (4.3)	9 (21.4)		
Serpentine signal voids							0.699
Yes	96 (88.1)	68 (71.6)	0.003	40 (87.0)	29 (69.0)	0.041	
No	13 (11.9)	27 (28.4)		6 (13.0)	13 (31.0)		

IHPC, intracranial hemangiopericytoma; P (Intra) is the result of univariable analyses between methylated and unmethylated groups; P (Inter) represents whether there exists significant difference between training and validation cohorts; IQR represents the interquartile range. Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

On the basis of this initial selection of promising variables, we then compared 64 radiomics modeling strategies including the 16 feature selection algorithms and 4 classifiers most commonly used in radiomics studies (12, 25). A detailed account of the 64 strategies is provided in **Supplementary Appendix E6**. Recursive feature elimination and random forest stood out as the optimal feature selection algorithm and classifier for radiomics signature construction.

The above radiomics pipeline was then conducted on T1WI-tumor, CE-T1WI-tumor, T2WI-tumor, T1WI-edema, CE-T1WI-edema, and T2WI-edema, respectively. Consequently, six radiomics signatures were acquired. A fusion radiomics signature was constructed by integrating the six single signatures by logistic regression modeling.

Integrated HMDT Model and Nomogram Construction

The HMDT was constructed by integrating effective clinic-radiological factors with the fusion radiomics signature. We adopted the Akaike information criterion (AIC) to select optimal incorporated factors and utilized logistic regression modeling to perform HMDT construction. In addition, a nomogram was drawn to manifest the contribution of each of the included parameters according to their weighted proportions in the model.

Model Assessment

Diagnostic Performance Assessment

The diagnostic power of the proposed models was evaluated by the receiver operating characteristic (ROC) curve, area under the curve (AUC), accuracy, sensitivity, and specificity. Comparisons between AUCs were performed with the Delong test, and comparisons between specificity and sensitivity were performed by Pearson's chi-square test. Calibration curves were plotted to evaluate the calibration power of the nomogram with the Hosmer Lemeshow test. To quantify the discrimination ability of the nomogram, Harrell's C-index was calculated.

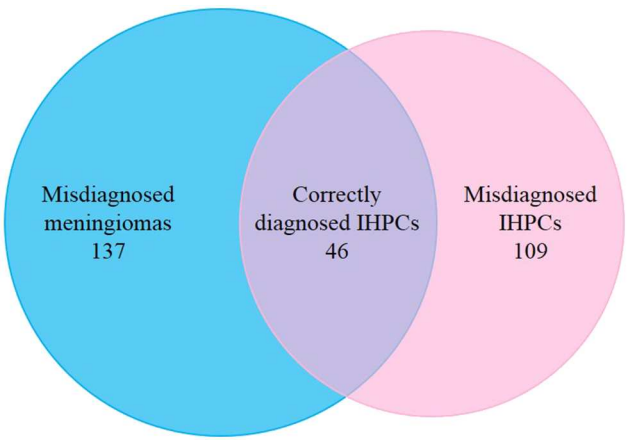


FIGURE 1 | Distribution of enrolled patients. Left circle represents cases of radiologically diagnosed IHPCs; right circle represents cases of pathologically diagnosed IHPCs. Intersection (purple) of two circles represents 46 cases of enrolled IHPCs, which were correctly diagnosed by radiology; 137 cases of pathologically diagnosed meningiomas were radiologically misdiagnosed as IHPCs (blue); 109 cases of pathological diagnosed IHPCs were radiologically misdiagnosed as meningiomas (pink).

Assessing the Diagnostic Robustness of HMDT

To test the model robustness, we randomly divided the enrolled cohorts into training and corresponding validation cohorts three times and labeled these Groups 1, 2, and 3. The division ratio remained 7:3 for each operation. AUCs were compared using the Delong test to show whether the change of dataset would affect the performance of the HMDT. At the same time, three-fold cross-validation was performed to elude the effect of sample divisions.

Stratification Analysis

In light of the need to consider subpopulations in which IHPC and meningioma diagnosis is more difficult, we performed stratification analysis based on age and radiological behavior (tumor shape and dural tail sign), as well as pathological grade and subtype. Considering the majority of IHPCs that were misdiagnosed using MRI were WHO grade I meningiomas, especially angiomatous meningiomas (AMs), we conducted additional subpopulation analysis of WHO grade I meningiomas and AMs.

Clinical Usefulness

The clinical validity of the HMDT was assessed by decision curve analysis. Furthermore, we developed a software embedded HMDT model with a user-friendly interface. This online tool can be freely downloaded and activated using the application file provide in the reference[1]. User instructions are provided in **Supplementary Appendix E7**.

Statistical Analysis

Statistical analysis was performed with PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA) and R software, version 3.4.1 (www.R-project.org). Statistical significance was defined with a two-sided $p < 0.05$.

RESULTS

Baseline Characteristics

The baseline characteristics are summarized in **Table 1**. There were no significant differences between the training and validation cohorts in terms of their demographic, clinical, or radiological characteristics ($p = 0.075$–0.997).

A total of 292 cases were enrolled in this study, of which 137 cases were pathologically diagnosed as meningiomas and 155 cases were pathologically diagnosed as IHPCs. Radiologically, all the enrolled meningiomas were misdiagnosed as IHPCs and 109 enrolled IHPCs were misdiagnosed as meningiomas. Only the remaining 46 cases of enrolled IHPCs were correctly radiologically diagnosed (**Figure 1**). Based on the 2016 WHO

[1] Available online at: http://www.radiomics.net.cn/post/118 (2019).

classification of CNS tumors, the pathological grades of these patients were as follows: 97 WHO grade II IHPCs, 58 WHO grade III IHPCs, 112 WHO grade I meningiomas, 22 WHO grade II meningiomas, and 3 WHO grade III meningiomas. There was no significant difference in the distribution of IHPC and meningioma between the training and validation cohorts ($p = 0.856$).

Selected Clinic-Radiological Factors

Seven clinical/radiological factors were selected as effective diagnostic parameters, which were the course of disease, location (frontal/posterior), location (supra/infra), dural tail sign, tumor margin, peritumoral edema, and serpentine signal voids. The AUC for each single clinic-radiological factor turned out to be <0.6 in the validation cohort. The result of uni- and multivariable analysis and AUC of each selected factor is shown in **Supplementary Table 1**.

Diagnostic Performance of the Clinical Model

Combining the seven single clinical/radiological factors into a multiparametric clinical model significantly increased the diagnostic power (training: $p < 0.001$; validation: $p = 0.002$). The AUCs of the clinical model were 0.841 and 0.766 in the training and validation cohorts, respectively. Detailed predictive indicators, the ROC curve, and the violin graph of the clinical model are shown in **Table 2**, **Figure 2**, and **Supplementary Figure 1**, respectively.

Diagnostic Performance of Quantitative Radiomics Signatures

When combining the six single radiomics signatures, the fusion signature reached satisfactory AUCs of 0.979 and 0.902 in the training and validation cohorts, respectively. The process of feature selection is shown in **Supplementary Table 2**. The selected radiomic features and their diagnostic performance are shown in **Supplementary Table 3**. Detailed predictive indicators, the ROC curve, and the violin graph of the radiomics signatures are shown in **Table 2**, **Figure 2**, and **Supplementary Figure 1**, respectively. The results from the 64 modeling strategies are shown in **Supplementary Table 4**. Decision trees of the six single radiomics signatures are shown in **Supplementary Figure 2**.

Diagnostic Performance of HMDT

The final integrated HMDT model produced extremely accurate diagnosis of IHPC and meningioma with AUCs of 0.985 and 0.917 in the training and validation cohorts, respectively. The HMDT showed a significant improvement in diagnostic power over the clinical model, with $p < 0.001$ and 0.002 in the training and validation cohorts, respectively. Comparing of the HMDT and the fusion radiomics signature showed a numerical increase, but it was not statistically significant in either the training ($p = 0.141$) or validation ($p = 0.133$) cohorts. Detailed predictive indicators, the ROC curve, and the violin graph of the HMDT are shown **Table 2**, **Figure 2**, and **Supplementary Figure 1**, respectively. The heatmap showing the correlation between clinical factors and the selected radiomic features is shown in **Supplementary Figure 3**.

TABLE 2 | Diagnostic ability of the developed models.

Model	Training cohort ($n = 204$)				Validation cohort ($n = 88$)			
	AUC (95% CI)	ACC	SEN	SPE	AUC (95% CI)	ACC	SEN	SPE
Clinical model	0.841 (0.787, 0.896)	0.760	0.734	0.790	0.766 (0.667, 0.863)	0.659	0.674	0.643
T1_tumor signature	0.859 (0.810, 0.908)	0.819	0.972	0.642	0.818 (0.732, 0.904)	0.716	0.891	0.524
T1_edema signature	0.768 (0.706, 0.829)	0.716	0.927	0.474	0.673 (0.569, 0.777)	0.648	0.957	0.310
T2_tumor signature	0.858 (0.809, 0.907)	0.794	0.927	0.642	0.762 (0.666, 0.858)	0.693	0.849	0.524
T2_edema signature	0.787 (0.727, 0.846)	0.750	0.936	0.537	0.711 (0.613, 0.809)	0.682	0.957	0.381
CE-T1_tumor signature	0.811 (0.752, 0.870)	0.755	0.725	0.789	0.731 (0.628, 0.835)	0.648	0.630	0.667
CE-T1_edema signature	0.760 (0.699, 0.821)	0.770	0.982	0.526	0.734 (0.652, 0.817)	0.659	1.000	0.286
Tumor signature	0.917 (0.877,0.958)	0.878	0.973	0.768	0.872 (0.799, 0.944)	0.750	0.848	0.643
Edema signature	0.808 (0.747, 0.869)	0.775	0.973	0.547	0.704 (0.597, 0.811)	0.659	0.978	0.310
Fusion signature	0.979 (0.959, 0.999)	0.956	0.991	0.916	0.902 (0.841, 0.964)	0.818	0.891	0.738
HMDT	0.985 (0.968, 1)	0.961	0.973	0.947	0.917 (0.861, 0.972)	0.852	0.848	0.857

AUC, area under the curve; CI, confidence interval; ACC, accuracy; SEN, sensitivity; SPE, specificity.

Robustness of HMDT

In the three randomly assigned training and validation subcohorts, the ROC curves for the clinical model, fusion radiomics signature, and the HMDT overlapped (**Figure 2**). The Delong test showed that there were no significant differences among the three subcohorts with a *p*-value all larger than 0.05. It revealed the robustness of the modeling process and the consistent performance of the models regardless of changes in the cohorts. Detailed performance indicators of the three models are shown in **Supplementary Table 5**. The result of the three-fold cross-validation is shown in **Supplementary Table 6**.

Stratification in Difficult-to-Diagnosis Subpopulations

In stratification analysis, the HMDT presented with satisfactory diagnostic power across subpopulations (**Table 3**). Importantly, in the highly misdiagnosed WHO grade I meningioma group, the HMDT still showed superior diagnostic ability with a high AUC of 0.988/0.914. Surprisingly, the HMDT demonstrated equally satisfactory diagnostic power even in the especially hard to diagnose AM group, with an AUC of 0.997/0.913.

Nomogram and Software Development for Clinical Use

The graphical nomogram is shown in **Figure 3**. The Hosmer Lemeshow test yielded no significant difference between the outcomes predicted by the HMDT and the actual histopathological outcomes with a $p < 0.801$ and 0.622 in the training and validation cohorts, respectively. Decision curve analysis showed that the HMDT performed with a net improvement of 0.21% with cutoff probability of 0% in the training cohort and 0.19% improvement with 18% cutoff probability in the validation cohort. Furthermore, examples for cases diagnosed using the developed HMDT online tool are provided in **Supplementary Appendix E7**.

Typical Case Analysis

Figure 4 presents four typical cases and description of their radiological characteristics. Cases A and B were strongly suspected to be IHPCs on the basis of radiological information, but pathological analysis later found that Case A was meningioma. Cases C and D were strongly suspected to be meningiomas, but Case C was later found to be IHPC. The HMDT successfully diagnosed the four cases in accordance with the pathological results, with high probabilities. The probabilities that Cases A and D would be IHPCs were 7.8 and 0.1%, respectively, and the probabilities that Cases B and C would be IHPCs were 98.2 and 98.4%, respectively. Other results predicted by the HMDT are shown in **Supplementary Table 7**.

As a further blind test of the added value of the HMDT over diagnoses based on current clinical practice, we asked five junior neurosurgeons (working experience<5 years), two senior neurosurgeons (working experience>10 years), and one expert (working experience>30 years) to distinguish IHPC and

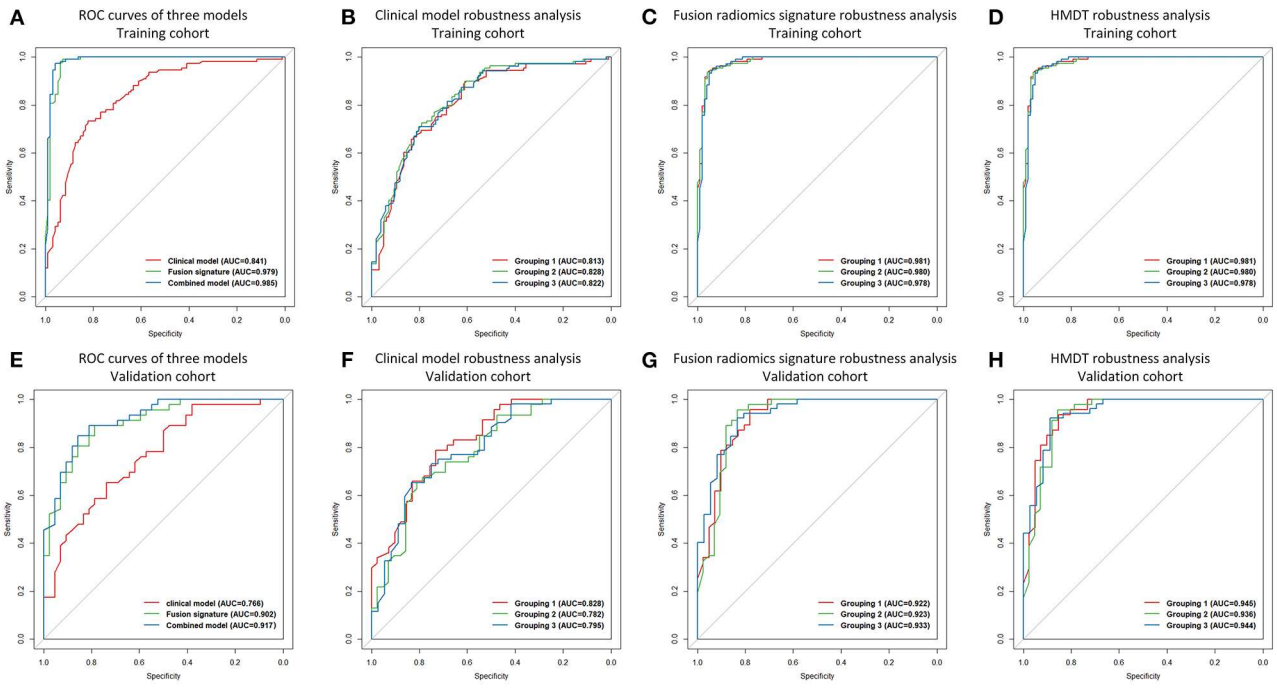


FIGURE 2 | ROC curves and robustness analysis results. ROC curves of the clinical model, the fusion radiomics signature, and the HMDT in the training cohort were shown in **(A)**, and the ROC curves of the three models in the validation cohort were shown in **(E)**. Robustness analysis for the clinical model, the fusion radiomics signature, and the HMDT in the training cohort were shown in **(B–D)**, respectively. For the validation cohort, robustness analysis for the three models were shown in **(F–H)**, respectively.

TABLE 3 | Stratification analysis of HMDT on training and validation cohorts.

Subpopulation	Training cohort ($n = 204$)				Validation cohort ($n = 88$)			
	AUC (95% CI)	ACC	SEN	SPE	AUC (95% CI)	ACC	SEN	SPE
Age								
<44	0.971 (0.921, 1)	0.941	0.946	0.933	0.894 (0.797, 0.990)	0.829	0.846	0.800
≥44	0.991 (0.948, 1)	0.966	0.982	0.954	0.933 (0.865, 1)	0.894	0.900	0.889
Tumor shape								
Yes	1	0.950	1	0.889	0.930 (0.805, 1)	0.667	1	0.500
No	0.983 (0.963,1)	0.962	0.980	0.941	0.924 (0.866,0.982)	0.863	0.829	0.906
Dural tail sign								
Yes	0.983 (0.957, 1)	0.929	1	0.904	0.944 (0.849, 1)	0.739	1	0.667
No	0.978 (0.945, 1)	0.970	0.989	0.930	0.904 (0.931, 0.976)	0.831	0.878	0.750
WHO grade I meningiomas	0.988 (0.968, 1)	0.968	0.973	0.961	0.914 (0.854, 0.973)	0.854	0.848	0.861
Angiomatous meningiomas	0.997 (0.992, 1)	0.978	0.991	0.920	0.913 (0.816, 1)	0.873	0.935	0.556

AUC, area under the curve; CI, confidence interval; ACC, accuracy; SEN, sensitivity; SPE, specificity.

meningioma for the four typical cases above. As expected, seven out of eight neurosurgeons wrongly diagnosed Case A as IHPC, and none of the eight neurosurgeons correctly diagnosed Case C as IHPC. The expert double-wrongly diagnosed Cases A and C. The diagnosed results of the eight neurosurgeons for the four cases are shown in **Supplementary Table 8**.

DISCUSSION

In this retrospective study, we explored the power of multihabitat and multisequence based radiomics for IHPC and meningioma preoperative diagnosis. The proposed effective tool, the HMDT, was developed by integrating clinic-radiological factors and the fusion radiomics signature. The HMDT improved the diagnostic accuracy with a high AUC of 0.985 in the training cohort and 0.917 in the validation cohort, which could enable a more reliable pretherapy diagnostic basis for subsequent treatment strategy making.

Over the past 30 years, previous studies exploring the use of radiological and/or clinical information in IHPC and meningioma preoperative diagnosis have shown some progress. He et al. have proved that the apparent diffusion coefficient (ADC) value was efficient for IHPC and AM (26). However, they concluded that conventional MRI and clinical factors fail to correlate with the pathological classification of IHPC and AM. Our rigorously proposed fusion radiomics signature derived from conventional MRI achieved superior performance with an AUC of 0.913 for IHPC and AM diagnosis, which was a significant improvement over the diagnostic power of the ADC value, which had an AUC of only 0.86. We acknowledge that, as other studies have shown, the ADC value contributes to IHPC and meningioma diagnosis (21, 26). However, in this paper, we demonstrate the unexploited power of conventional MRI data. Both conventional and functional MRI data should be fully utilized to increase the radiological diagnosis accuracy for IHPC and meningioma.

In our study, the dural tail sign was incorporated as the only clinic-radiological factor in the HMDT model. Previous studies have proved that narrow-based dural attachment and the absence of a dural tail sign were distinguishable factors in the diagnosis of IHPC and meningioma (8, 10, 11, 27). In our study, the dural tail sign presented a statistically different distribution in IHPCs and meningiomas with a $p < 0.01$. This was in concordance with previous results. Because the dural tail sign was associated with the chronic stimulation of meninges by the dural-attached lesion, although IHPC and meningioma are both dural-based tumors, their entirely different origin, growth rate, and malignancy may lead to such diversified manifestations of dural attachment and dural tail sign (27). Integrating the dural tail sign into the HMDT did not significantly improve its diagnostic ability, which implies that the quantified fusion radiomics signature has a more significant role in diagnosis than previously reported qualitative radiological factors. However, although it did not show a significant increase, adding the dural tail sign into the HMDT did boost its numerical accuracy. This shows the advantage of the integrated HMDT over the conventional radiological factor and single fusion radiomics signatures.

With regard to radiomic features, our results showed that the majority of selected features turned out to be wavelet features, which reflected multiscale information relating to tumor/edema areas. Through scale and translation operations, wavelet transformation could provide details focused on either high-frequency or low-frequency domains, leading it to be termed a "microscope in mathematics." Interestingly, we found

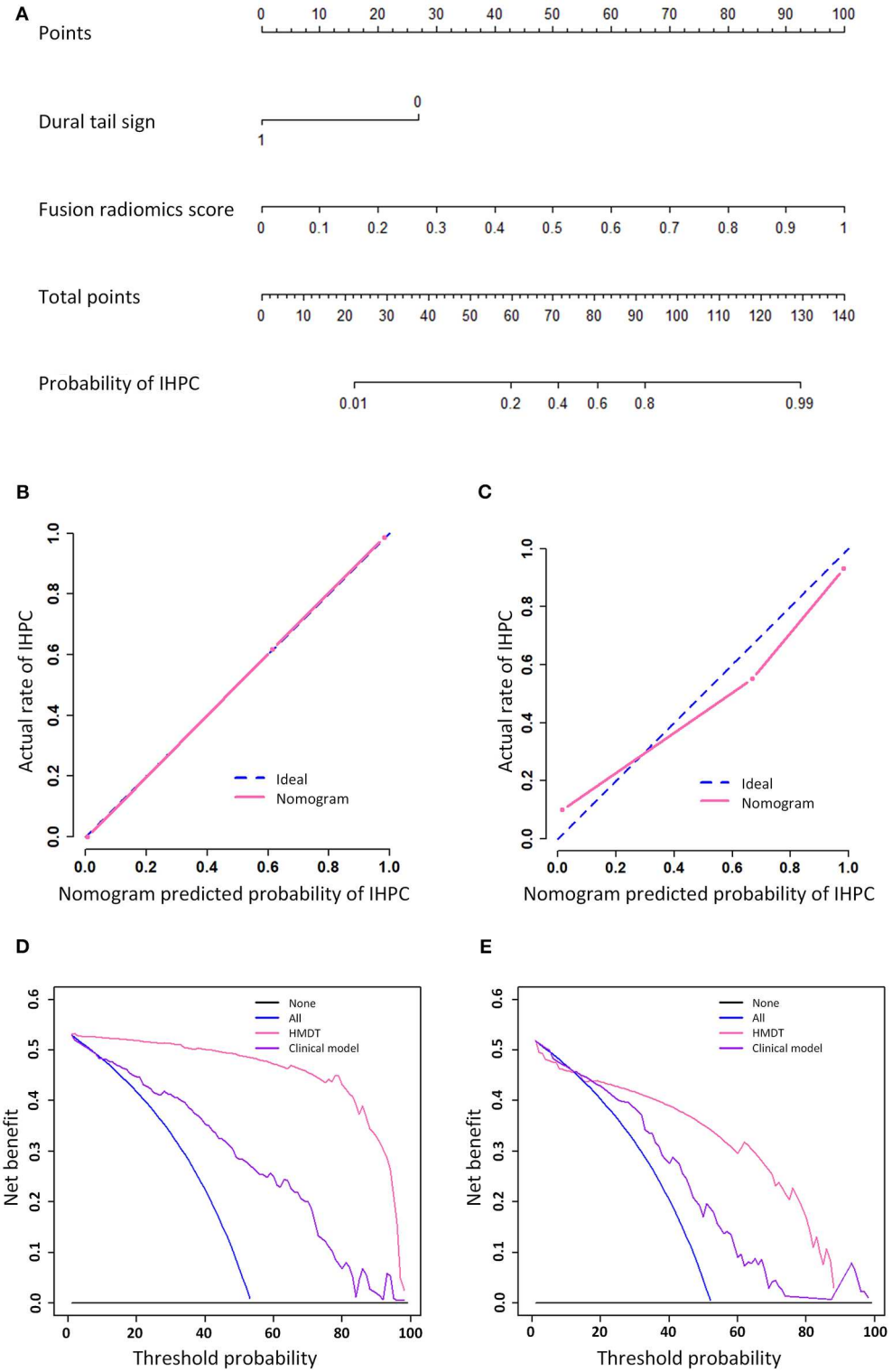


FIGURE 3 | Nomogram, calibration curve, and decision analysis curve. The nomogram that showed a linear presentation of the HMDT was shown in **(A)**. The calibration curves in training and validation cohorts were shown in **(B,C)**, respectively. Decision analysis curves in the training and validation cohorts were shown in **(D,E)**. The y-axis represents the net benefit and the x-axis represents the threshold probability.

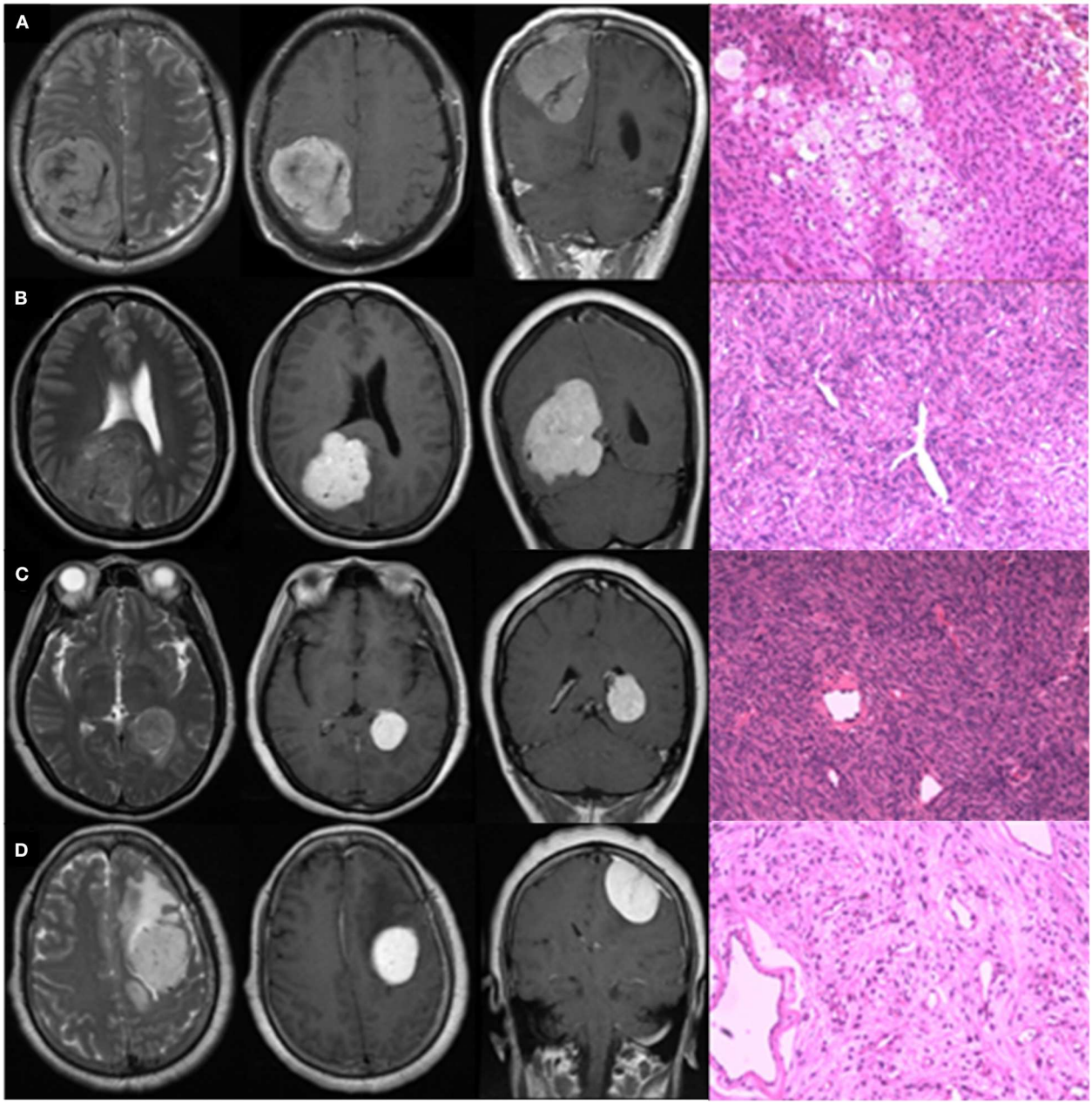


FIGURE 4 | Typical radiologically misdiagnosed cases. The four graphs in row were T2WI in axial view, CE-T1WI in axial and coronal view, and pathological image, respectively. Lesions in Cases **(A,B)** were supratentorial, posterior, and close to midline in location with internal serpentine signal voids, and absence of peritumoral edema on T2WI; irregular shape, unclear margin, and absence of the dural tail sign on CE-T1WI. Enhancement in Case **(A)** was heterogeneous, while in Case **(B)**, it was homogeneous. Lesions in Cases **(C,D)** were supratentorial and lateral in location with extensive peritumoral edema on T2WI; homogeneous enhancement, regular shape, and clear margin on CE-T1WI. Lesion in Case **(C)** grew in the lateral ventricle without apparent blood supply. Lesion in Case **(D)** located in the frontal, presenting with internal serpentine signal voids and clear dural tail sign. Actually, Cases **(A,D)** were pathologically confirmed meningiomas; Cases **(B,C)** were pathologically confirmed IHPCs.

that for tumor habitat on CE-T1WI, 9 out of 20 features were two-dimensional high-frequency transformation-based features. These features described the edge and details of the tumor region. Consistent with existing knowledge, after injection of Gd-DTPA, CE-T1WI could clearly display detailed radiological edge and intratumoral information including the boundary between the tumor and the normal brain tissue, intratumoral micronecrosis, blood supply, and capillary permeability. In terms of the tumor habitat on T2WI, 8 out of 20 features were, on the contrary, two-dimensional low-frequency transformation-based features. These features provided a general view of the tumor, but did not capture its detailed characteristics. Not surprisingly, compared

with CE-T1WI, T2WI focused more on the peritumoral edema area. Because of the lower contrast between the edema area and surrounding lesions/tissues, edge information would be weaker on T2WI, but it otherwise displayed the general intensity distribution of the ROI.

In our sample cohort, the majority of cases misdiagnosed as IHPCs were WHO grade I meningiomas, and AMs account for one third of these meningiomas. Thus, WHO grade I meningiomas, especially AMs, should be further stratified as a distinct subgroup. Previous studies have also pointed out the difficulty of AM and IHPC diagnosis (28–30). In this respect, the HMDT exceeded our expectations, displaying extremely satisfactory diagnostic ability with an AUC of 0.914 and 0.913 in the validation cohorts for WHO grade I meningioma and AM diagnosis, respectively. This showed that the HMDT not only successfully distinguishes IHPC and meningioma in the overall population but also can accurately diagnose IHPC in difficult cases, providing excellent preoperative guidance for clinicians.

Although this study achieved exciting initial results, a couple of limitations should be mentioned. First, only conventional MR sequences were used in the analysis. Functional MRI data are worthy of further exploration. Second, with a larger sample size, deep learning-based radiomics could be further applied. Third, manual segmentation to draw the tumor lesion was time consuming and labor intensive. Semiautomatic segmentation algorithms should be explored via a neuronetwork on both tumor and peritumoral edema areas.

In conclusion, the HMDT developed as the result of this study can realize high-accuracy diagnosis for IHPC and meningioma through machine learning–based radiomics analysis. The study results indicate that there is no doubt that the HMDT can be used as a clinical tool that has excellent robustness and subpopulation diagnostic power, and that will significantly improve the preoperative diagnosis of IHPC and meningioma, providing crucial information for the planning of subsequent treatment.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Beijing Tiantan Hospital, Capital Medical University, Beijing, China. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JWe and YH implemented the algorithm and software development, literature searching, and manuscript writing. LL implemented data collecting, ROI segmentation, literature searching, and manuscript writing. DG contributed to data analysis and figures making. QC and JZ identified the radiological characteristics of IHPCs and meningiomas, and estimated and adjusted the accuracy of ROIs. JWa reviewed and confirmed the pathological diagnosis of IHPC and meningiomas according to the 2016 WHO classification of CNS tumors. RL contributed to data collecting and ROI segmentation. DZ and JT conducted the design, quality control, and data interpretation of this study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.00534/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Anterior Clinoidal Meningiomas: Meningeal Anatomical Considerations and Surgical Implications

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Objective: Surgical removal of anterior clinoidal meningiomas (ACMs) remains a challenge because of its complicated relationship with surrounding meninges, major arteries and cranial nerves. This study aims to define the meningeal structures around the anterior clinoid process (ACP) and its surgical implications.

Methods: Five dry skulls and 19 cadavers were used in the anatomical study. Cadavers were prepared as transverse, coronal, and sagittal plastinated sections, and the meningeal architecture around the ACP was studied with dissecting and confocal microscopies. The database of meningiomas in one single center was retrospectively reviewed, and the patients with ACMs were collected for clinical analysis.

Results: The superior, lateral, medial surfaces, and the tip of ACP were covered by different layers and types of meninges. The ACMs were classified into four main types based on the sites of origin, possible extending pathways following meningeal dura. In the retrospective cohort of 131 ACMs, the percentage of types I, IIa, IIb, III, and IV were 42.0% (55/131), 19.8% (26/131), 9.2% (12/131), 16.8% (22/131), and 12.2% (16/131), respectively. We found that types IIa and I had higher chances for achieving Simpson grade 1–2 resection (92.3 and 85.4%, respectively), followed by type III (54.5%) and type IV (31.3%), while type IIb showed little chance of Simpson grade 1–2 resection. Univariate and multivariate analyses revealed ACM classification and tumor size (<3 cm) to be independent risk factors for achieving more extensive resection.

Conclusion: The meningeal architecture around the ACP may guide and determine the origin and extension of ACMs. The classification based on the meningeal architecture helps to understand surgical anatomy as well as predicting surgical outcomes.

Keywords: anterior clinoidal meningioma, meninges, classification, surgical anatomy, cavernous sinus, carotid artery, anterior clinoid process

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INTRODUCTION

Anterior clinoidal meningiomas (ACMs) were first reported in 1938 and compose about 34.0–43.9% of all sphenoid wing meningiomas (1). ACMs originate from the meninges attached to the anterior clinoidal process (ACP) and extend along the meningeal dura as they grow larger, displacing or even invading the surrounding neurovascular structures (2). The close relationship between the tumor and critical structures may result in high surgical morbidity and recurrence rate (2–5).

Because of the complex regional meningeal anatomy, meningiomas originated from different areas of ACP may present with varying patterns of growth and surgical outcomes. There were several anatomical studies on the ACP and its surrounding structures, especially the cavernous sinus and the carotid artery (6–9). However, few reports revealed the fine architecture of the meningeal coverings of the ACP, and few of the previously proposed classifications of ACMs differentiated the underlying relationship between the meningeal architecture and surgical implications.

In this study, we used some new anatomical techniques to investigate the fine meningeal architecture around the ACP, proposed a new classification based on anatomical findings, and analyzed the characteristics of different types of ACMs in 131 cases.

MATERIALS AND METHODS

Cadaveric Study

Five dry skulls and 19 cadavers (8 female and 11 male; age range, 54–89 years; mean age, 75 years) were used in this anatomical study. Written informed consent from the donor or the next of kin was obtained under the Human Tissues Act.

The dry skulls were used for studying the structural characteristics. The cadavers were prepared for 19 sets of plastinated sections. The thickness of the section was about 2.5–3.0 mm. Sheet plastination is a modern anatomical technique in which water and lipids of tissues and cells are replaced by curable and transparent resin. The plastination procedure was performed as previously described (10). The prepared section was examined under a Leica MZ8 stereoscopic dissecting microscope (Leica, Heerbrugg, Switzerland). The high-resolution images of the selected areas were scanned and collected with an Epson Perfection V750 Pro Scanner (Epson, Jakarta, Indonesia), in which the scanning resolution was set up at 1,200–6,400 dpi. The plastination process results in collagen fibers and neurofilaments being endogenously autofluorescent at the 488-nm excitation (11). Differentiation among those autofluorescent fibers is based upon their morphology, fluorescent intensity, and anatomical distribution. The plastinated section was observed under a Nikon AIR confocal laser scanning microscope (Nikon, Tokyo, Japan). The thickness of the optical section was set up at 16.7 μm under a 10 $\times$ objective, and the images were electronically recorded and montaged.

Clinical Study

The tumor registration database of Changzheng Hospital, Naval Medical University, Shanghai, China, was retrospectively reviewed. The clinical and pathological characteristics were extracted from the database and charts. The inclusion criteria were as follows: patients received surgery for removing the meningiomas and the diagnosis confirmed by magnetic resonance imaging (MRI), intraoperative findings, and pathological reports. The primary outcomes included the extent of tumor removal, cranial nerve function, and surgical-related morbidities. The extent of resection (Simpson grade) was recorded in the operative notes according to the chief surgeon's impression under the microscope, as well as confirmed by postoperative imaging study. Postoperatively, all patients underwent a brain computed tomography (CT) or MRI within 2 days after surgery. Follow-up was done with clinical and imaging examination of the patients. Two researchers (TX and YY) collected the data as well as classified the tumors with guidance from senior professors (YL and JC); any divergence was discussed and resolved.

Statistical Analysis

The clinical data were recorded and analyzed by SPSS 25.0 (Chicago, IL, USA). The univariate and multivariate analyses were performed using the logistic regression; $p < 0.05$ was regarded as statistically significant.

RESULTS

Zoning of the Anterior Clinoid Process

The ACP was the posteromedial extremity of the sphenoid ridge and appeared like an irregular triangular mass. It is located between the superior orbital fissure laterally and the optic canal medially. Based on these fixed bony landmarks, we could further divide ACP into four areas (**Figure 1A**). Following the lesser sphenoid wing, there is a ridge that separates the ACP into areas I and II. Area I was the superior surface of the ACP that was almost flat and continued with the planum sphenoidale and optic canal. Area II was the lateral surface that gradually curved down and then turned medially. Area III was the triangle posterior to the end of the ridge (tip of ACP). The interclinoid dural fold and the anterior petroclinoid dural fold were attached to the tip. Area IV was the medial surface of ACP that was adjacent to the optic canal anteromedially and the internal carotid artery (ICA) posteromedially. The inferior surface of ACP faced the clinoidal ICA and was not visible during surgery unless a total removal of ACP.

The Meningeal Architecture of the Anterior Clinoid Process

The meningeal architecture around the ACP varied (**Figures 1B–E**). Area I of the ACP was covered by the arachnoid and both the meningeal and periosteal dura (**Figure 1B**). The covering of area II of the ACP was complicated, as a multiple layered meningeal dura was sandwiched in between the arachnoid and periosteal dura (**Figures 1C,D**). The fiber orientations of these meningeal dura layers were various, but most of them were sagittal along a posteroanterior axis and inserted to the ACP. The superficial (or lateral) layer continued with the meningeal dura on the anterior and middle cranial fossae, the roof and lateral wall of the cavernous sinus

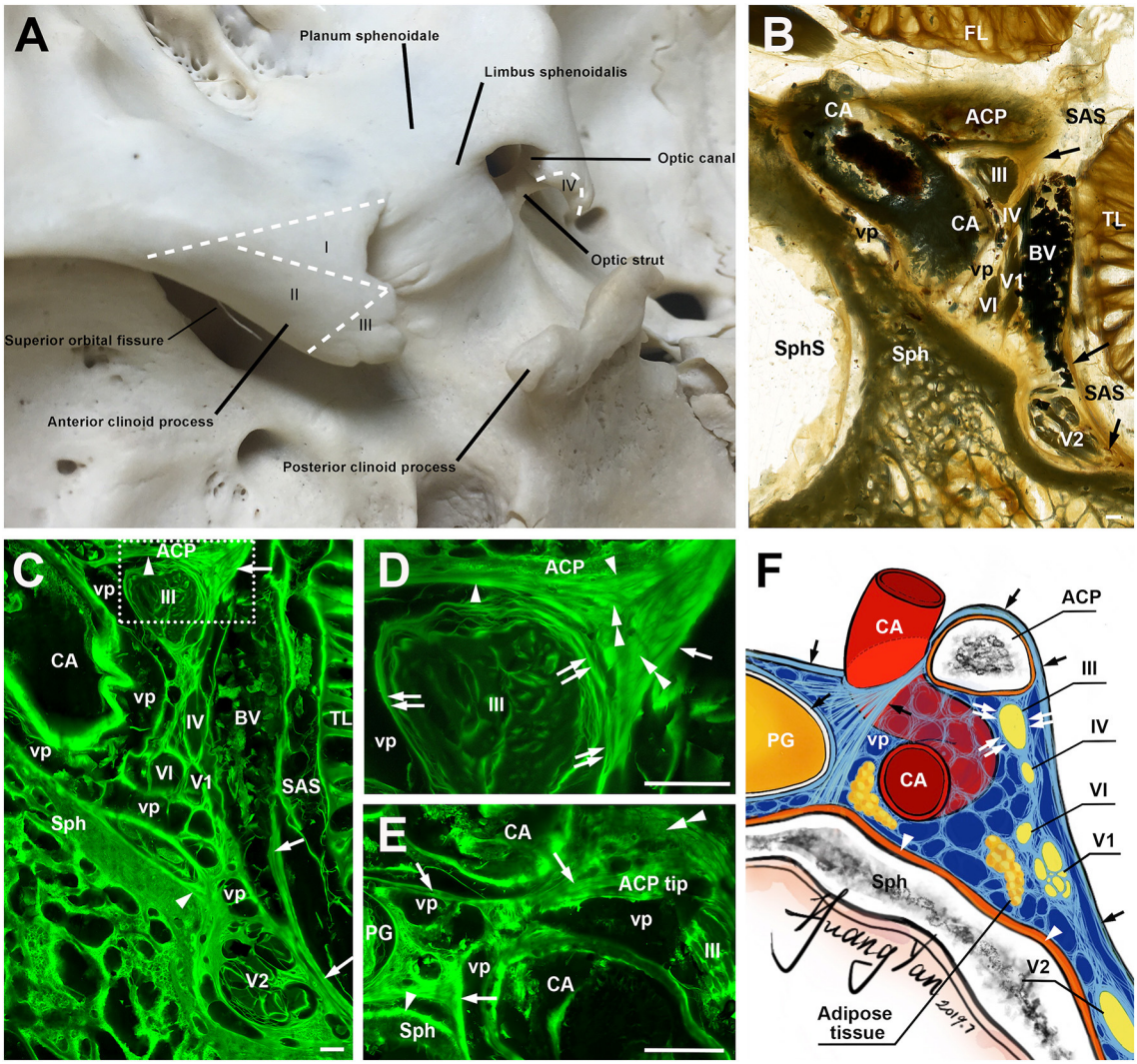


FIGURE 1 | The anterior clinoid process (ACP) and its meningeal coverings. **(A)** A posterosuperior view of the ACP, showing its four zones (I–IV). **(B)** A coronal sheet plastination section at the level of the clinoidal segment of the carotid artery (CA). Arrows point the lateral wall of cavernous sinus. **(C)** is the mirror confocal image of **(B)**. Arrowheads point to the periosteal dura. Arrows point to the meningeal dura. **(D)** is the higher magnification of the dashed line box of **(C)**, showing the meningeal architecture (single arrow and arrowheads) on the inferolateral surface of the ACP and its relationship with the dural sleeves (double arrows) of the ocular motor (III) and the lateral wall of the cavernous sinus. Double arrowheads point to sagittally orientated meningeal dural fibers, which originated from the tentorium and inserted to the ACP. **(E)** is from an adjacent section through the tip of the ACP, 3.4 mm posterior to **(D)**, showing the meningeal dural fibrous bundles (arrows) between C4 and C6 segments of the CA. **(F)** An illustration showing the meningeal architecture of the ACP and its surrounding structures that were mentioned in the previous images. BV, cerebral bridging vein; vp, venous plexus; Sph, sphenoid bone; SphS, sphenoid sinus; TL, temporal lobe; FL, frontal lobe; SAS, subarachnoid space; cranial nerves II, III, IV, V_1, V_2, and VI; bars = 1 mm.

(**Figure 1C**). The deeper (or medial) layers contributed to the meningeal dural sleeves of the ocular motor and trochlear nerves (**Figures 1C,D**) and the fibrous mesh network within the cavernous sinus.

The meninges covering area III include both periosteal and meningeal dura continued from areas I and II, mixed with fibers from the tentorium, which inserted into the tip of the ACP and serviced as the demarcation between the inferomedial and inferolateral surfaces of the ACP (**Figure 1E**). The oculomotor nerve pieced the single meningeal dura of the oculomotor triangle (roof of the cavernous sinus) and entered into the cavernous sinus just posteriorly to the ACP.

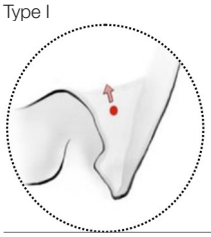
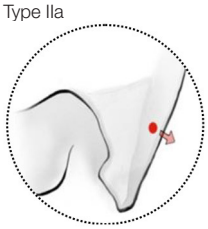
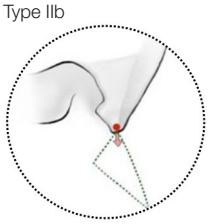
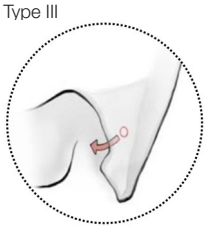
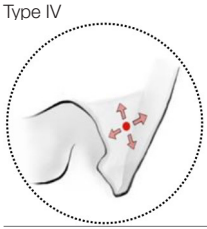
The meningeal dura of area I extended medially, forming the meningeal dural fibrous bundles (distal dural ring) between C4 and C6 segments of the CA, attached and fused with the external membrane (tunica adventitia) of the ICA (**Figure 1E**). Above this dural ring, the superior part of area IV was also covered by both the meningeal and periosteal dura, while the inferior surface of area IV was covered only by the periosteal dura (**Figures 1D,E**). The above findings are illustrated in **Figure 1F**.

Classification of ACMs and Its Surgical Relevance

We classified the ACMs into four types based on the location of their origin, meningeal architecture, extending pattern, as well as surgical implications (**Table 1**, **Figure 2**).

Type I ACMs originated from the meninges that cover the superior surface (area I) of the ACP, extended superiorly and laterally to the suprasellar space (**Figures 2A–C**). On the coronal view, the epicenter of the tumor laid superior and lateral to the clinoidal ICA and optic nerve. They may extend medially following the falciform ligament into the optic canal, resulting in vision decline. The branches of the middle cerebral artery (MCA) may be pushed superiorly and posteriorly and sometimes were even wrapped inside the tumor. For type I ACMs, standard

TABLE 1 | Classification of anterior clinoidal meningiomas and surgical implications.

Tumor classification	Common origin	Extending pattern	Recommended surgical techniques
Type I 	Superior surface of the ACP	Grow superiorly and laterally to the supraclinoidal space;	Frontal-temporal craniotomy +/– Anterior clinoidectomy +/– Unroof the optic canal
Type IIa 	Lateral surface of the ACP	Grow along the lateral wall of cavernous sinus;	Frontal-temporal craniotomy + Zygomatic osteotomy +/– Anterior clinoidectomy +/– Unroof the superior orbital fissure
Type IIb 	Tip of the ACP	Grow both inside and outside of the cavernous sinus following the meningeal dura near the oculomotor triangle;	Frontal-temporal craniotomy + Supraorbital osteotomy + Zygomatic osteotomy + Anterior clinoidectomy + Para-cavernous maneuvers
Type III 	Medial surface of ACP (above the distal dural ring)	Grow medially following the dural ring, diaphragm sellae.	Frontal-temporal craniotomy + Supraorbital osteotomy + Anterior clinoidectomy + Cutting distal dural ring +/– Drill tuberculum sellae +/– Unroof the optic canal
Type IV 	Difficult to be identified	Grow into multiple sellar and parasellar spaces, encasing the surrounding structures.	All the above surgical techniques. Carotid artery control is advocated. The patient may need a surgical plan with possible intentional partial resection to preserve important structures.

ACP, Anterior Clinoid Process; +, with; +/–, with/without.

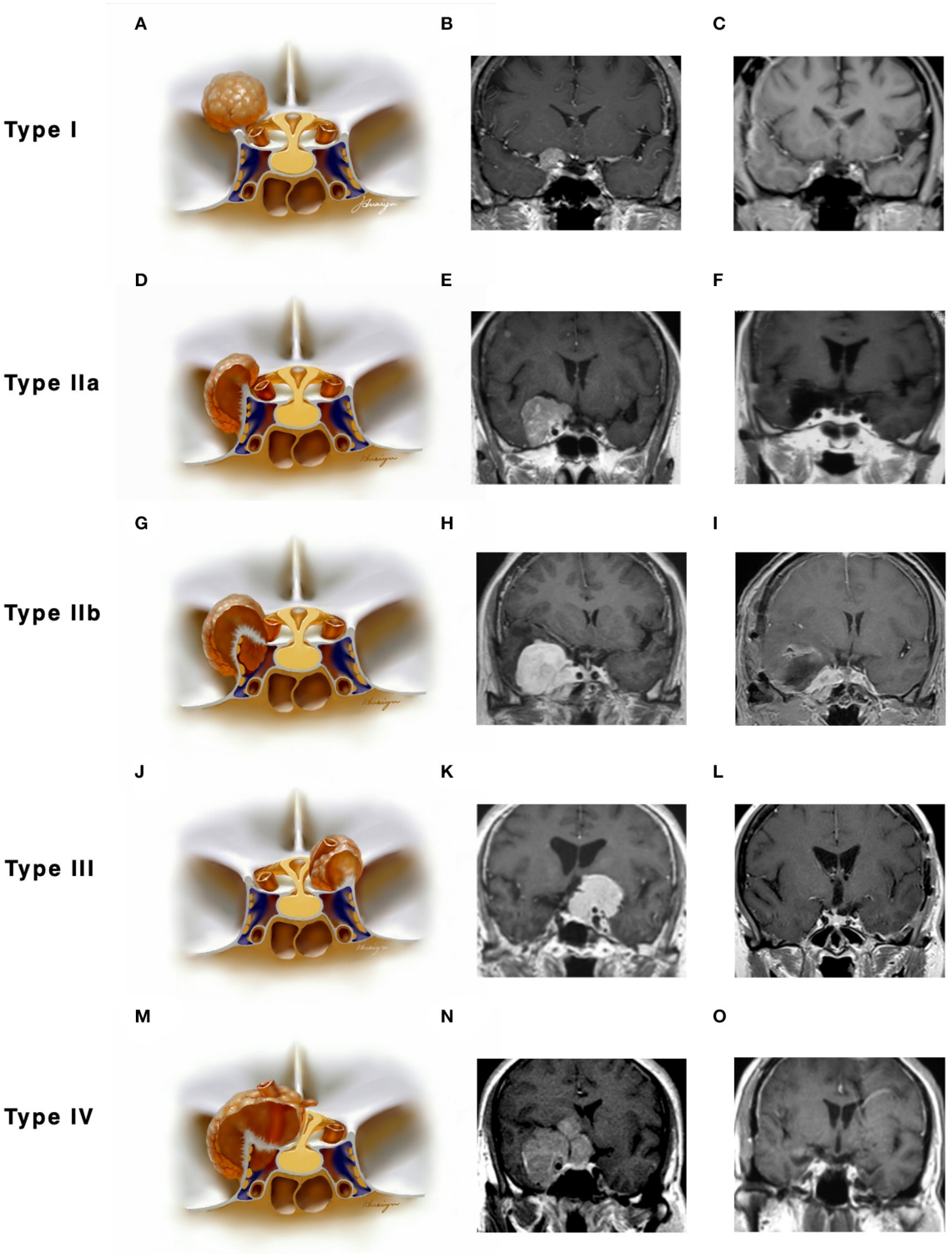


FIGURE 2 | Classifications of anterior clinoidal meningiomas (ACMs) based on meningeal anatomy of the anterior clinoid process (ACP). Each horizontal panel represents an illustration of coronal sectional view, a preoperative and postoperative MR images of a type of ACMs**. (A–C)** Type I ACMs originate from the superior surface of the ACP. Note that the tumor may invade into the optic canal following the falciform ligament. **(D–F)** Type IIa ACMs originate from the lateral surface of ACP. They "attach" and "push" rather than invade the cavernous sinus because of the thick and multilayer meningeal on the lateral wall of cavernous sinus. **(G–I)** Type IIb ACMs originate from the tip of the ACP and grow both inside and outside of the cavernous sinus following the meningeal dura near the oculomotor triangle. **(J–L)** Type III ACMs that originated from the medial surface of ACP; they could affect the distal dural ring and wrap the ICA from the very beginning. **(M–O)** Type IV ACMs that extend to multiple directions following the meninges.

frontal–temporal craniotomy offered enough surgical exposure; complete anterior clinoidectomy was not a must, and the extent of clinoidectomy could be tailored intradurally.

Type II ACMs were clinoidal-cavernous meningiomas, which were further divided into two subgroups (**Figures 2D–I**). Type IIa ACMs (**Figures 2D–F**) originated from the meninges that covered the lateral surface of ACP (area II), extended along the lateral wall of the cavernous sinus. Since the lateral wall of the cavernous sinus consisted of multilayers of the meningeal dura, tumors usually did not transgress this layer, so the cavernous sinus was compressed rather than invaded. The epicenter of these tumors laid laterally to the clinoidal ICA and the transcavernous cranial nerves. During surgery, a zygomatic osteotomy was needed in addition to frontal–temporal craniotomy in order to provide a "low-enough" surgical trajectory. Complete clinoidectomy was not mandatory, and the extent of bony removal could be tailored based on intraoperative findings.

Type IIb ACMs (**Figures 2G–I**) originated from the tip of the clinoid process (area III); they not only extended laterally to the middle cranial fossa like type IIa ACMs but also into the cavernous sinus and wrapped the neurovascular structures inside the sinus following the meninges that cover the roof of the cavernous sinus and the sleeves of the oculomotor and trochlear nerves, forming a "weak point" of the cavernous sinus. The coronal view of MRI was used to differentiate between type IIa and IIb ACMs. In type IIb ACMs, cranial nerve insufficiency was commonly seen. When performing the craniotomy, frontal–temporal craniotomy with complete clinoidectomy was essential for adequate exposure. The para-cavernous maneuvers need to be applied to facilitate tumor removal inside of the cavernous sinus.

Type III ACMs (**Figures 2J–L**) originate from the meninges that cover the medial wall of the ACP (area IV). The tumor extended medially to the diaphragm sellae, warped the supra-clinoidal segment of the ICA, pushed the optic nerve from above and/or below, and then extend into the sellar. On the coronal MRI, the epicenter of the tumor laid superior and medial to the ICA; the pituitary stalk was often pushed to the contralateral side. During surgery, complete anterior clinoidectomy was needed for adequate exposure, and the frontal–temporal craniotomy often required to be expanded with a supraorbital osteotomy to get a wider surgical angle. Drilling the tuberculum sellae was sometimes essential for removing the tumor inside the sellae.

Type IV ACMs (**Figures 2M–O**) were large tumors that extended to multiple sellar and parasellar spaces, thus were not included in types I–III ACMs. For type IV tumors, preoperative angiography was strongly warranted, and tumor-feeding vessels were embolized to decrease the risk during surgery. An orbital-zygomatic craniotomy with complete anterior clinoidectomy was applied for broad exposure. Much attention and energy were needed when dissecting the vessels that were encased by the tumor. Sometimes, a subtotal resection was done on purpose to minimize the surgical morbidity and preserve the functional outcome.

Surgical Outcomes of ACMs

A total of 2,654 patients with intracranial meningiomas were surgically treated from 1998 to 2019, while 131 patients were confirmed to be ACMs. According to the previously mentioned classification, 55 cases (42.0%), 26 cases (19.8%), 12 cases (9.2%), 22 cases (16.8%), and 16 cases (12.2%) were classified as types I, IIa, IIb, III, and IV, respectively. Their clinical and pathological features are summarized in **Table 2**. Type III and IV ACMs had the highest chance for presenting with vision decrease, followed by type I ACMs. Headache was mostly presented in 94% of type IV ACMs and 42% of type IIa ACMs.

Nearly 70% of patients had Simpson grade I and 2 resections (88/131), while the rest (43/131, 32.9%) got Simpson grade 3–4 resection. Types IIa and I had the highest chance of total resection (92.3 and 85.4%, respectively), followed by type III (54.5%) and type IV (31.3%), while type IIb showed no gross total resection in our case series. Univariate and multivariate analyses revealed ACM classification and tumor size (<3 cm) to be independent risk factors for achieving more extensive resection ($p = 0.024$ and $p = 0.025$, respectively, **Table 3**).

We had one perioperative death because of severe meningitis after surgery. Two cases of ICA rupture were found during operation when the chief operator was trying to dissect the tumor from the ICA with no arachnoid plane in between. Both cases were treated using compression and surgical glue repairing. On postoperative imaging, one patient (type I, **Figures 3A–C**) had total occlusion of the ipsilateral ICA but showed no neurological deficits. Another patient (type III, **Figures 3D–F**) showed a patent lumen of the ICA with no signs of a pseudoaneurysm. Both patients reported good status with no signs of recurrence (9 and 12 years after surgery, respectively).

For the patients with preoperative vision decrease, 52.6% got improved after surgery, while 42.1% were unchanged, and 5.3% had deterioration. A newly onset of vision loss after surgery was found in five cases (one case with type I, one case with type III, and the other three cases with type IV) of which two patients became better after treatment in the hyperbaric oxygen cabin. Oculomotor nerve dysfunction was found in three cases preoperatively and remained unchanged after surgery. A newly onset of oculomotor palsy was found in 18 cases (2 cases with type I, 3 cases with type IIa, 5 cases with type IIb, 1 case with type III, and the other 7 cases with type IV), of which 12 turned out to be temporary and had recovery gradually during follow-up.

The postoperative pathological study revealed most of the ACMs in our series to be WHO grade I (91.6%), with 7.6% diagnosed as WHO grade II and only one case confirmed to be WHO grade III. Of 90 tumor samples in which Ki-67 was tested, 81.1% showed <5% intensity, 16.7% showed intensity between 5 and 10%, and the rest 2.2% showed >10%.

Adjuvant radiotherapy was recommended to the patients with incomplete resection and/or high WHO grades. Of the 131 patients, 114 had the follow-up, with 13 cases of recurrent or regrowth (1 case of type I, 0 cases of type IIa, 2 cases of type IIb, 4 cases of type III, and 6 cases of type IV) and one death caused by the recurrent tumor (type IV, WHO grade III). Type III and IV ACMs had a higher

TABLE 2 | Clinicopathological characteristics of anterior clinoidal meningioma patients.

Characteristics	All patients ($n = 131$)	Type I ACMs ($n = 55$)	Type IIa ACMs ($n = 26$)	Type IIb ACMs ($n = 12$)	Type III ACMs ($n = 22$)	Type IV ACMs ($n = 16$)
Age (years)						
Range	27–76	33–73	27–76	27–73	33–60	38–64
Mean ± SD	53.66 ± 10.82	55.95 ± 9.68	57.31 ± 12.77	55.83 ± 12.04	46.77 ± 8.42	47.75 ± 6.78
Gender						
Male	45 (34.4%)	22 (40.0%)	8 (30.8%)	6 (50.0%)	8 (36.4%)	1 (6.3%)
Female	86 (65.6%)	33 (60.0%)	18 (69.2%)	6 (50.0%)	14 (63.6%)	15 (93.7%)
Presenting symptoms						
Vision decrease	57 (43.5%)	25 (45.5%)	1 (3.8%)	3 (25.0%)	16 (72.7%)	12 (75.0%)
Headache	45 (34.4%)	12 (21.8%)	11 (42.3%)	4 (33.3%)	3 (13.7%)	15 (93.7%)
Dizziness	32 (24.4%)	11 (20.0%)	8 (30.8%)	4 (33.3%)	3 (13.7%)	6 (37.5%)
Incidental finding	11 (8.4%)	5 (9.1%)	3 (11.5%)	1 (8.3%)	2 (9.1%)	0 (0%)
Seizure	7 (5.3%)	0 (0%)	3 (11.5%)	3 (25.0%)	0 (0%)	1 (6.2%)
Limb weakness	6 (4.6%)	1 (1.8%)	2 (7.7%)	0 (0%)	0 (0%)	3 (18.8%)
Diplopia	4 (3.1%)	0 (0%)	0 (0%)	2 (16.7%)	0 (0%)	2 (12.5%)
Ptosis	3 (2.3%)	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	2 (12.5%)
Tumor diameter						
≥3 cm	108 (82.4%)	40 (72.7%)	23 (88.5%)	12 (100%)	17 (77.3%)	16 (100%)
<3 cm	23 (17.6%)	15 (27.3%)	3 (11.5%)	0 (0%)	5 (22.7%)	0 (0%)
Resection degree (simpson)						
Grade 1–2	88 (67.2%)	47 (85.5%)	24 (92.3%)	0 (0%)	12 (54.5%)	5 (31.3%)
Grade 3–4	43 (32.8%)	8 (14.5%)	2 (7.7%)	12 (100%)	10 (45.5%)	11 (68.7%)
Tumor grades						
WHO grade I	120 (91.6%)	51 (92.7%)	25 (96.2%)	11 (91.7%)	20 (90.9%)	13 (81.3%)
WHO grade II	10 (7.6%)	4 (7.3%)	1 (3.8%)	1 (8.3%)	2 (9.1%)	2 (12.5%)
WHO grade III	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6.2%)
Ki-67 index	$n = 90$	$n = 37$	$n = 19$	$n = 11$	$n = 17$	$n = 6$
<5%	73 (81.1%)	32 (86.5%)	18 (94.7%)	8 (72.7%)	13 (76.5%)	2 (33.3%)
5–10%	15 (16.7%)	5 (13.5%)	1 (5.3%)	2 (18.2%)	4 (23.5%)	3 (50%)
>10%	2 (2.2%)	0 (0%)	0 (0%)	1 (10.1%)	0 (0%)	1 (16.7%)

chance of recurrence/regrowth, since most of these types of tumors did not get total resection. The remaining tumor in the cavernous sinus (type IIb) seemed relatively stable after radiotherapy; only 2 out of 12 cases had regrowth in the follow-up period.

DISCUSSION

Meningeal Architecture-Based Classification of ACMs

Meningiomas originate from the meningothelial cells at the dural–arachnoid junction (12) and tend to grow along with the meningeal layer of the dura (13, 14), so the meningeal architecture plays an essential role in determining the potential extending pathway and selecting appropriate surgical maneuvers for resection ACMs (15). In the present study, we used a novel morphological technology, the epoxy sheet plastination in combination with the confocal microscopy, to identify and trace the meningeal layers around the ACP and reveal their precise relationship with surrounding structures, e.g., the ICA, cranial nerves, and cavernous sinus (**Figure 1F**). The meningeal fibrous configuration of the ACP, optic canal, and cavernous sinus reported in this study and our previous studies provide an anatomical base for our new classification of the ACMs (16–18).

Several classification systems of ACMs were established in the past decades. AI-Mefty developed a grading system that divided the ACMs into group I for tumors arising proximal to the end of the carotid cistern, group II for tumors arising above the segment of the carotid invested in the carotid cistern, and group III for tumors originated from the optic foramen (1). Pamir modified this system by adding the diameter of tumors (<2, 2–4, and >4 cm) for each group (19). Goel invented a 2–10 scoring system based on the extent of visual impairment, size of the tumor, and tumor relationship with the ICA (20). Nakamura et al. divided the ACMs into only two groups: group 1 for tumors not invading cavernous sinus and group 2 for tumor involving the cavernous sinus (21). Nanda et al. established another grading system with total scores ranging from 1 to 10, then divide the patients into group 1 with scores <5 and group 2 with scores >5 (22).

TABLE 3 | Univariate and multivariate analysis for factors associated with extent of resection of ACMs.

Factors	Univariate analysis		Multivariate analysis		
	OR	*P*-value	OR	*P*-value	95% CI
Age (years)		0.326		0.729	
<40	1.000	1.000	1.348	0.774	0.175-9.366
40–60	0.552	0.171	0.735	0.639	0.202-2.671
>60	Reference	Reference		Reference	Reference
Type of ACMs		<0.001*		0.024*	
I	12.925	<0.001*	4.769	0.065	0.909–25.017
IIa	26.400	<0.001*	13.314	0.014	1.684–105.270
IIb	0.000	0.999	0.000	0.999	0
III	2.640	0.159	0.714	0.726	0.108–4.705
IV	Reference	Reference	Reference	Reference	Reference
Vision decrease (yes vs. no)	0.475	0.049*	0.800	0.703	0.254–2.517
Headache (yes vs. no)	0.456	0.042*	0.419	0.207	0.108–1.618
Dizziness (yes vs. no)	1.641	0.281	1.101	0.883	0.306–3.959
Tumor diameter (<3 cm vs. ≥3 cm)	0.071	0.011*	0.075	0.025*	0.008–0.724
Gender (female vs. male)	0.966	0.929	0.784	0.671	0.2552.408

**Statistically significant.*

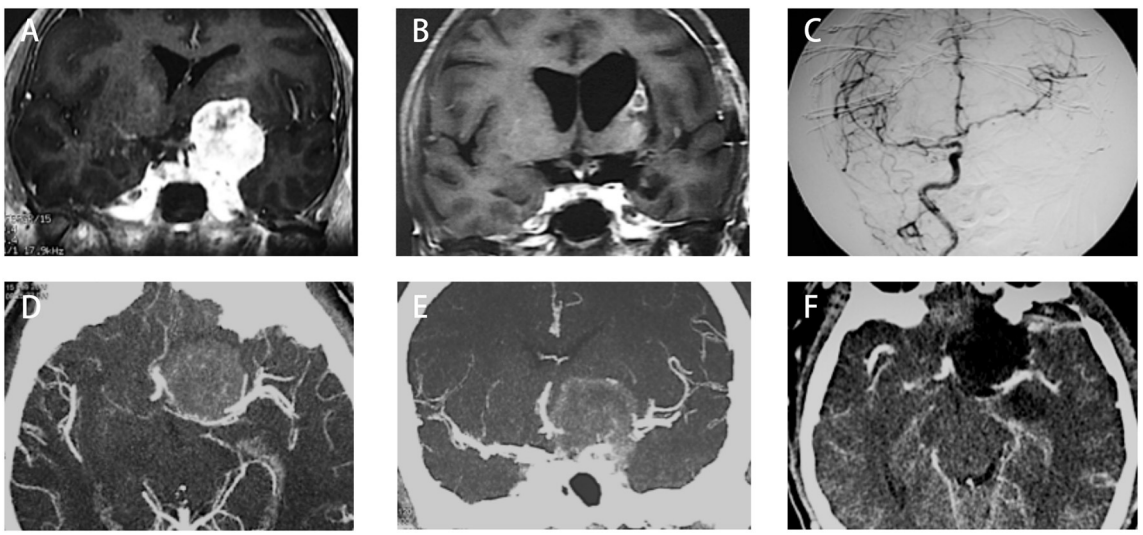


FIGURE 3 | Two cases with anterior clinoidal meningiomas (ACMs) that experienced intraoperative rupture of internal carotid artery (ICA). **(A)** Preoperative coronal MRI showed a type I ACM, which involved the supraclinoidal part of the left ICA. **(B)** Postoperative coronal MRI showed gross-total resection of tumor, with a small infarction near the left side lateral ventricle, indicating the occlusion of perforators supplying the head of the caudle nuclei. **(C)** Postoperative angiography showed complete occlusion of the left ICA. **(D,E)** Preoperative CT angiography showed a type III ACM, which engulfs the bifurcation of the left ICA. **(F)** Postoperative CT angiography showed patent branches of the ICA with gross total removal of the tumor.

There are some limitations to these classifications. First, a complicated scoring system is neither user-friendly nor easy to follow. Second, these classifications did not demonstrate the underlying relationship among the tumor, ACP, and surrounding structures that were linked by the meningeal anatomy. The classification system that we proposed herein provided another angle of view to the ACMs, in addition to the current knowledge of how ACMs originated, extended, presented, and resected. Different groups of ACMs may have different clinical presentations, requiring various surgical maneuvers and leading to different surgical outcomes. With the information provided by the classification, in addition to the diagnostic radiological findings, the surgeons can have a better preoperative estimation and a better prediction of the surgical outcomes for one specific case of ACM.

Surgical Approach for Removing ACMs

Many authors reported different approaches for removing ACMs, like lateral supraorbital approach (23), supraorbital

keyhole approach (24), standard or extended pterional approach (4, 25–27), frontal lateral approach (21), orbital-zygomatic approach (28–32), etc. **Table 4** summarized different surgical approaches and techniques as well as the outcomes that were published in the past decades. For ACMs, we believe that no universal approach could fit all the needs, nor do we advocate a routine clinoidectomy or unroofing the optic canal (34). Generally, a frontal–temporal craniotomy offers good anterior-lateral working trajectory and could be applied in most type I tumors, while other skull base techniques, like zygomatic osteotomy, orbital osteotomy, unroofing the optic canal, drilling the tuberculum sellae, etc., could be used either single or combined based on the tumor characteristics. The endoscopic endonasal route offers a different working angle, but current reports only limited in small size ACMs (35, 36).

Surgical Outcomes of ACMs

Up to date, many studies have reported the surgical treatment of ACM, but large series that include more than 100 patients with a long follow-up period were only seen in two series (21, 33). The rates of total resection ranging from 42.6 to 90.7%, with a varied chance of visual function improvement and tumor recurrence (**Figure 4**). In the present study, the total resection rate was 67%, with the visual function improved in 52.6% of patients and recurrent in 11.4% patients during the follow-up.

Arachnoid plane, as many authors have mentioned before, is the crucial factor for resectability. When an arachnoid plane is available, even when the vessels are encased by the tumor, experienced surgeons may still be able to dissect the vessels out of the tumor with microsurgical skills. Lack of arachnoid plane may cause firm adhesion between tumor and critical neurovascular

TABLE 4 | Literature review of recently published papers of anterior clinoidal meningiomas.

References	No. of patients	Mean/Median follow-up (months)	Total resection (%)	Post-operative visual function improvement (%)	Recurrence (%)	Surgical approach	Pathological findings
Al-Mefty. (1)	24	57	83.3	25	12.5	Pterional/subfrontal/ orbitocranial	NA
Kleinpeter Böck (5)	31	NA	77.4	NA	NA	NA	NA
Risi et al. (26)	34	22.8	58.8	32	21	Extended pterional	NA
Puzzilli et al. (25)	33	53.7	54.5	33.3	15.2	Pterional	WHO I, $n = 29$ WHO II, $n = 4$
Goel et al. (20)	60	26	70.0	69.1	1.6	Basal frontotemporal/ orbitozygomatic	NA
Nakamura et al. (21)	108	79	42.6	46.7	20.3	Pterional/frontolateral	WHO I, $n = 105$ WHO II, $n = 2$ WHO III, $n = 1$
Russell et al. (27)	35	153.6	68.6	63	9	Pterional	NA
Cui et al. (28)	26	22.3	61.5	61.5	0	Orbitozygomatic	NA
Pamir et al. (19)	43	39	90.7	84.6	11.7	Pterional	WHO I, $n = 42$ WHO II, $n = 1$
Sade and Lee (2)	52	NA	71.2	77	NA	Pterional + posterolateral orbitotomy + clinoidectomy	NA
Bassiouni et al. (33)	106	83	57.5	45.6	25.3	Pterional + optic nerve decompression + subdural clinoidectomy	WHO I, $n = 102$ WHO II, $n = 2$ WHO III, $n = 1$
Romani et al. (23)	73	36	78.1	28.2	4.1	Lateral supraorbital	WHO I, $n = 66$ WHO II, $n = 7$
Nagata et al. (29)	23	49.2	39.1	43.5	4.3	Pterional/orbitozygomatic	NA
Attia et al. (30)	22	56	59.1	66.7	13.6	Pterional/frontoorbital/ orbitozygomatic	WHO I, $n = 19$ WHO II, $n = 3$
Czernicki et al. (31)	30	83	63.3	43.8	36.8	Fronto-orbitozygomatic	WHO I, $n = 30$
Sughrue et al. (34)	29	90	20.7	17.2	6.9	Frontotemporal/ orbitozygomatic	WHO I, $n = 27$ WHO II, $n = 2$
Nanda et al. (22)	36	33	75.0	28	11.1	Pterional/orbitozygomatic	WHO I, $n = 36$
Kim et al. (32)	59	54.1	64.4	NA	18.6	Orbitocranial or orbitozygomatic/extended pterional/subfrontal	NA
Present study	131	76	67.2	52.6	11.4	Frontotemporal craniotomy with individualized skull base techniques	WHO I, $n = 120$ WHO II, $n = 10$ WHO III, $n = 1$

No., Number; NA, Not Applicable.

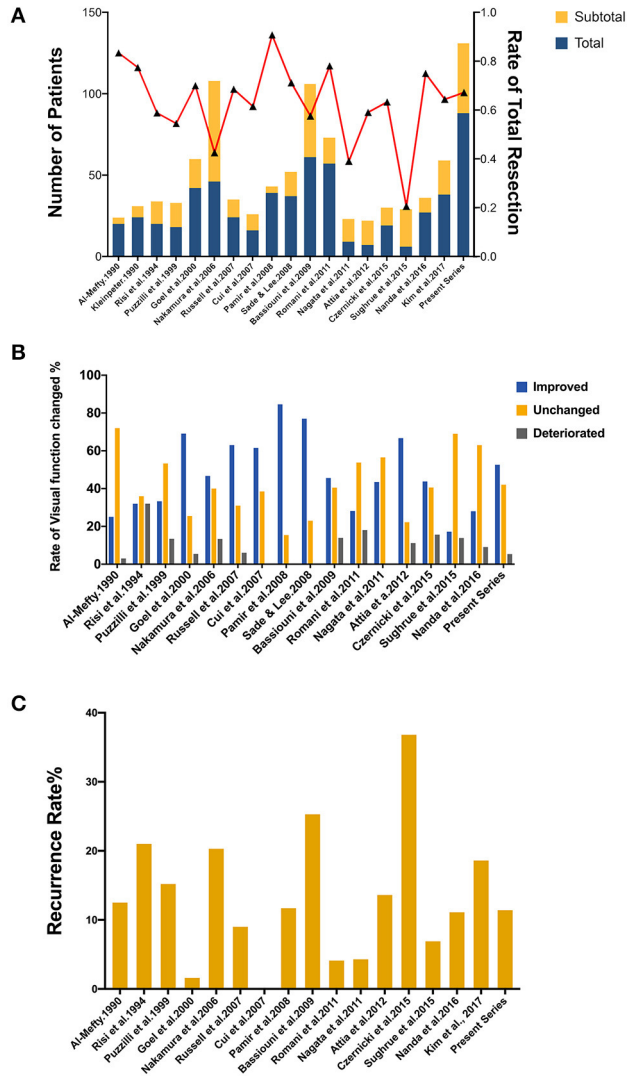


FIGURE 4 | Summary of literature on the extent of resection, visual function and tumor progression of ACMs. **(A)** A total of 18 studies (excluding the present study) reported the extent of resection of ACMs, ranging from 20.7–90.7%. **(B)** The rate of visual function improvement among 16 studies. 37.5% of studies (6/16) revealed improvements in visual function in more than 50% of patients. **(C)** The progression/recurrence rate varies from 0–36.8% in 16 studies.

structures, leading to a higher chance of complication during dissection.

Our anatomical study revealed a very close relationship between the distal dural ring (DDR) to ICA adventitia. Thus, type III ACMs can extend directly from the DDR to the surface of ICA, without leaving any arachnoid plane. Our finding was consistent with another histological study, which also found that the meningeal DDR eventually fuses with the adventitia of the ICA (37).

The genomic invasiveness might be another reason; some recently published studies found that even WHO grade I meningioma could show high invasive molecular behavior-like high-grade meningiomas, if they harbor specific genetic background. The tumor can cause severe edema (which indicated disruption of the arachnoid and pia), invasion to the brain, and easy recurrence, et al. (38, 39). This may explain the intraoperative ICA rupture case (type I, WHO grade I, **Figure 3A**). Future studies that focus on these low-grade but invasive meningiomas may help identify this subgroup of tumors before surgery.

ACMs Invading Cavernous Sinus

Cavernous sinus invasion rate of ACMs ranges from 0 to 63.9% (20, 21, 26, 40). The various ranges may be due to mixing tumors that compress the lateral wall with the tumors that truly invade into the cavernous sinus. In our study, we found that the "true" cavernous sinus invasion rate was 17.6%.

The meningeal anatomy of the lateral wall for the cavernous sinus has been extensively studied. The two-layer model was described by Umansky et al. (41), then widely accepted both anatomically and surgically (42–44). Janjua found that there is another intermediate layer between these two layers, which showed a distinct fiber direction of the other two layers (9). We reported that the lateral wall of the cavernous sinus is formed by the multiple-layered meningeal, which forms a relatively tight barrier for meningiomas to transgress the lateral wall, enters into the cavernous sinus, and engulfs the internal carotid artery (17).

The roof of the cavernous sinus is continuous with the superficial layer of the lateral cavernous wall, is relatively "weak," and can be pierced by the tumor. Via the roof, the meningioma can invade into the cavernous sinus, wrap the carotid artery and cranial nerves, making a total ACM resection much more complicated and riskier, which warrants a more conservative surgical therapeutic option. Adjuvant radiotherapy is strongly recommended for residual tumors in the cavernous sinus in order to prevent an early recurrence. Understanding of above-mentioned features helps the surgeon set up appropriate surgical goals for type IIa and IIb ACMs "involving" in the cavernous sinus.

Limitations

Our study has some limitations. First, because of the retrospective nature of this study, the effects or outcomes of applying either this classification or other previously reported schemes in ACM patients could not be evaluated. It still needs to be assessed by future perspective studies. We added that in the limits of our current study. Second, surgical outcomes are highly dependent on the operator. In the current study, the surgeries were performed by several senior surgeons; although all of them are experienced operators, their surgical techniques and principle are not precisely the same, and this type of bias cannot be adjusted in this study. Third, although we used group discussion to determine which type a specific case should be assign to, the process still had a subjective nature. In addition,

the pathological types and genomic background of each tumor were not included because of insufficient data. Future perspective studies are warranted to confirm the findings of the current study and evaluate the effect of applying this classification to the surgical outcomes.

CONCLUSION

The meningeal architecture around the ACP may guide and determine the origin and extension of ACMs. The classification based on the meningeal architecture helps to understand surgical anatomy as well as predicting surgical outcomes.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The cadaveric study was reviewed and approved by the Human Research Ethics Committee in University of Otago (H18/027), the clinical study was reviewed and approved by the IRB of Changzheng Hospital, 2018SL020. The patients/participants provided their written informed consent to participate in this study.

AUTHOR'S NOTE

Part of this work was accepted and presented in an oral presentation at the Special World Congress, World Federation of Neurosurgical Societies, Beijing, China, on Sep 10, 2019.

AUTHOR CONTRIBUTIONS

TX, YY, YL, MZ, and JC conceived or designed the work. TX, YY, ZG, LJ, HW, WL, LC, and HS acquired, analyzed, or interpreted data. TX, YY, and ZG drafted the paper. AE, YL, MZ, and JC revised it critically for important intellectual content. MZ and JC agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors provided approval for publication of the content.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Clinial Features, Individualized Treatment and Long-Term Surgical Outcomes of Skull Base Meningiomas With Extracranial Extensions

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Object: Skull base meningiomas with extracranial extensions are rarely described. This study describes the clinical features, surgical management and clinical outcomes of these rare tumors and investigates risk factors associated with progression-free survival (PFS).

Methods: The clinical data of 34 consecutive patients who underwent surgery for skull base meningiomas with extracranial extensions from 2007 to 2018 were retrospectively collected and analyzed.

Results: The mean patient age was 47.9 ± 13.9 years; 50.0% were male. The most common symptoms on admission were ophthalmic. All patients underwent a multidisciplinary consultation before surgery, and received individualized surgical management. The gross total resection (GTR) rate was 55.9% (19/34). Twelve patients received post-operative adjuvant radiotherapy (RT). Twelve patients experienced tumor recurrence during the follow-up period. The median PFS duration was 54 months. The mean overall survival (OS) duration was 111 months. By univariate analysis, a higher histological grade (WHO grade II and III), Ki-67 LI ≥ 5 and the extent of resection (EOR) were significantly associated with tumor recurrence. Multivariate analysis revealed Ki-67 LI ≥ 5, the EOR and adjuvant RT as prognostic factor of PFS.

Conclusions: These relatively rare meningiomas are difficult to resect and have a poor prognosis; they are more common in males and have a higher histological grade than intracranial meningiomas. Multidisciplinary collaboration and individualized surgical strategies are crucial for surgically managing these complex tumors. Total removal of the tumor remains challenging. Subtotal resection (STR) or partial resection (PR) followed by RT is a reasonable strategy when radical resection is infeasible. Adjuvant RT should be recommended especially for tumors with histopathological risk factors (Ki-67 LI ≥ 5 or high histological grade).

Keywords: clinical features, craniofacial, Ki-67, prognostic factors, progression-free survival, radiotherapy, skull base meningioma

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INTRODUCTION

Intracranial meningiomas are extracerebral, slow-growing, well-defined tumors that account for 13–26% of all primary intracranial neoplasms, and ∼25% of meningiomas arise in the cranial base (1). World Health Organization (WHO) grade II and III meningioma, ∼10–20% of all intracranial meningioma, exhibit a more aggressive biological behavior and a greater probability for recurrence than WHO grade I (WHO-I) meningioma (2).

Skull base meningiomas with extracranial extensions are a relatively rare clinical entity which extend into craniofacial structures (3). These complex tumors involve both intracranial and extracranial structures, such as the anterior or middle cranial fossa and the infratemporal fossa, nasal cavity, paranasal sinuses, orbits or neck, etc., so multidisciplinary cooperation and individualized surgical strategies are particularly required (4). A higher proportion of recurrent and non-benign tumor have been found in patients with such a special skull base meningioma (5), and RT is often needed after surgery. So, it is difficult to surgically manage this special entity, especially for a single disciplinary team. To the best of our knowledge, only a few reports have discussed this rare subtype of meningioma with consecutive patient series (3–16). Furthermore, most of them focused on the evaluation of sphenoorbital meningiomas or the outcome of a specific surgical approach. Individualized surgical approaches and the importance of multidisciplinary cooperation has not been highlighted. The clinical features and prognosis of these patients with skull base meningiomas with extracranial extensions, as well as comprehensive treatment strategies, have not yet been systematically well-documented.

Multidisciplinary cooperative treatment strategies for intra- and extra-cranial communicating tumors of the skull base have been explored at the Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College, and very good results have been achieved for dumbbell shaped jugular foramen schwannomas with neck extension surgically treated since 2005 (17, 18). In this study, we retrospectively analyzed the cases with pathologically confirmed skull base meningiomas with extracranial extensions that received multidisciplinary treatment at our center from 2007 to 2018, with focus on clinical features, individualized management paradigm and prognosis analysis.

TABLE 1 | Demographic, clinical, and radiological characteristics of 34 patients with skull base meningiomas with extracranial extensions.

Characteristics	Value (%)	Characteristics	Value (%)
Age at diagnosis (years)		Enhancement	
Mean	47.9 ± 13.9	Homogeneous	26 (76.5)
Range	14–72	Heterogeneous	8 (23.5)
Sex		Bone structure change on CT	22 (64.7)
Male	17 (50.0)	Pathology	
Female	17 (50.0)	WHO grade I	20 (58.8)
Duration from onset to admission		WHO grade II	12 (35.3)
Mean	19.2	WHO grade III	2 (5.9)
Range	7 days-10 years	Ki-67 LI	
Presenting symptoms		≥5%	17 (50.0)
Headache	4 (11.8)	<5%	17 (50.0)
Ophthalmic symptoms	21 (61.8)	EOR	
Mass on face or neck	8 (23.5)	GTR	19 (55.9)
Nasal obstruction or discharge	4 (11.8)	STR	9 (26.5)
Cranial nerve disorders	9 (26.5)	PR	6 (17.6)
Initial or recurrent lesion		Adjuvant RT	
Initial	14 (41.2)	Yes	12 (35.3)
Recurrent	20 (58.8)	No	21 (61.8)
Extracranial extensions		NK	1 (2.9)
Orbit	30 (88.2)	Tumor recurrence	12 (35.3)
Nasal cavity or paranasal sinus	20 (58.8)	Postoperative death	5 (14.7)
Infratemporal or pterygopalatine fossa	8 (23.5)	Died in perioperative period	1 (2.9)
Neck or parapharyngeal space	3 (8.8)	Died in follow-up period	4 (11.8)
		Median follow-up duration (months)	31

LI, label index; NK, not known; RT, radiotherapy.

MATERIALS AND METHODS

Patient Population

From 2007 to 2018, 271 patients with skull base meningiomas were surgically treated in the Department of Neurosurgery, Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College. Of these, 34 patients with skull base meningiomas with extracranial extensions were included. Twenty-nine patients underwent one operation, four patients underwent twice operations, and one underwent four operations for their recurrent tumors, and a total of 41 operative procedures had been performed in the series. The diagnosis of meningioma was confirmed by the neuropathologist according to either the 2007 or 2016 WHO grading criteria in all cases. The study was approved by the Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College Research Ethics Committee. Written consent from patients that are identifiable from the images have been obtained.

Clinical and Radiological Data

Clinical and radiological data were collected and analyzed. Clinical data included patient's age on admission, sex, and clinical manifestations (e.g., visual impairment, proptosis, headache, and neurological deficits). All patients underwent computed tomography (CT) and magnetic resonance imaging (MRI) scans during the diagnostic workup. High-resolution CT imaging with bone-window algorithm provided the best images of hyperostosis or erosion of the bone structure of the skull

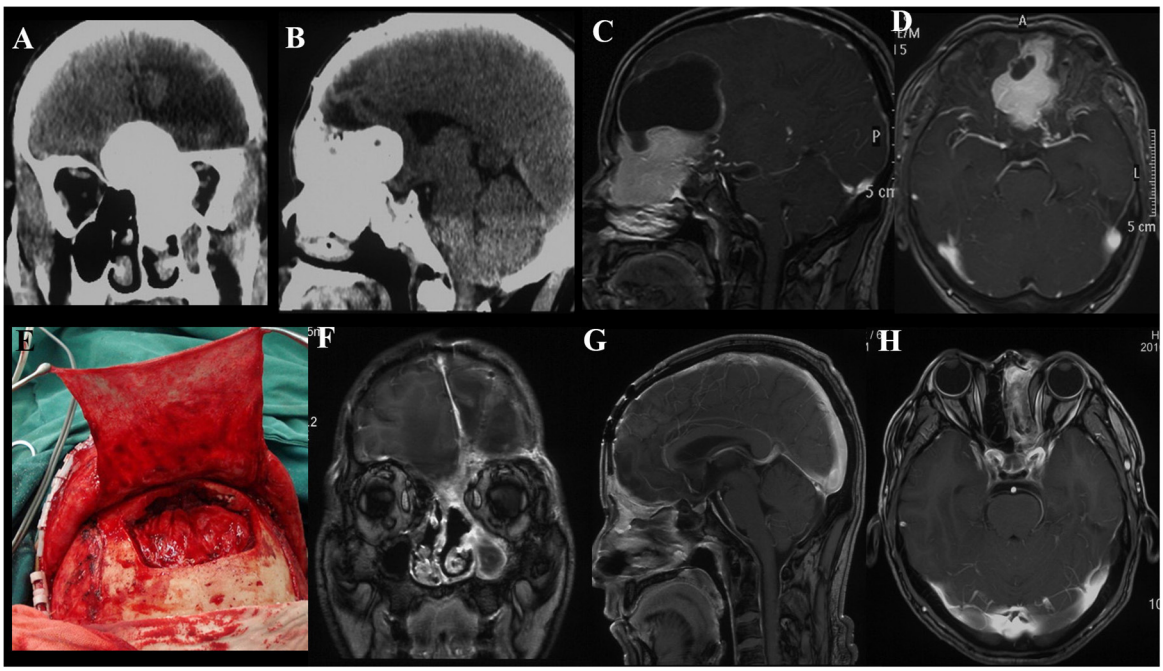


FIGURE 1 | Case illustrating the Derome approach. **(A,B)** CT scans show an anterior skull base tumor with nasal extension with significant calcifications. **(C,D)** T1-weighted sagittal and axial contrast-enhanced MRIs show the same tumor as A and B, the irregularly shaped lesion with heterogeneous enhancement and cystic changes. **(E)** A periosteal flap was prepared for repairing the skull base defect. **(F–H)** Postoperative contrast-enhanced MRIs indicated GTR of the tumor.

base. Gadolinium (Gd)-enhanced MRI sequence was used to confirm the intracranial and extracranial tumor portion and to evaluate the degree of dura involvement. Gd-enhanced MRIs were classified into two groups, including heterogeneous and homogeneous enhancement.

Pathological Examination

After operation, the dural attachment and areas of involved bone, nerve, skeletal muscle and mucosa were sent for pathological examination. Fresh paraffin-embedded tumor tissue was stained with hematoxylin and eosin (H&E) and immunohistochemistry for diagnosis and differential diagnosis. The ki-67 label index (Ki-67 LI) is the percentage of cells reactive to Ki-67, and the cutoff values for the Ki-67 LI were defined as 5% based on the results of our data and previous reports (2, 19).

Operative Procedures

Operative notes described the details of the surgical approach and the EOR. The surgical approach was selected depending upon the location of the tumor and the dimensions of its extracranial and intracranial components. Anterior skull base meningiomas with nasal extension were removed via a Derome approach. Sphenoid wing meningiomas with orbital extension were resected via a frontotemporal approach. Middle skull base meningiomas with infratemporal or pterygopalatine fossa extension were resected by a middle cranial fossa approach (the major part of tumor was intracranial) or a maxillary swing approach (the major part of tumor was extracranial). Midline skull base meningiomas with nasal extension were resected by a purely endoscopic endonasal approach. Dumbbell shaped jugular foramen meningiomas with neck extension were resected via a combined craniocervical approach. Cranial base meningiomas with extensive intra- and extra-cranial involvement were removed by a combined craniofacial approach or the undefined approach. The tumor resection was carried out according to the principle of microneurosurgery, that is, to devascularize the tumor first, to debulk the tumor, and then to remove the capsule and involved dura and bone. En bloc removal of the tumor is appreciated if possible. Skull base defects following by tumor resection were all reconstructed. During the operation, the neurosurgeons were mainly responsible for the craniotomy, intracranial tumor resection, skull base repair, and skull closure. The head and neck surgeons were mainly responsible for ligation of the external carotid artery or its branches, transfacial approach, extracranial tumor resection and free or pedicled myocutaneous flap transplantation. Based on a review of the surgery records, the EOR was subdivided into GTR, STR and PR. In general, GTR could be categorized as Simpson grade I or II, STR could be categorized as Simpson grade III or IV, and PR could be categorized as Simpson grade IV with significant residual tumor or V (20).

Follow-Up

Follow-up notes were collected and analyzed. Disease progression, defined as tumor recurrence after GTR or residual tumor enlargement after STR or PR, was evaluated using enhanced MRI scans. Complications, post-operative adjuvant RT, OS, and PFS were also recorded.

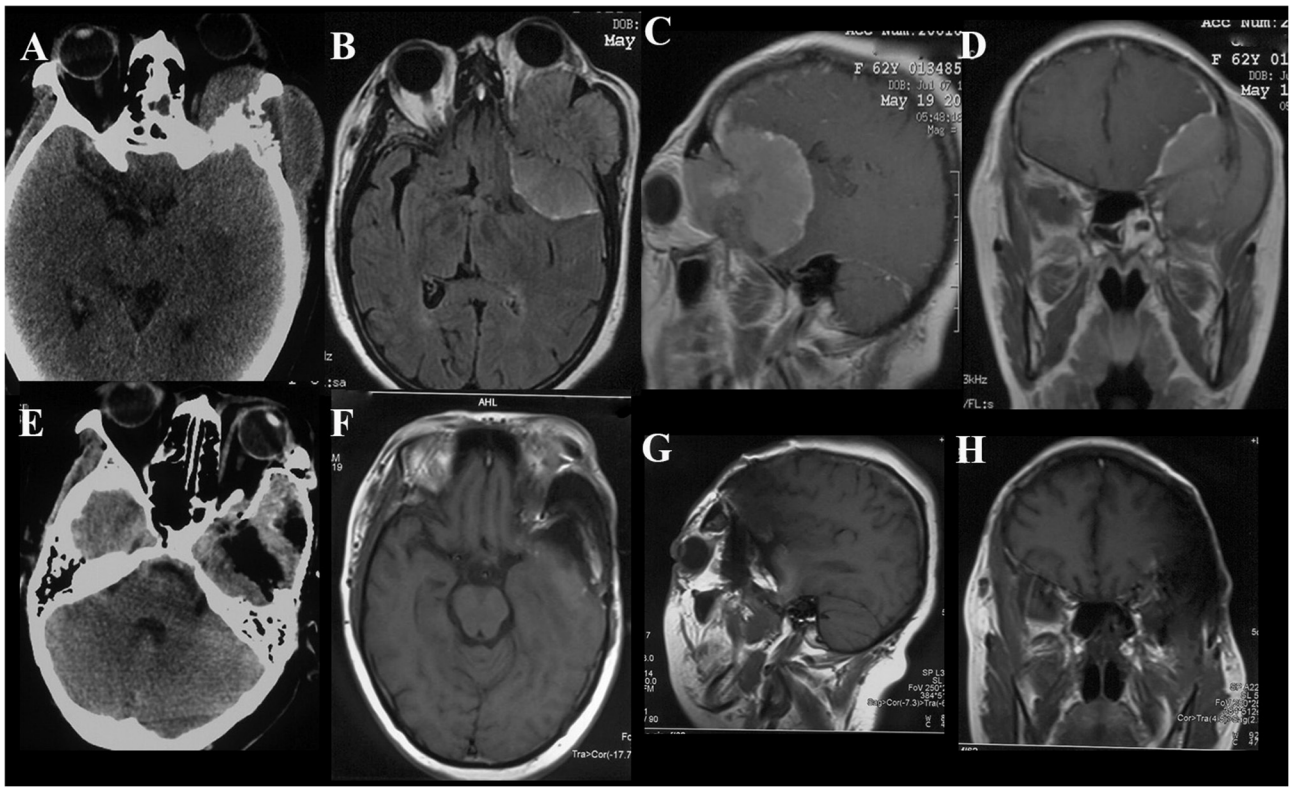


FIGURE 2 | Case illustrating the frontotemporal approach. **(A)** CT scan show bone hyperostosis and destructive absorption of the left sphenoidal wing and lateral wall. **(B–D)** T1-weighted axial, sagittal and coronal contrast-enhanced MRIs demonstrate the same tumor as A, the anterior and lateral cranial base meningioma with orbital extension with homogeneous enhancement. **(E–H)** Postoperative CT and MRI indicate satisfactory tumor resection.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation with a range. Categorical variables were described using frequencies and percentages. OS was determined from the date of surgery to death or the last follow-up. PFS was determined from the date of surgery to the date of documented progression. To assess predictors of PFS, we examined the following items: age, sex, lesion recurrence, enhancement on Gd-enhanced MRI, histological grade, Ki-67 LI, EOR, and adjuvant RT. The rates of PFS were estimated by Kaplan-Meier analysis (log-rank test). The Cox proportional hazards model and a stepwise regression analysis were used to assess the relevance between factors and recurrence. A $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS Statistics software (version 21.0; IBM Corp). It is noteworthy that one patient who died during the perioperative period was not included in the Kaplan-Meier analysis because he did not meet the purpose of the study and his death cannot reflect the natural course of this tumor.

RESULTS

Epidemiological and Clinical Data

Thirty-four cases of pathologically confirmed skull base meningioma with extracranial extensions were identified among 271 cases of surgically treated skull base meningiomas in our center in the study period. Thus, the ratio of this subtype of skull base meningiomas was 12.55%. The clinical characteristics are summarized in **Table 1**. The average patient age was 47.9 ± 13.9 years (range, 14–72 years). Seventeen patients were female, accounting for 50.0% of all patients (male: female ratio, 1:1). The most common presenting symptoms were ophthalmic symptoms, such as visual impairments, proptosis or retro-orbital pain, occurring in 21 patients (61.8%). Other tumor manifestations on admission were cranial nerve disorders in 9 patients (26.5%), a mass on the face or neck in 8 (23.5%), nasal obstruction or discharge in 4 (11.8%), and headache in 4 (11.8%). The mean duration of symptoms before surgery was 19.2 months (range, 7 days-10 years). Fourteen patients were initially treated in our center, and the other 20 patients with recurrent tumor had been surgically treated elsewhere before admission to our center.

Radiological Features

MRI or CT scans were used for the imaging diagnosis of meningioma and the evaluation of tumor resection. In this study, tumors often invaded different extracranial structures at the same time. Skull base meningiomas extended into orbital regions in 30 patients (88.2%), extended into the nasal cavity and/or paranasal sinuses in 20 (58.8%), invaded the infratemporal fossa or pterygopalatine fossa in 8 (23.5%), and involved the neck or parapharyngeal space in 3 (8.8%). Isointense or slightly

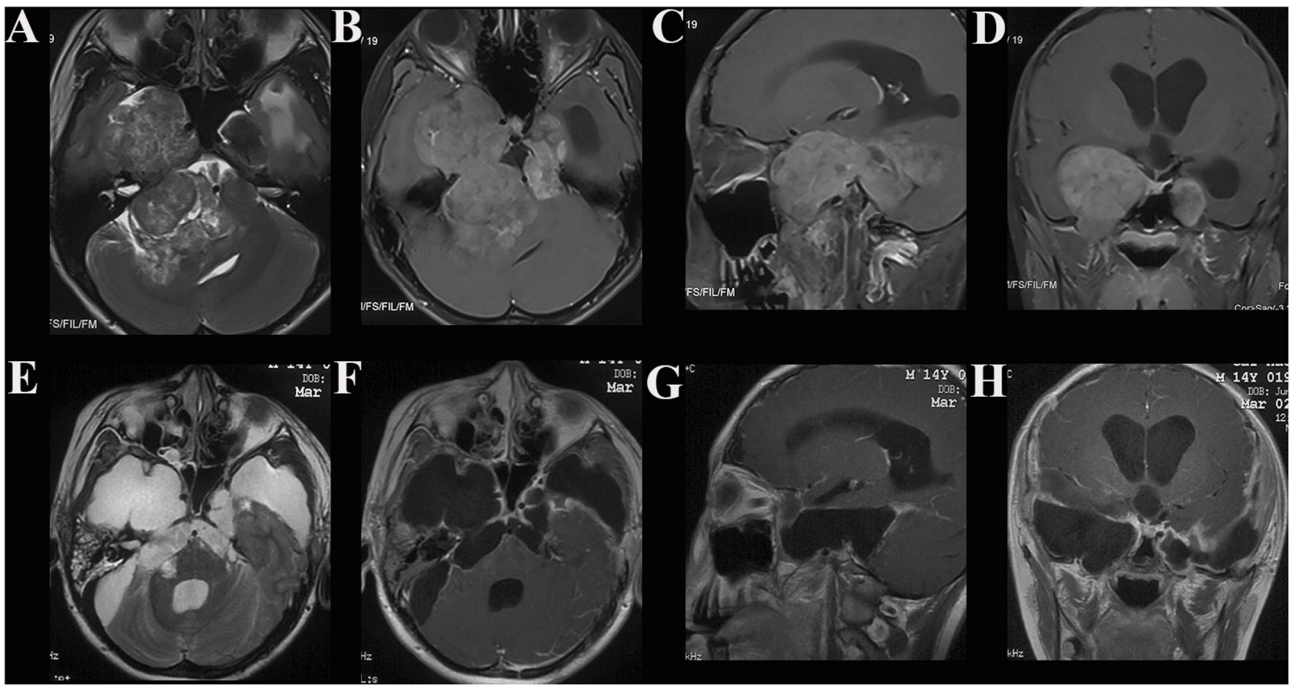


FIGURE 3 | Case illustrating the middle cranial fossa approach. **(A)** T2-weighted axial MRI show dumbbell shaped tumors in the bilateral middle and posterior cranial base with hyperintense and isointense. **(B–D)** T1-weighted axial, sagittal, and coronal contrast-enhanced MRIs demonstrate both tumors with heterogeneous enhancement, the dumbell shaped tumor on the right extended into infratemporal fossae **(B)**. **(E–H)** Postoperative contrast-enhanced MRI indicated satisfactory tumor resection.

hypointense on T1-weighted MRI and hyperintense or isointense on T2-weighted MRI were presented in most tumors. Gd-enhanced MRIs demonstrated significant enhancement in all patients, including heterogeneous enhancement in 10 cases (29.9%) and homogenous enhancement in 24 cases (70.1%). Tumor calcification was found on CT scans in 3 patients (8.8%) (**Figures 1A,B**). Cystic degeneration was revealed on MRI in 3 patients (8.8%) (**Figure 1C**). Distinct dural tail sign was found on enhanced MRI in 10 patients (29.4%) (**Figure 2**), whereas was not found in the other 24 (**Figure 3**). Changes in the bone structure of the skull base were found on CT scans with the bone-window algorithm in 22 patients (64.7%), including hyperostosis (63.6%) (**Figure 2A**) and destructive absorption (36.4%) (**Figure 5D**). In most patients, the bone hyperostosis areas were resected, as verified by post-operative CT. Fluid-attenuated inversion recovery imaging confirmed the existence of edema surrounding the tumor. Four patients in this series underwent preoperative angiography and embolization due to abundant tumor blood supply.

Surgical Records and Complications

All operations were performed by neurosurgeons, with the assistance of head and neck surgeons, if necessary. In all cases, therapies were tailored to individual patient after a multidisciplinary consultation. Eight patients underwent treatment by the Derome approach (**Figure 1**). In 1 of those 8 patients, a transnasal endoscopic approach was additionally required for the resection of tumors located in the ethmoid sinus and nasal cavity. Twelve patients were treated with the frontotemporal approach (**Figure 2**) and middle cranial fossa approach (**Figure 3**), three with the maxillary swing approach (**Figures 4H–L**), three with the combined craniocervical approach (**Figure 5**) and two with the purely endoscopic endonasal approach (**Figure 6**). A combined craniofacial approach (**Figures 4A–G**) was employed in 4 cases, and an undefined approach (**Figures 7A–G**) in 2 cases. GTR was achieved in 19 patients (55.9%), STR in 9 (26.5%), and PR in 6 (17.6%).

Surgical morbidities occurred in 10 patients, with 1 case of mortality; the patient died of brain stem dysfunction due to tumor invasion 15 days after the operation. Postoperative complications included new cranial nerve deficit in 3 cases (8.8%), cerebrospinal fluid (CSF) leakage requiring temporary lumbar CSF drainage in 2 (5.9%), subcutaneous hydrops in 2 (5.9%), intracranial infection in 2 (5.9%), post-operative cerebral infarction in 1 (2.9%) and skin flap necrosis requiring repeat free pedicle flap transplantation in 1 (2.9%). Except for hemiplegia after cerebral infarction and permanent neurological deficits in two patients, other complications gradually improved within a few months.

Histological Data

All tumors were verified as meningiomas on pathological examination. Among them, 20 tumors (58.8%) were classified as

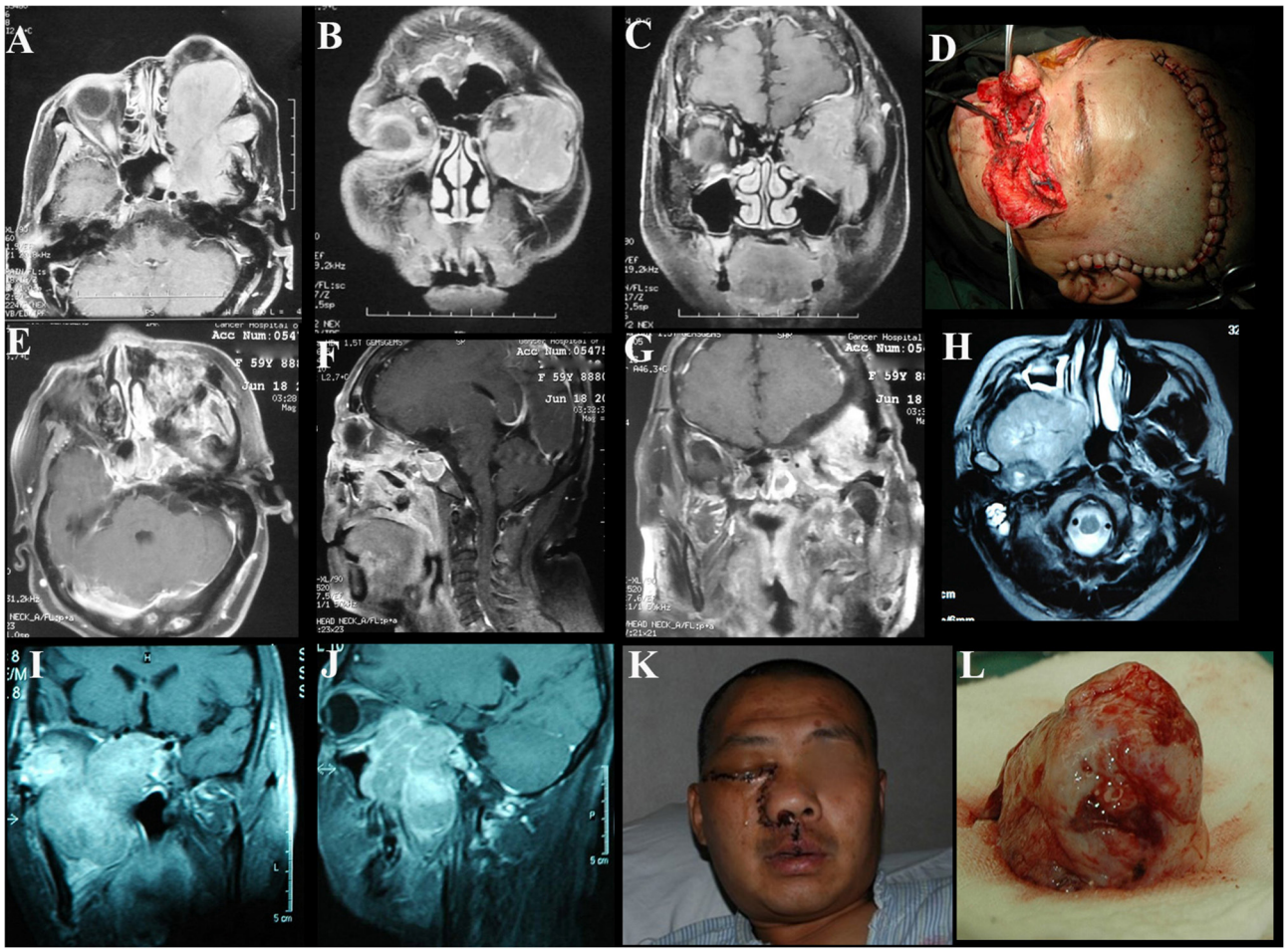


FIGURE 4 | Case illustrating the craniofacial and maxillary swing approaches. **(A–C)** T1-weighted axial and coronal contrast-enhanced MRIs demonstrate a tumor with homogeneous enhancement located in the anterior and lateral cranial base with extension to the orbits and infratemporal fossa. **(D)** The incision of the craniofacial approach. **(E–G)** Contrast-enhanced MRIs 1 week after the surgery indicate satisfactory tumor resection. **(H–J)** T1-weighted axial, coronal, and sagittal contrast-enhanced MRIs demonstrate a middle skull base meningioma extended into the right infratemporal and pterygopalatine fossae with significant enhancement. **(K)** The incision of the maxillary swing approach. **(L)** Photograph of the tumor sample. The maxillary swing approach can provide wide exposure and allow en bloc tumor resection.

WHO grade I, 12 (35.3%) were WHO grade II, and 2 (5.9%) were WHO grade III (**Figure 7H**). The Ki-67 LI in 17 cases was ≥5% and <5% in the other 17 cases (**Figure 7I**). Among the cases of ki-67≥5, there were 5 cases of WHO-I, 10 of WHO-II and 2 of WHO-III. The PFS decreased remarkably at a Ki-67 LI of 5%, demonstrating that the cutoff value of the Ki-67 LI was suitable for the analysis of this study, as previously reported (2, 19).

Follow-Up and Adjuvant RT

During the median follow-up period of 31 months (range, 3–133 months), 12 patients (35.3%) developed tumor recurrence, which occurred after an average of 19 ± 16.7 months (range, 3–54 months). The median PFS duration was 54 months (**Table 2**). The 3-, 5-, and 10-year PFS rate was 0.63, 0.47, and 0.47, respectively. Four patients died of recurrence during the follow-up period, and the mean OS duration was 111 months. The 3-, 5-, and 10-year OS rate was 0.87, 0.80, and 0.80, respectively. Twelve of 34 patients (35.3%) received adjuvant RT after surgical resection. Of the 12 patients who developed tumor recurrence during the follow-up period, 1 was treated by RT, and 5 were treated by repeat surgery and RT. One patient developed metastatic lung disease and received chemotherapy during the follow-up period.

Variables Associated With Recurrence

Age, sex, lesion recurrence, enhancement on Gd-enhanced MRI, histological grade, Ki-67 LI, EOR, and adjuvant RT were recorded and analyzed. Log-rank analysis and the Cox proportional hazards model were used to identify parameters significantly associated with shorter PFS. Univariate analysis revealed that a higher histological grade (**Figure 8A**), Ki-67 LI ≥ 5 (**Figure 8B**), and EOR (**Figure 8C**) were significantly associated with PFS, with $P = 0.001$, $P < 0.001$, and $P = 0.024$, respectively (**Table 3**). There was a trend toward increased recurrence in patients who were male ($P = 0.097$). Multivariate analysis confirmed Ki-67 LI≥5,

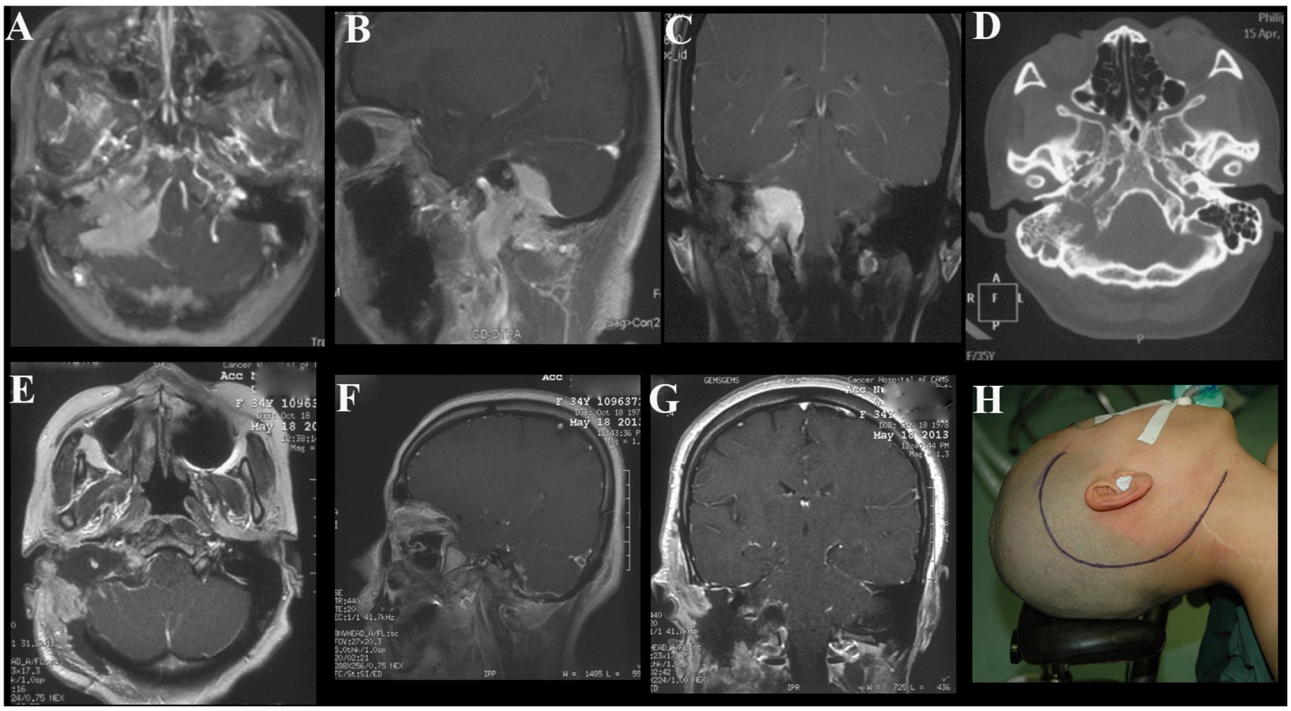


FIGURE 5 | Case illustrating the combined craniocervical approach. **(A–C)** T1-weighted contrast-enhanced MRIs demonstrate a tumor with homogeneous enhancement located in the right jugular foramen with both posterior cranial fossa and neck extensions, dural tail signs are found in the posterior fossa. **(D)** CT scan with the bone-window algorithm shows the enlarged jugular foramen with bone destructive change. **(E–G)** Postoperative contrast-enhanced MRIs indicate satisfactory tumor resection. **(H)** The incision of the combined craniocervical approach.

EOR (not GTR; NGTR) and adjuvant RT (absent) (**Figure 8D**) as risk factors of shorter PFS. To identify whether adjuvant RT was necessary for NGTR, the PFS data were analyzed by dividing all patients into two groups: those with or without a high Ki-67 LI. In the Ki-67 LI $\geq$ 5 group, adjuvant RT was significantly associated with longer PFS, while it was not in the Ki-67 LI<5 group (**Figures 9A,B**). On the contrary, GTR was significantly associated with longer PFS in the Ki-67 group LI<5, while was not in the Ki-67 LI$\geq$5 group (**Figures 9C,D**).

DISCUSSION

Research on meningiomas has never been popular. One reason could be the misunderstanding that these tumors are benign and curative. Neurosurgeons, especially skull base neurosurgeons, know this understanding to be wrong. Meningiomas have varying biological behaviors that range from completely benign to malignant. Moreover, even completely benign tumors occurring at the skull base are challenging to remove safely and can recur quickly (21).

Clinical and Radiological Characteristics

The mean age of the cohort was 47.9 years, slightly lower than 48.3–64 years reported in the literature (5–7, 10, 14, 15). It is well-known that the male: female ratio of intracranial meningiomas is 1:2 (22). In contrast, our cohort present no significant gender predilection. In our case series, the sex ratio (male: female) was ~1:1. This may be due to the high proportion of WHO grade II and III (non-benign) meningiomas (41.2%) in this series. Non-benign meningiomas are more common in males (22). This may be why there was a trend toward increased recurrence in men in the univariate analysis (P = 0.097). Furthermore, it has been demonstrated that patients with non-skull base lesions are more likely to have non-benign meningiomas (27 vs. 12%, P < 0.001) (23). Such a higher proportion of non-benign meningiomas in the cohort may be related to more recurrent cases included. In our case series, the proportion of recurrent tumors that had initially been treated elsewhere was 58.8%.The reason for such a high proportion of high-grade meningiomas deserves further research.

As reported by Taro Shimono et al. (24), the most common site invaded by skull base meningiomas is the orbit, and cervical extension is rare, occurring in only 1.4% of all cases of intracranial meningioma. In our cohort, the most common site of tumor invasion was the orbit (88.2%), and thus the most common symptoms were ophthalmic symptoms, which is consistent with what has been previously reported (3, 4, 15). Among these symptoms, proptosis is the most common clinical sign of meningioma with orbital extension. Proptosis can be explained either by the growth of an intraorbital tumor, the osseous invasion of a tumor in the orbital walls, or the

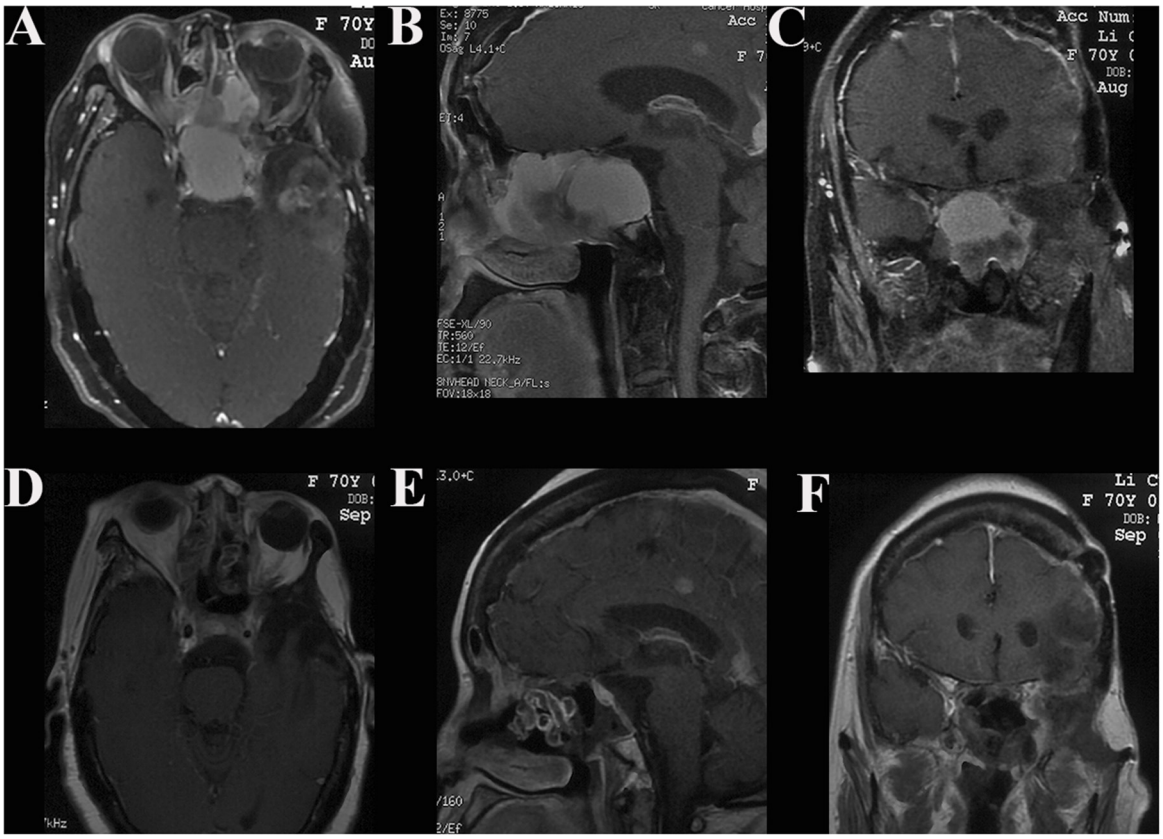


FIGURE 6 | Case illustrating the endoscopic endonasal approach. **(A–C)** T1-weighted axial, sagittal, and coronal contrast-enhanced MRIs demonstrate an anterior skull base tumor with extension to the sphenoid sinus, ethmoidal sinus, and nasal cavity with moderate enhancement. **(D–F)** Postoperative contrast-enhanced MRIs indicate satisfactory tumor resection.

reduction of venous drainage from the orbit on account of dural infiltration at the level of the superior orbital fissure (SOF) (7).

Heterogeneous enhancement was found on contrast-enhanced MRI in 10 cases (29.9%) (**Figures 7A–C**). Heterogeneous enhancement could be due to the existence of necrosis and cystic degeneration. On account of the rapid proliferation rate, the central area of the tumor often has insufficient blood circulation, resulting in ischemic necrosis or cystic degeneration (25). The necrotic area is usually larger in more invasive tumors (25). In the study, bone destructive absorption accounts for 36.4% of the bone changes in the skull base, which is much higher than that reported in the literature (6, 8). And that may be related to the higher pathological grade and poor biological behavior of the tumor. Some authors have suggested that the finding of hyperostosis of the cranial base represents true invasion of the bone (6, 10–12, 14). In conclusion, the clinical and radiological features of skull base meningiomas with extracranial extensions can be summarized as "6M": more often in males, more recurrent and non-benign cases, more orbital extension, more heterogeneous enhancement, and more bone destruction.

Multidisciplinary Cooperation and Individual Surgical Strategies

Although GTR is always our primary goal, this could be tempered if the tumor involves crucial neurovascular structures. In this cohort, the total resection rate is not so high (55.9%) due to more extensive cavernous sinus involvement cases (14/34) and more recurrent cases (20/34). We advocate that skull base meningiomas with both extra- and intra-cranial extensions should be surgically treated by a multidisciplinary skull base team. The team members include neurosurgeons, head & neck surgeons, plastic and reconstructive surgeons. Patients with such special meningiomas usually need staged operations without multidisciplinary cooperation. In this study, all cases received one-stage surgery through multidisciplinary cooperation, which alleviated the suffering and economic burden related to staged surgery. In addition, STR or PR of tumor should be followed by adjuvant RT, especially for the recurrent or non-benign cases. So, multidisciplinary cooperation is crucial for the management of skull base meningioma with extracranial extensions.

Individual Surgical Approach

Skull base meningiomas with extracranial extensions originate in different site at the skull base, and different intra- and

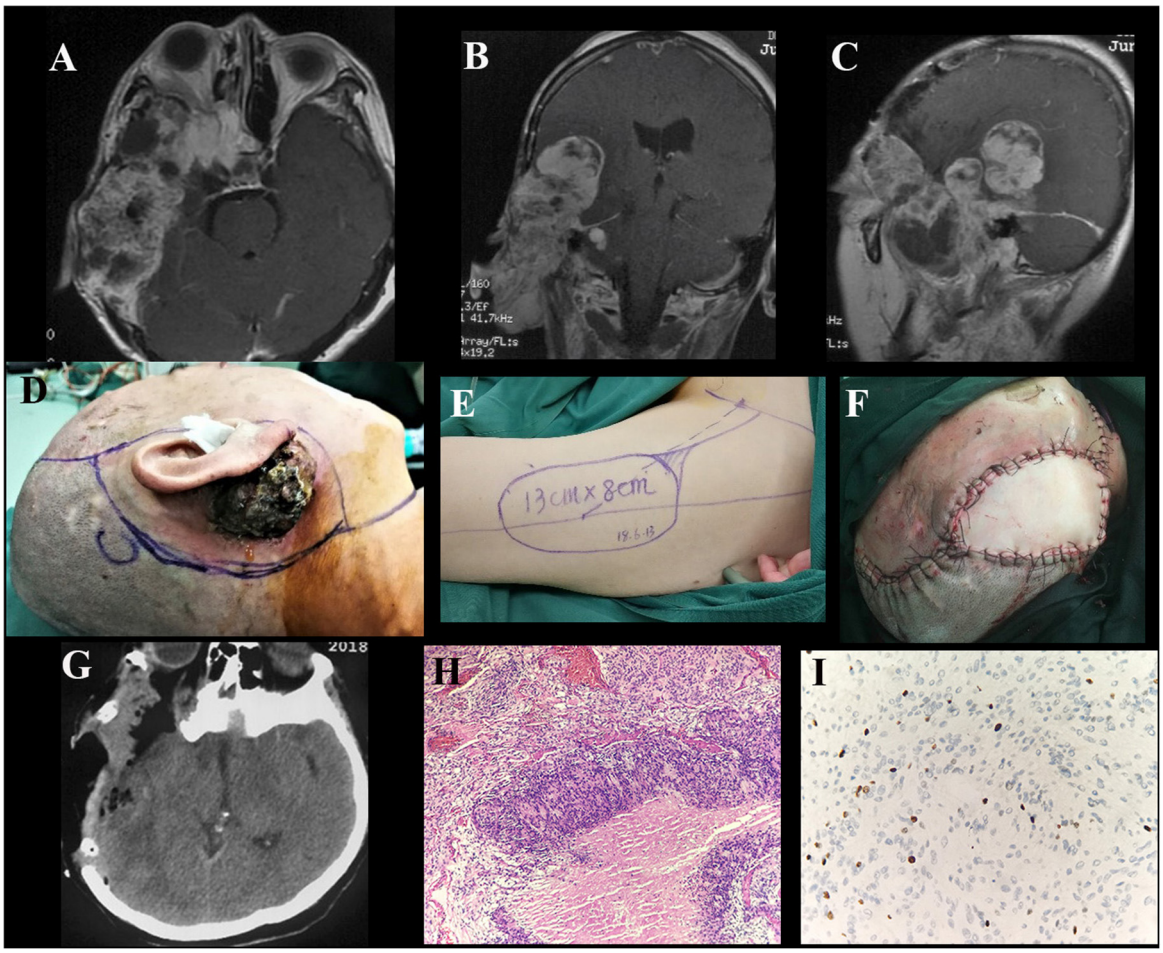


FIGURE 7 | Case illustrating an undefined approach. **(A–C)** T1-weighted axial and coronal contrast-enhanced MRIs demonstrate an irregularly shaped tumor originating in the right middle skull base with both intra- and extra-cranial extensions, invading the right ear with skin ulceration. The tumor enhanced heterogeneously after injection of contrast agent. **(D–F)** The incision surrounding the lesion and the free flap from the anterolateral thigh harvested to repair the defect. **(G)** Postoperative CT scan shows tumor and bone involvement resection. **(H)** H&E × 100 indicate atypical meningioma (WHO grade II). **(I)** Immunohistochemical staining shows Ki-67 ≥ 5.

TABLE 2 | PFS and OS of 33* meningioma patients.

PFS and OS	Value
3-, 5-, 10-PFS	0.63, 0.47, 0.47
PFS, median (months)	54
3-, 5-, 10-OS	0.87, 0.80, 0.80
OS, mean (months)	111

**One case of perioperative death was not included in the statistical analysis.*

extracranial vital structures involved, so an individual approach should be applied for the tumor resection. We have summarized eight approaches applicable for the treatment of these special entities, as outlined below. (a) The Derome approach (**Figure 1**) is usually used for tumors of anterior cranial fossa extending into the nasal cavity and paranasal sinus. We can gain access to the anterior skull base, the medial part of the maxillary sinus, and the nasal cavity directly through this approach. Blind spots underneath the orbits are the limitation of this approach, but increased visualization is facilitated by the additional use of endoscopy (9). (b) The endoscopic endonasal approach (**Figure 6**) can be used for tumors of midline cranial base extending into the nasal cavity and paranasal sinus. The endoscopic endonasal approach has many advantages, such as the lack of external incisions, reduced brain retraction, direct access to the tumor under the midline cranial base and an acceptable complication profile in contemporary series. Due to the development of this approach, the lateral rhinotomy gradually faded from view. Many authors have indicated that a purely or additional endoscopic endonasal approach is feasible and effective for the resection of anterior cranial base meningiomas with extracranial involvement in selected cases (3, 4, 15, 26). Almeida et al. (13) indicated that the transorbital endoscopic eyelid approach is a novel minimally aggressive option for the resection of sphenoorbital meningiomas with predominant hyperostosis. (c) The frontotemporal approach,

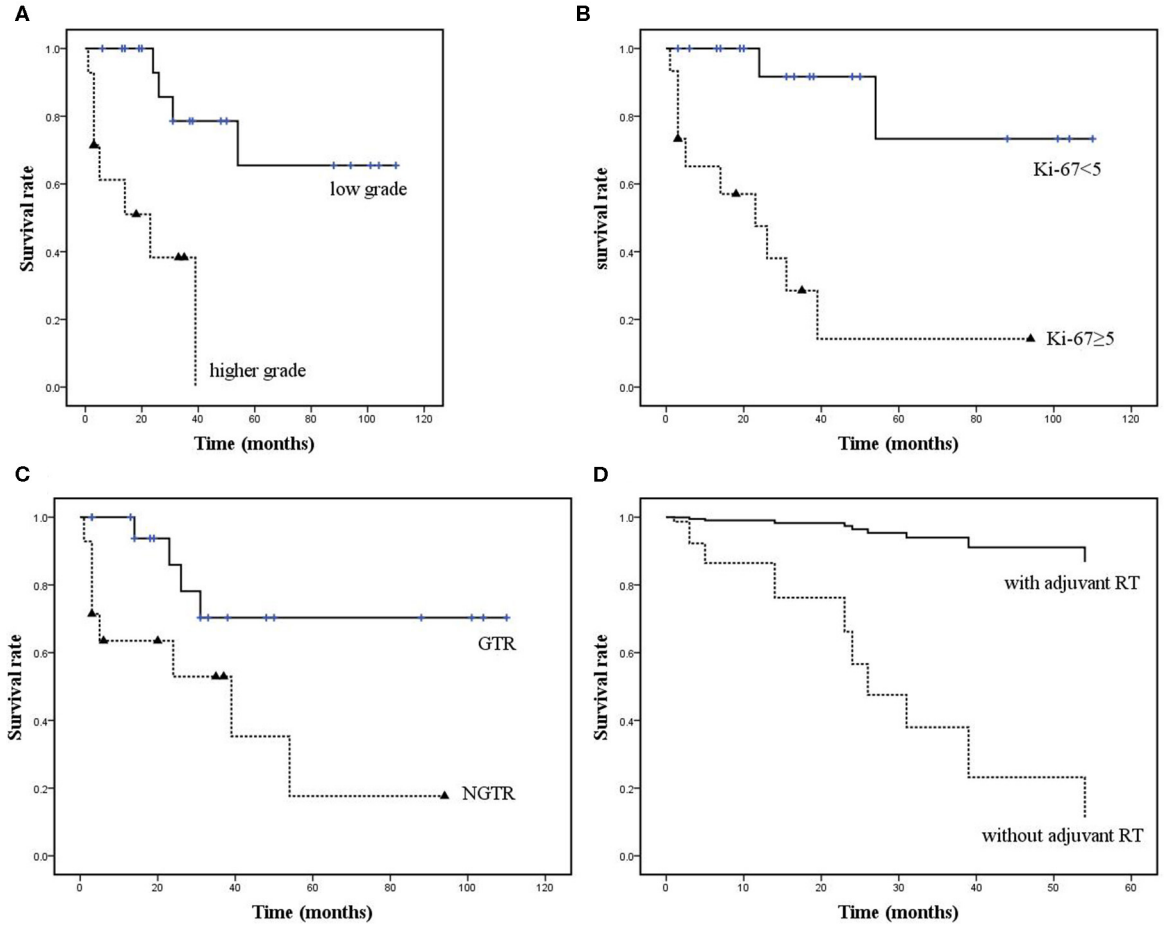


FIGURE 8 | (A–C) Kaplan-Meier curves showing statistically significant differences in PFS based on histological grade, Ki-67 LI and EOR ($P = 0.001$, $P < 0.001$, and $P = 0.024$, respectively). **(D)** Adjuvant RT was also significantly associated with PFS on multivariate analysis ($P = 0.024$, HR: 15.632, 95% CI: 1.441–169.524).

possibly in combination with additional orbital or zygomatic osteotomy (**Figure 2**), is used for anterolateral cranial base meningiomas invading sphenoid wing, petrous bone, orbit or fossae temporalis. The effectiveness of frontotemporal approach for excision of purely sphenoorbital meningiomas has been demonstrated by many reports (6–8, 11, 12, 14). (d) The maxillary swing approach (**Figures 4H–L**) is used for giant middle cranial fossa meningiomas extending into the infratemporal and pterygopalatine fossae, especially for those with heavy calcification and fibrosis. The advantages include wide tumor exposure, en bloc resection and less blood loss during operation (27). (e) The extended middle cranial fossa approach is suitable for meningiomas of which the major part locates in the middle skull base while a minor part extends to the infratemporal or pterygopalatine fossae. Middle cranial base meningiomas with both the infratemporal fossa and the posterior fossa extensions can be removed via this approach (**Figure 3**). (f) A combined craniofacial approach (**Figures 4A–G**) is only used for tumors with widely intracranial and extracranial involvement that cannot be removed by a single transcranial or transfacial approach. We agree with Emel Avci et al. (28) that the Barrow classification is a effective and simple system to understand the surgical anatomy better and refine the techniques for performing complex craniofacial approaches. However, the transfacial approach can be replaced by the endoscopic endonasal approach in selected cases. (g) The combined craniocervical approach (**Figure 5**) is used for dumbbell shaped jugular foramen tumors with cervical extensions. The vessels and nerves in the neck needed to be recognized and protected first, followed by extracranial tumor removal and exploration of jugular foramen. The intracranial and jugular foramen tumors were then removed by neurosurgeons via a suboccipital craniotomy. The advantages of this approach are that it is beneficial for protecting neurovascular structures and such an incision can provide an adequate vascularized muscle flap to reconstruct the skull base (17). (h) The undefined approach (**Figures 7A–G**). For tumors with extensive skull base invasion or skin ulceration, when existing surgical approaches cannot be applied, an undefined approach can be used to achieve radical tumor resection. And the large defect after tumor or ulcerative skin resection was reconstructed with the assistance of head and neck plastic surgeons.

Reconstruction of the Skull Base

The reconstruction of skull base mainly includes bone reconstruction and soft tissue reconstruction. The specific reconstructive procedure was selected based upon several key factors, including the location of the defect, the defect size, the tissue involved and whether post-operative radiotherapy is needed. Bony defects left after resection of skull base tumors rarely require hard support. Considering that some patients have received radiotherapy or need post-operative radiotherapy, we believe that soft tissue reconstruction is far more important than bone reconstruction. At present, it is controversial whether the orbital wall is reconstructed after orbital tumor resection. For the resection of sphenoorbital meningiomas in this group, the orbital rim was kept intact as much as possible for aesthetic reasons, so reconstruction of the orbit was unnecessary. There exists a high risk of osteonecrosis and bony resorption when an autologous free bone is used in orbital repair (29). We suggest using titanium mesh and vascularized soft tissue to remedy this problem. Oya et al. (6) suggested not attempting to radically resect portions of the tumor beyond the periorbita. They believe that there is no need to reconstruct the orbit if the periorbita remains attached to the orbital rim. Shrivastava et al. (8) advocated that if more than one orbital wall is removed, extensive reconstruction of the orbit is necessary to avoid extraocular muscle fibrosis, pulsating enophthalmos, and post-operative meningoceles.

TABLE 3 | Factors associated with PFS in 33 patients with skull base meningiomas with extracranial extensions.

Variables	Univariate	Multivariate	
	P-value	*P*-value	HR (95% CI)
Age (<50)	0.273	NA	
Sex (female)	0.097	0.159	0.375 (0.096–1.468)
Lesion recurrence	0.260	NA	
Heterogeneous enhancement	0.564	NA	
Higher histological grade	0.001*	0.37	2.314 (0.37–14.46)
Ki-67 LI ≥ 5	<0.001*	0.008*	9.774 (1.789–53.387)
EOR (NGTR)	0.024*	0.038*	10.937 (1.147–104.314)
Adjuvant RT (absent)	0.556	0.024*	15.632 (1.441–169.524)

**P < 0.05; HR, hazard ratio; EOR, extent of resection; NGTR, not GTR; NA, not applicable.*

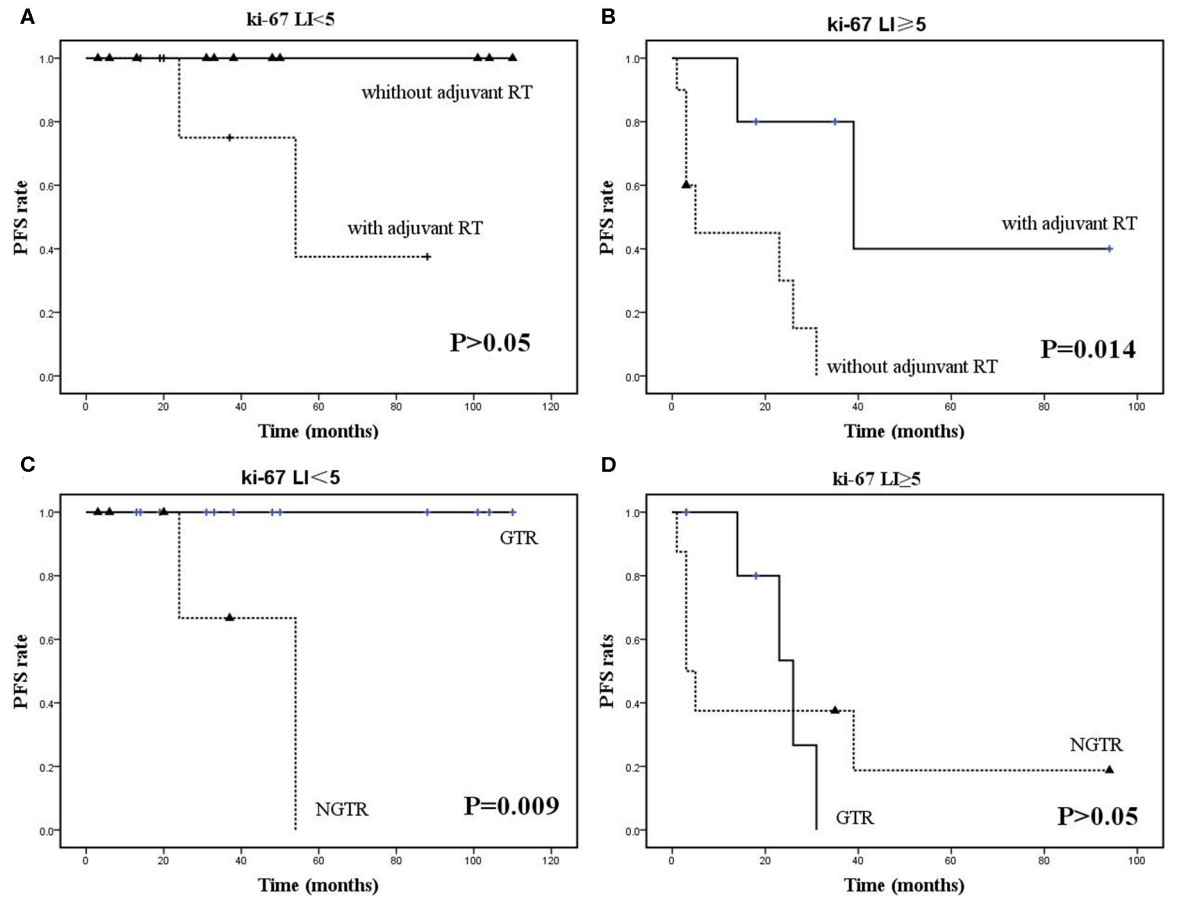


FIGURE 9 | Kaplan-Meier survival curves. **(A,B)** Adjuvant RT was significantly associated with longer PFS in the Ki-67 LI ≥ 5 group but not in the Ki-67 LI<5 group. **(C,D)** GTR was significantly associated with longer PFS in the Ki-67 LI<5 group but not in the Ki-67 LI ≥ 5 group.

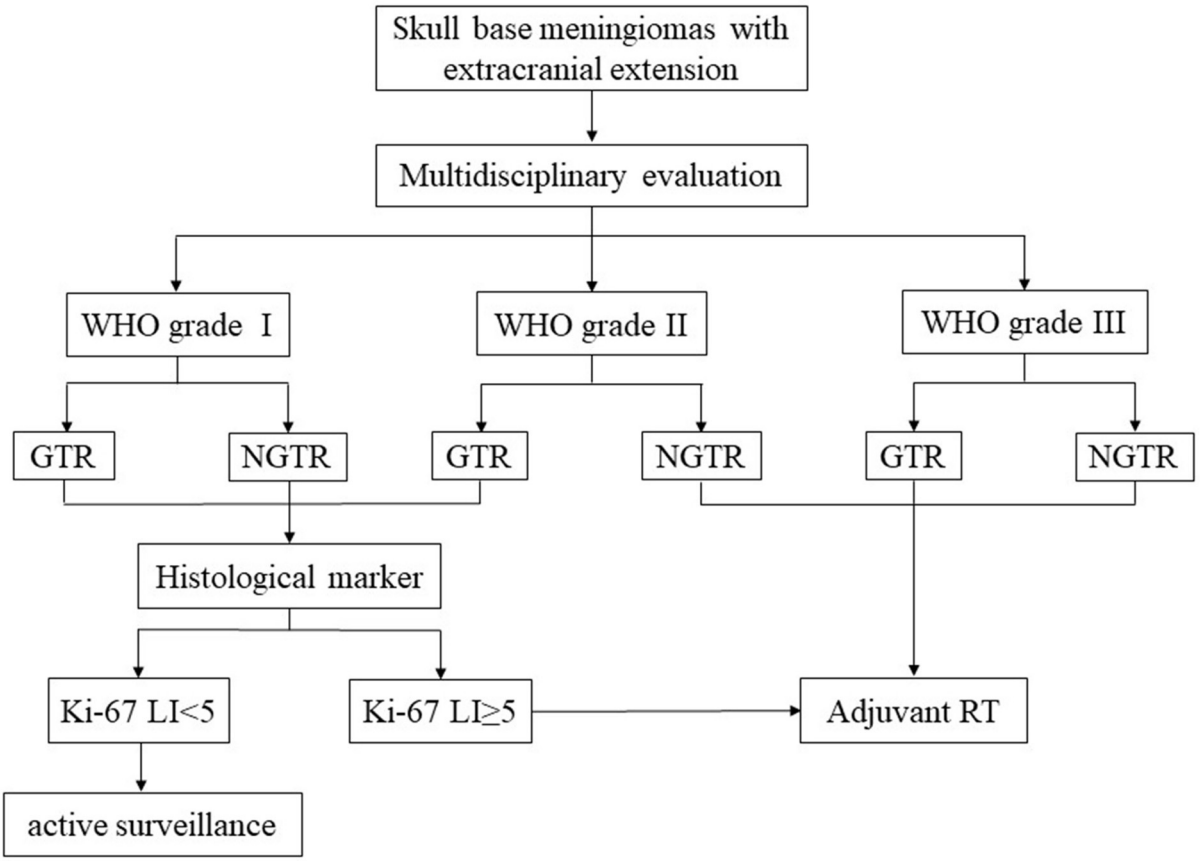


FIGURE 10 | Treatment algorithms for skull base meningiomas with extracranial extension.

Soft tissue repair mainly includes the following situations. (a) For small skull base defects after resection of the tumor by endoscopic approach or transfacial approach, autologous fat packing and nasoseptal flap can be used to repair the defect. Several reports have indicated that the use of pedicled septal flap and free fat grafts is an effective and safe technique for repairing skull base defects (30–33). (b) For a moderate skull base defects (generally no more than 4 cm in maximum diameter) left after transcranial approach, the dura mater can be repaired with autologous fascia and covered with adjacent pedicled myofascial flap. For example, the pedicled frontalis myofascial flap was used in the anterior approach (**Figure 1E**), the pedicled temporalis myofascial flap was used in the lateral approach, and the pedicled sternocleidomastoid myofascial flap was used in the combined craniocervical approach. It should be noted to avoid damaging the blood supply of the flap during operation. Feng et al. (34) also recommended temporalis muscle flap as a good choice for reconstruction of the lateral skull base. It has been reported that some flaps, such as the side-door temporoparietal fascia flap and the helmet-visor pericranial flap, can be used as a new option for skull base reconstruction (35, 36). (c) When large defects remain following tumor ablation (generally more than 4 cm in maximum diameter) or there is no available regional pedicled myofascial flap or skin defect, free flap transplantation can be used for repair. The free flap provides large and well-vascularized tissue, so it can effectively fill the dead space. And because the free flap does not have the attachment of a pedicle, it can be designed and placed in the desired position. Aksu et al. (37) have summarized six different types of free flaps used for cranial base reconstruction including anterolateral thigh flap, vertical rectus abdominis flap, radial forearm flap, fibula osteocutaneous flap, iliac osteocutaneous flap and tensor fasciae latae flap. The most commonly used flap in our center is the anterolateral thigh flap (**Figures 7E,F**). The superficial temporal artery, the facial artery or the occipital artery are the common recipient vessels. The flap can be harvested without changing intraoperative positioning, which allows both the recipient-site team and the donor-site team to operate simultaneously. Some studies have confirmed the effectiveness of the anterolateral thigh flap in repairing large skull base defects (29, 38). However, it has been reported that the failure rate of free flap repair is 2–9% (38). Advanced age and cardiovascular disease proved to increase the risk of flap ischemia (38). In the group, there is a patient with high risk of thrombosis who developed both necrosis of the flap and cerebral infarction after operation. After anticoagulatant

therapy and repeated flap transplantation, hemiplegia left by cerebral infarction was improved and the incision healed at the time of discharge. Therefore, we suggest that the risk of thrombosis should be assessed before flap transplantation and anticoagulatant therapy should be started as early as possible in high-risk patients.

Recurrence and Parameters Associated With Prognosis

In the literature, recurrence rates of 8–56.3% have been reported in several series (5, 7, 8, 39–41). In our series, 12 of 34 patients (35.3%) developed progression or recurrence during the median follow-up period of 31 months. The Kaplan-Meier univariate analysis showed a significantly decreased time to recurrence in patients with histological risk factors (higher WHO grade or Ki-67 LI) or NGTR. In addition, multivariate analysis revealed that adjuvant RT was a prognostic factor of PFS.

EOR and Adjuvant RT

The EOR remains a key factor in reducing early recurrence, as has been reported in previous studies (1, 5–7, 20, 41, 42). After the complete resection of cranial base meningiomas, the recurrence rate ranges from 20 to 22% at 10 years, and the recurrence rate of incomplete resection is significantly higher, ranging from 55 to 74% at 10 years (9). In our series, there were 4 cases (21.1%) of recurrence with GTR (4/19) and 8 cases (57.1%) of recurrence with NGTR (8/14). So, it's still our primary goal to achieve a GTR. Many authors have suggested that the combination of NGTR and adjuvant RT increased PFS with efficacy similar to that of GTR alone (1, 41, 43). Thus, NGTR followed by adjuvant RT can sometimes replace GTR. It is well-known that adjuvant RT is routinely used for WHO-III meningiomas and WHO-II meningiomas with NGTR. However, the role of adjuvant RT remains controversial for WHO-II meningiomas with GTR. Some authors have recommended adjuvant RT for WHO-II meningiomas regardless of the EOR (41, 44). In contrast, some authors do not support such aggressive use of adjuvant RT, only for tumors with NGTR (45, 46). We support the latter view. For tumors with GTR and Ki-67 $<$ 5, active surveillance is enough. But for the tumors with GTR while Ki-67 $\geq$ 5, it should also be candidates for RT.

Histological Grade and Biological Markers

The proportion of non-benign meningiomas in the skull base reported in the present study is significantly higher than that reported in the aforementioned literature (1, 5, 20, 43). This could be due to more recurrent cases included, more cases of extensive skull base destructive absorption, and limited cases with selection bias. Associations between histological grades and PFS have been reported in the literature, with recurrence rates of 7–25, 29–52, and 50–94% for WHO grades I, II, and III, respectively (1). The recurrence rates in our cohort were 21.1%, 58.5%, and 50.0%, respectively.

Nevertheless, meningiomas of the same pathological grade do not always show the same biological activity. Therefore, it is important to identify a useful marker for predicting the risk of tumor progression. The Ki-67 LI was examined in addition to the histological grade in our study. Many studies have shown that the recurrence of meningiomas is associated with the increased Ki-67 LI, in agreement with the present study (1, 19, 20, 47). In our cohort, adjuvant RT and the EOR showed different associations with PFS between the two groups (Ki-67 $\geq$ 5 or Ki-67 $<$ 5) (**Figure 9**), which may indicate that the effect of adjuvant RT on recurrence in patients with Ki-67 LI $\geq$ 5 was greater than that of the EOR; the conclusion was opposite in the other group. Thus, it enlightens us that skull base meningiomas with extracranial extensions with a high Ki-67 LI should be candidates for adjuvant RT to reduce recurrence. In the management of these complex tumors, Assessment of the Ki-67 LI should be recommended to determine subsequent treatment. However, this factor has not been included in the WHO diagnostic criteria for high-grade meningiomas.

Treatment Algorithms

Based on the evolving literature and our institutional data on the management of these rare meningiomas, we suggest those algorithms for the treatment of these complex tumors (**Figure 10**).

CONCLUSIONS

Skull base meningiomas with extracranial extensions are a relatively rare group of meningiomas that has a higher proportion of males and high histological grade compared with intracranial meningiomas. There are a low total resection rate and a high recurrence rate as different intracranial and extracranial structures involved by tumors. So, multidisciplinary collaboration, which may involve neurosurgery, head and neck/otolaryngology, plastic surgery and radiation oncology, is beneficial for the surgical management for these tumors. An individualized surgical strategy should be designed for each patient. Maximal tumor removal with minimal surgical morbidities remains the optimal treatment to minimize local recurrence. STR or PR followed by adjuvant RT is a reasonable strategy when radical resection is unavailable. RT for residual tumors should be considered in patients with histopathological risk factors, such as a high histological grade or Ki-67 $\geq$ 5. Active surveillance could be considered for patients without these risk factors.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

ETHICS STATEMENT

The study was approved by the Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical

College Research Ethics Committee. Written consent from patients that are identifiable from the images have been obtained.

AUTHOR CONTRIBUTIONS

JW conceived the idea. HL and FZ collected the data. HL analyzed the data and drafted the manuscript. All authors participated in the surgical procedure.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.01054/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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High Copy-Number Variation Burdens in Cranial Meningiomas From Patients With Diverse Clinical Phenotypes Characterized by Hot Genomic Structure Changes

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Meningiomas, as the most common primary tumor of the central nervous system, are known to harbor genomic aberrations that associate with clinical phenotypes. Here we performed genome-wide genotyping for cranial meningiomas in 383 Chinese patients and identified 9,821 copy-number variations (CNVs). Particularly, patients with diverse clinical features had distinct tumor CNV profiles. CNV burdens were greater in high-grade (WHO grade II and III) samples, recurrent lesions, large tumors (diameter >4.3 cm), and those collected from male patients. Nevertheless, the level of CNV burden did not relate to tumor locations, peritumoral brain edema, bone invasion, or multiple lesions. Overall, the most common tumor CNVs were the copy-number gain (CNG) at 22q11.1 and the copy-number losses (CNLs) at 22q13.2, 14q11.2, 1p34.3, and 1p31.3. Recurrent lesions were featured by the CNLs at 1p31.3, 6q22.31, 9p21.3, and 11p12, and high-grade samples had more CNVs at 4q13.3 and 6q22.31. Meanwhile, large tumors were more likely to have the CNVs at 1p31.3 and 1p34.3. Additionally, recurrence prediction indicated the CNLs at 4p16.3 ($p = 0.009$, hazard ratio = 5.69) and 10p11.22 ($p = 0.037$, hazard ratio = 4.53) were candidate independent risk factors.

Keywords: copy number variation, female prominence, multiple meningiomas, oncogenic driver, recurrence, tumor location

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INTRODUCTION

Meningiomas represent the most common primary intracranial tumor type, accounting for 37% of central nervous system neoplasms (1). They are believed to arise from progenitor cells of both the arachnoid cap cells of the arachnoid layer and fibroblasts that reside in the inner dura mater (2). Despite the identification of *NF2* mutations or loss of function, recent sequencing studies also

revealed mutations involving *TRAF7*, *KLF4*, *AKT1*, *SMO*, *POLR2A*, and the *ARID1A* and *TERT* promoters of in meningiomas (3–6). Cytogenetic changes, such as losses of chromosomes 22q, 14q, 1p, 1q, 10q, and 9q, are also commonly reported, some of which are related to tumor progression (7–12). Copy-number variations (CNVs) of cytobands located at 22q, 1p, and 14q were most common (12–14). In tumor development, losses of 6q and 4q have been reported to be significantly associated with high-grade lesions (13). Furthermore, meningiomas in specific locations may have featured CNVs; for instance, those at anterior skull base are likely to have intact chromosome 22q, which loses tumor suppressor gene *NF2* (15). However, as a relative benign tumor, meningioma had few data from a relatively large cohort to characterize genome-wide CNV changes, which limits efforts on applying them in tumor progression evaluation, prognosis, and the development of new treatments.

Although maximal but safe resection can cure the majority of meningiomas (16), tumor recurrence still occurs even after gross total resection (GTR) (17). The recurrence status cannot be completely predicted by histopathologic grade alone, as it is mainly based on histopathological characterizations of mitotic rate, cellular features of atypia, and local invasion (18). Meningiomas are well-known for their female-biased predominance (19), but tumors in male patients demonstrate not only a higher annual growth rate (20) but also a higher probability of recurrence (21–23). Previous studies have proposed molecular markers for prognostic scoring systems in recent years (14, 21, 24–26), and a better WHO classification of meningiomas integrated with independent molecular markers may help to predict the recurrence risk and adjust treatment plans for patients with meningiomas. Although genomic structure changes in neurologic tumors are common, extensive efforts are still required to evaluate roles of diverse recurrent CNVs in the models for tumor classification, prognosis scoring, and recurrence prediction.

To our knowledge, we here collected cranial meningiomas by far at the largest sample size in the Chinese population. We performed genome-wide genotyping for all these samples and identified diverse common CNVs. Along with detailed clinical information, we investigated their relations with gender difference, tumor location, grade classification, and recurrence, and we further proposed candidate predictors for tumor recurrence.

MATERIALS AND METHODS

Sample Collection

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital affiliated with Capital Medical University. Three hundred and eighty-three frozen meningioma samples were collected at Beijing Tiantan Hospital, Capital Medical University, between August 2008 and August 2017. Signed informed consent forms were acquired from all patients or their guardians before surgery. Tumor specimens from meningioma samples were stored in liquid nitrogen immediately following collection. Genomic DNA was purified from tumor samples using a Biomek 3000 automated workstation with an E.Z.N.A Mag-Bind Tissue DNA Kit (Omega Bio-Tek, Norcross, GA, USA). DNA quality and quantity were determined using a NanoDrop 1000 instrument (Thermo Scientific, Wilmington, DE, USA).

Clinical Data Collection and Follow-Up

Clinical information for 383 patients, including gender, age, primary or recurrent, degree of resection, tumor location, tumor diameter, bone invasion, peritumoral brain edema, pathological subtype, WHO grade, and follow-up results (recurrence and survival), was collected and summarized in **Table 1**. Pathological diagnosis was reviewed according to the 2016 WHO classification for meningiomas. Tumor recurrence was defined as tumor reemergence after GTR (gross total resection), or tumor regrowth with a minimum change of 25% increase of any tumor diameter after non-GTR based on contrast-enhanced MRIs (27). The degree of resection was decided according to the criteria of Simpson grading and classified as GTR (Simpson grade I to III) or STR (subtotal resection), verified by postoperative magnetic resonance images (MRIs) (28). Recurrence-free survival was defined as the period from the time of present surgery in our hospital to tumor recurrence (or last follow-up visit).

Whole-Genome Single-Nucleotide Polymorphism (SNP) Genotyping and Statistical Analysis

Whole-genome SNP array analysis for 383 meningioma samples was performed on Illumina Human Infinium CoreExome BeadChips (Illumina, San Diego, CA, USA). Raw intensity values were processed to obtain a normalized B allele frequency (BAF) and a log R ratio (LRR) for each probe using the GenomeStudio Software v2.0.4 (Illumina, San Diego, USA). LRR values were segmented with Genome Alteration Detection Analysis (GADA, Juan R. González, Barcelona, Spain) using parameters of $T > 10$ and segment lengths containing $\geq$50 continuous probes. For loss of heterozygosity (LOH) analysis, the sliding window approach was used with a window size of 100 informative SNPs. A window was considered to represent LOH if more than 80% of the SNPs had a minor allele frequency $\leq$0.9. A segment was defined either as normal or as having one of 3 types of alteration status based on the following criteria: (1) normal, $|\text{LRR}| < 0.075$ and retaining heterozygosity; (2) gain, $\text{LRR} \geq 0.075$; (3) loss, $\text{LRR} \leq -0.075$; and (4) copy-number neutral loss of heterozygosity (CNNLOH), $|\text{LRR}| < 0.075$.

To assess genome instability, the genomic fractions of CNVs, and CNNLOH were estimated by dividing the number of SNPs undergoing a specific alteration by the total number of SNPs present in the respective chromosome or in the respective sample. To identify minimal common regions (MCRs) of copy-number gains and losses, the Genomic Identification of Significant Targets in Cancer (GISTIC, Broad Institute, Boston, USA) algorithm was utilized. Thresholds of LRR were set at 0.1 and −0.1 to allow GISTIC to identify amplifications and deletions, respectively. *Q*-values of minimal common regions <0.01 were defined as significant, and 0.99 was used as the confidence level to determine

TABLE 1 | The clinicopathological features of the entire cohort and subcohort in the prognostic analysis for recurrence.

		Entire cohort	Subcohort
Gender	Female	265	198
	Male	118	69
History of surgery	Primary	338	267
	Recurrent	45	0
WHO grade	I	331	241
	II	46	26
	III	6	0
Pathological subtype	Anaplastic	6	0
	Angiomatous	14	11
	Atypical	18	8
	Chondroid	5	3
	Clear cell	5	2
	Fibrous	66	58
	Lymphoplasmacyte rich	1	0
	Meningothelial	117	74
	Metaplastic	1	1
	Transitional	140	100
	Microcystic	4	4
	Psammomatous	2	2
	Secretory	4	4
Tumor location	Skull base	239	148
	Non-skull base	144	119
Bone invasion	Yes	57	38
	No	326	229
Peritumoral brain edema	Yes	118	84
	No	265	183
Multiple meningiomas	Yes	24	16
	No	359	251
Tumor size	$>$ 4.3 cm	192	117
	$\leq$ 4.3 cm	191	150
Degree of resection	Simpson I	122	109
	Simpson II	132	120
	Simpson III	48	38
	Simpson IV	81	0

regions that contained potential driver genes. For genes within candidate CNV markers, the differential gene expression analysis was performed using NCBI GEO2R for the dataset GSE74385 in Gene Expression Omnibus (GEO) (29); the survival analysis for diverse tumors using the gene expression data and clinical information in The Cancer Genome Atlas (TCGA) project via the portal UALCAN (30).

Statistics

Chi-squared tests and Wilcoxon rank-sum tests were performed using *R* scripts. The two-sided significance level was set at $p \leq 0.01$, two-sided. Gene set enrichment analysis (GSEA) was performed using online tools (31), and the two-sided significance level was set at $q \leq 0.05$. Prognostic analyses were conducted using Kaplan–Meier analysis and a Cox proportional regression model. Before conducting the prognostic analysis, patients with history of surgery, or with STR, or with postoperative radiotherapy were excluded. The two-sided significance level was set at $p \leq 0.05$.

RESULTS

Patient Characteristics

A total of 383 meningioma patients were enrolled in this study, with the female-to-male ratio at 2.24 (265:118), consistent with previous observation. Their average age was 49 years old (18 to 81 years old). According to the 2016 WHO meningioma grading classification, meningiomas of WHO grade I accounted for 86% (331/383) of tumors, among which 89 were from male patients. Meningiomas of WHO grade II constituted 12% (19 in females compared with 27 in males) of tumors, while meningiomas of grade III were only 1.6%, with 4 from females and 2 from males. The median of tumor diameter was 4.30 cm, and 239 meningiomas located in the skull base. In all, 338 patients had primary meningiomas and 45 patients suffered from tumor recurrence. GTR was achieved in 302 patients and STR in 81 patients; meanwhile, 118 patients had peritumoral brain edema, and 57 had bone invasion. For the pathological subtypes of these meningiomas, there were 140 transitional, 117 meningothelial, 66 fibrous, 18 atypical, 14 angiomatous, 6 anaplastic, 5 chondroid, 5 clear cell, and 12 other types. The summarized clinicopathological features are shown in **Table 1**.

Landscape of CNVs in Meningiomas

A total of 9,821 high-confidence CNVs were identified, and each sample had 26 CNVs on average, including 6,416 gains and 3,405 losses (detailed information for each CNV, **Table S1**). Their sizes ranged from 298 bp to 198 Mb, with 6,722 over 500 kb and 2,869 over 5 Mb. According to MCRs covered by diverse CNVs (Materials and Methods), we identified 36 common losses (39 kb to 79 Mb) in 27 chromosomes and 28 common gains (2 kb to 20 Mb) in 23 chromosomes in these 383 meningiomas (**Figure 1** and **Table 2**). Copy-number losses (CNLs) were most likely to occur in 22q13.2 (31%), followed by 14q11.2 (29%). Moreover, chromosome 1 was also likely to lose fragments of its short arm, with three common losses of 1p34.3 (21%), 1p31.3 (19%), and 1p22.1 (16%). In comparison, copy-number gains (CNGs) were frequently detected at 22q11.1 (35%), 15q22.2 (16%), 14q11.2 (14%), 10q23.31 (14%), 8p11.22 (14%), and 7p12.3 (14%).

Particularly, four CNLs at 1p22.1, 8p11.22, 14q32.2, and 22q13.2 were more common in non-skull-base meningiomas, and a CNG at 22q11.1 more frequently occurred in skull-base meningiomas (**Figure 2**). These CNVs commonly led to the deletion of 737 genes and the amplification of 146 genes. Pathways over-represented by deleted genes were G2M checkpoint, IL6 JAK STAT3 signaling, TNFA signaling via NFKB, epithelial–mesenchymal transition, inflammatory response, and KRAS signaling (GSEA, Materials and Methods, **Table S1**).

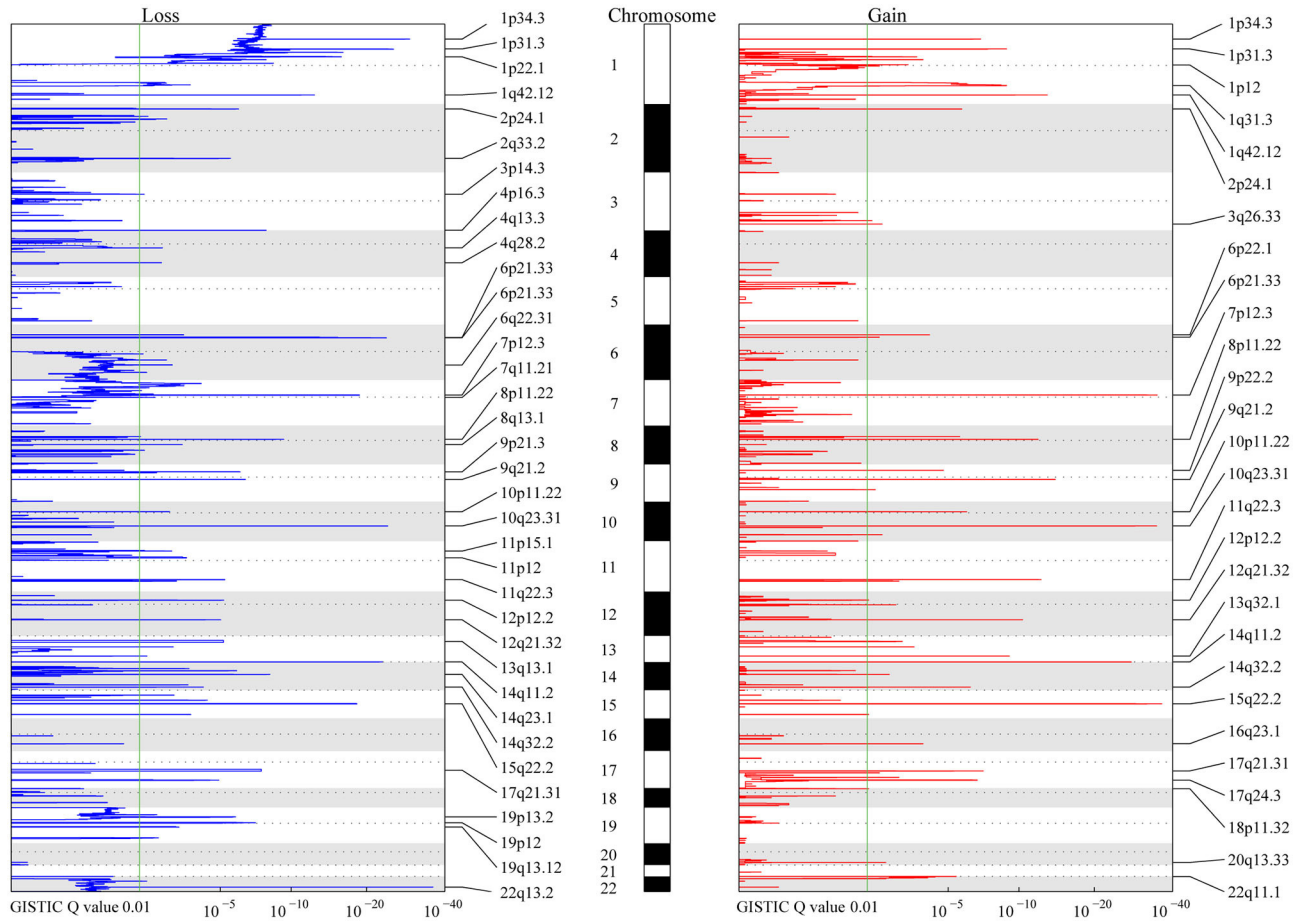


FIGURE 1 | MCR Profiling of CNVs in meningiomas. The peaks in red and blue represent consistent regions of gains and losses in meningiomas based on Genomic Identification of Significant Targets in Cancer (GISTIC), respectively. The GISTIC *Q*-value is shown at the bottom. The green lines indicate the *Q*-value (0.01) considered significant in the analysis. Chromosomes are shown in the middle with odd-numbered chromosomes as white and even-numbered chromosomes as gray.

High CNV Burdens in Either WHO Grade II and III Meningiomas or Recurrent Lesions Featured by Large CNVs Over 500 kb

In the grade I meningiomas, 331 samples had 7,416 CNVs (22 per sample); in the 46 grade II meningiomas, there were 2,048 CNVs (45 per sample); and 6 grade III meningiomas had 357 CNVs (60 per sample). Therefore, the number of CNVs was similar in grade II and grade III meningiomas (II and III together defined as high grade, $p = 0.374$, Wilcoxon rank-sum test), which was significantly higher than that in grade I ($p = 8.61 \times 10^{-4}$ and 6.74×10^{-3}, respectively, Wilcoxon rank-sum tests, **Figure 3A**). Moreover, the size of CNVs in high-grade meningioma was larger. The CNVs at 500–1,000 kb (5 vs. 6 vs. 2), 1–5 Mb (14 vs. 21 vs. 6), and >5 Mb (14 vs. 21 vs. 6) were more common in high-grade meningiomas than in grade I ($P < 0.01$, Wilcoxon rank-sum tests). Meanwhile, meningiomas at three grades had similar number of small CNVs (<500 kb) (grade I, 8; grade II, 11; and grade III, 11). Overall, large CNVs contributed to the higher CNV burden in WHO grade II and III meningiomas. In all, we found 15 common CNVs with differential incidences among different grades of meningiomas (**Table 3**). Interestingly, two CNLs at 4q13.3 and 6q22.31, both larger than 19 Mb, were most commonly observed in high-grade samples ($P = 4.01 \times 10^{-7}$, 4.05×10^{-10}, respectively, Chi-square tests). A CNL at 4q13.3 covered 104 genes, which were over-represented in pathways including inflammatory response, IL6 JAK STAT3 signaling, TNFA signaling via NFKB, epithelial–mesenchymal transition, KRAS signaling up, and angiogenesis (**Table S1**). For 397 genes affected by the CNL at 6q22.31, the enriched pathways were Hypoxia, IL2 STAT5 signaling, and androgen response (**Table S1**).

Recurrent meningiomas had significantly more CNVs (39 per sample) than primary ones (24 per sample, $p = 2.08 \times 10^{-3}$, Wilcoxon rank-sum test, **Figure 3B**). Meanwhile, recurrent lesions also had more CNVs over 500 kb (31 vs. 16, $p = 3.03 \times 10^{-4}$, Wilcoxon rank-sum test). Among seven common CNVs differentially distributed between recurrent and primary meningiomas ($P < 0.01$, chi-squared tests, **Table 3**), four CNVs of 1p31.3, 6q22.31, 9p21.3, and 11p12 were over 500 kb. Chromosome fragment losses at

TABLE 2 | List of MCRs of CNVs in meningiomas.

Cytoband	CNV	Boundaries	Size (kb)	Number of genes	Frequency (%)
1p12	Gain	chr1:117631472–121239762	3,608	29	2.87
1p31.3	Gain	chr1:62921155–63282308	361	3	10.44
1p34.3	Gain	chr1:35453772–35870648	417	4	10.44
1q31.3	Gain	chr1:196525315–199864159	3,339	22	11.75
1q42.12	Gain	chr1:225137135–225458504	321	1	12.01
2p24.1	Gain	chr2:20078572–20173435	95	3	6.01
3q26.33	Gain	chr3:180322742–180397085	74	2	4.96
6p21.33	Gain	chr6:31237665–31322196	85	2	8.09
6p22.1	Gain	chr6:29910981–29913077	2	1	6.79
7p12.3	Gain	chr7:48313001–48318810	6	1	13.58
8p11.22	Gain	chr8:38971607–39678651	707	6	13.58
9p22.2	Gain	chr9:17269438–17484335	215	1	6.27
9q21.2	Gain	chr9:79827895–80010024	182	1	9.66
10p11.22	Gain	chr10:32740815–33165314	424	1	5.22
10q23.31	Gain	chr10:91469746–91505720	36	1	13.58
11q22.3	Gain	chr11:103004336–103153757	149	1	10.70
12p12.2	Gain	chr12:21011481–21417898	406	4	11.23
12q21.32	Gain	chr12:88465703–88566416	101	3	12.01
13q32.1	Gain	chr13:96506648–96705463	199	1	10.70
14q11.2	Gain	chr14:1–20425050	20,425	16	13.58
14q32.2	Gain	chr14:96756059–96813532	57	1	7.05
15q22.2	Gain	chr15:62202415–62332979	131	1	16.45
16q23.1	Gain	chr16:75766089–76806431	1,040	1	6.27
17q21.31	Gain	chr17:41256213–41276031	20	1	11.75
17q24.3	Gain	chr17:66878095–67324998	447	7	10.97
18p11.32	Gain	chr18:2533131–2831495	298	4	7.83
20q13.33	Gain	chr20:58405221–58519202	114	4	8.09
22q11.1	Gain	chr22:1–18300886	18,301	27	35.25
1p22.1	Loss	chr1:93620394–94027864	407	4	15.67
1p31.3	Loss	chr1:62767954–63632517	865	4	19.06
1p34.3	Loss	chr1:35444038–35900519	456	5	20.63
1q42.12	Loss	chr1:224916594–225590674	674	1	11.75
2p24.1	Loss	chr2:20076455–20197016	121	2	6.27
2q33.2	Loss	chr2:203621938–204193687	572	5	10.18
3p14.3	Loss	chr3:57187079–57994564	807	8	5.22
4p16.3	Loss	chr4:1–493146	493	8	9.66
4q13.3	Loss	chr4:58064465–77139509	19,075	104	7.83
4q28.2	Loss	chr4:128748468–129193525	445	4	8.88
6p21.33	Loss	chr6:31324926–31467364	142	3	11.75
6p21.33	Loss	chr6:31239830–31368124	128	1	10.18
6q22.31	Loss	chr6:73934060–152442820	78,509	397	7.05
7p12.3	Loss	chr7:48147076–48981328	834	2	7.05
7q11.21	Loss	chr7:57531190–64451645	6,920	19	7.57
8p11.22	Loss	chr8:39142265–39771450	629	5	15.14
8q13.1	Loss	chr8:67577141–68113721	537	11	6.79
9p21.3	Loss	chr9:21865843–22447070	581	4	4.44
9q21.2	Loss	chr9:79783752–80039005	255	2	9.66
10p11.22	Loss	chr10:32634973–33190566	556	1	4.96
10q23.31	Loss	chr10:91405045–91592197	187	2	15.14
11p12	Loss	chr11:36680720–43605303	6,925	7	5.22

(Continued)

TABLE 2 | Continued

Cytoband	CNV	Boundaries	Size (kb)	Number of genes	Frequency (%)
11p15.1	Loss	chr11:17062455–17408024	346	5	6.79
11q22.3	Loss	chr11:102935067–103734644	800	2	9.66
12p12.2	Loss	chr12:21069809–21417617	348	2	12.27
12q21.32	Loss	chr12:88439501–88890670	451	2	11.23
13q13.1	Loss	chr13:32886039–32977098	91	1	17.23
14q11.2	Loss	chr14:1–20443750	20,444	16	28.98
14q23.1	Loss	chr14:58734239–59101447	367	4	14.10
14q32.2	Loss	chr14:96731074–96846091	115	1	12.01
15q22.2	Loss	chr15:61509172–62359861	851	1	15.14
17q21.31	Loss	chr17:41180695–41278115	97	1	4.96
19p12	Loss	chr19:19906363–23958291	4,052	42	12.53
19p13.2	Loss	chr19:11842324–12757476	915	25	10.44
19q13.12	Loss	chr19:36950172–38319896	1,370	34	8.36
22q13.2	Loss	chr22:42518427–42557362	39	2	30.55

MCRs, minimal common regions.

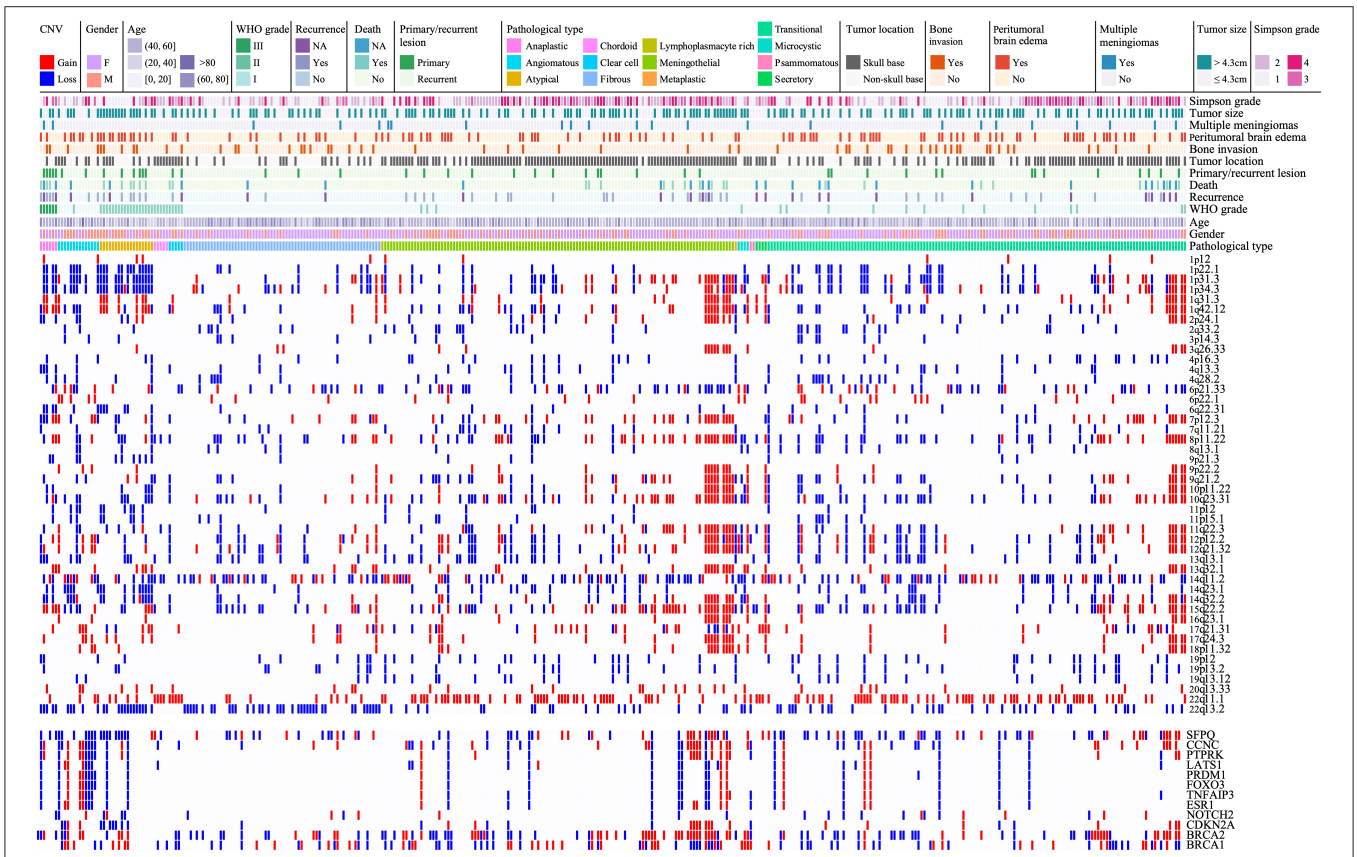


FIGURE 2 | Landscape of CNVs in meningiomas. The solid bar in the same column represents a single MCR of a CNV with colors of red for gain, blue for loss, and white for normal. Different clinical information is represented at the top, which includes gender, age, WHO grade, death state, recurrent state, primary/recurrent lesions, pathology subtype, tumor location (skull base and non-skull base), bone invasion, peritumoral brain edema, multiple lesions, tumor size (>4.3 cm), and Simpson grade with colors as shown in the figure legends.

these sites were more common in recurrent meningiomas. For disrupted genes in each site (Sheet 3, **Table S1**), 6q22.31 covers nearly 400 genes. Other sites have much less genes affected, including four genes in 1p31.3 (*USP1*, *ANGPTL3*, *ATG4C*, and *DOCK7*), four in 9p21.3 (*CDKN2A*, *CDKN2B*, *C9orf53*, and *CDKN2B-AS1*), and seven in 11p12

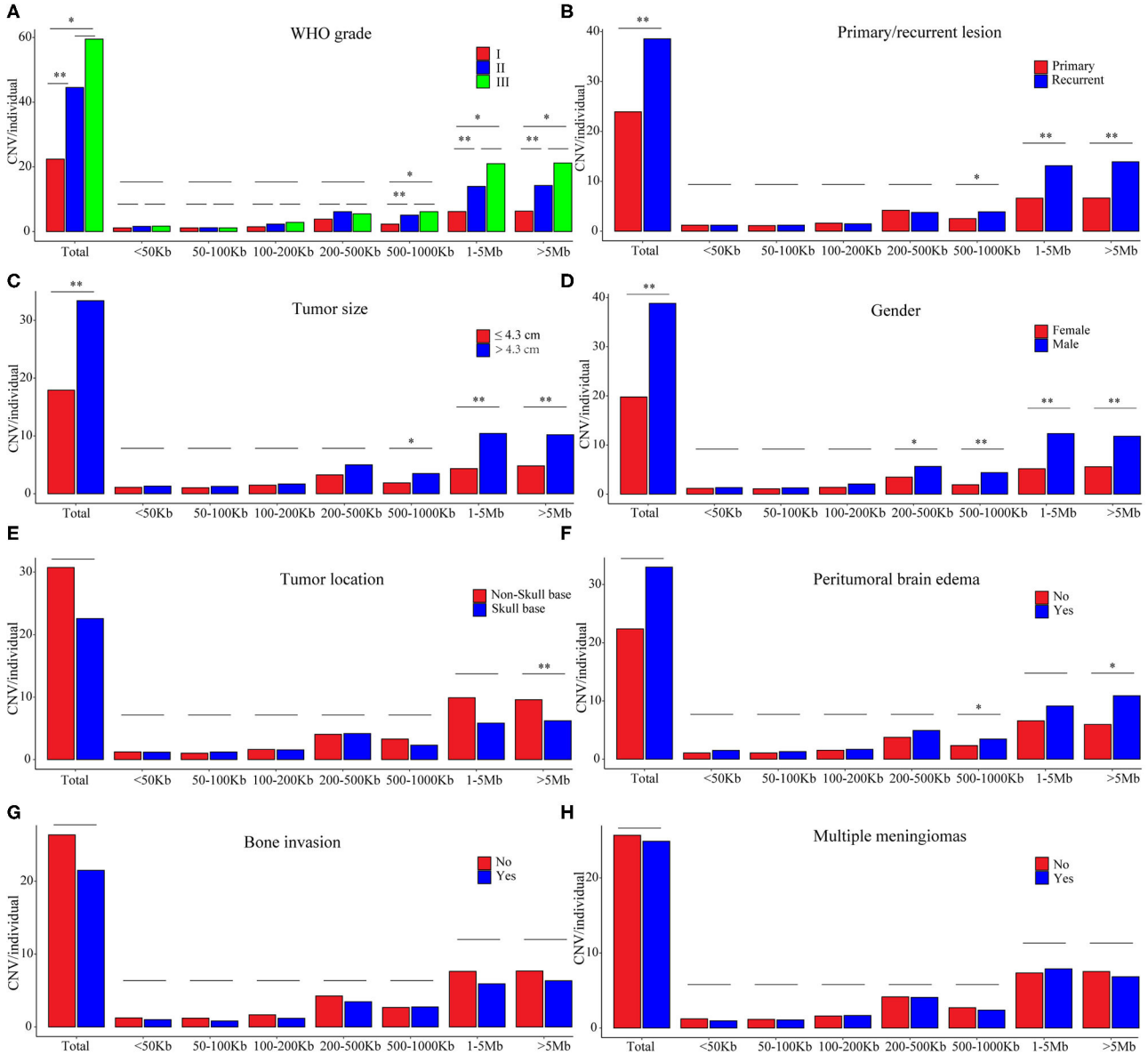


FIGURE 3 | CNV burdens in meningiomas with different clinical features. *P*-values were calculated with Wilcoxon rank-sum test at each size range. $^{*}P < 0.01$; $^{**}P < 0.001$. **(A)** Average number of CNVs in meningiomas of different WHO grades. **(B)** Average number of CNVs in meningiomas of primary and recurrent lesions. **(C)** Average number of CNVs in meningiomas of different tumor sizes. **(D)** Average number of CNVs in meningiomas of different gender. **(E)** Average number of CNVs in meningiomas of different positions. **(F)** Average number of CNVs in meningiomas with or without peritumoral brain edema. **(G)** Average number of CNVs in meningiomas with or without brain edema. **(H)** Average number of CNVs in single or multiple lesions.

(*API5*, *TTC17*, *LRRC4C*, *HNRNPKP3*, *MIR129-2*, *MIR670*, and *LOC100507205*).

High CNV Burdens in Meningiomas of Large Diameter and Male Patients

According to the median of tumor diameter (4.30 cm), we grouped these tumors into large (>4.3 cm) and small groups (≤4.3 cm). The large group had 191 samples with 33 CNVs on average, significantly higher than the observation in the small group (192 samples with 18 CNVs on average, $P = 7.51 \times 10^{-4}$, Wilcoxon rank-sum test, **Figure 3C**). Besides, large meningiomas also had more CNVs over 500 kb (24 vs. 11, $p = 4.84 \times 10^{-4}$, Wilcoxon rank-sum test). Large lesions had more CNVs of 1p31.3 and 1p34.3, and only one CNV, either loss or gain, was over 500 kb locating at 1p31.3 (four genes affected, **Table S1**).

Meningiomas from male patients had significantly more CNVs (118 samples, 39 CNVs on average) than those in female patients (265 samples, 20 CNVs on average; $p = 4.11 \times 10^{-6}$, Wilcoxon rank-sum test, **Figure 3D**). Moreover, these CNVs in male samples were larger, more of which were over 200 kb (male:

TABLE 3 | MCRs of CNVs differently distributed in meningiomas of different WHO grade, history of surgery, and tumor size.

Cytoband	CNV	WHO grade			*P*	History of surgery		*P*	Tumor size		*P*
		I	II	III		Primary	Recurrent		Small	Large	
1p22.1					$9.42 \times 10^{-7**}$			$1.75 \times 10^{-6**}$			
	Loss	40	16	4		42	18				
	No change	291	30	2		296	27				
1p31.3					$1.90 \times 10^{-5**}$			$3.38 \times 10^{-6**}$			$2.10 \times 10^{-3*}$
	Loss	50	19	4		52	21		26	47	
	No change	244	24	2		249	21		151	119	
	Gain	37	3	0		37	3		15	25	
1p34.3					$9.30 \times 10^{-5**}$			$3.50 \times 10^{-7**}$			$9.65 \times 10^{-6**}$
	Loss	56	18	4		55	23		25	53	
	No change	243	21	2		247	19		155	111	
	Gain	32	7	0		36	3		12	27	
1q31.3					$2.20 \times 10^{-4**}$						
	No change	300	35	3							
	Gain	31	11	3							
1q42.12					$7.64 \times 10^{-6**}$						
	Loss	36	8	1							
	No change	264	27	1							
	Gain	31	11	4							
2p24.1					$1.88 \times 10^{-4**}$						
	Loss	19	2	3							
	No change	294	39	3							
	Gain	18	5	0							
4q13.3					$4.01 \times 10^{-7**}$						
	Loss	22	4	4							
	No change	309	42	2							
6q22.31					$4.05 \times 10^{-10**}$			$2.31 \times 10^{-5**}$			
	Loss	15	8	4		17	10				
	No change	316	38	2		321	35				
7p12.3					$3.49 \times 10^{-5**}$						
	Loss	18	6	3							
	No change	266	37	1							
	Gain	47	3	2							
9p21.3					$1.55 \times 10^{-5**}$			$1.16 \times 10^{-4**}$			
	Loss	9	6	2		10	7				
	No change	322	40	4		328	38				
10p11.22					$4.48 \times 10^{-3*}$						
	Loss	12	5	2							
	No change	301	39	4							
	Gain	18	2	0							
11p12					$1.86 \times 10^{-3*}$			$9.10 \times 10^{-4**}$			
	Loss	12	7	1		13	7				
	No change	319	39	5		325	38				
14q23.1					$4.00 \times 10^{-3*}$			$2.00 \times 10^{-3*}$			
	Loss	39	13	2		41	13				
	No change	292	33	4		297	32				
14q32.2					$2.44 \times 10^{-5**}$						
	Loss	29	14	3							
	No change	277	30	3							
	Gain	25	2	0							
22q13.2					$7.92 \times 10^{-4**}$						
	Loss	91	21	5							
	No change	240	25	1							

*MCRs, minimal common regions. P-values were calculated with chi-square tests. *P < 0.01; **P < 0.001. WHO grade was in accordance with 2016 WHO classification of meningiomas. Tumor size was dichotomized at median value of 4.30 cm. CNV, copy-number variation.*

34 vs. female: 16, $p = 3 \times 10^{-6}$, Wilcoxon rank-sum test). Seven common CNVs showed significant gender difference ($P < 0.01$, chi-squared tests, **Table 4**). Five out of them were over 200 kb including the CNVs of 1p22.1, 1p31.3, 1p34.3, 14q23.1, and 19p12. The CNLs at these sites were more common in meningiomas from male patients. For genes affected by these

TABLE 4 | MCRs of CNVs differently distributed in meningiomas of different gender, tumor location, and with or without peritumoral brain edema.

Cytoband	CNV	Gender		*P*	Tumor location		*P*	PBE		*P*
		F	M		Non-skull base	Skull base		No	Yes	
1p22.1				$4.55 \times 10^{-4**}$			$2.00 \times 10^{-3*}$			$1.37 \times 10^{-3*}$
	Loss	30	30		33	27		31	29	
	No change	235	88		111	212		234	89	
1p31.3				$6.98 \times 10^{-4**}$						
	Loss	37	36							
	No change	198	72							
	Gain	30	10							
1p34.3				$1.38 \times 10^{-5**}$						
	Loss	37	41							
	No change	201	65							
	Gain	27	12							
4p16.3										$4.41 \times 10^{-3*}$
	Loss							18	19	
	No change							247	99	
6p21.33				$1.77 \times 10^{-3*}$						
	Loss	50	20							
	No change	204	81							
	Gain	11	17							
8p11.22							$2.20 \times 10^{-3*}$			
	Loss				28	30				
	No change				107	166				
	Gain				9	43				
9p21.3										$1.96 \times 10^{-3*}$
	Loss							6	11	
	No change							259	107	
14q23.1				$5.23 \times 10^{-9**}$						$7.83 \times 10^{-3*}$
	Loss	19	35					29	25	
	No change	246	83					236	93	
14q32.2				$1.77 \times 10^{-4**}$			$2.15 \times 10^{-4**}$			
	Loss	20	26		27	19				
	No change	223	87		114	196				
	Gain	22	5		3	24				
19p12				$6.05 \times 10^{-3*}$						
	Loss	25	23							
	No change	240	95							
20q13.33										$6.07 \times 10^{-4**}$
	No change							252	100	
	Gain							13	18	
22q11.1							$3.45 \times 10^{-5**}$			
	No change				112	136				
	Gain				32	103				
22q13.2							$4.63 \times 10^{-7**}$			
	Loss				66	51				
	No change				78	188				

MCRs, minimal common regions. P-values were calculated with chi-square tests. $^{*}P < 0.01$; $^{**}P < 0.001$. CNV, copy-number variation; M, male; F, female; PBE, peritumoral brain edema.

CNVs (**Table S1**), there were four located in 1p22.1 (*DR1*, *FNBP1L*, *CCDC18*, and *LOC100131564*), four in 1p31.3 (*USP1*, *ANGPTL3*, *ATG4C*, and *DOCK7*), four in 14q23.1 (*ARID4A*, *KIAA0586*, *TIMM9*, and *TOMM20L*), five in 1p34.3 (*SFPQ*, *ZMYM4*, *ZMYM6*, *ZMYM1*, and *ZMYM6NB*), and 42 in 19p12.

The Number of CNVs in Meningiomas Was Independent of Tumor Locations, Peritumoral Brain Edema, Bone Invasion, and Single or Multiple Lesions

Skull-base meningiomas (239 samples, 23 CNVs per sample) had a similar number of CNVs to with non-skull-base lesions (144 samples, 31 CNVs per sample; $p = 0.013$, Wilcoxon rank-sum test, **Figure 3E**). Overall, extremely large CNVs (>5 Mb) were more likely to present in non-skull-base meningiomas ($p = 7.18 \times 10^{-5}$, Wilcoxon rank-sum test). Nevertheless, a CNG at 22q11.1 of this type was preponderant in skull-base meningiomas ($p = 3.45 \times 10^{-5}$, chi-squared test, **Table 4**), affecting 27 genes in the region (**Table S1**).

TABLE 5 | The MCRs of CNVs differently distributed in meningiomas of single or multiple lesions.

Cytoband	CNV	Meningiomas		*P*
		Single	Multiple	
10q23.31				3.49×10^{-3}*
	Loss	58	0	
	No change	257	16	
	Gain	44	8	

*MCRs, minimal common regions. P-values were calculated with chi-square tests. *P < 0.01. CNV, copy-number variation.*

Patients present with peritumoral brain edema (118 samples, 33 CNVs on average) showed no significantly difference in number of CNVs with those without (265 samples, 22 CNVs on average; $P > 0.01$, Wilcoxon rank-sum test, **Figure 3F**). However, more large CNVs (500 kb−1 Mb and >5 Mb) were observed in meningiomas with peritumoral brain edema ($P = 3.48 \times 10^{-3}$, 5.29×10^{-3}, respectively, Wilcoxon rank-sum tests). The featured one with most significance located at 9p21.3, which was a CNL covering four genes (*CDKN2A*, *CDKN2B*, *C9orf53*, and *CDKN2B-AS1*) ($p = 1.96 \times 10^{-3}$, chi-square test; **Table 4** and **Table S1**).

In tumors with or without bone invasions ($P = 0.597$) or single or multiple lesions ($P = 0.869$), the CNV burdens were similar (Wilcoxon rank-sum tests; **Figures 3G,H**). No CNVs were more prevalent in meningiomas with bone invasions. Nevertheless, a CNG at 10q23.31 had a higher incidence in multiple lesions (multiple, 33% vs. single, 12%; $p = 3.49 \times 10^{-3}$, chi-squared test, **Table 5**), which only covers one gene *KIF20B*.

Identification of Independently Significant Prognostic CNVs in Predicting Tumor Recurrence

Based on common CNVs, we tried to predict the tumor recurrence. After excluding patients with recurrent lesions, with subtotal resection, or having postoperative radiotherapy, 267 patients were included for further prognostic analysis, and the detailed clinicopathological features of this subcohort are shown in **Table 1**. In the follow-up (mean period, 60 months), 12 patients suffered from tumor recurrence. All common CNV regions and clinical features were included in univariate Cox analysis of tumor recurrence. As shown in **Table 6**, skull-base lesions ($p = 0.040$), loss of 1p22.1 ($p = 0.039$), 1p34.3 ($p = 0.024$), 4q13.3 ($p = 0.029$), 4p16.3 ($p = 0.001$), 7q11.21 ($p = 0.015$), 10p11.22 ($p = 0.003$), 14q23.1 ($p = 0.032$), 19q13.12 ($p = 0.013$), and 19p12 ($p = 0.01$) were significant risk factors

TABLE 6 | Significant factors for tumor recurrence of meningiomas in subcohort for prognostic analysis.

	Risk factor		P	HR	95% CI	
Univariate cox analysis						
Tumor location	skull base	Yes vs. no	0.040	4.99	1.08	23.11
1p22.1	Loss	Yes vs. no	0.039	3.65	1.07	12.47
1p34.3	Loss	Yes vs. no	0.024	3.92	1.20	12.85
4q13.3	Loss	Yes vs. no	0.029	4.38	1.16	16.51
4p16.3	Loss	Yes vs. no	0.001	7.96	2.33	27.22
7q11.21	Loss	Yes vs. no	0.015	5.18	1.37	19.52
10p11.22	Loss	Yes vs. no	0.003	7.48	1.98	28.20
14q23.1	Loss	Yes vs. no	0.032	3.83	1.12	13.09
19q13.12	Loss	Yes vs. no	0.013	5.39	1.43	20.33
19p12	Loss	Yes vs. no	0.010	5.05	1.48	17.26
Multivariate cox analysis						
4p16.3	Loss	Yes vs. no	0.009	5.69	1.53	21.13
10p11.22	Loss	Yes vs. no	0.037	4.53	1.10	18.67

HR, hazard ratio; CI, confidence interval.

for tumor recurrence. In particular, most significant independent risk factors for recurrence were loss of 4p16.3 ($p = 0.009$, HR = 5.69, multivariate Cox analysis) and 10p11.22 ($p = 0.037$, HR = 4.53). As shown in **Figure 4,** patients with losses of both 4p16.3 and 10p11.22 were more likely to suffer from tumor recurrence than patients with loss of either one, or patients with neither of these CNV changes. Calculated by Cox analysis, the hazard ratio (HR) increased by 5.10 (95% CI: 2.35–11.08, $p = 3.7 \times 10^{-5}$) for each additional prognostic CNV.

Eight genes located within these two CNLs: *ZNF141*, *ABCA11P*, *ZNF595*, *ZNF721*, *ZNF718*, *ZNF876P*, *ZNF732* in 4p16.3, and *CCDC7* in 10p11.22 (**Table S1**). In differential gene expression analysis between non-recurrent (grade I, 13 and grade II, 6) and recurrent (grade I, 7 and grade II, 8) lesions in a public gene expression dataset of meningioma (Method), *ZNF141* and *ZNF595* showed the tendency to have lower expression levels in recurrent samples (unadjusted $p < 0.05$, **Table S1**). We further examined the effects of expression levels of these eight genes on survival time for 31 tumor types in TCGA (Method) and identified 28 associations with significance ($p < 0.05$, **Figure S1**). All of these genes had lower expression levels in certain tumor types from patients with shorter survival, which indicated their decreased functions related to malignant phenotypes. Particularly, most of these genes (five out of eight) had the same effects on patient survival in head and neck squamous cell carcinoma (HNSC), and the low expression of *ZNF718* ($p = 0.0027$), *CCDC7* ($p = 0.01$), *ZNF141* ($p = 0.012$), *ZNF721* ($p = 0.029$), and *ZNF732* ($p = 0.045$) all demonstrated significant associations with the shorter survival of patients.

DISCUSSION

In the present study, we clarified the CNV characteristics of cranial meningiomas in 383 Chinese patients. Particularly, we compared the CNV burdens of meningiomas in diverse phenotypes. We found more CNVs in the samples of high-grades, recurrent lesions, tumor diameter over 4.3 cm, and samples from male patients. Meanwhile, CNV burden may not relate to tumor locations, peritumoral brain edema, bone invasion, and multiple lesions. Moreover, we also identified featured CNVs in each clinical group. Besides, we found two candidates as independent prognostic CNVs in predicting tumor recurrence.

Based on a relatively large cohort of cranial meningiomas, we observed that CNVs of 22q (61%), 14q (54%), and 1p (38%) were the most prevalent, followed by 15q (32%), 6p (30%), 8p (29%), 10q (29%), and 1q (25%). In previous studies, CNVs of 22q, 14q, and 1p are always among the

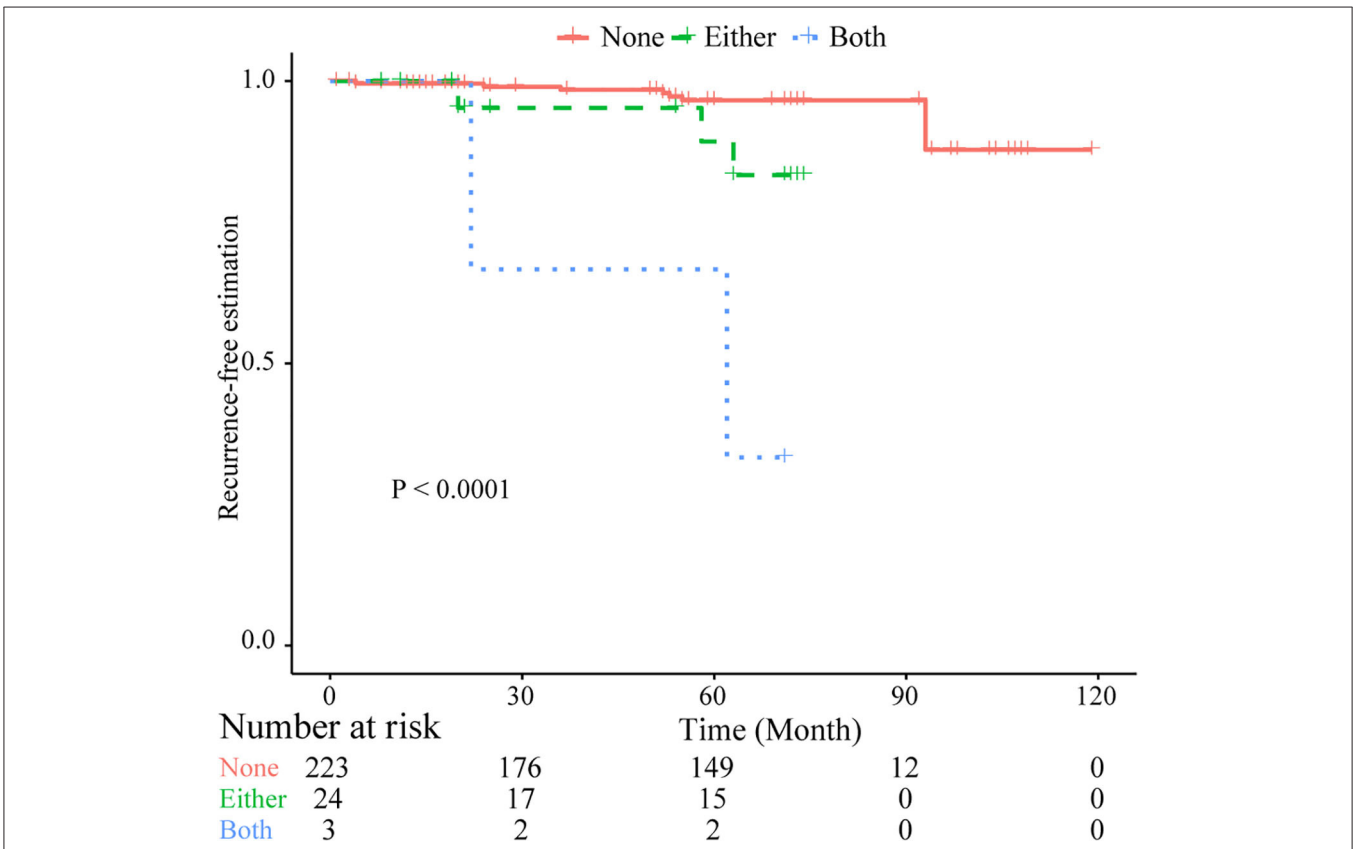


FIGURE 4 | Kaplan–Meier plots of combined losses involving the CNLs at 4p16.3 and 10p11.22 as risk factor of tumor recurrence. Log-rank test was used. Both, with CNLs identified at both sites; Either, with CNLs identified at only one of two sites; None, no CNLs at both sites.

most frequent CNVs of meningiomas (7, 10, 12, 14, 15, 24, 32), which is in accordance with our observation. For instance, a recent study reported the top three CNVs in their samples located at 1p (71%), 22q (64%), and 14q (42%) (14). By far, no differences were noted among different ethnic groups.

The CNVs frequently identified in patients with distinct clinical features hold clues for further functional studies. For instance, two CNLs of 1p31.3 and 1p34.3, commonly seen in meningiomas of high-grade and recurrent or large lesions, contain a lot of genes with functional importance. At 1p34.3, the *SFPQ* gene participates in transcriptional regulation, DNA double-strand break repairs, and suppression of RNA:DNA-hybrid-related telomere instability (33, 34). At 1p31.3, the *USP1* gene, involved in multiple DNA repair pathways, can function as a key senescence regulator controlling genomic integrity (35); autophagy protein *ATG4C* participates in controlling the unregulated cell growth (36). Reduced levels of autophagy have been described as being linked to malignant tumors (37). Functional changes related to these genes may also contribute to the progression of meningiomas, which needs further studies for validation.

The CNG at 10q23.31 was the only CNV more commonly seen in multiple meningiomas rather than in single lesions. It covers only one gene, *KIF20B*, an oncogene involved in cytokinesis. A recent study suggested to target the *KIF20B* gene in the treatment for hepatocellular carcinoma (38). Inhibition of KIF20B can block mitosis at both metaphase and telophase, which enhance the cytotoxicity of two chemotherapeutic drugs, hydroxycamptothecin, and mitomycin C (39). The role of *KIF20B* in tumorigenesis of meningiomas, especially multiple lesions, suggests that its suppression might be a novel strategy in the treatment for multiple meningiomas in the future. Moreover, the CNG at 6p21.33, more frequently found in lesions from male patients, is where *HLA-B* and *HLA-C* are located, indicating the existence of immune factors underlying gender difference of meningioma occurrence; the CNG at 20q13.33, more frequently identified in patients with peritumoral brain edema, covers the *SYCP2* gene, which is related to the depth of cervical invasion in squamous cell carcinoma (40).

Tumor recurrence is an important issue for patients with meningiomas, and patients with meningiomas prone to recurrence need adjuvant radiation therapy or close follow-up. Meanwhile, patients with low risk of tumor recurrence could be spared from the toxicity of radiation therapy. Nevertheless, these patients are not accurately identified by WHO grading (41). Here, we demonstrated the potential of CNV profiling in recurrence prediction. Loss of 1, 4, 9, and 10p and gain of 1q or other chromosomal regions have been revealed to be risk factors for tumor recurrence in previous studies (7–11, 14, 21, 24). In our observation, the CNLs of 4p16.3 and 10p11.22 were independent risk factors for cranial meningioma recurrence. The CNL of 4p16.3 covers MiR-571, *ABCA11P*, *ZNF141*, *ZNF595*, *ZNF718*, *ZNF721*, *ZNF732*, and *ZNF876P*. A recent study identified miR-571 as the first miRNA that prevents aberrant DNA replication, and the *Cdk2-c-Myc*-miR-571 axis was identified as a new pathway for regulating DNA replication, cell cycle, and genomic stability in cancer cells (42). As a result, loss of miR-571 may lead to genomic instability. Although some studies have reported differential expression or mutation occurrence of *ZNF595* (43), *ZNF721* (44), *ZNF718* (45), and *ZNF141* (46), their functions remain unclear. Besides, potential roles of *ABCA11P*, *ZNF732*, and *ZNF876P* are novel in meningioma recurrence. In the 10p11.22, CCDC7, also known as Biot2, highly expressed in CD133-positive stem cells, functions as a risk factor for poor prognosis in colorectal cancer (47, 48). In our study, the CNL at 10p11.22 (*CCDC7*) was an independent risk factor of tumor recurrence, and the underlying mechanisms need further investigation.

The cross-sectional analysis in the entire cohort compared primary and recurrent lesions from different groups of patients, and some primary tumors may also harbor CNVs contributing to tumor recurrence. It may undermine the ability to identify CNVs related to recurrence, which may explain the missing of the CNLs of 4p16.3 and 10p11.22 in the comparison. Meanwhile, the comparison results may be cofounded by differential CNVs present in the early stage of tumor development between two groups of patients. Therefore, the follow-up study provides us an opportunity to identify those CNVs related to recurrence. The recurrence rates of patients with these two CNVs were over 20% (loss of 4p16.3, 21%, 4/19; loss of 10p11.22, 27%, 3/11), significantly higher than the recurrent rate (about 4%) in patients without them. Nevertheless, only 12 patients (4.5%, 12/267) had tumor recurrence during a mean follow-up period of 5 years in our subcohort for prognostic analysis. Although it is similar to previous observation, which is 3% for WHO grade I meningiomas and 30% for WHO grade II meningiomas in GTR patients (28), the prediction power of these two candidate markers requires further evaluation in a larger group of patients with tumor recurrence in the future follow-up. Besides, the recurrence factors may have heterogeneity, and 4p16.3 and 10p11.22 together accounted for the 13% (loss of 4p16.3, 4/45; loss of 10p11.22, 4/45, losses of both, 2/45) recurrent lesions in the cross-sectional analysis. It needs further efforts to dissect other CNVs related to tumor recurrence.

CONCLUSIONS

Based on a large number of patients with cranial meningiomas, we identified that the CNVs of 22q, 1p, and 14q were the most prevalent. Meningiomas of high WHO grades, recurrent tumors, large size, and male gender were likely to have more CNVs, especially of large size (>500 kB). Additionally, the CNLs at 4p16.3 and 10p11.22 were promising candidates as independent risk factors for tumor recurrence prediction.

DATA AVAILABILITY STATEMENT

The datasets in this study have been publicly deposited. They can be accessed at: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE147673.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Beijing Tiantan Hospital Affiliated with Capital Medical University. Signed informed consent forms were acquired from all patients or their guardians.

AUTHOR CONTRIBUTIONS

LW, DZ, JM, YH, ZW, JZ, LZ, and WC designed this study. JM, YH, KT, DL, KW, YY, and JD conducted the experiments and acquired data. JM, YZ, YC, LS, and LC conducted the follow-up and acquired data. JM and YH analyzed and interpreted data. JM, YH, KT, DL, KW, YY, JD, YZ, YC, LS, and LC drafted the manuscript. LW, DZ, ZW, JZ, WC, and LZ revised the manuscript. All authors have seen and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.01382/full#supplementary-material

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REVIEW
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An Overview of Managements in Meningiomas

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Meningioma is the most frequent primary tumor of the central nervous system. Important advances have been achieved in the treatment of meningioma in recent decades. Although most meningiomas are benign and have a good prognosis after surgery, clinicians often face challenges when the morphology of the tumor is complicated or the tumor is close to vital brain structures. At present, the longstanding treatment strategies of meningioma are mainly surgery and radiotherapy. The effectiveness of systemic therapy, such as chemotherapy or targeted therapy, has not been confirmed by big data series, and some clinical trials are still in progress. In this review, we summarize current treatment strategies and future research directions for meningiomas.

Keywords: meningioma, surgery, radiotherapy, stereotactic radiosurgery, target therapy

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INTRODUCTION

Meningioma is the most common central nervous system tumor originating from arachnoid cap cells. Meningioma account for about 30% of all primary intracranial tumors in adults, but are rare in children and adolescents (0.4–4.6%) (1). The total incidence of meningiomas is 83/100,000. Meningiomas are more common in women (female-biased sex ratio 2–4: 1) (2). The annual incidence of meningioma increased with age, from 0 to 19-years (0.14/100,000) to 75–84-years (37.75/100,000) (3). The median annual incidence of meningioma is lowest in African Americans (3.43 per 100,000 persons) and highest among Whites (9.52 per 100,000 persons) (4). However, the multivariate analysis results shows that African Americans are independent risk factors for relapse compared with Whites, Hispanics, and Asians (5).

Eighty to ninety percentage of meningiomas are benign (WHO grade I) and can be routinely followed up for the long term or cured by surgery and radiotherapy (2). The rest include atypical meningioma (WHO grade II) and anaplastic meningioma (WHO grade III or "malignant meningioma"), and the therapeutic effect is not satisfactory whether surgery, radiotherapy, or traditional chemotherapy is used.

The aim of this study is to review the current advancement of meningioma treatment. A comprehensive review has been made to collect all the articles related to meningioma treatment since 1993 until 2020. MEDLINE and PubMed database searches were performed. Related articles cited in the chosen studies were also investigated. We summarized the current treatment strategies of meningioma in the figure (**Figure 1**). Details of each treatment will be presented in the corresponding section.

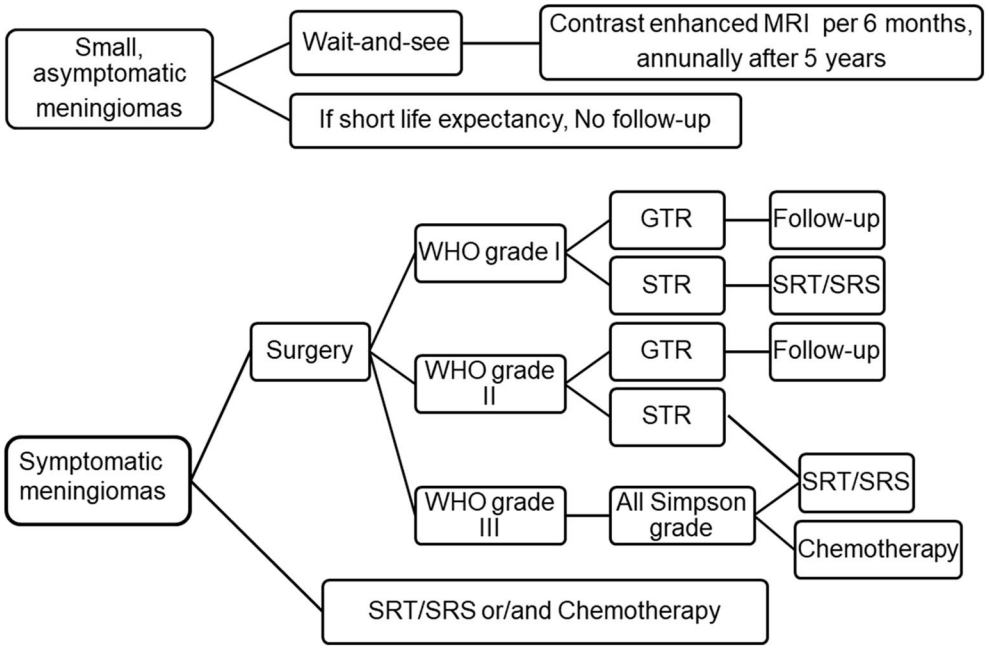


FIGURE 1 | Current treatment strategies for meningioma. For small and asymptomatic meningiomas, an strategy of "wait and see" is recommended, clinical and MRI evaluation was performed every 6 months after an initial observation. If patients do remain asymptomatic, annually after 5 years. If the patient's life expectancy is short, follow-up may not be necessary. Symptomatic meningioma should be removed to the maximum extent. Patients who are unwilling to undergo surgery, the elderly or obviously disabled can choose SRT/SRS or chemotherapy. Patients with WHO grade I meningioma were followed up after GTR, and SRT/SRS was recommended after STR. For WHO grade II meningioma, intimate follow-up is recommended after GTR, while SRT/SRS is recommended after STR. For WHO grade III meningiomas, adjuvant radiotherapy are recommended regardless of the grade of resection. Adapted from Goldbrunner et al. (6). EANO guidelines for the diagnosis and treatment of meningiomas. WHO, world health organization; GTR, gross total resection; STR, subtotal resection; SRT, stereotactic radiotherapy; SRS, stereotactic radiosurgery.

"WAIT-AND-SEE" STRATEGIES

Small (tumor diameter $\leq$3 cm), asymptomatic (few or no symptoms or signs) meningiomas can be carefully observed and followed with regular Magnetic Resonance Imaging (MRI) scans. The approach is also applicable to old patients and patients with severe complications or poor physical conditions. The European Association of Neuro-Oncology (EANO) suggests that for asymptomatic or small meningioma, 6 months after the initial diagnosis, the dynamic changes in tumor should be evaluated with contrast enhanced MRI. If the patient remains asymptomatic, the patient is evaluated annually thereafter. After 5 years, this interval can be doubled. For patients with short life expectancy due to old age or severe complications, if the radiological diagnosis of benign meningioma is clear, follow-up is not required (6). However, if the tumor significantly enlarged or presents symptoms during follow-up period, active treatment is recommended. Tumor diameter $\geq$3 cm, peritumoral edema (PTE), age <60 years, lack of calcification, T2 hyperintense lesion are significantly correlated with the risk of symptom progression (7–11).

SURGERY

Surgical resection is the primary treatment choice for symptomatic meningiomas. The purpose of the operation is to relieve symptoms caused by the tumor, change the natural course of the tumor, and improve quality of life. The tumor should be removed surgically in patients with obvious mass effect and increased intracranial pressure. The factors that affect the surgical strategy are as follows: (1) surgical benefits; (2) surgical risks; (3) biological characteristics of tumor; (4) tumor mass effect or clinical symptoms; (5) subjective wishes of patients. Surgical risks were assessed based on the patient's general condition, tumor location, age, tumor size, and symptoms (2, 12). The location of the tumor is very important for the assessment of surgical risk. The surgical approach and resection of convex meningiomas are relatively simple and of low risk. The full exposure of surgical field and the careful separation of tumor capsule can protect the structure of artery and vein to the greatest extent, improve the success rate of operation of convex meningiomas, and reduce the disability rate. If the tumor is located in the olfactory sulcus, adjacent to the sagittal sinus, intraventricular, cerebellopontine angle, and falx cerebrum, the surgery has moderate risk. The removal of meningiomas involving the dural sinus, blood vessels, or cranial nerves is a great challenge for surgeons. The surgery for meningiomas originating from the clinoid process, cavernous sinus, and tuberculum sellae is of high risk (13). The petroclival area is the position where cranial nerves, cavernous sinus segment of internal carotid artery, basilar artery, superior cerebellar artery, and posterior cerebral artery converge. Tuberculum

sellae meningiomas usually involve optic nerve and anterior cerebral artery complex. These complex structures often wrap around the surface of the tumor and adhere to the tumor tightly. Therefore, special attention should be taken during the operation.

Gross total resection (GTR) of meningiomas involving cortical veins or venous sinuses may damage the venous circulation. Subtotal resection (STR) can be performed when the venous sinuses are partially unobstructed (14). At present, it is generally recommended to resect the tumor outside the superior sagittal sinus. The residual tumor may recur. Imaging follow-up or adjuvant radiosurgery may be given for the residual tumor (15). For the tumors that invade the superior sagittal sinus without affecting the patency of the sinus, it is suggested that only the tumor outside the venous sinus be removed, and then the residual tumor in the venous sinus should be followed up regularly. It is recommended to resect the tumor after radiotherapy if the tumor is enlarged during the follow-up period. If the venous sinus has been completely occluded and the vein collateral circulation has been established, the occluded venous sinus can be removed by surgery after the detailed evaluation of these collateral veins, and these formed collateral veins should be protected during the operation. Traditional experience has shown that the risk of complete removal of the invaded sinus is not high and there is no need to reconstruct the venous circulation. Some scholars claim to reconstruct the venous circulation system on the basis of total tumor resection. The reconstruction of venous sinuses has potential benefits for patients with venous compensation affected or even patients with complete occlusion of venous sinuses. However, the safety and effectiveness have not been confirmed in multicenter randomized studies. The injury of unobstructed venous sinus may be followed by cerebral infarction, intracerebral hemorrhage, visual loss, infection, and other consequences. In our experience, total removal of meningiomas invading the venous sinus should not be the ultimate goal of surgery. No matter which operation method is chosen, the anatomy and compensation of the collateral vein and the invasion of the venous sinus must be clearly understood before the operation if we want to deal with the venous sinus during the operation.

Surgery microscope, neuronavigation technology, intraoperative neurophysiological monitoring, intraoperative imaging, adaptive hybrid surgery, and cavitational ultrasonic aspirators have greatly improved the success rate of surgery. The operation of skull base meningioma is challenging. Many skull base meningiomas cannot be completely resected even if the latest surgical methods are fully utilized. Endonasal approach can reach the ventral side of the deep skull base tumor, avoid the pulling of brain tissue during the operation, which is conducive to the safe resection of lesions, and even achieve Class Simpson I resection in some patients. The endonasal approach is more suitable for the removal of small meningiomas growing beside or below the optic chiasm. The endonasal approach are not suitable for large meningiomas, asymmetric meningiomas, or meningiomas which surround major vascellum and optic nerve. The narrow and limited operation space increases the risk of operation in the key anatomical position. The blood supply of skull base meningioma mainly comes from the ventral vessels of the tumor. The dura and its surface vessels in the basal region of the tumor can be exposed preferentially by endonasal approach. Endoscopic endonasal approach can be divided into standard endoscopic endonasal approach (SEEA) and expanded endoscopic endonasal approach (EEEA). EEEA can not only avoid pulling brain tissue, but also minimize the damage of optic nerve, reduce the congestion and edema of brain tissue, and maintain the integrity of appearance.

Meningiomas of skull base suitable for endoscopic treatment include olfactory sulcus meningioma, tuberculum sellae meningioma, petroclival meningioma, foramen magnum meningioma, etc. Cerebrospinal fluid leakage (9.5%), infection (5.4%), nerve injury (4.1%), vascular injury (2.7%) is a major complications of endoscopic endonasal approach (16). Endoscopic endonasal approach should be the primary choice for tuberculum sellae meningiomas with suspected involvement of the optic canal. The tuberculum sellae meningioma often grows into the optic canal through the medial edge of the cranial opening of the optic canal, which is the main reason for postoperative recurrence. Endoscopic treatment of tumors on the ventral side of the optic canal has natural anatomical advantages. However, whether transcranial approach or endoscopic endonasal approach should be used remains controversial (17). The biggest challenge of endonasal approach is the reconstruction of skull base, especially for the wide base meningioma. The incidence of cerebrospinal fluid leakage is as high as 30% (18). At present, it is considered that the multi-layer repair method of skull base reconstruction is more effective than the single-layer repair method, the tissue patch with blood supply is more beneficial than that without blood supply. The most commonly used patch is the self nasal septum mucosa flap with vascular pedicle, which can meet the needs of reconstruction of most skull base defects and reduce the incidence of cerebrospinal fluid leakage to $<5\%$ (19). The efficacy of endonasal approach depends on many factors, including the size, growth pattern, invasion degree, and transfer status of meningioma. Strict control of indications and contraindications of endonasal approach also has a certain impact on the prognosis of the operation. Endoscopic endonasal approach may be more suitable for small meningiomas located in midline anterior cranial fossa and may improve the visual impairment caused by tumors (20). However, if meningioma is too large, surrounded by blood vessels or calcified, endoscopic endonasal approach is not recommended (21). It is generally considered that the invasion of the medial side of the optic canal or the growth of tumor to the lateral part of the optic nerve is the contraindication of the endonasal approach. Endonasal approach should not be adopted when meningioma involves internal carotid artery, anterior cerebral artery, or anterior communicating artery. In order to maintain a clear field of vision, remove the lesion to the greatest extent, and avoid the damage of key nerves and blood vessels and adjacent anatomical structures in the operation area, the skull base bone should be removed as much as possible to open up a wide operation channel. The

effect of surgery is also closely related to the professional skills of surgeons.

Up to date, there are several limited data comparing the effectiveness of endoscopic and microsurgery for meningiomas. Gaedner reported the combined use of endoscopy and microscopy in 35 cases of anterior skull base meningiomas (22). Devitiis reported the results of 51 cases of tuberculum sellae meningioma resected by transcranial approach and endoscopic surgery (23). The results of the two studies are consistent. Both believe that the early neurological complications of patients in the endoscopic endonasal approach group are lower, compared with traditional craniotomy, but the long-term recurrence rate and survival rate need to be further evaluated. More importantly, both reports indicate that the degree of resection is not affected by the approach, but by the patient's condition and tumor factors. Another study found that there was no significant difference between transcranial approach and endoscopic approach in perioperative mortality and incidence of GTR (24). The visual function of patients with tuberculum sellae meningioma improved more significantly after endoscopic surgery. However, the incidence of cerebrospinal fluid leakage after endoscopic surgery was higher than transcranial approach, olfactory groove meningiomas (25.1 vs. 10.5%) (25, 26) and tuberculum sellae meningiomas (19.3 vs. 5.81%) (17), which is almost three times of that of patients undergoing transcranial surgery. It is clear that further research is needed to determine the recurrence rate of these two methods, and with the development of endoscopy, it may be matched with craniotomy in terms of recurrence risk 1 day. We think that the choice of approach depends on the understanding of local anatomy and clinical experience of the surgeon. The imaging examination of the skull base structure before operation is helpful to know the size, location, blood supply, texture, adhesion status, and the adjacent structures such as nerves, blood vessels, and dura mater, which is very important for the choice of the approach. Combined approach, which combines the advantages of surgical microscope and endoscope, may be the future of meningioma surgery.

Meningiomas are usually resected to the maximal extent according to Simpson's criteria. The key point of the operation is to protect the normal brain tissue beside the tumor. It is difficult to completely remove tumors that are closely adhered to venous sinus or neurovascular tissue of cranial base without serious complications (27, 28). At present, STR is accepted by more and more neurosurgeons as a strategy to preserve the integrity of vein and nerve function (29).

Most meningiomas are rich in blood vessels. Selective vascular embolization is helpful to improve the GTR of skull base meningiomas, shorten the operation time, decrease the bleeding and reduce the incidence of postoperative complications. The vascular pedicle of many skull base meningiomas is located in the ventral side of the surgical approach, and the surgical channel is narrow and deep, which makes the surgical resection more difficult (30). Preoperative embolization can improve the safety of the operation and fully expose the tumor during the operation. Moreover, the ischemic necrosis and softening of tumor tissue caused by embolization can reduce the traction of peripheral nerve tissue during the operation. Therefore, vascular embolization may facilitate the completion of a surgical approach more safely. It can be used as a separate treatment for some patients who are not suitable for craniotomy, can slow down or prevent tumor growth, and can also be used as an adjuvant treatment before surgery. The safety and effectiveness of embolization alone for meningiomas have been questioned (31). For meningiomas with multiple blood supply, it is not recommended to embolize all the blood supply arteries, embolization of the primary artery is an appropriate choice. The complication of cerebral infarction is easy to appear in internal carotid artery branch embolism (32). For large meningiomas, meningiomas with blood supply mainly from the branches of the external carotid artery, or meningiomas located in difficult surgical sites with abundant blood supply, the maximum benefit may be achieved from preoperative selective embolization (31). Preoperative embolization is suggested in the following situations: complicated blood supply vessels, severe PTE affecting the identification of tumor boundary, tumor proximity to functional areas, and the dural sinus, scalp, and skull are involved (33). With the progress of interventional therapy techniques, the risk of preoperative embolization has decreased year by year. Studies have shown that the complication rate of preoperative embolization is only 2.6–12% (34, 35). Severe neurological dysfunction after preoperative embolization of meningiomas includes occlusion of distal vessels, reflux of embolic materials, bleeding, and swelling of tumors caused by occlusion of blood vessels. Therefore, the potential benefits and adverse consequences of embolization must be carefully evaluated before embolization. The incidence of hemorrhagic complications after vascular embolization is higher than that of ischemic complications (36). The deep infiltration of embolic particles and the necrosis caused by blood flow blocking make the tumor easy to bleed (36). The dissolution of granules and the remission of vasospasm may lead to ineffective reperfusion of vascular bed and aggravate the edema and swelling of tumor. Therefore, the intracranial mass effect caused by very large meningiomas may be aggravated after embolization. It is reported that the interval time between embolization and surgery ranges from 1 day to more than 1 week (37). Extending the interval between embolization and surgery may maximize the benefit of embolization. Some experts suggested that the best time for operation is 7–9 days after embolization (38). However, recanalization or collateral circulation may occur at more than 1 week after embolization. Therefore, most centers perform surgery within 7 days (37).

5-aminolevulinic acid (5-ALA) is an indirect fluorophore, which can be absorbed by tumor and converted into a fluorescent substance protoporphyrin IX (PP IX). The surgeon can directly see the fluorescence of tumor through fluorescence microscope and other equipment. 5-ALA can calibrate cancer cells, make them fluoresce, and can improve tumor resection rate. It has been applied to different types of central nervous system tumors, including ependymoma, hemangioblastoma, metastatic brain tumor, and intracranial meningioma. 5-ALA fluorescence guided tumor resection has been proved to be one of the

effective methods to improve the "gross resection rate" of high-grade gliomas (39). However, the influence of histopathological grading and previous treatment on the fluorescence ability of meningioma cells remians still unclear. The effectiveness of 5-ALA mediated Fluorescence-guided surgery for meningiomas a needs further evaluation in the future (40, 41).

The postoperative complications of meningioma include cerebral hemorrhage, infection, neurological deficit, brain edema, epilepsy, etc. The incidence of postoperative intracranial hemorrhage is about 2.6%. The mechanism includes abnormal coagulation function, small vessel injuries caused by excessive pulling of brain tissue, bleeding of surgical wound, blood pressure fluctuation post operation, or other potential diseases. The incidence of postoperative infection was 2.7%. The location of the tumor is a predictor of postoperative infection, the incidence of infection in skull base meningiomas is four times higher than that in non-skull base meningiomas. Prolonged operation time is also associated with an increased risk of infection (42). Normative surgery practice, adequate rinsing of surgical site, and prophylactic application of antibiotics can reduce the postoperative infection rate. The incidence of postoperative neurological deficits directly related to surgery is 2–30%, which depends on the location and resection range of the tumor. Meningiomas in non-functional areas are usually completely removed with minimal complications. Surgery of cranial base meningiomas may injure the cranial nerve. When the tumor invades the venous sinus, surgery may accidentally injure the superior sagittal sinus and the diploic veins, resulting in postoperative venous infarction. PTE can be seen in about 46–92% of meningiomas in different degrees. PTE can cause clinical symptoms and complicate surgery, which is closely related to poor prognosis after surgery. Preoperative PTE may be a risk indicator for poor prognosis of the elderly (43). PTE is caused by tumor compression, tumor features such as invasiveness, high histological grade, histopathology as secretory type, microcystic type and/or hemangioma type, and high expression of vascular endothelial growth factor (VEGF). Corticosterone steroid hormone is the predominant drug for the treatment of PTE. Anti-angiogenic therapy (e.g., bevacizumab) may be considered in case of poor hormone effect (44). Studies have shown that early postoperative hyperbaric oxygen therapy can significantly reduce PTE, improve Karnofsky Performance Score (KPS), and reduce the incidence of neurological dysfunction (45).

In patients with meningiomas, the rate of new seizure after surgery is about 12–19% (46). Epilepsy after meningiomas surgery may be related to meningiomas themselves or craniotomy. It has demonstrated that maximum diameter >1 cm of PTE, WHO grade II and III tumors and low-range resection (Simpson grades III-v) are independent predictors of postoperative poor seizure outcomes (47). Preventive application of antiepileptic therapy remains controversial. A recent meta-analysis shows that preventive use of anti-epileptic drugs is ineffective for meningiomas patients who have no previous history of epilepsy (48). The American Academy of Neurology recommends that patients with no previous history of epilepsy should stop prophylactic antiepileptic therapy 1 week after surgery (49). Reducing brain tissue or vascular injury during operation can reduce postoperative neurological deficits and improve seizures (50). Whether postoperative epilepsy is related to tumor STR remains controversial. Non-enzyme-induced antiepileptic drugs are recommended for patients who have experienced one or more meningioma-related seizures. Levetiracetam and gabapentin have good efficacy and tolerance for patients with persistent epilepsy.

In addition, MR-guided laser ablation therapy (MR-LITT) is one of the most promising minimally invasive surgical techniques. MR-LITT can accurately ablate meningiomas lesions and avoid damage to surrounding tissues. For patients with PTE symptoms, LITT may be a feasible alternative therapy if drug therapy is not good enough (51). However, these effects still need further randomized controlled studies to confirm.

RADIATION THERAPY

Radiation therapy (RT) is suitable for the following patients: patients diagnosed with WHO grade II or grade III meningioma; patients after STR; patients who have lost the opportunity of surgery for various reasons or have a recurrence and are not suitable for resection (52). The purpose of radiotherapy is to reduce its proliferation ability and control its progress. Fractionated radiotherapy increases the tolerance dose of important intracranial structures (such as visual pathways) and reduces the side effects of radiotherapy as much as possible. Conventional fractionated radiotherapy for STR postoperative and recurrent meningiomas can significantly improve the local tumor control rate. Unconventional fractionated radiotherapy includes hypofractionated radiotherapy and Hyperfractionated radiotherapy. There are few studies on hyperfractionated radiotherapy in the treatment of meningiomas.

With the development of computer technology, radiotherapy is more accurate and individualized. Precision radiotherapy technology includes three-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), Image guided radiotherapy (IGRT), real-time dynamic radiotherapy, etc. Stereotactic radiotherapy (SRT) is an improvement of conformal radiotherapy. SRT technology can irradiate a specific target with a large dose once, the attenuation of radiation dose outside the target area is steep, and normal tissues around the focus are not damaged. Fractionated stereotactic radiotherapy (FSRT) can reduce the exposure dose of peripheral normal brain tissue in high dose radiation. Compared with conventional radiotherapy, FSRT has similar therapeutic results. Stereotactic radiosurgery (SRS) was developed by combining radiotherapy and stereotactic. SRS is suitable for meningiomas with a maximum diameter of <3 cm and located more than 3 mm from radiosensitive structures such as optic nerve (53). Early SRS devices used only a single fractionated therapy. Current radiosurgery devices can use frameless radiosurgery techniques, allowing repeated fractionated therapy or large fractionated radiosurgery (54).

The recurrence rate of WHO grade I meningioma after GTR is relatively less, and most experts advocate that postoperative

adjuvant radiotherapy is not required. However, WHO grade I meningioma has a high recurrence rate after STR surgery. Radiotherapy is recommended if salvage total resection is not possible in the future. Grade II and III meningiomas are invasive tumors. Even after obvious Simpson I resection, the risk of recurrence is still high, reaching 30–40% and 50–80%, respectively, after 5 years (10). Therefore, in the initial treatment, surgery is often combined with radiotherapy. Radiotherapy for WHO II meningiomas remains controversial, and trials are currently underway to confirm the role of postoperative radiotherapy for completely resected WHO II meningiomas (6). For WHO III meningiomas, routine radiotherapy is recommended after surgery regardless of the surgical method. Our point of view is the potential benefits of "radiotherapy" need to be carefully weighed against the side effects of "radiotherapy" after total atypical meningioma resection. For atypical meningioma patients with STR, we recommend "radiotherapy" rather than observation. Metastasis of meningiomas is rare, if the number of metastatic meningiomas is too large to be removed completely, or the patient's physical condition is not suitable for surgery, fractionated radiotherapy can be used (55).

Tanzler et al. (56) reported that PFS of primary radiotherapy for patients with grade I meningioma for 5 and 10 years was 99% (postoperative RT was 96 and 93%). Santacroce et al. (57) reported a PFS incidence rate of 92.7% in 10 years after nearly 3,000 meningioma patients received radiotherapy alone without surgery. Pollock et al. (58) found no difference between SRS and GTR in 7-year PFS rate (both >95%). Kokubo reported a 5-year local control rate of 41% for benign meningiomas and 30% for atypical or malignant recurrent meningiomas (59). It is not clear whether the PFS after radiotherapy is related to previous surgery. In a retrospective observational study, the PFS in the radiotherapy group is superior to Simpson's 2–5 stage resections when comparing surgical resection and radiotherapy for meningiomas smaller than 35 mm in diameter.

Metellus et al. (60) reported the long-term follow-up results of 53 cases with cavernous sinus meningiomas who received conventional fractionated 3D-CRT. Twenty-eight cases (52.8%) were treated with radiotherapy alone, 25 cases (47.2%) were treated with postoperative adjuvant therapy. The average follow-up time was 6.9 years. PFS rates in 5 and 10 years were 98.1%, 95.8%, 31 cases (58.5%) were improved in clinical symptoms, 20 cases (37.7%) were stable in symptoms, 3 cases (57%) had acute radiation reaction, and 1 case (19%) had late injury. Hemmati et al. analyzed 99 patients with atypical meningioma (WHO grade II), of which 19 patients received IMRT after tumor resection and the remaining 80 patients only underwent surgical resection. The median follow-up period was 37 months. The results showed that the median PFS of patients receiving IMRT was significantly longer than that of the simple operation group (64 vs. 37 m) (61).

A retrospective study of 5,300 meningioma patients from 15 centers showed that the PFS rates of SRS in 5 and 10 years were 95.2–97% and 88.6–94%, respectively (62), and the complication rate was 6.6% (57). A review shows that the 5-year rates of gamma-knife SRS, LINAC SRS, and FRT PFS are 93.6,95.6, and 97.4%, respectively ($P = 0.32$). SRS is twice higher than FRT in tumor volume reduction rate, tumor recurrence or progression rate is 3–5.8%, and there is no statistical difference between the two methods ($p > 0.05$) (63). WHO grade and previous radiotherapy history are reliable long-term predictors of overall prognosis of gamma -knife SRS therapy (64). The overall 5-year control rate of WHO grade I meningioma patients receiving gamma knife adjuvant therapy was 93%. The total PFS rate after STR followed with SRS seems to be equivalent to GTR (65). The tumor control rates of adjuvant SRS therapy for WHO grade II and III tumors are 50 and 17%, respectively (66). For STR meningioma (Simpson Grade II-IV), the 3 and 7-year PFS rate of SRS were better than surgery (58). Adjuvant radiotherapy can improve the long-term control and overall survival of WHO grade III meningiomas. PFS increased from 28% of GTR to 57% of GTR followed by adjuvant radiotherapy at 5 years. Aghi et al. (67) described that 8 atypical meningioma patients (108 in total) did not relapse after receiving GTR plus radiotherapy, while the relapse rate of GTR alone was 30% (average follow-up 3 years).

Factors affecting the effect of SRS on meningiomas include WHO classification of tumor, tumor location and size, patient age, time interval between SRS, and initial tumor resection and radiation dose, etc. (68). Tumor volume >8 cm^3 is the most important factor for poor prognosis of benign meningiomas treated by SRS (69). The improvement of clinical symptoms in non-single-session gamma knife radiosurgery (non-SS GKS) patients may be twice as much as that in single-session gamma knife radiosurgery (SS GKS) patients. However, with the increase of SRS treatment volume for high-grade meningiomas, the incidence of radiotherapy-related complications increases (5–23%) (70). The most common adverse reactions were epilepsy (12.0%) (71), cranial nerve injury (5.5%), and PTE (5.3%) (72).

The timing and method of radiotherapy are still controversial. There was no difference in overall survival in patients with STR or STR plus radiotherapy. It is safe to wait for the disease to progress before radiotherapy (73). At present, there is no data showing that radiotherapy timing will affect the long-term survival rate. It is suggested that small asymptomatic meningiomas can be observed first, and radiotherapy should be performed if tumor progresses. For benign meningiomas invading venous sinus, it is necessary to weigh early radiotherapy, surgical resection and observation. It is not clear whether SRT or SRS should be used for atypical meningiomas (AM) (74). There are many factors that determine SRS or SRT in the treatment of meningiomas. Physical factors (tumor size, margin, optimal dose), biological factors (histology of metastatic tumor, use of systemic drugs) and clinical factors (life expectancy, complications) all play a role in decision-making (75). A study found that in 50 patients with atypical meningiomas, the average follow-up time was 86 months. Twenty-one patients (42%) received SRS. The local control rates of tumor for 2 and 5 years were 91 and 88% respectively. Twenty-nine patients (58%) received SRT. The local control rates of tumor for 2 and 5 years were 71 and 69%, respectively. There was no significant difference between SRS and SRT.

Compared with photon radiation therapy, proton radiation therapy, and neutron radiation therapy can irradiate the target

more accurately and greatly reduce the radiation toxicity to surrounding normal tissues, but they are still in the development stage.

CHEMOTHERAPY

Drug therapy can only be carried out when surgery and radiotherapy strategies are no longer available, such as recurrent or progressive meningiomas. There are a variety of chemotherapy drugs and molecular targeted drugs for the treatment of non-benign meningiomas, such as alkylating agents, tyrosine kinase inhibitors, endocrine drugs, interferon, targeted molecular pathway inhibitors, etc. (**Figure 2**). Although many drugs have shown efficacy in preclinical studies and some clinical applications, there is no consistently effective drug found in different clinical studies (76).

Hydroxyurea (HU) is a ribonucleic acid reductase inhibitor, which induces apoptosis of meningiomas cells by preventing the growth of S phase of cell cycle. HU has been used as adjuvant therapy for meningiomas that have not been completely resected or recurred. Weston et al. found that although HU may prevent some patients from progressing, it does not reduce the tumor size and causes significant side effects (77). Chamberlain published a retrospective case series study. This study retrospectively analyzed 35 patients with high-grade meningiomas who relapsed after surgery and radiotherapy (WHO Grade II, 22 cases; WHO Grade III, 13 cases), the total PFS rate at 6 months was 3%, and the median PFS was only 2.0 months (78). It shows that HU has very limited activity although it is well-tolerated.

Temozolomide (TMZ), an alkylating agent, failed to prolong PFS of recurrent meningiomas. Chamberlain et al. (79) treated 16 patients with refractory meningiomas with temozolomide. Tumor progression time was 2.5–5.0 months (median 5.0 months). The survival time ranged from 4 to 9 months (median 7.5 months). Irinotecan is a topoisomerase I inhibitor, which can cause DNA double strand breaks. A pre-clinical study found that irinotecan can inhibit the growth of meningeal cells (80). However, the subsequent Phase II trial failed to prove its clinical efficacy.

It has been reported that recombinant interferon α-2b is effective for a few malignant meningiomas patients (81). A study observed the therapeutic effect of interferon on 35 patients with recurrent WHO grade I meningiomas. PFS rate were 54 and 31% at 6 and 12 months, respectively, and the median progression time was 7 months, suggesting that interferon is an effective drug for the treatment of recurrent low-grade meningiomas (82). However, other studies have not reached a consistent conclusion.

Genomics studies have confirmed the importance of mutations such as NF2, TRAF7, KLF4, AKT1, SMO, PI3KCA, and POLR2A in the occurrence and development of meningiomas (83). Fifty to sixty percentage of meningiomas patients have mutation of tumor suppressor gene neurofibromatosis type 2 (NF2) (84). The NF2 gene product merlin is a tumor suppressor and mediates inhibition of cell proliferation (85). Gene mutations drive key mitogenic pathways, including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (AKT), mechanistic target of rapamycin (mTOR), extracellular signal-regulated kinase (ERK), etc. (86). Gene mutation can also overexpress receptor tyrosine kinases (RTKs), so more and more receptor tyrosine kinase inhibitors are used in targeted therapy (87).

The high expression of platelet-derived growth factor receptor (PDGFR) is closely related to the development of malignant meningiomas and atypical meningiomas. Imatinib combined with HU was used to treat recurrent or invasive meningiomas. Of the 21 patients receiving combined therapy, 67% had no imaging progress. The results showed that imatinib combined with HU was well-tolerated, but had little effect on grade II or III meningiomas (88). Sunitinib is a small molecule tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor and PDGF. A prospective, multicenter, single-arm phase II clinical trial of sunitinib in the treatment of malignant meningiomas showed that 42% of patients achieved no tumor progression within 6 months. MR perfusion imaging confirms that sunitinib can reach the location of the lesion and play a role in the vascular system of the tumor, however, further study is needed to confirm whether these effects can produce beneficial clinical effects (89).

Over-expression of epidermal growth factor receptor (EGFR) is found in over 60% of meningiomas (90). Receptor activation of epidermal growth factor (EGF) or transforming growth factor-a (TGF-a) can promote *in vitro* proliferation of meningiomas cells (91). In a study of 25 patients with recurrent meningiomas treated with the EGFR inhibitors Gefitinib and Erlotinib. Although the treatment is well-tolerated, neither gefitinib nor erlotinib has no obvious activity on recurrent meningiomas. It suggests that EGFR alone may not be a valuable therapeutic target. Therefore, it is necessary to evaluate the combined application of multi-target inhibitors and EGFR inhibitors with other targeted molecular agents (76, 92).

VEGF was found expression in 84% of meningiomas, and VEGF receptor (VEGFR) was expressed in 67% of meningiomas (93). The expression level of VEGF and VEGFR in meningiomas increases with the increase of tumor grade. Inhibition of VEGF and VEGFR may have significant anti-tumor effect. Studies have shown that bevacizumab, a VEGF inhibitor, has clinical benefits in meningiomas with no response to surgery or radiotherapy, and can improve the survival rate of patients (94). However, due to the lack of strong clinical evidence for improving survival rate and related toxicity, the treatment of meningiomas with bevacizumab should be carefully evaluated. An ideal randomized controlled trial is needed to better determine the effect of this drug in the treatment of meningiomas (95). Vatalanib can effectively inhibit VEGFR and PDGFR and has anti-tumor activity in grade II and III meningiomas (87).

mTORC1 can attenuate RTK signals through PI3K and Akt pathway, thus forming a negative feedback loop. Inhibitors of mTOR pathway such as Temsirolimus and Everolimus have been proved to be effective in preventing meningiomas progression (96, 97). In addition, *in vitro* studies have demonstrated that retinol-like compounds such as Fenretinide can bind to the retinoic acid receptor (RAR) to induce apoptosis in meningiomas cells (98). Clinical trials of Vismodegib and Afureserib, specific

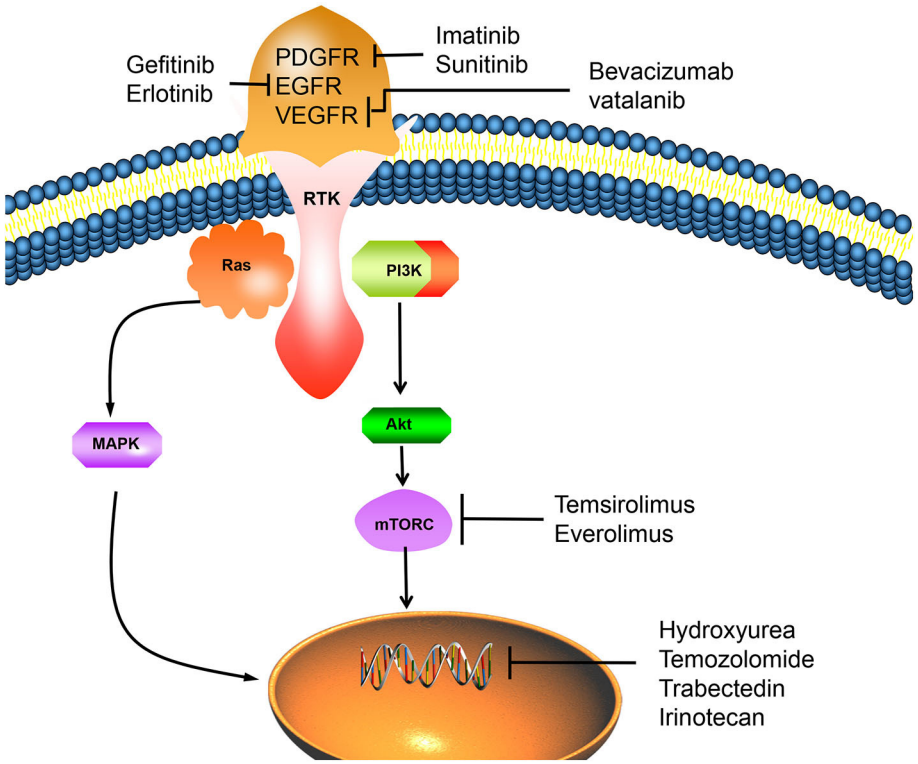


FIGURE 2 | The overexpression of RTK can activate important mitogenic pathways, including Ras, MAPK, PI3K-Akt, Mtor, and other intracellular signals, which can promote the proliferation of tumor cells. However, PDGFR/EGFR/VEGFR inhibitors can inhibit the activation of RTK, thus reverse this process and lead to tumor cell apoptosis. Chemotherapy drugs such as hydroxyureae and temozolomide can act on cell nucleus, inhibit tumor cells proliferation by inducing cell apoptosis. PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; RTK, receptor tyrosinekinase; Ras, PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen activated protein kinase; Akt, protein kinase B; mTORC, mammalian target of rapamycin C.

drugs for meningiomas with mutations in SMO and AKTl genes, are under way. This trial is the first to target a specific mutant meningioma, and the results remain to be seen (99).

Studies have shown that there is a strong relationship between sex hormones and meningiomas. Estrogen receptor (ERs) is expressed at a low level in about 10% of meningiomas patients, while progesterone (PRs) and androgen receptor are expressed in 70% of meningiomas patients (100). Due to the low expression level of ERs, the treatment of ERs antagonist tamoxifen has not shown any effective results. The results of antiprogestin mifepristone study are also mixed (101). There have been no reports of androgen receptor antagonists in meningiomas. Somatostatin (SST) plays an important role in regulating the proliferation of normal cells and tumor cells. Long half-life SST analogs are now recommended for systemic treatment of unresectable or radiorefractory relapsed meningiomas (102). A recent study analyzed the efficacy of everolimus and octreotide in the treatment of recurrent meningiomas, and the results showed that the overall PFS6 was 55%. The 6 and 12-month survival rates were 90 and 75%, respectively. After 3 months of treatment, the growth rate of 78% tumor volume decreased significantly, that is the decrease was more than 50%. The study suggests that the combination of everolimus and octreotide has better anti-meningioma activity (103).

GENE THERAPY

Gene therapy is the introduction of genetic material (DNA or RNA) into human cells to correct or compensate for gene defects and abnormalities in order to achieve therapeutic purposes. Researchers found that adenovirus virus and herpes virus can be effectively transduced into meningiomas cells. Herpes simplex virus is the first oncolytic virus effective in treating meningiomas (104). Due to the short duration of therapeutic effect and uncontrollable insertion mutation, only a few preclinical studies have been reported, which also provides a new direction for gene therapy of meningiomas.

PROGNOSIS AND RECURRENCE

The most reliable prognostic factors for meningiomas are histological grade (WHO grade) and resection degree (Simpson grade) (105). Meningiomas are mostly benign. The results of surgical treatment vary with the location and treatment of

meningiomas. The tumors located in the medial sphenoid ridge, cavernous sinus, and clivus have poor prognosis, high operative mortality, many postoperative sequelae and poor quality of life (106).

Recurrence rate of meningiomas after operation is usually between 13 and 40%. Recurrence rate of meningiomas has a great correlation with Simpson classification degree of resection (10). The recurrence rate of Simpson grade I surgery patients is 9%, grade II is 19%, and grade III is 29%. Postoperative patients should receive regular imaging examination due to the recurrence rate of meningiomas also increases with the extension of follow-up time. After STR of the lesion (Simpson IV grade), almost all patients relapsed after more than 15 years of followed up, of which 60% died, and most occurred within 10 years.

Robert Sumkovski et al. found that sex, age, Karnofsky score etc. have predictive value for recurrence of different types of meningiomas (107). Histological grading of meningiomas also affects its recurrence, and with the increase of pathological grading, the recurrence rate increases greatly. The recurrence rate of WHO grade I meningiomas is 7–23%, WHO grade II meningiomas is 50–55%, and WHO grade III meningiomas is 72–78% in 5 years after total resection (70). The gene distribution of meningiomas varies with tumor location and may also affect prognosis. When recurrent meningiomas have symptoms, surgery should be considered first, and SRS/RT adjuvant therapy should be given after surgery. In the 16 patients with recurrent meningioma treated by radiotherapy, the disease-free survival rate was 78%, compared with only 11% for those treated with surgery alone (108).

OUTLOOK

With the continuous progress of skull base surgery, anesthesia technique, MR, neurovascular reconstruction and ultrasound, the GTR of meningiomas, and the prognosis of the patients have been greatly improved. Patients with meningiomas should be treated individually in multiple disciplines, modes and stages, and tumors should be removed and controlled to the greatest extent on the basis of ensuring the cranial nerve function and quality of life of patients. Stereotactic techniques, including gamma knife, linear accelerator, and proton beam radiotherapy, enable meningiomas to be treated with radiotherapy while preserving important nerve structures. Chemotherapy, targeted therapy, and immunotherapy for meningiomas are also under exploration. DNA methylation is closely related to tumors, and its characteristics can provide important basis for individualized treatment of different subtypes of meningiomas (109). Lymphocyte telomere length (LTL) is significantly correlated with increased risk of meningiomas (110). These studies may explain the causes of the occurrence and progression of brain tumor lesions in the future, thus enriching the treatment methods for meningiomas at all levels and bringing better prognosis to patients.

AUTHOR CONTRIBUTIONS

WZ and LZ collected, analyzed the clinical data, and wrote part of the manuscript. ZG, JW, YH, and CW participated in the data analysis and interpretation. PW worked on the manuscript revision. All authors read and approved the final manuscript.

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CORRECTION
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Corrigendum: An Overview of Managements in Meningiomas

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In the original article, there were mistakes in the order of **Figure 1** and **Figure 2** as published. The positions of the two figures were reversed. The corrected **Figure 1** and **Figure 2** appear below.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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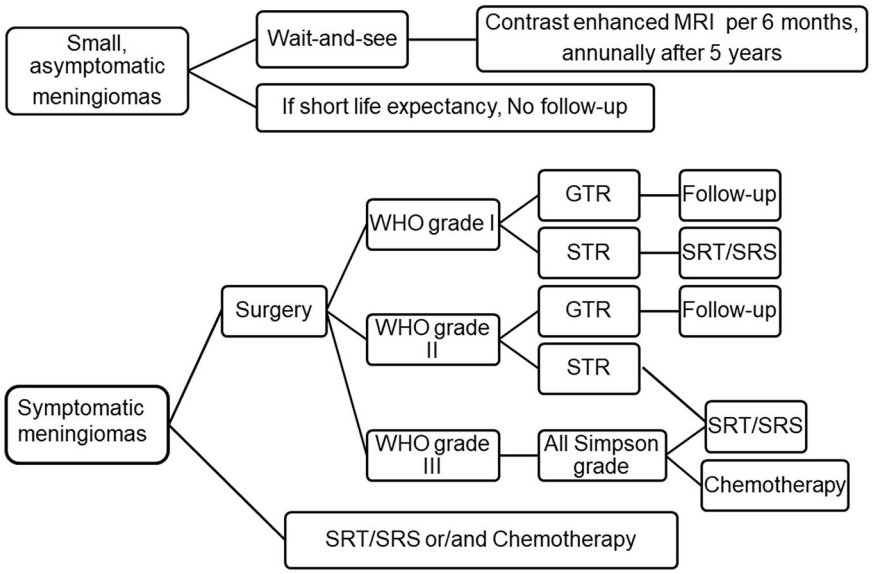


FIGURE 1 | Current treatment strategies for meningioma. For small and asymptomatic meningiomas, an strategy of "wait and see" is recommended, clinical and MRI evaluation was performed every 6 months after an initial observation. If patients do remain asymptomatic, annually after 5 years. If the patient's life expectancy is short, follow-up may not be necessary. Symptomatic meningioma should be removed to the maximum extent. Patients who are unwilling to undergo surgery, the elderly or obviously disabled can choose SRT/SRS or chemotherapy. Patients with WHO grade I meningioma were followed up after GTR, and SRT/SRS was recommended after STR. For WHO grade II meningioma, intimate follow-up is recommended after GTR, while SRT/SRS is recommended after STR. For WHO grade III meningiomas, adjuvant radiotherapy are recommended regardless of the grade of resection. Adapted from Goldbrunner et al. (6). EANO guidelines for the diagnosis and treatment of meningiomas. WHO, world health organization; GTR, gross total resection; STR, subtotal resection; SRT, stereotactic radiotherapy; SRS, stereotactic radiosurgery.

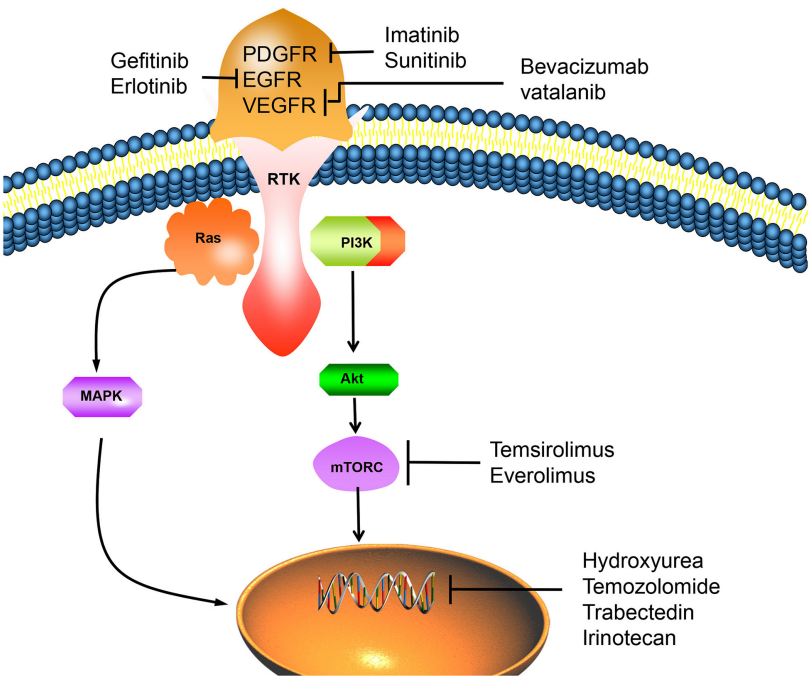


FIGURE 2 | The overexpression of RTK can activate important mitogenic pathways, including Ras, MAPK, PI3K-Akt, Mtor, and other intracellular signals, which can promote the proliferation of tumor cells. However, PDGFR/EGFR/VEGFR inhibitors can inhibit the activation of RTK, thus reverse this process and lead to tumor cell apoptosis. Chemotherapy drugs such as hydroxyureae and temozolomide can act on cell nucleus, inhibit tumor cells proliferation by inducing cell apoptosis. PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; RTK, receptor tyrosinekinase; Ras, PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen activated protein kinase; Akt, protein kinase B; mTORC, mammalian target of rapamycin C.

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The Preferred Locations of Meningioma According to Different Biological Characteristics Based on Voxel-Wise Analysis

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Objective: Meningiomas presented preferred intracranial distribution, which may reflect potential biological natures. This study aimed to analyze the preferred locations of meningioma according to different biological characteristics.

Method: A total of 1,107 patients pathologically diagnosed with meningiomas between January 2012 and December 2016 were retrospectively analyzed. Preoperative MRI were normalized, and lesions were semiautomatically segmented. The stereospecific frequency and p value heatmaps were constructed to compare two biological phenotypes using two-tailed Fisher's exact test. Age, sex, WHO grades, extent of resection (EOR), recurrence, and immunohistochemical markers including p53, Ki67, epithelial membrane antigen (EMA), progesterone receptor (PR), and CD34 were statistically analyzed. Recurrence-free survival (RFS) were analyzed by Kaplan–Meier method.

Result: Of 1,107 cases, convexity (20.8%), parasagittal (16.1%), and falx (11.4%) were the most predominant loci of meningiomas. The *p*-value heatmap suggested lesion predominance in the left frontal and occipital convexity among older patients while in the left sphenoid wing, and right falx, parasellar/cavernous sinus, and middle fossa among younger patients. Lesions located at anterior fossa and frontal structures were more frequently seen in the male while left parietal falx and tentorial regions, and right cerebellopontine angle in the female. Grades II and III lesions presented predominance in the frontal structures compared with grade I ones. Meningiomas at the left parasagittal sinus and falx, tentorium, intraventricular regions, and skull-base structures were significantly to receive subtotal resection. Lesions with p53 positivity were statistically located at the left frontal regions and parasellar/cavernous sinus, higher Ki67 index at the left frontal and bilateral parietal convexity and right parasellar/cavernous sinus, EMA negativity at the right olfactory groove and left middle fossa, and CD34 positivity at the sellar regions and right sphenoid wing. Tumor recurrence rates for grades I, II, and III were 2.8, 7.9, and 53.8%, respectively. Inferior RFS, higher

Ki67 index, grades II and III, and a larger preoperative volume were observed in older patients. Recurrent meningiomas were more frequently found at the occipital convexity, tentorium, sellar regions, parasagittal sinus, and left sphenoid wing.

Conclusion: The preferred locations of meningioma could be observed according to different biological characteristics, which might be helpful for clinical decisions.

Keywords: meningiomas, magnetic resonance imaging, voxel-wise analysis, lesion location preference, recurrence

INTRODUCTION

Meningiomas account for 37.6% of all primary central nervous system (CNS) tumors and 53.3% of non-malignant intracranial tumors, with an incidence rate of 8.6 per 100,000 (1). Meningiomas originate from the arachnoidal cap cell and are histologically divided into grades I, II (atypical), and III (anaplastic), according to the 2016 WHO classification (2, 3). Approximately 80% of the meningiomas are grade I with benign behaviors, while the high-grade lesions (grades II and III) tend to recur and metastasize (4). Surgery is recognized as the first option for treating patients with meningioma, pursuing the primary goal of complete resection (Simpson grade I) (5). Patients with lesions in favorable locations (e.g., convexity meningiomas) presented improved recurrence-free survival (RFS) by extensive resection (6). Besides surgery, however, radiotherapy or radiosurgery is required for meningiomas in uneasily accessible locations (5). Moreover, the meningioma locations are related to the symptoms, tumor histology, and the prognostic value of Simpson classification. Skull-base lesions insult memory more seriously than convexity ones do (7). Atypical meningiomas are associated with a location on the convexity, and Simpson grade is correlated to the high risk of recurrence for tumors in this location instead of falx and posterior fossa (8–10). Therefore, the location-specific difference in meningioma greatly influences clinical decisions and therapeutic strategies.

The spatial distribution of meningioma has long been investigated with clinical interest to explore the location-specific difference. A study in the 1930s suggested that the anterior one-third of the superior sagittal sinus was commonly affected (11). Moreover, this result was verified by Hirayama et al. using voxel-based lesion mapping for 260 meningiomas (12). The authors also discovered more frequent distribution in skull-base structures and regions around central sulcus and the sylvian fissure. Given this, the voxel-wise analysis based on MRI is a valuable method to show the spatial landscape of brain tumors, which have been applied in glioblastoma, brain metastases, and primary CNS lymphoma (13–16). Notably, the preferred locations of glioblastoma were statistically compared and visualized by atlas in terms of biological features and genetic alterations (13, 14). Similarly, biological and clinical characteristics are of great importance for meningiomas and might be associated with the location. A study indicated that WHO grades, Ki67-MIB1, and progesterone receptor (PR) expression differed depending on tumor locations (17).

The present study, therefore, used a large surgery-treated patient cohort at our institution and applied voxel-wise mapping and Fisher's exact test to visualize the preferred locations of meningioma according to different biological characteristics. Location analysis might improve the clinical understanding of meningiomas.

MATERIALS AND METHODS

Patient Cohort

Patients with meningiomas who received surgery between January 2012 and December 2016 at our institution were reviewed. Preoperative contrast-enhanced T1-weighted MRI (CE-T1WI) and histopathological reports were consecutively extracted from the institutional medical database. A total of 1,107 patients were included. The extent of resection (EOR), including gross total resection (GTR, Simpson grades I and II) and subtotal resection (Simpson grades III and IV), was classified according to surgical records and the recheck of postoperative MRI, which were reviewed by a senior neuroradiologist (BJ). The biological characteristics include age, sex, WHO grade, EOR, recurrence, and the expression of p53, Ki67, epithelial membrane antigen (EMA), PR, and CD34.

Patient Consent

The inclusion process was approved by the institutional ethical committee on human clinical research. A general informed consent agreement, stating that the clinical, pathological, and imaging data with privacy protection might be used for teaching and scientific research, was signed by every patient as soon as hospitalized. Because of the retrospective nature of the current study with no clinical intervention, the specific informed consent agreement to a project was waived by the ethical committee. Medical records were desensitized for privacy protection.

Magnetic Resonance Imaging

The patients underwent an either 1.5-(Signa Excite, GE Healthcare, Milwaukee, Wisconsin) or 3.0-T (Discovery 750, GE Healthcare, Milwaukee, Wisconsin) MRI. Intravenous injection of gadodiamide (0.2 ml/kg body weight, up to a maximum of 20 ml, Omniscan, GE Healthcare) was used to obtain the CE-T1WI. The last scan before surgery demonstrating meningioma was used for analyses.

Definition of Tumor Location

The locations of meningioma were identified according to the surgical description and the dura mater attached with a tumor in imaging. Locations were classified as the previous study with modifications (12). These included convexity, parasagittal sinus, falx, tentorium, cerebellar convexity, cerebellopontine angle, sphenoid wing, parasellar/cavernous sinus, tuberculum sellae/planum sphenoidale/anterior clinoid process, middle fossa, olfactory groove, clival–petroclival, foramen magnum, intraventricular, and other types (multiple/orbital/jugular foramen). A neurosurgeon (CS) and a neuroradiologist (BJ) reviewed the results.

Image Normalization and Segmentation

Images were exported in the standard Digital Imaging and Communications in Medicine (DICOM) format. They then were converted into the Neuroimaging Informatics Technology Initiative (NIfTI) format using dcm2nii converter software (University of Nottingham School of Psychology, Nottingham, UK). The axial images were selected. Statistical Parametric Mapping Software version 12 (SPM12, Institute of Neurology, University College London, London, UK) in MATLAB (version R2012a, The MathWorks, Natick, MA, USA) was used to register the images to a standard brain template (MNI152; Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada) for normalization (15, 16). The regions of interest (ROIs) in normalized images were semiautomatically segmented using 3D Slicer (version 4.10.0; http://www.slicer.org/) and its "Grow from Seed" module (18). The segmentation was performed by two neurosurgeons and reviewed by another neurosurgeon and the neuroradiologist.

Stereospecific Frequency and p-value Heatmaps

MRIcron (University of Nottingham School of Psychology, Nottingham, UK) was used to superimpose the ROIs on MNI152 to construct stereospecific frequency heatmaps. The p value heatmaps were created to compare two different phenotypes under one characteristic (e.g., comparing old with young patients) and calculate the significance of a voxel. The two-tailed Fisher's exact test was performed with custom Python scripts, as previously described by Ellingson et al. (13, 14).

$$p = \frac{(a+b)!\,(c+d)!\,(a+c)!\,(b+d)!}{a!b!c!d!n!}$$

In the formula, "a" is the frequency of tumor occurrence under phenotype A, "b" is the frequency of tumor occurrence under phenotype B, "c" is the frequency of tumor-free patients under phenotype A, "d" is the frequency of tumor-free patients under phenotype B, and "n" is the total number of patients.

Statistical Analyses

The normalized tumor volume was calculated by multiplying the number of voxels within the ROI by the volume of a single voxel (0.08 mm^3) in MNI152, approximating to the lesion volume before normalization. Recurrence-free survival (RFS) was determined by the Kaplan–Meier analysis with the log-rank test. The Kruskal–Wallis and Dunn's multiple comparison test were used when appropriate, and data were presented as mean ± standard error of the mean (SEM). GraphPad Prism (version 8.0.2; GraphPad Software, San Diego, CA, USA) and SPSS (version 22.0; IBM SPSS Statistics, Armonk, NY, USA) were used for all statistical analyses. $p < 0.05$ was deemed significant.

RESULTS

Demographics

Among the 1,107 patients, the median age was 56 years, and the ratio of male to female was 3:7. According to the WHO classification, 993 (89.7%), 101 (9.1%), and 13 (1.2%) were

TABLE 1 | Demographics of 1,107 patients with meningiomas.

Characteristics	Number (%)
Age	
Range	13–85
Median	56
Sex	
Male	322 (29.1)
Female	785 (70.9)
WHO grades	
I	993 (89.7)
II	101 (9.1)
III	13 (1.2)
Locations	
Convexity	230 (20.8)
Parasagittal sinus	179 (16.1)
Falx	126 (11.4)
Tentorium	94 (8.5)
Cerebellar convexity	10 (0.9)
Cerebellopontine angle	86 (7.7)
Sphenoid wing	109 (9.8)
Parasellar/cavernous sinus	32 (2.9)
Tuberculum sellae/planum sphenoidale/anterior clinoid process	84 (7.6)
Middle fossa	14 (1.3)
Olfactory groove	66 (6.0)
Clival-petroclival	21 (1.9)
Foramen magnum	3 (0.3)
Intraventricular	22 (2.0)
Others (multiple/orbital/jugular foramen)	31 (2.8)
Extent of resection*	
Gross total resection	945 (90.0)
Subtotal resection	105 (10.0)
Recurrence rates#	
I	28 (2.8)
II	8 (7.9)
III	7 (53.8)

**The results of EOR were lost in 57 patients; thus, the EOR was evaluated in 1,050 patients.*

#The recurrence rates were calculated based on the number of patients of the corresponding WHO grade.

grades I, II, and III, respectively. WHO grade I consisted of 717 female (72.2%) and 276 male (27.8%). WHO grades II and III consisted of 68 female (59.6%) and 46 male (40.4%). The gender distribution according to different WHO grades was significantly different (**Supplementary Figure 1**, $p = 0.005$). Convexity (20.8%), parasagittal (16.1%), and falx (11.4%) were the three most common locations affected by meningiomas, followed by skull-base structures including sphenoid wing (9.8%), cerebellopontine angle (CPA, 7.7%), tuberculum sellae/planum sphenoidale/anterior clinoid process (7.6%), and olfactory groove (6.0%). Ninety percent of the patients received GTR (Simpson grades I and II). Forty-three patients had recurrence during the follow-up visits, and the recurrence rates for grades I, II, and III were 2.8, 7.9, and 53.8%. The demographics are summarized in **Table 1**.

Tumor Volume

The median preoperative tumor volume after normalization was 22.828 cm^3 (95% confidence interval, 20.64–25.37). Although no significance of tumor volume was found comparing non-skull-base with skull-base meningiomas, convexity meningiomas were statistically smaller than the parasagittal and tentorial ones (**Figure 1A**). Further comparison among skull-base lesions demonstrated a larger volume of the sphenoid wing and olfactory groove meningiomas than lesions at other locations (**Figure 1B**).

Stereospecific Frequency Heatmap

Stereospecific frequency heatmap was constructed by ROIs overlapping to visualize the spatial landscape of meningiomas. The color ranging from dark blue to red indicated the tumor frequency from 0 to 5% and above (**Figure 2**). The results indicated that lesions preferred to distribute at the anterior two-thirds of the superior sagittal sinus and falx, olfactory groove, tuberculum sellae/planum sphenoidale/anterior clinoid process, parasellar/cavernous sinus, and CPA. Although convexity meningiomas accounted for the largest proportion of all the cases, no particularly densely distributed area was observed in the convexity. Mild left lateralization was found. The laterality was further analyzed according to locations and biological characteristics, including age, sex, and WHO grade, but no significance was found (**Supplementary Figure 2** and **Supplementary Table 1**).

p-value Heatmaps

Biological characteristics including age, sex, WHO grade, EOR, and expression of p53, Ki67, EMA, PR, and CD34 were statistically analyzed. Two different phenotypes under one characteristic were compared, and significant voxels were visualized to explore the preferred locations. The median age of 56 years was set as the cutoff value to stratify the patients. Results suggested statistically significant clusters in the left frontal and occipital convexity in older patients while in the skull-base structures including sphenoid wing, and right falx, parasellar/cavernous sinus and middle fossa in younger patients (**Figure 3A**). Tumor frequency results showed the predominance of the anterior fossa, frontal structures, and tentorial regions in the male sex compared to female sex with the predominance of the left parietal falx, tentorium, and cerebellar convexity, and right CPA (**Figure 3B**). *p*-value heatmap based on the WHO classification identified clusters in the frontal structures and left parietal and

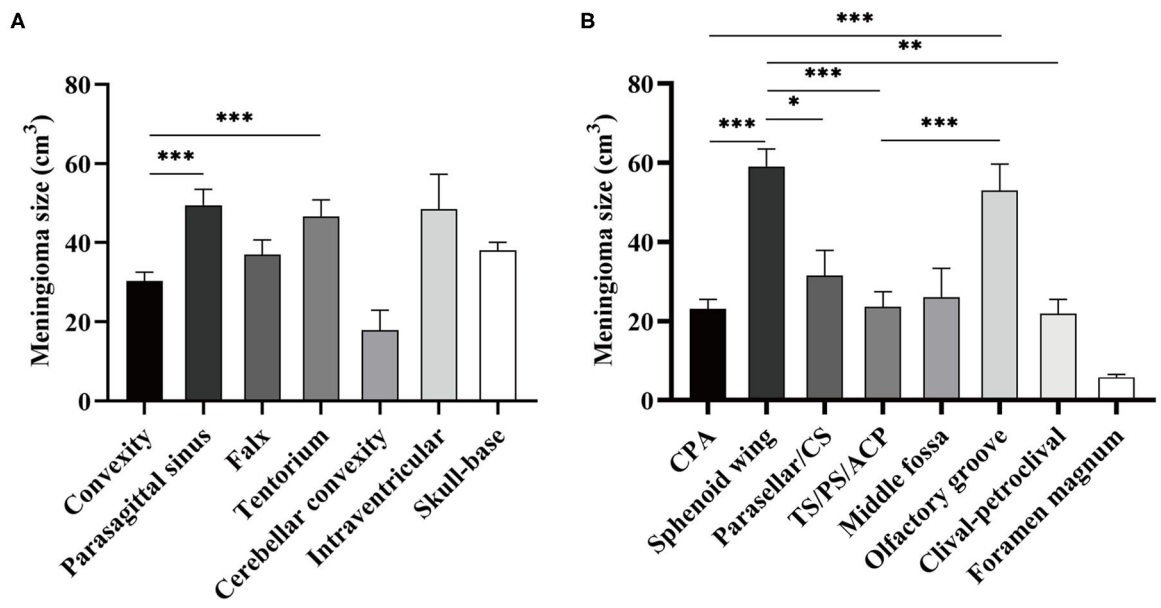


FIGURE 1 | Comparison of normalized tumor volume according to the locations of meningioma. **(A)** Meningioma size was compared between skull- and non-skull-base locations. **(B)** Meningioma size was compared among eight skull-base locations. CS refers to cavernous sinus; TS/PS/ACP refers to tuberculum sellae/planum sphenoidale/anterior clinoid process. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$, respectively.

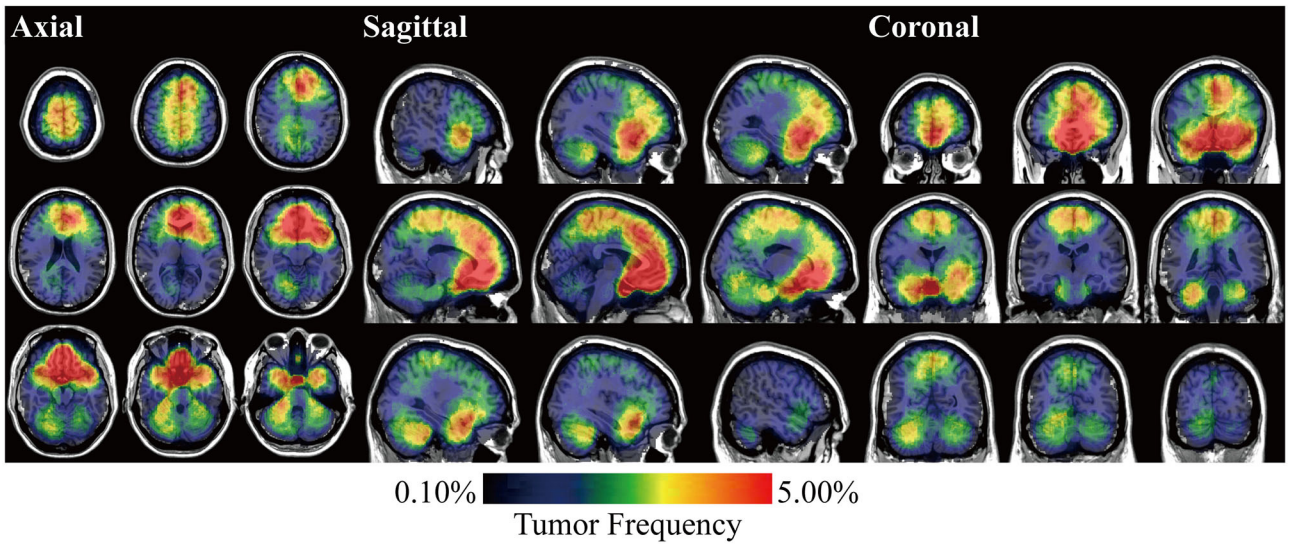


FIGURE 2 | Stereospecific frequency heatmap of meningiomas with axial, sagittal, and coronal positions. Lesions in 1,107 patients were normalized, segmented, and superimposed on the MNI152. The color ranging from dark blue to red indicated the tumor frequency from 0 to 5% and above.

occipital convexity as more frequently associated with high-grade meningiomas (grades II and III) and clusters in the left parasagittal sinus, right CPA, and sellar regions as more frequently associated with grade I meningiomas (**Figure 4A**). Significant clusters in the left parasagittal sinus and falx, tentorium, intraventricular regions, and skull-base structures (e.g., sellar regions and sphenoid wing) were identified as more frequently associated with meningiomas received subtotal resection (**Figure 4B**).

The spatially distinct regions in the left falx and parasellar/cavernous sinus occurred at a significantly higher frequency in lesions with positive expression of p53 (**Figure 5A**). The predominance in the left frontal and bilateral parietal convexity and right parasellar/cavernous sinus was significantly associated with Ki67 > 5% (**Figure 5B**). Lesions with negative expression of EMA frequently occurred in the right olfactory groove and left middle fossa (**Figure 6A**). Tumor frequency results showed the predominance of sellar regions and right sphenoid wing in lesions with positive expression of CD34 (**Figure 6B**). No significant location was found for PR.

Tumor Recurrence

Inferior RFS was observed in older patients ($p = 0.0324$, **Figure 7A**), high-grade lesions ($p < 0.001$, **Figure 7B**), Ki67 > 5% ($p = 0.0052$, **Figure 7C**), and a larger preoperative size ($\geq$22.828 cm^3, $p = 0.0003$, **Figure 7D**). The relation between EOR and RFS was not significant (**Figure 7E**). Clusters in occipital convexity, tentorium, sellar regions, parasagittal sinus, and left sphenoid wing were identified containing high a proportion of recurrent meningiomas (**Figure 7F**).

DISCUSSION

The present study visualized the preferred locations of meningioma in 1,107 patients according to different biological characteristics by voxel-wise constructing stereospecific frequency and *p*-value heatmaps, which could be a valuable reference for clinical decisions.

The high incidence rates and surgical difficulties for uneasily accessible locations of meningioma challenge the clinicians despite the benign nature of this tumor. As symptoms and treatment strategies largely depend on the location, it is indispensable to analyze the role of lesion location in clinical investigation of meningiomas (19, 20). A visual-perceivable graphic pattern is required for identifying and visualizing tumor locations rather than complicated table analyses. Voxel-based image normalization and segmentation are practical methods to comprehensively show the frequency of spatial distribution (15). The voxel-wise method was applied by Hirayama et al. (12) for meningioma mapping. The preferred locations of meningioma at the anterior two-thirds of the superior sagittal sinus and falx, olfactory groove, tuberculum sellae/planum sphenoidale/anterior clinoid process, parasellar/cavernous sinus, and cerebellopontine angle in our results were in accordance with the findings by Hirayama et al. The present study increased the sample size and objectively indicated the laterality of meningioma, overcoming their limitation of the intentional assumption that lesions distributed equally between hemispheres. The result that numerous lesions located at the middle third of the sagittal plane was reported in another study and was associated with a high risk of perioperative complications (21). The key points of surgery of these lesions were handling the feeding artery,

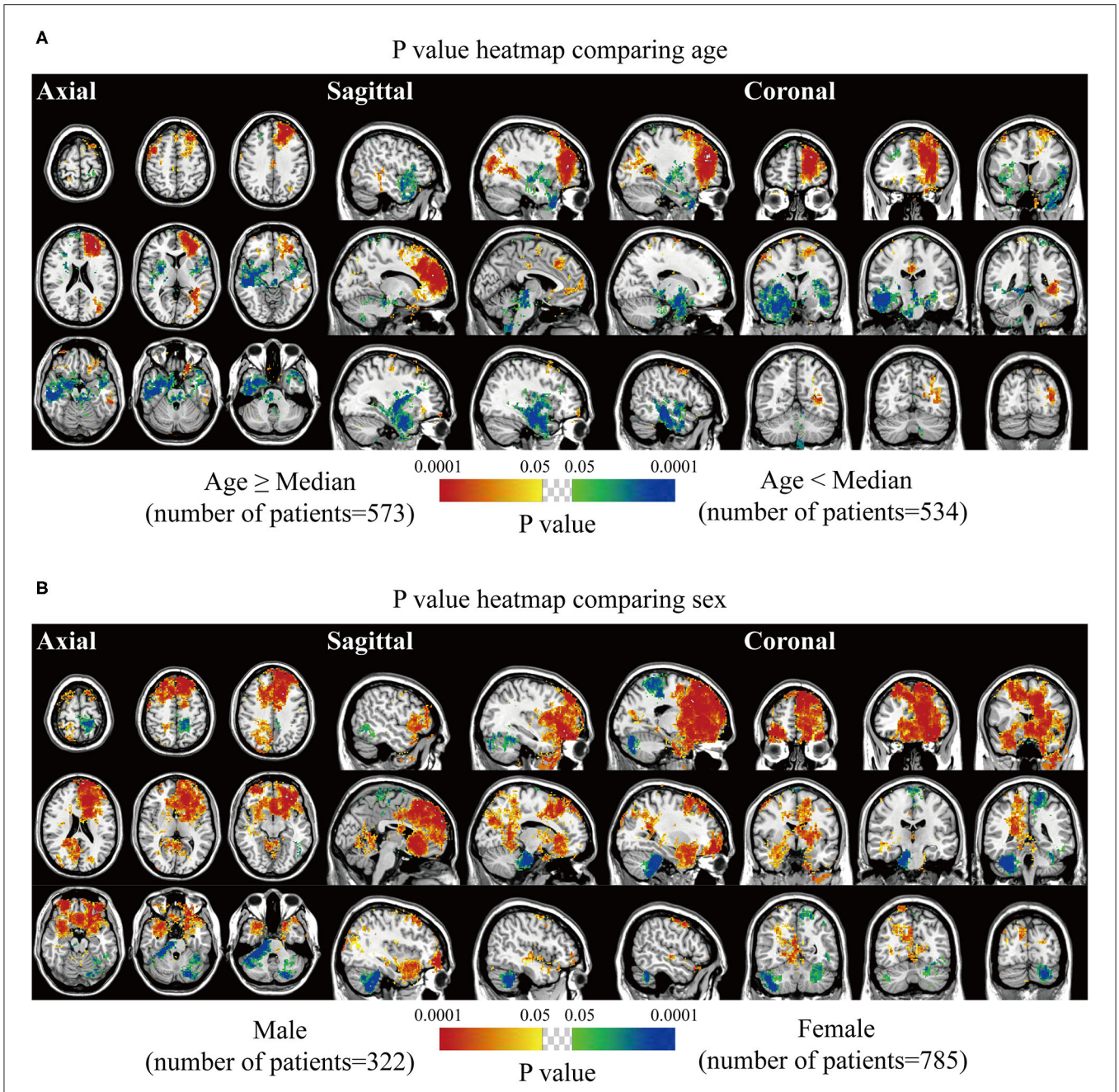


FIGURE 3 | *p*-value heatmaps of meningioma comparing age and sex. **(A)** *p*-value heatmap showed statistically significant clusters after comparing older (age ≥ 56 years) with younger (age < 56 years) patients. **(B)** *p*-value heatmap showed statistically significant clusters after comparing male with female patients. The color ranging from green to dark blue, and bright yellow to red, both indicated the *p*-value from 0.05 to 0.0001.

protecting the central sulcus vein, and treating affected sagittal sinus (22). The distinct distribution in these areas could be explained by regionally thick arachnoid membranes with high risk of developing neoplasms. This theory was also verified by the large tumor size in the parasagittal sinus, tentorium, sphenoid wing, and olfactory groove by our results.

The Fisher's exact test was used for further exploration of the correlation between locations and biological characteristics of meningioma, for the significance calculation of voxels, and for the comparison of the two phenotypes. The method was proposed by Ellingson et al. (13, 14) for the laterality study of glioblastoma in terms of particular molecular and genetic profiles. In our study, age, sex, WHO grade, and extent of resection and recurrence were considered for comparison. Several interesting clusters were highlighted. The frontal and occipital structures were frequently associated with older and

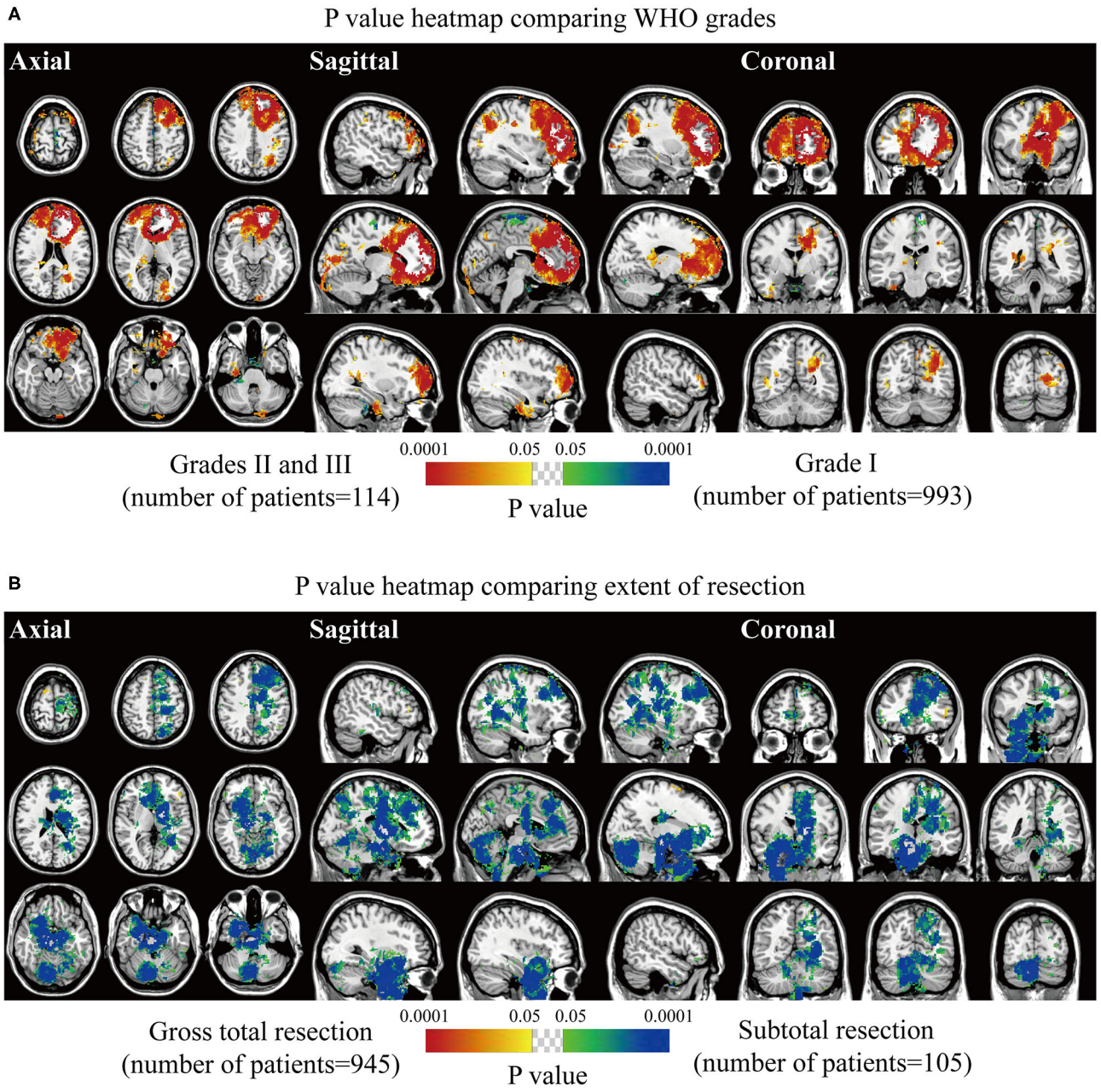


FIGURE 4 | *p*-value heatmaps of meningioma comparing WHO grade and extent of resection. **(A)** *p*-value heatmap showed statistically significant clusters after comparing grade I lesions with grades II and III ones. **(B)** *p*-value heatmap showed statistically significant clusters after comparing patients received gross total resection with ones received subtotal resection. The color ranging from green to dark blue, and bright yellow to red, both indicated the *p*-value from 0.05 to 0.0001.

male patients and high-grade meningiomas, as previously described (23). A predominance in the right CPA was observed in the female sex, and lesions in this region were statistically prone to be WHO grade I. Although skull-base clusters also significantly indicated grade I lesions, they were identified as the most frequent occurrence in subtotal resection. It has been well-documented that skull-base meningioma was a risk factor for incomplete resection (24). Moreover, the p value heatmap suggested the skull-base lesions presented a significant inclination to recur. Therefore, more appropriate surgical approaches should be taken in skull-base lesions resection to decrease recurrence.

The meningiomas were histologically categorized into 15 subtypes, according to the 2016 WHO classification (2). The subtype is an important biological characteristic of meningiomas. However, over classification into 15 categories will decrease the

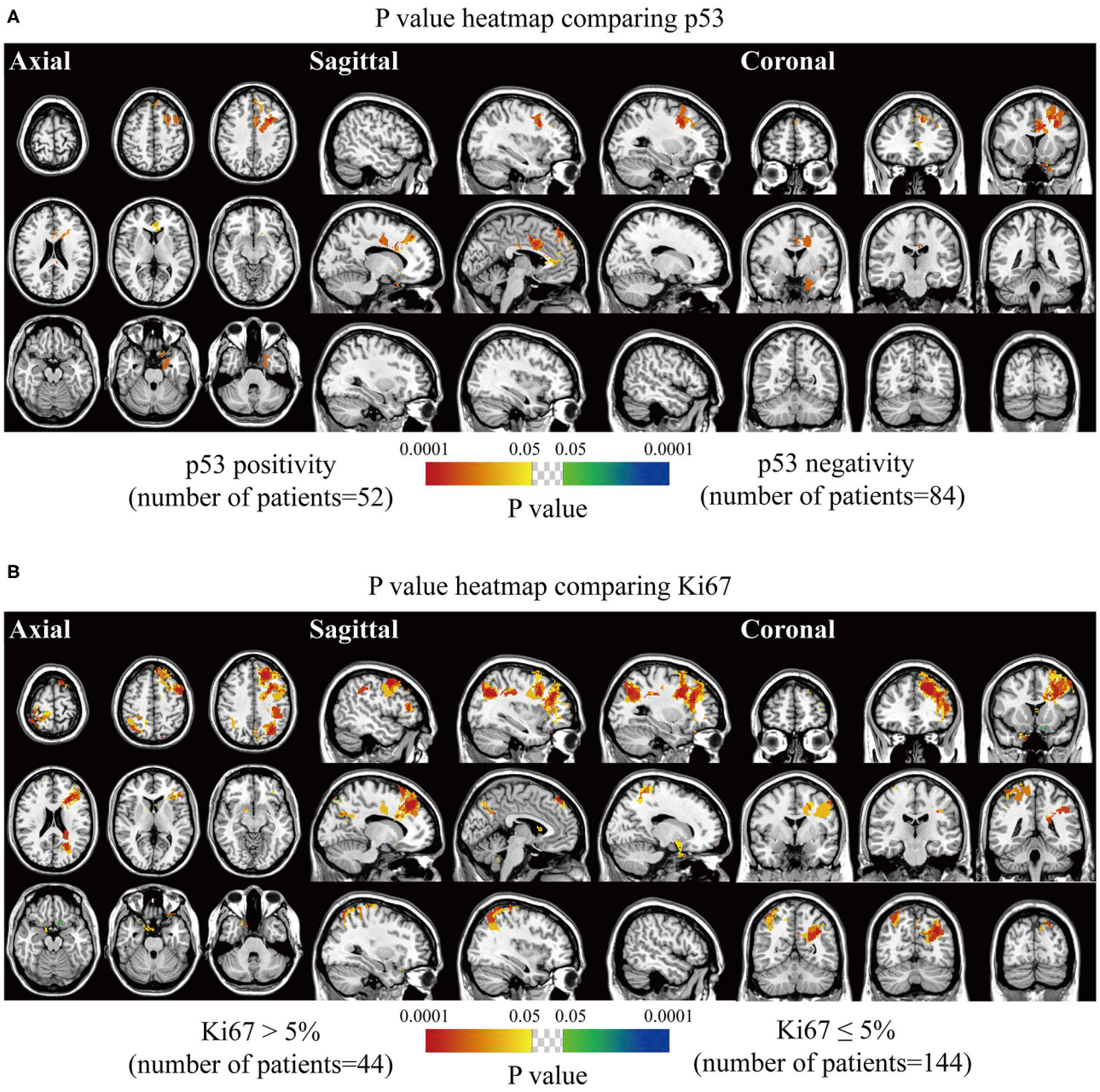


FIGURE 5 | *p*-value heatmaps of meningioma comparing immunohistochemical p53 and Ki67. **(A)** *p*-value heatmap showed statistically significant clusters after comparing p53 positivity with negativity. **(B)** *p*-value heatmap showed statistically significant clusters after comparing Ki67 > 5% lesions with Ki67 ≤ 5% ones. The color ranging from green to dark blue, and bright yellow to red, both indicated the p value from 0.05 to 0.0001.

statistical power. Another two reasons for not including the subtypes are the following: (1) the methodology of the voxel-wise analysis requires paired features (like WHO grade I vs. WHO grades II and III), and analyzing up to 15 categories simultaneously is difficult; and (2) some early pathological reports did not provide detailed subtype information. Future studies may focus on the different subtypes of meningiomas using other statistical methods.

As the molecular alterations might be responsible for the heterogeneity of meningioma, the expression of p53, Ki67, PR, EMA, and CD34 were further speculated to be related to the preferred locations of meningioma (23, 25). Expression of p53 is an indicator of the possible mutation of tumor suppressor gene *p53*, and Ki67 antigen protein is a cellular proliferative marker. The two markers predicted oncogenic ability and malignant degree (26, 27). EMA and PR were described as markers

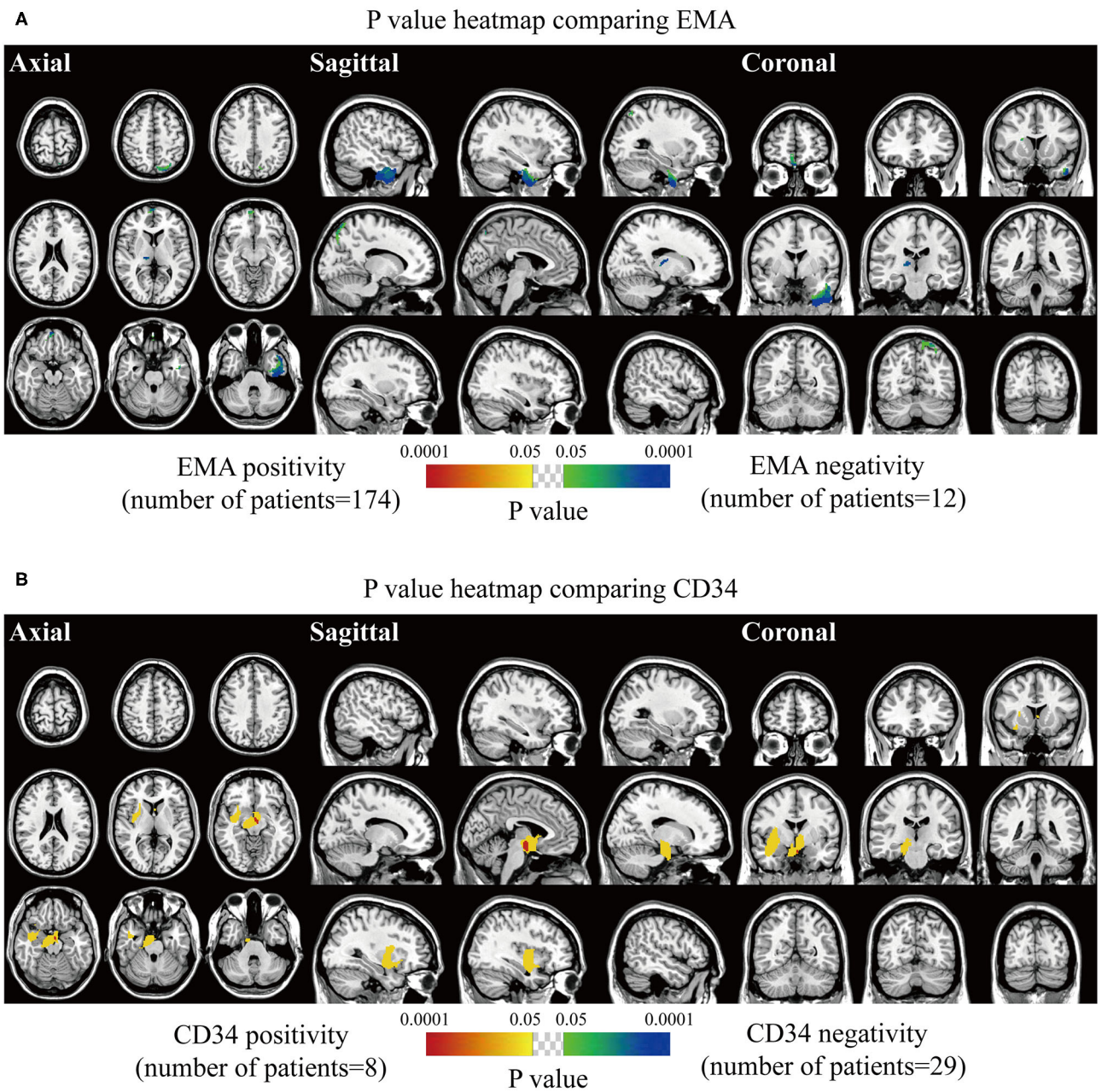


FIGURE 6 | *p*-value heatmaps of meningioma comparing immunohistochemical epithelial membrane antigen (EMA) and CD34. **(A)** *p*-value heatmap showed statistically significant clusters after comparing EMA positivity with negativity. **(B)** *p*-value heatmap showed statistically significant clusters after comparing CD34 positivity with negativity. The color ranging from green to dark blue, and bright yellow to red, both indicated the *p*-value from 0.05 to 0.0001.

identifying a more advanced differentiated state (23). CD34 is commonly used for evaluating neovascularity and tumor behavior (23). Our results revealed that positive p53 and higher Ki67 lesions presented strong predominance in the falx, frontal and parietal convexity, and bilateral parasellar/cavernous sinus, which was consistent with the investigation by Maiuri et al. (17). This is probably associated with the distinct distribution of high-grade meningiomas. No significant cluster was noticed for PR, and meningioma with negative EMA predominantly located at the olfactory groove and middle fossa. However, Maiuri et al. pointed out that 75% of cases with PR expression >50% were located at the medial skull base (17). The high incidence of female patients was associated with the expression of PR in meningiomas. Furthermore, our results interestingly found that the proportion of male patients in the higher grades subgroup was significantly increased compared with that in the grade

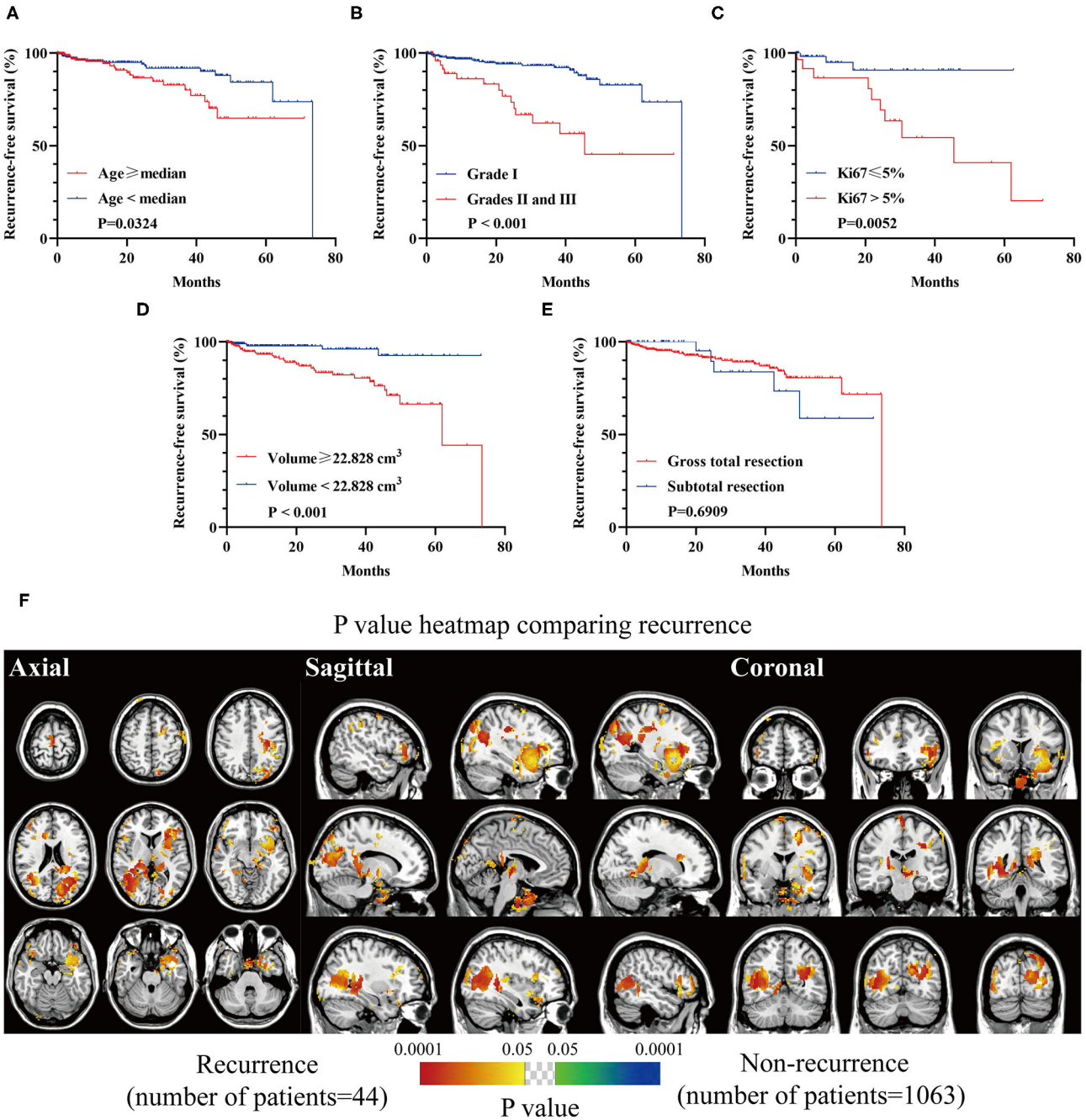


FIGURE 7 | Recurrence-free survival (RFS) analyses of biological characteristics and *p*-value heatmap of meningioma comparing recurrence. **(A)** RFS analysis comparing older (age ≥ 56 years) with younger (age < 56 years) patients. **(B)** RFS analysis comparing WHO grade I lesions with grades II and III ones. **(C)** RFS analysis comparing Ki67 > 5% lesions with Ki67 ≤ 5% ones. **(D)** RFS analysis comparing larger preoperative lesions (≥22.828 cm^3) with smaller ones (<22.828 cm^3). **(E)** RFS analysis comparing gross total resection with subtotal resection. **(F)** *P*-value heatmap showed statistically significant clusters after comparing gross total resection with subtotal resection. The color ranging from green to dark blue, and bright yellow to red, both indicated the *p*-value from 0.05 to 0.0001.

I subgroup, partially in accordance with the previous study (28). Higher CD34 levels were found in skull-base meningioma compared to the non-skull-base lesion by Haciyakupoglu et al. (29) and similar findings were found in sellar regions and sphenoid wing in our study.

According to the prognosis, there were expected findings that older patients, higher Ki67 expression, high-grade lesions, and a larger preoperative volume resulted in shorter RFS. Falcine and tentorial meningiomas were reported to have a high chance of recurrence, partially in agreement with our results (30). However,

no superior RFS was shown in the gross total resection group. The role of the Simpson grading system for predicting recurrence was questioned, but Nanda et al. (6) maintained its prognostic value. It was reported that a higher risk of recurrence could be observed in STR for convexity lesions. In contrast, the recurrence was not correlated with the EOR for falx and posterior fossa lesions, leading to the unequally prognostic value of Simpson grading in terms of tumor locations (9). Further studies are needed to investigate the prognostic value of the Simpson grading system.

There are several limitations in the present study. First, the retrospective nature of the current study can be challenging. A prospective study, controlling field strength, imaging-section thickness, and applying fully automatic segmentation to improve accuracy, and analyzing more clinical characteristics [e.g., presenting symptoms, Karnofsky performance status (KPS), and postoperative radiotherapy] to improve prognostic prediction, is warranted. Notably, it is believed that obtaining a Simpson grade I resection for the skull-base meningiomas is difficult, and it may be inaccurate to evaluate the Simpson grade based on surgical reports or pre- and postoperative MRI. Thus, complete surgical video records might be more accurate for further evaluating the EOR of skull-base lesions in a retrospective study. Following that, the mechanism of preferred locations (e.g., laterality) of meningioma should be investigated in the future. Additionally, the genomic mutations were not analyzed in the present study. The clinical significance of the mutations of NF2, KLF4, and TRAF7 were proven in meningiomas, and studies have shown a significant association between mutations and specific locations (5, 31). The preferred locations of meningioma according to distinct mutations are to be analyzed in our following study. Lastly, it was not reported in the previous literature whether the voxel-wise Fisher's exact tests have multiple comparison problem when applied in multiple hypotheses testing. The implications of our research via Fisher's exact tests may give a hint to the nature of meningiomas but need further test by more prudent statistical analysis.

In conclusion, this is the first study visualizing the preferred locations of meningioma according to different biological characteristics by voxel-wise constructing stereospecific frequency and *p*-value heatmaps in a large surgery-treated patient cohort. Our findings might be a valuable reference for clinical decisions.

DATA AVAILABILITY STATEMENT

The data for this study can be acquired with appropriate request to the corresponding author.

ETHICS STATEMENT

The inclusion process was approved by the ethical committee on human clinical research of the Second Affiliated Hospital of Zhejiang University. A general informed consent agreement, stating that the clinical, pathological, and imaging data with privacy protection might be used for teaching and scientific research, was signed by every patient as soon as hospitalized. Because of the retrospective nature of the current study with no clinical intervention, the specific informed consent agreement to a project was waived by the ethical committee. Medical records were desensitized for privacy protection.

AUTHOR CONTRIBUTIONS

CS and GC designed the study. JZ, QY, and XW collected the medical data. HZ, CZ, and YP made normalization and segmentation. ZD, JW, and FY analyzed data and constructed heatmaps. XY and JL performed survival and statistical analyses. CS and ZD wrote the manuscript. YI, BJ, QX, and GC reviewed all the data, results, and manuscript. All authors read and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.01412/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Next-Generation Sequencing Analysis of ctDNA for the Detection of Glioma and Metastatic Brain Tumors in Adults

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Background and aims: The next-generation sequencing technologies and their related assessments of circulating tumor DNA in both glioma and metastatic brain tumors remain largely limited.

Methods: Based largely on a protocol approved by the institutional review board at Peking University International Hospital, the current retrospective, single-center study was conducted. Genomic DNA was extracted from blood samples or tumor tissues. With the application of NextSeq 500 instrument (Illumina), Sequencing was performed with an average coverage of 550-fold. Paired-end sequencing was employed utilized with an attempt to achieve improved sensitivity of duplicate detection and therefore to increase the detection reliability of possible fusions.

Results: A total of 28 patients (21 men and 7 women) with brain tumors in the present study were involved in the study. The patients enrolled were assigned into two groups, including glioma group ($n = 21$) and metastatic brain tumor group ($n = 7$). The mean age of metastatic brain tumor group (59.86 ± 8.85 y), (43.65 ± 13.05 y) reported significantly higher results in comparison to that of glioma group (45.3 ± 12.3 years) ($P < 0.05$). The mutant genes in metastatic brain tumor group included *ALK*, *MDM2, ATM, BRCA1, FGFR1, MDM4* and *KRAS*; however, there were no glioma-related mutant genes including *MGMT*, *IDH1*, IDH2, *1p/19q*, and BRAF et al. Interesteringly, only two patient (28.3%) was detected blood ctDNA in metastatic brain tumor group; In contrast, blood ctDNA was found in ten glioma patients (47.6%) including 1p/19q, *MDM2, ERBB2, IDH1, CDKN2A, CDK4, PDGFRA, CCNE1, MET*. The characterizations of *IDH* mutations in the glioma included *IDH1* mutation (p.R132H) and IDH2 mutation (p.R172K). The mutation rate of IDH in tumor tissues was 37.06 ± 8.32%, which was significantly higher than blood samples ($P < 0.05$).

Conclusion: The present study demonstrated that the mutant genes among glioma and metastatic brain tumors are shown to be different. Moreover, the ctDNAs in the metastatic brain tumors included *ALK* and *MDM2*, and glioma-related ctDNAs included 1p/19q and *MDM2* followed by frequencies of *ERBB2, IDH1, CDKN2A, CDK4, PDGFRA, CCNE1, MET*. These ctDNAs might be biomarkers and therapeutic responders in brain tumor.

Keywords: ctDNA, brain tumors, NGS, MGMT, IDH1/2

BACKGROUND

Brain tumors are a highly heterogeneous disease with significant morbidity and mortality, which contains a collection of neoplasms arising largely from within the brain (glioma). On the other hand, brain tumors can also occur because of systemic tumors that have metastasized to the brain (metastatic brain tumors) (1). As for adults, primary brain tumors are predicted to represent 1.4% of all new cancer diagnoses and account for 2.6% of all cancer deaths (2). The overall incidence of glioma throughout the globe is estimated to be 6.4 per 100,000 persons annually, and the disease has been reported with an overall 5-year survival rate of 33.4%.

In addition, age between 55 and 64 years is considered as peak prevalence, and glioma is the most common primary brain tumor in adults (3). Metastatic brain tumors are estimated to occur as much as 10 times more frequently in comparison to glioma, which is ∼53.7 per 100,000 persons (4). Either glioma or metastatic brain tumors are associated with poor prognosis (median overall survival of only 4–15 months), progressive neurological deterioration, and reduced quality of life (5, 6). Therefore, the early diagnosis, accurate differentiation, and dynamic monitoring progression of primary and metastatic brain tumors are of great importance. However, traditional methods, such as clinical examination, magnetic resonance imaging, and histopathological biopsy, are often limited to meet the requirement for clinical practice (7).

Non-invasive or minimal invasive technology to detect circulating tumor DNA (ctDNA) derived from blood (liquid biopsy) has several advantages. First, the technology is able to reduce invasive damages and avoid spatial heterogeneity and difficulties of harvesting brain tumor tissues. Second, it is more feasible and accessible, allowing for repeat blood sampling and providing dynamic insight of brain tumors progression, which becomes a promising and convincing tool to analyze the genomic characterization of brain tumors (8, 9). Recently, according to the revised fourth edition of the World Health Organization (WHO) classification of central nervous system (CNS) tumors, the integration of histology and genetic analysis for the diagnosis of specific neoplastic entities are recommended, such as isocitrate dehydrogenase 1 and 2 (*IDH1/2*) mutations, 1p/19q chromosomal codeletion, point mutations in tumor protein 53 (*TP53*), and O6-methylguanine methyltransferase (*MGMT*) promoter methylation for adults diffuse glioma (10). Other genetic alterations are meaningful for the molecular characterization of different types of brain tumors, including mutation in the promoter of telomerase reverse transcriptase (*TERT*) for oligodendroglioma, the v-RAF murine sarcoma viral oncogene homolog B1 (*BRAF*) *V600E* mutation for non-diffuse glioma, and v-rel avian reticuloendotheliosis viral oncogene homolog A (*RELA*) fusion for supratentorial ependymomas (11, 12). Recently, the next-generation sequencing (NGS) technologies have drawn increasing attention as a result of several advantages, such as globally interrogating the genetic composition of biological samples, significantly reduced sequencing cost, improved accuracy of detection, and real-time monitoring progression of tumors, with high sensitivity for detecting extremely low levels of mutation frequency; therefore, the technology allows early screening and diagnosis of brain tumors (13). However, limited reports exist considering the NGS-related assessments in both glioma and metastatic brain tumors.

In the present study, the genetic characterization of both glioma and metastatic brain tumors was comprehensively analyzed by using tumor tissue or blood samples based on the NGS technology, including mutant gene, microsatellite instability (MSI), mismatch repair, tumor mutational burden (TMB), and PD-L1 expression. Our research was conducted to help provide insight for the genetic alterations in both primary and metastatic brain tumors.

METHODS

Participants

Based on a protocol approved by the institutional review board at Peking University International Hospital, the current retrospective, single-center study was performed according to the Good Clinical Practice guidelines, as well as the principles of the Declaration of Helsinki. The medical records of adult patients harboring brain tumors were reviewed. The patients enrolled undergoing the whole treatments in this hospital from August 2018 to June 2019 ($N = 213$). In order to be included in the current study, the following inclusion criteria should be met: (1) patients with age ranging from 18 to 75 years old; (2) patients were pathologically confirmed with primary or metastatic brain tumors, and with 5-year cancer-free history (excluding melanoma); (3) patients with normal functions of multiple vital organs (including heart, liver, lung, kidney, and bone marrow) without severe or vital illness; (4) patients scored from 0 to 1 based on the Eastern Cooperative Oncology Group (ECOG); (5) patients were in agreement with complete ctDNA tests for tissue or blood samples; (6) informed consent form was signed voluntarily by participants. The exclusion criteria included history of other malignant tumors or CNS benign tumors within 5 years (excluding melanoma), participating

in other clinical trials within 3 months, organ transplant or blood transfusion recipients within 3 months, pregnant or lactating women, hepatitis B virus/hepatitis C virus/human immunodeficiency virus positive, autoimmune diseases, severe or vital illness, ECOG scoring from 2 to 5, incomplete clinical evaluations, incomplete ctDNA tests, unsigned informed consent form, and other unsuitable circumstances.

Sampling and Sequencing

Genomic DNA was extracted from blood samples or tumor tissues. As for blood sampling, at least 10 mL of peripheral blood (anticoagulated with EDTA) was drawn from participants and separated through centrifugation (1,600 × *g*, 10 min) at room temperature. Circulating tumor DNA of blood samples was extracted with the use of QIAamp Circulating Nucleic Acid Kit (Qiagen, Hilden, Germany). As for tumor tissues, ctDNA from 10-μm formalin-fixed paraffin-embedded (FFPE) tissue was extracted through the use of QIAamp DNA FFPE Tissue Kit (Qiagen) following manufacturer's instructions. After DNA quantification, take more than 20 ng of DNA from the instructions of the kit for DNA library construction (Kapa HTP library preparation kit). The steps include ctDNA large fragment separation, small fragment recovery, DNA end repair and a-connector connection, adding special connector of Illumina sequencing kit (California, USA) at both ends of DNA, magnetic bead screening according to the required DNA fragment size, polymerase chain reaction (PCR) amplification library for probe hybridization capture, and sequencing experiment. In the panel, the target region is designed according to the reference genome sequence of Hg 19 to detect point mutation, insertion, fusion, and deletion. With the application of a NextSeq 500 instrument (Illumina), sequencing was performed with an average coverage of 550-fold. When choosing the respective adapters, the sample in the panel could be generally detected on other sequencing devices. Flow cells were selected on the basis of desired read length (150 bp), number of samples, and required target coverage for the Illumina reagent selection algorithm. The sequencing data are first processed by base calling to extract base information, and then data quality control is carried out, including removing low-quality data, tailoring data, removing poly X and other error information; data comparison, deduplication, and error correction are processed by RWA, PICARD algorithms; GATK and VarScan2 are used for variation information, genotype information, SNP, indel, et al. (14–16) are obtained. Finally, annotate the variation information. The specific methods are as follows: RAW sequencing reads were preprocessed by fastp v0.18.0 and then aligned to the reference genome (hg19/GRch37) using BWA-MEM v0.7.15 with default settings. Gencore v0.12.0 was used to remove duplicated reads. Pileup files for properly paired reads with mapping quality ≥60 were generated using Samtools v0.1.19. Somatic variants were called by VarScan2 v2.3.8 and GATK 4.0. The called somatic variants were filtered with following criteria: read depth >20 ×; variant allele frequency (VAF) ≥2% for tumor tissue DNA and ≥0.05% for cfDNA from blood samples; somatic $P \leq 0.01$; strand filter ≥1. Allele frequencies were calculated with all bases of quality >Q30. CNVkit v0.9.3 was applied for copy number variation detection, and GeneFuse v0.6.1 was used to detect actionable gene fusions. Paired-end sequencing was employed and applied in order to improve the sensitivity of duplicate detection as well as increase the detection reliability of possible fusions (17).

Statistics Analysis

The present study applied Statistical Product and Service Solutions software (SPSS 15.0, Inc., Chicago, IL, USA) for statistical analysis. The aggregated results were expressed as mean ± standard deviation (SD). We also utilized one-way analysis of variance (ANOVA) and two-way ANOVA and Student *t*-test for continuous data, and χ^2 test was used for categorical data. In addition, Kruskal–Wallis test and Wilcoxon two-sample tests were used for non-normal distribution samples. $P < 0.05$ represented significant statistical difference.

RESULTS

Demographic Characteristics

The current retrospective study involved a total number of 28 patients (21 men and 7 women) harboring brain tumors. The patients enrolled in the present study were divided into two groups including primary brain tumor group ($n = 21$) and metastatic brain tumor group ($n = 7$). The average age of all included 28 patients was 47.5 ± 13.8 years (range, 22–75 years). The mean age of patients in metastatic brain tumor group (61.2 ± 9.4 years) was calculated to be significantly higher when comparing that in primary brain tumor group (Age: glioma 43.65 ± 13.05, Metastatic brain tumor: 59.86 ± 8.85) ($P < 0.05$). As laid out in **Table 1**, the pathological type of all glioma was diffuse glioma, and the pathological types of metastatic brain tumors included lung adenocarcinoma, lung squamous carcinoma, renal cell carcinoma, intestinal adenocarcinoma, and endometrial cancer.

TABLE 1 | Demographic characteristics of patients with brain tumors.

Variable	All	Glioma tumor	Metastatic brain tumor
Number, *n* (%)	28	21(75.0%)	7 (25.0%)
Age (y)	47.5 ± 13.8	43.65 ± 13.05	59.86 ± 8.85[a,b]
Gender			
Male, *n* (%)	21 (75.0 %)	16 (76.2%)	5 (71.4%)
Female, *n* (%)	7 (25.0%)	5 (23.8%)	2 (28.6%)
Pathological type, *n* (%)		Diffuse glioma, 22 (100%)	Lung adenocarcinoma, 3 (42.9%) Renal cell carcinoma, 1 (14.3%) Endometrial cancer, 1 (14.3%) Intestinal adenocarcinoma, 1 (14.3%) Lymphoma, 1(14.3%)

Data presented as mean ± SD or n (%) and P < 0.05 was considered statistically significant. [a]P < 0.05 vs. All; [b]P < 0.05 vs. Primary brain tumor.

Data Processing Results

The results of data processing are shown in **Tables 2**, **3**. The raw data and mapped data of cfDNA in patients' peripheral blood are shown in **Table 2**. All patients had more than 99.90% mapped rate and 92.00% unique mapped rate, among which patient 11 had the lowest unique mapped rate (92.40%). Patient gDNA data information is shown in **Table 3**. All patients had mapped rate >99.8% and unique mapped rate >98.00%.

Genetic Alterations

As seen in **Figure 1**, the most frequent genetic alterations identified were *MGMT* (46.7%), followed by *IDH1* (26.7%), *TP53* (26.7%), *CDKN2A* (16.7%), *H3F3A* (13.3%), *MDM2* (13.3%), *1p/19q* (10%), *ATM* (10%), *EGFR* (10%), *ALK* (6.7%), *BRAF* (6.7%), *CDK4* (6.7%), *ERBB2* (6.7%), *MDM4* (6.7%), *MET* (6.7%), *NF1* (6.7%), *PDGFRA* (6.7%), *PTEN* (6.7%), *ARID1A* (3.3%), *BRCA1* (3.3%), *CCNE1* (3.3%), *FGFR1* (3.3%), *IDH2* (3.3%), *KIT* (3.3%), *KRAS* (3.3%), and *PIK3CA* (3.3%). Different somatic mutations occur in all genes, including amplification and fusion, chromosomal structural variation, insertion and deletion, and point mutation; among them, germline mutations occur in genes *ATM*, *BRCA1*, *IDH1*, *PTEN*, *EGFR*, *IDH2*, and *TP53*; ctDNA mutation rate is lower than tissue, among which *TP53*, *ATM*, *BRAF*, and *PTEN* do not occur in ctDNA.

The genetic alterations in metastatic brain tumors are shown in **Table 4**. The mutant genes in this group included *ALK*, *MDM2*, *ATM*, *BRCA1*, *FGFR1*, and *KRAS*. Among them, ALK mutation is the fusion of EML4-exon6 and ALK-exon 20 genes, MDM2 and FGFR1 mutation is copy number variation; ATM and BRCA1 mutations are germline heterozygous variants. The results of peripheral blood and tissue were basically similar. MDM2 did not detect variation in tissue, but the copy number in peripheral blood was 4. FGFR1 in the same patient did not detect variation in peripheral blood, but the copy number in tissue was 3.8. However, there were no glioma-related mutant genes. Remarkably, the MSI type of endometrial cancer metastatic brain tumor is MSI-H; the other MSI type of metastatic brain tumor is MSS.

As seen in **Figure 2**, glioma-related mutant genes included *MGMT* ($n = 14$), *IDH1* ($n = 8$), *IDH2* ($n = 1$), *1p/19q* (n = 3), *BRAF* ($n = 2$), and *TP53*($n = 6$) in the glioma group. Among them, *MGMT* methylation, *IDH* mutation, *1p/19q* deletion, *BRAF* mutation, *TP53* mutation or splicing mutation, and all patients with *IDH* mutation showed *MGMT* methylation positive. All genes have different somatic mutations; among them, the genes causing germline variation are *IDH1*, *PTEN*, *EGFR*, *BRAF*, *IDH2*, and *TP53*. In the detection of glioma gene mutation, it was found that there was a great difference between the tissue mutation rate and the peripheral blood mutation rate.

TABLE 2 | Patient cfDNA raw data and mapped data.

Sample/cfDNA	Raw data	Clean data	Mapped data			
			Mapped reads	Mapped rate (%)	Unique mapped	Unique mapped rate (%)
1	63635109	62867246	62776621	99.86	62561967	99.51
2	82706726	81569670	81522163	99.94	81442332	99.84
3	54898315	54309126	54272482	99.93	54154609	99.72
4	93141659	92242771	92196539	99.95	92045800	99.79
5	63580115	62986487	62967226	99.97	62889967	99.85
6	53309568	52834976	52820040	99.97	52767748	99.87
7	116543183	114868302	114760711	99.91	106935843	93.09
8	66168658	65159095	65082262	99.88	64932280	99.65
9	28897366	28456160	28424382	99.89	28029058	98.50
10	25802218	25289301	25238625	99.80	24949636	98.66
11	115953874	114392151	114298549	99.92	105693584	92.40
14	61003326	60465008	60446509	99.97	60377546	99.86
16	49393646	48364871	48335596	99.94	48253531	99.77
17	109574934	108354095	108284996	99.94	108180033	99.84
18	59292893	58632937	58589463	99.93	57963273	98.86
19	41871323	41284423	41268391	99.96	40798788	98.82
20	137472397	135922473	135833229	99.93	135324076	99.56
21	146248056	143746431	143605635	99.90	143424774	99.78
22	67027604	66500690	66436931	99.90	66348527	99.77
23	67628547	66881607	66857604	99.96	66774953	99.84
24	62477626	61435056	61388961	99.92	61300629	99.78
25	94187189	93238733	93186439	99.94	93078384	99.83
26	91145779	89820387	89754604	99.93	89493803	99.64
28	76629466	76077872	76011800	99.91	75816732	99.66

TABLE 3 | Patient gDNA raw data and mapped data.

Sample/gDNA	Raw data	Clean data	Mapped data			
			Mapped reads	Mapped rate (%)	Unique mapped	Unique mapped rate (%)
1	66531967	65792013	65749464	99.94	65632495	99.76
2	39757181	39389673	39377443	99.97	39107803	99.28
3	35659785	34971757	34916499	99.84	34292628	98.06
4	30846537	29820218	29819198	100.00	29604650	99.28
5	29785822	29452871	29442446	99.96	29198601	99.14
6	81906016	81165609	81139259	99.97	80985694	99.78
7	50105179	49626011	49599260	99.95	49290266	99.32
8	70699970	69740194	69645649	99.86	69549091	99.73
9	43816628	43234047	43186976	99.89	42671838	98.70
10	41371341	39679044	39606057	99.82	38928846	98.11
11	111206589	109842532	109715630	99.88	109549959	99.73
12	48371223	47853335	47818179	99.93	47326009	98.90
13	45418688	42619589	42604633	99.96	42291776	99.23
14	34771950	34388704	34373003	99.95	33956643	98.74
15	114586944	110555929	110492789	99.94	109482466	99.03
16	19845365	19607222	19596907	99.95	19337713	98.63
17	47985546	47471783	47422382	99.90	45783988	96.4
18	60162428	59435412	59385430	99.92	58713449	98.79
19	42419153	41979994	41967147	99.97	41567125	99.02
20	46667933	46194675	46135923	99.87	45027230	97.47
21	80715730	79762969	79688969	99.91	79535799	99.72
22	33602295	33297637	33284888	99.96	33051096	99.26
23	36249446	35951141	35940380	99.97	35639912	99.13
24	59931926	59306786	59276075	99.95	58739233	99.04
25	100346154	99222412	99162043	99.94	98564904	99.34
26	67050678	66345831	66292803	99.92	65789276	99.16
27	28267255	27957878	27944746	99.95	27656077	98.92
28	35401850	35051830	35039088	99.96	34714611	99.04

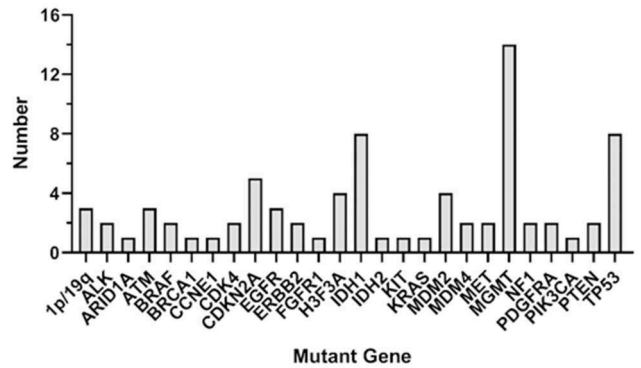


FIGURE 1 | Genetic alterations in the whole participants. The figure shows the overall gene mutation statistics of 28 patients, among which MGMT has the greatest mutation probability, with a total of 14 patients; IDH1 and TP53 have the second mutation in eight patients each; CDK4 gene mutation in five patients; H3F3A and MDM2 have mutations in four patients each; 1p/19q, ALM, EGFR have mutations in three patients each, and the number of mutations in other genes is small.

In general, the tissue mutation rate was higher than the peripheral blood mutation rate (**Table 5**). And *TP53* gene was found to be highly variable in tissue in patients with *TP53* mutation detected. Interestingly, 47.6% of glioma patients were detected ctDNA, but only two metastatic patients were found with somatic mutations in ctDNA. Glioma-related ctDNAs included 1p/19q, *MDM2, ERBB2, IDH1, CDKN2A, CDK4, PDGFRA, CCNE1, MET*. Among ctDNA positive glioma patients, 30% of them were detected 1p/19q codeletion and *MDM2* amplification in both tissue and blood.

The genetic alterations in glioma were laid out in **Table 6**. The mutant genes in this group included *MGMT*, *IDH1*, IDH2, *1p/19q*, *BRAF*, *TP53*, *CDKN2A*, *H3F3A*, *MDM2*, *ATM*, *EGFR*, *ALK*, *CDK4*, *ERBB2*, *MDM4*, *MET*, *NF1*, *PDGFRA*, *PTEN*, *ARID1A*, *BRCA1*, *CCNE1*, *FGFR1*, *KIT*, *KRAS*, and *PIK3CA*. Based on **Table 7**, the characterizations of *IDH* mutations in the glioma included *IDH1* mutation (p.R132H) and *IDH2* mutation (p.R172K). The mutation abundance of *IDH* in tumor tissues was $37.06 \pm 8.32\%$, which was significantly higher in comparison to that in blood samples ($P < 0.05$).

TABLE 4 | Genetic alternations in metastatic brain tumors.

Pathologic types	Sample type	Mutant genes	Variation	Variation rate of tissue	Variation rate of peripheral blood	MSI	TMB (muts/Mb)	PD-L1
Lung adenocarcinoma	Fresh tissue/peripheral blood	*ALK,*	*EML4-exon6-ALK-exon20* fusion	33.24%	49.82%	MSS	5.22	5%
		MDM2	Amplification		4 copies		0.87	
Lung adenocarcinoma	Fresh tissue/peripheral blood	*ALK*	*EML4-exon6-ALK-exon20* fusion	13.07%	0	MSS		–
Renal cell carcinoma	Fresh tissue/peripheral blood	*ATM*	Heterozygous (germline) c.5919-2A>G			MSS	0	–
Intestinal adenocarcinoma	Fresh tissue/peripheral blood	*KRAS*	Amplification	7.20%		MSS	2.61	1%
Lung adenocarcinoma	Fresh tissue/peripheral blood	*FGFR1*	Amplification	3.8 copies		MSS	8.7	–
Lymphoma	Fresh tissue/peripheral blood	*MDM4*	Amplification	3.8 copies	2copies	MSS	3.82	1%
Endometrial cancer	Fresh tissue/peripheral blood	*BRAC1*	Hheterozygous (germline) p.E1304fs			MSI-H	3.48	10%

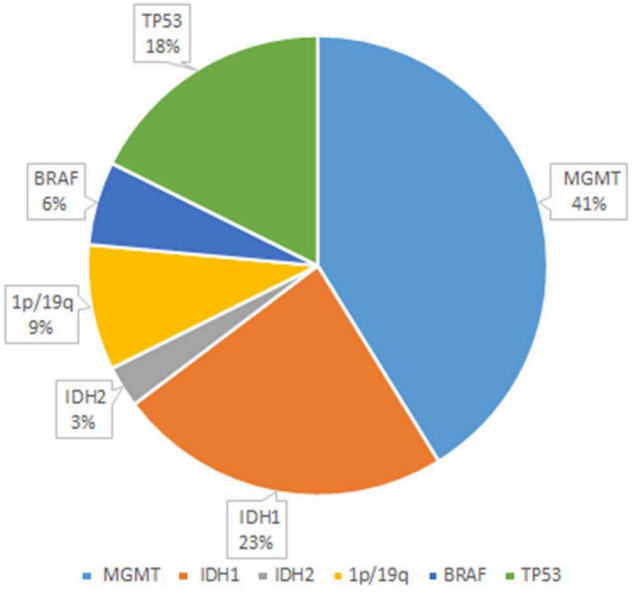


FIGURE 2 | Glioma-related mutant genes. The figure shows several genes with higher probability of mutation and their respective probability of occurrence in 22 glioma patients. Among them, the genes prone to mutation were MGMT, IDH1, IDH2, 1p/19q, BRAF, and TP53, and their mutation changes were 41, 23, 3, 9, 6, and 18%, respectively.

DISCUSSION

The accurate differentiation of primary and metastatic brain tumors is considered pivotal, considering that the intervention and therapy approaches for patients with these two types of tumors are remarkably different for clinical practice (18, 19). The cancers with the highest propensity in terms of metastasizing to the brain are lung (50%), followed by breast (15%) and melanoma (5–10%), accounting for ∼80% of all brain metastases (20). In this study, we found that the mutant genes in the metastatic brain tumors included *ALK*, *MDM2*, *ATM*, *BRCA1*, *FGFR1*, and *KRAS*, and there were no glioma-related mutant genes (*MGMT*, *IDH1*, *IDH2*, *1p/19q*, *BRAF*, and *TERT*). According to the aggregated result, NGS-based genetic analysis might become a promising tool to differentiate primary and metastatic brain tumors. Based on a report supported by Bettegowda et al. (21), the sensitivity of ctDNA was 87.2% for detection of clinically relevant *KRAS* gene mutations, with specificity of 99.2% in the detection of metastatic cancers. Wang et al. (22) suggested that liquid biopsy such as ctDNA could be regarded a feasible alternative approach in terms of identifying sensitizing genomic alterations, and ALK translocation could be identified in the diffuse brain metastases. However, in this study ALK, MEM2 and MDM4 were detected in ctDNA of only two brain metastatic patients. It might be due to sample size, and we plan to expand the sample size in further study. Moreover, the results showed that glioma-related mutant genes included *MGMT* ($n = 14$), *IDH1* ($n = 8$), *IDH2* ($n = 1$), *1p/19q* ($n = 3$), and *BRAF* ($n = 2$). As a DNA repair protein, MGMT is able to remove the alkylation of the O6 position of guanine which is also the most cytotoxic lesion induced by alkylating agent chemotherapy (23). Hypermethylation of the promoter of *MGMT* is considered to have predictive value to respond to the alkylating agent temozolomide among patients harboring glioblastoma (24). Piccioni et al. (25) reported that 50% of patients with glioma had ≥1 somatic alteration detected. Additionally, 61 genes were found with single-nucleotide variants, and amplifications were detected in *EGFR MET*, *ERBB2*, and others, indicating that plasma cfDNA genomic analysis might be used as a viable approach for clinical practice to identify genomically driven therapy options. According to the study of Schwaederle et al. (26), the most frequent alterations among diverse cancers were reported to be *TP53* (29.8%), followed, respectively, by *EGFR* (17.5%), *MET* (10.5%), *PIK3CA* (7%), and *NOTCH1* (5.8%). In addition, detectable ctDNA aberrations existed among 65% of diverse cancers (as well as 27% of glioblastomas), with the majority theoretically actionable by an approved agent. In this study, 47.6% of glioma patients were detected ctDNA including 1p/19q, *MDM2, ERBB2, IDH1,*

TABLE 5 | Gene mutations in tissues and peripheral blood of patients with glioma.

Pathologic diagnosis	Sample type	Mutant gene	Variation	Variation rate of tissue (%)	Variation rate of peripheral blood (%)
Glioma	Peripheral blood/Fresh tissue	*IDH1*	p.R132H	31.3	0.79
		MGMT	Methylation		
Glioma	Peripheral blood/Fresh tissue	*MGMT*	Methylation		
Glioma	Peripheral blood/Fresh tissue	*IDH1*	p.R132H	33.31	0
		MGMT	Methylation		
Glioma	Peripheral blood/Fresh tissue	*IDH1*	p.R132H	28.43	0
		MGMT	Methylation		
Glioma	Peripheral blood/Fresh tissue	*MGMT*	Methylation		
		EGFR	Amplification	44.5 copies	
		PTEN	p.R130*	33.76	0
		EGFR	p.A289v	11.67	0
Glioma	Peripheral blood/Fresh tissue	*MGMT*	Methylation		
		IDH1	p.R132H	31.03	0
		1P/19q	Codeletion	1.25 copies	2
Glioma	Peripheral blood/Fresh tissue	*MGMT*	Methylation		
		BRAF	p.D594N	14.89	0
		MDM2	Amplification	3 copies	2 copies
Glioma	Peripheral blood/Fresh tissue	*1P/19q*	Codeletion	1.26 copies	2 copies
		IDH2	p.R172K	36.06	0
		MGMT	Methylation		
Glioma	Peripheral blood/Fresh tissue	*MGMT*	Methylation		
		1P/19q	Codeletion	1.18 copies	2 copies
		IDH1	p.R172H	37.25	0
Glioma	Peripheral blood/Fresh tissue	*MGMT*	Methylation		
		IDH1	p.R132H	35.82	0
		TP53	p.H168Q	34.06	0
		TP53	Splice mutation	36.18	0
		EGFR	Amplification	27.5 copies	
Glioma	Peripheral blood/Fresh tissue	*CDKN2A*	Defect	0.4 copies	
		PTEN	p.N184Kfs*6	56.31	
		MGMT	Methylation		
		CDK4	Amplification	7 copies	
		CDKN2A	Defect	0.4 copies	
Glioma	Peripheral blood/Fresh tissue	*MGMT*	Methylation		
Glioma	Peripheral blood/Fresh tissue	*H3F3A*	p.K28M	44.24	0
		TP53	c.994-1G>A	85.77	0
		CDKN2A	Defect	1.2 copies	2 copies
		ERBB2	Amplification	3.9	2.1
		MDM2	Amplification	3.4	2
Glioma	Peripheral blood/Fresh tissue	*IDH1*	p.R132H	55.18	
		MGMT	Methylation		
		TP53	p.R273H	86.16	
		CDKN2A	Defect	0.4 copies	
		MET	Amplification	4.2 copies	
		PDGFRA	Amplification	79.5 copies	
		KIT	Amplification	79.5 copies	
Glioma	Peripheral blood/Fresh tissue	*H3F3A*	p.K28M	44.36	0
		CDK4	Amplification	4 copies	2 copies
		MDM2	Amplification	6 copies	2 copies
		ARID1A	p.E1787Kfs*11		

(Continued)

TABLE 5 | Continued

Pathologic diagnosis	Sample type	Mutant gene	Variation	Variation rate of tissue (%)	Variation rate of peripheral blood (%)
Glioma	Peripheral blood/Fresh tissue	*TP53*	p.R248Q	44.28	0
		TP53	p.V157L	46.99	0
		PDGFRA	Amplification	13.4 copies	2 copies
		ATM	p.I1422Qfs*4	46.34	0
		ATM	c.6347 + 1G > A	9.52	0
Glioma	Peripheral blood/Fresh tissue	*BRAF*	p.V600E	3.56	0
		CCNE1	Amplification	4 copies	2 copies
		ERBB2	Amplification	3 copies	2 copies
Glioma	Paraffin section/Peripheral blood	*H3F3A*	p.K28M	42.81	
		NF1	p.?	39.83	
		NF1	p.Q2507Nfs*20	33.47	
Glioma	Peripheral blood/Fresh tissue	*TP53*	p.R249	4.25	0
Glioma	Peripheral blood /FFPE	*PIK3CA*	p.H1047L	9.59	
		H3F3A	p.K28M	61.83	
		MDM4	Amplification	3 copies	
Glioma	Peripheral blood/Fresh tissue	*IDH1*	p.R132H	45.15	0
		MGMT	Methylation		
		TP53	p.R248W	91.06	0
		MET	Amplification	3.2	2

TABLE 6 | Genetic alternations in primary brain tumors.

Number	Mutant genes	MSI	MMR	TMB (muts/Mb)	PD-L1 (%)
1	*IDH1, MGMT*	MSS	pMMR	3.48	–
2	*MGMT*	MSS	pMMR	3.48	–
3	*IDH1, MGMT*	MSS	pMMR	4.35	1
4	*IDH1, MGMT*	MSS	pMMR	3.48	<1
5	*MGMT, EGFR, PTEN*	MSS	pMMR	1.74	–
6	*MGMT, IDH1, 1p/19q*	MSS	pMMR	3.48	–
7	*MGMT, BRAF, MDM2*	MSS	pMMR	2.61	30
8	*MGMT. IDH2, 1p/19q*	MSI-H	pMMR	2.61	<1
9	*MGMT, IDH1, 1p/19q*	MSS	pMMR	3.48	–
10	*MGMT, IDH1, TP53*	MSS	pMMR	2.61	<1
11	*MGMT, EGFR, PTEN, CDK4, CDKN2A*	MSS	pMMR	4.35	40
12	*MGMT*	MSS	pMMR	0	1
13	*H3F3A, TP53, CDKN2A, MDM2, ERBB2*	MSS	pMMR	2.29	–
14	*MGMT, IDH1, TP53, CDKN2A, MET, KIT, PDGFRA*	MSS	pMMR	2.29	1
15	*H3F3A, CDK4, MDM2, ARID1A*	MSS	pMMR	2.29	<1
16	*TP53, PDGFRA, ATM*	MSS	pMMR	5.34	1
17	*BRAF, CCNE1, ERBB2*	MSS	pMMR	0	15
18	*NF1, H3F3A*	MSS	pMMR	3.05	<1
19	*TP53*	MSS	pMMR	0	<1
20	*H3F3A, PIK3CA, MDM4*	MSS	pMMR	1.1	1
21	*MGMT, IDH1, TP53, MET*	MSS	pMMR	1.53	<1

CDKN2A, CDK4, PDGFRA, CCNE1, MET. These ctDNAs might be biomarkers and therapeutic responders in glioma and be worthy of further investigation.

Furthermore, we found that the characterizations of *IDH* mutations in the glioma included *IDH1* mutation (p.R132H) and *IDH2* mutation (p.R172K). The mutation abundance of *IDH* in tumor tissues was 37.06 ± 8.32%, which reported evidently higher results in comparison to that in blood samples ($P < 0.05$). *IDH*-mutated results were found in at least 80% of WHO grades II and III infiltrating astrocytomas and secondary GBMs,

TABLE 7 | IDH mutations in the glioma.

Mutant gene	Characterization	Mutation Abundances in tumor tissues (%)	Mutation Abundances in blood (%)
IDH1	p.R132H	31.30	0.79
IDH1	p.R132H	33.31	0
IDH1	p.R132H	28.43	0
IDH1	p.R132H	31.03	0
IDH1	p.R132H	37.25	0
IDH1	p.R132H	35.82	0
IDH1	p.R132H	55.18	0
IDH1	p.R132H	45.15	0
IDH2	p.R172K	36.06	0

whereas all oligodendrogliomas were *IDH*-mutated and 1p/19q co-deleted (27). Similar results were observed in the study of Hartmann et al. (28) that codon 132 of the *IDH1* gene, known as the R132H variant, was reported to account for 92.7% of *IDH* mutation, followed by R132C (4.1%), R132S (1.5%), R132G (1.4%), and R132L (0.2%). Moreover, residue R172 in exon 4 of the *IDH2* gene was homologous to R132 in the *IDH1* gene, and the most common *IDH2* mutations included R172W (16%), R172M (19%), and R172K (65%). In current study, three glioma patients were oligodendrogliomas, and 1p/19q codeletion was detected in both blood and tissue of these patients. Interestingly, copy number of 1p/19q is higher in blood than tissue. Thus these findings provide new insights into verification 1p/19q codeleciton to glioma patient via a noninvasive approach. Lots of focus has been paid to the predictive value of TMB as biomarker in terms of the response to immune checkpoint blockade therapy among many clinical trials (29). High TMB was consistently selected for beneficial outcome with immune checkpoint blockade therapy, and we found that the mean TMB of glioma was 2.55 mutations per Mb. According to the study supported by Johnson et al. (30), 43 to 575 mutations per Mb existed in hypermutated gliomas characterized by TMBs.

CONCLUSION

The present study demonstrated that the mutant genes among glioma and metastatic brain tumors include are different. Moreover, the ctDNAs in the metastatic brain tumors included *ALK* and *MDM2*, and glioma-related ctDNAs included 1p/19q and *MDM2* followed by frequencies of *ERBB2, IDH1, CDKN2A, CDK4, PDGFRA, CCNE1, MET*. These ctDNAs might be noninvasive biomarkers and therapeutic responders in brain tumor.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://bigd.big.ac.cn/search?dbId=&q=HRA000141, with accession no: HRA000141.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at Peking University International Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JL, WZ, CL, and DL carried out the experiments. DL, PL, and JZ participated in data analysis. CL, XY, and YZ participated in the clinical investigation of the patient. JL, PL, and DY drafted the manuscript. JL, JZ, and DY offered opinions for discussions and reviewed the manuscript. YZ and DY critically reviewed the overall manuscript as well as supervised the study. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MicroRNA-221/222 Inhibits the Radiation-Induced Invasiveness and Promotes the Radiosensitivity of Malignant Meningioma Cells

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The controversy of adjuvant radiotherapy of meningiomas is at least partially due to the insufficient understanding on meningioma cells' response to irradiation and the shortage of radiosensitivity-promotion methods. *MicroRNA-221* and *microRNA-222* were identified as critical regulators of radiosensitivity in several other tumors. However, their effect in meningiomas has yet to be confirmed. Therefore, the malignant meningioma IOMM-Lee cells were adopted, transfected with *microRNA-221/222* mimics or inhibitors, and irradiated with different dosages. The effects of radiation and *microRNA-221/222* were then assessed *in vitro* and *in vivo*. Radiation dose increases and *microRNA-221/222* downregulation synergistically inhibited cell proliferation and colony formation, prevented xenograft tumor progression, and promoted apoptosis, but antagonistically regulated cell invasiveness. Pairwise comparisons revealed that only high-dose radiations (6 and 8 Gy) can significantly promote cell invasiveness in comparison with unirradiated counterparts. Further comparisons exhibited that downregulating the *microRNA-221/222* expression can reverse this radiation-induced cell invasiveness to a level of untransfected and unirradiated cells only if cells were irradiated with no more than 6 Gy. In addition, this approach can promote IOMM-Lee's radiosensitivity. Meanwhile, we also detected that the dose rate of irradiation affects cell cycle distribution and cell apoptosis of IOMM-Lee. A high dose rate irradiation induces G0/G1 cell cycle arrest and apoptosis-promoting effect. Therefore, for malignant meningiomas, high-dose irradiation can facilitate cell invasiveness significantly. Downregulating the *microRNA-221/222* level can reverse the radiation-induced cell invasiveness while enhancing the apoptosis-promoting and proliferation-inhibiting effects of radiation and promoting cell radiosensitivity.

Keywords: invasiveness, radiosensitivity, microRNA-221/222, IOMM-Lee, dose rate, epithelial–mesenchymal transition-inducing transcription factors

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INTRODUCTION

Meningiomas, one of the most common primary intracranial neoplasms, are classified into WHO grades I–III on the basis of local invasiveness and cellular features of atypia (1). Surgical resection is the primary treatment. As an important component of the therapeutic management of meningiomas, external beam radiotherapy aims to control tumor growth of surgically inaccessible tumors and in residual or recurrent lesions after surgery, ideally to achieve safe dose escalation and effective toxicity avoidance (e.g., necrosis of brain parenchyma, neurocognitive dysfunction, hypopituitarism, radiation-induced tumors, and malignant transformation) (2). However, radiotherapy has always been controversial, for instance, its necessity for WHO grade II lesions with different extents of resection (2–8), the optimal dosage (9–13), timing (7, 12, 14), etc. Thus, elucidation of how radiation exposure affects meningioma cells and exploration of the possible regulatory mechanism of radiosensitivity are indispensable for improved treatment.

MicroRNAs (miRs) are a family of endogenously synthesized small non-coding RNAs that regulate gene expression by influencing the protein translational machinery and/or inducing degeneration of target messenger RNAs (mRNAs) (15, 16). Genome-wide studies have demonstrated that miRNA genes are frequently located in cancer-associated genomic regions, indicating the potential roles of miRNAs in tumorigenesis (17). Previous studies on meningioma have suggested that several miRNAs participate in the regulation of cell proliferation (18–21), apoptosis (19, 22), invasiveness (19, 23), migration (19, 24), tumor recurrence (25–27), and histopathological progression (18, 19, 25, 27–29). However, no miRNAs have been verified to affect the radiosensitivity of meningiomas. *MiR-221* and *miR-222*, both located on the X chromosome with the same seed sequences, were confirmed to be involved in regulating the radiosensitivity of glioblastoma (30), gastric carcinoma (31), colorectal carcinoma (32, 33), and nasopharyngeal carcinoma (34). However, relevant research on the radiosensitivity of meningioma is lacking. In the present study, we aimed to reveal the effect of radiation on meningioma cells and the role of *miR-221/222* in regulating meningioma radiosensitivity.

MATERIALS AND METHODS

Cells and Cell Culture

The meningioma cell line IOMM-Lee (ATCC Cat. No. CRL-3370, RRID: CVCL_5779) was kindly provided by Professor Jin-Hong Mei (Nanchang University, China) and was authenticated completely match with IOMM-Lee in the American Type Culture Collection (ATCC) short tandem repeat (STR) database without any cross-contamination of other human cell lines before and after this research. Cells were grown in Dulbecco's modified Eagle's medium (DMEM; HyClone, USA) supplemented with 10% fetal bovine serum at 37°C in a 5% CO_2 atmosphere.

Cell Transfection

The *miR-221/222* mimics and inhibitors were chemically synthesized by RiboBio Co., Ltd. (Guangzhou, China) and were transfected into IOMM-Lee cells with ribo*FECT*™ CP reagent according to the manufacturer's instructions. Scrambled oligonucleotides (GenePharma Co., Ltd., Shanghai, China) were also transfected as a negative control. The expression levels of *miR-221* and *miR-222* in transfected IOMM-Lee cells were identified by quantitative real-time PCR.

Radiation Exposure

Irradiation was performed at room temperature in a linear accelerator (Varian600, Varian, USA) at a dose rate of 3.2 Gy/min (31, 33). Cells were plated into six-well plates and exposed to the specified dose (0, 2, 4, 6, and 8 Gy) of X-rays.

Clonogenic Assay

A clonogenic assay was applied to determine the radiosensitivity of IOMM-Lee cells. A predetermined number of viable cells (1,000 cells for 0, 2, and 4 Gy; 2,000 cells for 6 and 8 Gy) were seeded in six-well culture plates and incubated at 37°C for 24 h. Next, the cells were irradiated with different doses and then incubated for 7 days to allow colony growth. Then, colonies were stained with crystal violet, and those containing 50 or more cells were counted. The plating efficiency was calculated by dividing the average number of counted colonies by the number of seeded cells. Survival fractions (SFs) were calculated by normalization to the plating efficiency of the respective unirradiated controls (32). After estimation of the SF at different radiation doses, the survival curve (log of SF vs. the radiation dose) was plotted, and the D_0 value for each group was calculated using the following equation: $SF = 1 - (1 - e^{D/D0})^n$(32). The D_0 value, which represents the radiation dose required to reduce the SF from 100 to 37%, is considered a measure of the intrinsic radiosensitivity of cells (33). The sensitization enhancement ratio for each treated group was determined by the ratio of the D_0 of the control group to that of the treated group (33).

Cell Proliferation Assay

Cells were seeded into 96-well plates at a density of 2×10^3 cells per well and cultured for 12 h. Cell proliferation was assessed using a Cell Counting Kit-8 assay (Fluorescence, Beijing, China) according to the manufacturer's instructions. Absorbance was measured at a wavelength of 450 nm on a Model 550 microplate reader (Bio-Rad Laboratories, Hercules, CA, USA).

Cell Cycle and Apoptosis Analyses by Flow Cytometry

The effects of *miR-221/222* and irradiation on the cell cycle and apoptosis in IOMM-Lee cells were examined by flow cytometry. Pretreated IOMM-Lee cells in the log phase of growth were stained with Annexin V/fluorescein isothiocyanate (FITC) and propidium iodide (Beyotime, China). Cell cycle and apoptotic rate were examined with a fluorescence-activated cell-sorting

Abbreviations: DMEM, Dulbecco's modified Eagle's medium; FACS, fluorescence-activated cell-sorting; miR, microRNA; SER, sensitization enhancement ratio; SF, survival fraction.

(FACS) flow cytometer (BeamCyte, China), and the data were analyzed using CellQuest Software. The percentages of cells in G0/G1 phase and the apoptotic rate were measured by calculating the ratio of the number of corresponding cells and that of total cells. For each sample, 10,000 cells were measured.

Invasion Assay

The invasive potential of the pretreated cells was evaluated by measuring the number of cells that invaded Matrigel-coated Transwell chambers. Prior to the experiment, Transwell inserts with 8-μm pores were coated with Matrigel and reconstituted with fresh medium for 2 h. Cells (1×10^5/ml) were seeded into the upper chambers in 200 μl serum-free DMEM, while DMEM supplemented with 10% fetal bovine serum (700 μl) was placed in the lower chamber. After incubation for 48 h, cells that degraded the Matrigel and invaded the lower surface of the Matrigel-coated membrane were fixed with 70% ethanol, stained with hematoxylin, and counted in five random fields at a magnification ×200 under an optical microscope.

Dual Luciferase Reporter Assay

The 3′-untranslated region (UTR) of phosphatase and tensin homolog (PTEN), which contains the predicted binding sites of *miR-221/222*, were cloned into the *Xho*I site of the psi-check2 reporter vector (Biomed, Beijing, China). For the luciferase reporter assays, IOMM-Lee cells were cultured in 24-well plates with three replicates, incubated for 24 h, and transfected with 500 ng of psi-check2-PTEN or psi-check2-control plasmids with/without 100 nM *miR-221* mimics or *miR-222* mimics using Lipofectamine 3000. Luciferase activity was measured 48 h after transfection using dual-luciferase reporter assay system (Promega, WI, USA) according to the manufacturer's procedures. Data were normalized by Firefly/Renilla luciferase activity.

Western Blot Analysis

Protein of IOMM-Lee cells from each subgroup was extracted using radioimmunoprecipitation assay (RIPA) buffer (Beyotime, Shanghai, China). Their concentration was determined using a BCA Protein Assay Kit (Beyotime, Shanghai, China). Equal amounts of protein (5 μg) were then subjected to 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) followed by transfer of protein to polyvinylidene fluoride (PVDF) membranes (Millipore, Darmstadt, Germany). Membranes were subsequently blocked in Tris-buffered saline containing 0.1% Tween-20 and 5% skimmed milk powder and were incubated with primary antibodies against PTEN (1:1,000 dilution) and β-actin (1:4,000 dilution) (Cell Signaling Technology, MA, USA) overnight at 4°C. Horseradish peroxidase (HRP)-conjugated secondary antibodies for PTEN (1:2,000 dilution) and β-actin (1:4,000 dilution) (Cell Signaling Technology, MA, USA) were used afterward. The blots were detected using Pierce™ ECL Western Blotting Substrate (Thermo Fisher Scientific, Rockford, USA), and the membranes were developed using a ChemiDoc MP imaging system (Bio-Rad, Hercules, CA).

In vivo Studies

All animal studies were conducted in accordance with an approved institutional animal care and use committee protocol of our hospital (202001014). IOMM-Lee cells (5×10^6) were injected subcutaneously into the flank position of 5-week-old female BALB/c nude mice. When the tumors reached 5 mm in diameter, animals were randomly divided into 4 groups of 16 mice each and were, respectively treated with intratumoral injections of saline, scramble oligonucleotides, *miR-221/222-3p* agomirs, and *miR-221/222-3p* antagomirs (RiboBio, Guangzhou, China) every 4 days for a total of three doses (3 nmol/dose). Eight animals from each group were radiated with two doses of 4 Gy during the intervals between injections. The entire mouse body except the tumor area was covered with lead sheets to avoid exposure to radiation during treatments. Vernier caliper was used to measure the length and width of tumors on alternate days, and tumor volumes were calculated as $\pi/6 \times (\text{length} \times \text{width}^2)$. Regression in subcutaneous tumor growth was followed, and mice were euthanized when tumor rupture and hemorrhage were observed in unradiated-control group. Immediately after the removal of the tumors, half of each tumor was stored in liquid nitrogen for the subsequent quantification of *miR-221* and *miR-222* by using quantitative real-time PCR (qRT-PCR); the other half was fixed in buffered formaldehyde and was sectioned and subjected to the later H&E and immunohistochemical staining for PTEN.

Statistical Analysis

The abovementioned experiments were performed at least in triplicate, and data are presented as the mean ± standard deviation. The effects of *miR-221/222* expression level and radiation dose on IOMM-Lee cells *in vitro* and *in vivo* were tested with two-way analysis of variance. Simple effect and pairwise comparisons with Bonferroni posttest were performed if the interaction between the factors appeared significant; otherwise, main effect and multiple comparisons with Bonferroni posttest were performed. Further comparisons of invasive cell numbers between the inhibitor group and the control/scramble group exposed to different radiation doses were analyzed by independent-sample *t*-tests. Multiple comparisons of xenograft tumor volumes between different treatment groups were analyzed by ANOVA with Bonferroni posttest. All *P* values are two-sided, and significance was defined using a threshold of 0.05. Statistical analyses were performed with SPSS version 19.0 (IBM Corp. Armonk, New York, USA).

RESULTS

Modulation of *miR-221/222* Expression in IOMM-Lee Cell Line

IOMM-Lee cells were transfected with *miR-221/222* mimics or inhibitors. qRT-PCR revealed that no significant difference in *miR-221* and *miR-222* expression between the control and the scramble group (*miR-221*: $P = 0.7640$, *miR-222*: $P = 0.0856$). Compared with that in either the control or the scramble group, the expression of *miR-221* and *miR-222* increased significantly in the *miR-221/222*-mimic group (*miR-221*: vs. control, $P < 0.0001$;

vs. scramble, $P < 0.0001$; *miR-222*: vs. control, $P < 0.0001$; vs. scramble, $P < 0.0001$), while it decreased significantly in the *miR-221/222*-inhibitor group (*miR-221*: vs. control, $P < 0.0001$; vs. scramble, $P < 0.0001$; *miR-222*: vs. control, $P < 0.0001$; vs. scramble, $P < 0.0001$) (**Figures 1A,B**).

Radiation Dose and Expression Level of *miR-221/222* Synergistically Modulate IOMM-Lee Cell Proliferation, Apoptosis, and Cell Cycle Distribution

With an increase in radiation dose or a decrease in *miR-221/222* expression level, the absorbance and colony number of IOMM-Lee cells decreased gradually, while apoptotic percentage and G0/G1 phase percentage increased; however, their invasive cell number increased as the radiation dose increased and decreased as the *miR-221/222* expression level decreased (**Table 1**, **Figure 1**). Two-way ANOVA revealed significant simple effects of radiation dose and *miR-221/222* expression level and their significant interactions in the proliferation, colony formation, apoptosis, and invasiveness of IOMM-Lee cells, while it exhibited their significant main effects in the sub-G0/G1 population, yet without significant interactions (**Table 2**).

Increasing radiation dose and downregulating *miR-221/222* expression have synergistic effects on inhibiting proliferation and promoting apoptosis of IOMM-Lee cells (**Tables 1**, **2**). Significant decrease in cell absorbance and colony number appears at each step-up of irradiation dose or each fall of the *miR-221/222* expression (**Tables 3**, **5** and **Figures 1C,I**), indicating that the proliferation-inhibiting effect of radiation can be significantly enhanced by downregulating *miR-221/222* expression.

As to the apoptosis of IOMM-Lee cells, pairwise comparisons of different groups revealed that, by irradiating with the same dosage, the apoptosis rate was significantly increased with downregulation of *miR-221/222* expression (**Table 5** and **Figures 1D,E**). Meanwhile, (1) the radiation dose that initially significantly promoted cell apoptosis was much higher in the *miR-221/222*-mimic group (6 Gy) than in the other groups (2 Gy) compared to their respective unirradiated cells; (2) within irradiated IOMM-Lee cells, the significant increase in apoptotic rate caused by each step-up of irradiation dose, which can be seen in cells with regular or decreased *miR-221/222* expression, was not observed as the expression of *miR-221/222* promoted; (3) in the comparisons between two irradiated subgroups with an incremental gradient of 4 or 6 Gy, the apoptosis rate increased significantly in the control, scramble, and *miR-221/222*-inhibitor group, whereas no significant differences were detected in the *miR-221/222*-mimic group (**Table 3** and **Figures 1D,E**). These findings, from different perspectives, suggest that the apoptosis-promoting effect of radiation can be significantly enhanced by downregulating *miR-221/222* expression in IOMM-Lee cells.

Further analysis of cell cycle distribution exhibits that the sub-G0/G1 population was positively correlated with radiation dose but negatively correlated with *miR-221/222* expression (**Table 4**, **Figures 1F,G**). No corresponding effects on the sub-G2/M population were found. Although a significant effect of radiation dose on the S phase population was presented with an interaction with the *miR-221/222* expression level (**Table 2**), no obvious radiation dose-dependent trend was explored in pairwise comparisons (**Table 3**).

Radiation Dose and Expression Level of *miR-221/222* Antagonistically Modulate IOMM-Lee Cell Invasion

Increased radiation dose and downregulated *miR-221/222* have antagonistic effects on cell invasiveness (**Tables 1**, **2**). Pairwise comparison analysis revealed that (1) invasive cell number at 8 Gy was significantly higher than that at lower radiation doses in the control or the scramble group, while invasive cell number at 6 Gy was only significantly higher than that of the unirradiated/2 Gy-irradiated control groups and unirradiated scramble group, respectively; (2) in the *miR-221/222*-mimic group, the invasive cell number for cells irradiated with a dose no lower than 4 Gy was significantly higher than that at lower radiation doses. However, in the *miR-221/222*-inhibitor group, the invasive cell number was significantly increased only in the comparison of 0 vs. 8 Gy (**Table 3** and **Figure 1H**); (3) the expression level of *miR-221/222* had no significant effect on cell invasiveness at a low radiation dose ($\leq$2 Gy) compared to that of the control or the scramble group. Only at high radiation doses did the high expression of *miR-221/222* exhibit a significant invasion-promoting effect ($\geq$4 Gy), while the low expression of *miR-221/222* presented a significant invasion-inhibiting effect ($\geq$6 Gy) (**Table 5** and **Figure 1H**).

By further comparing the invasive cell numbers of the inhibitor group and the control/scramble group exposed to different irradiation doses, it was revealed that although failed to completely reverse the 8-Gy-promoted invasiveness to a low-dose radiation-induced level, downregulation of *miR-221/222* expression can completely reverse the 6-Gy-induced cell invasiveness to a level, which is without significant increase compared with that of the low-dose-irradiated control groups or unirradiated/low-dose-irradiated scramble groups (**Tables 1**, **6**).

Downregulation of *miR-221/222* Expression Promotes Radiosensitivity of IOMM-Lee Cells

The effect of genetic manipulation of *miR-221/222* on radiosensitivity of IOMM-Lee cells was investigated using a clonogenic assay. The D_0 value of the control, scramble, *miR-221/222*-mimic, and *miR-221/222*-inhibitor groups are 5.4242, 5.0970, 5.6025, and 4.1296 Gy, respectively. The sensitization enhancement ratio (SER) was 1.0642, 0.9682, and 1.3135 for the scramble, *miR-221/222*-mimic, and *miR-221/222*-inhibitor groups, respectively (**Table 7**, **Figure 1J**). These results revealed a negative correlation between the SER and the *miR-221/222* expression, which provides strong evidence that downregulation of *miR-221/222* expression can promote the radiosensitivity of IOMM-Lee cells.

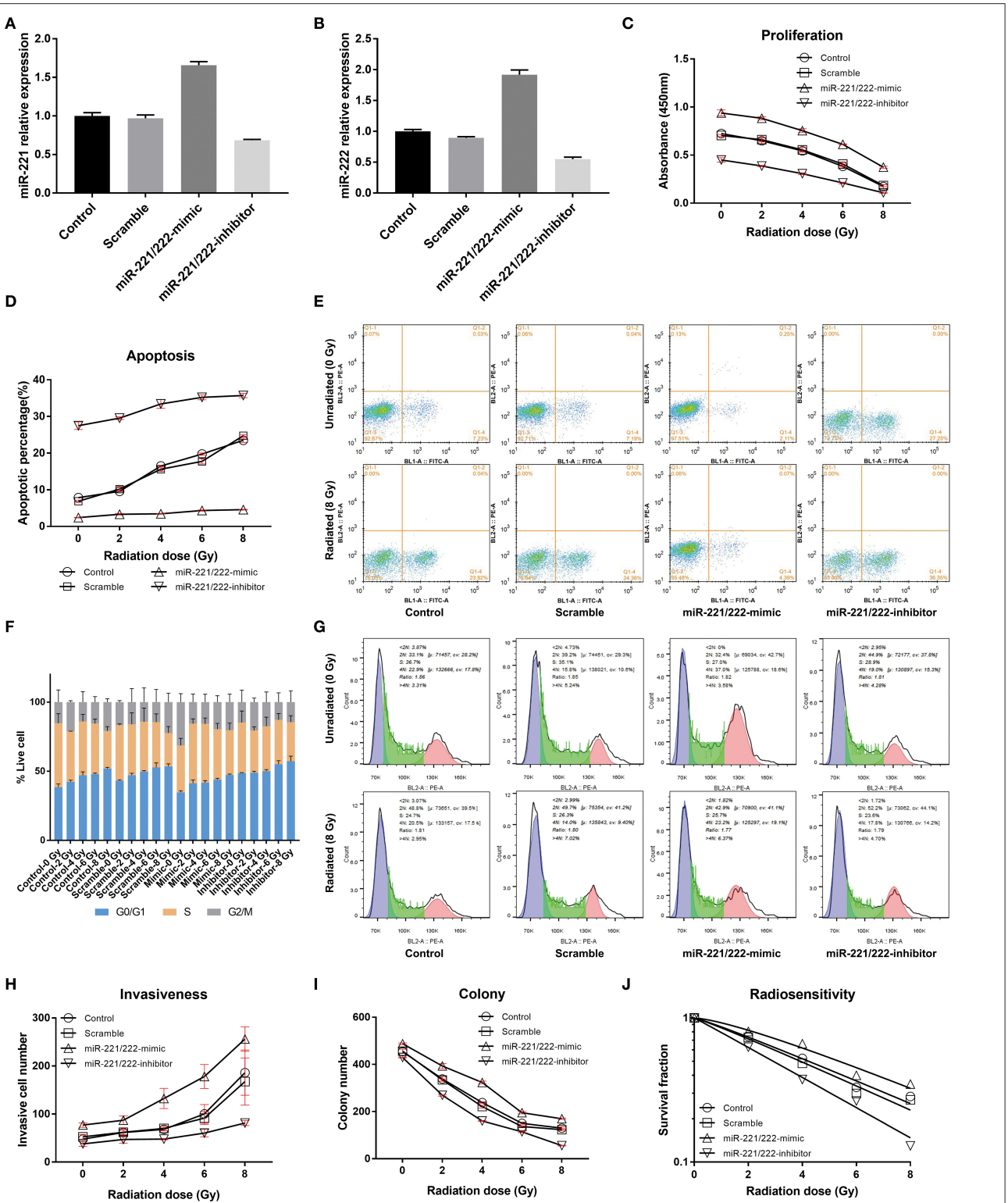


FIGURE 1 | The effects of the expression of *miR-221/222* and radiation dose on IOMM-Lee cells *in vitro*. **(A,B)** Present the relative expressions of *miR-221* and *miR-222* in different groups after transfection, respectively. **(C)** Shows that increasing the radiation dose and downregulating *miR-221/222* expression level can synergistically inhibit the proliferation of IOMM-Lee cells, while **(D,E)** show their synergistical promotion on cell apoptosis. **(F,G)** Exhibit that both increasing the radiation dose and downregulating *miR-221/222* expression level can separately increase the sub-G0/G1 population and induce G0/G1 cell cycle arrest. **(H,I)** Revealed that increasing the radiation dose and downregulating *miR-221/222* expression level can antagonistically regulate the cell invasiveness, while synergistically inhibit the colony formation, respectively. Furthermore, **(J)** exhibits that downregulating the *miR-221/222* expression enhances the radiosensitivity of IOMM-Lee cells. The abovementioned experiments were performed at least in triplicate.

TABLE 1 | Descriptive statistics of various assays of IOMM-Lee cells.

Different assays	Number	Group (Mean ± Standard deviation)			
		Control	Scramble	Mimic	Inhibitor
Absorbance (450 nm)					
0 Gy	3	0.724 ± 0.008	0.705 ± 0.011	0.938 ± 0.032	0.450 ± 0.023
2 Gy	3	0.649 ± 0.029	0.660 ± 0.023	0.883 ± 0.016	0.387 ± 0.006
4 Gy	3	0.545 ± 0.007	0.555 ± 0.024	0.754 ± 0.020	0.307 ± 0.009
6 Gy	3	0.383 ± 0.016	0.406 ± 0.022	0.612 ± 0.005	0.210 ± 0.008
8 Gy	3	0.174 ± 0.021	0.183 ± 0.010	0.374 ± 0.011	0.108 ± 0.006
Colony number					
0 Gy	3	454.333 ± 8.021	456.333 ± 8.021	487.667 ± 3.786	429.000 ± 2.000
2 Gy	3	338.333 ± 9.713	334.000 ± 4.583	393.000 ± 10.536	269.000 ± 3.606
4 Gy	3	238.000 ± 3.000	221.000 ± 5.568	323.333 ± 5.686	160.333 ± 2.082
6 Gy‡	3	150.000 ± 3.606	136.667 ± 2.517	195.000 ± 5.000	114.000 ± 3.000
8 Gy‡	3	129.667 ± 4.933	123.333 ± 4.163	169.667 ± 3.055	55.667 ± 1.528
Apoptotic percentage (%)					
0 Gy	3	7.850 ± 0.684	6.897 ± 0.302	2.407 ± 0.057	27.473 ± 1.033
2 Gy	3	9.587 ± 0.023	10.190 ± 0.710	3.313 ± 0.201	29.540 ± 0.376
4 Gy	3	16.490 ± 0.154	15.607 ± 0.580	3.457 ± 0.068	33.413 ± 1.196
6 Gy	3	19.743 ± 0.321	17.750 ± 0.700	4.340 ± 0.147	35.213 ± 0.671
8 Gy	3	23.503 ± 0.588	24.743 ± 0.337	4.570 ± 0.101	35.717 ± 0.611
Cell cycle distribution (%)¶					
G0/G1 phase					
0 Gy	3	38.412 ± 2.400	43.192 ± 0.614	34.748 ± 1.102	48.659 ± 0.316
2 Gy	3	42.388 ± 1.074	47.115 ± 1.426	41.311 ± 2.411	48.919 ± 1.052
4 Gy	3	46.981 ± 2.555	49.741 ± 0.699	41.694 ± 1.472	50.139 ± 1.066
6 Gy	3	47.949 ± 0.743	52.801 ± 3.184	43.921 ± 0.920	55.094 ± 2.479
8 Gy	3	51.974 ± 0.791	53.391 ± 1.913	47.220 ± 0.725	57.241 ± 3.615
S phase					
0 Gy	3	46.262 ± 6.932	36.459 ± 0.114	39.013 ± 5.147	36.517 ± 3.209
2 Gy	3	27.145 ± 3.136	40.027 ± 0.962	36.787 ± 8.346	35.985 ± 9.891
4 Gy	3	32.658 ± 5.989	24.266 ± 4.618	33.796 ± 5.214	43.053 ± 3.468
6 Gy	3	42.525 ± 4.232	36.462 ± 4.193	32.500 ± 5.032	36.545 ± 8.268
8 Gy	3	30.511 ± 2.680	32.301 ± 6.639	31.983 ± 4.564	28.289 ± 4.606
G2/M phase					
0 Gy	3	15.326 ± 8.769	21.153 ± 0.962	14.006 ± 7.538	15.534 ± 3.943
2 Gy	3	20.881 ± 2.394	16.782 ± 1.038	16.099 ± 9.762	14.274 ± 10.200
4 Gy	3	14.540 ± 9.162	22.343 ± 6.500	31.456 ± 6.072	15.637 ± 5.816
6 Gy	3	15.781 ± 5.692	19.617 ± 4.586	20.280 ± 5.735	14.796 ± 8.574
8 Gy	3	20.570 ± 2.853	17.560 ± 7.330	12.924 ± 6.696	14.470 ± 8.155
Invasive cell number					
0 Gy	5	47.800 ± 1.643	52.600 ± 4.980	77.000 ± 4.583	37.800 ± 5.215
2 Gy	5	61.600 ± 4.827	62.000 ± 6.403	87.200 ± 9.039	47.000 ± 7.517
4 Gy	5	68.200 ± 3.194	70.200 ± 4.658	132.400 ± 20.959	47.800 ± 1.304
6 Gy	5	100.400 ± 19.424	91.600 ± 13.334	178.200 ± 25.024	60.400 ± 7.893
8 Gy	5	186.200 ± 47.108	167.600 ± 48.993	256.000 ± 25.318	81.400 ± 5.320

‡*These results were normalized as the colony numbers per 1000 seeded cells.*

¶*These results, after the exclusion of "< 2N" and "> 4N" parts, were normalized by using the geometric proportion method to achieve the sum of persentages of G0/G1, S, G2/M phases of each subgroup is 100%.*

TABLE 2 | Radiation dose and expression level of miR-221/222 co-modulate IOMM-Lee cells.

Different assays	Source	df	*F*	*P*	Partial eta squared
Absorbance (450 nm)	Group	3	1458.879	**<0.0001***	0.991
	Radiation dose	4	1567.872	**<0.0001***	0.994
	Group × Radiation dose	12	19.320	**<0.0001***	0.853
	Error	40			
Colony number	Group	3	1032.021	**<0.0001***	0.987
	Radiation dose	4	8088.989	**<0.0001***	0.999
	Group × Radiation dose	12	33.749	**<0.0001***	0.910
	Error	40			
Apoptotic percentage	Group	3	2089.699	**<0.0001***	0.998
	Radiation dose	4	238.783	**<0.0001***	0.988
	Group × Radiation dose	12	26.278	**0.0038***	0.963
	Error	40			
Cell cycle distribution					
G0/G1 phase	Group	3	93.727	**<0.0001***	0.875
	Radiation dose	4	71.541	**<0.0001***	0.877
	Group × Radiation dose	12	1.870	0.0691	0.359
	Error	40			
S phase	Group	3	0.511	0.6767	0.037
	Radiation dose	4	4.643	**0.0036***	0.317
	Group × Radiation dose	12	3.256	**0.0024***	0.494
	Error	40			
G2/M phase	Group	3	1.406	0.2551	0.095
	Radiation dose	4	0.982	0.4283	0.089
	Group × Radiation dose	12	1.297	0.2584	0.280
	Error	40			
Invasive cell number	Group	3	97.670	**<0.0001***	0.786
	Radiation dose	4	124.624	**<0.0001***	0.862
	Group × Radiation dose	12	8.406	**<0.0001***	0.558
	Error	80			

**Indicates statistical significance, and relevant P values are emphasized in bold.*

PTEN Is a Target Gene of the *miR-221/222* Cluster

Dual luciferase reporter assay revealed that cotransfection of *miR-221* or *miR-222* mimics with psi-check2-PTEN significantly decreased luciferase activity compared to scramble or control-treated cells (*miR-221*: $P < 0.0001$; *miR-222*: $P < 0.0001$) (**Figures 2A,B**). Western blot analysis showed that PTEN was upregulated gradually as the *miR-221/222* expression level decreased or the radiation dose increased (**Figures 2C,D**). All these data demonstrated that PTEN is a target gene of the *miR-221/222* cluster.

Downregulation of *miR-221/222* Expression and Irradiation Suppress Tumor Growth *in vivo*

Dramatic reductions in tumor volume were observed in irradiated control (38.66%), scramble (38.56%), *miR-221/222*-mimic (33.78%), and *miR-221/222*-inhibitor (20.08%) groups as compared with their respective unirradiated counterparts (**Figure 3**), indicating a significant inhibitory effect of irradiation on the volume of subcutaneous IOMM-Lee xenografts in nude mice ($P < 0.0001$, partial $\eta^2 = 0.474$). For unirradiated animals, tumor volume in the *miR-221/222*-inhibitor group decreased by 85.21, 80.38, and 90.15% as compared with the control, scramble, and *miR-221/222*-mimic groups. The corresponding reduction rates in irradiation groups were 80.74, 74.48, and 88.11%. These suggest that the tumor volume can be suppressed by inhibiting the expression of *miR-221/222 in vivo* ($P < 0.0001$, partial $\eta^2 = 0.862$). Furthermore, these two treatments have a synergistic effect on preventing tumor growth *in vivo* ($P = 0.002$, partial $\eta^2 = 0.232$).

In addition to further proving these abovementioned results, multiple comparisons of tumor volumes at the last measure also revealed that no significant difference between the radiated-mimics group and the unradiated-control or unradiated-scramble group, indicating the antagonistic effect between radiation and upregulated *miR-221/222* expression *in vivo* (**Table 8**). A same situation was also found in the comparison between the unradiated-inhibitor group and the

TABLE 3 | Pairwise comparisons between IOMM-Lee cells irradiated with different dosages in various assays.

Pairwise comparisons	Increased dosage	Control			Scramble			Mimic			Inhibitor		
		P	95% CI		*P*	95% CI		*P*	95% CI		*P*	95% CI	
Absorbance (450 nm)													
0 Gy vs. 2 Gy	2 Gy	**<0.0001***	0.033	0.118	**0.0313***	0.002	0.087	**0.0036***	0.013	0.098	**0.0007***	0.021	0.106
2 Gy vs. 4 Gy	2 Gy	**<0.0001***	0.062	0.147	**<0.0001***	0.063	0.148	**<0.0001***	0.086	0.171	**<0.0001***	0.038	0.122
4 Gy vs. 6 Gy	2 Gy	**<0.0001***	0.120	0.204	**<0.0001***	0.106	0.191	**<0.0001***	0.100	0.185	**<0.0001***	0.054	0.139
6 Gy vs. 8 Gy	2 Gy	**<0.0001***	0.167	0.251	**<0.0001***	0.329	0.414	**<0.0001***	0.195	0.280	**<0.0001***	0.060	0.145
0 Gy vs. 4 Gy	4 Gy	**<0.0001***	0.137	0.222	**<0.0001***	0.108	0.192	**<0.0001***	0.142	0.226	**<0.0001***	0.101	0.186
2 Gy vs. 6 Gy	4 Gy	**<0.0001***	0.224	0.309	**<0.0001***	0.211	0.296	**<0.0001***	0.229	0.314	**<0.0001***	0.134	0.219
4 Gy vs. 8 Gy	4 Gy	**<0.0001***	0.329	0.413	**<0.0001***	0.181	0.266	**<0.0001***	0.338	0.423	**<0.0001***	0.157	0.241
0 Gy vs. 6 Gy	6 Gy	**<0.0001***	0.299	0.384	**<0.0001***	0.256	0.341	**<0.0001***	0.284	0.369	**<0.0001***	0.198	0.282
2 Gy vs. 8 Gy	6 Gy	**<0.0001***	0.433	0.518	**<0.0001***	0.435	0.519	**<0.0001***	0.467	0.551	**<0.0001***	0.237	0.321
0 Gy vs. 8 Gy	8 Gy	**<0.0001***	0.508	0.593	**<0.0001***	0.479	0.564	**<0.0001***	0.522	0.607	**<0.0001***	0.300	0.385
Colony number													
0 Gy vs. 2 Gy	2 Gy	**<0.0001***	103.053	128.947	**<0.0001***	109.386	135.281	**<0.0001***	81.719	107.614	**<0.0001***	147.053	172.947
2 Gy vs. 4 Gy	2 Gy	**<0.0001***	87.386	113.281	**<0.0001***	100.053	125.947	**<0.0001***	56.719	82.614	**<0.0001***	95.719	121.614
4 Gy vs. 6 Gy	2 Gy	**<0.0001***	75.053	100.947	**<0.0001***	71.386	97.281	**<0.0001***	115.386	141.281	**<0.0001***	33.386	59.281
6 Gy vs. 8 Gy	2 Gy	**0.0003***	7.386	33.281	**0.0394***	0.386	26.281	**<0.0001***	12.386	38.281	**<0.0001***	45.386	71.281
0 Gy vs. 4 Gy	4 Gy	**<0.0001***	203.386	229.281	**<0.0001***	222.386	248.281	**<0.0001***	151.386	177.281	**<0.0001***	255.719	281.614
2 Gy vs. 6 Gy	4 Gy	**<0.0001***	175.386	201.281	**<0.0001***	184.386	210.281	**<0.0001***	185.053	210.947	**<0.0001***	142.053	167.947
4 Gy vs. 8 Gy	4 Gy	**<0.0001***	95.386	121.281	**<0.0001***	84.719	110.614	**<0.0001***	140.719	166.614	**<0.0001***	91.719	117.614
0 Gy vs. 6 Gy	6 Gy	**<0.0001***	291.386	317.281	**<0.0001***	306.719	332.614	**<0.0001***	279.719	305.614	**<0.0001***	302.053	327.947
2 Gy vs. 8 Gy	6 Gy	**<0.0001***	195.719	221.614	**<0.0001***	197.719	223.614	**<0.0001***	210.386	236.281	**<0.0001***	200.386	226.281
0 Gy vs. 8 Gy	8 Gy	**<0.0001***	311.719	337.614	**<0.0001***	320.053	345.947	**<0.0001***	305.053	330.947	**<0.0001***	360.386	386.281
Apoptotic percentage													
0 Gy vs. 2 Gy	2 Gy	**0.0038***	−3.068	0.406	**<0.0001***	−4.624	−1.962	0.4969	−2.238	0.424	**0.0004***	−3.398	−0.736
2 Gy vs. 4 Gy	2 Gy	**<0.0001***	−8.234	−5.572	**<0.0001***	−6.748	−4.086	1.0000	−1.474	1.188	**<0.0001***	−5.204	−2.542
4 Gy vs. 6 Gy	2 Gy	**<0.0001***	−4.584	−1.922	**0.0002***	−3.474	−0.812	0.5557	−2.214	0.448	**0.0025***	−3.131	−0.469
6 Gy vs. 8 Gy	2 Gy	**<0.0001***	−5.091	−2.429	**<0.0001***	−8.324	−5.662	1.0000	−1.561	1.101	1.0000	−1.834	0.828
0 Gy vs. 4 Gy	4 Gy	**<0.0001***	−9.971	−7.309	**<0.0001***	−10.041	−7.379	0.2414	−2.381	0.281	**<0.0001***	−7.271	−4.609
2 Gy vs. 6 Gy	4 Gy	**<0.0001***	−11.488	−8.826	**<0.0001***	−8.891	−6.229	0.2726	−2.358	0.304	**<0.0001***	−7.004	−4.342
4 Gy vs. 8 Gy	4 Gy	**<0.0001***	−8.344	−5.682	**<0.0001***	−10.468	−7.806	0.1723	−2.444	0.218	**0.0001***	−3.634	−0.972
0 Gy vs. 6 Gy	6 Gy	**<0.0001***	−13.224	−10.562	**<0.0001***	−12.184	−9.522	**0.0010***	−3.264	−0.602	**<0.0001***	−9.071	−6.409
2 Gy vs. 8 Gy	6 Gy	**<0.0001***	−15.248	−12.586	**<0.0001***	−15.884	−13.222	0.0773	−2.588	0.074	**<0.0001***	−7.508	−4.846
0 Gy vs. 8 Gy	8 Gy	**<0.0001***	−16.984	−14.322	**<0.0001***	−19.178	−16.516	**0.0002***	−3.494	−0.832	**<0.0001***	−9.574	−6.912
Cell cycle distribution (S phase)													
0 Gy vs. 2 Gy	2 Gy	**0.0009***	6.031	32.204	1.0000	−16.654	9.519	1.0000	−10.860	15.313	1.0000	−12.555	13.618
2 Gy vs. 4 Gy	2 Gy	1.0000	−18.600	7.573	**0.0092***	2.674	28.848	1.0000	−10.096	16.077	1.0000	−20.154	6.019
4 Gy vs. 6 Gy	2 Gy	0.3071	−22.953	3.220	0.0848	−25.283	0.890	1.0000	−11.790	14.383	1.0000	−6.579	19.594
6 Gy vs. 8 Gy	2 Gy	0.0943	−1.073	25.100	1.0000	−8.925	17.248	1.0000	−12.569	13.604	0.6819	−4.831	21.343
0 Gy vs. 4 Gy	4 Gy	**0.0365***	0.517	26.690	0.0849	−0.893	25.280	1.0000	−7.870	18.303	1.0000	−19.623	6.55
2 Gy vs. 6 Gy	4 Gy	**0.0118***	−28.467	−2.294	1.0000	−9.522	16.651	1.0000	−8.800	17.373	1.0000	−13.646	12.527
4 Gy vs. 8 Gy	4 Gy	1.0000	−10.940	15.234	0.7559	−21.122	5.052	1.0000	−11.273	14.900	**0.0176***	1.677	27.85
0 Gy vs. 6 Gy	6 Gy	1.0000	−9.349	16.824	1.0000	−13.090	13.083	1.0000	−6.574	19.600	1.0000	−13.115	13.058
2 Gy vs. 8 Gy	6 Gy	1.0000	−16.453	9.720	0.8707	−5.361	20.813	1.0000	−8.283	17.890	0.8825	−5.39	20.783
0 Gy vs. 8 Gy	8 Gy	**0.0093***	2.664	28.838	1.0000	−8.928	17.245	1.0000	−6.056	20.117	0.6910	−4.859	21.314
Invasive cell number													
0 Gy vs. 2 Gy	2 Gy	1.0000	−48.644	21.044	1.0000	−44.244	25.444	1.0000	−45.044	24.644	1.0000	−44.044	25.644
2 Gy vs. 4 Gy	2 Gy	1.0000	−41.444	28.244	1.0000	−43.044	26.644	**0.0034***	−80.044	−10.356	1.0000	−35.644	34.044
4 Gy vs. 6 Gy	2 Gy	0.0924	−67.044	2.644	0.8002	−56.244	13.444	**0.0029***	−80.644	−10.956	1.0000	−47.444	22.244
6 Gy vs. 8 Gy	2 Gy	**<0.0001***	−120.644	−50.956	**<0.0001***	−110.844	−41.156	**<0.0001***	−112.644	−42.956	0.8572	−55.844	13.844
0 Gy vs. 4 Gy	4 Gy	0.9488	−55.244	14.444	1.0000	−52.444	17.244	**0.0002***	−90.244	−20.556	1.0000	−44.844	24.844
2 Gy vs. 6 Gy	4 Gy	**0.0188***	−73.644	−3.956	0.1636	−64.444	5.244	**<0.0001***	−125.844	−56.156	1.0000	−48.244	21.444
4 Gy vs. 8 Gy	4 Gy	**<0.0001***	−152.844	−83.156	**<0.0001***	−132.244	−62.556	**<0.0001***	−158.444	−88.756	0.0670	−68.444	1.244
0 Gy vs. 6 Gy	6 Gy	**0.0004***	−87.444	−17.756	**0.0179***	−73.844	−4.156	**<0.0001***	−136.044	−66.356	0.6479	−57.444	12.244
2 Gy vs. 8 Gy	6 Gy	**<0.0001***	−159.444	−89.756	**<0.0001***	−140.444	−70.756	**<0.0001***	−203.644	−133.956	0.0556	−69.244	0.444
0 Gy vs. 8 Gy	8 Gy	**<0.0001***	−173.244	−103.556	**<0.0001***	−149.844	−80.156	**<0.0001***	−213.844	−144.156	**0.0053***	−78.444	−8.756

**Indicates statistical significance, and relevant P values are emphasized in bold.*

TABLE 4 | Multiple comparisons of the persentage of G0/G1 phase between different IOMM-Lee cell groups.

Multiple comparisons	*P*	95% CI	
0 Gy vs. 2 Gy	**0.0001***	−5.841	−1.520
2 Gy vs. 4 Gy	**0.0423***	−4.366	−0.045
4 Gy vs. 6 Gy	**0.0041***	−4.963	−0.642
6 Gy vs. 8 Gy	**0.0130***	−4.676	−0.355
0 Gy vs. 4 Gy	**<0.0001***	−8.046	−3.726
2 Gy vs. 6 Gy	**<0.0001***	−7.169	−2.848
4 Gy vs. 8 Gy	**<0.0001***	−7.478	−3.157
0 Gy vs. 6 Gy	**<0.0001***	−10.849	−6.528
2 Gy vs. 8 Gy	**<0.0001***	−9.684	−5.363
0 Gy vs. 8 Gy	**<0.0001***	−13.364	−9.043
Control vs. Scramble	**<0.0001***	−5.512	−1.902
Mimic vs. Control	**<0.0001***	−5.567	−1.957
Mimic vs. Scramble	**<0.0001***	−9.274	−5.664
Inhibitor vs. Control	**<0.0001***	4.664	8.275
Inhibitor vs. Scramble	**0.0008***	0.957	4.568
Mimic vs. Inhibitor	**<0.0001***	−12.037	−8.426

**Indicates statistical significance, and relevant P values are emphasized in bold.*

radiated-inhibitor group (**Table 8**). This may be explained by the observation that the effect of inhibiting the *miR-221/222* expression on preventing tumor progression has already been too obvious to reflect the effect of radiation.

Downregulation of *miR-221/222* Expression and Irradiation Promote the Expression of PTEN *in vivo*

Immunohistochemical analysis of tissue sections of xenografts reflects a gradually increased immunoreactivity of PTEN as the *miR-221/222* expression decreases (**Figure 4**); meanwhile, tissue sections from radiation-treated xenografts exhibited higher expression levels of PTEN compared to their corresponding unirradiated counterparts (**Figure 4**). These are consistent with the results of *in vitro* studies.

DISCUSSION

In the present study, both radiation dose and expression level of *miR-221/222* significantly contributed to the regulation of the proliferation, colony formation, apoptosis, invasiveness, and subcutaneous xenografts of IOMM-Lee cells with significant interactions present, whereas they significantly regulated the sub-G0/G1 population without an interaction (**Table 2**). Increasing the radiation dose and downregulating *miR-221/222* expression level can synergistically inhibit the proliferation and colony formation, prevent subcutaneous xenografts progression, and promote the apoptosis of IOMM-Lee cells, while they antagonistically regulate the cell invasion (**Tables 1**, **2**, **8** and **Figures 1**, **3**). In addition, inhibiting the *miR-221/222* expression in IOMM-Lee cell can promote its radiosensitivity (**Table 7**). Consequently, downregulating the expression level of *miR-221/222* can promote the strengths of radiation and circumvent its weaknesses in IOMM-Lee cell treatment.

Paradoxical Effects of Ionizing Radiation on IOMM-Lee Cells

The radiation dose-dependent apoptosis-promoting and proliferation-inhibiting effects of radiation on IOMM-Lee cells provide theoretical bases for utilizing postoperative radiation therapy to control the growth of residual or recurrent meningiomas in the clinic (**Tables 1–3**, **8**, **Figures 1C–E**, **3**). However, the radiation-induced invasiveness of IOMM-Lee cells may explain the unsatisfactory recurrence-free survival or even some toxicities of clinical adjuvant radiotherapy (**Tables 1–3** and **Figure 1H**).

It has been revealed in several cancer cells (including breast, lung, and liver cancer, and glioma cells) that ionizing radiation (IR) enhances their migratory and invasive properties by inducing the epithelial–mesenchymal transition (EMT) (35–40). This IR-induced EMT is mediated by EMT-inducing transcription factors (EMT-TFs) (e.g., Snail, ZEB, and Twist families) that are activated by a network of signaling pathways (41–44). These EMT-TFs possess two potentials in cancer cells: (1) prometastatic potential—the aforementioned IR-enhanced migration and invasiveness reflect their prometastatic role. They regulate the expression level of proteins that is implicated in cell polarity, cytoskeletal structural maintenance, cell–cell contact, and extracellular matrix degradation, and they suppress key epithelial genes (e.g., E-cadherin) (41–44); (2) oncogenic potential: they are implicated in inducing malignant transformation (41, 45), stemness properties (41, 45), and oncogenic metabolism (41, 44). Hence, it is logical to assume that the present radiation-enhanced invasiveness of IOMM-Lee cells may be caused by the IR-induced EMT. In addition, we revealed in our previous clinical study that malignant progressed atypical meningiomas are more likely to exhibit low connexin 43 expression in their preradiotherapeutic tissues (46). Malignant transformation is one of the toxicities of radiotherapy in meningiomas (2). Connexin 43, the most abundant connexin isoform in the central nervous system (47, 48), oligomerizes to form gap junctions between adjacent meningioma cells (49, 50). These two points, as well as the present radiation-induced invasiveness of IOMM-Lee cells, all correspond to the prometastatic and oncogenic capacities of EMT-TFs. Al-Mefty et.al discovered the same complex genetic alterations that they saw in histologically higher-grade meningiomas already apparent in the early, benign stages of those tumors (51). Arishima et al. reported that different subtypes of meningiomas express different levels of connexin 43 (52). These findings raises the possibility that meningioma cells' inherent expression levels of certain moleculars and the intrinsic regulation level of EMT-TFs may determine whether this meningioma will undergo invasiveness enhancement, tumor recurrence, or malignant progression after radiotherapy.

TABLE 5 | Pairwise comparisons between IOMM-Lee cells with different miR−221/222 expression levels in various assays.

Pairwise comparisons	0 Gy			2 Gy			4 Gy			6 Gy			8 Gy		
	P	95% CI		*P*	95% CI		*P*	95% CI		*P*	95% CI		*P*	95% CI	
Absorbance (450 nm)															
Control vs. Scramble	1.0000	−0.020	0.059	1.0000	−0.050	0.028	1.0000	−0.049	0.029	0.6205	−0.063	0.016	1.0000	−0.049	0.030
Mimic vs. Control	**<0.0001***	0.175	0.253	**<0.0001***	0.195	0.273	**<0.0001***	0.170	0.249	**<0.0001***	0.190	0.268	**<0.0001***	0.161	0.240
Mimic vs. Scramble	**<0.0001***	0.194	0.273	**<0.0001***	0.184	0.262	**<0.0001***	0.160	0.239	**<0.0001***	0.166	0.245	**<0.0001***	0.152	0.230
Inhibitor vs. Control	**<0.0001***	−0.314	−0.235	**<0.0001***	−0.302	−0.223	**<0.0001***	−0.277	−0.199	**<0.0001***	−0.212	−0.133	**0.0002***	−0.105	−0.027
Inhibitor vs. Scramble	**<0.0001***	−0.294	−0.215	**<0.0001***	−0.313	−0.234	**<0.0001***	−0.287	−0.209	**<0.0001***	−0.236	−0.157	**<0.0001***	−0.115	−0.036
Mimic vs. Inhibitor	**<0.0001***	0.449	0.528	**<0.0001***	0.457	0.536	**<0.0001***	0.408	0.487	**<0.0001***	0.362	0.441	**<0.0001***	0.227	0.306
Colony number															
Control vs. Scramble	1.0000	−14.096	10.096	1.0000	−7.763	16.430	**0.0021***	4.904	29.096	**0.0237***	1.237	25.430	0.9235	−5.763	18.430
Mimic vs. Control	**<0.0001***	21.237	45.430	**<0.0001***	42.570	66.763	**<0.0001***	73.237	97.430	**<0.0001***	32.904	57.096	**<0.0001***	27.904	52.096
Mimic vs. Scramble	**<0.0001***	19.237	43.430	**<0.0001***	46.904	71.096	**<0.0001***	90.237	114.430	**<0.0001***	46.237	70.430	**<0.0001***	34.237	58.430
Inhibitor vs. Control	**<0.0001***	−37.430	−13.237	**<0.0001***	−81.430	−57.237	**<0.0001***	−89.763	−65.570	**<0.0001***	−48.096	−23.904	**<0.0001***	−86.096	−61.904
Inhibitor vs. Scramble	**<0.0001***	−39.430	−15.237	**<0.0001***	−77.096	−52.904	**<0.0001***	−72.763	−48.570	**<0.0001***	−34.763	−10.570	**<0.0001***	−79.763	−55.570
Mimic vs. Inhibitor	**<0.0001***	46.570	70.763	**<0.0001***	111.904	136.096	**<0.0001***	150.904	175.096	**<0.0001***	68.904	93.096	**<0.0001***	101.904	126.096
Apoptotic percentage															
Control vs. Scramble	0.2373	−0.290	2.197	1.0000	−1.847	0.640	0.3334	−0.360	2.127	**0.0004***	0.750	3.237	0.0510	−2.484	0.004
Mimic vs. Control	**<0.0001***	−6.687	−4.200	**<0.0001***	−7.517	−5.030	**<0.0001***	−14.277	−11.790	**<0.0001***	−16.647	−14.160	**<0.0001***	−20.177	−17.690
Mimic vs. Scramble	**<0.0001***	−5.734	−3.246	**<0.0001***	−8.120	−5.633	**<0.0001***	−13.394	−10.906	**<0.0001***	−14.654	−12.166	**<0.0001***	−21.417	−18.930
Inhibitor vs. Control	**<0.0001***	18.380	20.867	**<0.0001***	18.710	21.197	**<0.0001***	15.680	18.167	**<0.0001***	14.226	16.714	**<0.0001***	10.970	13.457
Inhibitor vs. Scramble	**<0.0001***	19.333	21.820	**<0.0001***	18.106	20.594	**<0.0001***	16.563	19.050	**<0.0001***	16.220	18.707	**<0.0001***	9.730	12.217
Mimic vs. Inhibitor	**<0.0001***	−26.310	−23.823	**<0.0001***	−27.470	−24.983	**<0.0001***	−31.200	−28.713	**<0.0001***	−32.117	−29.630	**<0.0001***	−32.390	−29.903
Invasive cell number															
Control vs. Scramble	1.0000	−37.453	27.853	1.0000	−33.053	32.253	1.0000	−34.653	30.653	1.0000	−23.853	41.453	0.7634	−14.053	51.253
Mimic vs. Control	0.1069	−3.453	61.853	0.2221	−7.053	58.253	**<0.0001***	31.547	96.853	**<0.0001***	45.147	110.453	**<0.0001***	37.147	102.453
Mimic vs. Scramble	0.2793	−8.253	57.053	0.2399	−7.453	57.853	**<0.0001***	29.547	94.853	**<0.0001***	53.947	119.253	**<0.0001***	55.747	121.053
Inhibitor vs. Control	1.0000	−42.653	22.653	1.0000	−47.253	18.053	0.5693	−53.053	12.253	**0.0083***	−72.653	−7.347	**<0.0001***	−137.453	−72.147
Inhibitor vs. Scramble	1.0000	−47.453	17.853	1.0000	−47.653	17.653	0.4029	−55.053	10.253	0.0693	−63.853	1.453	**<0.0001***	−118.853	−53.547
Mimic vs. Inhibitor	**0.0102***	6.547	71.853	**0.0079***	7.547	72.853	**<0.0001***	51.947	117.253	**<0.0001***	85.147	150.453	**<0.0001***	141.947	207.253

**Indicates statistical significance, and relevant P values are emphasized in bold.*

TABLE 6 | Comparisons between the invasive cell numbers of the miR-221/222-inhibitor and the control/scramble group exposed to different radiation doses.

	0 Gy-Inhibitor		2 Gy-Inhibitor			4 Gy-Inhibitor			6 Gy-Inhibitor			8 Gy-Inhibitor		
	P	95% CI		*P*	95% CI		*P*	95% CI		*P*	95% CI		*P*	95% CI
0 Gy-Control	**0.0035***	4.361	15.639	0.8266	-8.434	10.034	1.0000	-2.163	2.163	**0.0219***	-22.304	−2.896	**<0.0001***	−39.342	−27.858
2 Gy-Control				**0.0065***	5.388	23.812	**0.0003***	8.644	18.956	0.7792	-8.341	10.741	**0.0003***	−27.208	−12.392
4 Gy-Control							**<0.0001***	16.842	23.958	0.0929	-1.837	17.437	**0.0014***	−19.599	−6.801
6 Gy-Control										**0.0070***	16.284	63.716	0.0935	−4.777	42.777
8 Gy-Control													**0.0011***	55.909	153.691
0 Gy-Scramble	**0.0018***	7.363	22.237	0.2023	-3.699	14.899	0.0706	-0.509	10.109	0.0986	-17.425	1.825	**<0.0001***	−36.315	−21.285
2 Gy-Scramble				**0.0094***	4.817	25.183	**0.0013***	7.461	20.939	0.7339	-8.882	12.082	**0.0008***	−27.985	−10.815
4 Gy-Scramble							**0.0002***	16.700	28.100	**0.0438***	0.348	19.252	**0.0076***	−18.492	−3.908
6 Gy-Scramble										**0.0020***	15.220	47.180	0.1508	−4.605	25.005
8 Gy-Scramble													**0.0166***	25.562	146.838

**Indicates statistical significance, and relevant P values are emphasized in bold.*

TABLE 7 | Impact of miRNA-221/222 expression on IOMM-Lee cell radiosensitivity.

Group	D_0	Dq	SF_2	SER
Control + irradiation	5.4242	0.6797	0.7364	
Scramble + irradiation	5.0970	0.5713	0.7160	1.0642
miRNA-221/222-mimic + irradiation	5.6025	2.0211	0.8220	0.9682
miRNA-221/222-inhibitor + irradiation	4.1296	0.1000	0.6250	1.3135

D_0 is a dose that reduces the survival fraction from 100% to 37%; Dq, quasi-threshold dose; SF2, survival fraction at 2 Gy; SER, the sensitization enhancement ratio.

Downregulation of *miR-221/222* Expression Enhances the Apoptosis-Promoting Effect and Proliferation-Inhibiting Effect of Radiation and Promotes Radiosensitivity of IOMM-Lee Cells

The radiosensitization of downregulating the *miR-221/222* cluster has been certified in several human tumors: Zhang et al. successively discovered that tumor radiosensitivity could be promoted by the knockdown of *miR-221* and *miR-222* in gastric cancer cell line SGC7901 (31) and glioblastoma cell line U251, and demonstrated that PTEN is a target gene of the *miR-221/222* cluster (31); Sun and Khoshinani confirmed that *miR-221* (33) and *miR-222* (32) mediated the radiosensitivity of colorectal cancer cells by regulating PTEN, respectively; consistent results were reported by Wu and his colleague in their study of nasopharyngeal carcinoma (34). The radiosensitivity enhancement of *miR-221/222* downregulation and PTEN as the target gene of these two miRNAs were also confirmed in our present study of IOMM-Lee meningioma cells.

The PTEN gene, located at 10q23.3, was identified as one of the most commonly mutated tumor suppressor in human cancers, second only to p53 (53). Its encoded PTEN protein exhibits phosphoinositide 3-phosphatase activity toward phosphatidylinositol 3,4,5-trisphosphate and antagonizes phosphatidylinositol 3-kinase (PI3K) functions to negatively regulate cell proliferation and promote cell apoptosis (54). Loss-of-function mutations in the PTEN gene result in the inactivation of the PTEN protein, which further gives rise to oncogenic transformation of cells, resistance, and relapse in response to conventional therapeutic agents (55, 56).

IR exerts its therapeutic effect mainly by generating DNA damages (57). These IR-induced DNA damages, primarily double-strand breaks, trigger a number of DNA damage response and repair signaling cascades and subsequently phosphorylate p53 protein (58–61). Activated p53 upregulates the transcriptional and translational levels of several genes (including PTEN) to cause cell cycle arrest, apoptosis, autophagy, or senescence according to the severity of the DNA damage and the cell type (42, 62–65). Meanwhile, accumulation of PTEN, in turn, remarkably enhances p53 DNA binding and transcriptional activity by interacting with its C-terminal domain (66). Briefly, IR can induce PTEN

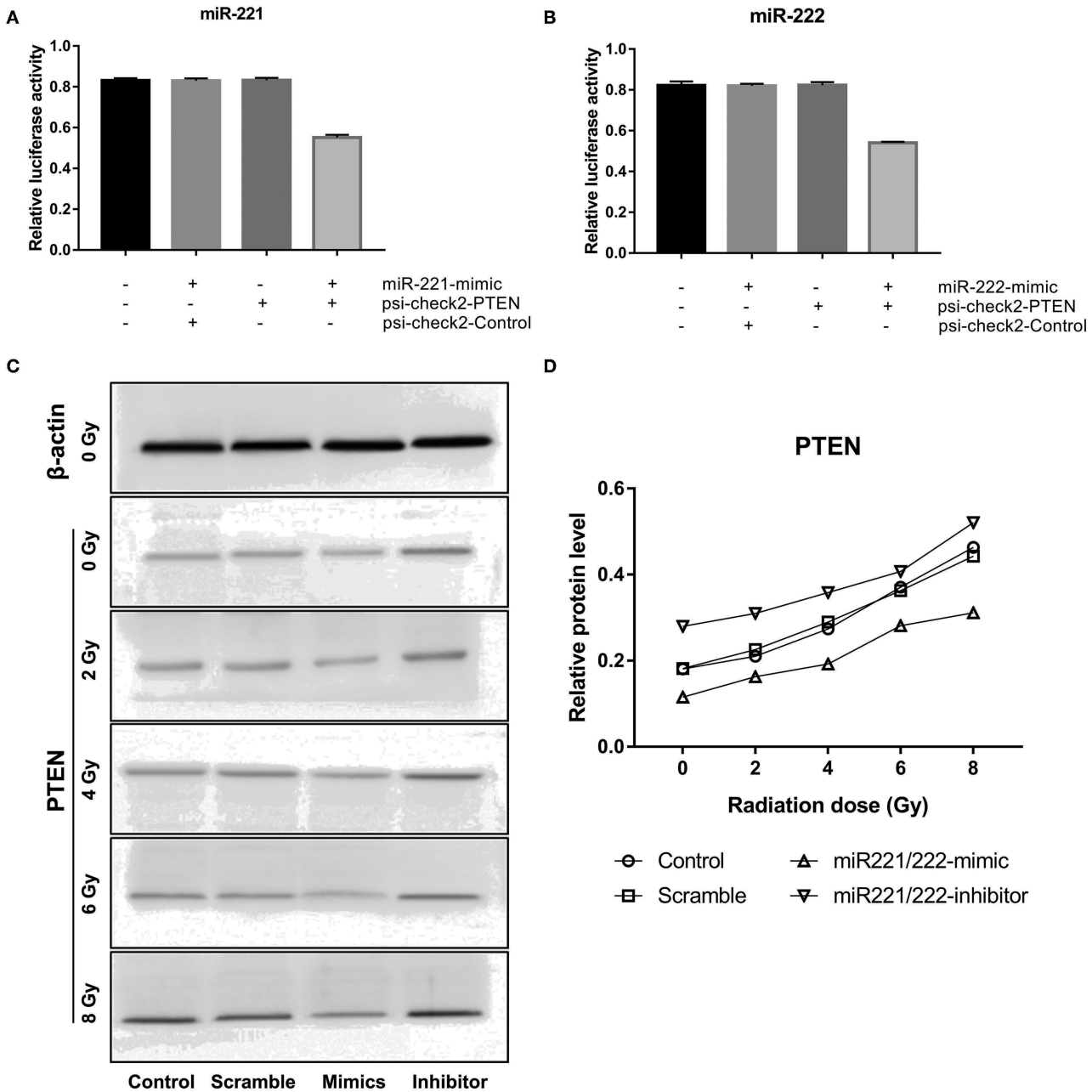


FIGURE 2 | Phosphatase and tensin homolog (PTEN) is a target gene of *miR-221* and *miR-222* in IOMM-Lee cells. **(A,B)** Significantly decreased luciferase activities were revealed after the cotransfection of *miR-221* mimics or *miR-222* mimics and psi-check2-PTEN in dual luciferase reporter assay. **(C,D)** Western blot analysis exhibited that the expression of PTEN was positively correlated with radiation dose but negatively correlated with *miR-221/222* expression.

accumulation to facilitate its therapeutic effects in some tumors. H460 cells obtained enhanced PTEN expression after irradiation in Il Lae Jung's previous research of nonsmall cell lung cancer (67). Similarly, the present radiation dose-dependent increase in PTEN in the IOMM-Lee cells suggests that the abovementioned mechanisms were activated during radiotherapy in meningiomas. Moreover, improved radiotherapeutic response in meningiomas can be achieved by further upregulation of PTEN through inhibiting the miR-221/222 expression.

The radiosensitization of PTEN has also been reported in previous literature: Rosser et al. identified forced expression of PTEN as a valuable approach to achieve radiosensitization in prostate cancer cells (68); multiple studies confirmed that the radioresistance of nasopharyngeal carcinoma could be enhanced by suppressing the expression of PTEN (69–71); consistent

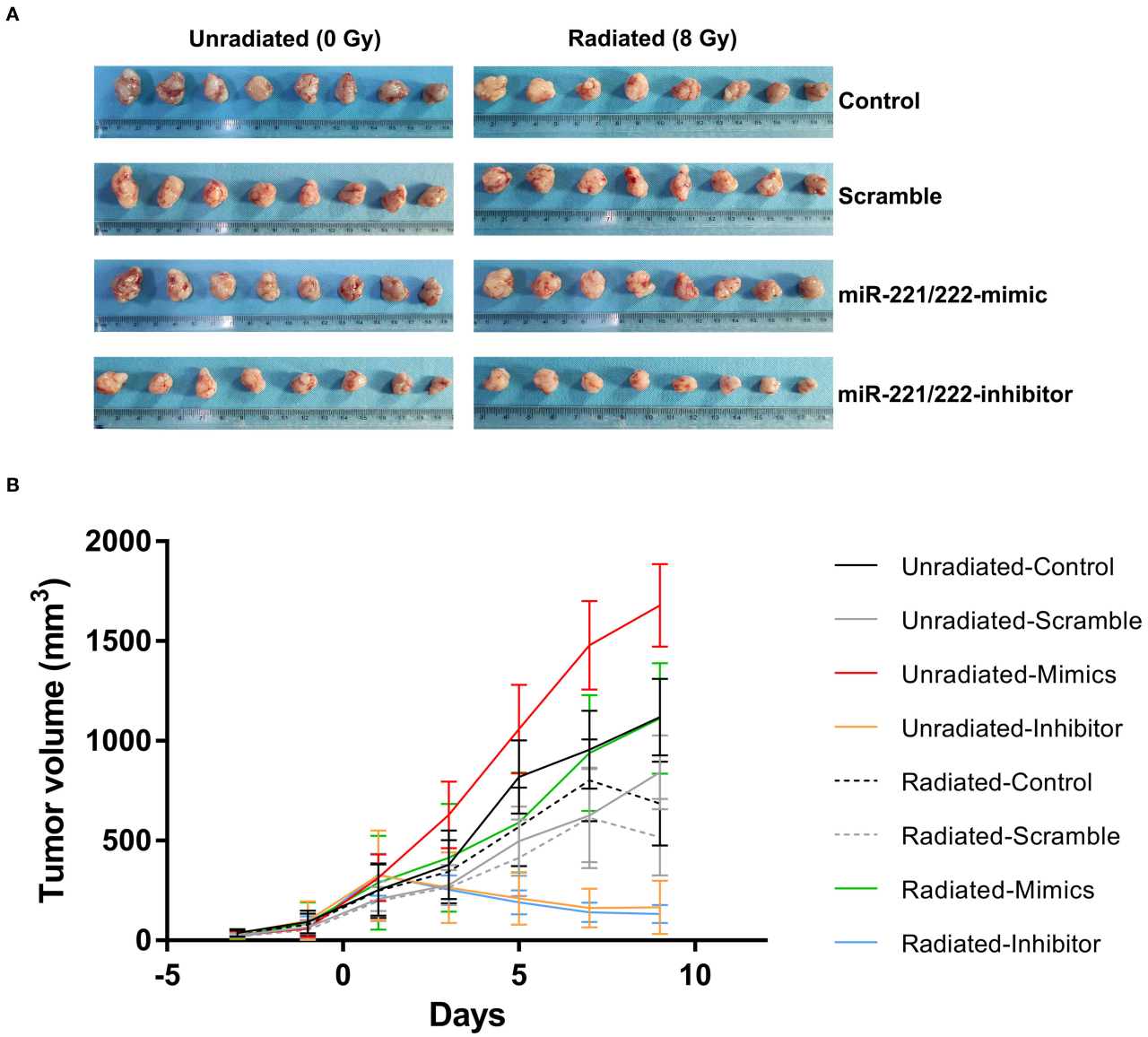


FIGURE 3 | Downregulating *miR-221/222* expression along with radiation suppresses subcutaneous tumor growth *in vivo*. **(A)** Exhibits the xenograft tumors from different treatment subgroups. **(B)** Reveals that both inhibition of the *miR-221/222* expression level and ionizing radiation significantly suppress tumor growth in nude mice.

conclusions were obtained in the corresponding researches of non-small cell lung carcinoma (72), hepatocellular carcinoma (73), and esophageal cancer (74). Accordingly, the present observations indicate that the radiosensitization of *miR-221/222* inhibition in IOMM-Lee cells was achieved by its further upregulation of PTEN expression on the basis of IR-induced PTEN accumulation.

Downregulation of *miR-221/222* Expression Can Reverse Radiation-Induced Cell Invasiveness

The IR-induced invasiveness of IOMM-Lee cells enhanced significantly as radiation dosage increased. Downregulation of miR-221/222 could promote the expression of PTEN and reverse the IR-enhanced cell invasiveness. As previously described, the IR-enhanced cell invasiveness is associated with EMT. Aside from their abovementioned radiosensitivity-regulatory effect, *miR-221* and *miR-222* have also been revealed to promote EMT (75) and increase migration and invasion in several other tumors (76). As a target of the miR-221/222 cluster, PTEN has been verified to possess the ability of reversing EMT in Jin's radioresistant esophageal cancer cells study (74). Therefore, it is conceivable that miR-221/222 downregulation reverses the radiation-induced cell invasiveness and is achieved by the EMT-reversion effect of accumulated PTEN. However, the underlying mechanisms of PTEN-regulated EMT in meningiomas require further investigations.

TABLE 8 | Time-varing tumor volumes of IOMM-Lee xenograft tumors in various treatment groups.

Days	Description	Unradiated groups (Mean ± Standard deviation)				Radiated GROUPS (Mean ± Standard deviation)			
		Control	Scramble	Mimics	Inhibitor	Control	Scramble	Mimics	Inhibitor
−3	1st Pre-treat	37.046 ± 18.881	25.701 ± 10.108	27.921 ± 13.966	34.697 ± 23.985	32.867 ± 18.433	18.493 ± 5.085	20.396 ± 15.011	20.432 ± 15.302
−1	2nd Pre-treat	92.979 ± 57.307	65.933 ± 33.077	59.935 ± 42.045	99.533 ± 97.297	78.893 ± 55.275	52.566 ± 25.984	89.624 ± 103.919	64.602 ± 57.082
0	1st -injection								
1	1st-measure	252.025 ± 129.423	207.469 ± 60.287	313.998 ± 116.227	325.252 ± 224.913	248.363 ± 137.236	198.245 ± 100.424	288.830 ± 235.379	329.696 ± 104.858
2	1st -IR								
3	2nd-measure	378.611 ± 171.727	277.653 ± 100.420	628.602 ± 167.446	264.124 ± 176.213	344.355 ± 158.887	266.415 ± 88.061	414.844 ± 269.869	253.916 ± 71.315
4	2nd -injection								
5	3rd-measure	819.921 ± 184.435	497.531 ± 173.248	1059.213 ± 222.273	211.468 ± 132.266	569.421 ± 196.957	414.461 ± 192.684	590.938 ± 250.908	190.157 ± 60.905
6	2nd -IR								
7	4th-measure	956.500 ± 195.499	626.219 ± 233.596	1478.570 ± 223.009	162.200 ± 97.474	801.723 ± 206.409	613.421 ± 252.433	939.645 ± 290.516	140.574 ± 47.782
8	3rd -injection								
9	5th-measure	1118.742 ± 191.996	843.166 ± 185.583	1679.081 ± 206.211	165.412 ± 134.343	686.242 ± 211.075	518.079 ± 192.757	1111.826 ± 277.750	132.189 ± 44.762
Multiple comparisons (the 5th-measure), *P*-value									
Unradiated-Control			0.157	**<0.0001***	**<0.0001***	**0.001***	**<0.0001***	1.000	**<0.0001***
Unradiated-Scramble				**<0.0001***	**<0.0001***	1.000	**0.035***	0.191	**<0.0001***
Unradiated-Mimics					**<0.0001***	**<0.0001***	**<0.0001***	**<0.0001***	**<0.0001***
Unradiated-Inhibitor						**<0.0001***	**0.014***	**<0.0001***	1.000
Radiated-Control							1.000	**0.001***	**<0.0001***
Radiated-Scramble								**<0.0001***	**0.005***
Radiated-Mimics									**<0.0001***

IR, ionizing radiation; Pre-treat, Pre-treatment.

**Indicates statistical significance, and relevant P values are emphasized in bold.*

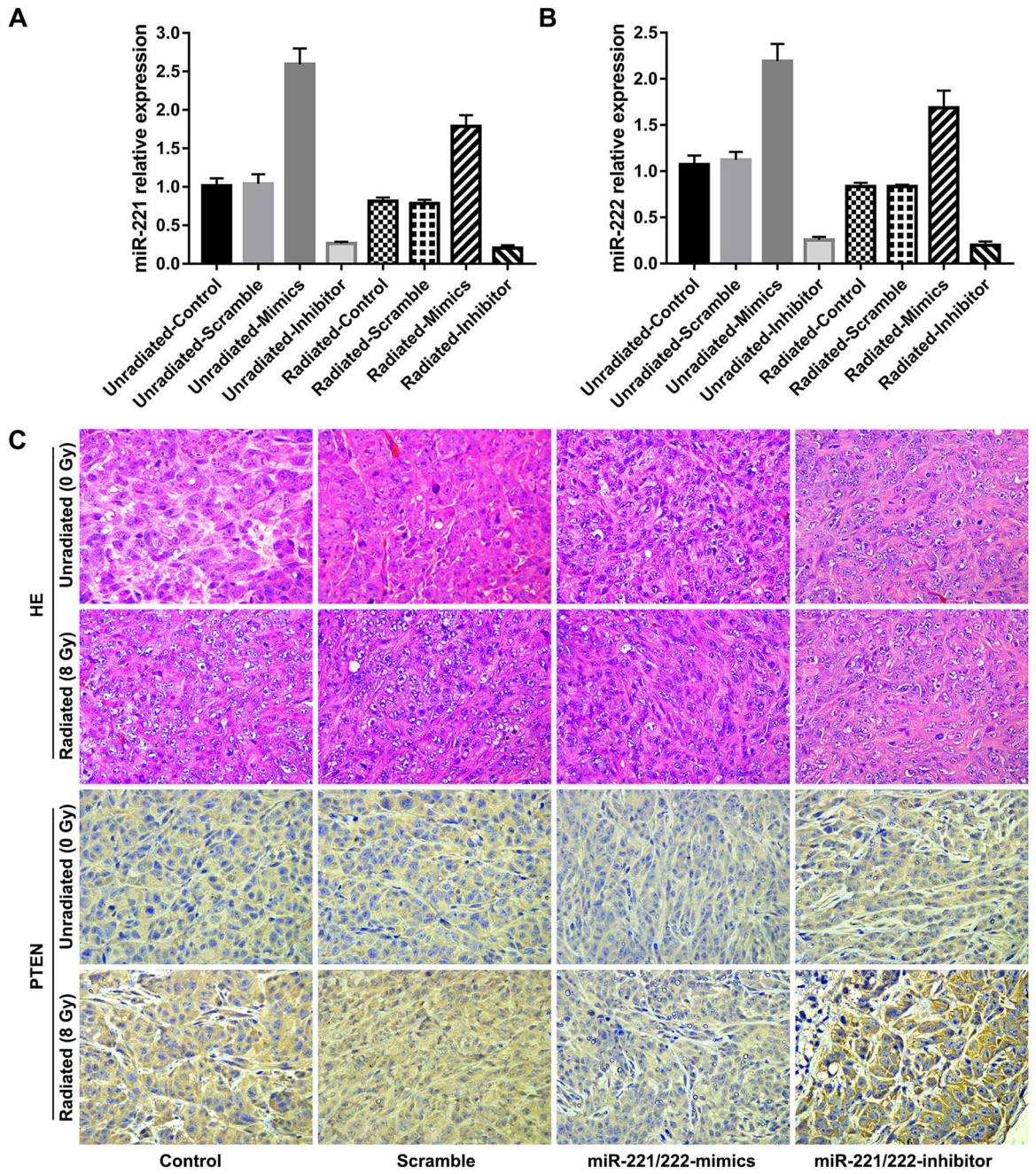


FIGURE 4 | Downregulation of *miR-221/222* expression and ionizing radiation promote the expression of phosphatase and tensin homolog (PTEN) *in vivo*. **(A,B)** Show the relative expressions of *miR-221* and *miR-222* in subcutaneous tumors of different subgroups, respectively. **(C)** Exhibits immunohistochemical staining for PTEN (bottom, 400×) and their corresponding H&E staining (top, 400×) of tissue sections from each subgroup.

Dose Rate of Irradiation Affects Cell Cycle Distribution of IOMM-Lee

In previous studies of IOMM-Lee cells, (1) Gogineni et al. indicated that radiation treatment (7 Gy) induced G2/M cell cycle arrest and a resultant decrease in the G0/G1 or S phase when evaluated against the unirradiated cells, as well as an insignificant cell-death-promoting effect (77). (2) However, by comparing the 5-Gy irradiated cells with unirradiated cells, Winson et al. exhibited a cell cycle distribution consist of an increased G0/G1, a decreased S, and an increased G2/M population, accompanied by an increment in apoptosis rate (78). The present results of radiation-induced G0/G1 cell cycle arrest and apoptosis-promoting effect are consistent with Winson's research while opposite to Gogineni's study (**Tables 1–4** and

Figures 1D–G). To determine the underlying causes of these opposites, we compared the data and discovered that the main difference is the dose rate, which was 0.71 and 3.2 Gy/min in the Gogineni's study (77) and the present study, respectively, while Winson et al. did not provide theirs (78).

According to Hall's revised and updated illustration of the dose-rate effect (79), the dose–response curve becomes progressively shallower as the dose rate reduces, indicating an increment in sublethal damage repair. Cells rest on their cell cycle phase without progression. However, a further reduction in dose rate in a limited range allows cells to progress through the cycle and accumulate in G2, resulting in the inverse dose-rate effect. The critical dose rate of IOMM-Lee initiating this effect has not been determined. With a higher dose rate in the present study, the capability of cells to repair sublethal damage was restrained, which further leads to an increase in apoptotic rate with a fixed cell cycle distribution. The dose rate used by Gogineni et al. is lower, which might have triggered the inverse dose-rate effect. This dose rate might not significantly increase cell death but have gradually accumulated cells to rest on G2 phase, and these may explain their cell cycle and apoptosis results.

In Kurpinski's research of differential effects of X-rays on human mesenchymal stem cells (80), it is proved that X-ray at a high dose rate (1 Gy/min) induces a significant increase in population of G0/G1 phase, a decrease in S phase, and no significant changes in G2/M phase in comparison with a low dose rate counterpart (0.1 Gy/min). We observed that the sub-G0/G1 population, which is referred to as an indicator of cell death, increased following a high dose rate radiation in IOMM-Lee cell (**Tables 1**, **2**, **4** and **Figures 1F,G**). Combine with the dose-rate effect, these indicate that, within certain range, a higher dose-rate radiation treatment induces G0/G1 arrest and a relevant increased sub-G0/G1 population.

LIMITATIONS

It is noteworthy that the present research is based only on one single meningioma cell line IOMM-Lee, which may not comprehensively reflect other cell lines. Acquisition of other meningioma cell lines is beyond our ability, and the corresponding assays should be performed for comprehensive evaluation.

CONCLUSION

Radiation inhibits proliferation and promotes apoptosis and invasiveness in IOMM-Lee cells. Downregulating *miR-221/222* expression can reverse this radiation-induced cell invasiveness while enhancing the apoptosis-promoting and proliferation-inhibiting effects of radiation and promoting cell radiosensitivity. Meanwhile, the dose rate of irradiation was also revealed to affect cell cycle distribution and cell apoptosis of IOMM-Lee. A high dose-rate irradiation induces G0/G1 cell cycle arrest and apoptosis-promoting effect. These findings suggest that the downregulation of *miR-221/222* is a promising method of improving radiotherapeutic efficacy and preventing postradiotherapeutic tumor recurrence. Future investigations of meningioma cells may focus on the interaction mechanisms between *miR-221/222* and IR-induced EMT and EMT-TFs, which may improve the understanding of radiotherapeutic toxicities and achieve more effective toxicity avoidance.

DATA AVAILABILITY STATEMENT

The datasets generated for this study can be found in the article/supplementary material.

ETHICS STATEMENT

The animal study was reviewed and approved by Animal Welfare Ethics Committee of Beijing Neurosurgical Institute (202001014).

AUTHOR CONTRIBUTIONS

QZ and L-RS: experimental implementation and acquisition of data. QZ, L-RS, X-LH, LW, G-BZ, S-YH, H-WJ, and C-LK: analysis and interpretation of data. QZ: drafting the article. J-TZ and G-JJ: approved the final version of the manuscript on behalf of all authors. J-TZ, G-JJ, WJ, ZW, LW, and B-NX: administrative, technical, and material support. All authors: conception and experimental design, critically revising the article, reviewed submitted version of manuscript, and study supervision.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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WHO Grade I Meningioma Recurrence: Identifying High Risk Patients Using Histopathological Features and the MIB-1 Index

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Objective: In this study, we identify clinical, radiographic, and histopathologic prognosticators of overall, early, and post-median recurrence in World Health Organization (WHO) grade I meningiomas. We also determine a clinically relevant cutoff for MIB-1 to identify patients at high risk for recurrence.

Method: A retrospective review of WHO grade I meningioma patients with available MIB-1 index data who underwent treatment at our institution from 2007 to 2017 was performed. Univariate and multivariate analyses, and recursive partitioning analysis (RPA), were used to identify risk factors for overall, early (within 24 months), and post-median (>24 months post-treatment) recurrence.

Result: A total of 239 patients were included. The mean age was 60.0 years, and 69.5% of patients were female. The average follow-up was 41.1 months. All patients received surgery and 2 patients each received either adjuvant radiotherapy (2/239) or gamma knife treatment (2/239). The incidence of recurrence was 10.9% (26/239 patients), with an average time to recurrence of 33.2 months (6–105 months). Posterior fossa tumor location ($p = 0.004$), MIB-1 staining ($p = 0.008$), nuclear atypia ($p = 0.003$), and STR ($p < 0.001$) were independently associated with an increased risk of recurrence on cox-regression analysis. RPA for overall recurrence highlighted extent of resection, and after gross total resection (GTR), a MIB-1 index cutoff of 4.5% as key prognostic factors for recurrence. Patients with a GTR and MIB-1 >4.5% had a similar incidence of recurrence as those with STR (18.8 vs. 18.6%). Variables independently associated with early recurrence on binary logistic regression modeling included STR ($p = 0.002$) and nuclear atypia ($p = 0.019$). RPA confirmed STR as associated with early recurrence.

Conclusion: STR, posterior fossa location, nuclear atypia, and elevated MIB-1 index are prognostic factors for WHO grade I meningioma recurrence. Moreover, MIB-1 index >4.5% is prognostic for recurrence in patients with GTR. Verification of our findings in larger, multi-institutional studies could enable risk stratification and recommendations for adjuvant radiotherapy following resection of WHO grade I meningiomas.

Keywords: meningioma, WHO grade I, recurrence, MIB-1, benign, early recurrence, late recurrence

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INTRODUCTION

Meningiomas are the most common primary central nervous system (CNS) neoplasm and account for over 37% of all primary brain tumors (1). Management options for meningiomas include observation, surgery, and radiotherapy (2, 3). While a minority of meningiomas are aggressive, including World Health Organization (WHO) grades II and III, over 80% are WHO grade I, and often called "benign" (4). However, even WHO grade I meningiomas can recur, with previous studies highlighting a recurrence rate of up to 47% with long-term follow-up (4, 5). Meningioma recurrence frequently necessitates treatment with additional surgery or salvage radiotherapy, leading to potential morbidity (6, 7). As a result, the ability to predict recurrence is a crucial component of WHO grade I meningioma management to make recommendations regarding the frequency of surveillance imaging, or the use of adjuvant radiotherapy.

In addition to the Simpson grade achieved at resection, a number of tumor characteristics have been evaluated as possible predictors of recurrence, with a focus on histopathological findings (8). These include the MIB-1 index (a marker of cell proliferation), brain invasion, and the presence of atypical histologic features, including increased cellularity, sheeting, foci of spontaneous necrosis, and nuclear atypia (9–13). Indeed, the 2016 WHO classifications exclusively use pathological findings to determine tumor grade with grade II defined by brain invasion and increased mitosis over 4/10 high powered field (HPF) (4). In addition, three atypical features together result in an increased tumor grade (4). Looking forward, meningioma molecular characteristics have recently been associated with risk of recurrence, and will likely be used in meningioma grading in the future (14–16).

While the WHO classifications synthesize the available literature to create clear delineators between tumor grades, the literature surrounding WHO grade I meningioma recurrence remains mixed. For example, while brain invasion alone can result in an increase of tumor grade from WHO grade I–II, a number of subsequent studies have not found a relationship between brain invasion and recurrence, highlighting the need for additional research into predictors of recurrence (10, 17, 18). The utility of the MIB-1 index in predicting meningioma recurrence is also controversial; a study in WHO grade I meningiomas only suggested a higher recurrence risk with a MIB-1 index of >3%, but other literature including all WHO grades have demonstrated a higher incidence of recurrence at >5% or >10% (9–11). Previous studies have also proposed a MIB-1 cutoff of >3% only in patients with a Simpson II or III resection, further demonstrating the variety in MIB-1 cutoffs and their usage (13). In comparison, a limited number of studies have investigated the impact of atypical features in WHO grade I meningioma recurrence; although, they have suggested a higher risk of recurrence in WHO grade I tumors displaying atypical features upon pathologic analysis (9).

Therefore, the goal of this study was to investigate clinical, radiographic, and pathologic predictors of recurrence in WHO grade I meningiomas. Given the lack of consensus on the use of MIB-1 in WHO grade I meningiomas, we also utilize recursive partitioning analysis to identify a clinically relevant cutoff for the MIB-1 index. We then identify predictors of early and post-median recurrence in WHO grade I tumors.

METHODS

Patient Population

Patients who underwent treatment for a WHO grade I meningioma from 2007 to 2017 were retrospectively identified using an institutional database. This study was formally approved by the University of California, San Francisco Institutional Review Board (IRB#13-12587). Patients without MIB-1 index values available in the electronic medical record were excluded. Early in the study period, MIB-1 was obtained at the discretion of the attending neuropathologist, but, as time progressed, MIB-1 was obtained on all WHO grade I meningioma patients.

Clinical Data

Patient demographics, clinical, and treatment characteristics, histopathological data, and clinical outcomes were retrospectively reviewed and collected. Clinical data collected included patient age, sex, Karnofsky Performance Status (KPS) at treatment, clinical presentation, and previous history of meningioma treatment. Histopathologic data included MIB-1 index, sheeting/loss of architecture, increased cellularity, necrosis, nuclear atypia, and the presence of bone invasion. Progesterone receptor (PR), Epithelial Membrane Antigen (EMA), CD34, S100, glial fibrillary, and acidic protein (GFAP) staining results were collected when available. Pathologic data was extracted from the pathology report generated at the time of surgical intervention. Tumor location, size, and the presence of preoperative peritumoral edema were determined using preoperative MRI imaging. Anterior-posterior (AP), superior-inferior (SI), and transverse (TV) diameters were collected. Preoperative tumor volume was calculated using the equation for non-spherical tumor volume. Treatment type was similarly collected. Simpson grade was determined through the operative report. Gross total (GTR) and Subtotal resection (STR) were determined using post-operative magnetic resonance imaging (MRI) scans.

The primary outcomes of interest were tumor recurrence and time to recurrence. Recurrence was determined on post-operative radiography as a local recurrence or progression of residual tumor. Time to recurrence was determined from the patient's date of treatment. Length of follow-up was calculated from the date of treatment to the last visit with the neurosurgery clinic. Secondary outcomes included early and post-median recurrence. Early recurrence was defined as within 2 years of initial treatment (19). Post-median recurrence was defined as occurring >2 years [based on previous literature (19) and the median time to recurrence in the cohort] following initial treatment.

Statistical Analysis

Chi-square and Student's *t*-test were utilized for the comparison of categorical and continuous variables, respectively. A multivariate backward likelihood Cox regression model for

recurrence was constructed using variables with $p < 0.200$ on univariate analysis. Similarly, multivariate backward likelihood binary logistic models were constructed to predict early and post-median recurrence using variables with $p < 0.200$ on univariate analysis. Recursive partitioning analysis (RPA) was used to further identify key risk factors of overall, early, and post-median meningioma recurrence. A $p < 0.050$ was used as a threshold of statistical significance. All statistical analysis was performed with SPSS 26.

RESULTS

Overall Patient Demographics and Clinical Outcomes

Overall patient demographics, histopathological features, and clinical outcomes can be seen in **Table 1**. In total, 239 patients with WHO grade I meningiomas were included in the study. The average age was 60.0 years, and 69.5% of patients were female. The most common presenting symptom was headache (30.5%), followed by a focal neurologic deficit (27.6%). The majority of patients underwent surgery alone (98.3%), with 2 patients each receiving adjuvant radiation therapy (0.8%) or gamma knife (0.8%) treatments. Peritumoral edema was present on the preoperative MRIs of 38.1% of patients. The average calculated tumor volume was 30.6 cm^3 (range = 0.23–215.73 cm^3), and the average largest tumor dimension was 3.8 cm (range = 0.6–11.3 cm). Overall, 91 (38.1%) tumors were located on the skull base, 57 (23.8%) were convexity tumors, 43 (18.0%) had a falx/parasagittal location, and 55 (23.0%) had another location. Most patients received a gross total resection (63.6%). The incidence of Simpson I, II, III, and IV resection were 31.4, 29.7, 2.5, and 35.6%, respectively. Atypical features were present in a number of patients; the most common atypical features were bone invasion (18.0%) and sheeting/loss of architecture (8.4%). Mean follow-up was 41.1 months (range: 0–147 months).

Predictors of WHO Grade I Meningioma Recurrence

A total of 26 patients recurred with a median time to recurrence of 24.5 months (**Table 1**). A comparison between patients with a recurrence and those without can be found in **Table 2**. There was no difference in age (60.2 vs. 58.8, $p = 0.582$) or female gender (61.5 vs. 70.4%, $p = 0.353$) between patients with tumors that recurred and non-recurrent patients. Treatment characteristics were similar between the groups, with most patients in each group receiving surgery alone (100.0 vs. 98.1%, $p = 1.000$). However, patients with recurrent tumors had a higher incidence of STR (61.5 vs. 32.7%, $p = 0.004$) and a lower incidence of Simpson grade I resection (11.5 vs. 34.1%, $p = 0.019$). The incidence of peritumoral edema, tumor size, and tumor volume were similar between the groups. On histopathologic analysis, patients with recurrence trended toward increased nuclear atypia (19.2 vs. 7.5%, $p = 0.061$). Patients with recurrence also had a higher mean follow-up (68.9 vs. 37.7 months, $p = 0.001$).

TABLE 1 | Patient characteristics, histopathological features, radiography, and outcomes.

Variable	*N* = 239
Age (years)	
Mean (range)	60.0 (27–90)
Number of female patients	166 (69.5%)
Follow-up	
Mean (range)	41.1 (0–147)
Presenting symptoms	
Headache	73 (30.5%)
Seizure	35 (14.6%)
Cognitive changes	23 (9.6%)
Focal neurologic deficit	66 (27.6%)
Extremity weakness	28 (11.7%)
Ataxia	14 (5.9%)
Vertigo	25 (10.5%)
Proptosis	9 (3.8%)
None (incidental)	53 (22.2%)
KPS at treatment (*N* = 237)	84.7 (30–100)
Tumor location	
Falx/parasagittal	43 (18.0%)
Convexity	57 (23.8%)
Skull base	91 (38.1%)
Posterior fossa	18 (7.5%)
Middle fossa	55 (23.0%)
Anterior fossa	22 (9.2%)
Other	55 (23.0%)
Recurrent tumor	7 (2.9%)
Radiographic characteristics	
Peritumoral edema	91 (38.1%)
Tumor volume (*N* = 164) (range)	30.6 (0.23–215.73)
Largest tumor dimension (*N* = 199) (range)	3.8 (0.6–11.3)
Histopathology	
MIB-1 (average)	3.3 (0.0–18.11)
Sheeting/loss of architecture	20 (8.4%)
Increased cellularity	16 (6.7%)
Necrosis	24 (10.0%)
Nuclear atypia	21 (8.8%)
Bone invasion	43 (18.0%)
Treatment characteristics	
Surgery	235 (98.3%)
Surgery + radiation therapy	2 (0.8%)
Surgery + gamma knife	2 (0.8%)
Preoperative embolization	41 (17.2%)
Simpson grade	
I	76 (31.8%)
II	71 (29.7%)
III	6 (2.5%)
IV	86 (36.0%)
EOR	
STR	86 (36.0%)
GTR	153 (64.0%)
Recurrence	26 (10.9%)
Mean months to recurrence	33.2 ± 23.7
Median months to recurrence (range)	24.5 (6–105)
Multiple recurrence	5 (2.1%)

TABLE 2 | Comparison of patients with recurrent meningiomas vs. non-recurrent meningiomas.

Variable	Non-recurrent $N = 213$	Recurrent $N = 26$	*P*-value
Age (years)			
Mean	58.81 ± 12.30	60.23 ± 13.02	0.582
Number of female patients	150 (70.4%)	16 (61.5%)	0.353
Follow-up (months)			
Mean (range)	37.72 ± 30.62	68.85 ± 42.25	0.001
KPS at treatment	86.02 ± 11.72	85.77 ± 10.27	0.917
Tumor location			
Falx/parasagittal	38 (17.8%)	5 (19.2%)	0.792
Convexity	53 (24.9%)	4 (15.4%)	0.283
Skull base	80 (37.6%)	11 (42.3%)	0.638
Posterior fossa	14 (6.6%)	4 (15.4%)	0.108
Middle fossa	52 (24.4%)	3 (11.5%)	0.141
Anterior fossa	18 (8.5%)	4 (15.4%)	0.274
Other	49 (23.0%)	6 (23.1%)	0.993
Previously treated tumor	5 (2.3%)	2 (7.7%)	0.127
Radiographic characteristics			
Peritumoral edema	82 (38.5%)	9 (34.6%)	0.700
Tumor volume ($N = 164$)	30.48 ± 36.21	32.61 ± 38.79	0.834
Largest tumor dimension ($N = 239$)	3.22 ± 2.03	2.8 ± 2.58	0.358
Histopathology			
MIB-1 (%)	3.22 ± 2.23	4.27 ± 3.70	0.168
Sheeting/loss of architecture	17 (8.0%)	2 (11.5%)	0.464
Necrosis	20 (9.4%)	4 (15.4%)	0.309
Increased cellularity	13 (6.1%)	3 (11.5%)	0.295
Nuclear atypia	16 (7.5%)	5 (19.2%)	0.061
Bone invasion	36 (16.9%)	7 (26.9%)	0.209
Treatment characteristics			
Surgery	209 (98.1%)	26 (100.0%)	1.000
Preoperative embolization	36 (16.9%)	5 (19.2%)	0.784
Simpson grade			
I	73 (34.3%)	3 (11.5%)	0.019
II	65 (30.8%)	6 (23.1%)	0.417
III	5 (2.4%)	1 (3.8%)	0.506
IV	70 (32.9%)	16 (61.5%)	0.004
EOR			0.004
STR	70 (32.9%)	16 (61.5%)	
GTR	143 (67.1%)	10 (38.5%)	

A subsequent backward likelihood cox-regression analysis highlighted an independent relationship between recurrence and posterior fossa tumor location (HR = 5.25, CI 1.71–16.17, $p = 0.004$), MIB-1 index (HR = 1.18, CI 1.05–1.34, $p = 0.008$), nuclear atypia (HR = 5.24, CI 1.73–15.92, $p = 0.003$), and STR (HR = 5.66, CI 1.30–13.92, $p < 0.001$; **Table 3**). Kaplan-Meier curves highlighting recurrence free survival for posterior fossa location ($p = 0.007$), nuclear atypia ($p = 0.137$), extent of resection ($p = 0.001$), and MIB-1 >4.5% ($p = 0.001$) are shown in **Figures 1A–D**.

TABLE 3 | Cox regression analysis for recurrence.

Variable	Hazard ratio	95% CI	*P*-value
Tumor location			
All other tumor locations	Ref		
Middle fossa location	0.326	0.093–1.14	0.080
Posterior fossa location	5.27	1.71–16.20	0.004
MIB-1 staining	1.18	1.05–1.34	0.008
Nuclear atypia			
No nuclear atypia	Ref		
Nuclear atypia	5.26	1.73–15.97	0.003
Extent of resection			
Gross total resection	Ref		
Subtotal resection	5.68	2.31–13.97	<0.001

Predictors of Early vs. Post-median WHO Grade I Meningioma Recurrence

A comparison between non-recurrent patients and patients with tumors that recurred early or post-median is presented in **Table 4**. Patients with an early recurrence had a higher incidence of subtotal resection (76.9 vs. 32.7%, $p = 0.001$). They also trended toward a higher incidence of nuclear atypia (23.1 vs. 7.5%, $p = 0.084$) on histopathology (**Table 4**). Patients with a post-median recurrence trended toward an increased incidence of posterior fossa tumor location (23.1 vs. 6.6%, $p = 0.063$) and a higher incidence of bone invasion (38.5 vs. 16.9%, $p = 0.064$) as well as a higher MIB-1 index (5.55 vs. 3.22%, $p = 0.098$). There was no significant difference between Simpson grading or GTR rates in patients with post-median recurrence vs. non-recurrent patients (**Table 4**).

Two multivariate backward likelihood binary logistic models were used to identify predictors of early vs. post-median recurrence (**Table 5**). Independent predictors of early tumor recurrence included nuclear atypia on histopathology (OR = 6.45, CI 1.34–31.07, $p = 0.020$) and STR (OR = 8.92, CI 2.18–36.46, $p = 0.002$). The sole independent predictor of post-median recurrence was MIB-1 index (OR = 1.24, CI 1.05–1.45, $p = 0.010$), although posterior fossa location approached significance (OR = 4.42, CI 0.954–20.49, $p = 0.058$; **Table 5**).

Recursive Partitioning Analysis of Recurrence

RPA was performed to identify key risk factors of meningioma recurrence (**Figure 2**). Consistent with the cox-regression analysis, STR was the first partition when predicting overall recurrence: 18.6% of patients with an STR resection recurred as compared to 6.5% with a GTR. The next decision node within only GTR patients involved a MIB-1 cutoff of 4.5%, as 18.8% of patients with a MIB-1 >4.5% recurred vs. 3.3% of patients with a MIB-1 ≤4.5% (**Figure 2A**). With regards to post-median recurrence specifically, RPA identified the first decision node as a MIB-1 cutoff of 5.83%: 22.2% of patients with MIB-1 >5.83% recurred vs. 3.3% of patients with a MIB-1 ≤5.83%. The subsequent decision node utilized a posterior fossa tumor

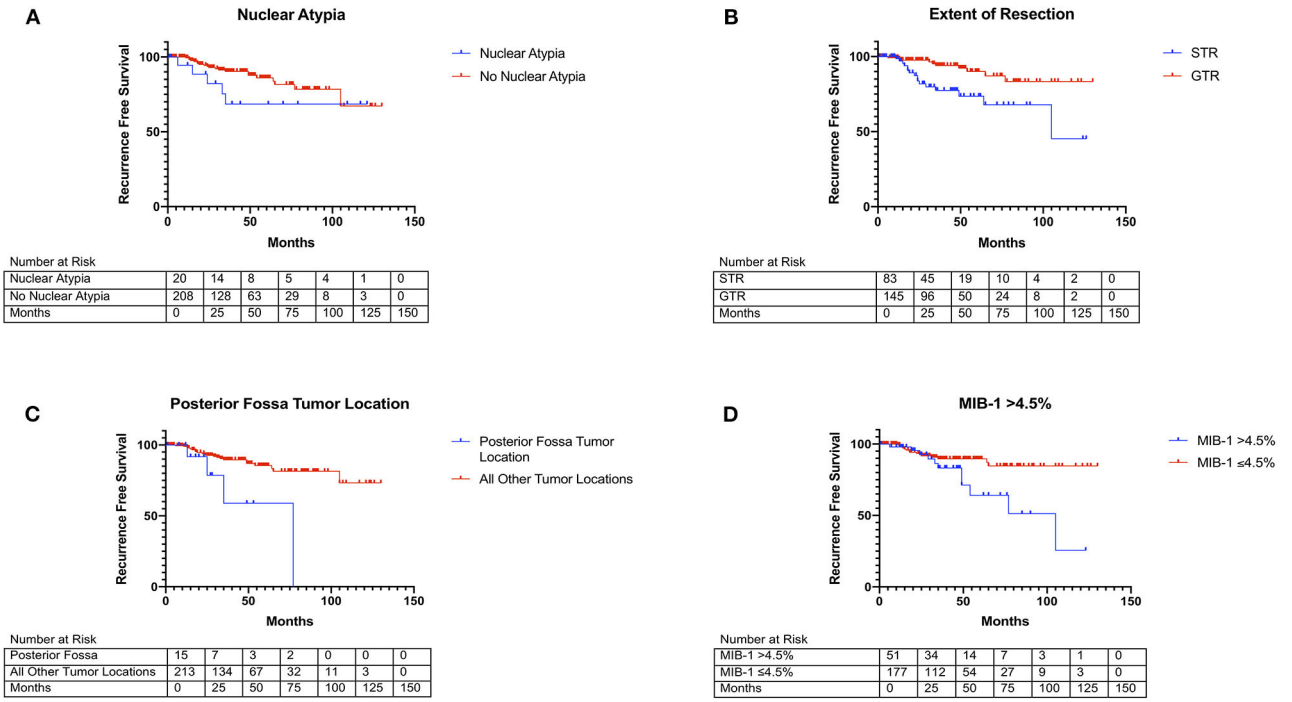


FIGURE 1 | Kaplan Meier curves of risk factors for WHO grade I meningioma recurrence. **(A)** Nuclear atypia (blue line) vs. no nuclear atypia (red line) ($X^2 = 2.21$, $p = 0.137$). **(B)** Posterior-fossa tumor location (blue line) vs. other locations (red line) ($X^2 = 10.36$, $p = 0.001$). **(C)** MIB-1 index >4.5% (blue line) vs. ≤4.5% (red line) ($X^2 = 6.17$, $p = 0.013$). **(D)** STR (blue line) vs. GTR (red line) ($X^2 = 10.46$, $p = 0.001$).

location: 13.3% of patients with a posterior fossa tumor recurred vs. 2.5% of other tumor locations (**Figure 2B**). RPA for early recurrence identified extent of resection as the primary decision node: 11.6% of patients with STR recurred vs. 2.0% of GTR patients. The following decision node utilized falx or parasagittal location: 36.4% of falx or parasagittal tumors recurred vs. 8.1% of other tumor locations (**Figure 2C**).

DISCUSSION

Key Results

WHO grade I meningioma recurrence is independently associated with MIB-1 index, posterior fossa tumor location, the presence of nuclear atypia, and STR. More specifically, a MIB-1 index of 4.5% was identified as a clinically relevant cutoff in risk-stratifying WHO grade I meningioma patients following GTR. Patients with a >4.5% MIB-1 index and GTR of their WHO grade I meningioma had a similar risk of recurrence as those patients with an STR. Further analysis highlighted MIB-1 as a critical factor associated with post-median recurrence while extent of resection was the main driver of early recurrence.

Predictors of WHO Grade I Meningioma Recurrence

Previous studies have similarly assessed the relationship between histopathological features, clinical characteristics, and recurrence in all meningioma WHO grades. In a study of 901 patients (716 WHO Grade I, 174 Grade II, and 11 Grade III), Gousias et al. demonstrate a higher risk of recurrence in meningiomas with a MIB-1 index of >10%, higher WHO grade, tumor size >6 cm, petroclival or cavernous sinus location, and multiplicity (11). However, Gousias et al. did not assess the relationship between the presence of atypical features on histology and tumor recurrence. In WHO grade I meningiomas specifically, Marciscano et al. utilized a cohort of 148 WHO grade I meningioma patients with complete pathological analysis to identify variables associated with recurrence, with a focus on the impact of atypical pathologic features on recurrence risk (9). Interestingly they identify the presence of atypical features as an independent risk factor in addition to MIB-1 index >3% and Simpson resection. Our study similarly highlights surgical GTR and nuclear atypia, an atypical feature, as independent predictors of recurrence (**Table 3**), although we assessed each atypical feature independently. We also consider tumor location in our cox-regression model, further identifying posterior fossa location of the tumor as an independent risk factor of recurrence. While Marciscano et al. did not include tumor location in their analysis of predictors of progression, Gousias et al. similarly demonstrate petroclival tumor location as a risk factor for recurrence, albeit when considering all WHO meningioma grades (9, 11). The higher risk of recurrence associated with posterior fossa location may be due to the increased prevalence of NF2 mutations in the posterior fossa (14, 15, 20), although we are unable to fully explore this as we do not routinely perform genetic testing of

TABLE 4 | Early vs. post-median recurrence.

Variable	Non-recurrent $N = 213$	Early $N = 13$	*P*-value (vs. non-recurrent)	Post-median $N = 13$	*P*-value (vs. non-recurrent)
Age (years)					
Mean	58.81 ± 12.30	57.00 ± 13.98	0.609	63.46 ± 11.63	0.186
Number of female patients	150 (70.4%)	9 (69.2%)	1.000	7 (53.8%)	0.224
Follow-up (months)					
Mean (range)	37.72 ± 30.62	55.92 ± 39.24	0.125	81.77 ± 42.63	0.003
Tumor location					
Falx/parasagittal	38 (17.8%)	4 (30.8%)	0.269	1 (7.7%)	0.703
Convexity	53 (24.9%)	1 (7.7%)	0.311	3 (23.1%)	1.000
Skull base	80 (37.6%)	4 (30.8%)	0.772	7 (53.8%)	0.241
Posterior fossa	14 (6.6%)	1 (7.7%)	0.601	3 (23.1%)	0.063
Middle fossa	52 (24.4%)	1 (7.7%)	0.309	2 (15.4%)	0.738
Anterior fossa	18 (8.5%)	3 (23.1%)	0.108	1 (7.7%)	1.000
Other	49 (23.0%)	4 (30.8%)	0.509	2 (15.4%)	0.738
Recurrent tumor	5 (2.3%)	1 (7.7%)	0.302	1 (7.7%)	0.302
Radiographic characteristics					
Peritumoral edema	82 (38.5%)	7 (55.8%)	0.272	2 (15.4%)	0.139
Tumor volume ($N = 158$) ($N = 156$)	30.48 ± 36.21	26.03 ± 22.17	0.732	41.38 ± 55.34	0.480
Largest tumor dimension ($N = 226$)	3.22 ± 2.03	2.39 ± 2.14	0.157	3.25 ± 2.99	0.978
Histopathology					
MIB-1	3.22 ± 2.23	2.99 ± 1.82	0.722	5.55 ± 4.65	0.098
Sheeting/loss of architecture	17 (8.0%)	2 (15.4%)	0.300	1 (7.7%)	1.000
Necrosis	20 (9.4%)	1 (7.7%)	1.000	3 (23.1%)	0.134
Increased cellularity	13 (6.1%)	1 (7.7%)	0.575	2 (15.4%)	0.210
Nuclear atypia	16 (7.5%)	3 (23.1%)	0.084	2 (15.4%)	0.277
Bone invasion	36 (16.9%)	2 (15.4%)	1.000	5 (38.5%)	0.064
Treatment characteristics					
Surgery	209 (98.1%)	13 (100.0%)	1.000	13 (100.0%)	1.000
Preoperative embolization	36 (16.9%)	2 (15.4%)	1.000	3 (23.1%)	0.474
Simpson grade ($N = 224$)					
I	73 (34.3%)	1 (7.7%)	0.065	2 (15.4%)	0.229
II	65 (30.8%)	2 (15.4%)	0.353	4 (30.8%)	1.000
III	5 (2.4%)	0 (0.0%)	1.000	1 (7.7%)	0.304
IV	70 (32.9%)	10 (76.9%)	0.002	6 (46.2%)	0.370
EOR			0.001		0.370
STR	70 (32.9%)	10 (76.9%)		6 (46.2%)	
GTR	143 (67.1%)	3 (23.1%)		7 (53.8%)	
Time to recurrence					
Mean (range)		16.4 ± 5.2	<0.001*	50.1 ± 23.0	<0.001*

**Post-median vs. early recurrence.*

meningioma at our institution. Regardless, additional studies with larger WHO grade I meningioma patient cohorts are needed to investigate this relationship.

MIB-1 Index and WHO Grade I Meningioma Recurrence

Similar to previous studies (9, 11, 13, 21) we then also evaluated the relationship between the MIB-1 index of a tumor and its risk of recurrence. We first evaluated MIB-1 index in a cox-regression model for overall recurrence, as previously discussed. In agreement with previous studies, we found that higher MIB-1 index was independently associated with an overall increased risk of recurrence. Given the discrepancies in cutoff values for MIB-1 between the literature and the inter-laboratory variability, we initially evaluated MIB-1 as a continuous variable. We next sought to determine the cutoff for MIB-1 index in our patient population by utilizing RPA to model overall recurrence, which identified a MIB-1 cutoff value of 4.5% in patients with GTR (**Figure 2A**). Interestingly, these patients had a similar risk of recurrence as patients with an STR, demonstrating the

TABLE 5 | Binary logistic model for post-median and early tumor recurrence.

	Variable	Odds ratio	95% CI	*P*-value
Post-median tumor recurrence	Tumor location			
	Non-posterior fossa location	Ref		
	Posterior fossa location	4.42	0.954–20.49	0.058
	MIB-1 staining	1.24	1.05–1.45	0.010
	Peritumoral edema			
	No peritumoral edema	Ref		
	Peritumoral edema present	0.266	0.055–1.29	0.101
Early tumor recurrence	Extent of resection			
	Gross total resection	Ref		
	Subtotal resection	8.87	2.17–36.28	0.002
	Nuclear atypia			
	No nuclear atypia	Ref		
	Nuclear atypia present	6.53	1.37–31.43	0.019

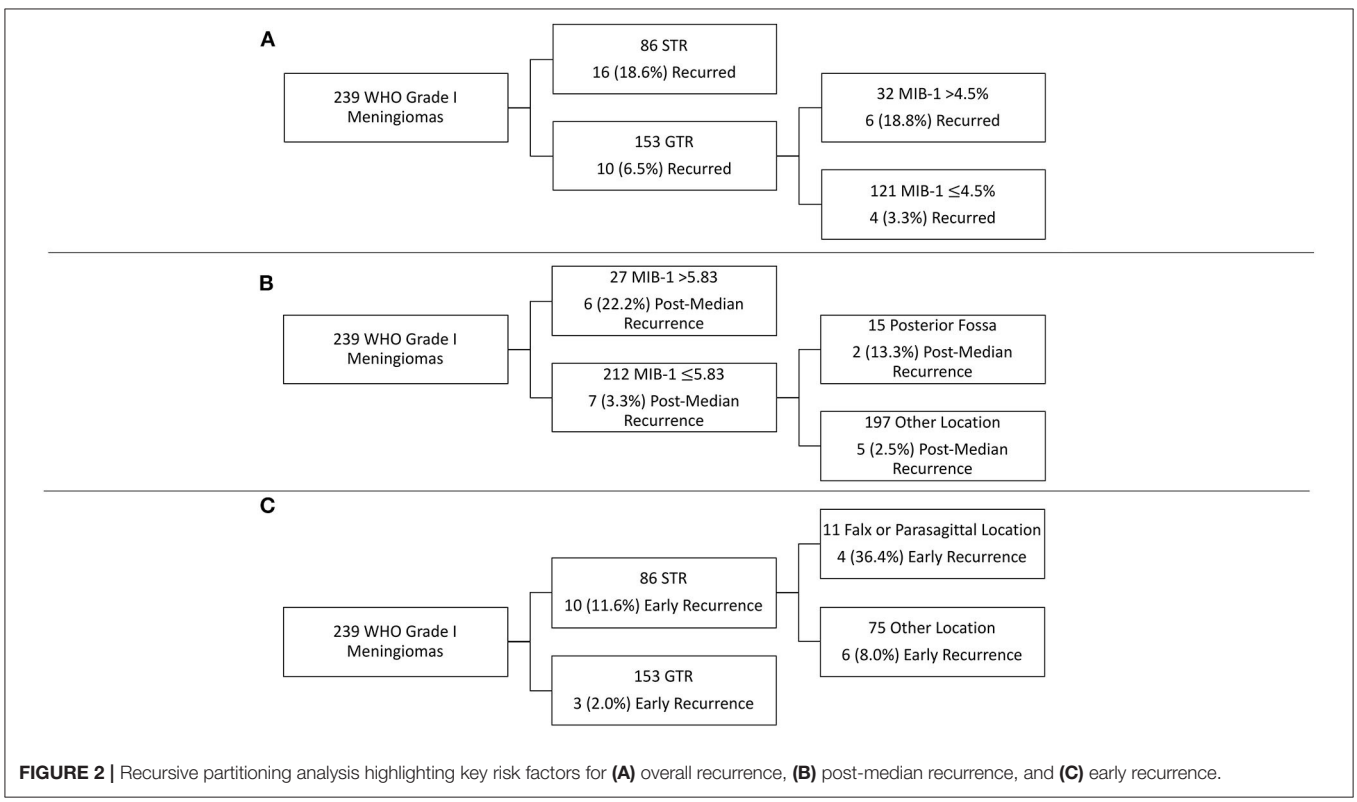


FIGURE 2 | Recursive partitioning analysis highlighting key risk factors for **(A)** overall recurrence, **(B)** post-median recurrence, and **(C)** early recurrence.

utility of MIB-1 in patients following GTR. Perry et al. similarly identifies a MIB-1 index of 4.2% as associated with recurrence following GTR on univariate analysis, albeit when considering all meningioma grades (22).

The recurrence rate of 18.8% in patients with a GTR and MIB-1 >4.5%, highlights the need for close surveillance of these patients or even the consideration of adjuvant radiation therapy, depending on patient preference. Adjuvant radiation therapy following resection for WHO grade I meningioma has been shown to reduce recurrence, especially following STR (23–25), although observation following STR remains standard practice (8). In a study of 92 WHO grade I meningiomas, Soyuer et al. demonstrated a 91% progression-free survival (PFS) in patients who received adjuvant radiotherapy following STR, which was significantly higher than the 38% PFS in those patients who had not received adjuvant radiotherapy (24). As patients in our study with an STR had a similar risk of recurrence as those with a GTR and MIB-1 >4.5%, adjuvant radiotherapy for both groups may reasonable. However, larger studies are needed to further validate our MIB-1 cutoff and the associated clinical implications. Prospective studies investigating the use of adjuvant radiotherapy in WHO grade I meningiomas are also needed.

Predictors of Early and Post-median WHO Grade I Meningioma Recurrence

Given the trend toward a later recurrence in patients with an elevated MIB >4.5% (**Figure 1C**), we then sought to investigate differences in predictors between patients who recurred early (defined as within 2 years of treatment) or post-median (those who recurred >2 years following treatment). Few studies in the literature have investigated predictors of early recurrence in meningiomas. A study by Budohoski et al. identifies parafalcine location, STR, and peritumoral edema on radiographic imaging as predictors of early recurrence in a cohort of 220 atypical meningiomas (26). A similar study by Maillo et al., in WHO grade I meningiomas, utilizes interphase fluorescence *in situ* hybridization (FISH) and pathological features to identify risk factors for early recurrence (defined as 2.5 years after treatment) and found larger tumor size, karyotype abnormalities, patient age, and abnormalities of chromosome 10 to be associated with increased risk of recurrence (19). However, the authors did not consider the presence of atypia on pathology or MIB-1 index. Using a cohort of WHO grade I meningioma patients with more granular pathologic and clinical data, we identified extent of resection and nuclear atypia on pathology as independent predictors of early recurrence on binary logistic regression modeling (**Table 5**). RPA similarly revealed the importance of extent of resection in risk-stratifying patients for early recurrence (**Figure 2C**). Interestingly, it also highlighted the increased risk associated with falx/parasagittal tumor location, corresponding with the findings of Budohoski et al. (26). The only significant predictor of post-median tumor recurrence on binary logistic regression modeling was MIB-1 index, although posterior fossa location of the tumor approached significance. This was further demonstrated on RPA (**Figure 2B**). Surprisingly, extent of resection was not an independent predictor of post-median recurrence, as the majority of post-median recurrences had undergone a GTR. Post-median recurrences may highlight a category of WHO grade I meningioma that is molecularly more aggressive and recurs despite GTR, given their elevated MIB-1 index and posterior fossa location [potentially indicating an underlying NF2 mutation (20)]. Early recurrences are significantly more impacted by extent of resection and, as a result, likely represent the continued growth of residual tumor as opposed to the recurrence of previous completely resected tumor, as seen in post-median recurrences. Thus, our results potentially represent two different molecular WHO grade I meningioma subtypes. However, future studies with larger patient cohorts and molecular tumor data are needed to further investigate the underlying differences in molecular alterations between early and post-median recurrences.

Limitations

The limitations of our study include its retrospective nature and low incidence of recurrence. Our study also includes patients beginning in 2007 and, as a result, spans both the 2007 and 2016 WHO CNS classification schemes. However, the only significant change between the two classifications was the addition of brain invasion as a lone criterion for WHO grade II status. Only two of the patients included in our cohort had brain invasion noted on pathological analysis, and neither patient recurred. As a result, we do not believe the inclusion of patients graded using the 2007 classification scheme had a significant impact on our findings. In addition, our study relies on the pathologic reports following initial resection, without a central re-review of pathologic slides. This may lead to increased variability in the pathologic variables, such as nuclear atypia and other similar pathologic findings which can demonstrate interobserver variability (27, 28). However, MIB-1 is a relatively objective measure with lower inter-observer variability between pathologists using the same method within a pathology laboratory (29). Practice patterns regarding MIB-1 testing also changed during the study time-period from individual pathologist preference, which varied depending on the pathologist, to testing in all patients. Factors considered by pathologists when deciding on MIB-1 testing included the atypical features included in our study, thus minimizing their potential impact on our findings. In addition, all meningiomas included in our study are WHO Grade I. As a result, we believe any bias introduced into the study based on these changes in practices patterns is minimal. Finally, while we include detailed clinical and pathologic characteristics, our patient cohort lacks information regarding tumor genetic and molecular changes, which have been shown to have a significant impact on tumor outcomes (15, 30–32). Thus, there remains a need for additional large multi-institutional studies with molecular/genetics data in addition to traditional pathologic and clinical variables when predicting overall recurrence of WHO grade I meningiomas. This includes consideration of molecular/genetic prognosticators, such as genome-wide methylation patterns (33, 34), TERT promoter mutations (35), and additional tumor molecular data given our findings, future investigations into unique genetic/molecular, clinical, and pathologic predictors of early and later recurrences are warranted as well, given the potential impact on therapeutic decision making by physicians.

Nevertheless, our study provides detailed insight into clinical and histopathological predictors of recurrence, specifically in WHO grade I meningiomas. In addition, we identify patients with a MIB-1 >4.5% as being at high risk for recurrence following GTR. We also leverage our data to provide insight into differences between early and post-median WHO grade I meningioma recurrences, potentially identifying different WHO grade I meningioma molecular subgroups. Our results suggest that patients with an elevated MIB-1 index and nuclear atypia on pathologic analysis, posterior fossa location of their tumor, and STR are at higher risk for recurrence and should be considered for closer follow-up or even adjuvant radiotherapy. In addition, patients with a MIB-1 over 4.5% are at a similar risk for recurrence as those who have undergone STR of their tumors and should also potentially be considered for adjuvant radiotherapy.

CONCLUSION

There remains a paucity of literature on specific predictors of recurrence in WHO grade I meningiomas. The findings

of this study highlight posterior fossa tumor location, MIB-1 index, nuclear atypia, and extent of resection as independently associated with recurrence of grade I meningiomas. We also demonstrate that patients with a MIB-1 >4.5% and GTR have a similar risk of recurrence as patients with an STR. Finally, differential analysis of early and post-median recurrences revealed the association of MIB-1 index and posterior fossa location in post-median recurrences, while early recurrences were more significantly impacted by extent of resection. Additional studies validating our findings and including molecular/genetic data are needed to identify additional predictors of recurrence in WHO grade I meningiomas. Such studies could provide a more accurate framework to risk-stratify patients and aid with therapeutic decision making, including the potential for adjuvant radiotherapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UCSF Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AH: conceptualization, methodology, formal analysis, investigation, writing—original draft, writing—review and editing, and visualization. JY: conceptualization, methodology, and writing—review and editing. IK and SS: investigation. J-SC: visualization and formal analysis. DR and MM: writing—review and editing. SM: writing—review and editing, conceptualization, and methodology. MA: writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer BB declared a past co-authorship with the authors DR, MM, and SM to the handling editor.

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Multi-Omics Analysis in Initiation and Progression of Meningiomas: From Pathogenesis to Diagnosis

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Meningiomas are common intracranial tumors that can be cured by surgical resection in most cases. However, the most disconcerting is high-grade meningiomas, which frequently recur despite initial successful treatment, eventually conferring poor prognosis. Therefore, the early diagnosis and classification of meningioma is necessary for the subsequent intervention and an improved prognosis. A growing body of evidence demonstrates the potential of multi-omics study (including genomics, transcriptomics, epigenomics, proteomics) for meningioma diagnosis and mechanistic links to potential pathological mechanism. This thesis addresses a neglected aspect of recent advances in the field of meningiomas at multiple omics levels, highlighting that the integration of multi-omics can reveal the mechanism of meningiomas, which provides a timely and necessary scientific basis for the treatment of meningiomas.

Keywords: meningiomas, biomarker, genomics, epigenomics, transcriptomics, proteomics

INTRODUCTION

Meningiomas account for 13–36.6% of the primary malignant tumors of the central nervous system (1). Although the reported incidence is around 7.8/100,000 (2), the rate of recurrence increases dramatically to 32% with progressive/higher grade meningiomas (∼20% of all meningiomas) (3). Coupled with the high treatment costs (∼$83,838 per person) (4), meningioma is increasingly recognized as a serious, worldwide public health concern (5). Since the publication of revised WHO guidelines in 2016, the diagnosis of meningioma is mainly divided into three grades based on the morphological features (6). Unfortunately, this grading system does not ultimately predict the clinical behavior of meningiomas, especially long-term recurrence of atypical meningiomas (7).

Recent advances in omics technologies (genomics, transcriptomics, epigenomics, and proteomics) contribute to large screening of biomarkers for meningioma by tissue microarray to predict biological behavior of meningiomas (8). Notably, integration of multi-omics with clinical data represents an accurate and promising methodology to provide very accurate prediction models for meningioma progression (**Figure 1**), suggesting the potential of early and accurate diagnosis, effective therapeutic strategies, and favorable prognosis of meningioma (9, 10).

GENOMICS

Accurate and comprehensive sequencing of personal genomes is an important technical advance based on bioinformatics analysis (11), which is crucial to genetic studies of complex human diseases (12). Deep understanding of genetic alterations relating to meningioma development and progression may provide new insights into meningioma classification and personalized treatment (13).

As early as 2011, a sequencing-based genome-wide association study (GWAS) of 859 patients with meningioma and a control group ($n = 704$) identified MLLT10 as a new susceptibility locus (14). It is worth mentioning that, in the last decades, the role of *MLLT10* in the pathogenesis and progression of meningioma has been well-established (15, 16). In that same year, an expanded genome-wide association study of meningioma, including 2,000 patients and 6,000 controls, was initiated by the National Institutes of Health (17), which earned a significant contribution in understanding genetic factors of meningioma. Notably, the results, including an inverse relationship between hormones and allergies, provided a clear framework and direction for further meningioma study as well as the establishment of comparative oncology (18–20). Furthermore, a genotype analysis in 65 samples using high-density single nucleotide polymorphism (SNP) arrays found associations between meningiomas and variation in *PIAS2*, *KATNAL2*, *TCEB3C*, *TCEB3CL*, and *CTNNA3*, especially *TARDBP* mutations with amyotrophic lateral sclerosis (21), which further improves the identification of susceptible sites of meningioma by genomics. Subsequently, a GWAS involving 1,606 meningioma patients and 9,823 controls provided additional support for the link between obesity and risk of recurrence in meningioma (22), which laid a solid foundation for meningioma characteristics, including risk factors and epidemiology (23, 24). To further illustrate the genetic basis and construct a genetic linkage map of meningioma, Claus et al. identified a new meningioma susceptibility site at 11p15.5 through a combined reference panel from UK10K data including a total of 2,138 and 12,081 controls and 1,000 genomic projects in 2018 (25). It is worth pointing out that the susceptible site included a new pathogenic mutation in *RIC8A*, which is necessary for the development of cranial neural crest-derived structures. Therefore, this study suggests the cytogenetic relationship between meningiomas and nerve sheath structures (26) (**Figure 2**).

In addition to the potential role of genetic factors on meningioma, genomics has been applied in the diagnosis and classification of meningioma. Clinically, in the case of a meningioma specimen that contains atypical tumor regions that are difficult to assess, molecular marker techniques for patient genome analysis, such as array comparative genomic hybridization (aCGH) and expression array profiles, can be used for histopathological grading (27). The first instance from a whole genome sequencing project of malignant subtypes revealed mutational signatures and frequently altered genes in malignant meningiomas, including *NF2*, *MN1*, *ARID1B*, *SEMA4D*, and *MUC2*, which confirmed the role of pathogenic *NF2* mutations in the development of meningiomas, and expression of *MN1* may be a valuable diagnostic tool for determining the potential in malignant transformation (28).

So far, genomics has made a tremendous contribution to the criteria for diagnosis, staging, risk stratification, and response assessment of meningiomas (**Table 1**). Regrettably, some aspects of genetic factors in meningioma have been ignored, and the gene regulatory network leading to meningioma remains unclear. Further pooling research in genomics will advance the field of meningiomas' genetic basis and pathological mechanisms, which may also provide novel research horizons and suggestions for intervention strategies and clinical practice of meningioma.

EPIGENOMICS

Epigenetic factors, mainly DNA methylation and histone modification, have considerable effects on the pathogenesis of meningioma (29). In the last few years, developments in multi-omics technologies provide tools for high-throughput and high-density molecular analyses, which has provided a novel view regarding the functional organization of the molecular layer. The pathogenic role of chromosome markers in gene regulation and other processes were also inferred by it (30).

WHO classification of meningiomas is based on histologic characteristics. However, part of malignant meningiomas was histologically described to benign meningiomas (31); therefore, novel diagnostic strategies are urgently required while DNA methylation assessment has considerable potential to reconstruct the grade of meningioma. Expression profiles of 10,422 genes at the early stage of meningioma using cDNA microarray indicate hypermethylation of gene subsets are critical in tumor development (32). Further research identified 64-CpG meningioma methylation predictor (64-MMP), which is responsible for tumor recurrence (hazard ratio = 12.16) (33). In 2017, Sahm et al. compiled a genome-wide mapping of differentially methylated regions by DNA methylation profiling from 497 meningioma and 309 extra-axial skull tumors that might histologically mimic meningioma variants. On this basis, six different clinically relevant methylation types of meningioma were distinguished, and they relate to typical mutations, cytogenetics, and gene expression patterns (34). Notably, the classification by methylation provides more precise prognostication of progression-free survival outcomes at 10

Abbreviations: WHO, World Health Organization; GWAS, Genome Wide Association Study; UK, United Kingdom; aCGH, array comparative genomic hybridization; 64-MMP, 64-CpG meningiomas methylation predictor; HRR, homologous recombination repair; PTX3, Recombinant Pentraxin 3; MN1, meningioma 1; miRNA, microRNA; snoRNA, small nucleolar RNA; sncRNA, small interfering RNA; siRNA, small interfering RNA; HMGN5, high-mobility group nucleosome-binding protein 5; K-Ras, K-rat sarcoma; SELDI-TOF MS, surface-enhanced laser desorption/ionization time-of-flight mass spectrometry; ITRAQ, isobaric tags for relative and absolute quantification; ESI-Q-TOF, electrospray ionization- quadrupole-time of flight; Q-Exactive MS, thermo scientific Q exactive; SELDI, surface-enhanced laser desorption/ionization time-of-flight mass spectrometry; AKAP12, a-kinase anchor protein 12; FoxM1, Forkhead Box M1; ITP, immune thrombocytopenia; TNF-α, tumor necrosis factor α; NF2, Neurofibromatosis Type 2.

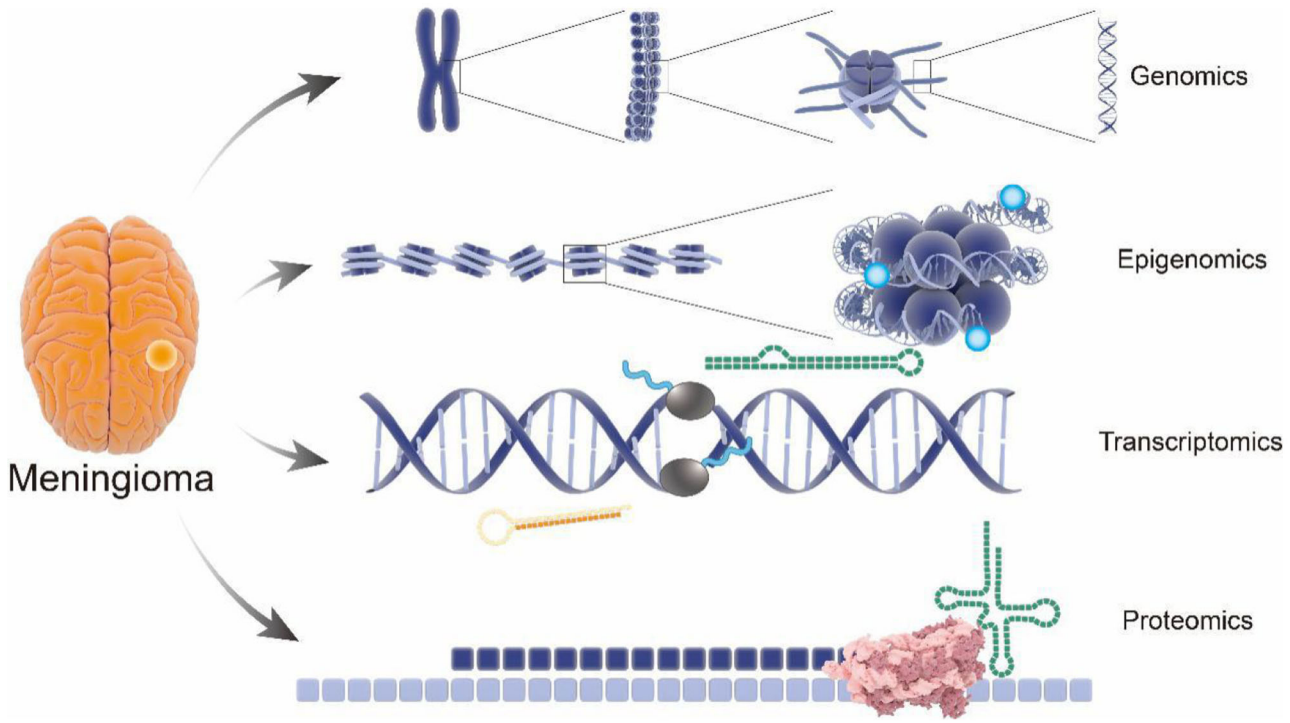


FIGURE 1 | Comprehensive analysis of pathology and molecular genetics of meningioma from multi-omics perspective. Structure of gene with the meningioma pathogenic variants have been revealed by genomics; performance of the epigenomics showing the influence of the genetic modification on meningioma; pathological gene expression in meningioma were analyzed by transcriptomics; applications of proteomics visually show the endocranial shape changes during meningioma. From genomics to proteomics, the pathological process and potential therapeutic targets involved in meningioma progression will be revealed as never before.

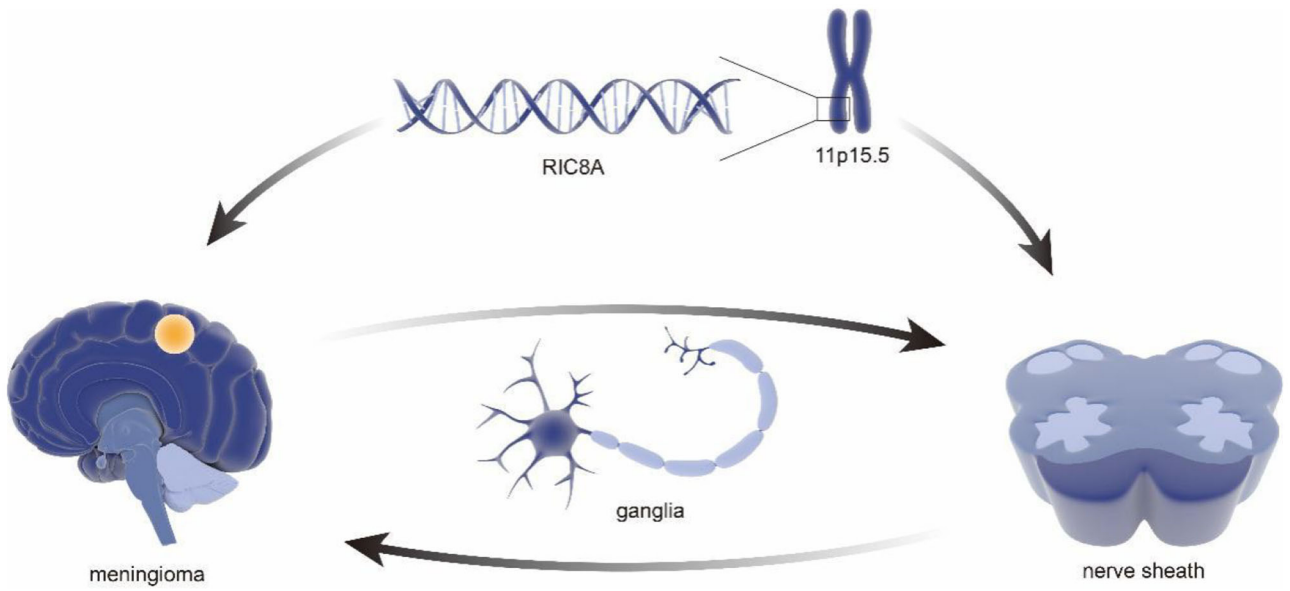


FIGURE 2 | Genetic association of the nerve sheath development and meningioma. The RIC8A located in area 11p15.5 were revealed to be associated with pathological phenotypes in meningioma. It is important to mention that the same genes have been confirmed to be related to cranial neural crest-derived structures. Consider the correlation between nerve sheath and ganglia, which might explain a series of cases of nerve sheath meningioma and ganglia intraparenchymal meningioma.

TABLE 1 | Genomics research associated with meningiomas.

Phenotype	Sample size (case, control)	Tissue/tissue	Ethnicity	Tested genes/techniques	Major results	PMID
Meningiomas and normal	*N* = 1,563	Meningiomas tissue (I, II, III)	German	10p12.31, MLLT10	Marker of meningiomas with WHO grade I, II, III	21804547(14)
Meningiomas and normal	*N* = 14,219	Meningiomas tissue (I, II, III)	German	RIC8A	Marker of meningiomas with WHO grade I, II, III	29762745(25)
Meningiomas	*N* = 9	Meningiomas tissue (III)	China	NF2	Important marker of meningiomas with WHO grade III	25549701(28)
Meningiomas	*N* = 9	Meningiomas tissue (III)	China	MN1	Candidate gene for malignant transformation of meningioma	25549701(28)
Meningiomas	*N* = 9	Meningiomas tissue (III)	China	ARID1B	Marker of meningiomas with WHO grade III	25549701(28)
Meningiomas	*N* = 9	Meningiomas tissue (III)	China	SEMA4D	Marker of meningiomas with WHO grade III	25549701(28)
Meningiomas	*N* = 9	Meningiomas tissue (III)	China	MUC2	Marker of meningiomas with WHO grade III	25549701(28)

years' follow-up compared to WHO grading, which highlights the diagnostic and prognostic implications of malignant meningioma by assessing methylation status.

Importantly, epigenetic profiles in meningioma contribute to the construction of an individualized prediction model of early progression and recurrence in meningioma (35). For example, DNA methylation profiles of 282 clinically annotated meningioma samples were used for construction of a prediction model of 5-year recurrence-free survival (RFS) in meningioma. Notably, the recurrence model provides important prognostic information (hazard ratio = 7.7, area under curve = 0.82), which is more accurate than prediction based on clinical factors, including extent of resection and WHO grade (Δ area under curve = 0.25) (36).

In addition to the roles in tumor classification, a comprehensive understanding of epigenetic regulation that has characterized meningioma development and progression may also provide useful guidance for targeted therapies. So far, methylation of *TIMP3*, *CDKN2*, and other genes that can regulate the progression of meningiomas have been identified by genome-wide methylation DNA analysis (37); further work reveals the connection between the H3K27me3 signal and hypermethylated phenotype in meningiomas, integrating with microarray analysis of the transcriptional network controlled by *E2F2* and *FOXM1*. This study makes recommendations for potential targets for therapeutic intervention (38).

The progress in epigenetic research on meningioma have proved to be a valuable tool in pathological classification and intervention of meningiomas (**Supplementary Table 1**) (21). However, recent advances in epigenomics of meningioma have mainly focused on DNA methylation; the role of histone modification and chromosome organization have been neglected. It is also worth noting that chromosomes are associated with homologous recombination repair (HRR) defects, which has been confirmed as a primary causative factor of meningioma (39, 40), suggesting that histone modification has great potential in the development of novel meningioma prevention and intervention measures.

TRANSCRIPTOMICS

By comparing the transcriptome differences between meningioma patients and controls, transcriptomics can screen out the specific expression differences with diagnostic significance, which can be used in the diagnosis and early intervention of meningiomas.

Since the occurrence and development of meningiomas are often caused by the accumulation of multiple gene changes, transcriptome can detect the gene expression differences between normal tissues and meningiomas from the transcriptional level (**Supplementary Table 2**) (41–45). In 2017, a genome-wide array comparing microRNAs expression in meningioma from 50 patients showed that miRNA-21 expression increased significantly with increasing histopathologic grade with reduction of miRNA-107 (41, 46). Notably, upregulated miR-29c-3p coupled with reduction of its predicted target recombinant pentraxin 3(*PTX3*) was observed in the same year using whole transcriptome microarray chips, which indicated the level of tumor suppressor *PTX3* is inhibited by miR-29c-3p (42). Interestingly, *PTX3* overexpression was frequently observed in high-grade gliomas and meningiomas with poor prognosis, which suggests that *PTX3* may be an important contributor to meningioma cell proliferation and invasion (47). The conflicting results have been obtained, which remind us that further studies of changes in transcriptome of meningioma is necessary.

As mentioned earlier, due to its high recurrence rate and poor prognosis, a lot of work on the research of malignant meningioma is required (48), and it is associated with shorter progression-free and overall survival after complete resection (49). Fortunately, novel markers of malignant meningiomas identified through differential gene expression analyses can be achieved through transcriptomics. For example, an illumina expression microarray to assess gene expression levels from a sample set of 19 resected meningiomas identified dense coexpression subnetworks in meningioma and detected carcinogenic modules associated with malignant meningioma. Among the 23 identified coexpression modules, a module involving 356 genes is highly correlated with occurrence of

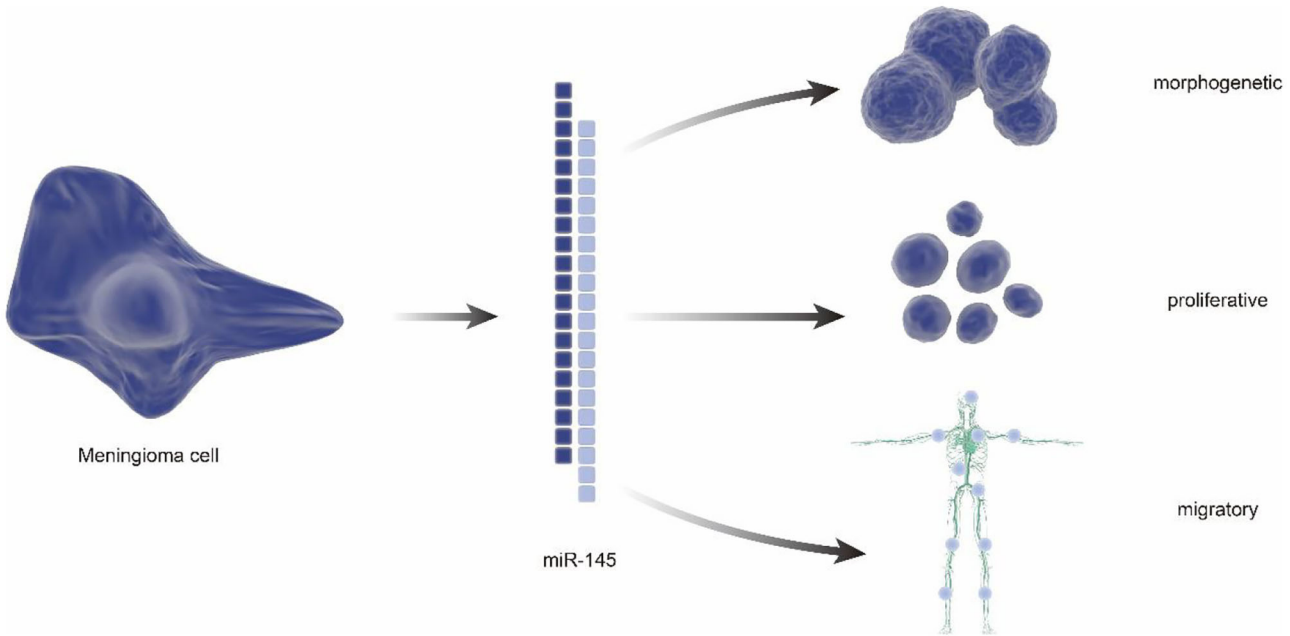


FIGURE 3 | The regulatory role of miRNA in meningiomas. miRNA has a reduced expression in atypical and anaplastic meningiomas, which increases cell proliferation and reduces apoptotic susceptibility. In addition, reduced miRNA reduces migration, invasion, and adhesion of meningioma cells. It can also alter meningioma cell morphology, resulting in low elongation and adhesion.

meningioma. It should be noted that putative meningioma tumor suppressive meningioma 1 (MN1) in this module was differentially expressed between malignant and benign meningioma (43), indicating it can be used as a predictor of meningioma classification.

In addition to characterization of differentially expressed genes, some RNAs were also found to have potential meaning in classification of benign and malignant meningiomas. In 2013, a tissue microarray indicated reduced expression of miR-145 in WHO grade II/III meningiomas using frozen samples from 42 meningiomas. Notably, the follow-up studies demonstrated the antiproliferation, morphogenesis, and antimigration effects of miR-145 in meningioma cells, suggesting the proposed role of the miR-145 in restraining meningioma progression (44) (**Figure 3**). Besides, the small nucleolar RNAs(snoRNAs), such as SNORA46 and SNORA48, were also found differentially expressed between grade I and grade II/III meningiomas, which is identified by RNA sequencing (RNA-seq) analysis after numerous genes were found differentially expressed by real time-PCR (45).

In addition, miRNAs belong to small ncRNAs (sncRNAs), and small interfering RNA (siRNAs) are functionally similar to miRNA, modulating post-transcriptional gene expression by binding to specific mRNAs (50). But transcriptomics studies focused on miRNAs are much more than that on siRNAs although siRNA has been found to relate to some meaningful molecules in meningiomas. For example, siRNA can decrease the expression of high-mobility group nucleosome-binding protein 5 (HMGN5), which has a positive association with meningioma histological grade (51). As for snoRNA, more and more evidence reveal the importance of snoRNA in tumorigenesis (52, 53), such as SNORD50A/B (C/D box), which can directly bind to and inhibit K-rat sarcoma (K-Ras), is deleted in many cancer types (54). However, the lack of transcriptomic studies pertaining to the expression of siRNAs and snoRNAs or relative pathways suggest that transcriptomic studies taking siRNA into consideration are required in the field of meningioma research.

PROTEOMICS

Proteomics is a large-scale study of protein properties, including protein expression levels, post translation modification, protein–protein interaction, etc., which has been proven to be a useful tool in the identification between varieties of meningeal neoplasms (55).

Proteomics can detect the differential expression of proteins in different grades or types of meningiomas (**Supplementary Table 3**) (56–58). As early as 2006, the pure meningioma cell population was sequenced to indicate the differentially expressed proteins of each WHO grade meningioma. This study identified the 15 proteins that were significantly related to atypical meningioma, and nine proteins can be used to discriminate atypical from anaplastic meningiomas (57). Similar biomarkers were also reported in 2014; the expression of galectin-3, vimentin was decreased significantly in meningiomas, and the expression of 40S ribosomal protein S12 and glutathione S-transferase was increased significantly (59). It is worth mentioning that the function of galectin-3 was further investigated in 2017;

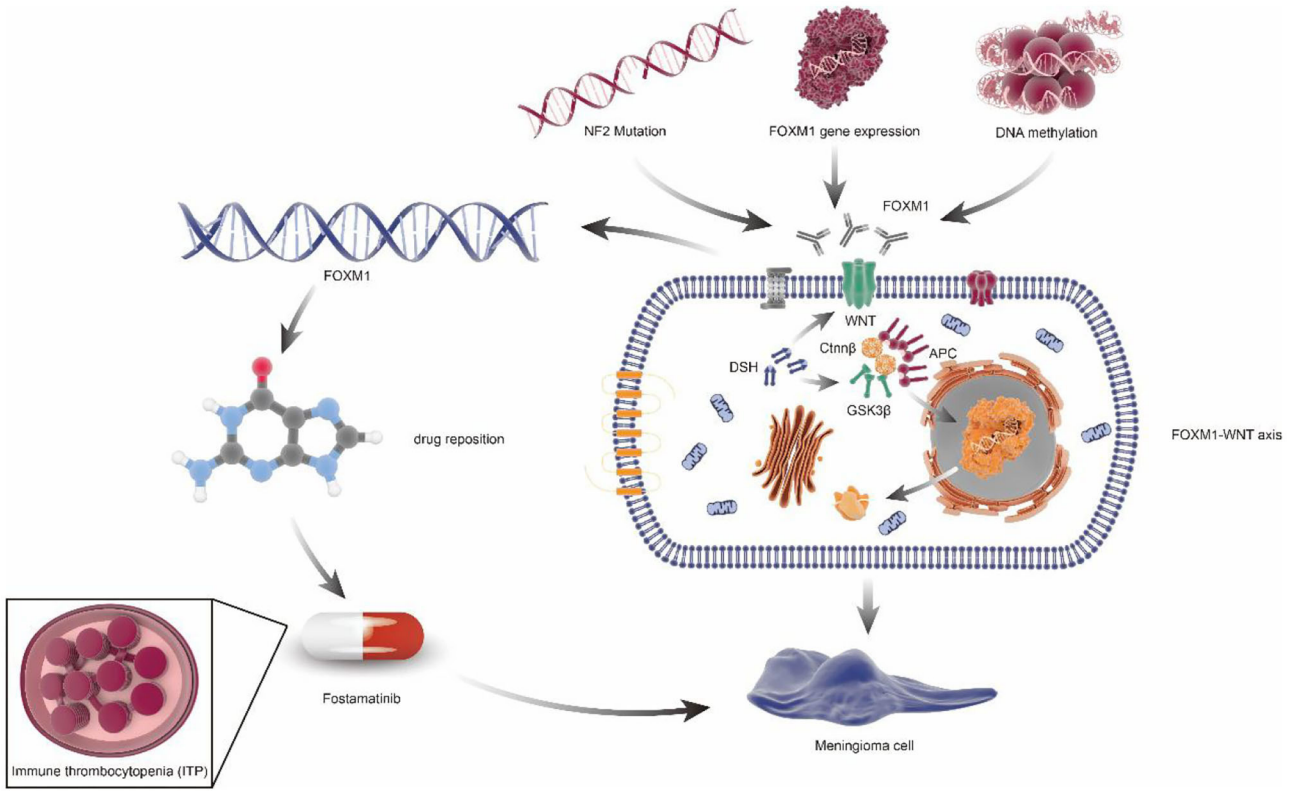


FIGURE 4 | FOXM1/Wnt signaling axis drives meningioma prolife ratio and tumor growth. NF2 mutation, FOXM1 gene expression, and DNA methylation can cause the increase of FOXM1 expression or activity, which would activate the FOXM1/WNT signaling axis, resulting in primary or aggressive meningioma cell proliferation. In addition, through the principle of drug repositioning, fostamatinib, a kind of medicine aimed at chronic immune thrombocytopenia (ITP), which targets the FoxM1, may also be used in the treatment of meningiomas.

high expression of galectin-3 was observed in meningioma infiltration and recurrence (60). However, the role of galectin-3 in meningioma remains controversial; there is still a need for further studies to confirm the exact mechanism of galectin-3 in meningioma. Recently, with highly sensitive instruments in proteomics, low-abundance proteins could be found to be meaningful in different grades of meningiomas. For example, comparative tissue proteomic analysis was performed by isobaric tags for relative and absolute quantification (ITRAQ)-based quantitative proteomics by using electrospray ionization-quadrupole-time of flight (ESI-Q-TOF) and thermo scientific Q exactive (Q-Exactive MS), which quantified many transmembrane receptors and transcription factors, such as activated RNA polymerase II transcriptional coactivator p15 in pathology of meningioma (61).

In addition, proteomics analysis has also been used to identify different subtypes of meningiomas. To explore the different protein expression patterns of bone-infiltrating and non-invasive meningioma, the researchers used a protein spectrum combined with surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI), and the results show meaningful differences in fibrous and meningothelial grade I meningiomas that contribute to distinguish the two types of meningiomas (60). Therefore, invasive and non-invasive growth behavior of grade I fibrous and meningothelial meningioma can be distinguished by analyzing the protein profile of benign meningioma. Notably, the early diagnosis of invasive grade I meningioma is thought to contribute to follow-up policies and the issue of radiotherapy (62).

In addition to protein expression, proteomics studies about post-translational modifications have also been conducted to map the mechanisms of aggressiveness of meningiomas. By using two high-throughput technologies: unbiased iTRAQ LCMS/MS and biased Pamchip peptide arrays, it was found that the A-kinase anchor protein 12 (AKAP12) protein (a phosphoprotein) is downregulated in all grades of meningioma (58). Further studies have shown that knocking down AKAP12 in benign meningioma cells promotes proliferation, migration, and invasion, suggesting that AKAP12 is a central regulator of invasive meningioma progression (58). However, although studies have provided increasing evidence that post-translational modification is closely connected with cell-based functional characterization, which has a close connection with function and malignancy of the disease, phospho-proteomes are rarely studied in meningiomas (61, 63, 64).

MULTI-OMICS STUDIES IN MENINGIOMAS

Despite a valuable contribution, the results from single omics are unable to map the comprehensive meningioma-related signaling pathways and networks. Therefore, advantages of integrated analysis using multi-omics data have been gradually revealed. For example, the *FoxM1* target gene in the case of increased *FoxM1* mRNA expression was identified by RNA sequencing, DNA methylation sequencing, and target gene expression profile from meningiomas with low survival rate and high local recurrence rate (65). In addition, integration of multi-omics data contributes to the identification of radiation-induced meningioma, an uncommon late risk of cranial irradiation with higher recurrence rate and pathologically malignant features compared to the sporadic meningioma (66). For example, comparative genome hybridization was used for the identification of chromosome 1p loss in radiation-induced meningioma (67). Notably, NF2 rearrangement in radiation-induced meningioma was identified through exome, methylation, and RNA-seq analysis from 31 cases, which can be used for the differentiation of radiation-induced meningioma from sporadic meningioma as neurofibromatosis type 2 (NF2) rearrangement has still not been reported in sporadic meningioma (68).

The target gene identified by multi-omics studies can potentially be used in drug repositioning in meningiomas (**Supplementary Table 4**), which appeared to be cheaper, quicker, and more effective (69). For example, Fostamatinib, targeting *FoxM1*, has been approved by the FDA for the treatment of chronic immune thrombocytopenia (ITP). Given the same putative drivers of disease associations, Fostamatinib may improve meningioma via regulating synthesis and secretion of tumor necrosis factor α(TNF-α) (70) (**Figure 4**).

CONCLUSION

In 2016, the World Health Organization included the molecular standards into the classification of meningiomas (71). Soon after this, accurate pathological diagnosis and treatment decisions at the molecular level depend on powerful clinical molecular detection using genome, epigenome, and transcriptome tools is highly applied in clinical studies (72). Although it is necessary to carry out molecular detection of brain tumors in medicine, there are still great differences in the acquisition and utilization of molecular diagnosis technology in various institutions, and the lack of compensation for such detection is still a major obstacle (72). Notably, the important role of omics studies in the molecular level pathological study and grading of meningiomas has potential value in clinical diagnosis and treatment. Therefore, there is no doubt that multi-omics studies will shed further light on the novel strategies for the prediction, prevention, and treatment of meningiomas.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.01491/full#supplementary-material

Supplementary Table 1 | Summary of epigenomics studies for meningiomas.

Supplementary Table 2 | Research on meningiomas in transcriptomics.

Supplementary Table 3 | Proteomics research on meningiomas.

Supplementary Table 4 | Meningioma driver genes-based drug-repositioning.

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Corrigendum: Multi-Omics Analysis in Initiation and Progression of Meningiomas: From Pathogenesis to Diagnosis

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In the published article, affiliation 3 "Department of Neurology, Shanxi Medical University, Taiyuan, China" was added in error. It should be deleted.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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REVIEW
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Clinical Significance of Somatostatin Receptor (SSTR) 2 in Meningioma

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Somatostatin receptor (SSTR) 2, widely expressed in meningioma, is a G-protein-coupled receptor and can be activated by somatostatin or its synthetic analogs. SSTR2 is therefore extensively studied as a marker and target for the diagnosis and treatment of meningioma. Accumulating studies have revealed the crucial clinical significance of SSTR2 in meningioma. Summarizing the progress of these studies is urgently needed as it may not only provide novel and better management for patients with meningioma but also indicate the direction of future research. Pertinent literature is reviewed to summarize the recent collective knowledge and understanding of SSTR2's clinical significance in meningioma in this review. SSTR2 offers novel ideas and approaches in the diagnosis, treatment, and prognostic prediction for meningioma, but more and further studies are required.

Keywords: meningioma, SSTR2, somatostatin, somatostatin analogs, diagnosis, treatment, prognosis

INTRODUCTION

Meningiomas, arising from the dura mater of the brain and spinal cord, are currently the most frequent primary intracranial tumors (1). Meningiomas have an estimated annual incidence of 7.86 cases per 100,000 people, accounting for up to 30% of all primary intracranial tumors (2–4). The majority of meningiomas are histologically benign and slow growing and correspond to World Health Organization (WHO) grade I, while up to 20% of the tumors are classified as WHO grade II or grade III meningiomas on account of features of increased malignancy and local invasiveness (5, 6). Progressive enlargement of the tumor and compression of adjacent neural tissue lead to clinical manifestations, such as generalized or focal seizure disorders, focal neurological deficits, and neuropsychological decline (3). The preliminary radiological diagnosis and precise localization of meningioma mainly depend on magnetic resonance imaging (MRI) nowadays (1, 7).

Abbreviations: ^{111}In, 111-indium; ^{177}Lu, 177-lutetium; ^{90}Y, 90-yttrium; CNS, central nervous system; CT, computed tomography; DOTATATE, DOTA-D-Phe1-Tyr3-octreotate; DOTATOC, DOTA-(Tyr3)-octreotide; IGF-1: insulin-like growth factor-1; MRI, magnetic resonance imaging; PET, positron emission tomography; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SHP1, SH2-containing phosphatase-1; SHP2, SH2-containing phosphatase-2; SPECT, single-photon emission computed tomography; SRS, somatostatin receptor scintigraphy; SSTR, somatostatin receptor; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

Surgical resection remains the standard treatment for meningiomas; however, observation should be considered as a therapeutic option if the clinical situation permits; meanwhile, radiotherapy is becoming increasingly important in the treatment of meningiomas, especially for those surgically inaccessible tumors; in addition, large-scale clinical trials for pharmacotherapy have not presented positive results yet (1, 8–10).

Somatostatin receptors 1–5 (SSTR1–5) pertain to the family of seven-transmembrane G protein-coupled receptors and are widely expressed in both normal tissues and solid tumors (11, 12). These five receptors share some common features underlying structure and signaling mechanisms, but their cellular/subcellular localization and mode of regulation vary from one to another (12, 13). Among these receptors, the overexpression of SSTR2 was the most frequent in meningiomas compared with the other SSTR subtypes (14). In recent years, accumulating studies have reported the correlation between SSTR2 expression and meningiomas. However, to the best of our knowledge, no literature review has been published to summarize it thus far. Hence, we provide a detailed summary of the current understanding of the clinical significance of SSTR2 in meningioma in this review.

SYNOPSIS OF SSTR2

The encoding gene for SSTR2 is localized at chromosome 17q25.1 and comprises two exons. The first exon contains the 5′ untranslated region while exon 2 contains the entire coding region and 3' untranslated region (13). The SSTR2 gene has a strong tolerance to sequence variations; hardly any disease-related mutations have been discovered in the SSTR2 gene (13, 15). The transcribed SSTR2 mRNA is spliced to produce two isoforms of SSTR2 named SSTR2A (the long form) and SSTR2B (the short form), which differ in the length of the cytoplasmic tail (12, 16). Human tissues include the SSTR2A variant exclusively (13). Typical seven-transmembrane segments and four putative N-glycosylation sites could be displayed in the SSTR2 protein of 369 amino acids (13). The protein can be detected by Western blot as a characteristic band of 70–80 kDa (13, 17, 18). SSTR2 is ubiquitously distributed in normal tissues especially in the central nervous system (CNS) and endocrine system (12, 19–21). SSTR2 is also expressed widely and represents manifold functions in various tumor tissues including neuroendocrine tumors, pituitary adenomas, breast cancer, melanoma, thyroid cancer, and meningioma (20, 22–25). Nevertheless, the expression level of SSTR2 between normal tissues and tumor tissues is different. For instance, SSTR2 was identified as significantly highly expressed in meningioma tissues compared with normal tissues by Anne et al. (26). The expression of SSTR2 can routinely be detected through reverse-transcription polymerase chain reaction and immunohistochemistry (**Table 1**); the vast majority of meningiomas express SSTR2 (14, 25–32). SSTR2 mediates diverse physiological effects when activated by somatostatin or its synthetic analogs, such as regulating the physiologic secretion of insulin, glucagon, thyroid-stimulating hormone, and growth hormone (GH); protecting retina nerves; and regulating neuronal excitability (13, 23, 33–36).

SSTR2-RELATED DIAGNOSIS APPROACHES FOR MENINGIOMA

A preliminary diagnosis of meningioma typically relies on MRI and computed tomography (CT); further diagnosis includes histological classification, grading, and molecular features (1, 3, 7). However, because the results of CT and MRI are sometimes ambiguous and because biopsy carries potential risks of bleeding, additional approaches (**Figure 1**) for the diagnosis of meningioma are needed (37). Besides, this "integrated diagnosis" era also calls for other novel and efficient diagnostic methods for accurate diagnoses of meningioma (38, 39).

Somatostatin receptor 2A was found to be a more sensitive diagnostic marker for meningioma than epithelial membrane antigen—a conventional meningioma marker (40). Since then, accumulating evidence has emerged to support the diagnosis value of SSTR2A as it is a highly sensitive and specific marker for meningioma (41, 42). A case report has shown that SSTR2A, combined with epithelial membrane antigen, provides assistance for the diagnosis of an unusual skull tumor with psammomatoid bodies (43).

Moreover, given that SSTR2 is expressed in almost 100% meningiomas (14, 26, 30, 44, 45), radiolabeled SSTR2 ligands have been widely utilized in the modern radiological diagnosis of meningioma (**Table 2**).

Positron emission tomography (PET)-based imaging (including PET, PET/CT, and PET/MRI) applying radiolabeled somatostatin agonists such as ^{68}Ga-DOTATATE (DOTA-D-Phe1-Tyr3-octreotate) and ^{68}Ga-DOTATOC (DOTA-[Tyr3]-octreotide) has been presented to be a precise diagnostic means; this technology is helpful in target volume delineation, radio/surgical treatment planning, diagnosing small meningiomas, and monitoring tumor growth rate, etc. (46–51). Recent researches demonstrated a higher sensitivity of ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE PET or PET/CT by comparison with contrast-enhanced MRI or fluoroethyl-tyrosine PET in diagnosing meningiomas (52–54). Additionally, the exact delineation seems challenging in some cases with low CT and MRI contrast as a result of osseous infiltration or in skull base meningiomas. PET-based imaging with radiolabeled SSTR2 ligands shows superiority in overcoming this diagnostic difficulty due to the highly specific binding of SSTR2 ligands to SSTR2 in meningiomas and the extremely low absorption in adjacent structures such as bone and brain tissue (7, 53, 55, 56). Furthermore, in the case of atypical meningioma or a rare type of meningioma like optic nerve sheath meningioma, SSTR2-related PET/CT is also deemed to be a useful noninvasive diagnostic method (57–59).

Single photon emission CT (SPECT) somatostatin receptor scintigraphy (SRS) using ^{111}In-octreotide is another valuable tool for the diagnoses of meningiomas based on the general expression of SSTR2 in all meningiomas. SPECT SRS with ^{111}In-octreotide is considered a highly specific imaging approach,

TABLE 1 | Studies regarding the detection methods and expression of SSTR2 in meningiomas.

Subjects										
No. of meningiomas	40	60	20	50	42	22	26	35	68	148
Detection methods	IHC	IHC	RT-PCR	RT-PCR	RT-PCR	IHC	RT-PCR	IHC	IHC	IHC
SSTR2 expression (%)*	70	100	100	100	79	64	100	74	87	100
References	(14)	(25)	(26)	(27)	(28)	(29)		(30)	(31)	(32)

**The results stand for the percentage of SSTR2-expressing meningiomas. IHC, immunohistochemistry; RT-PCR, reverse transcription-polymerase chain reaction.*

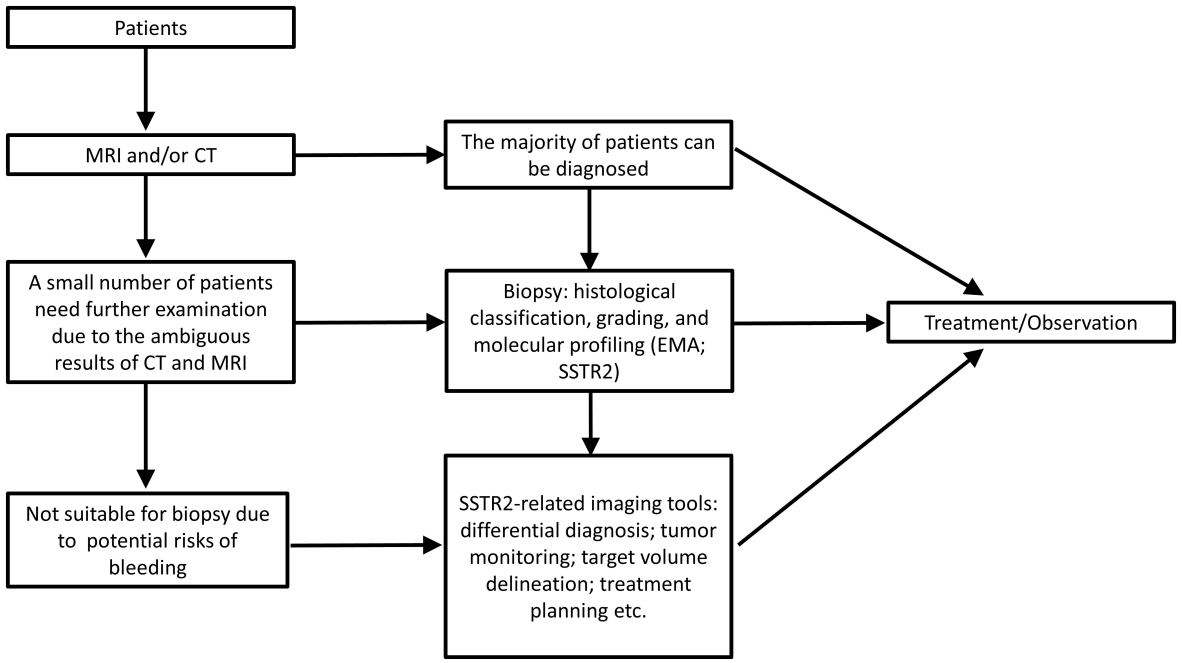


FIGURE 1 | The diagnosis process and application scenarios of meningioma with the utilization of SSTR2.

and it plays an important role in post-treatment follow-up in meningioma patients (60, 61). Hildebrandt et al. have shown that *in vivo* detection of SSTRs by ^{111}In-octreotide scintigraphy in meningioma patients had a high sensitivity as a high density of SSTRs was detected in all cases (62). Regarding differential diagnosis in meningioma and other CNS tumors such as craniopharyngiomas, schwannomas, and ependymomas or other cranial dural-based lesions, SPECT SRS with ^{111}In-octreotide has also proven its values (63–66). In the meantime, SPECT SRS could offer aid in the differential diagnosis between meningiomas and radionecrosis or postoperative scar at the skull base, which is meaningful for recurrence screening of meningioma (64). As for cases with an atypical presentation, SPECT SRS can offer support in distinguishing optic nerve sheath meningioma from alternative orbital masses (67, 68).

Other SSTR2-related imaging tools also exhibit diagnostic values. For instance, SPECT/CT SRS using ^{99m}Tc-HYNIC-octreotide specifically binding to SSTR2 in meningioma can diagnose primary optic nerve sheath meningioma or allow differentiation of meningiomas from inactive pituitary adenomas, which is seemingly elusive by conventional MRI (69, 70).

These studies suggest that SSTR2-related imaging tools with radiolabeled somatostatin agonists are valuable for precise-positioning tumor detection, evaluation of disease extension, differential diagnosis, and tumor monitoring even in small, asymptomatic, or rare cases.

SSTR2-RELATED TREATMENT APPROACHES FOR MENINGIOMA

Individualized precision treatment regimens should be employed in treating patients with meningioma since heterogeneity between meningiomas exists and clinical outcomes for different patients vary greatly (1). Correct decision making in the management of meningioma patients is significant in order to achieve optimal clinical consequence and long-time survival (71–73). Surgery is the main treatment for most meningiomas; however, effective treatment modalities for patients with unresectable or recurrent meningioma remain elusive. It is of interest that SSTR2-related/targeted treatments could provide novel therapeutic interventions against meningiomas beyond

TABLE 2 | Clinical studies using radiolabeled SSTR2 ligands for meningioma diagnosis.

Image diagnostic method	Radiolabeled SSTR2 ligand	Sample size	Major/novel functions	References
PET	^{68}Ga-DOTATATE	21 pts (81 Ms)	Discriminating meningioma and tumor-free tissue even in recurrent tumors after previous therapy.	(46)
		64 Ms	Selecting the time point for treatment initiation; predicting tumor growth rate	(48)
		30 pts (49 Ms)	Discriminating meningioma and post-treatment change; improving diagnosis and extent of disease evaluation.	(50)
	^{68}Ga-DOTATOC	3 pts (8 Ms)	Offering excellent imaging properties and a very high tumor-to-background ratio even in small meningiomas.	(49)
		21 pts	Showing higher specificity for meningioma diagnosis than FET PET.	(54)
PET/CT	^{68}Ga-DOTATATE	82 pts	Improving detection of the transosseous extension of intracranial meningiomas.	(53)
	^{68}Ga-DOTATOC	26 pts	Improving target volume delineation for IMRT especially for skull base meningioma and recurrent disease after surgery	(47)
		134 pts	Providing additional information in patients with uncertain or equivocal results on MRI; helping to confirm MRI-based diagnosis of meningiomas in cases of biopsy limitations.	(52)
PET/MRI	^{68}Ga-DOTATOC	10 pts	Sketching treatment target volume; benefiting radiosurgical treatment planning.	(51)
SPECT SRS	^{111}In-octreotide	27 pts	Discriminating meningioma and nonspecific hyperperfusion; displaying remaining tumor tissue or relapse of meningioma in postsurgical follow-up.	(60)
		22 pts	Detecting Ms with an extremely high sensitivity (100%).	(62)
		47 pts	Discriminating Ms and other CNS tumors, combined with MRI.	(63)
		70 pts	Discriminating Ms and other tumors, postoperative scar or radionecrosis at the skull base.	(64)
		95 pts	Discriminating Ms and other CNS tumors.	(65)
		50 pts	Discriminating Ms and other cranial dural-based lesions, combined with MRI.	(66)
SPECT/CT SRS	^{99m}Tc-HYNIC-octreotide	30 pts	Showing high meningioma radioactivity accumulation with a sensitivity of 100 %.	(70)

CNS, central nervous system; DOTATATE, DOTA-D-Phe1-Tyr3-octreotate; DOTATOC, DOTA-(Tyr3)-octreotide; FET, fluoro-ethyl-tyrosine; IMRT, intensity modulated radiotherapy; ^{111}In, 111-Indium; MRI, Magnetic Resonance Imaging; Ms, meningiomas; PET, Positron emission tomography; pts, patients; SPECT, single-photon emission computed tomography; and SRS, Somatostatin receptor scintigraphy.

traditional therapies, especially for those inoperable or recurrent patients.

The exact biological function of SSTR2 in meningioma is hitherto not very sharply defined, but its activation may be correlated to an antiproliferative effect (28, 74–77). Native somatostatin is rapidly metabolized and has a short half-life (1–3 min) *in vivo*, which limits its clinical use, whereas synthetic somatostatin analogs like octreotide are much more stable (20). Somatostatin analogs have already achieved promising effects in the treatment of high-SSTR2-expression tumors, such as gastroenteropancreatic neuroendocrine tumors and GH-secreting pituitary adenomas (78, 79). The therapeutic efficacy of somatostatin analogs for meningiomas *in vitro* has been confirmed in various studies (27, 77, 80, 81). For example, Graillon et al. demonstrated that octreotide significantly decreased proliferation in 88% of fresh primary meningioma cells (82). Nonetheless, octreotide has been shown not to induce apoptosis of meningioma cells (82).

The direct and indirect antitumor mechanisms (**Figure 2**) of the SSTR2 ligands–somatostatin analogs for the treatment of meningioma have been explored in several preclinical researches. Somatostatin or its analogs bind to SSTR2, leading to the activation of specific tyrosine phosphatases (SHP1 and SHP2) and the inhibition of the PI3K/Akt pathways, which mediate its direct antitumor effects through the induction of cyclin-dependent kinase inhibitors and cell cycle arrest (27, 80, 81, 83–87). The indirect antitumor mechanisms of somatostatin analogs incorporate (1) reduction of angiogenesis, particularly by inhibiting vascular endothelial growth factor (VEGF) secretion; (2) suppression of growth factors and hormone secretion that will drive tumor growth; and (3) stimulation of natural antitumor mechanisms (27, 84, 86–88). The synthesis of VEGF, one of the dominant proangiogenic factors, was decreased in meningioma cells by somatostatin analogs, indicating their antiangiogenic effects (27, 84, 86, 87). Somatostatin analogs can inhibit the release of GH from

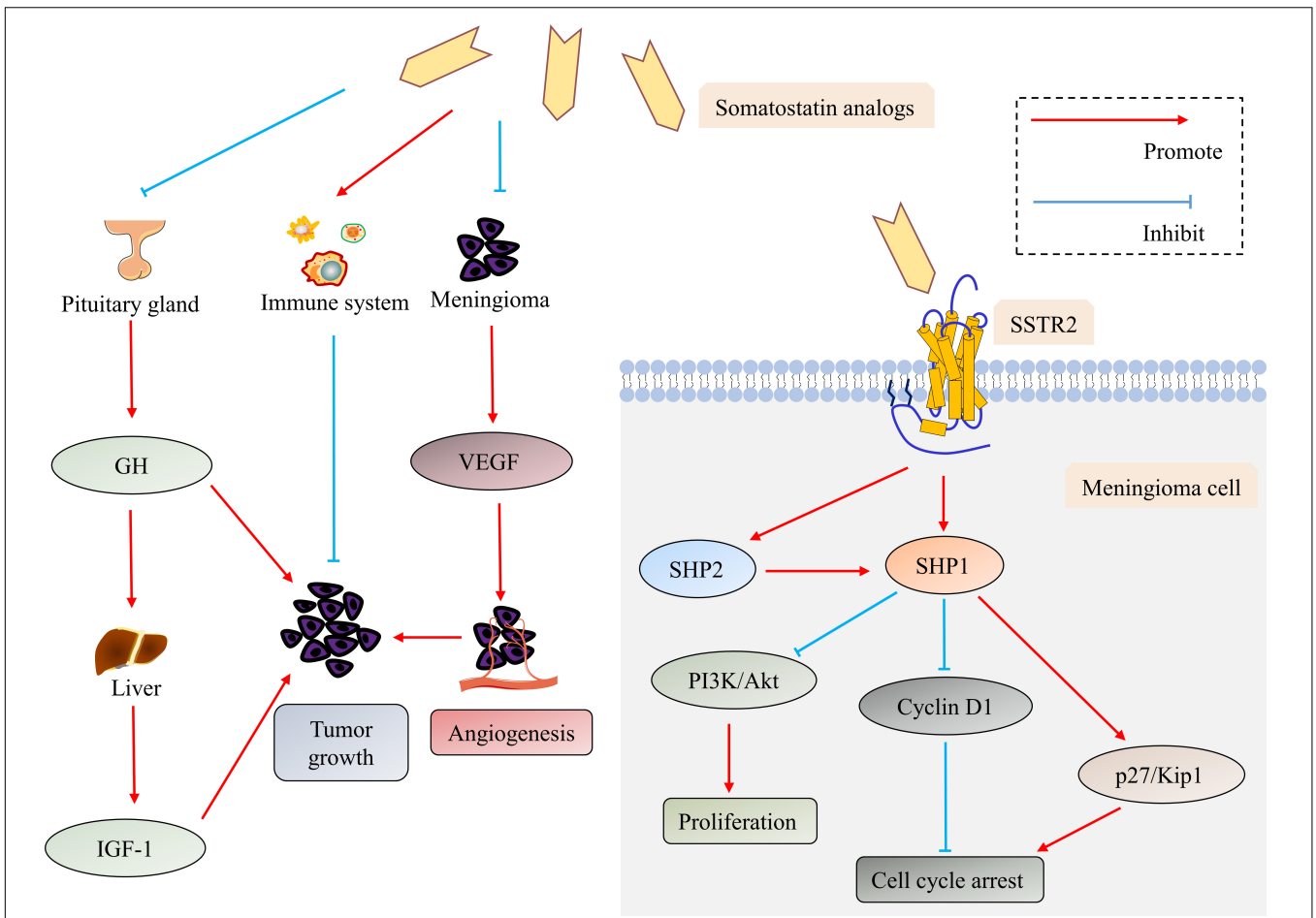


FIGURE 2 | The direct and indirect antitumor mechanisms of the somatostatin analogs in meningioma. Somatostatin analogs exert their direct antitumor effects by binding to SSTR2, which leads to the activation of SHP1 and SHP2. SHP2 can further activate SHP1. SHP1 mediates antiproliferative action through inhibiting the PI3K/Akt pathway and induces cell cycle arrest through down-regulating cyclin D1 while up-regulating p27/Kip 1. Suppressing secretion of VEGF and GH/IGF-1 and activating the immune system are involved in indirect antitumor mechanisms of somatostatin analogs. Abbreviations: Akt, protein kinase B; GH, growth hormone; insulin-like growth factor-1 (IGF-1); PI3K, phosphatidylinositol 3-kinase; SHP1, SH2-containing phosphatase-1; SHP2, SH2-containing phosphatase-2; SSTR, somatostatin receptor; and VEGF, vascular endothelial growth factor.

the pituitary gland, which causes the suppression of hepatic production of insulin-like growth factor-1 (IGF-1) (84, 86, 87). Both GH and IGF-1 have been proven to be tumor-promoting factors for meningioma (84, 86–88). Somatostatin and its analogs are also capable of activating the immune system, for SSTR2 are expressed in some immune cells (84, 86, 87, 89).

In some cases, considerable efficacy of somatostatin analogs could even be achieved in the treatment of unresectable or recurrent meningiomas (90–92). Rammo et al. reported a patient with progressive anaplastic meningioma treated with octreotide. Prior to octreotide therapy, repeated surgery and radiation therapy did not help stop the progression of the disease, but surprisingly, this patient remained in remission for over 3 years following octreotide treatment (90).

A few clinical studies have been carried out to evaluate the efficacy and safety of somatostatin analogs in the treatment for patients with meningioma (**Table 3**). A prospective pilot trial was carried out by Chamberlain et al. with a sustained-release somatostatin analog (Sandostatin LAR) treating 16 recurrent meningioma patients. The median overall survival (OS) was 7.5 months; 31% of patients achieved partial radiographic response, and 44% achieved 6 months progression-free survival (PFS); the toxicity of Sandostatin LAR was small (74). These results revealed that Sandostatin LAR might be a useful and tolerable alternative therapy option for recurrent meningiomas. Johnson et al. conducted a phase II study of subcutaneous octreotide treatment for recurrent meningioma patients. The results of this study were less satisfactory: even though octreotide was well tolerated and 2 of 11 patients experienced prolonged stability, it had not been able to produce objective tumor response (93). Complete resection of skull base meningiomas is always challenging; to this end, Schulz et al. treated patients harboring a progressive residual meningioma after surgery with a somatostatin analog. Disregarding the fact that no case of tumor disappearance was observed, the disease appeared to have stabilized in all cases (94). This study offered a perspective on additional therapy for post-surgery skull base meningiomas with somatostatin analogs. Regretfully, it was not a randomized controlled prospective clinical trial. For the treatment of recurrent high-grade meningioma, the efficacy of somatostatin analog might be limited, according to a phase II study showing that none of nine patients achieved radiographic partial response (82). In another trial, a somatostatin analog called pasireotide LAR (SOM230C) was prescribed monthly to patients with recurrent or progressive meningioma; unfortunately, it also failed to increase the proportion of patients with 6 months PFS significantly (95). Studies have manifested that the low levels of Raf kinase inhibitory protein or the mutations of aryl hydrocarbon receptor interacting protein were related to the unsatisfactory response to somatostatin analogs for the treatment of GH-secreting pituitary adenomas (96, 97), notwithstanding the fact that there is a paucity of similar studies in meningioma. Taken collectively, somatostatin analogs represent a safe but undefined therapeutic option in meningioma management. Notably, these clinical trials suffer from limited

TABLE 3 | Clinical studies using somatostatin analogs for meningioma treatment.

Subjects	No. of pts	Somatostatin analog	Dose	mTCs	Tumor response			Survival			TT due to AEs	References
					PR	SD	PD	PFS6	mPFS /TTP (months)	mOS (months)		
Recurrent M	16	Sandostatin LAR	30 mg/4 weeks	4.5	5	5	6	44%	5	7.5	0	(74)
Recurrent high-grade M	9	Sandostatin LAR	30–40 mg/4 weeks	3	0	3	6	44%	4.2	18.7	0	(82)
Recurrent or progressive M	11	Sandostatin LAR	500 μg 3 times/day	NA	0	8	3	30%	3.9	NA	0	(93)
Progressive residual M after surgery	8	Sandostatin LAR	30 mg/4 weeks	NA	0	8	0	100%	NA	NA	1	(94)
Recurrent or progressive M	34	Pasireotide LAR	60 mg/4 weeks	NA	0	24	8	32%	4.2	NA	0	(95)

AEs, adverse events; M, meningioma; mOS, median overall survival; mPFS, median progression survival; mTCs, median treatment cycles; NA, not-available; PFS6, 6 months progression survival; PR, partial response; Pts, patients; PD, progressive disease; SD, stable disease; TT, treatment interruption; and TTP, time to progression.

sample size and short duration, so more and larger trials are urgently warranted.

SSTR2-directed peptide receptor radionuclide therapy (PRRT) has also exhibited their potential therapeutic use for patients with meningiomas. Beta-emitters 90-yttrium (^{90}Y) and 177-lutetium (^{177}Lu) are the most widely used radiometals in PRRT at present (98). Certain amounts of clinical studies (**Table 4**) have investigated the therapeutic effect of SSTR2-targeted PRRT in treating meningioma patients. In a clinical study, five meningioma patients, among which three had tumors that were very large with standard medical therapies that all failed, were treated with ^{177}Lu-octreotate. Consequently, two of them had stable disease (SD) while three of them had progressive disease after PRRT treatment (99). A retrospective study also presented the activity of SSTR2-targeted PRRT using ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC in patients with meningioma, with the results that 10 of 20 patients achieved SD for a median time of 17 months (100). Gerster-Gilliéron et al. have recommended ^{90}Y-DOTATOC as a second- or third-line option for recurrent or progressive meningiomas, since median PFS (**Figure 3**) of patients receiving systemic ^{90}Y-DOTATOC treatment was 57 months and the treatment was safe (101). Moreover, the results of a phase II prospective clinical trial, in which 67.6% of patients achieved SD and the mean survival of all enrolled patients was 8.6 years, lent further support to the use of SSTR2-directed PRRT in patients with progressive unresectable meningioma (102). Many more clinical studies have confirmed the efficacy and safety of SSTR2-targeted PRRT in the treatment of meningiomas (103–105). Indeed, the recent European Association of Neuro-Oncology guidelines on meningioma have declared PRRT a promising approach to treat refractory meningiomas across all WHO grades in the future (1). The selective accumulation of radiolabeled somatostatin analogs in meningioma cells enhances the efficacy while reducing the toxicity of PRRT. Nevertheless, because these traces are mainly excreted by the kidney, renal toxicity seems inevitable, which may limit the application of PRRT (98, 106, 107). Generally, in patients with recurrent or complex unresectable meningiomas, especially in those where standard treatments have failed, the use of SSTR2-targeted PRRT should be considered; for those who accept PRRT, we should pay close attention to their renal function, and renal protection should be provided.

Taken together, SSTR2-related/targeted treatments are promising approaches for the treatment of unresectable or refractory meningiomas. Somatostatin analogs can only inhibit the proliferation but fail to induce the apoptosis of meningioma cells; meanwhile, somatostatin analog treatment for meningioma exhibits efficacy *in vitro* and some special cases, but clinical studies have not achieved satisfactory results. Consequently, the effectiveness of somatostatin analog treatment for meningioma is actually controversial currently; further studies are required to identify and select the patients in whom treatment with somatostatin analogs is potentially effective. Importantly, SSTR2-targeted PRRT has shown an effect on the treatment of meningiomas in some clinical studies.

TABLE 4 | Clinical studies of PRRT treatment for meningioma.

Subjects	No. of pts	Intervention	Dose (GBq)	Cycles	Tumor response				mPFS (months)	Other main results/conclusions	References
					CR	PR	SD	PD			
Recurrent or progressive Ms	5	^{177}Lu-octreotate	14.8–29.6	2–4	0	0	2	3	NA	177Lu-octreotate can have therapeutic effects in meningioma.	(99)
Progressive Ms	20	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	13.7–27.6	1–4	0	0	10	10	5.4	PFS6 was 42%; treatment was well tolerated.	(100)
Recurrent or progressive Ms	15	^{90}Y-DOTATOC	1.35–14.8	2–4	0	0	13	2	24	Toxicity was moderate.	(101)
Progressive unresectable Ms	34	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	1.5–22.2	1–4	0	0	23	11	NA	The mean survival 8.6 years; treatment was well tolerated,	(102)
Recurrent Ms	29	^{90}Y-DOTATOC	5–15	2–6	0	0	19	10	21	Median OS was 40 months; treatment was well tolerated.	(103)
Recurrent Ms	8	^{111}In-Pentetreotide	4.8–29	2–4	0	2	5	1	NA	Treatment was well tolerated.	(104)
Advanced symptomatic Ms	10	EBRT + ^{177}Lu-DOTATATE or DOTATOC	7.0–7.9	1	1	1	8	0	13.4	The combination treatment was safe and effective.	(105)

CR = complete response; DOTATOC = DOTA-(Tyr3)-octreotide; DOTATATE = DOTA-D-Phe1-Tyr3-octreotate;EBRT = External beam radiotherapy; 111In = 111-Indium; 177Lu = 177-Lutetium; mPFS = median progression survival; Ms = meningiomas; NA = not-available; OS = overall survival; PD = progressive disease; PFS6 = 6 months progression survival; PR = partial response; Pts = patients; SD = stable disease; 90Y = 90-Yttrium.

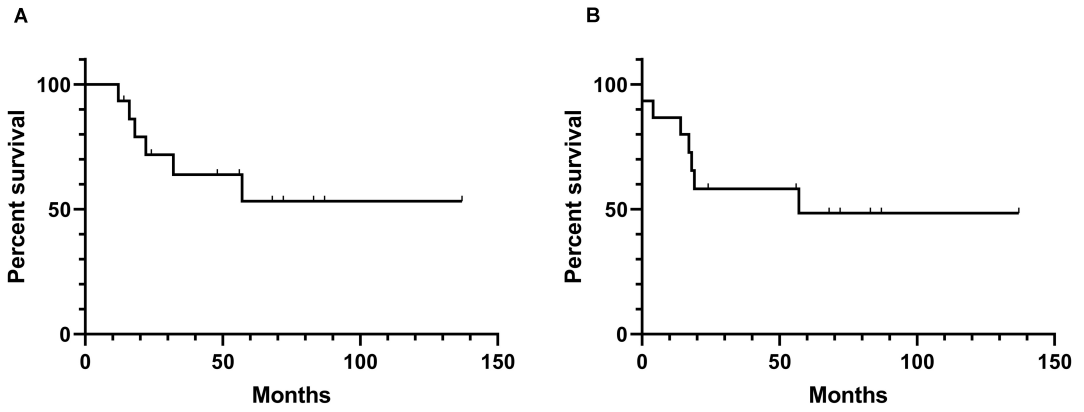


FIGURE 3 | Kaplan–Meier curves of overall survival and progression-free survival of the reported effects (101) of SSTR-related radiation therapy. **(A)** Overall survival. **(B)** Progression-free survival.

SSTR2 IN PROGNOSTIC PREDICTION OF MENINGIOMA

It is of clinical importance to predict the prognosis of meningioma patients, since it can provide a valuable reference for the proper management of patients, such as making treatment and follow-up strategies. Previous studies have manifested several potential prognostic indicators for meningioma, including the WHO tumor grade, the extent of resection, expression of progesterone and estrogen receptors, mitotic index, and bone involvement (72, 108–111). However, additional prognostic factors are still sorely needed to better predict the outcomes of meningioma patients.

Barresi et al. have attempted to draw the association between SSTR2 and tumor grade by analyzing SSTR2 immunohistochemical expression in 35 different-grade meningiomas; their results have shown that SSTR2 was frequently expressed in high-grade meningiomas and related to higher microvessel density (30). Explicitly, 57% grade I, 75% grade II, and 66% grade III meningiomas were characterized by a high expression of SSTR2 (30). Somatostatin or its analogs might be effective in the therapy of meningiomas by reducing their blood supply based on this study (112). Nevertheless, Durand et al. have found that SSTR2 levels were not grade related but histotype related, with significantly higher expression levels in the meningothelial subtype than in the fibroblastic subtype (29). This finding may support the use of somatostatin or its analogs to treat this subtype. Silva et al. have argued that SSTR2 levels might correlate to the risk of recurrence because the high expression of SSTR2 was observed in partially resected meningiomas with tumor regrowth (25). Additionally, Seystahl et al. have also observed that the expression level of SSTR2 was not correlated with the WHO grade of meningiomas; yet the expression level of SSTR could be a predictive biomarker for the outcome of meningioma patients treated with PRRT; a higher expression of SSTR2 was revealed to be associated with better PFS after PRRT treatment (100). These researches indicate that whether SSTR2 levels are grade related in meningiomas remains controversial; meanwhile, SSTR2 could still offer some implications for prognosis prediction in spite of this controversy.

CONCLUSION AND PROSPECTS

Meningiomas are the most frequent intracranial tumors. SSTR2 expressed in almost all meningiomas, which provides novel ideas and approaches in the diagnosis, treatment, and prognostic prediction for meningiomas. Certain progress regarding the clinical significance of SSTR2 in meningioma has been made in the past few decades. SSTR2-related imaging tools with radiolabeled somatostatin agonists, including PET, PET/CT, PET MRI, SPECT SRS, and SPECT/CT SRS, have significant value in (preclinical) diagnosis, differential diagnosis, and disease evaluation. Despite accumulating evidence that SSTR2-related/targeted treatments (e.g., somatostatin analogs and SSTR2-targeted PRRT) are promising and safe therapeutic options for unresectable or refractory meningiomas, several controversial areas remain. More and larger multicenter long-term follow-up and randomized prospective trials are urgently needed, especially in uncovering the precise underlying signaling pathways of SSTR2 ligands–somatostatin analogs' antitumor effects as well as identifying and selecting candidate patients who may benefit from these treatments.

AUTHOR CONTRIBUTIONS

YZ, WW, and AS conceptualized the research project. WW, YZ, YW, and LL drafted the manuscript. YW and JL drew the figures. PZ and AS reviewed and modified the manuscript. AS, YD, and PZ supervised the research and led the discussion. All authors approved the final version of the manuscript.

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A Novel Scoring System Based on Preoperative Routine Blood Test in Predicting Prognosis of Atypical Meningioma

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Purpose: The aim of this study was to explore the correlation and clinical significance of preoperative fibrinogen and neutrophil-lymphocyte ratio (F-NLR) scoring system with 3-year progression-free survival (PFS) of patients with atypical meningioma.

Materials and Methods: Clinical, pathological, radiological, and laboratory variables were collected to analyze their correlation with 3-year PFS in the training set with 163 patients. Patients were classified by different F-NLR scores (0, 1, or 2). External validation for the predictive value of F-NLR scoring system was performed in the validation set with 105 patients.

Results: Overall, 37.3% (100 of 268) of the enrolled patients were male. The scoring system showed good performance in predicting 3-year PFS (AUC = 0.872, 95%CI = 0.811–0.919, sensitivity = 66.1%, specificity = 93.3%, and *Youden* index = 0.594). DeLong's test indicated that the AUC of F-NLR scoring system was significantly greater than that of fibrinogen level and NLR ($Z = 2.929$, $P = 0.003$; $Z = 3.376$, $P < 0.001$). Multivariate Cox analysis revealed that tumor size (HR = 1.39, 95%CI = 1.10–1.76, $P = 0.007$), tumor location (HR = 3.11, 95%CI = 1.60–6.95, $P = 0.001$), and F-NLR score (score of 1: HR = 12.78, 95%CI = 3.78–43.08, $P < 0.001$; score of 2: HR = 44.58, 95%CI = 13.02–152.65, $P < 0.001$) remained significantly associated with 3-year PFS. The good predictive performance of F-NLR scoring system was also demonstrated in the validation set (AUC = 0.824, 95%CI = 0.738–0.891, sensitivity = 62.5%, specificity = 87.9%, and *Youden* index = 0.504).

Conclusion: Our study confirmed the correlation and clinical significance of preoperative F-NLR scoring system with 3-year PFS of patients with atypical meningioma. A prospective and large-scale study is required to validate our findings.

Keywords: atypical meningioma, fibrinogen, neutrophil-lymphocyte ratio, progression-free survival, prognosis

INTRODUCTION

Meningioma is a common type of intracranial tumor with three grades of malignancy (1). Atypical meningioma is considered as a transitional type between benign and malignant meningioma. To some extent, the WHO grade II meningioma presents a malignant tendency with an approximately recurrence rate of 40% (2, 3). Patients with atypical meningioma had an average rate of 50% for 5-year progression-free survival (PFS) (4). The optimal management of patients with atypical meningioma remained controversial mainly because of the difficulty for predicting tumor recurrence. The existing studies suggested that surgical resection, imaging, postoperative radiation therapy (PORT), and pathologic features could be reliable predictors for atypical meningioma (5–8). However, there is no general consensus on which predicative factor is most clinically effective and meaningful.

The important roles of systemic inflammatory response and coagulation cascade have been confirmed (9). Recently, studies have emphasized that hyperfibrinogenemia is related to the malignant behaviors and poor prognosis in various types of tumor (10–13). Inflammatory biomarkers like neutrophil-lymphocyte ratio (NLR) in peripheral blood could reflect the state of body inflammatory response and have been confirmed to be related with recurrence in many malignancies (14–17). However, the clinical significance of plasma level of fibrinogen and NLR has not been clarified for patients with atypical meningiomas.

The present study is aimed to explore the correlation and clinical significance of preoperative F-NLR scoring system with 3-year PFS of patients with atypical meningioma.

MATERIALS AND METHODS

Study Population

This study was performed at the Department of Neurosurgery of The First Affiliated Hospital of Fujian Medical University, the Department of Neurosurgery of The Affiliated Hospital of Putian University and the Department of Neurosurgery of Zhengzhou University People's Hospital. It was approved by local Ethics Committee of all participating hospitals and conformed to the Ethical guidelines of the Declaration of Helsinki. The requirement of informed consent was waived due to its retrospective design. Patients with atypical meningioma admitted to the three institutions between January 2007 and January 2017 were enrolled in this retrospective observational study. Possible related factors for 3-year PFS were identified on data from 163 patients operated between January 2007 and December 2013 (training set). External validation was performed with data from 105 patients operated from January 2014 to January 2017 (validation set). The cohort consisted of 268 patients meeting the following inclusion criteria: (1) age >18 years old; (2)a preoperative diagnosis of meningioma based on imaging analysis and a confirmed diagnosis of atypical meningioma based on pathological results; (3) peripheral blood test was performed within 7 days before surgery. Exclusion criteria were: (1) incomplete medical information such as missing the peripheral blood test; (2) history of other tumors; (3) patients had previous atypical meningioma surgery or other surgery; (4) evidence of infection or previous use of steroids, antitumor drugs, antiplatelet or anticoagulant drugs, or immunosuppressants; (5) combined with other neurological diseases or systemic diseases.

Pathological Examination

All patients met the diagnostic criteria of atypical meningioma. The 2007 WHO histological criteria included (18): (1) three or more of the five histological features: high cellularity, geographic necrosis, nuclear pleomorphism, foci of small hyperchromatic cells, and uninterrupted pattern-less or sheet-like growth; (2) a mitotic index of four or higher per ten high-power fields (HPF). Brain invasion was supplemented as an additional criterion in the 2016 WHO edition (1). We extracted the value of mitotic index per ten HPF, Ki-67 index, and presence or absent of brain invasion for all patients.

Radiological Examination

For each case, preoperative magnetic resonance imaging (MRI) or computed tomography (CT) scan was performed to evaluate the site and diameter of tumor. Tumor site was classified into skull base group and non-skull base group (19). Tumor originating from cavernous sinus, anterior clinoid, tuberculum sella, optic sheath, planum sphenoidale, medial tentorial, petroclival, foramen magnum, bony foramina, lateral/middle sphenoid wing, posterior petrous, orbital roof, and lateral tentorial were assigned into skull base group. Non-skull base group contained tumor arising from convexity, parasagittal, falcine, cerebellar convexity, intraventricular, and pineal. Medical records and postoperative imaging data within 1 month after surgery were retrieved to classify the extent of surgical resection based on Simpson's scale (20). Because of the insufficient samples in the Simpson grade IV and Simpson grade V, all patients were divided into Simpson grade I-II group and Simpson grade III-V group to distinguish the extent of surgical excision for the further analysis. Except for the above-mentioned characteristics, two neuroradiologists blinded to the medical data also independently analyzed the preoperative and postoperative MRI or CT images to determine the extent of peritumoral edema.

Clinical and Laboratory Variables

Patient data including history of present illness, past medical history, general demographics, treatment regimens (PORT), and other related data were collected. All patients underwent general preoperative blood tests including routine blood examinations according to standard laboratory test procedures within 1 week before surgery. The normal values for fibrinogen range from 1.8 to 3.5 g/L. Based on the cut-off value, we classified the F-NLR scores as 0[neither hyperfibrinogenemia (fibrinogen-lymphocyte ratio >2.95) nor high NLR(>2.74)], 1[hyperfibrinogenemia or high NLR], or 2[both hyperfibrinogenemia and high NLR].

Follow-Up Evaluation

All patients underwent contrast-enhanced CT scan or MR imaging within 1 month after surgery. The subsequent intervals

of follow-up ranged from 3 to 6 months. Progression-free survival in this manuscript was defined as the time from surgery to relapse. At the end point, the 3-year PFS of patients after surgery were estimated. Patients with growing residual tumor or new lesions on a follow up contrast-enhanced MR imaging or CT were included into the recurrence group. The other patients were included into the non-recurrence group.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS, Inc., Chicago, Illinois, United States). Continuous variables, described as mean ± standard deviation, were analyzed using 2-sample *t*-test. Categorical variables, expressed as counts (percentage), were analyzed using Pearson χ^2 test or Fisher exact test. All available variables were included in univariate logistic regression analysis for their association with 3-year PFS. Variables which had univariate association of $P < 0.10$ were included for further multivariate analysis. Backward stepwise multivariate regression was performed to create the final model of which the variables had $P < 0.05$. The predictive value of variables was assessed by the receiver operating characteristic (ROC) curve analysis. The best threshold of predictor was determined with its sensitivity, specificity, and *Youden* index. DeLong's test was used to assess the model performance of area under the curve (AUC). Kaplan-Meier curve analysis was performed to evaluate 3-year PFS rate after surgery. *P*-value for comparing survival curves was calculated with the log-rank test. The univariate and multivariate Cox proportional models were utilized to assess the prognostic significance of included factors. A value less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

In this study, atypical meningioma patients were divided into a recurrence group ($n = 78$, 29.10%) and a non-recurrence group ($n = 190$, 70.90%). Overall, the average age of patients was 54.00 ± 11.69 years old; 37.3% (100 of 268) of the enrolled patients were male and 62.7% of them were female.

The entire cohort including 268 patients was divided into the training set and the validation set. Forty-five cases of recurrence were observed in 163 patients of the training set (27.6%) and thirty-three cases were observed in the 105 patients of the validation set (31.4%).

Table 1 shows the demographics and baseline characteristics of the 163 patients in the training set. Age, neutrophil count, lymphocyte count, NLR, plasma fibrinogen level, tumor size, and extent of resection were significantly different between the two groups. The difference of tumor location for the two 3-year PFS rate groups was not significant with $P = 0.082$, so did the PORT with $P = 0.095$.

Univariate and Multivariate Analysis of the Factors Related With 3-Year PFS

Parameters with significant univariate association ($P < 0.10$) for 3-year PFS were shown in **Table 2**, including age, NLR, plasma fibrinogen level, tumor size, tumor location, extent of resection, and PORT. After multivariate analysis, NLR (OR = 0.77, 95%CI = 0.62–0.99, $P = 0.025$), and plasma fibrinogen level (OR = 0.27, 95%CI = 0.15–0.48, $P < 0.001$) were still significant after adjusting for confounders. In addition, tumor size (OR = 0.59, 95%CI = 0.43–0.81, $P = 0.001$), and extent of resection (OR = 3.43, 95%CI = 1.12-10.51, $P = 0.031$) remained significant and independent of 3-year PFS.

Comparison of the Prognostic Value of Preoperative Plasma Biomarkers

Utilizing ROC curve analysis, **Figure 1** shows the prognostic value of the 4 preoperative plasma biomarkers. The best cut-off value of fibrinogen level for predicting 3-year PFS was 2.95 g/L. The predictive performance was represented with AUC = 0.786 (95%CI = 0.715–0.846), sensitivity = 77.1%, specificity = 71.1%, and *Youden* index = 0.482. Based on the best cut-off value of 4.00 × 10∧9/L, the predictive performance of neutrophil count (AUC = 0.652, 95%CI = 0.574–0.725, sensitivity = 72.0%, specificity = 64.4%, and *Youden* index = 0.365) was also calculated by ROC curve analysis (**Figure 1**). The best cut-off value of lymphocyte count for predicting 3-year PFS was 1.65 × 10∧9/L. The predictive performance was represented by AUC = 0.630 (95%CI = 0.551–0.704), sensitivity = 67.8%, specificity = 57.8%, and *Youden* index = 0.256. The cut-off value was 2.74 for NLR (AUC = 0.743, 95%CI = 0.669–0.808, sensitivity = 87.3%, specificity = 73.3%, and *Youden* index = 0.606).

DeLong's test indicated that the AUC of fibrinogen level was comparable with that of NLR ($Z = 0.711$, $P = 0.477$). The AUC of NLR was significantly greater than that of neutrophil count ($Z = 3.153$, $P = 0.002$) and lymphocyte count ($Z = 2.138$, $P = 0.033$).

Relationship Between F-NLR Score and Prognosis in the Training Set

Figure 2 showed the predictive performance of F-NLR scoring system compared to fibrinogen level and NLR. Based on the cut-off value of 0, the scoring system had an AUC of 0.872 (95%CI = 0.811–0.919), a sensitivity of 66.1%, a specificity of 93.3%, and a *Youden* index of 0.594. DeLong's test indicated that the AUC of F-NLR scoring system was significantly greater than those of fibrinogen level and NLR ($Z = 2.929$, $P = 0.003$; $Z = 3.376$, $P < 0.001$).

The F-NLR scores were 0, 1, and 2 in 81 (49.7%), 58 (35.6%), and 24 (14.7%) of the 163 patients, respectively. The F-NLR score was significantly different in the patients with and without tumor recurrence at 3 years after surgery ($P < 0.001$). Patients with F-NLR score of 0–2 had significantly different 3-year PFS rate (96.3%, 78/81; 65.5%, 38/58; 8.3%, 2/24; $P < 0.001$, **Figure 3**). The mean 3-year PFS was 35.36 (95%CI = 34.64–36.08) months, 29.79 (95%CI = 27.36–32.22) months, 23.00 (95%CI = 19.75–26.50) months, respectively ($P < 0.001$, **Figure 3**).

TABLE 1 | Comparison of demographic and clinical variables in patients with PFS < 3 and PFS ≥ 3 in the training set.

Parameter	Total	PFS < 3 year (*n* = 45)	PFS ≥ 3 year (*n* = 118)	*P*-value
Age	54.45 ± 11.68	57.87 ± 11.13	53.15 ± 11.67	0.021
Sex				0.404
Male	59 (36.2%)	14 (31.1%)	45 (38.1%)	
Female	104 (63.8%)	31 (68.9%)	73 (61.9%)	
Hypertension				0.649
No	134 (82.2%)	36 (80.0%)	99 (83.1%)	
Yes	29 (17.8%)	9 (20.0%)	20 (16.9%)	
Diabetes mellitus				0.566
No	155 (95.1%)	44 (97.8%)	111 (94.1%)	
Yes	8 (4.9%)	1 (2.2%)	7 (5.9%)	
WBC count 10∧9/L	6.57 ± 2.29	6.92 ± 2.39	6.44 ± 2.26	0.238
NEU count 10∧9/L	4.25 ± 2.16	4.99 ± 2.31	3.97 ± 2.03	0.007
RBC count 10∧12/L	4.53 ± 0.57	4.57 ± 0.49	4.52 ± 0.60	0.585
MON count 10∧9/L	0.40 ± 0.43	0.32 ± 0.26	0.43 ± 0.48	0.178
LYM count 10∧9/L	1.83 ± 0.55	1.64 ± 0.48	1.91 ± 0.56	0.004
PLT count 10∧9/L	239.77 ± 82.33	246.33 ± 70.55	237.28 ± 86.55	0.532
HGB g/L	133.75 ± 15.63	133.06 ± 14.42	134.01 ± 16.12	0.730
FIB g/L	2.99 ± 0.91	3.61 ± 1.16	2.73 ± 0.65	< 0.001
NLR	2.55 ± 1.70	3.24 ± 1.39	2.29 ± 1.75	0.001
Tumor size cm	4.93 ± 1.44	5.55 ± 1.34	4.69 ± 1.41	0.001
Tumor location				0.082
Non-skull base	124 (76.1%)	30 (66.7%)	94 (79.7%)	
Skull base	39 (23.9%)	15 (33.3%)	24 (20.3%)	
Extent of resection				0.012
Simpson Grade I-II	141 (86.5%)	34 (75.6%)	107 (90.7%)	
Simpson Grade III-V	22 (13.5%)	11 (24.4%)	11 (9.3%)	
Skull invasion				0.321
No	97 (59.5%)	24 (53.3%)	73 (61.9%)	
Yes	66 (40.5%)	21 (46.7%)	45 (38.1%)	
Peritumoral edema				0.321
Mild (≤1 cm)	66 (40.5%)	21 (46.7%)	45 (38.1%)	
Severe (>1 cm)	97 (59.5%)	24 (53.3%)	73 (61.9%)	
Brain invasion				0.692
No	72 (44.2%)	21 (46.7%)	51 (43.2%)	
Yes	91 (55.8%)	24 (53.3%)	67 (56.8%)	
Mitotic level				0.132
<4/HPF	102 (62.6%)	24 (53.3%)	78 (66.1%)	
≥4/HPF	61 (37.4%)	21 (46.7%)	40 (33.9%)	
Ki-67 index				0.563
<5	100 (61.3%)	26 (57.8%)	74 (62.7%)	
≥5	63 (38.7%)	19 (42.2%)	44 (37.3%)	
PORT				0.095
No	136 (83.4%)	34 (75.6%)	102 (86.4%)	
Yes	27 (16.6%)	11 (24.4%)	16 (13.6%)	

Values are reported as number, number(%), and mean ± standard deviation. PFS, progression-free survival; WBC, white blood cell; NEU, neutrophil; RBC, red blood cell; MON, monocyte; LYM, lymphocyte; PLT, platelet; HGB, hemoglobin; FIB, fibrinogen; NLR, neutrophil-lymphocyte ratio; PORT, postoperative radiation therapy.

In the univariate Cox hazard regression analysis, age (HR = 1.03, 95%CI = 1.00–1.06, $P = 0.024$), tumor size (HR = 1.46, 95%CI = 1.17–1.82, $P = 0.001$), tumor location (HR = 1.85, 95%CI = 0.99–3.43, $P = 0.053$), extent of resection (HR = 2.59, 95%CI = 1.31–5.12, $P = 0.006$), and F-NLR score ($P < 0.001$) were all significantly associated with 3-year PFS. Furthermore, multivariate Cox analysis revealed that tumor size (HR = 1.39, 95%CI = 1.10–1.76, $P = 0.007$), tumor location (HR = 3.11, 95%CI = 1.60–6.95, $P = 0.001$), and F-NLR score (score of 1: HR = 12.78, 95%CI = 3.78–43.08, $P < 0.001$; score of 2: HR = 44.58, 95%CI = 13.02–152.65, $P < 0.001$) remained associated with 3-year PFS (**Table 3**).

TABLE 2 | Univariate and multivariate analysis of 3-year PFS with possible predictive factors in the training set.

Parameter	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*-value	OR	95%CI	*P*-value
Age	0.96	0.93–1.00	0.023			
NLR	0.73	0.59–0.91	0.004	0.77	0.61–0.99	0.025
FIB	0.26	0.15–0.45	<0.001	0.27	0.15–0.48	<0.001
Tumor size cm	0.64	0.49–0.84	0.001	0.59	0.43–0.81	0.001
Tumor location	0.85	0.23–1.10	0.085			
Extent of resection	3.15	1.25–7.90	0.015	3.43	1.12-10.51	0.031
PORT	2.06	0.87–4.88	0.099			

OR, odds ratio; CI, confidence interval; NEU, neutrophil; LYM, lymphocyte; FIB, fibrinogen; NLR, neutrophil-lymphocyte ratio; PORT, postoperative radiation therapy.

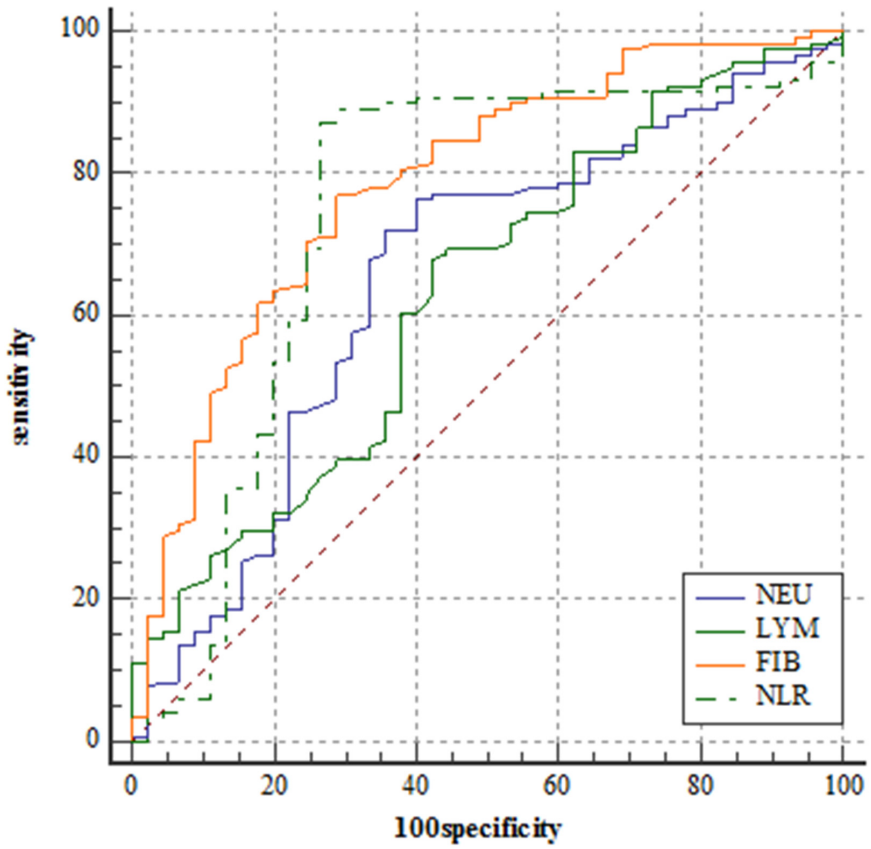


FIGURE 1 | Receiver operating characteristic curve analyses comparing neutrophil counts, lymphocyte counts, fibrinogen level, and neutrophil-lymphocyte ratio for predicting patients reaching 3-year progression-free survival in the training set.

Relationship Between F-NLR Score and 3-Year PFS by Subgroup Analysis Based on Extent of Resection and Tumor Location

A significant interaction effect was found between extent of resection and F-NLR score, $P < 0.001$. In patients with Simpson grade I-II, Kaplan-Meier curves analysis revealed that patients with F-NLR score of 0–2 were significantly different in 3-year PFS rate (97.4%, 74/76; 66.7%, 32/48; 5.9%, 1/17) and mean 3-year PFS (35.58 months, 95%CI = 35.00–36.16; 29.95 months, 95%CI = 27.31–32.60; 24.12 months, 95%CI = 20.81–27.42) ($P < 0.001$, **Figure 4**). In patients receiving Simpson grade III-V resection, those with F-NLR score of 0–2 were not significantly different in 3-year PFS rate (80.0%, 4/5; 60.0%, 6/10; 14.3%, 1/7) and mean 3-year PFS (32.00 months, 95%CI = 24.99–39.01; 29.00 months, 95%CI = 22.94–35.06; 20.29 months, 95%CI = 12.93–27.64) ($P = 0.045$, **Figure 4**).

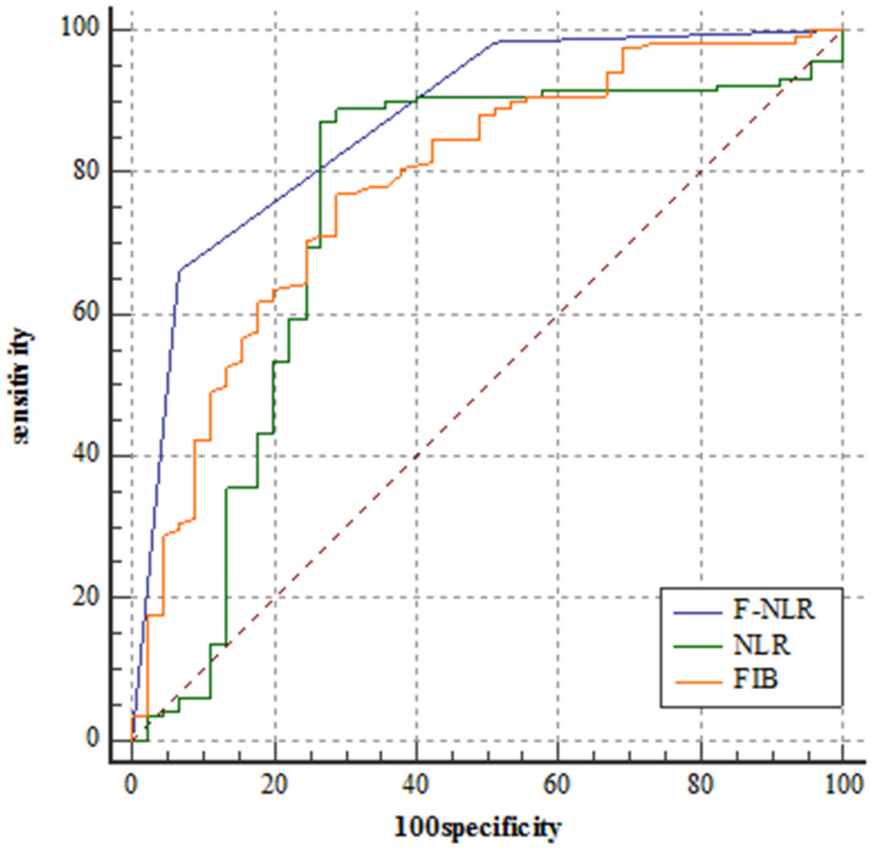


FIGURE 2 | Receiver operating characteristic curve analyses comparing fibrinogen and neutrophil-lymphocyte ratio scoring system, fibrinogen level, and neutrophil-lymphocyte ratio for predicting patients reaching 3-year progression-free survival in the training set.

A significant interaction effect between tumor location and F-NLR score was also found for 3-year PFS, $P < 0.001$. In the Kaplan-Meier curves analysis of subgroups based on tumor location, F-NLR score was still associated with 3-year PFS ($P < 0.001$, **Figure 4**). For patients with non-skull base tumor, the 3-year PFS rates in F-NLR score 0–2 were 96.8% (60/62), 76.7% (33/43), and 5.3% (1/19), respectively; the mean 3-year PFS were 35.45 (95%CI = 34.69–36.21), 31.77 (95%CI = 29.34–34.21), and 24.32(95%CI = 21.13–27.51), respectively. For the other patients with skull base tumor, the 3-year PFS rate for F-NLR score 0, 1, 2 was 94.7%(18/19), 33.3%(5/15), and 20.0%(1/5), respectively; the mean 3-year PFS were 35.05 (95%CI = 33.25–36.86) months, 24.20 (95%CI = 18.89–29.51) months and 18.00 (95%CI = 9.50–26.50) months, respectively.

External Validation of F-NLR Score for Predicting Prognosis

Table 4 shows the demographics and the main baseline characteristics between the training set and the validation set. There was no significant difference in age, sex, hypertension, diabetes, FIB level, NLR level, tumor size, tumor location, extent of resection, PORT, 3-year PFS rate, and F-NLR score between the two sets.

In the validation set with 105 patients, the score of 0, 1, and 2 comprised 49 (46.7%), 35 (33.3%), and 21 (20.0%), respectively, and accounted for 45, 23, and 4 cases achieving 3-year PFS. Patients with F-NLR score of 0–2 had significantly different 3-year PFS rate both in the training set and the validation set ($P < 0.001$, $P < 0.001$, **Table 5**). The distribution of patients with different F-NLR scores in the two groups was similar between the training set and the validation set (**Figure 5**).

Figure 6 showed the predictive performance of F-NLR scoring system compared to fibrinogen level and NLR in the validation set. Based on the cut-off value of 0, the scoring system had an AUC of 0.824 (95%CI = 0.738–0.891), a sensitivity of 62.5%, a specificity of 87.9%, and a *Youden* index of 0.504. The AUC for fibrinogen level and NLR were 0.722 (95%CI = 0.627–0.805) and 0.630 (95%CI = 0.530–0.722), respectively. DeLong's test indicated that the AUC of F-NLR scoring system was significantly greater than those of fibrinogen level and NLR ($Z = 2.462$, $P = 0.014$; $Z = 4.075$, $P < 0.001$).

DISCUSSION

Tumor recurrence could increase morbidity and result in decreased survival (2). Even after gross total excision, atypical

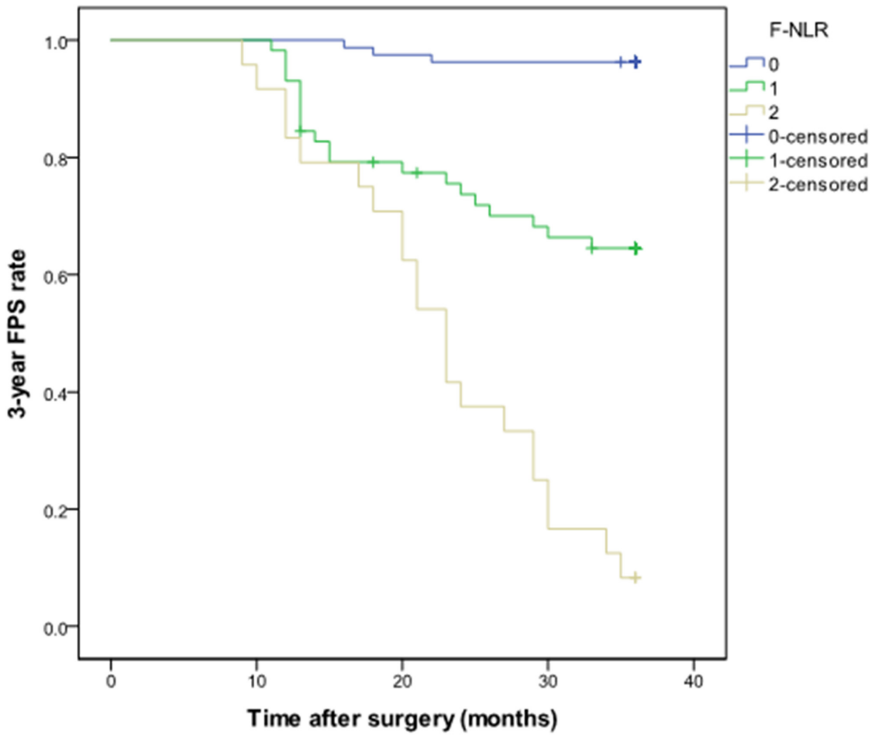


FIGURE 3 | Kaplan-Meier curve of the 3-year progression-free survival rate in patients with different fibrinogen and neutrophil-lymphocyte ratio score from 0 to 2 in the training set.

TABLE 3 | Univariate and multivariate cox hazard regression analysis of 3-year PFS with possible predictive factors in the training set.

Parameter	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age	1.03	1.00–1.06	0.024			
Tumor size cm	1.46	1.17–1.82	0.001	1.39	1.10–1.76	0.007
Tumor location	1.85	0.99–3.43	0.053	3.11	1.60–6.95	0.001
Extent of resection	2.59	1.31–5.12	0.006			
F-NLR score			<0.001			<0.001
0	1.00	Reference		1.00	Reference	
1	12.09	3.59–40.71	<0.001	12.78	3.78–43.08	<0.001
2	44.35	13.15–149.58	<0.001	44.58	13.02–152.65	<0.001

HR, hazard ratio; CI, confidence interval; F-NLR, fibrinogen and neutrophil-lymphocyte ratio.

meningioma reached a high 5-year recurrence rate of 30 to 40% (2, 3). Barrett et al. reported that recurrence occurred in 30.3% of atypical meningioma patients with gross total resection at 3 years (6). Not only that, but the tumor also shows heterogeneity with variable growth rates. Hence, there is a great need to determine prognostic factors for stratifying recurrence risk of patients. Although significant progress on diagnosis and treatment of atypical meningioma has been made, there are still lots of difficulties on classifying recurrence risk of these patients. Personalized medicine based on genome sequencing may change the future of medical services. However, the procedure is invasive and may not capture the full spatial and temporal heterogeneity of the tumor. In contrast, preoperative non-invasive plasma biomarkers have enormous potential in risk stratification of tumor recurrence because they could guide surgeon to perform early and reasonable interventional therapy. Furthermore, these biomarkers could also be analyzed by conventional equipment rendering their practicability and inexpensiveness. We hypothesize that preoperative peripheral blood biomarkers could predict recurrence of atypical meningioma, allowing stratification of the extent of resection, adjuvant treatment, and tumor location.

In this study, we assessed the prognostic value of the preoperative plasma fibrinogen level and preoperative blood test in the training set with 163 atypical meningioma patients. Recurrence rate at 3 years after surgery was 29.10% in our cohort,

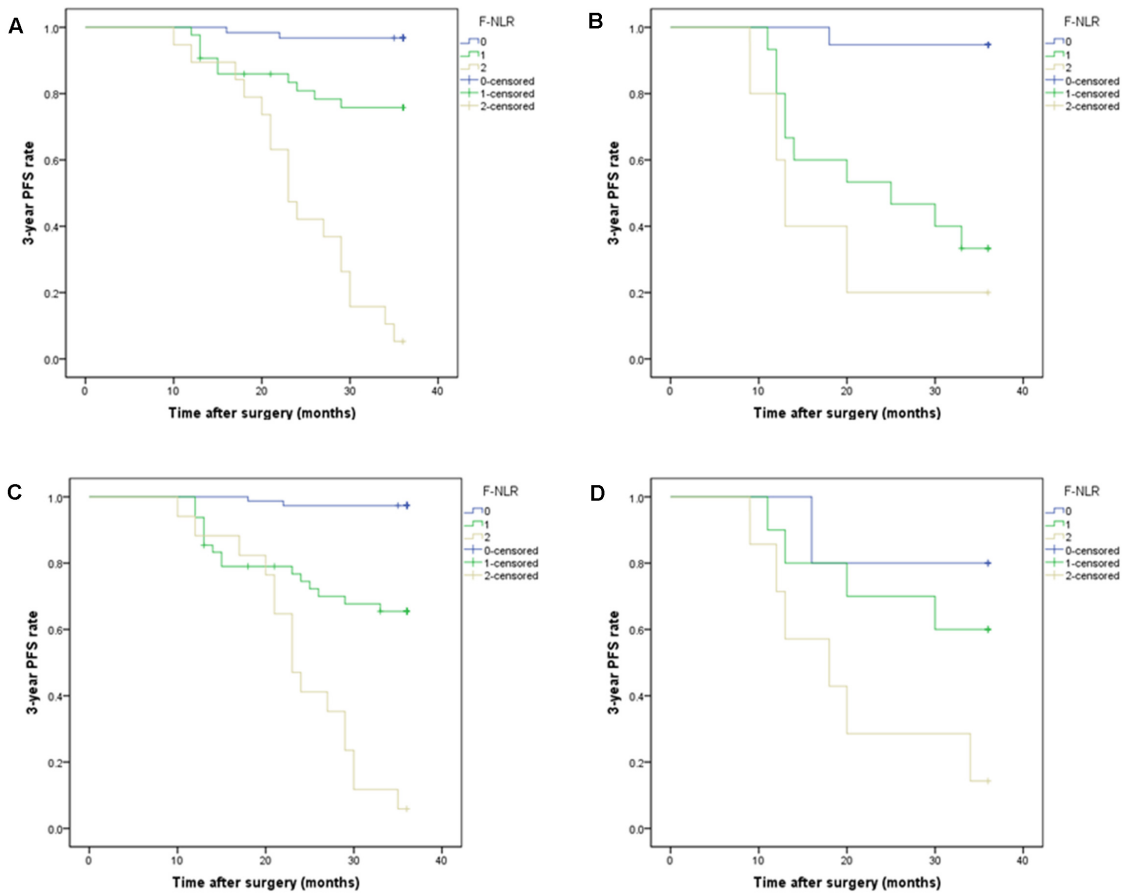


FIGURE 4 | (A,B) Subgroup analysis of Kaplan-Meier curve of the 3-year progression-free survival rate in patients with different fibrinogen and neutrophil-lymphocyte ratio score from 0 to 2 based on tumor location in the training set. **(A)** F-NLR score was associated with 3-year PFS in non-skull base tumors, $P < 0.001$. **(B)** F-NLR score was associated with 3-year PFS in skull base tumors, $P < 0.001$. **(C,D)** Subgroup analysis of Kaplan-Meier curve of the 3-year PFS rate in patients with different F-NLR scores based on extent of resection. **(C)** F-NLR score was associated with 3-year PFS in patients with Simpson grade I-II resection, $P < 0.001$. **(D)** F-NLR score was not associated with 3-year PFS in patients with Simpson grade III-V resection, $P = 0.045$.

which was similar to that reported in other studies (6). In the training set, we found a moderate predictive value of fibrinogen level (AUC = 0.786, 95%CI = 0.715–0.846, sensitivity = 77.1%, specificity = 71.1%, and *Youden* index = 0.482) in atypical meningioma relapsing at 3 year after surgery. In addition, a comparable predictive value was found in NLR (AUC = 0.743, 95%CI = 0.669–0.808, sensitivity = 87.3%, specificity = 73.3%, and *Youden* index = 0.606). Although the values of fibrinogen and NLR in predicting the 3-year PFS rate in patients with atypical meningioma were, respectively, proven, a single parameter may be not comprehensive enough. Therefore, we combined these two parameters to build a novel F-NLR scoring system and obtained a significantly elevated AUC. To the best of our knowledge, this is the first report to determine the predictive value for prognosis of F-NLR scoring system in patients with atypical meningioma. The scoring system proved its value in risk stratification of atypical meningioma recurrence at 3 years after surgery. The 3-year PFS rate decreased as the F-NLR score increased. Multivariate Cox analysis based on a multicenter retrospective study of 163 atypical meningioma patients revealed that F-NLR score was an independently related factor of 3-year PFS rate. Patients with score 1 had 12.78-fold risk of relapse than those with score 0. In addition, the risk of recurrence in patients with score 2 increased by 44.58-fold. After calculating the interaction effects, we performed subgroup analysis based on tumor location and extent of resection. Subgroup analysis based on tumor location revealed that F-NLR remained valuable in predicting 3-year PFS rate ($P < 0.001$). Kaplan-Meier curve analysis revealed that for patients with Simpson grade I-II and Simpson grade III-V, different F-NLR scores were both associated with significantly different 3-year PFS rates ($P < 0.001$, $P = 0.045$). This result strengthened the idea that F-NLR scoring system and 3-year PFS were closely related. In addition, the good predictive performance of F-NLR scoring system was also demonstrated in the validation set with 105 patients (AUC = 0.824, 95%CI = 0.738–0.891, sensitivity = 62.5%, specificity = 87.9%, and *Youden* index = 0.504). As the similar baseline characteristics and F-NLR score distribution between the training set and the validation set, we had reason to believe the predictive

TABLE 4 | Comparison of demographic and clinical variables in patients between training set and validation set.

Parameter	Training set year (*n* = 163)	Validation set year (*n* = 105)	*P*-value
Age	54.45 ± 11.68	52.19 ± 11.61	0.122
Sex			0.638
Male	59 (36.2%)	41 (39.0%)	
Female	104 (63.8%)	64 (61.0%)	
Hypertension			0.585
No	134 (82.2%)	89 (84.8%)	
Yes	29 (17.8%)	16 (15.2%)	
Diabetes mellitus			0.772
No	155 (95.1%)	99 (94.3%)	
Yes	8 (4.9%)	6 (5.7%)	
FIB g/L	2.97 ± 0.91	3.11 ± 1.16	0.292
NLR	2.55 ± 1.70	2.86 ± 1.81	0.167
Tumor size cm	4.93 ± 1.44	4.69 ± 1.41	0.190
Tumor location			0.613
Non-skull base	124 (76.1%)	77 (73.3%)	
Skull base	39 (23.9%)	28 (26.7%)	
Extent of resection			0.222
Simpson Grade I-II	141 (86.5%)	85 (81.0%)	
Simpson Grade III-V	22 (13.5%)	20 (19.0%)	
PORT			0.936
No	136 (83.4%)	88 (83.8%)	
Yes	27 (16.6%)	17 (16.2%)	
FPS			0.501
<3 years	45 (27.6%)	33 (31.4%)	
≥3 years	118 (72.4%)	72 (68.6%)	
F-NLR score			
0	81 (49.7%)	48 (46.7%)	0.529
1	58 (35.6%)	35 (33.3%)	
2	24 (14.7%)	21 (20.0%)	

Values are reported as number, number(%), and mean ± standard deviation. FIB, fibrinogen; NLR, neutrophil-lymphocyte ratio; PORT, postoperative radiation therapy; PFS, progression-free survival; F-NLR, fibrinogen and neutrophil-lymphocyte ratio.

TABLE 5 | The 3-year PFS rates in patients with different F-NLR scores.

	Total	PFS < 3 year (*n* = 78)	PFS ≥ 3 year (*n* = 190)	*P*-value
Training set	163 (100.0%)	45 (27.6%)	118 (72.4%)	
F-NLR score				<0.001
0	81 (49.7%)	3 (3.7%)	78 (96.3%)	
1	58 (35.6%)	20 (34.5%)	38 (65.5%)	
2	24 (14.7%)	22 (91.7%)	2 (8.3%)	
Validation set	105 (100.0%)	33 (31.4%)	72 (68.6%)	
F-NLR score				<0.001
0	49 (46.7%)	4 (8.2%)	45 (91.8%)	
1	35 (33.3%)	12 (34.3%)	23 (65.7%)	
2	21 (20.0%)	17 (81.0%)	4 (19.0%)	

Values are reported as number, number(%). PFS, progression-free survival; F-NLR, fibrinogen and neutrophil-lymphocyte ratio.

value of F-NLR scoring system in prognosis of patients with atypical meningioma.

Accumulating evidence demonstrates the important pathophysiological role of activation of coagulation cascade in tumor progression. Fibrinogen, a key component in the coagulation system, has been confirmed as an important regulator of systemic inflammatory response and cancer development in various types of tumor. Many studies reported the association between hyperfibrinogenemia and invasiveness of malignancy (9–13). Plasma fibrinogen level was also confirmed to be significantly lower in WHO grade I meningioma compared to that of glioblastomas and metastases (21). In meningioma of different grades, immunohistochemical analysis revealed that fibrinogen staining scores were significantly elevated from grade

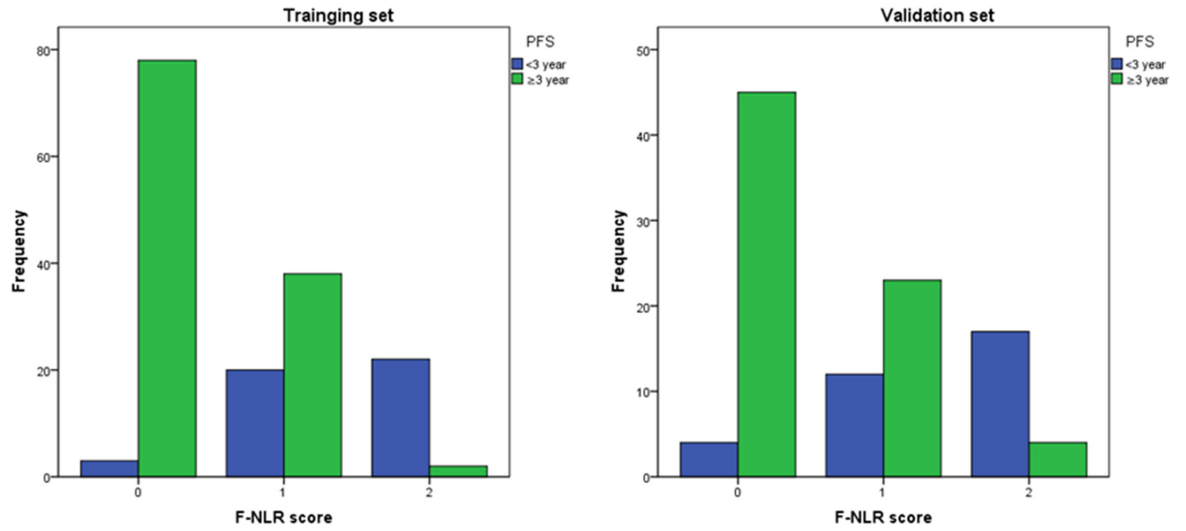


FIGURE 5 | The distribution of patients with different F-NLR scores in the recurrence group and non-recurrence group was similar between the training set and the validation set.

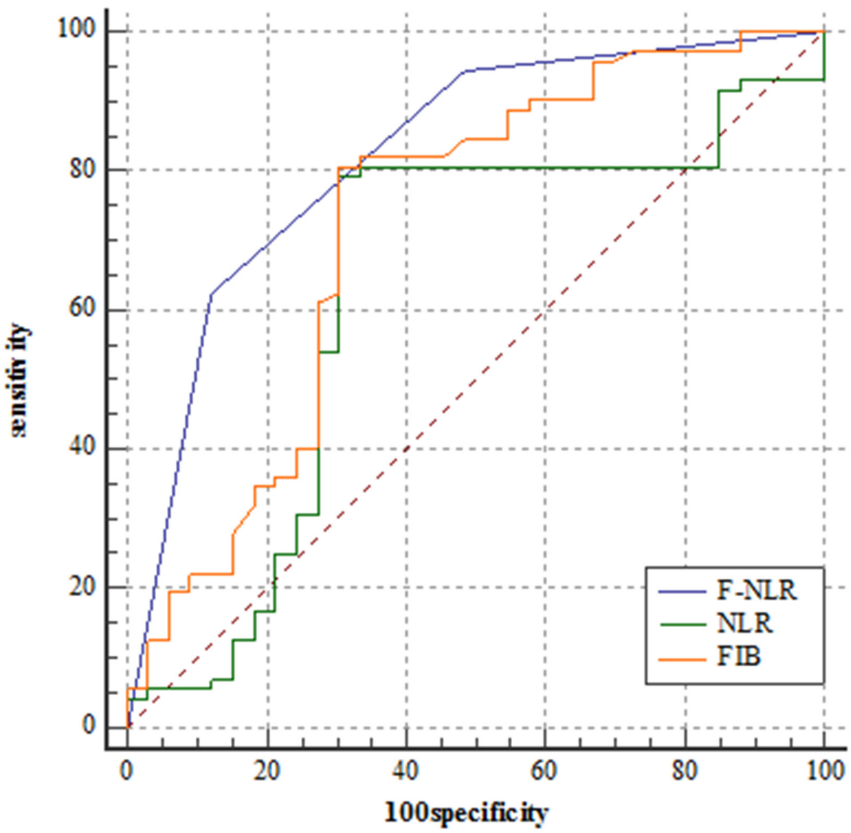


FIGURE 6 | Receiver operating characteristic curve analyses comparing fibrinogen and neutrophil-lymphocyte ratio scoring system, fibrinogen level, and neutrophil-lymphocyte ratio for predicting patients reaching 3-year progression-free survival in the validation set.

I to grade III. These pathological or clinical evidences provide a theoretical basis for application of fibrinogen level in predicting prognosis in patients with atypical meningioma.

However, the mechanism of regulation remains unclear, with the following possible explanations. First, a "web" built by fibrinogen in the extracellular matrix could promote cell

adhesion, migration, and invasion of tumor (22, 23). Second, the physical barrier formed by platelet-fibrin deposition surrounding tumor cells could prevent them from the killing contact of NK cells (24). In atypical meningioma, fibrinogen was observed to surround tumor cells in a fibrillary pattern (25). Third, as an acute-phase reactant released in malignancy and systemic inflammation, fibrinogen could be synthesized by tumor cells and promoted to be released by interleukin-6 (26). In turn, the released fibrinogen promotes tumor cell proliferation by the combined effects with vascular endothelial growth factor and fibroblast growth factor-2 (27, 28). In our study, patients with higher preoperative fibrinogen level had lower 3-year PFS rate than the others. Hence, fibrinogen could be a reliable predictor for the prognosis of atypical meningioma.

In recent years, systemic inflammation has attracted significant attention in tumor occurrence and progression. The predictive value of NLR, a representative indicator of tumor-related inflammation, for intracranial tumor prognosis has been confirmed (12, 29). Neutrophils are known for playing a positive role in tumor growth and angiogenesis (30). Conversely, lymphocytes make a significant contribution in inhibiting tumor proliferation (31). Therefore, the neutrophil-lymphocyte ratio could enhance the efficacy for predicting recurrence risk in malignant tumor. For meningioma, the value of preoperative blood test in predicting tumor grades has been confirmed (32). Our study revealed that atypical meningioma patients with high NLR had lower 3-year PFS rate than those with low NLR. Therefore, NLR could be used as a predictor to evaluate the recurrence risk of atypical meningioma.

In our study, we also evaluated the predictive value of several other clinic-pathological factors on the tumor recurrence of atypical meningioma. In variable types of tumor, elevated Ki-67 index and mitotic level played a key role in aggressiveness and tendency to recurrence (33, 34). Brain invasion and high mitotic index has been shown to be linked with higher risk of recurrence in atypical meningioma (5). Similarly, as a cellular biomarker of proliferation, Ki-67 index has been successfully applied in predicting local recurrence of an atypical meningioma cohort following gross total resection (6). Unfortunately, our study did not find the association between Ki-67 index and 3-year PFS in patients with atypical meningioma. The relationship between brain invasion, mitotic index and 3-year PFS was also not statistically significant in univariate analysis. That may be due to insufficient sample size. Extent of resection was highly influential on atypical meningioma recurrence which has been confirmed in many studies (7, 35, 36). Thus, it is recommended that atypical meningioma should be completely resected based on Simpson grade. In our study, we divided the patients into Simpson grade I-II group and Simpson III-V group due to small number of cases in Simpson grade IV-V. Multivariate logistic regression analysis showed the strong relation between extent of resection and 3-year PFS. The Simpson grade III-V group had 2.59-fold risk of relapse than the other group in the univariate Cox hazard regression analysis. However, after multivariate analysis, extent of resection lost statistical significance possibly due to the insufficient sample in the training set. Actually, we have also created a rating scale incorporating all those independent prognostic factors that resulted significant at the multivariate analysis before updating the manuscript. But we found the predictive value of that rating scale was similar to our F-NLR scoring system (AUC = 0.895, 95%CI = 0.838–0.938 vs. AUC = 0.872, 95%CI = 0.811–0.919; Z = 1.140, P = 0.254). And the rating scale incorporating all the independent prognostic factors was not convenient in the clinical application. Our F-NLR scoring system incorporating two preoperative blood test parameters was relatively objective and easy to access. Therefore, we retained the F-NLR scoring system to predict prognosis of patients in our study.

Many potential factors contribute to the formation of peritumoral edema with complex mechanism. Peritumoral edema also demonstrated significant link with histopathological grade and aggressive growth of tumor in some studies (8, 37). However, others also showed negative investigations on the uncertain relationship (38, 39). Similarly, our study showed that peritumoral edema of atypical meningioma was not correlated with tumor recurrence. On the other hand, prior studies have demonstrated that larger tumor size was correlated with high tumor proliferative potential (35, 40). Our findings confirmed the higher risk of recurrence in larger tumor in both univariate and multivariate analyses. Tumor location could affect the difficulty of surgery and the extent of resection. Atypical meningioma in skull base is more difficult to be completely resected, which contributes to the tendency of recurrence. In our study, tumor locating in skull base was confirmed as an independent risk factor for 3-year PFS in multivariate analysis. Fukushima et al. reported that skull base location was independently associated with tumor recurrence in patients following Simpson Grade IV resection (41). Another study also validated the higher recurrence rate of skull base tumor in a Grade I-V cohort (42). These studies shed light on our findings and our study also extended theirs.

Given the potential toxicities of upfront PORT, there is no consensus on the necessity for patients with atypical meningioma taking it as a conventional therapy. The European Association of Neuro Oncology guidelines recommend that adjuvant radiation therapy should be considered in tumor with incomplete resection (43). On the other hand, a Phase III trial conducted by the European Organization for Research and Treatment of Cancer is currently ongoing to clarify the value of PORT in patients after complete resection (44). However, prior studies were contradictory on whether PORT decreases the risk of recurrence in atypical meningioma patients. Some studies affirmed the efficacy of PORT while others showed a non-significant association between PORT and tumor recurrence (36, 45, 46). In our cohort, we did not find the value of PORT in decreasing the risk of tumor recurrence.

Several limitations existed in our study. First, although the acquired data were from multiple centers, the retrospective design of study suffered potential selection bias. Second, other molecular markers were not included in our study because of

incomplete immunohistochemical analysis in early cases. Third, the minimum duration of follow-up was not long enough to evaluate further PFS rate and overall survival of patients. Therefore, a multicenter prospective study with more thorough and comprehensive data should be carried out to validate the reliability of F-NLR scoring system in patients with atypical meningioma again.

CONCLUSION

Our study confirmed the correlation and clinical significance of preoperative F-NLR scoring system with 3-year PFS of patients with atypical meningioma. Extent of resection, tumor size, and tumor location also showed their association with 3-year PFS. The F-NLR scoring system could serve as a useful tool for predicting prognosis of patients with atypical meningioma. A prospective and large-scale study is required to validate our findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Fujian Medical University, The Affiliated Hospital of Putian University, and the Henan Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CD, DK, and JG performed and designed the experiments, analyzed and interpreted the data, and wrote the manuscript. XC, GW, JZ, GZ, YL, and ZL collected and interpreted the data. All authors were involved in drafting the article and reviewed and approved the final manuscript.

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Is DNA Methylation a Ray of Sunshine in Predicting Meningioma Prognosis?

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Meningioma is the most common intracranial tumor, and recent studies have drawn attention to the importance of further research on malignant meningioma. According to the World Health Organization (WHO) grading, meningioma is classified into 15 subtypes with three grades of malignancy. However, due to a lack of descriptions of molecular subtypes, genetic mutations, or other features, there were deficiencies in the WHO classification. The DNA methylation-based meningioma classification published in 2017 used DNA copy number analysis, mutation profiling, and RNA sequencing to distinguish six clinically relevant methylation classes, which contributed to a better prediction of tumor recurrence and prognosis. Further studies indicated that gene variation and gene mutations, such as those in neurofibromin 2 *(NF2)* and *BRCA1*, were related to the high WHO grade, malignant invasion, and recurrence. Among the mutant genes described above, some have been associated with differential DNA methylation. Herein, we searched for articles published in PubMed and Web of Science from January 2000 to May 2020 by entering the keywords "meningioma," "methylation," and "gene mutation," and found a number of published studies that analyzed DNA methylation in meningiomas. In this review, we summarize the key findings of recent studies on methylation status and genetic mutations of meningioma and discuss the current deficits of the WHO grading. We also propose that a methylation-based meningioma classification could provide clues in the assessment of individual risk of meningioma recurrence, which is associated with clinical benefits for patients.

Keywords: meningioma, methylation, classification, prognosis, gene

INTRODUCTION

Meningiomas, tumors of the meningeal coverings of the brain and spinal cord, are the most common intracranial tumors. According to the World Health Organization (WHO) classification, 80% of meningiomas are grade I and are considered benign. The remaining 20% are grade II and III with a malignant histological tendency (1). Although the WHO grade is considered to be the

most reliable indicator in predicting meningioma prognosis (2, 3), there is significant variation with regards to the risk of recurrence for individual patients (4, 5).

Recently, many studies have demonstrated that epigenetic changes, especially DNA methylation, as well as genetic mutations are related to tumor prognosis (4) (**Table 1**). A totally new classification based on DNA copy number analysis, mutational profiling, and RNA sequencing has been used to distinguish six individual clinically relevant methylation classes (6) to better predict tumor recurrence and prognosis. A series of studies have identified methylation profiling as a marker of malignancy or poor survival rates and genetic mutations as an indicator of histology grade. However, there has been no significant evidence illustrating a relationship between DNA methylation and genetic mutation. The most recent papers suggest that many potential genes, like *NDRG2* and *MAL2,* are related to DNA methylation, but whether they can predict prognosis remains controversial.

METHODS

We reviewed the relevant literature on PubMed and Web of Science that had been published between January 2000 and May 2020. We identified 599 studies addressing aberrant DNA methylation and genetic mutation in meningiomas. The words we searched included "meningioma," "methylation," and "gene mutation." After analyzing all relevant articles, we found genes-of-interest and searched those genes on PubMed and Web of Science to acquire pertinent information.

THE GENETIC MUTATIONS IN WHO GRADE

In recent years, several aberrant gene mutations have been reported in meningiomas. The new WHO grade (2016 version) adds this molecular feature to its criteria and tries to give a clear description of different histological subtypes (1). Although the WHO grade defines characteristics of each subtype, the deficiencies of this classification have gradually been revealed.

The WHO Grade – Subtypes and Molecular Features

To better predict the prognosis of meningiomas, the WHO grade 2016 criteria, which emphasized mitotic activity and brain invasion, classified meningiomas into three pathological grades with 15 subtypes (**Table 2**). These included grade I tumors of nine subtypes (meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacytic-rich, and metaplastic subtypes), grade II of three histological subtypes (chordoid, clear cell, and atypical), and grade III meningiomas of three subtypes (papillary, rhabdoid, and anaplastic) (7). Each grade has unique molecular features that have been reviewed by previous studies (1, 8). Grade I meningiomas show high mutation rates of some genes (**Table 2**), including neurofibromin 2 (*NF2*), the proto-oncogene v-Akt murine thymoma viral oncogene homolog 1 (*AKT1*), the ubiquitin ligase tumor necrosis factor receptor-associated factor 7 *(TRAF7*), the oncogene phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), the pluripotency transcription factor Kruppel-like factor 4 (*KLF4*), and the gene for the catalytic subunit of RNA polymerase II (*POLR2A*) (9, 10). *TRAF7* mutations occur in 25% of WHO grade I and II meningiomas (11). Other genetic mutations have also been reported, including phosphatase and tensin homolog (*PTEN*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), and cyclin-dependent kinase inhibitor 2B (*CDKN2B*) genes which can be found in grade III meningiomas (12). High-grade meningiomas are characterized by more mutations than grade I meningiomas (9).

Different histological subtypes of meningiomas also harbor various characteristics. For example, secretory meningiomas show frequent co-mutations of the *KLF4* and *TRAF7* genes (13, 14), while clear cell meningiomas show SWI/SNF-related, matrix-associated, actin-dependent regulators of chromatin, subfamily e, member 1 (*SMARCE1*) mutations (15). A subset of rhabdoid meningiomas reveals poor outcomes by inactivating the *BAP1* gene, compared to patients with *BAP1*-negative rhabdoid meningiomas (16). Therefore, adding genetic mutations into the WHO classification system allows each subtype of meningiomas to be more precisely characterized.

Regarding prognosis, histologic grade (the WHO grade) and the extent of surgical resection (the Simpson grade) were considered the two most important prognostic variables (3, 17). Heald et al. showed that gross-total resection significantly decreases the risk of recurrence (2), suggesting the importance of the Simpson grade in meningioma recurrence. Studies have also demonstrated that, with the exception of other external conditions (i.e., therapeutic regimens), a combination of the WHO grade and the Simpson grade has better clinical value to predict the prognosis of different grades of meningiomas. Grade I meningiomas have a 10-year overall survival rate of 80% and a progression-free survival rate (PFS) of approximately 74 to 96% (18–20). Grade II meningiomas have an easier tendency for recurrence, and their 10-year overall survival (OS) and PFS are between 53–79% and 23–78%, respectively. Comparatively, grade III meningiomas are more aggressive and significantly associated with brain invasion, with a 10-year OS of 14 to 34% and PFS of 0%, even for those that undergo gross-total resection (3, 5). These results show that a higher histologic grade is associated with a poorer survival rate, and for patients with a WHO grade III meningiomas, subtotal resection indicates a worse prognosis. Clinicians have utilized these methods to predict the prognosis of patients. However, some deficits in the WHO grading system remain.

The Deficiencies of WHO Grade

Usually, the risk of recurrence is predicted based on the WHO grade. However, as many malignant tumors are underestimated in clinical practice, the actual risk of recurrence is higher than the predicted risk. Thus, a new grading system is needed. Based on clinical experience, meningiomas of the same grade can exhibit totally different biologic behaviors. For example, some meningiomas that are designated as benign can recur within

TABLE 1 | Key findings on meningiomas in the last two decades.

Year	Number of meningiomas sample					Key findings	References
	Total	Grade I	Grade II	Grade III	Comment		
2004	72	/	/	/	58 benign, 10 atypical and 4 anaplastic meningiomas	The relationship between p53 gene mutation and p14 (ARF) gene methylation	(6)
	50	20	14	16	/	The methylation of p16 (INK4a)	(7)
	60	33	24	3	/	The methylation of TP73	(8)
2005	48	/	/	/	16 benign, 19 atypical, and 13 anaplastic meningiomas	The promoter hypermethylation is associated with atypical and anaplastic meningiomas; the methylation of MGMT	(9)
	44	15	11	8	10 meningiomas (grade I and grade II)	Hypermethylation of the NDRG2 promoter	(10)
2006	25	/	/	/	Meningiomas without NF2 involvement	The methylation of NF2, p14 (ARF), CDH1, BRCA1, RB1	(11)
2007	40	22	11	7	/	The methylation status of p73 or RASSF1A along with 1p LOH may result in the malignant transformation of a meningioma	(12)
2009	26	10	7	9	209 tumors from 13 other tumor types; two human malignant meningioma cell lines: IOMM-Lee21 and KT21-MG1	Aberrant methylation of the CpG island of WNK2 was associated with decreased expression in primary tumors	(13)
2010	50	27	11	12	/	The methylation of TIMP3	(14)
2011	65	26	27	12	/	uPA Promoter Methylation	(15)
2012	131	100	28	3	/	The methylation of HOXA 7, 9, and 10 were associated with histopathology and clinical aggressiveness parameters	(16)
	36	16	17	3	/	The methylation of MGMT, CDKN2A, GSTP1, and THBS1	(17)
	50	20	16	14	/	Hypermethylation of the promoter of hMLH1 is associated with the tumor grade	(18)
2013	33	30	2	1	Discovery set	The methylation of IGF2BP1 and PDCD1	(19)
	12	6	5	1	Verification set		
	19	10	5	4	/	Global DNA hypomethylation and the MAL2 gene	(20)
2015	44	33	2	9	/	The methylation of CDKN2B, RASSF1A, RUNX3, AND GATA6	(21)
2016	/	/	/	/	*de novo* tumors: 41 meningiomas and 33 hemangiopericytomas; recurrent tumors: 37 meningiomas and 5 hemangiopericytomas	The promoter methylation of hTERT was positively correlated with WHO grade and hTERT expression	(22)
2017	497	/	/	/	309 samples of other extra-axial skull tumors	DNA Methylation-Based Classification	(23)
	89	54	34	1	Test group	Robust DNA methylation signatures in meningioma were correlate with CNAs and could stratify patients by recurrence risk	(24)
	51	36	9	6	Validation group		
2019	282	/	/	/	Training cohort: 228; the first validation cohort: 54	Established a 5-year meningioma recurrence score	(4)

TABLE 2 | The WHO grade (2016 criteria) (8).

WHO grade (2016 criteria)	Histological subtype	Gene mutations
I	Meningothelial	TRAF7, AKT1, POLR2A, PIK3CA
	Fibrous (fibroblastic)	NF2
	Transitional (mixed)	NF2, AKT1, PIK3CA
	Psammomatous	NF2
	Angiomatous	–
	Microcystic	–
	Secretory	KLF4, TRAF7
	Lymphoplasmacyte-rich	–
	Metaplastic	–
II	Chordoid	–
	Clear cell	SMARCE1
	Atypical	NF2, TRAF7, AKT1
III	Papillary	–
	Rhabdoid	BAP1
	Anaplastic (malignant)	NF2

a short amount of time, while other meningiomas with high-grade features may hardly ever exhibit recurrence (21, 22). It has also been reported that some grade I meningiomas exhibit early or frequent recurrence and metastasis to distant organs, such as the lungs (23–26). As the prediction of outcomes through the use of the WHO and Simpson classifications to predict the prognosis of meningiomas has been inconsistent with overall results, there appear to be other factors affecting the progression of meningiomas.

Observations of Epigenetic Alteration and Gene Methylation in Meningiomas

Indeed, there is an urgent need for a more accurate subclassification covering histological and surgical resection assessments that reflects the potential malignant characteristics of meningiomas. Recently, it has become a trend to study the molecular features of different meningioma subtypes to find out potential biomarkers that suggest worse progression. Chromosomal structural variation and genetic mutations have become a research hotspot. Mawrin et al. found few chromosomal alterations in WHO grade I tumors, but frequent alterations of karyotype and copy number in WHO grade II tumors. Losses of chromosomes 1p, 6q, 9p, 10, 14q, and 18q, and gains of chromosomes 1q, 9q, 12q, 15q, 17q, and 20q have been found across grade III meningiomas (27). Different genes contribute to different meningiomas' subtypes. These genes include *TRAF7*, *AKT1*, *POLR2A*, *PIK3CA*, *SMO*, *KLF4*, *SMARCB1*, *BAP1,* and *NF2* (11, 16, 28–32). Each subtype of meningiomas has its own molecular features, but some genetic mutations (including *NF2*, *TRAF7*, *AKT1,* and *PIK3CA*) can be found among several subtypes of meningiomas, which confuse the judgment of tumor evolution.

Additionally, epigenetic alteration has become increasingly important in tumor occurrence and evolution. These alterations appear in meningiomas without causing the aforementioned gene mutations (33–35). Epigenetic changes caused by complicated mechanisms modulate heritable gene expression without altering the primary sequence of DNA (36). These changes include DNA methylation, microRNA interactions, histone packaging, and chromatin restructuring. Among these, abnormal DNA methylation is a chemical modification process mediated by DNA methyltransferase (DNMT). It can cause gene silencing and a decline in expression by blocking the transcriptional machinery from accessing the DNA (37, 38). As aberrant DNA methylation often occurs in the early stage of tumorigenesis, it can be detected in the early stage of disease (37, 39). The methods currently used to detect DNA methylation include bisulfite methods [such as whole-genome bisulfite sequencing (WGBS), reduced representation bisulfite sequencing (RRBS)], and Illumina EPIC methylation array profiling) and non-bisulfite methods (40). According to research data, global detection of abnormal methylation genes can provide biomarkers of clinical potential for the prognosis of certain cancers, such as lung cancer and colorectal cancer (41, 42). Actually, DNA methylation is a common event in meningiomas, as approximately 77% harbor at least one differentially methylated gene and 25% experience alterations of three or more genes (33). Although gene methylation can be detected across all grades of meningiomas, the frequency varies between benign and malignant tumors, and genes (e.g., *TIMP3*, *GSTP1*, *MEG3*, *HOXA6*, *HOXA9*, *PENK*, *WNK2,* and *UPK3A* genes) have an increased frequency according to the WHO grade (12). Several studies indicate that a large number of genes are methylated in meningiomas (43–46) and uncover the relationship between genes and WHO grade, which lays a solid foundation for the methylation classification of this tumor type.

THE METHYLATION CLASSES IN MENINGIOMAS

For meningiomas, a large proportion of previous studies (45–48) have focused on aberrantly methylated genes, but few have studied classification based on methylation. The methylation grading may not be being utilized effectively. In 2017, new methylation classes were published and were considered a more reliable classification system compared to the WHO's grading. Some newly discovered genes were not included in this classification; subsequent supplementary experiments are in preparation.

The Old Methylation Classes

Based on methylation profiling, one study subclassified WHO grade I and II meningiomas into three methylation clusters (39), and they did not include grade III meningiomas. Another study used robust methylation signatures (283-bMMC model) to distinguish two clinical–biological subgroups, including one clinically favorable prognostic subgroup (MM-FAV) and another clinically unfavorable meningioma methylation subgroup (MM-UNFAV) (**Table 3**). The Kaplan–Meier survival analysis showed that tumors in the MM-UNFAV group had significantly shorter recurrence times compared to MM-FAV. After adjusting for

TABLE 3 | The 283-bMMC model subgroups (2017).

Basic Methylation Classifier (bMMC)	Subgroups	CNA Patterns	Median RFS (in validation groups)
283-bMMC	MM-FAV	+1p, −22q	16.35 years
	MM-UNFAV	−1p, +1q, −2p, −3p/+3, −4, +5, −6q, +9, −10, +12, +13q, −14q, +15q, −16, −18, +20, +21q, +22q	8.27 years

relevant morphological, clinical, and molecular variables, 283-bMMC subgroups did not show significance in predicting recurrence, but a subset (64-MMP) proved to be a meningioma methylation predictor (22). Both studies provide innovative classifications of risk-related meningiomas, suggesting a proof-of-concept that DNA methylation profiles act as an important prognostic marker in meningiomas (33, 49).

The New Methylation Classes

Sahm et al. established a totally new classification on meningiomas, characteristics of which included DNA copy number analysis, mutational profiling, and RNA sequencing. After studying 497 meningiomas and 309 samples of other extra-axial skull tumors, they found that using DNA methylation data clearly distinguishes meningiomas from other tumors, indicating the specificity of DNA methylation for meningiomas. Based on the molecular spectrum of meningiomas, 497 meningiomas were divided into two major groups:group A and B. Tumors in group A followed a mainly benign clinical course, while tumors in group B showed an intermediate to malignant clinical course. However, whether these two groups develop from distinct cells of origin needs to be confirmed.

In additional studies, researchers found four subgroups in group A and two subgroups in group B. The six methylation classes were designated as MC ben-1, MC ben-2, MC ben-3, MC int-A, MC int-B, and MC mal (**Table 4**). MC ben-1, MC ben-2, and MC ben-3 were benign tumors. MC int-A and MC int-B were intermediate tumors and had higher rates of progression and recurrence. MC mal was distinguished as a malignant tumor with a high possibility of progression and recurrence. Generally, the DNA-based classification is different from the WHO grade. However, researchers noted an enrichment of grade I tumors in MC ben-1, MC ben-2, and MC ben-3. When methylation subgroups were scattered among all WHO grades, the new classification covered more molecular features, such as DNA methylation profile. The new classification was likely to predict meningioma prognosis better, and its predicted Kaplan-Meier survival curves were more accurate than those predicted by the WHO grade (6). For example, in the 497 samples collected by Sahm et al., most WHO grade II tumors belonged to the MC int-A and MC int-B classes, while a portion of them belonged to the MC ben-1 methylation class. The survival time in the MC ben-1 methylation class was lower compared to the MC int-A and MC int-B classes. Analogously, most of the WHO grade III tumors belonged to the MC mal methylation class. However, a subset of WHO grade III tumors were also classified as MC int-B. For this tumor type, data demonstrated a significant difference between the PFS of two methylation classes, with MC mal tumors showing a worse PFS than MC int-B tumors. This conclusion was in accordance with that of Sievers et al., who used 28 chordoid meningiomas to illustrate that DNA methylation classification had higher accuracy in outcome prediction than the WHO grading (50).

Compared to the WHO grade, applying methylation profiling for meningioma classification may have a higher value as it helps identify progressive tumors among low-grade meningiomas and stable tumors among high-grade meningiomas. It signifies a potential capability to reduce undertreatment or overtreatment. For instance, a patient with a WHO grade I meningioma may be treated by clinicians as a patient with benign tumors due to histological identification, but there is still a small chance of recurrence. This means the traditional WHO grading cannot distinguish the potential malicious tumors from stable tumors within the same grade. Therefore, malignant tumors that are considered as benign may be underrated (6). In conclusion, the new methylation classification can help clinicians choose optimal treatment regimens (including chemotherapy, radiotherapy, or molecular targeted therapy) for patients with the same grade and different methylation profiles.

Besides meningiomas, methylation classification has been proven to be more relevant than histological grading in other solid tumors, such as gliomas (1, 51), thus revealing the importance of methylation profiling in tumor classification. Although the new parameters for predicting prognosis exhibited

TABLE 4 | The methylation-based classification (2017) and associations with WHO grade.

Epigenetic groups	Methylation class	Subgroups	WHO grade
Group A	Benign	MC ben-1	Fibroblastic, Transitional, Atypical
		MC ben-2	Secretory, Transitional, Meningothelial
		MC ben-3	Angiomatous, Transitional, Atypical
	Intermediate	MC int-A	Fibroblastic, Transitional, Atypical
Group B		MC int-B	Atypical, Anaplastic
	Malignant	MC mal	Anaplastic

advantages over other methods, it still has some limitations. First, the collected 497 meningiomas were retrospectively analyzed, making the results not so convincing. It is necessary to conduct a prospective study to put this new classification into practice and track the results, as well as learn the feasibility of the new classification. Second, insufficient clinical data and technical limitations have made the result not very reliable. In the study, only 228 samples' clinical data were obtained, and only 303 samples have been sequenced to study the relationship between genetic mutations and methylation classes. Third, as this study does not include new genes discovered in recent years, such as *PPM1D* and *POLR2A*, tumors exhibiting these features were not classified into any subgroups.

Overall, the new classification system brings a new way to stratify, classify, and treat meningiomas. Although it is better than the previous grading system, more prospective studies that incorporate new genes are needed to improve its use clinically.

METHYLATION CLASS AND HISTOLOGICAL SUBTYPES

Methylation classification based on the methylation profiles shows an improved predictive ability compared to the WHO grade and Simpson system. When discussing the relationship between these groups, the two independent systems overlap in some features. The newest studies have identified a lot of genes that could be used as biomarkers for meningiomas, and some of them may influence the progression via DNA methylation. Others may have distinctive mechanisms. The genes that are methylated in meningiomas have different functions on tumor progression. However, some of them, such as *MGMT*, need more research in order to prove their function on meningiomas.

The Relationship Between Methylation Class and Histological Subtypes

There are two different patterns that characterize methylation class and histological subtypes (**Table 4**). First, methylation class is significantly associated with a subset of histological subtypes. MC int-A and MC int-B classes are mainly composed of atypical meningiomas (WHO grade II), while the remaining (23%) of atypical meningiomas belong to the benign class MC ben-1. Additionally, 76% of MC mal were anaplastic meningiomas (WHO grade III), but anaplastic meningiomas also exist in both MC int-B (47%) and MC int-A (12%). Second, methylation class samples widely exist among all corresponding variants, including the rhabdoid and papillary meningiomas (MC ben-3, MC int-B, and MC int-A), transitional meningiomas (MC int-A and MC int-B), fibroblastic meningiomas (MC ben-1), and meningothelial meningiomas (MC ben-2) (6). High-grade meningioma histology more frequently appears in higher methylation classes (MC int-A is higher than MC ben-2). The aforementioned two patterns show that the relationship between methylation classes and histological types is complex. Even when the features of genetic mutation in each methylation subgroups were studied, results were only able to roughly indicate which subgroup harbored which kind of aberrant genes or cytogenetics. Although Paramasivam et al. have studied mutation patterns in epigenetic subgroups (52), we cannot infer the inner connections due to the limited amount of studies. Hence, future studies should analyze large-samples with integrated data in each methylation class.

Nevertheless, this issue has remained controversial due to a study that reported that DNA methylation of a gene is not strongly correlated to gene expression during the malignant transformation of meningiomas (49). Nowadays, the hypothesis is accepted that both mechanisms can occur independently or co-exist in one sample, while various meningiomas harbor different situations. For example, WHO Grade I and II meningiomas present relatively more aberrantly methylated loci than genetically altered loci (53). As previously shown, aberrant promoter methylation of CpG islands via IL-1b can silence the *NF2* gene, which has pivotal roles in tumorigenesis and the development of WHO grade I meningiomas (35, 54). However, a recent study found the *NF2* promoter methylation in only one of 49 tumors examined, and only one of 40 examined CpG sites harbors the feature of this tumor, suggesting that *NF2* methylation did not play a major role in meningioma development (55). Similar to the *MEG3* gene, biallelic loss and promoter methylation has been observed in high-grade meningiomas, but only allelic loss correlated with gene silencing (53). Therefore, it is difficult to deny that both mechanisms are involved in this process, though it is necessary to know which one plays a more essential role. Some alterations of genes are affected by DNA methylation, while others are affected by different mechanisms.

Other Aberrantly Methylated Genes

It is well known that epigenetic changes can affect both gene expression and the function of a protein product (56). To date, several studies have reported that the methylation of gene promoter CpG dinucleotides (CpG islands) have been connected to the WHO grades and prognosis in meningiomas. They have shown that the inactivation of transcription occurs when the promoter region of a tumor-related gene has been methylated, leading to the silencing of gene expression (53, 57, 58). Other studies have reported that global methylation might have an influence on tumor recurrence (22, 49). Generally, alterations of DNA methylation in meningiomas have two mechanisms: hypermethylation and hypomethylation. Hypomethylation, however, is much less common compared with hypermethylation (53). Each type of methylation has its own target genes that cause a change in meningioma aggression. Sometimes, these two mechanisms may co-exist in one sample. Therefore, additional studies are needed to figure out which mechanism is more important, even though both mechanisms have a function on gene mutation. In addition, some studies have shown that non-CpG island methylation plays an important function in gene expression (59, 60). However, further studies are warranted to establish the mechanism and function of non-CpG island methylation.

The Possibility of Using These Genes as Predictors of Prognosis

Given results from previous studies, a large number of genes have been found to have aberrant methylation, some of which have influenced gene expression, resulting in tumorigenesis. Promoter methylation is the most common event in meningiomas and several genes are related to this pattern. Hence, in this section, we divide mechanisms into two groups (hypomethylation and hypermethylation) for further discussion (**Table 5**).

Hypomethylation

Global methylation

To the best of our knowledge, global methylation has not been widely studied in meningiomas, and only a few groups have reported it (39, 49, 61). Among them, Gao et al. were the first to analyze whole-genome DNA methylation across three subtypes of meningiomas. After assessing DNA methylation in 19 primary brain tumor samples (10 benign, five atypical, and four malignant meningiomas), they found increased global DNA hypomethylation from grade I through III meningiomas, which was in line with gene expression results. These results were similar to Vengoechea et al. The latter concluded that high-grade meningioma harbored more global hypomethylation (49, 61, 62). Although global DNA hypomethylation can distinguish malignant meningiomas from atypical and benign ones, it cannot separate atypical and benign tumors. Thus, it may potentially serve as diagnostic biomarkers for only malignant tumors.

Aggression: urokinase plasminogen activator (uPA) and PAI-1

The uPA system plays an important role *in vivo*, such as in wound healing, embryogenesis and tumor progression, and metastasis (63). The expression of uPA has been linked to methylation of the uPA promoter in breast and prostate cancers (64, 65). PAI-1 is an inhibitor of uPA, and uPA/PAI-1 has been reported to contribute to glioma invasion and malignant progression (66, 67). Kandenwein et al. studied 65 tissue samples of meningiomas from 58 patients and found that the relationship between the expression of uPA and PAI-1 reached significance. Both protein expressions were significantly correlated with WHO grade. However, PAI-1 showed a highly significant correlation with prognosis, when setting 6 ng/ml as a cut-off of PAI-1 levels. The samples below this level were not recurrent in this study, demonstrating PAI-1 as a possible prognostic marker for meningiomas. Nevertheless, there was no correlation between the clinicopathological data and uPA promoter methylation (43). In fact, on the contrary, Arai et al. identified that uPA expression was inversely correlated with uPA promoter methylation levels (68).

According to results from some studies, the increased expression of uPA proteins has been shown to have a significant negative correlation with promoter methylation and positively correlated with WHO grade, malignant invasion, and recurrence (43, 69). Some studies even show a radiation-induced overexpression of uPA in meningioma cells, suggesting an additional level of regulation (70, 71). Velpula et al. (72) and Goetz et al. (73) pointed out that the expression of uPA has been related to radiation-induced hypomethylation. Therefore, patients with aberrant uPA gene methylation should carefully consider radiotherapy.

TABLE 5 | Aberrant genes in meningiomas.

Gene	Altered DNA methylation	Role
uPA	Hypomethylation	Aggression
IGF2BP1, PDCD1	Hypermethylation	Increase malignant potential
HOXA7/HOXA9/HOXA10	Co-methylation	Progression and aggression
P73, RASSF1A, MAL2	Hypermethylation	Malignant transformation
p53, p14ARF, MEG3	Hypermethylation	Progression
CDKN2A, NDRG2, TIMP3	Hypermethylation	Progression and recurrence
THBS1	Hypermethylation	Angiogenesis
MGMT, WNK2	Hypermethylation	Unclear

Hypermethylation

DNA hypermethylation means a specific site, that is unmethylated under normal conditions, has become methylated. And it always occurs in promoter CpGs islands. In meningiomas, several genes have an association with this epigenetic mechanism and show various influences on its progression and recurrence.

Increased malignant potential: IGF2 mRNA binding protein 1 (IGF2BP1), programmed cell death 1 (PDCD1/PD-1), NDRG2 and TIMP3

IGF2BP1, which belongs to the VICKZ family, is an RNA-binding protein that is implicated in tumorigenesis by influencing the translocation and stability of mRNA in some cancers (74). PDCD1 is a negative regulator of immune responses and likely plays an important role in the progression of many diseases (75), such as rheumatoid arthritis (76). Vengoechea et al. analyzed 49 samples from three grades of meningiomas and identified nine genes that exhibited the largest absolute difference in methylation intensity. Among them, the expression of IGF2BP1 and PDCD1 proteins were sharply decreased, indicating that both these genes were associated with the malignant potential of the tumor. These results suggest the potential ability of CDKN2A as a recurrence predictor. However, Aydemir et al. did not find any statistically significant relationship between hypermethylation of the *CDKN2A* gene and histopathologic subtype, WHO grade, and recurrence (77). Therefore, studies encompassing a larger series still need to evaluate whether or not CDKN2A alterations can be used as biomarkers of recurrence in meningioma.

Regarding *NDRG2*, previous research has indicated potential associations between this gene and the malignant progression of tumors. Several studies have documented that the loss of NDRG2 expression is significantly associated with hypermethylation of the NDRG2 promoter (78–82). Lusis et al. pointed out that hypermethylation of the NDRG2 promoter is described in a subset of lower-grade meningiomas, including clinically aggressive atypical meningiomas (78). Das et al. found that NDRG2 was marginally expressed or even undetectable in anaplastic meningiomas (83). Skiriute et al. demonstrated that the expression of the *NDRG2* gene was significantly reduced in primary and recurrent atypical/WHO grade II compared

with primary benign/WHO grade I meningiomas (47). However, Majchrzak-Celińska et al. questioned the reliability of NDRG2 as a diagnostic biomarker due to the fact that its methylation levels were only slightly elevated in comparison to the common brain tissue (84). Overall, these studies illustrate the heterogeneity of *NDRG2* methylation, and further studies are needed to determine the function of *NDRG2*.

TIMP3 is located on 22q12.3 and codes for a protein that can specifically inhibit matrix metalloproteinases *(MMPs)* via covalent binding to the active site of the enzymes and reduces the invasiveness of tumor cells (85, 86). *MMPs* contain several classes of proteases and the expression of *MMPs* correlates with tumor stage, increased invasion, and metastasis (87). The allelic losses on 22q12 are associated with *TIMP3* hypermethylation and transcriptional downregulation. The promoter hypermethylation of *TIMP3* was associated with a more aggressive and higher-grade meningioma phenotype and poor prognosis (88, 89). There is a growing body of evidence indicating that *TIMP3* methylation could be an epigenetic marker of meningioma progression. Pham et al. analyzed 50 meningiomas (27 Grade I patients, 11 Grade II patients, and 12 Grade III patients) and found that hypermethylation of *TIMP3* varied between anaplastic (67%), atypical (22%), and benign (17%) meningiomas (90). Bello et al. reported that Grade I tumors had less aberrant methylation than Grade II or III meningiomas (33). In contrast, Liu et al. investigated the same chromosomal region but did not find any hypermethylation of *TIMP3* in meningiomas (35). Though there was some evidence to indicate that the methylation of *TIMP3* gene is associated with a shorter time to recurrence, Linsler et al. pointed out that there was no correlation of *TIMP3* hypermethylation with tumor recurrence or WHO grade (88). Due to the non-uniform approach needed to detect DNA methylation, several studies have observed different results and further research needs to be conducted in order to establish a standard definition for methylation to solve the contradictions in the *TIMP3* gene.

Angiogenesis: the thrombospondin 1 (THBS1)

The *THBS1* gene is thought to inhibit angiogenesis by disrupting the motility of endothelial cells and inducing their apoptosis (91). Transcriptional silencing of THBS1 has been shown to be related to promoter hypermethylation (92, 93). One study reported that the silencing of this gene via hypermethylation can promote angiogenesis in tumor cells (94). However, this remains controversial. Bello et al. found that 54% of Grade III meningiomas and 30% of intracranial meningiomas demonstrated hypermethylation of the *THBS1* gene. However, they did not find any association between hypermethylation and WHO grade (33). Liu et al. did not find any *THBS1* gene hypermethylation (33), and the true role of the *THBS1* gene in meningiomas remains a mystery.

Unclear function: WNK lysine deficient protein kinase 2 (WNK2) and O6-methylguanine–DNA methyltransferase (MGMT)

Many genes have been found to be methylated in meningiomas, but whether they correlate with tumor progression remains a mystery. This is particularly true for two genes: *WNK2* and *MGMT*.

WNK2 is a member of the WNK subfamily of protein kinases (95, 96), which negatively regulates EGF-induced activation of the ERK/MAPK-pathway and the downstream cell cycle progression (97). In recent years, studies have shown that *WNK2* is a specific tumor-suppressor gene for brain tumors and its downregulation is significantly correlated with the presence of promoter methylation (98). Jun et al. analyzed 22 meningioma samples, suggesting that WNK2 was aberrantly methylated in a large proportion of grade II and III meningiomas. With further study, they found that dense aberrant methylation was associated with decreased WNK2 expression in these meningiomas and that aberrant DNA methylation existed in approximately 60 CpGs in the 3′ part of the island, with very little methylation in the 5′ region. Therefore, aberrant methylation of the 3′ region may silence WNK2 expression (99). As in infiltrative gliomas, WNK2 has been identified to be silenced by promoter methylation in most samples (100). These studies show WNK2 as a candidate predictor of meningiomas but also put forward that other mechanisms, such as signal path interference, might affect the expression of WNK2.

Research has shown that promoter hypermethylation of the *MGMT* gene can be a predictor in glioblastoma multiform (GBM) (101). Recently, several studies have reported hypermethylation of MGMT in meningiomas. Liu et al. reported 6% MGMT promoter hypermethylation in a group of 48 meningioma cases (35). Aydemir et al. (77) and Bello et al. (33) showed that MGMT was methylated in 11.1 and 16%, respectively, of their samples, though they did not find any significant correlation between methylation and tumor grade. However, Robles et al. had an entirely different outcome. They showed that none of the samples harbored MGMT promoter methylation (102), similar to Jabini et al. (103).

There are many studies that suggest opposite opinions, and the functions of these two genes in meningiomas still need to be uncovered. There need to be subsequent studies to figure out the relationship and mechanisms between these genes and meningiomas.

The Role of Methylation in Meningiomas

Studies have shown that molecular subsets of meningiomas could be identified by their epigenetics (22, 49), and epigenetics can uncover tumor progression. In this review, we discuss DNA methylation in meningiomas. From previous studies, we can conclude two major roles of methylation in meningiomas.

Prediction

The first role of methylation in meningiomas is the ability to predict tumor recurrence. Genes like *NDRG2* and *TIMP3* have been proven to be associated with recurrence (47, 88). Meningiomas with these methylated genes indicate a shorter time to recurrence. In order to prove the role of DNA methylation in meningiomas, Nassiri et al. used DNA methylation profiles of clinically annotated tumor samples among multiple institutions to develop a methylome model of 5-year recurrence-free survival (RFS). They also combined a methylome model with established

prognostic clinical factors to obtain a 5-year meningioma recurrence score through a nomogram. They found that adding the methylome predictor enhanced the discriminatory ability of the nomogram (4). Additionally, a scoring system established on a scale of 5–15 points that was comprised of three stages depending on the methylation values of the five chosen genes [*HOXA6*, *HOXA9*, *PENK*, *UPK3A,* and *IGF2BP1* (39)] also verified the value of methylation in meningiomas. The samples in their study that had scored lower than 9 points demonstrated significant differences in the PFS curve compared to samples that scored more than nine points (22). Due to the non-uniform cognition of aberrantly methylated genes, studies up to now have been independent of each other, but both types of studies have uncovered the potential of DNA methylation to predict the recurrence of meningiomas.

Risk Stratification

The secondary role of DNA methylation is to stratify meningiomas. It is hard to classify meningiomas into three groups like benign, middle, and malignant using only histological grading. The new methylation-based classification has demonstrated the ability to divide tumors into different risk groups (6). Genes like *MAL2* and *RASSF1A* have been connected to malignant transformation (34, 49, 84) and the benign tumors harboring these genes have the potential ability to become malignant. Therefore, these tumors should be taken seriously. However, using methylation profiling alone to assess the tumor was not precise because other factors should be taken into consideration as well, such as Ki-67 and clinical characters. Moreover, with a deepening of research, the importance of methylation to stratify high-risk patients gradually emerged. For example, the presence of three or more hypermethylated TSGs has been shown to be a useful biomarker for risk stratification in meningiomas (104). Hence, utilizing methylation profiling to identify high-risk patients is possible, but more integrated and supportive studies are needed.

HYPOTHESIS: METHYLATION PROFILES COULD BE USED IN ADDITION TO THE WHO GRADE AND SIMPSON GRADE TO IDENTIFY TUMOR RECURRENCE MORE ACCURATELY?

Nowadays, clinicians often judge the characteristics of meningiomas by histological grade alone. While most patients choose to undergo a pathological examination, some patients may have gene detection after the operation. According to NCCN clinical guidelines, subgroups of patients should receive radiotherapy after the operation, such as those with a WHO grade III tumor and those who have undergone partial excision of a WHO grade II tumor. Some patients who detect the abnormal genes could accept molecular targeting treatment, while other therapies, such as chemotherapy and hormonotherapy, depend on the situation. The follow-up plan depends on the WHO grade, Simpson grade, and personal situations, but all these criteria are very general and sometimes the decision depends largely on the clinicians' experience. Although the new methylation-based classification may take a long time to be applied in regular clinical practice, it may improve treatment decisions as the methylation-based classification is more accurate than WHO grading (6). Our review has highlighted certain genes that are associated with the progression and prognosis of meningiomas through DNA methylation. Gene expression is controlled via hypermethylation or hypomethylation which, in turn, affects tumor evolution. Based on previous studies, methylation signatures have been proven to be a predictor of meningioma prognosis and the use of methylation signatures to stratify meningiomas has yielded better results than using WHO grade or Simpson grade (6). Hence, methylation profiles could be used in addition to WHO grade and Simpson grade to identify tumor recurrence more accurately.

If we combine the aforementioned scoring system with the WHO and Simpson systems, using *HOXA6*, *HOXA9*, *PENK*, *UPK3A*, and *IGF2BP1* genes to distinguish patients with a high probability for recurrence, these patients may receive more aggressive treatment and more frequent follow-up plans, and some recurrence can be detected earlier than before. However, this scoring system has certain drawbacks in that the chosen five genes are not typical for all grades of tumors. It is also hard to detect the global gene methylation profile for every patient due to economic capacity and technical conditions. Currently, there are several techniques for global DNA methylation profiling, such as WGBS and RRBS. For now, WGBS is the gold standard method to investigate every CpG site in the genome (105). However, an analysis showed more than 70% of sequenced reads did not give useful information (106). For one sample, WGBS needs two lanes of sequencing using the Illumina HiSeq system to obtain a tenfold average coverage of CpG sites, which costs ∼US$6000 (107). Due to the substantial cost and large volume of raw data, applying WGBS in clinical practice is not possible in the short term. Other methods such as RRBS are cost-effective, but the region is limited to the enzyme recognition sites (108). Though new technologies are constantly being invented, these are not the best methods for clinical application. Therefore, it is necessary to establish a reliable system that contains the chosen aberrantly methylated genes that are associated with the invasiveness of meningiomas. It is important to divide these genes into several groups according to their function on the progression of meningiomas; benign tumors which harbor *TP73*/*RASSF1A* hypermethylation, for example, are more likely to turn malignant while the hypermethylation of *TIMP3* marks a shorter time to recurrence. We hypothesize that putting the same functional genes together and choosing landmark genes for detection can help create a special report for each patient with regards to tumor aggressiveness and risk of recurrence. This information can help clinicians set an optimal therapeutic regimen and follow-up plan for each patient (**Figure 1**).

With further studies, an increasing number of genes are found to be methylated during the meningioma progression. Additionally, controversial genes such as *THBS1* and *MGMT* can be added to this system to help clinicians judge the situation of each tumor. Though the correlation between methylated genes and histological subtypes has not yet been found, the relationship

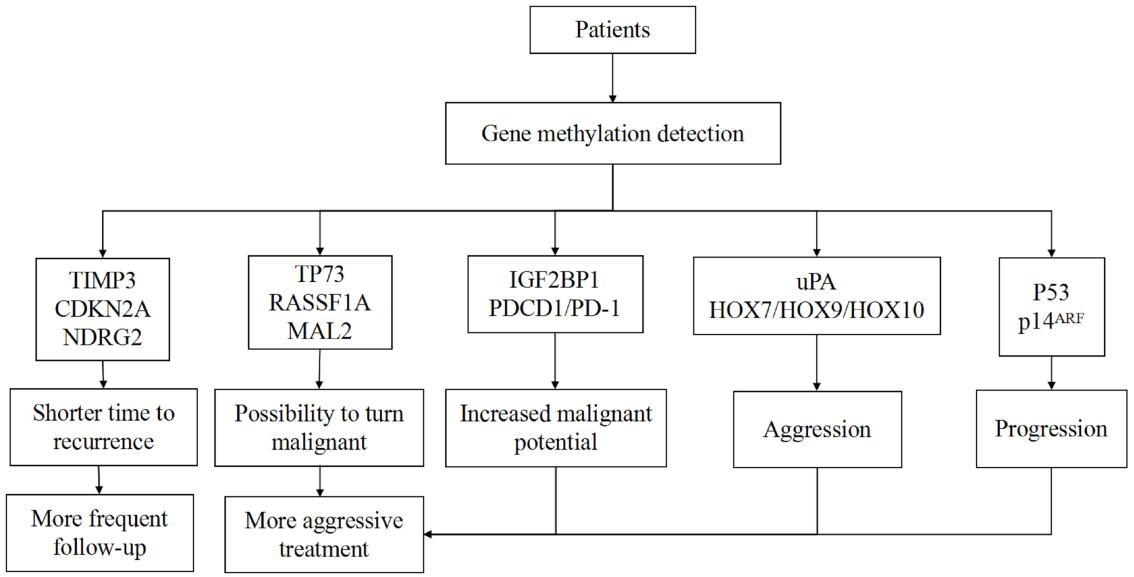


FIGURE 1 | Patient classification based on genes.

between the WHO grade and DNA methylation class has been explored in several studies (6). Other relationships, such as the relevance between specific histological subtype and methylation class, have been studied as well (50). Further studies should continue to focus on this hotspot. Therefore, the system can be improved to accurately correspond to each subtype and specific abnormal genes can be detected in limited conditions. It is more efficient for doctors to describe the features of tumors using methylation profiles, genetic mutations, or histological subtypes. As it takes a long time to establish criteria based on methylation, the emphasis now should be on forming a system that contains useful genes that can improve the existing grading. There needs to be a uniform standard to define methylation and a large number of samples of whole grade tumors. It may take a long time, but it can be established step-by-step.

CONCLUSION AND PERSPECTIVES

Several genes have come to be considered as involved in the progression of meningiomas through methylation. With the results from the detection of gene methylation, an increasing amount of new genes are connected to tumorigenesis. During this research, it has been shown that different genes have different functions. While some genes already have a clear role, other genes (i.e., TIMP3, THBS1, and MGMT) remain controversial and need more research. The incorporation of several genes has been studied successfully to predict survival times and recurrence risk in meningioma patients. A new classification system focused on DNA methylation is able to identify meningiomas more accurately. Though there are lots of grading systems, it seems they are independent of each other and it is difficult to integrate them or make a comprehensive standard for the identification of various meningiomas. Thus, there needs to be a revised system that can improve present grading. Based on conclusions from other studies, we believe that combining a new system that contains several remarkable methylated genes with current grade systems (WHO grade and Simpson grade) can help clinicians choose an individualized therapeutic regimen (like surgery, radiotherapy, or chemotherapy) and follow-up plan for each patient. We have reviewed several grading systems and a series of methylated genes in meningiomas and concluded the ability of methylation profiling to identify various meningiomas. This leads us to put forward a hypothesis that methylation profiling can serve as a supplement to clinical predictors and provide a more accurate prediction of recurrence risk.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AS, XW, and LC supervised the research, led the discussion, and wrote and revised the manuscript. All authors participated in analyzing and discussing the literature, commenting on, and read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Molecular Mechanism and Approach in Progression of Meningioma

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Meningioma is the most common tumor of the central nervous system, most of which is benign. Even after complete resection, a high rate of recurrence of meningioma is observed. From in-depth study of its pathogenesis, it has been found that a number of chromosomal variations and abnormal molecular signals are closely related to the occurrence and development of malignancy in meningioma, which may provide the theoretical basis and potential direction for accurate and targeted treatment. We have reviewed advances in chromosomal variations and molecular mechanisms involved in the progression of meningioma, and have highlighted the association with malignant biological behavior including cell proliferation, angiogenesis, increased invasiveness, and inhibition of apoptosis. In addition, the chemotherapy of meningioma is summarized and discussed.

Keywords: meningioma, mechanism, genetics, chromosomal abnormality, apoptosis, invasiveness, angiogenesis

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INTRODUCTION

The meninges consist of the dura mater, arachnoid and pia mater, which envelope the surface of the brain and spinal cord. A tumor produced in the meninges is known as a meningioma (1). According to the latest statistical report of the Central Brain Tumor Registry of the United States (CBTRUS), meningioma has become the tumor with the highest rate of incidence of the central nervous system, accounting for approximately 37.1% (2). Meningioma is common in elderly patients, the median age of diagnosis being 66 years of age. Females are approximately 2.2-fold more likely to develop meningioma than males, except in atypical and anaplastic meningioma, where males outnumber female patients (2). The World Health Organization (WHO) classifies meningioma into grade I benign meningioma (>80%), grade II atypical meningioma (15–20%), and grade III anaplastic meningioma (1.0–3.0%) (2, 3). Meningioma can be further divided into 15 subtypes according to histopathology (4). Among them, meningothelial, fibroblastic, and transitional meningioma are the most common subtypes of the WHO (5). By comparing the immunophenotypes of normal arachnoid and meningiomas, research data indicate that arachnoid cap cells are likely to be the precursor cells of meningioma (6). Finally, a study established that prostaglandin D2 synthase (PGDS) positive arachnoid cells are the origin cells of meningiomas (7). Surgical resection can cure 70–80% of meningioma. However, atypical and anaplastic meningioma often have high

recurrence rates, strong invasiveness and poor prognosis. Even after complete resection, the rate of recurrence of atypical and anaplastic meningioma is still as high as 50% and 80%, respectively (8). Furthermore, approximately 20% of meningioma with benign histology are likely to in fact be invasive and recurrent, which affects the treatment of the tumor (9). Previous studies have identified multiple molecular targets and genetic alterations that contribute to its progression, including those related to cell proliferation, increased invasiveness, angiogenesis, and inhibition of apoptosis. These molecular targets may be targeted in future to improve the therapeutic effect. Here, we summarize the molecular mechanisms that drive the biological behavior and relative medical treatment of meningioma.

CYTOGENETICS

The most common chromosomal abnormality in meningioma is in chromosome 22, observed in 40–70% of grade I meningioma. Beyond the loss of chromosome 22, few other chromosomal abnormalities have been observed in benign meningioma (10). In an analysis of chromosome 22 in 44 sporadic meningiomas, researchers found that in 43 cases, all or part of the chromosome had been deleted, the majority of deletions occurring in the neurofibromatosis type 2 (NF2) region, suggesting that the mutation on NF2 leads to the occurrence of meningioma (11). In addition, a number of studies have demonstrated that loss of gene function of NF2 contributes to develop schwannoma, ependymomas, and malignant mesothelioma (12–14). Mice lacking NF2 are prone to develop cancers such as osteosarcoma, lymphoma, lung adenocarcinoma, hepatocellular carcinoma (HCC), and fibrosarcoma (15). Research has suggested that NF2 promotes contact inhibition and tumor suppression by suppressing mitogenic signaling at the cellular cortex (16). Therefore, the inactivation of NF2 plays an important role in early oncogenic events. Atypical and anaplastic meningioma exhibit a greater number of chromosomal abnormalities than benign meningioma, but the frequency of the NF2 gene mutations is almost the same as in benign meningioma, indicating that NF2 may not be related to the progression of meningioma (17). Loss of chromosome 1 is detected more often in atypical and anaplastic meningioma, and is the second most common deletion site in meningioma (1). The rate of deletion of 1p is significantly correlated with grade of meningioma (grade I meningioma: 13–26%; grade II: 40–76%; and grade III: 70–100%). Loss of 1p is also associated with malignant progression of meningioma (18). In atypical meningioma, chromosomal loss of 1p, 6q, 10, 14q, and 18q, and gains at 1q, 9q, 12q, 15q, 17q, and 20q have been observed. On the basis of the mutations described above, losses are more frequent at 6q, 9p, 10, and 14q with amplification of 17q23 in anaplastic meningioma (3) (**Figure 1**). In terms of chromosomal mutation and incidence of relapse in meningioma, researchers have used fluorescence *in situ* hybridization (iFISH) analysis on 302 meningioma samples, finding that alterations in 1p, 1q, 7, 9, 10, 14, 18, and 22 chromosome were significantly related to the incidence of relapse (19). Chromosomal variations provide a genetic basis for the stepwise progression of meningioma, which greatly assists in the diagnosis of grade and prognosis. Recent studies have also shown that the location of meningiomas is related to mutational profile. Compared with other anatomic locations, NF2 mutations are more common in the lateral regions and posterior skull base meningiomas, while the most majority of non-NF2 meningiomas often locate in the anterior, medial, or skull base regions (1, 20). For example, meningiomas with Smoothened (SMO) mutation are more likely to localize to the medial anterior skull base, near the midline (20). Meningiomas with Krueppel-like-factor 4 (KLF4)/TNF receptor-associated factor 7 (TRAF7) mutation often locate in the medial skull base and v-akt murine thymoma viral oncogene homolog 1 (AKT1)/TRAF7 mutation in the anterior skull base (21).

GENETIC ALTERATIONS WITH CLINICAL PROGNOSIS

The genetic changes of meningioma is associated with the poor prognosis. A study have shown that activating mutations in the promoter of the telomerase reverse transcriptase (TERT) gene promote the aggressiveness of meningiomas and reduce the survival of patients (22). Patients with TERT promoter mutation had significantly shorter overall survival (53.8 vs 115.6 months; $P = 0.0006$). Another study also demonstrated that patients with TERT promoter mutation had a higher risk of recurrence and a shorter time to progression, regardless of WHO grade (23). In a study of 169 meningioma samples, Dystrophin-encoding and Muscular Dystrophy-associated gene (DMD) inactivation (by genomic deletion or loss of protein expression) was detected in 32% of patients with progressive meningiomas. Patients with DMD inactivation had significantly shorter overall survival than wild-type counterparts [5.1 years (95% CI 1.3–9.0) vs. median not reached (95% CI 2.9–not reached), $p = 0.006$] (24). Breast cancer (BRCA)1-associated protein-1 (BAP1) is a tumor suppressor gene encoding for a deubiquitylating enzyme. A study have demonstrated that BAP1-deficient meningiomas are more aggressive and have a poor prognosis (25).

MOLECULAR MECHANISMS OF CHANGE IN BIOLOGICAL BEHAVIOR

Abnormal Cell Growth and Proliferation

The growth and proliferation of tumor cells are closely related to cell cycle dysregulation. For example, abnormal expression of cyclin, cyclin dependent kinases or their inhibitors often leads to enhanced proliferation and differentiation of meningioma cells (26, 27). The cyclin-dependent kinase inhibitor 2A (CDKN2A) gene can encode a variety of cell cycle regulating proteins including p16 [inhibitor of CDK4 (INK4a)] and p14 [alternative reading frame (ARF)] that inhibit the growth of tumor cells. Of these, the former principally inhibits the activity of cyclin dependent kinase 4 (CDK4) and 6 (CDK6), while the latter inhibits the degradation of tumor suppressor protein p53 that

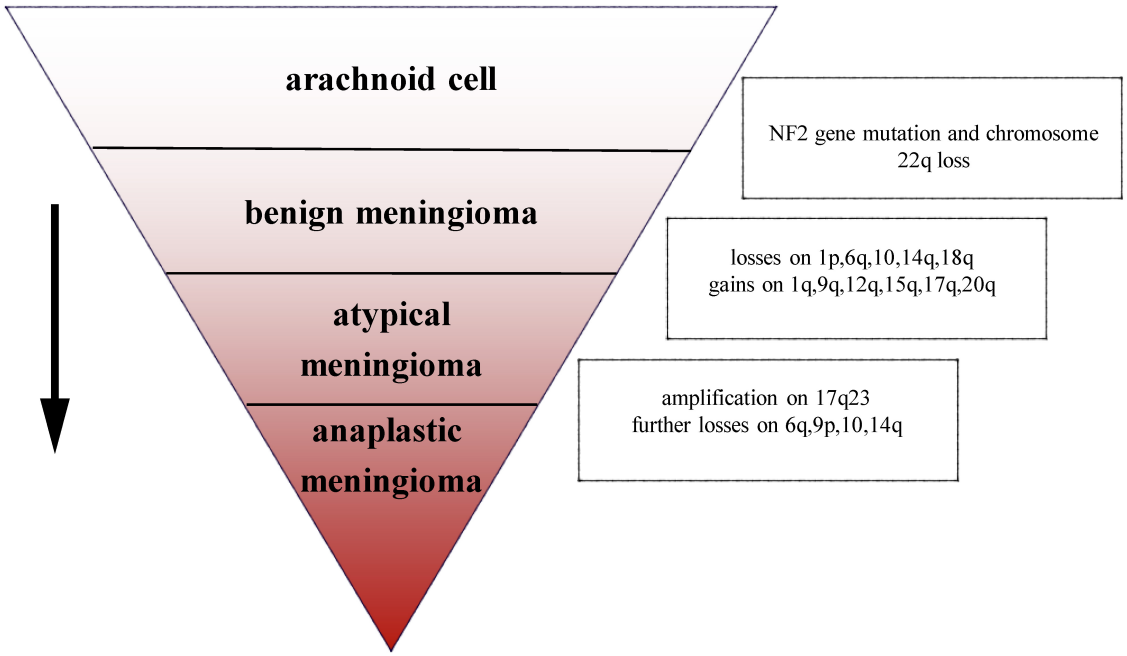


FIGURE 1 | Chromosomal abnormalities in the progression of meningioma.

controls G1/S phase transition (8, 26). One study that compared the gene coding sequences of recurrent and non-recurrent meningioma found that changes in the CDKN2A gene were only observed in recurrent meningioma (28). The deletion of the CDKN2A gene promoted the malignant progression of meningioma, indicating poor outcome (29). Cyclin D1 (CCND1) controls the transition of the cell cycle, principally regulating the G1-S phase, and playing an important role in the transcription of tumor genes and cell proliferation (30). It has been reported that cyclin D1 is overexpressed in meningioma, and positively correlated with the degree of malignancy and rate of recurrence in meningioma. Knockdown of cyclin D1 expression in the meningioma cell lines IOMM-Lee and CHl57 demonstrated inhibition of the growth and proliferation of the cells (27). Forkhead box protein M1 (FoxM1) is a pro-mitotic transcription factor, which plays a positive regulatory role in the G1/S and G2/M transition of the cell cycle, ensuring smooth progression of mitosis (31). A separate study showed that an increase in FoxM1 expression can be observed in higher-grade meningioma, promoting the expression of β-catenin and cyclin D1, finally leading to proliferation and colony formation in meningioma cells (32). Similarly, overexpression of FoxM1 was also found in recurrent meningioma (32). A single transcriptome analysis, including the analysis of 280 human meningioma samples, demonstrated that FoxM1 plays a critical role in the proliferation of meningioma, indicating poor clinical prognosis (33). Cell cycle related proteins topoisomerase IIα and mitosin control the condensation and separation of mitotic chromosomes (34). A retrospective study of 160 meningioma patients found that patients with high topoisomerase IIα and mitosin expression suffered a higher risk of recurrence (35). Rapamycin [mammalian target of rapamycin (mTOR)] is mainly regulated by the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) pathway, and is over-activated in both sporadic and hereditary brain tumors, related to cell growth, differentiation and tumorigenesis (36) (**Figure 2**). A study of human meningioma cell lines found that meningioma with over-expression of osteoglycin (OGN) exhibited higher cell proliferation, cell cycle activation and colony formation rate, activities closely associated with the PI3K/Akt/mTOR pathway (37). Inhibition of this pathway significantly suppressed abnormal cell proliferation and increased cell death. Yesilöz et al. analyzed 93 samples of skull base meningiomas, finding that over-activation of the mTOR signaling pathway was closely associated with the recurrence of meningioma (38). Another study demonstrated that the high expression of mTOR in atypical meningioma led to an increase in mitotic index, and meningioma which had high expression of mTOR exhibited worse prognosis (39).

Increased Cell Invasiveness

The adhesiveness of malignant cells is usually lower than that of normal cells. It was found that various cell adhesion molecules are expressed abnormally during the malignant invasion of meningioma. E-cadherin (encoded by CDH1 at 16q22.1) is a calcium-dependent adhesion molecule, mediating their interaction with epithelial cells (40). It relies on β-catenin to play a role in cell adhesion, which is considered an indirect regulator of the Wnt signaling pathway (10). E-cadherin and β-catenin comprise the E-cadherin/catenin complex that regulates cell adhesion and maintains cell polarity and stability (40). A low expression or absence of E-cadherin leads to the

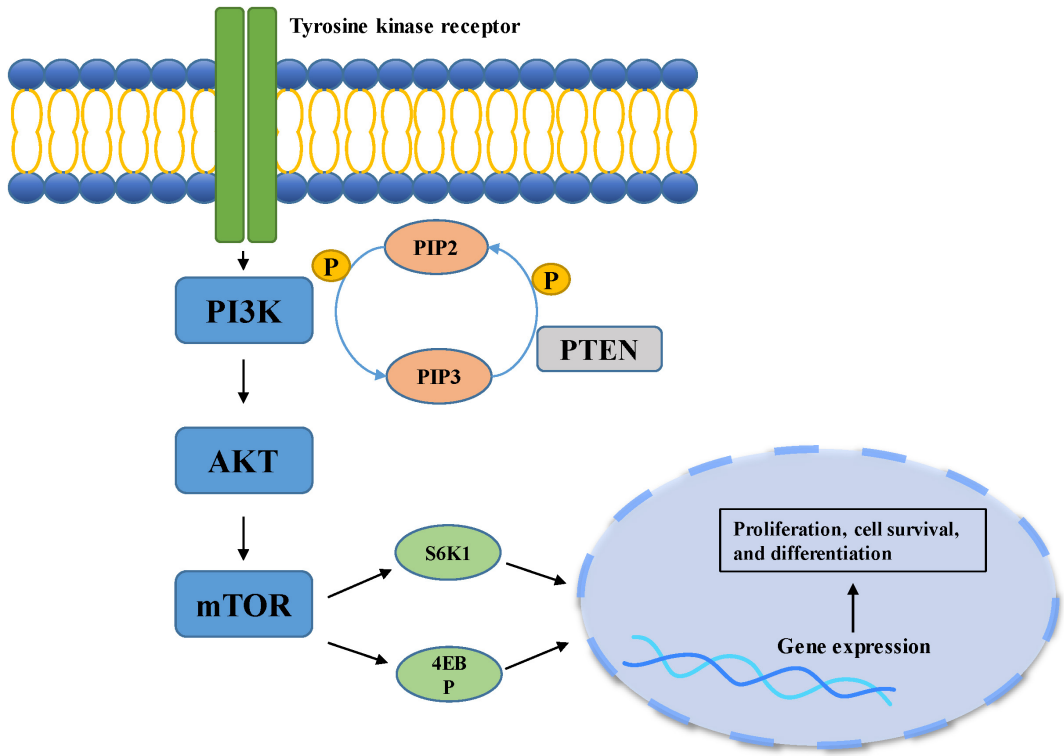


FIGURE 2 | PI3K/Akt pathway is involved in cell growth, differentiation, and tumorigenesis. When the ligand binds to the membrane receptor, the receptor activates PI3K, which then catalyzes the formation of PI3P from PIP2 on the inner surface of the membrane. As the second messenger, PI3P further activated Akt. Akt can activate the downstream mTOR pathway, which can phosphorylate and activate S6K1 and 4EBP, and finally participate in gene expression.

reduced formation of the complex, contributing to a decrease in adhesion between epithelial cells, the loss of intercellular connections, in addition to the weakening of contact inhibition, eventually leading to the uncontrolled growth of tumor cells and invasion of surrounding tissues (41, 42). Immunostaining of E-cadherin in 60 meningioma samples demonstrated that the expression of E-cadherin was down-regulated in 73% of meningioma. Moreover, E-cadherin has a more apparent down-regulatory effect in grade II and III meningiomas (43). Other studies of E-cadherin in meningioma have drawn similar conclusions. One study demonstrated negative expression of E-cadherin in all atypical meningioma, concluding that the increased invasiveness of meningioma is partly due to the loss of E-cadherin (44). Another study reported a positive correlation between the low expression of E-cadherin and the invasiveness of meningioma (45). Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases involved in the degradation of the extracellular matrix and tissue reconstruction, found to be closely associated with malignant invasion and distant metastasis of tumor cells (46). A number of reports have suggested that MMP-9 can promote the occurrence and development of tumors (47–50). Previous studies have shown that the expression of MMP-9 in meningioma is significantly correlated with the degree of malignancy and invasiveness. In the malignant meningioma cell lines IOMM-Lee and CH157-MN, MMP-9 has been shown to be significantly up-regulated with increased expression of the lncRNA LINC00460, leading to the progression of meningioma (51). The expression of MMP-9 in different grades of meningiomas has also been studied (52). Results of immunohistochemical analysis indicated that more MMP-9 was expressed in grade II and III meningiomas. Another study showed increased expression of MMP-9 in meningioma cells following irradiation (53). The authors confirmed increased invasiveness of the cells through spheroid migration and Matrigel invasion assays. The ability of cells to invade was reversed by the down-regulation of MMP-9. Petermann et al. found that loss of density-enhanced phosphatase-1 (DEP-1; a transmembrane protein-tyrosine phosphatase) reduced the adhesion of cell matrix, and enhanced the migration and invasive growth of meningioma cells (54). In the following experiments, Petermann et al. studied the relationship between DEP-1 and the invasiveness of meningioma cells (55). They found increased MMP-9 expression in DEP-1-depleted meningioma cells using zymography, suggesting that up-regulation of MMP-9 may contribute to the aggressive growth of meningioma. A recent study also demonstrated that the deficiency of DEP-1 promotes the progression of meningioma (56). A separate study demonstrated that the expression levels of tissue inhibitor of metalloproteinases-1 (TIMP-1) in invasive meningioma is significantly lower than that in non-invasive meningioma, possibly related to the inhibition of MMP-9 activity by TIMP-1 (57). The expression of A-kinase anchor protein 12 (AKAP12)

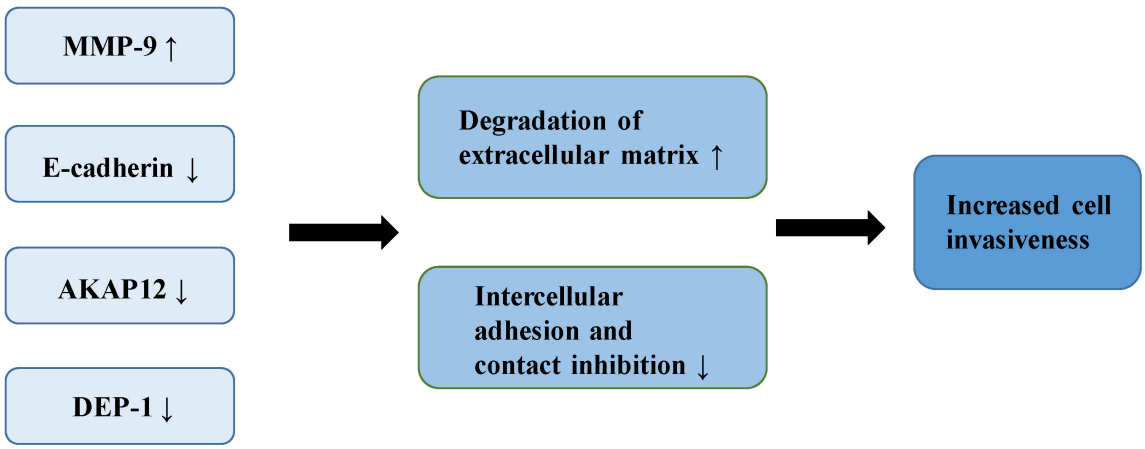


FIGURE 3 | The mechanism of increased invasiveness in meningioma.

increased in actively migrating cells, believed to play an important role in actin dynamics and actin filament-based migration (58). It is known that the expression of AKAP12 is inhibited in a number of human malignant tumors, such as melanoma, HCC, gastric cancer and BRCA (59–62). It has been found that knock-down of AKAP12 can promote the migration and invasion of meningioma cells, indicating that AKAP12 plays a possible role in inhibition of the progression of meningioma (63) (**Figure 3**).

Angiogenesis

Meningioma is a vascular-rich type of tumor, especially atypical and anaplastic meningioma, which are likely to relapse, suggesting that angiogenesis plays an important role in its malignant-type behavior (64). In a study of the molecular mechanism of tumor angiogenesis, Bergers proposed the theory of an "angiogenic switch," that is, the dynamic balance of angiogenic and antiangiogenic factors which becomes broken, allowing the interaction of these factors to affect the biological behavior of meningioma, such as angiogenesis and invasion (65). Vascular endothelial growth factor (VEGF) is considered among the most important angiogenic factors, involved in multiple physiological and pathological pathways of angiogenesis. One study established that VEGF and its receptor are up-regulated in the hypoxic tissues of recurrent meningioma, inducing new angiogenesis to alleviate the hypoxia. Microvessel density (MVD) is closely related to poor prognosis in meningioma (66). In a study of 40 meningioma samples, a group of researchers found positive correlation between VEGF expression and pathological grade of meningiomas by immunohistochemistry (67). Hypoxia inducible factor-1 alpha (HIF-1α), an upstream regulator of a variety of signaling pathways, regulates many tumor metabolic processes, such as glycolysis, apoptosis, angiogenesis, and promotion of tumor growth (68). HIF-1α activates VEGF transcription via the PI3K/Akt signaling pathway, up-regulating VEGF expression and promotes endothelial cell proliferation in meningioma (69). In addition, over-expression of HIF-1α can increase the stability of VEGF and its receptor, and promote neovascularization (70). One study found that silencing of HIF-3α (an HIF-1α inhibitor) suppresses angiogenesis and proliferation in meningioma (71). As the upstream regulatory gene of VEGF, signal transducer and activator of transcription factor 3 (Stat-3), it regulates the expression of VEGF through the JAK/STAT signaling pathway combined with the promoter of VEGF, promoting tumor angiogenesis (72). Kwon et al. confirmed that MMP-9 is expressed to a significant level in meningioma, closely related to neovascularization and tumor cell migration (73). A study of malignant meningioma cell lines found that the expression of MMP-9 was silenced by small interfering RNA (siRNA) which could inhibit the formation of a capillary network (74). MMP-9 creates the space and stimulation for angiogenesis by promoting the degradation of extracellular matrix and releasing the VEGF embedded in the extracellular matrix. MMP-9 also enhances the binding function of VEGF and its receptor, and up-regulates the bioavailability of VEGF (74). In 1999, a number of researchers found a type of microcirculatory duct without endothelial cells in melanoma, termed tumor vasculogenic mimicry (VM). Blood is able to flow normally in these acellular tubular structures (75). The VM phenomenon has also been reported in malignant meningioma (76) (**Figure 4**).

Inhibition of Apoptosis

Inhibition of apoptosis is closely associated with the occurrence, development and prognosis of tumors in meningioma. Several studies have found that the Wnt signaling pathway plays an important role in the development of meningioma, which is involved in apoptosis (77–79). The main pathway comprises three branches: the classical Wnt/β-catenin signal transduction pathway, the planar cell polarity (PCP) pathway and the Wnt-Ca^{2+} pathway (10). Members of the classical pathway include the extracellular Wnt factor, transmembrane receptor, β-catenin, glycogen synthase kinase-3β (GSK3β), adenomatous polyposis coli (APC), Axin, and casein kinase-1 (CK1) (10, 80). When the classical Wnt pathway is unactivated, GSK3β in the cytoplasm can phosphorylate β-catenin in the form of a complex with APC, Axin, and CK1 (81). By recognition of the phosphorylation site

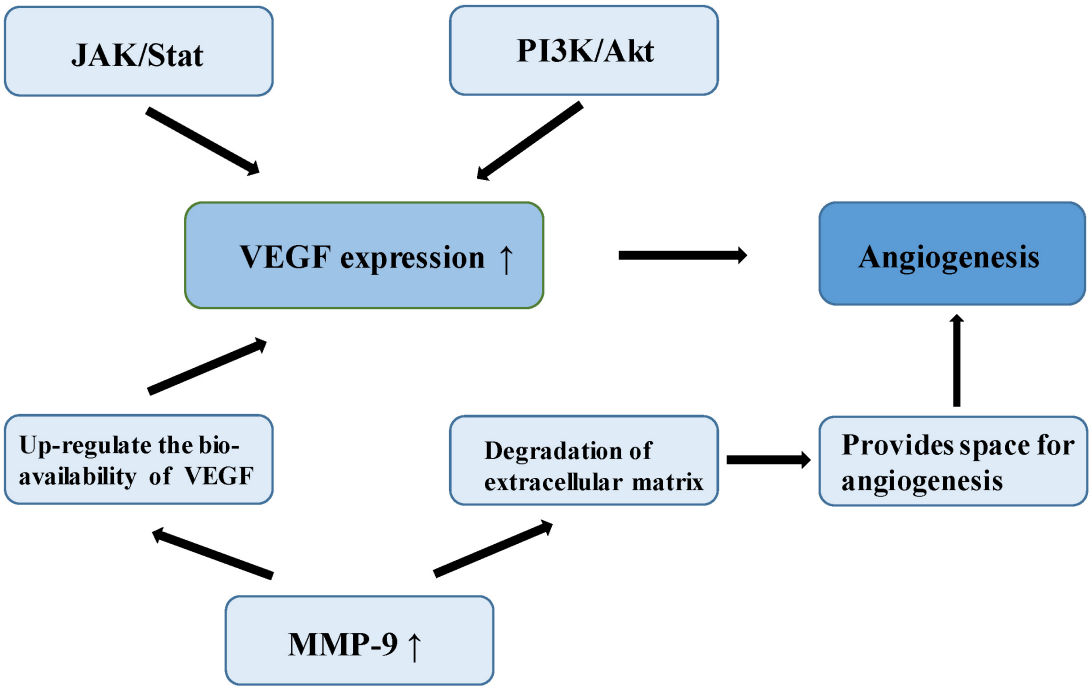


FIGURE 4 | The mechanism of angiogenesis in meningioma.

of β-catenin, β-TrCP can ubiquitinate β-catenin, then degrade it through a proteasome, and maintain a low level of β-catenin in cells (82). When Wnt signaling is activated, the Wnt protein binds with the extracellular domain of Frizzled (Fz). Through the synergistic effect of the low density lipoprotein receptor related protein (LRP 5/6), dishevelled protein (DVL) in the cytoplasm becomes translocated to the cellular membrane. DVL can phosphorylate GSK3β and lead to disintegration of the complex. In this case, β-catenin cannot be degraded, and a large number of free β-catenin aggregates in the cytoplasm and enters the nucleus (83). After β-catenin is combined with lymphoid enhancer factor (LEF)/T cell factor (TCF) to form a complex, suppression of LEF/TCF is reduced, and transcription of downstream target genes is specifically activated, including c-myc, cyclin D1, CD44, Bcl2, c-jun, etc. (84, 85) (**Figure 5**).

Multiple studies have shown that activation of the Wnt signaling pathway inhibits neural cell apoptosis (86–90). One study of meningioma found that lncRNA SNHG1 can inhibit apoptosis in BEN-1-1 and IOMM-Lee cells via the Wnt pathway, as found through the measurement of TUNEL-positive cells and caspase-3 activity (77). Knockdown of SNHG1 inhibited cell proliferation and promoted apoptosis. In another study, in which down-regulation of lncRNA LINC00702 inhibited Wnt signal activity in malignant meningioma, induction of apoptosis and decreased meningioma cell proliferation were observed (78). Unfortunately, there are few studies of the inhibition of apoptosis via the Wnt signaling pathway in meningioma. However, a large number of reports have been published concerning inhibition of apoptosis through the Wnt signaling pathway in glioma, neuroblastoma, spinal cord injury, and cerebral hemorrhage (85–91). Therefore, we can reasonably assume that the Wnt signaling pathway plays a role in inhibition of apoptosis in meningioma cells.

Many studies have explored the potential target of anti-apoptotic mechanisms in meningioma. One study assessed the expression of CD163 in 50 samples of meningioma (92). Researchers found that 48.5% and 71.4% of grade I and II meningioma, respectively, were positive for CD163. They also found human meningioma cell lines in which CD163 was overexpressed exhibited a decrease in apoptosis and hematopoietic cytokines, demonstrating that CD163 prevents apoptosis by production of granulocyte colony-stimulating factor (G-CSF). Other researchers compared the rate of apoptosis in meningioma between the FTS (a Ras inhibitor) group and control group by flow cytometric analysis, finding that apoptosis increased in the FTS group, indicating that Ras inhibition induced apoptosis (93). It has been reported that the expression of let-7d is down-regulated in meningioma, and that its overexpression induces apoptosis (94). In a recent study, researchers found a new oncogenic protein, N-myc downstream-regulated gene 4 (NDRG4), which is overexpressed in aggressive meningioma. After removal of NDRG4, the cells mostly died due to apoptosis (95).

MEDICAL TREATMENT FOR MENINGIOMA

For the majority of patients with benign meningioma, surgical resection combined with stereotactic radiotherapy is effective in

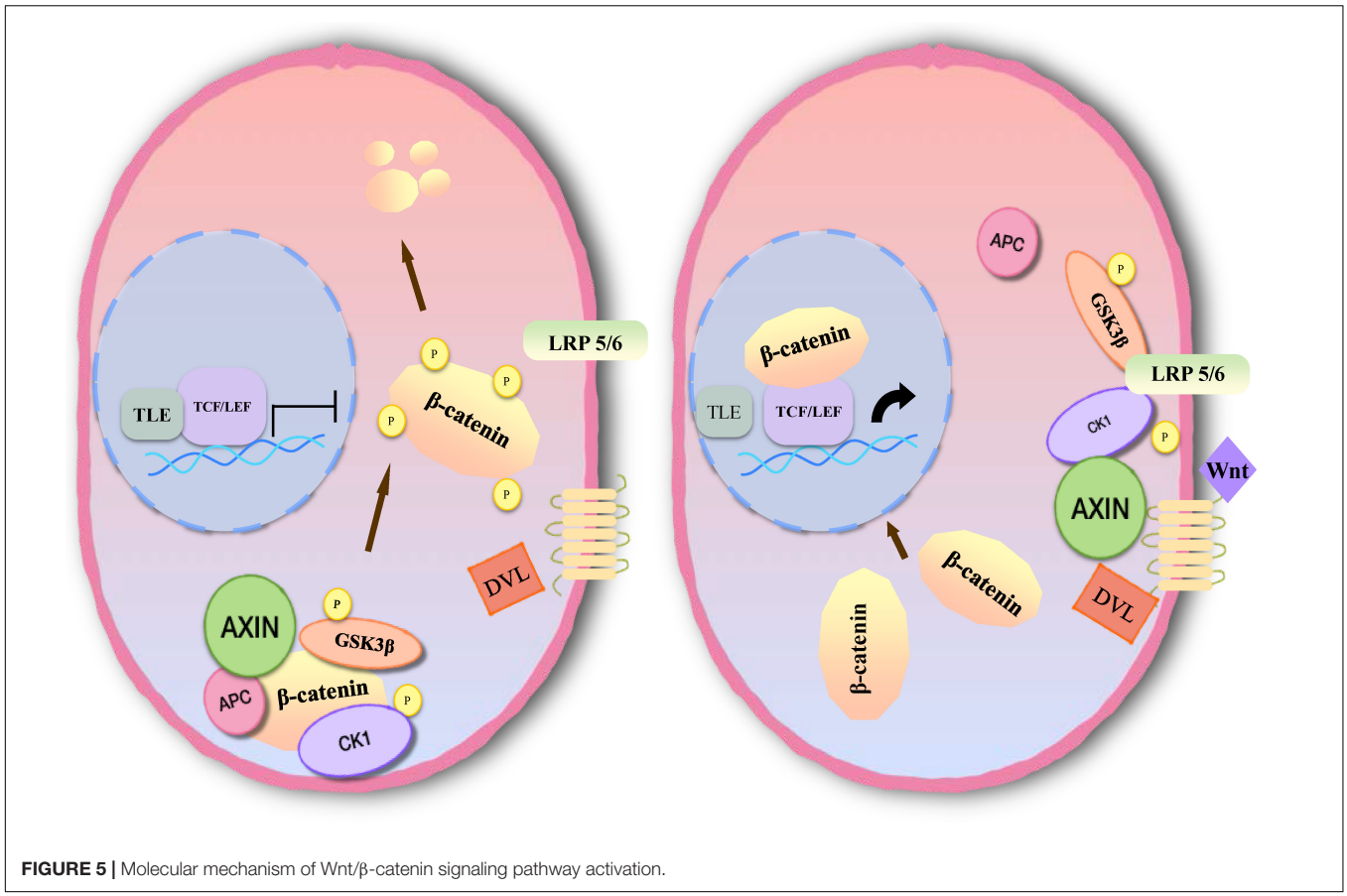


FIGURE 5 | Molecular mechanism of Wnt/β-catenin signaling pathway activation.

controlling the disease. However, no standardized treatment for recurrent or progressive meningioma has yet been published. Methods of treatment for meningioma include chemotherapy, molecular targeted therapy, immunotherapy, and hormone therapy, etc. (96).

Molecular Targeted Therapy

A large number of studies have confirmed that the PI3K/Akt/mTOR pathway is overactive in meningioma, which has a close association with cell growth, differentiation and tumorigenesis, suggesting that mTOR is a potential therapeutic target for meningioma. In an *in vitro* experiment, eight mice with subcutaneous IOMM-Lee xenografts were treated with mTOR inhibitors (97). Growth of the tumor cells was significantly inhibited. A recent phase II trial of progressive meningioma achieved satisfactory results (98). Twenty patients with meningioma (including 18 non-benign meningioma) were treated with everolimus (an mTOR inhibitor) and octreotide (a somatostatin agonist). The overall PFS-6 was 55%, and a 6- and 12-month overall survival was 90% and 75%, respectively. Tumor growth rate decreased significantly after 3 months in 78% patients, and median tumor growth rate decreased from an initial 16.6% to 0.02%. Octreotide inhibits the phosphorylation of the PI3K/Akt pathway and activates tyrosine phosphatase, which can inhibit the proliferation of tumor cells *in vitro* (99). One study demonstrated that octreotide promotes the antitumor effect of everolimus in aggressive meningioma (100). Because a meningioma is a vascular-rich tumor, reduction in angiogenesis may be beneficial for treatment. VEGF is an important angiogenic regulatory molecule, which positively correlates with the pathological grade of meningioma. The expression levels of VEGF in atypical and anaplastic meningioma have been found to be 2 and 10 times higher than in benign meningioma, respectively (101). A retrospective study of 15 patients of atypical or anaplastic meningioma treated with bevacizumab (a VEGF inhibitor) found that the progression-free survival (PFS) rate was 43.8% at 6 months, with a median PFS of 26 weeks (102). Similarly, another retrospective study in which 14 patients with progressive meningioma were enrolled (including 5 patients with grade I meningioma) found that PFS at 6 months following treatment with bevacizumab was 86% (103). A phase II clinical trial evaluated the response of patients with advanced meningioma to combination treatment consisting of bevacizumab and everolimus (104). A total of 17 patients were treated, 15 of whom exhibited stable disease progression, with a median disease stabilization period of 10 months. An ongoing phase II clinical trial (NCT02847559) aims to test the efficacy of the combination of electric field therapy and bevacizumab in patients with recurrent or progressive meningioma. A separate phase II clinical trial recruited 36 patients with high-grade meningioma who were treated with sunitinib [a VEGF and

platelet derived growth factor (PDGF) inhibitor], finding that median PFS was 1.4 and 6.4 months in VEGFR2 negative and positive patients, respectively (105). Despite the significant side effects (grade 3 or higher toxicity in 60% of patients), this clinical trial provides strong evidence for the potential targeting of VEGF in meningioma treatment.

Other Treatments

Chemotherapy is not effective for the treatment of malignant meningioma, and is usually only used when the initial treatment fails or the tumor relapses (106). Timozolomide and irinotecan, which are efficient therapies for specific intracranial tumors, had no apparent therapeutic effect on meningioma (107, 108). Hydroxyurea is the most well-studied chemotherapeutic drug in advanced meningioma, and this exhibits a certain therapeutic effect (109). Interferon-alpha is a biologic agent able to inhibit DNA synthesis. In the early experiments of meningioma *in vitro*, interferon-alpha exhibited inhibitory activity toward the growth of tumor cells (110). A phase 2 study evaluated the efficacy of interferon-alpha in the treatment of WHO grade I recurrent meningioma, and found that the PFS rate was 54% at 6 months, demonstrating pharmaceutical activity (111).

Immunotherapy is a potential treatment regimen for malignant meningioma. It has been found that the expression of programmed death-ligand receptor (PD-L1) is increased in meningioma, especially in anaplastic meningioma (112). Therefore, two phase 2 clinical trials of treatments for high-grade meningioma are in progress, using nivolumab (NCT02648997), and pembrolizumab (NCT03016091), respectively. With the discovery of progesterone receptor (PR) in meningioma cells, the use of mifepristone (an antagonist of progesterone) in the treatment of meningioma patients has gradually attracted the attention of researchers (113). It has been reported that in 3 cases of meningioma treated with mifepristone, 2 cases exhibited radiological regression and 1 case was stable (114). A phase II clinical study showed moderate clinical improvement following treatment with mifepristone in meningioma (115). However, the first and only randomized phase III trial for unresectable meningioma demonstrated the opposite result. There was no significant difference in PFS in the mifepristone and placebo groups 10 months (95% CI 7–13 months) vs. 11 months (95% CI 6–18 months) (116). The failure of these chemotherapy agents in clinical studies is probably due to the wide molecular heterogeneity of meningiomas.

Unfortunately, at present, there are no strong clinical data showing that medical therapy has a significant effect on meningiomas. Moreover, the sample size of most relevant clinical trials is less than 20 patients. If we consider WHO grade, we will find that these clinical trials also include grade I meningiomas that do not normally require such second-line treatment. These data may influence the real beneficial effects of medical therapy on meningiomas. A greater number of randomized clinical trials are required to provide evidence for the medical treatment of meningioma.

CONCLUSION

Meningioma is the most common tumor of the central nervous system, and most are considered benign. However, meningioma has a high recurrence rate, and the treatment of malignant meningioma is limited. Specially, the research on molecular mechanism and genetics treatment is insufficient compared with glioma. In this review, we focus on the molecular mechanism to elucidate the changes of biological behavior in the meningioma progression, including cell proliferation, increased invasiveness, angiogenesis, and inhibited apoptosis. Related signaling pathways and protein biomarkers may provide the direction and theoretical basis for the accurate targeted therapy of meningioma in the future.

AUTHOR CONTRIBUTIONS

ZS, YZ, ST, and YP drafted the manuscript. AS and JZ reviewed and modified the manuscript. LL, SY, and QW revised the manuscript. All authors agreed on the final version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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High Tumor Mitochondrial DNA Content Correlates With an Improved Patient's Outcome in WHO Grade III Meningioma

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Background: Studies have shown mitochondrial genome content (mtDNA content) varies in many malignancies. However, its distribution and prognostic values in high-grade meningioma remain largely unknown. In this retrospective study, we sought to assess a putative correlation between the mtDNA content and clinical characteristics.

Methods: Mitochondrial DNA was extracted from 87 World Health Organization grade III meningioma samples using a qPCR method. The distribution of mtDNA content in WHO grade III meningioma and its correlations with clinical variables were assessed. Furthermore, we prognostic values were also determined.

Results: Mean mtDNA content was 617.7 (range, 0.8–3000). There was no mtDNA distribution difference based on the histological subtypes ($P = 0.07$). Tumors with preoperative radiation were associated with lower mtDNA content ($P = 0.041$), whereas no correlations with other clinical variables were observed. A high mtDNA content was associated with significantly better PFS ($P = 0.044$) and OS ($P = 0.019$). However, in patients who received postoperative radiotherapy, low mtDNA content was associated with better PFS ($P = 0.028$), while no difference in OS was observed ($P = 0.272$). Low mtDNA content was also associated with better OS and PFS in subgroups of patients with ER negative status (PFS, $P = 0.002$; OS, $P = 0.002$).

Conclusions: Consistent with other tumors, high mtDNA content was associated with better outcome in WHO grade III meningioma in our cohort. However, for patients who received post-operative radiation therapy, low mtDNA content was associated with better PFS. These findings suggest that mtDNA content may further be explored as a potential biomarker for high-grade meningioma patients and for those who received postoperative radiation therapy.

Keywords: meningioma, MtDNA content, grade III meningioma, prognosis, radiation, malignant meningioma

INTRODUCTION

Tumors of the meninges constitute approximately a third of all primary intracranial neoplasms (1). Meningiomas are thought to arise from the arachnoid cap cells of the intracranial and spinal regions. According to the newest WHO 2016 Central Nervous System (CNS) tumor grading criterion, meningiomas are classified to three WHO grades and fifteen histological subtypes (2). Although the majority of meningiomas are benign and slowly growing tumors, there exist a subset of tumors manifesting aggressive and malignant biological behaviors, usually accompanied with higher tumor grade. The histological grading is strongly associated with tumor recurrence and clinical outcome, with five-year survival rates ranging only 28–61% from reported studies. Although grade III meningioma constitutes only a small proportion (1–2%) of all meningiomas, the malignancy and the clinical outcome remains dismal, with a median overall survival ranging from 2.6 to 5.8 years, compared with the other two lower grade meningioma (3–8). Grade III meningioma is defined by a mitotic index equal or higher than 20 mitoses per 10 high power fields and is further classified to three different subtypes based on the histological features, namely anaplastic, papillary, and rhabdoid (2). The anaplastic subtype is the most common in grade III meningioma, representing about 80% of all grade III meningiomas, while the papillary and rhabdoid constitute about 10%, respectively (9).

The mainstream treatment for grade III meningioma involves radical surgical resection followed by stereotactic radiotherapy or radiotherapy (10). Unfortunately, a considerable proportion of grade III meningioma patients still suffer from recurrence despite in time radiation therapy applied (11, 12). Great efforts have been made to investigate potential medical treatment and identify the predictors for radiation sensitivity. To the best of our knowledge, very few have been identified and none of them are applied for clinical use.

Although genetic and cellar studies have identified a number of genes, proteins, and molecules implicated in the tumor genesis, progression and malignant transformation of meningioma during the last several decades, most molecules studied are concerned with nuclear DNA alternations (13). The role of mitochondria in meningioma has not been well deciphered. Mitochondria contain their own genome, encode their own transitional machinery and 13 critical proteins for the oxidative phosphorylation system, which plays a vital role in reactive oxygen production, redox signaling, apoptosis, and many other biological processes (14). Each mitochondrion possesses multiple copies of a mitochondria genome. The functional component of mitochondrial DNA in a cell depends mainly on the content of mitochondrial genomes and the integrity of each mtDNA molecule. Broad ranges of mtDNA content in cells have been reported, from a few in embryonic to several thousands in cardiac myocytes (15). Studies have demonstrated that alterations of mtDNA content are involved in the development and progression of cancer, and the mtDNA content is often changed in tumors compared to non-neoplastic tissues (16–24). Although the content of mtDNA varies in a variety of tumors, it has never been reported in meningioma before, let alone in grade III meningioma. There is only one study investigating the mutational status of mtDNA and they concluded that mtDNA instabilities is relate to tumorogenesis of meningioma (25).

In this retrospective study, we investigated mtDNA content in a cohort of grade III meningioma patients and its association with clinical characteristics, treatment status and prognosis.

Abbreviations: mtDNA, mitochondrial genome content; GTR, gross total resection; STR, subtotal resection; WHO, World Health Organization; ER, estrogen receptor; PR, progesterone receptor; PFS, progression free survival; OS, overall survival.

PATIENTS AND METHODS

Studies and Patients

Samples from eighty-seven meningioma patients (44 males and 43 females) with WHO grade III meningioma who underwent surgical resection between 2003 and 2008 at the Neurosurgical Department of Huashan Hospital, Fudan University, were included in the current analysis (**Table 1**). Based on their histology, the meningiomas were assigned to one of three WHO groups: 63 anaplastic, 12 papillary, and 12 rhabdoid meningiomas. Among those, 59 (67.8%) were primary tumors and 28 (32.2%) were recurrent. The histopathological results were independently re-evaluated and confirmed by two experienced neuro-pathologists (Dr. Yin Wang and Dr. Hong Chen) according to the WHO 2016 meningioma grading criterion. All participants gave their written informed consent and ethical approval for the study was obtained from the Human Subjects Institutional Review Board at Huashan Hospital, Fudan University (KY-2012-17).

DNA Extraction

All paraffin-embedded meningioma tissues used for DNA extraction were reviewed by Dr. Yin Wang to ensure that at least 50% of the cells were neoplastic. DNA was extracted using the GenElute™ FFPE DNA Purification Kit (Sigma-Aldrich, Kenilworth, USA) according to the manufacturer's instructions and reported other authors (26). Briefly, the tissues were treated with xylene first to remove paraffin, and then were subjected to digestion and DNA subsequently isolated from the digested tissues. The concentration and purity of the DNA were assessed using a Nanodrop 2000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA) and all samples were diluted to a concentration of 0.2 ng/μL DNA and stored at −80°C before mtDNA content analysis.

mtDNA Content

mtDNA content was determined using a quantitative real-time PCR method. This assay measures relative mtDNA content by measuring the ratio of mitochondrial copy number to single copy nuclear gene. The mitochondrially encoded NADH dehydrogenase subunit 1 gene (MT-ND1) and nuclear single copy gene β-globin were used in our study. The specific sequences of primers and TaqMan probes used for the amplification were as follows: MT-ND1 forward (MT-ND1-F),

TABLE 1 | Association between mtDNA content and clinicalpathological variables of Grade III meningioma patients.

Characteristics	mtDNA low *n* (%)	mtDNA high *n* (%)	*P*
Gender			0.546
Male	20 (46.5%)	24 (54.5%)	
Female	23 (53.5%)	20 (45.5%)	
Age			0.283
≤60	32 (74.4%)	36 (83.7%)	
>60	11 (25.6%)	8 (18.6%)	
Tumor location			0.107
Skull base	13 (30.2%)	20 (45.5%)	
Non-skull base	30 (69.8%)	24 (54.5%)	
KPS score			0.438
≤80	13 (30.2%)	15 (34.1%)	
>80	30 (69.8%)	29 (65.9%)	
Tumor status			0.223
Primary	27 (62.8%)	32 (67.4%)	
Recurrent	16 (37.2%)	12 (32.6%)	
Preoperative radiation			0.041*
Yes	8 (18.6%)	2 (4.5%)	
No	35 (81.4%)	42 (95.5%)	
Malignant transformation			0.520
Yes	7 (16.3%)	8 (25.6%)	
No	36 (83.7%)	36 (74.4%)	
Extent of resection			0.241
GTR	35 (81.4%)	32 (72.7%)	
STR	8 (18.6%)	12 (27.3%)	
ER			0.290
Positive	24 (55.8%)	30 (68.2%)	
Negative	19 (44.2%)	14 (31.8%)	
PR			0.290
Positive	5 (11.6%)	8 (18.2%)	
Negative	38 (88.4%)	36 (81.8%)	
Ki-67			0.093
≤5	10 (23.2%)	17 (38.6%)	
>5	33 (76.7%)	27 (61.4%)	

*ER, estrogen receptor; PR, progesterone receptor; *p<0.05 considered statistically significant.*

5′-CCCTAAAACCCGCCACATCT-3′; MT-ND1 reverse (MT-ND1-R), 5′-GAGCGATGGTGAGAGCTAAGGT-3′; β-globin forward (β-globin-1), 5′-GTGCACCTGACTCCTGAGGAGA-3′; β-globin reverse (β-globin−2), 5′-CCTTGATACCAACCT GCCCAG-3′. The TaqMan probes were labeled with 5′-FAM (6-carboxyfluorescein, fluorescent reporter) and 3′-TAMRA (6-carboxy-tetramethylrhodamine, fluorescent quencher). qPCR amplification for each sample was performed using TaqMan™ Universal Master Mix II on the Applied Biosystems (Foster City, CA) Quantstudio 6 real-time PCR system. All samples were run in triplicate for both mitochondrial and nuclear genes on a 384 well plate with a 7500 Fast Real-time PCR system (qRT-PCR; PE7500 real-time PCR instrument; Applied Biosystems, Foster City, CA, USA). Proper positive and negative controls, a calibrator DNA and a standard curve, were also included in each run to monitor the performance of PCR reactions. The thermal conditions for both primers were 95°C for 30 s, followed by 35 cycles of 94°C for 30 s, 58°C for 30 s, and 72°C for 50 s with signal acquisition. The results were analyzed with the 7500v2.0.4 software (Applied Biosystems). The ratio of MT-ND1 copy number to β-globin copy number was calculated for each sample from standard curves. Furthermore, the ratio of each sample was normalized to a calibrator DNA to standardize between different runs, and it was defined as relative mtDNA content.

Immunohistochemistry

Immuno-histochemical staining was carried out by using monoclonal antibodies, including Ki-67, ER and PR (Signal way [SAB], Shanghai, China; 1:200 dilution). Immuno-histological staining of these antigens was evaluated by two experienced neuro-pathologists as descried above. The tumor was considered ER or PR positive if > 10% of the tumor nuclei showed staining; weak positive when 1–9% of the tumor nuclei were stained; and negative for tumors with no nuclei staining (27, 28).

Statistical Analysis

All statistical computations used in this study were performed using Stata 13.3 for Windows. mtDNA content distribution was tested with the Shapiro-Wilk test. Fisher's exact test was used to analyze associations between the clinical variables and mtDNA content. The association between mtDNA content and Ki-67 labeling index was tested using the logistic regression model. Continuous variables with skewed distribution were compared with Mann-Whitney U test. Survival curves were drawn as Kaplan-Meier survival plots and analyzed with log-rank test. Cox proportional hazards regression model was applied for the univariate, multivariate and stratified prognostic analysis. A P value < 0.05 was considered to be statistically significant.

RESULTS

mtDNA Content Distribution and Its Association With Clinical Variables

The mtDNA content was measured using a real-time PCR based method in a cohort of 87 WHO grade III meningiomas. The mean mtDNA quantity was 617.7 (range, 0.8–3000) mtDNA per cell. The mean mtDNA quantity was 955.8 (range, 0.8–3000) in anaplastic meningioma, 988.8 (range, 548.5–2336.8) in papillary subtype, and 612.7 (range, 460.2–1815.2) in rhabdoid subtype. No significant difference in the distribution of mtDNA was observed between the three histological subtypes ($p = 0.07$, Kruskal-Wallis test). Therefore, we combined these three histological subtypes together for further statistical analysis. Linear regression model was performed to see whether the mtDNA distribution is associated with tumor proliferation marker (Ki-67 labeling index). No correlation between these two parameters was observed ($P = 0.056$, $r = 0.031$). Since mtDNA content was not normally distributed ($P < 0.0001$, Shapiro-Wilk test), we classified the cohort into two groups based on the median of mtDNA content (median, 782.2), resulting in mtDNA low group (43 tumors) and high group (44 tumors).

To evaluate the clinical relevance of mtDNA, we then compared the mean mtDNA with various clinicopathological characteristics. As shown in **Table 1**, no significant differences were observed between mtDNA and gender, age, tumor location (skullbase vs. convexity), preoperative KPS score, tumor recurrent status, malignant transformation, extent of tumor resection, ER status, PR status, or Ki-67 labeling index ($P > 0.05$, Fisher's exact test). However, there was a significant difference with regard to preoperative radiation therapy; patients who received radiation therapy before surgery ($N = 10$) were more prevalent in the mtDNA low group (**Figure 1**, $P = 0.041$, Fisher's exact test).

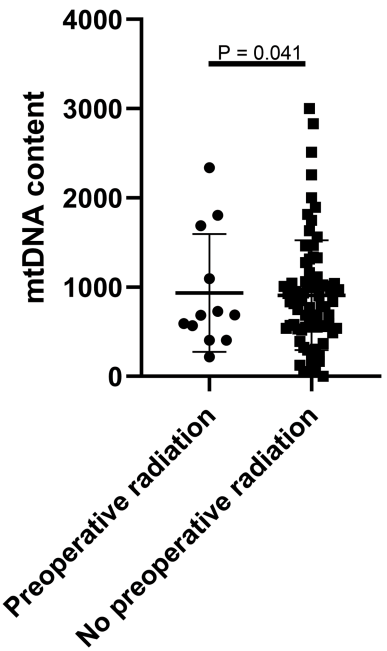


FIGURE 1 | mtDNA content was significantly lower in patients with preoperative radiation therapy.

Prognostic Analysis of mtDNA Content in Grade III Meningioma Patients

We next studied the association between mtDNA content and progression free survival (PFS) and overall survival (OS). As shown in **Figure 2**, patients with high mtDNA content showed a significantly longer PFS ($P = 0.044$, log-rank test) as well as OS ($P = 0.019$, log-rank test). The median PFS in mtDNA low and high group were 43.93 months (range, 1–136 months) and 68.14 months (range, 3–160 months, $p = 0.049$), respectively, while the median OS was 58.19 (range, 1–138 months) and 78.89 (range, 4–160 months, $p = 0.023$), respectively. Univariate Cox proportional hazards model revealed that patients with high mtDNA content had a significantly better outcome regarding extent of resection (GTR) and negative ER (**Table 2**). We next performed multiple Cox proportional hazards model by testing a number of prognostic factors including ER status (5, 29). Here, we found that along with ER, mtDNA was also an independent prognostic factor for both PFS ($P = 0.002$) and OS ($P = 0.002$) (**Table 2**).

Prognostic Analysis of mtDNA Content in Grade III Meningioma Patients Receiving Postoperative Radiation

Radiation therapy has been frequently associated with mitochondria damage (30). Therefore, we analyzed the prognostic factors in patients who received postoperative radiation therapy. A total of 47 patients in our cohort received either gamma knife or external beam radiation after tumor resection. The tumor mtDNA content in patients who underwent postoperative radiation therapy was not normally distributed ($P < 0.0001$, Shapiro-Wilk test). In this subgroup, we further classified patients into mtDNA low and high group based on the median mtDNA content in this group, which was 295.7 per cell. Three patients who previously harbored meningiomas with low mtDNA in the initial 87 patients cohort were reclassified as mtDNA high tumors in this 47 patients group.

No statistically significant differences were observed between the clinical variables and the mtDNA content, including

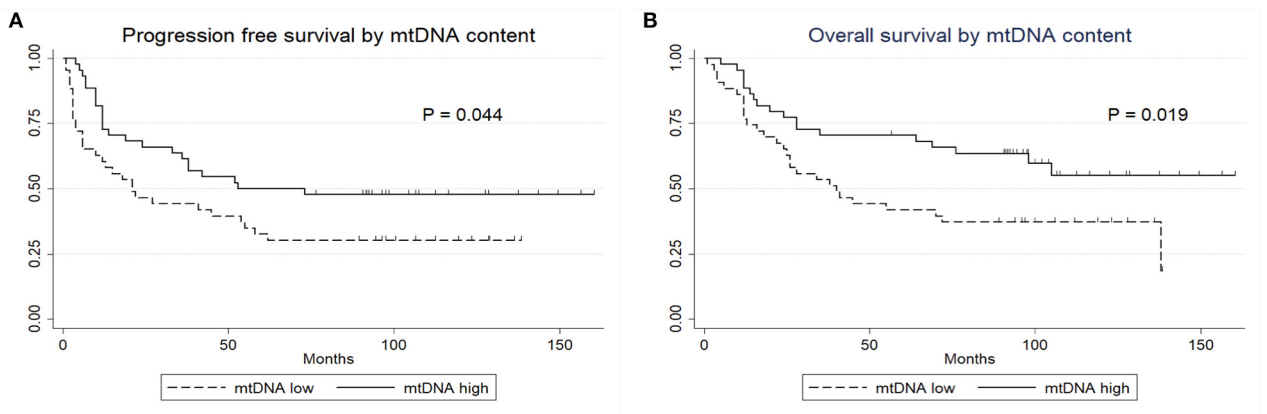


FIGURE 2 | Kaplan-Meier survival curves. **(A)** PFS of patients by mtDNA content. **(B)** OS of patients by mtDNA content.

TABLE 2 | Univariate and multivariate analysis of prognostic factors for WHO grade III meningioma patients.

	Univariate Analysis				Multivariate Analysis			
	PFS		OS		PFS		OS	
Variable	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***P***	**HR (95% CI)**	***p***	**HR(95% CI)**
Age (<60/≥60)	0.819	1.062 (0.636–1.733)	0.974	1.012 (0.502–2.039)				
Gender (female/male)	0.669	0.911 (0.593–1399)	0.275	1.388 (0.252–0.921)				
Preoperative KPS (<80/≥80)	0.877	0.958 (0.555–1.654)	0.987	1.005 (0.540–1.870)				
Extent of resection (GTR/STR)	0.001*	0.412 (0.246–0.692)	0.027*	0.481 (0.252–0.921)	0.013*	2.697 (1.232–5.900)		
Location (skull base/non-skull base)	0.006*	1.887 (1.195–2.978)	0.043*	1.824 (1.018–3.269)				
Radiation (no/yes)	0.433	0.841 (0.544–1.298)	0.034*	0.532 (0.297–0.953)				
Ki-67 index (<5%/≥5%)	0.958	0.988 (0.621–1.570)	0.847	1.064 (0.567–1.995)				
ER (−/+)	0.001*	2.884 (1.508–5.514)	0.002*	2.966 (1.466–6.001)	0.002*	3.366 (1.558–7.271)	0.002*	3.523 (1.559–7.962)
PR (−/+)	0.884	0.946 (0.446–2.007)	0.539	0.763 (0.323–1.805)				
Recurrent (no/yes)	0.000*	2.532 (1.539–4.167)	0.107	1.637 (0.899–2.981)	0.039*	1.841 (1.032–3.283)		
mtDNA content (low/high)	0.049*	0.579 (0.336–0.998)	0.023*	0.502 (0.277–0.909)	0.002*	0.378 (0.202–0.706)	0.002*	0.349 (0.178–0.683)

*KPS, karnofsky performance score; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; GTR, gross total resection; ER, estrogen receptor; PR, progesterone receptor; *p < 0.05 considered statistically significant.*

TABLE 3 | Association between mtDNA content and clinical-pathological variables of Grade III meningioma patients who receive post-operative radiation therapy.

Characteristics	**mtDNA low *n* (%)**	**mtDNA high *n* (%)**	***P***
Gender			0.096
Male	16 (66.7%)	13 (56.5%)	
Female	8 (33.3%)	10 (43.5%)	
Age			0.609
≤60	19 (79.2%)	18 (78.3%)	
>60	5 (20.8%)	5 (21.7%)	
Tumor location			0.092
Skull base	6 (25.0%)	11 (47.8%)	
Non-skull base	18 (75.0%)	12 (52.2%)	
KPS score			0.598
≤80	6 (25.0%)	6 (26.1%)	
>80	18 (75.0%)	17 (73.9%)	
Tumor status			0.340
Primary	18 (75.0%)	15 (65.2%)	
Recurrent	6 (25.0%)	8 (34.8%)	
Preoperative radiation			0.525
Yes	4 (16.7%)	3 (13.0%)	
No	20 (83.3%)	20 (87.0%)	
Malignant transformation			0.375
Yes	5 (20.8%)	3 (13.0%)	
No	19 (79.1%)	20 (87.0%)	
Extent of resection			0.221
GTR	20 (83.3%)	16 (69.6%)	
STR	4 (16.7%)	7 (30.4%)	
ER			0.092
Positive	10 (41.7%)	15 (65.2%)	
Negative	14 (58.3%)	8 (34.8%)	
PR			0.325
Positive	3 (12.5%)	5 (21.7%)	
Negative	21 (87.5%)	18 (78.3%)	
Ki-67			0.234
≤5	6 (25.0%)	9 (39.1%)	
>5	18 (75.0%)	14 (60.9%)	

ER, estrogen receptor; PR, progesterone receptor.

preoperative radiation status ($P > 0.05$, Fisher's exact test, **Table 3**). Interestingly, the univariate Cox proportional survival analysis revealed that low mtDNA content in the irradiated tumor group was associated with better PFS ($P = 0.035$) (**Table 4**), which was further confirmed by Kaplan-Meier analysis ($P = 0.028$) (**Figure 3**). However, it was not associated with OS ($P = 0.272$) (**Figure 3**). Our multivariate analysis of patients with post-operative radiation did not identify mtDNA content as a significant independent factor for PFS or OS, while ER status was found to be a very significant prognostic factor (**Table 4**). Stratified analysis revealed that, for patients who received postoperative radiation therapy, low mtDNA content was associated with longer OS and PFS in patients with ER negative status (PFS, $P = 0.002$; OS, $P = 0.002$) (**Figure 4**).

TABLE 4 | Univariate and Multivariate Analysis of Prognostic Factors for WHO grade III meningioma patients receiving post-operative radiation therapy.

	Univariate Analysis				Multivariate Analysis			
	PFS		OS		PFS		OS	
Variable	*P*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
Age (<60/≥60)	0.984	0.991 (0.397–2.471)	0.625	0.763 (0.258–2.258)				
Gender (female/male)	0.528	0.778 (0.357–1.696)	0.774	0.884 (0.382–2.048)	0.013*	0.272 (0.097–0.762)		
Preoperative KPS (<80/≥80)	0.854	0.922 (0.387–2.194)	0.960	0.976 (0.381–2.501)				
Extent of resection (GTR/STR)	0.009*	2.970 (1.313–6.720)	0.250	1.738 (0.678–4.456)				
Location (skull base/non-skull base)	0.025*	2.421 (1.117–5.244)	0.084	2.106 (0.904–4.906)				
Ki-67 index (<5%/≥5%)	0.354	0.688 (0.312–1.518)	0.515	0.749 (0.313–1.790)				
ER (−/+)	0.001*	4.875 (1.937–12.270)	0.008*	3.587 (1.393–9.238)	0.000*	10.202 (3.019–34.468)	0.002*	6.692 (2.056-21.784)
PR (−/+)	0.218	1.779 (0.711–4.453)	0.831	1.126 (0.380–3.334)				
Recurrent (no/yes)	0.006*	2.994 (1.371–6.539)	0.049*	2.362 (1.005–5.553)				
mtDNA content (low/high)	0.035*	2.414 (1.066–5.466)	0.278	1.607 (0.682–3.783)				

*KPS, karnofsky performance score; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; GTR, gross total resection; *p<0.05 considered statistically significant.*

DISCUSSIONS

WHO grade III meningioma are rare and represent 1–2% of all meningiomas. Initial standard-of-care therapy for malignant meningiomas is surgical resection followed by radiation therapy. Nevertheless, the majority patients with malignant meningiomas devlope recurrent tumors and have a dismal outcome (3, 5). Extensive efforts have been made to explore possible prognostic factors that can predict the outcome in malignant meningiomas (31–36). In addition, we previously reported that ER is an independent negative prognostic factor for WHO grade III meningioma (5). In this study, we explored the distribution of mtDNA content and its prognostic value in a total of 87 patients with WHO grade III meningioma. We demonstrated that patients with high intratumoral mtDNA content had a significantly better outcome regarding both OS and PFS. However, in the subgroup of patients who received postoperative radiation therapy, low mtDNA content was associated with better PFS, although it was not an independent prognostic factor in multivariate analysis.

mtDNA content variation has been reported to play an important role in the development of several malignancies. As early as 1996, Liang et al. demonstrated high mtDNA content is associated with more proliferative abilities (37). Since then, an increasing number of studies focused on mtDNA copy number variation and its correlations with tumors. In our cohort, mtDNA content distribution was not associated with the Ki-67 labeling index. This is in concordance with previous studies that demonstrated no correlation between the Ki-67 labeling index and outcomes in grade III meningioma (5, 38). In tumors, the mtDNA content has been shown to be altered compared to adjacent non-neoplastic tissues, including breast, esophageal and prostate cancers (16–18). In addition, a progressive decrease in mtDNA content has been observed during malignant transformation in glioma, breast, prostate, endometrial and head and neck cancers (17–19, 21, 22, 39). We analyzed distribution of mtDNA content between the three histological subtypes within the WHO grade III meningioma and no difference was observed, which was consistent with our previous study demonstrating no difference in the clinical features between the three distinct histological subtypes (5). We did not separately analyze the mtDNA content by the histological subtype was that there were two few papillary and habdoid meningioma patients in the cohort which would lead to statistical bias. Zhang et al. revealed that in their series of 151 glioma patients, mtDNA content was associated with recurrent status in glioma, which was confirmed by two recent studies (40, 41). In breast cancer, Marjolein reported low mtDNA content was more prevalent in ER positive breast cancers (20). In our cohort, however, we did not find any correlations between mtDNA content and major tumor clinical characteristics including tumor recurrence, malignant transformation, and ER status. Nevertheless, low mtDNA content was more prevalent in patients who received preoperative radiation therapy, which may be explained by the radiation-induced DNA damage in the mitochondrial genome combined by impaired enzyme synthesis.

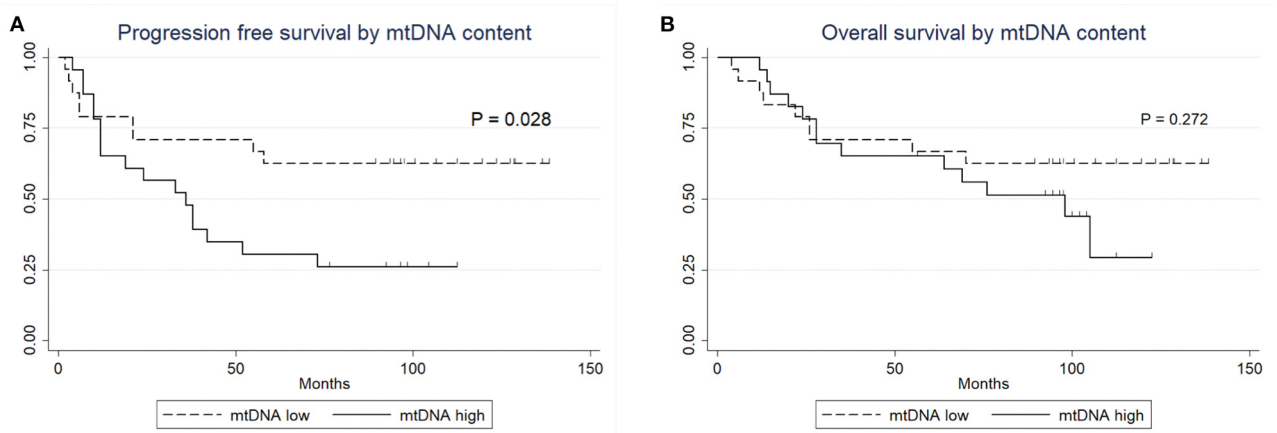


FIGURE 3 | Kaplan-Meier survival curves. **(A)** PFS of patients with post-operative radiation therapy by mtDNA content. **(B)** OS of patients with post-operative radiation therapy by mtDNA content.

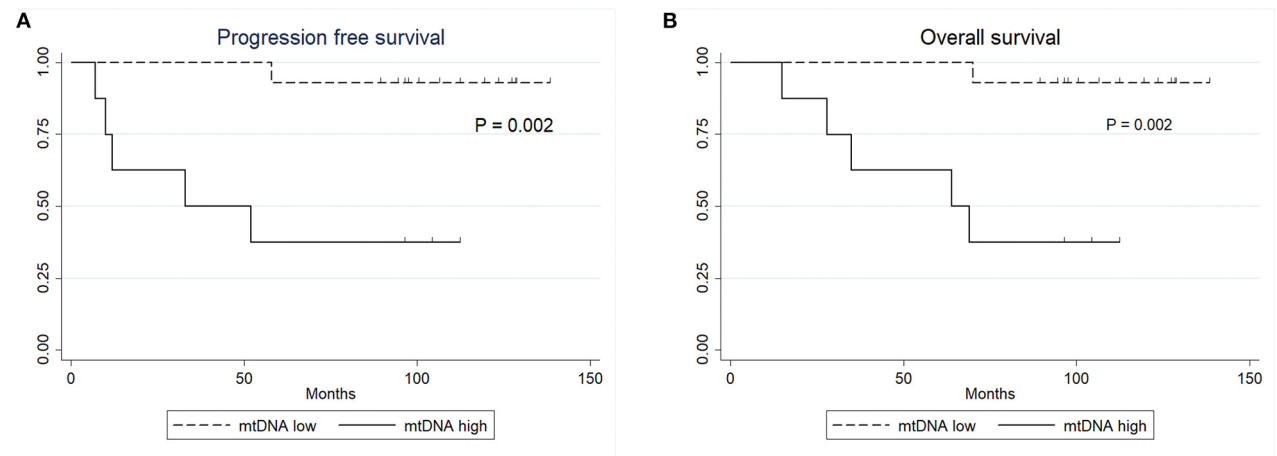


FIGURE 4 | Kaplan-Meier survival curves. **(A)** PFS of patients with ER negative status by mtDNA content. **(B)** OS of patients with ER negative status by mtDNA content.

Although most studies revealed that high mtDNA content was associated with better outcome in cancer, some studies showed contrary data (18, 42–51). Thus, the role of mtDNA in cancer prognosis remains controversial. Consistent with the results reported in breast, prostate, and esophageal cancer and glioma, we found a strong correlation between outcome and mtDNA content in our cohort. High mtDNA content was associated with both better PFS and OS of patients with grade III meningioma. In addition, along with ER status, mtDNA content was an independent prognostic factor for both PFS and OS, suggesting that alterations in mitochondria genome might be associated with progression in high grade meningioma.

Interestingly, our survival analysis demonstrated that in patients who received postoperative radiation ($n = 47$), low tumor mtDNA content was associated with better PFS, whereas no OS difference was observed. Consistently, studies in breast cancer demonstrated that low tumor mtDNA content is associated with better outcome after receiving chemotherapy due to induction of mitochondrial damage. Likewise, as radiation can induce mitochondrial damage (52), a suitable hypothesis is that tumors with low mtDNA content may be more susceptible to mitochondrial damage induced by radiation than those with high mtDNA content.

A recent work by Soon et al. reported that mitochondrial DNA is mutated in several glioma cells and could subsequently induce mitochondrial dysfunction and higher oxidative stress (53). Mitochondrion dysfunction has been theorized as a crucial player in many tumors by increasing the production of reactive oxygen species (ROS) through the activity of the mitochondrial electron transport chain (54). This altered

cellular respiratory system may generate excessive reactive oxygen species, and further lead to a vicious cycle of DNA damages. This hypothesis was also proved in pediatric high-grade glioma in a recent study by Shen et al. (41). In their study, higher mtDNA content was associated with better outcome while reducing mtDNA content induced inhibited tumor growth. Reducing mtDNA content in combination with radiation demonstrated synergistic effect. Their study gave us a hint that in grade III meningioma, treatment strategies using pharmacological inhibition of mtDNA content in combination of radiation could also be effective. Pharmacological agents such as DCA can reduce tumor mtDNA content and inhibit meningioma growth, while reduced mtDNA content may render these tumors more sensitive to postoperative radiotherapy.

The main limitation of our study is the small patient number included, especially in the radiation subgroup, which may limit the statistical power of survival and stratified analyses. Moreover, meningioma patients with lower histological grade were excluded. Consequently, the distribution of mtDNA content in different grades of meningioma cannot be evlautaed.

CONCLUSIONS

In conclusion, our study highlights the prognostic association of mtDNA content in WHO grade III meningioma. High mtDNA content was an independent prognostic factor for better PFS and OS. However, for patients who received postoperative radiation therapy, low mtDNA content was associated with better PFS. Tumor mtDNA content may serve as a marker to predict the outcome of patients with WHO grade III meningioma. Further studies are warranted to explore the mtDNA distribution in lower WHO grade tumors and the possible role of the mitochondrial genome in the progression of meningioma and response to radiation therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Huashan Hospital Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LH, HZ, YG, and QX: study concepts. LH: study design and manuscript preparation, quality control of data and algorithms. LH, HZ, JD, and SS: data acquisition. LH, TJ, HW, and QX: data analysis and interpretation. LH, TJ, and HW: statistical analysis. TJ, HW, and QX: manuscript editing. HW, YG, and QX: manuscript review. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Quantified Risk-Scoring System for the Recurrence of Meningiomas: Results From a Retrospective Study of 392 Patients

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Aim: This study aimed to identify the independent risk factors of recurrence in patients undergoing primary resection of meningioma and construct a scoring system for the prediction of the risk of postoperative recurrence.

Materials and Methods: The clinical data of 591 patients who underwent primary surgical resection for meningioma at the First Affiliated Hospital of Wenzhou Medical University between November 2010 and December 2016 were retrospectively reviewed. The clinical, radiological, and pathological characteristics were evaluated, and the independent risk factors for recurrence were identified via receiver operating characteristic (ROC) curve and logistic analyses. A scoring system that included these independent risk factors was used to construct a risk-predicting model that was evaluated via a ROC curve analysis. The recurrences of different subgroups were observed by Kaplan-Meier's curves.

Results: The clinical data of 392 patients with meningioma were used to construct the scoring system. The logistic analysis showed that sex (OR = 2.793, 95% CI = 1.076–7.249, $P = 0.035$), heterogeneous tumor enhancement (OR = 4.452, 95% CI = 1.714–11.559, $P = 0.002$), brain invasion (OR = 2.650, 95% CI = 1.043–6.733, $P = 0.041$), Simpson's removal grade (OR = 5.139, 95% CI = 1.355–19.489, $P = 0.016$), and pathological grade (OR = 3.282, 95% CI = 1.123–9.595, $P = 0.030$) were independent risk factors for recurrence. A scoring system was developed and used to divide the patients into the following four subgroups: subgroup 1 with scores of 0–75 ($n = 249$), subgroup 2 with scores of 76–154 ($n = 88$), subgroup 3 with scores of 155–215 ($n = 46$), and subgroup 4 with scores of 216–275 ($n = 9$). The incidences of recurrence in each subgroup were as follows: subgroup 1, 1.2%; subgroup 2, 5.7%; subgroup 3, 26.1%; and subgroup 4, 66.7% ($P < 0.001$). The scoring system reliably predicted the postoperative recurrence of meningioma with a high area under the ROC curve.

Conclusions: Our scoring system is a simple and reliable instrument for identifying meningioma patients at risk of postoperative recurrence and could help in optimizing individualized clinical treatment.

Keywords: meningioma, recurrence, prognosis, risk model, scoring system

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INTRODUCTION

Meningioma is the most prevalent primary intracranial tumor and accounts for ∼15–30% of all primary intracranial neoplasms (1). According to the current 2007 World Health Organization (WHO) classification system, most meningiomas are benign (∼80%). The WHO classification distinguishes three histological grades (I-II-III) and 15 subtypes (2). Currently, the method most commonly used in the clinic to predict recurrence is risk stratification based on the WHO grade as the tumor histological grade has been demonstrated to predict the postoperative risk of recurrence following treatment (3, 4). Some studies have also reported other risk-related factors for recurrence, including radiological characteristics, age and Simpson's removal grade (5, 6). However, despite current studies investigating the prognosis of meningioma, a reliable prediction system is still lacking (7, 8). Therefore, we retrospectively analyzed data obtained from patients with WHO grades I, II, or III meningiomas who were treated in our hospital. The aims of this study were to identify the prognostic factors that influenced the postoperative recurrence of tumors, construct a new scoring system and risk-rating model for the prediction of postoperative recurrence, and support the optimization of treatment strategies for patients.

MATERIALS AND METHODS

Patients and Data

Patients with meningioma who underwent primary surgical treatment at the Department of Neurosurgery at the First Affiliated Hospital of Wenzhou Medical University between November 2010 and December 2016 were enrolled in this retrospective study. Among all 591 patients enrolled in our study, the demographic and clinical data were retrospectively collected using all available inpatient and outpatient reports and records. The follow-up period was up to October 2019 or the first recurrence after primary tumor resection. The inclusion criteria were as follows: (1) an age ≥18 years; (2) available preoperative and postoperative magnetic resonance imaging (MRI) (including T1-weighted, T2-weighted, and contrast-enhanced T1-weighted) data; (3) pathologically confirmed meningioma based on the WHO histological grading system; and (4) complete postoperative follow-up data. The exclusion criteria included a lack of complete imaging data, loss to follow-up, and multiple meningiomas. Based on these criteria, 392 of the 591 patients were included in the study analyses (**Figure 1**). This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Given the retrospective nature of the study, patient informed consent was waived.

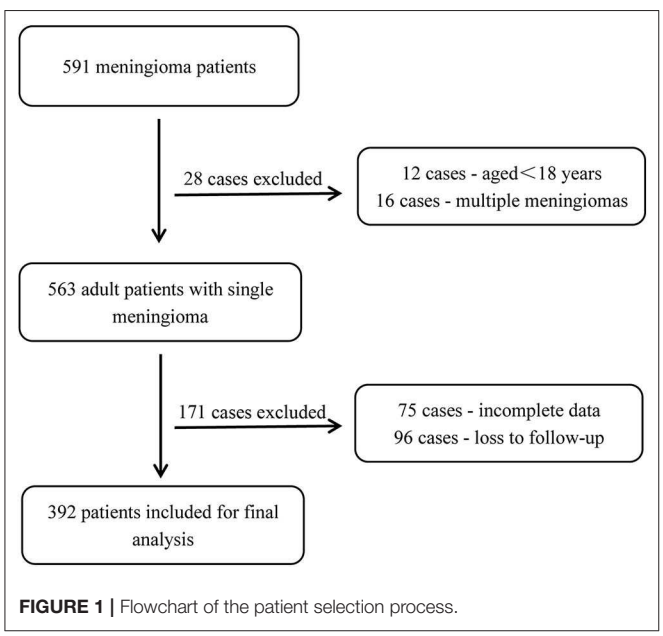


FIGURE 1 | Flowchart of the patient selection process.

Recorded Variables

We collected the patients' clinical, radiological, and pathological characteristics, including sex, age, preoperative Karnofsky performance scale (KPS), tumor location, tumor size, tumor shape, peritumoral edema, dural tail sign size, tumor calcification, tumor-surrounding vessels, tumor basal size, heterogeneous tumor enhancement, tumor–cortex interface, Simpson's removal grade, pathological grade, brain invasion, and Ki-67 index.

In our study, a regular tumor shape was defined according to MRI as round or oval, and an irregular tumor shape included fusiform and other irregular shapes. Peritumoral edema was evaluated based on T2 predominant sequences obtained in MR screenings. The edema–tumor volume ratio was defined according to the Edema Index (EI). We estimated the tumor and edema volume based on the results of the MR scan as follows: the maximum perpendicular diameters were measured on axial images, and the extent in the coronal direction was estimated as the number of axial images that displayed the structure multiplied by the slice thickness. The relationship between peritumor brain edema (PTBE) and the tumor volume was defined as $EI = (V_{Edema}+V_{Tumor})/V_{Tumor}$; when there was no edema, the result was 1 (9, 10). T2 predominant MR screenings were used to examine the tumor-cortex interface, which was classified as follows: (1) marked interspace when there was a distinct interval (>1 mm wide) between at least 50% of the tumor and the surrounding cortical surface; (2) a regular border when there were no gaps or irregular boundaries between the tumor and the subcortical surface, but regular boundaries were observed across more than 50% of the surface; and (3) an irregular border when there was no clear cortical contour on more than 50% of the surface of the tumor (11, 12). The tumor-surrounding vessels were defined based on a T2-weighted image in which the sign of empty blood vessels surrounded the tumor blood vessel. Heterogeneous tumor enhancement was defined based on T1-weighted contrast images when the tumors were enhanced inhomogenously, and no apparent hyperintensity in the part of the tumor-involved area was observed on a postcontrast T1-weighted image. The tumor size, dural tail sign size and tumor basal size were measured on T1-weighted contrast images.

Tumor recurrence was defined as the formation of a new contrast-enhanced nodule in the previous resection cavity, the

formation of a 95% isodose line or residual tumor progression in patients who underwent subtotal resection. During the follow-up period, relapse was assessed by a senior neurosurgeon and an experienced neuroimaging specialist.

Statistical Analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution uniformity of the continuous parameters. The normally distributed data are expressed as the mean ± standard deviation, and the non-normally distributed data are expressed as the median and interquartile range (IQR). An independent *t*-test and Mann-Whitney *U*-test were used to analyze the differences between the groups in the continuous variables, while the chi-square test and Fisher's exact test were used to analyze the differences between the groups in the categorical variables. We plotted receiver operating characteristic (ROC) curves and selected the maximal value of the Youden index as the cutoff point for the tumor size, tumor basal size and total risk scores. The patients were grouped according to this cutoff point. Based on the univariate analysis, a multiple logistic regression analysis was conducted to calculate the odds ratio (OR) and 95% confidence interval (CI) of the independent variables. The area under the ROC curve (AUC) was used to evaluate the accuracy of our scoring system based on the clinicopathological characteristics of the individuals. Kaplan-Meier's curves with a log-rank test were performed to observe the recurrence of meningioma in different subgroups. Statistical significance was indicated by $P < 0.05$. The statistical analyses were carried out using SPSS software (SPSS 22.0 Inc., Chicago, IL).

RESULTS

Patient Characteristics

The clinical, radiological and pathological data of 392 meningioma patients were systematically reviewed. The median follow-up duration was 60 months (IQR = 46–78 months). The baseline characteristics are shown in **Table 1**. The majority of patients were female ($n = 268$, 68.4%), and the median age of all patients was 55 years (IQR = 47–63 years). The tumor sites included the cranial convexity (167, 42.6%), skull base (122, 31.1%), parasagittal sinus (51, 13.0%), and other locations (52, 13.3%). The pathological grades included WHO grade I (362, 92.4%), WHO grade II (26, 6.6%), and WHO grade III (4, 1%) meningioma. Of the 392 patients included in the analyses, 26 cases (6.6%) experienced recurrence after surgery.

TABLE 1 | Clinical characteristics.

Characteristic	Value ($N = 392$)
Sex	
Female	268 (68.4%)
Male	124 (31.6%)
Age (y)	55 (47-63)*
Preoperative KPS	
>70	345 (88.0%)
≤70	47 (12.0%)
Tumor location	
Convexity	167 (42.6%)
Skull base	122 (31.1%)
Parasagittal sinus	51 (13.0%)
Other	52 (13.3%)
Tumor size (mm)	
>42	140 (35.7%)
≤42	252 (64.3%)
Simpson's removal grade	
I	137 (34.9%)
II-IV	255 (65.1%)
Pathological grade	
I	362 (92.4%)
II	26 (6.6%)
III	4 (1.0%)
Recurrent	
Yes	26 (6.6%)
No	366 (93.4%)

**The values in the table are the number of patients, except for age, age in the table presented as the median (IQR). IQR, interquartile range; KPS, Karnofsky performance scale.*

Univariate Analysis

A chi-square test was used to examine the associations between the clinical characteristics and postoperative recurrence. The results of the univariate analysis of the entire cohort of patients is shown in **Table 2**. Sex (female vs. male, $P = 0.001$), preoperative KPS (>70 vs. ≤70, $P = 0.006$), tumor size (>42 mm vs. ≤42 mm, $P = 0.001$), tumor shape (regular vs. irregular, $P = 0.028$), peritumoral edema (EI > 4 vs. EI ≤ 4, $P = 0.011$), tumor surrounding vessels ($P = 0.032$), tumor basal size (>42 mm vs. ≤42 mm, P<0.001), heterogeneous tumor enhancement ($P < 0.001$), tumor–cortex interface (marked interspace vs. regular border vs. irregular border, $P < 0.001$), brain invasion ($P < 0.001$), Simpson's removal grade (I vs. II-IV, $P = 0.010$), pathological grade (I vs. II-III, $P < 0.001$), and Ki-67 index (≥5% vs. <5%, $P < 0.001$) were identified as prognostic factors for recurrence. There were no significant associations between recurrence and age, tumor location, dural tail sign size (mm) or tumor calcification.

Multivariate Analysis

The independent risk factors for recurrence were identified by a multivariate logistic regression analysis. As shown in **Table 3**, sex (OR = 2.793, $P = 0.035$), heterogeneous tumor enhancement (OR = 4.452, $P = 0.002$), brain invasion (OR = 2.650, $P = 0.041$), Simpson's removal grade (OR = 5.139, $P = 0.016$), and pathological grade (OR = 3.282, $P = 0.030$) independently predicted recurrence.

Scoring System

To establish a scoring system for the accurate prediction of recurrence, we used the independent risk factors identified in the multiple logistic regression analysis. The risk score of each risk factor was calculated by logarithmic transformation and multiplied by 100, resulting in the following risk calculation

TABLE 2 | Univariate analysis of the risk of recurrence.

Factors	Recurrent	Non-recurrent	*P*
Sex			0.001
Female	10(3.7%)	258(96.3%)	
Male	16(12.9%)	108(87.1%)	
Age (y)			0.854
≤60	18(6.8%)	247(93.2%)	
>60	8(6.3%)	119(93.7%)	
Preoperative KPS			0.006
>70	18(5.2%)	327(94.8%)	
≤70	8(17.0%)	39(83.0%)	
Tumor location			0.059
Convexity	10(6.0%)	157(94.0%)	
Skull base	10(8.2%)	112(91.8%)	
Parasagittal sinus	6(11.8%)	45(88.2%)	
Other	0(0.0%)	52(100.0%)	
Tumor size(mm)			0.001
≤42	9(3.6%)	243(96.4%)	
>42	17(12.1%)	123(87.9%)	
Tumor shape			0.028
Regular	14(4.9%)	270(95.1%)	
Irregular	12(11.1%)	96(88.9%)	
Peritumoral edema			0.011
EI ≤ 4	15(4.9%)	290(95.1%)	
EI>4	11(12.6%)	76(87.4%)	
Dural tail sign size(mm)			0.088
≤10	15(5.3%)	268(94.7%)	
>10	11(10.1%)	98(89.9%)	
Tumor calcification			0.572
NO	22(7.0%)	293(93.0%)	
Yes	4(5.2%)	73(94.8%)	
Tumor-surrounding vessel			0.032
No	15(5.1%)	280(94.9%)	
Yes	11(11.3%)	86(88.7%)	
Tumor basal size(mm)			<0.001
≤42	13(4.2%)	295(95.8%)	
>42	13(15.5%)	71(84.5%)	
Heterogeneous tumor enhancement			<0.001
No	14(4.1%)	324(95.9%)	
Yes	12(22.2%)	41(77.8%)	
Tumor–cortex interface			<0.001
Marked interspace	11(3.7%)	284(96.3%)	
Regular border	7(12.1%)	51(87.9%)	
Irregular border	8(20.5%)	31(79.5%)	
Brain invasion			<0.001
No	11(3.6%)	298(96.4%)	
Yes	15(18.1%)	68(81.9%)	
Simpson's removal grade			0.010
I	3(2.2%)	134(97.8%)	
II-IV	23(9.0%)	232(91.0%)	
Pathological grade			<0.001
I	16(4.4%)	346(95.6%)	
II-III	10(33.3%)	20(66.7%)	
Ki-67 index			<0.001
<5%	8(2.4%)	322(97.6%)	
≥5%	18(29.0%)	44(71.0%)	

The values in the table are the number of patients. KPS, Karnofsky performance scale. EI, Edema Index.

TABLE 3 | Multivariate analysis to evaluate potential predictive factors for recurrence and the scoring of these factors.

Factors	OR	95%CI	*P*	Risk score
Sex				
Female	1			0
Male	2.793	1.076–7.249	0.035	45
Heterogeneous tumor enhancement				
No	1			0
Yes	4.452	1.714–11.559	0.002	65
Brain invasion				
No	1			0
Yes	2.650	1.043–6.733	0.041	42
Simpson's removal grade				
I	1			0
II-IV	5.139	1.355–19.489	0.016	71
Pathological grade				
I	1			0
II-III	3.282	1.123–9.595	0.030	52

CI, confidence interval; OR, odds ratio.

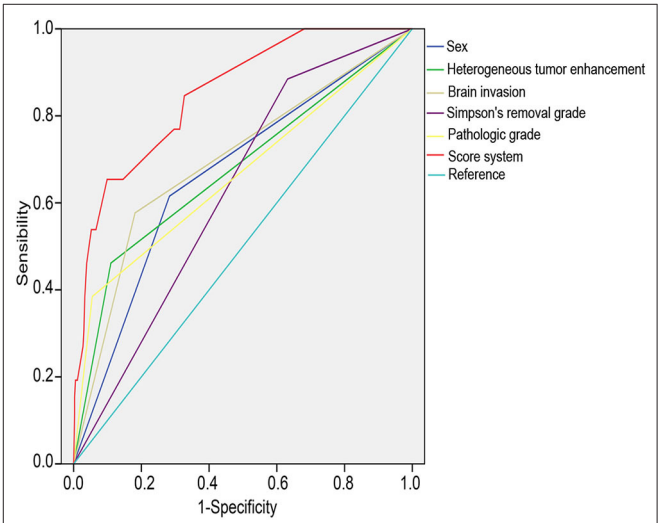


FIGURE 2 | Receiver operating characteristic (ROC) curves of the risk factors. ROC curves evaluating the probability of postsurgical recurrence according to sex, heterogeneous tumor enhancement, brain invasion, Simpson grade, and pathological grade for both individual and combined risk factors.

equation: risk scores = 100*log(X), where X = OR (**Table 3**); these values were summed to determine the composite score. Compared with the individual scores, the composite score improved the accuracy of the prediction of recurrence (i.e., a larger AUC) as follows: combined score, 0.849, 95% CI = 0.776–0.923; sex, 0.660, 95% CI = 0.548–0.772; heterogeneous tumor enhancement, 0.673, 95% CI = 0.551–0.796; brain invasion, 0.696, 95% CI = 0.580–0.911; Simpson's removal grade, 0,625, 95% CI = 0.528–0.722; and pathological grade, 0.665, 95% CI = 0.538–0.792 (**Figure 2**).

Development of the Scoring System

We plotted the ROC curves of the subjects, and the value with the maximal Youden index was selected as the cutoff point for the total scores in each patient; then, the patients was divided into four subgroups (**Table 4**). The incidences of postoperative recurrence in the patients with scores of 0–75 ($n = 249$), 76–154 ($n = 88$), 155–215 ($n = 46$), and 216–275 ($n = 9$) were 1.2, 5.7, 26.1, and 66.7%, respectively. Consistently, the result of the Kaplan-Meier's curves also showed that postoperative recurrence differed among the four subgroups (**Figure 3**). The patients with high scores, especially those with scores over 155, had a high risk of postoperative recurrence.

TABLE 4 | The postoperative recurrence of different risk groups based on score system.

Subgroup	Score	% (fraction) experiencing postoperative recurrence
Low-risk	0–75	1.2% (3/249)
Medium-risk	76–154	5.7% (5/88)
High-risk	155–215	26.1% (12/46)
	216–275	66.7% (6/9)

The table showed the percentage of patients experiencing postoperative recurrence based on the score system. Ratios were significantly different between the different risk groups (chi-square tests).

DISCUSSION

Meningiomas are the most common primary brain tumors in adults (13). Currently, the main treatment is surgery, and patients at a high risk of recurrence based on pathological reports or postoperative residuals receive adjuvant radiotherapy. However, identifying the patients who could actually benefit from this approach is controversial. Although several studies have reported the factors associated with postoperative recurrence (3, 14), no comprehensive system is available for the prediction of patients who are a high risk (7, 8) In this study, we combined the clinical, radiological, and pathological characteristics obtained from 392 patients to construct a system for the prediction of postoperative recurrence risk in meningioma. Our data reveal that sex, heterogeneous tumor enhancement, Simpson's removal grade, brain invasion, and pathological grade are independent predictors of meningioma recurrence after surgery. Furthermore, we constructed a new, simple and reliable scoring system and risk-rating model for the prediction of the postoperative recurrence of meningioma.

Independent Risk Factors and Recurrence

Previous studies have investigated the relationship between sex and recurrence risk. Escribano et al. found that the male sex was an independent risk factor for meningioma recurrence and that men were 2–3 times more likely than women to relapse (15). Wang C's research also revealed that male patients were

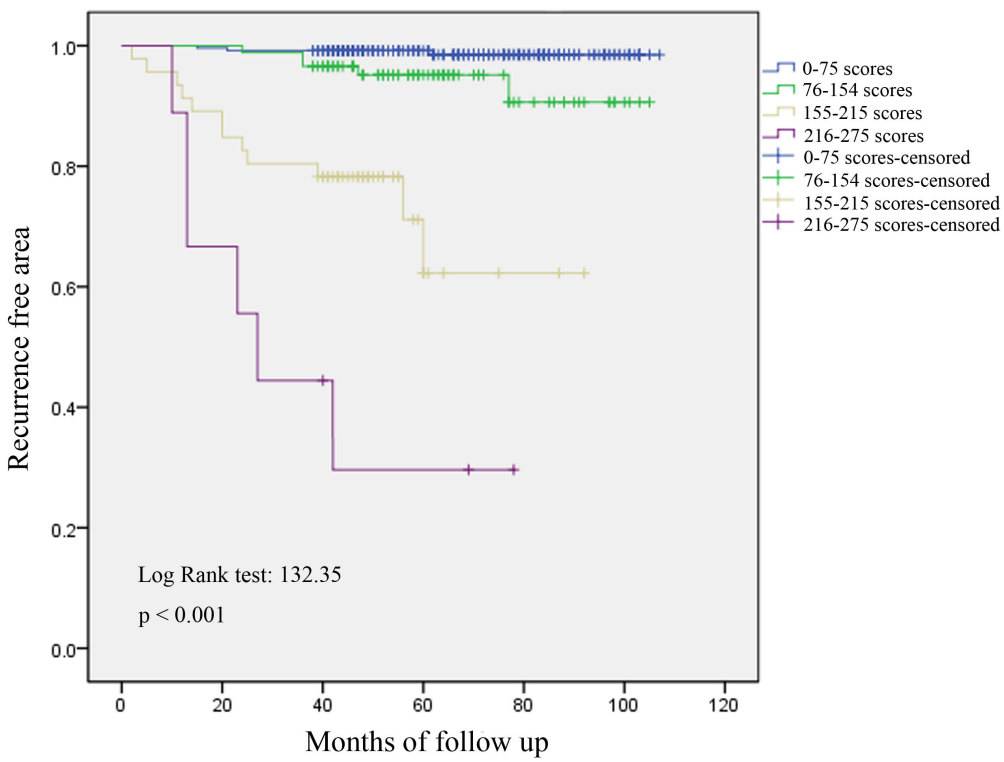


FIGURE 3 | Analysis of recurrence by Kaplan-Meier's curves in four subgroups. Postoperative recurrence differed among the four subgroups, and patients with high scores, especially over 155, had a high risk of postoperative recurrence.

at a higher risk of recurrence (16). In contrast, in WHO grade II atypical meningioma, Fernandez C et al. showed that the recurrence rates in the females were significantly higher than those in the male patients in their study, which was published in 2016 (17). In our study, we found that males had a higher proportion of WHO grade II-III meningiomas and were more likely to experience recurrence than the female patients. However, the effect of sex on meningioma recurrence remains unclear and may be related to the geographical distribution. A larger cohort study is needed to further investigate this issue.

Advances in radiography technology have made it increasingly important to analyze all radiology results, especially contrast-enhanced MRI, in meningioma. Some previous studies have also described a correlation between heterogeneous tumor enhancement and high-grade meningiomas. Lin et al. reported that heterogeneous enhancement was an independent predictor of high-grade meningioma (5). Durand also observed that all meningiomas with heterogenous enhancement (16/199 cases) were high-grade meningiomas (6). In our study, heterogeneous tumor enhancement was an independent predictor of meningioma recurrence. This finding may indicate local necrosis and higher malignancy in meningioma, which is consistent with previous studies and similar results reported in glioblastoma patients (18).

In the 2016 edition of the WHO Classification of Central Nervous System tumors, brain invasion was added as an independent criterion for atypia meningiomas, which may affect the grading and application of indirect adjuvant therapy. Therefore, this study lays the groundwork for exploring the crucial role of brain invasion, which can influence considerations regarding meningioma patients' postoperative treatment and prognosis (19). Many recent studies have also reported that a correlation exists between brain invasion and prognosis or recurrence (20–25), and our study confirms this finding. We found that brain invasion, Simpson's removal grade and the pathological grade were independent predictors of meningioma recurrence. To date, several studies have suggested that the most important prognostic factor for tumor recurrence is the histological grade (26–28). While focusing on grade I tumors, Marciscano et al. (26) demonstrated that a relationship exists between the recurrence rate and histological grade as follows: in WHO grade I tumors, the chance of recurrence was 7–25%; in grade II, the chance of recurrence was 29–59%; and in grade III, the chance of recurrence was 60–94%. Additionally, some studies have indicated Simpson's removal grade is closely correlated with the risk of recurrence (29, 30). Aizer et al. reviewed 575 and 64 patients diagnosed with atypical and malignant meningioma, respectively, and assessed the adjusted impact of gross total resection (GTR) and subtotal resection (STR) on all-cause mortality. The results showed that the extent of resection was an important index for predicting the prognosis of patients with atypical and malignant meningiomas (31). Currently, in clinical practice, Simpson's removal grade and the pathological grade are the parameters most commonly used by neurosurgeons to assess postoperative recurrence. Some studies found that the Ki-67 index was an important risk factor; however, the Ki-67 index was not an independent risk factor in our study. We believe that there may have been interference between the variables.

Prediction Model

According to the results of the univariate and multivariate analyses, we constructed a predictive scoring system and risk-rating model of meningioma recurrence. As shown in **Figure 2**, the AUC of the combined scores was significantly higher than that of the individual scores, indicating that the model was able to screen patients with a high risk of recurrence. Based on the scoring system, the patients were divided into four subgroups with scores of 0–75, 76–154, 155–215, and 216–275. According to the recurrent curves shown in **Figure 3** and the incidences of postoperative recurrence, we consider that the subgroup scoring 0–75 is at a low risk level, and postoperative adjuvant therapy is not required; the subgroup scoring 76–154 is at a medium risk level, and postoperative adjuvant therapy should be determined based on the clinical features and follow-up; the subgroups scoring 155–215 and 216–275 are at a high risk level, and further adjuvant therapy is recommended after surgery. Therefore, this model could help optimize the treatment strategies and the adoption of comprehensive adjuvant therapy in high-risk patients with the aim to decrease or slow tumor recurrence.

In a recent study, Escribano et al. reviewed 125 patients with parasagittal meningiomas and constructed a binary logistic regression model. These authors concluded that the male sex, tumor size and histologic type were independent risk factors for recurrence (15). Chohan and colleagues retrospectively analyzed the clinical data of 60 patients with histologic atypia/anaplasia at the time of the first recurrence of meningioma. A competitive risk regression model was used to analyze the predictors of second recurrence. These authors suggested increasing radiation therapy to better control the tumor and challenged the importance of the extent of resection in the first recurrence (32). Both above-described studies built a model and predicted the recurrence of meningiomas; however, compared to our study, these two previous studies included fewer patients, focused only on the risk factors and did not further quantify or classify the results. In 2014, Domingues and colleagues conducted a comprehensive and in-depth analysis of 302 meningioma patients. These authors included clinical, imaging, pathology and results and genetic testing and were the first to model, quantify and build a new prognostic classification for meningioma patients. Although these authors provided different strategies for the treatment of meningioma (33), in clinical practice, it is not easy to obtain all the information used in their study, especially the data of whole exome sequencing (WES) of the tumor tissue. In our study, routinely collected data ***were*** used, rendering our approach more accessible, more practical and easier to implement and promote in clinical practice with high accuracy.

Limitations

Our study has some limitations. First, the sample size was not large, and the level of loss to follow-up was relatively high, which may have led to statistical bias. Furthermore, this study was a retrospective study performed in a single institution, and the follow-up duration was not long enough for benign tumors.

Therefore, it is necessary to conduct a large-scale multicenter study to further validate our scoring system before it can be used in daily practice.

CONCLUSIONS

In our study, we identified the independent risk factors for postoperative recurrence of meningioma and constructed a scoring system for recurrence. This scoring system is a simple and reliable instrument that can be used to identify meningioma patients at risk of postoperative recurrence and could help optimize individualized treatment in a clinical setting, especially for high-risk patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Given the retrospective nature of the study, patient informed consent was waived.

AUTHOR CONTRIBUTIONS

ZS and WZ: conception and design, approved the final version of the manuscript on behalf of all authors, administrative/technical/material support, and study supervision. ZZ, CW, JX, CW, LX, QL, JL, and LC: acquisition of the data. ZS, ZZ, CW, JX, QL, JL, LC, and LX: analysis and interpretation of the data. ZS, WZ, and ZZ: drafting of the article. All authors: critical revision of the article, reviewed submitted version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Outcome of Tumor-Associated Proptosis in Patients With Spheno-Orbital Meningioma: Single-Center Experience and Systematic Review of the Literature

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Objective: Tumor-associated proptosis comprises a frequent phenomenon that negatively impacts quality of life in patients suffering from spheno-orbital meningioma (SOM). Therefore, proptosis outcome represents an important measure in meningioma surgery. In the current study, we analyzed our institutional database in order to evaluate the recovery of tumor-associated proptosis in patients with SOM.

Methods: Between 2009 and 2019, 32 patients with SOM underwent surgical treatment at the authors' institution. The exophthalmos index (EI) was calculated by means of preoperative and postoperative tumor-associated proptosis. Patients with preoperative EI $\geq$ 1.1 were included in further analysis. Further, we performed a systematic review of the contemporary literature. Favorable proptosis outcome was defined as postoperative decreased EI compared with preoperative EI.

Results: Overall, 25 of 32 patients with SOM (78%) suffered from preoperative proptosis in the present series. Preoperative mean EI of 1.37 $\pm$ 0.18 decreased after surgical treatment to a postoperative mean EI of 1.15 $\pm$ 0.1 during follow-up ($p < 0.0001$). Systematic review of the literature revealed three studies with individual data on preoperative and postoperative EI measurements leading to a total of 103 patients; 100 of 103 patients (97%) with SOM and preoperative proptosis achieved favorable outcome.

Conclusions: The EI provides a comparable standard in evaluation of surgical outcome in patients with tumor-associated proptosis due to SOMs. The large dataset consisting of pooled individual patient data from the systematic review of the literature and the present case series support the assumption that surgical treatment is highly effective in the treatment of tumor-associated proptosis in SOM.

Keywords: spheno-orbital meningioma, skull base surgery, proptosis-outcome, exophthalmos index, review of the literature

INTRODUCTION

Tumor-associated proptosis is a typical presenting symptom in patients suffering from spheno-orbital meningiomas (SOMs) (1, 2). In patients with SOM or other skull base meningiomas, proptosis is often perceived as cosmetically and/or functionally attenuating (2). Despite microsurgical resection representing the standard treatment modality for clinically manifest meningiomas, several previous reports have discussed the optimal surgical approach, extent of resection, and the need for orbital reconstruction (2–5). However, standardized evaluation and comparability of initial characteristics and postoperative outcome of tumor-associated proptosis were cumbersome until the implementation of the exophthalmos index (EI) by Scarone et al. in 2009 (1). Therefore, patient data that enable a robust comparability of surgical results in the case of tumor-associated proptosis in patients with SOM are scarce.

Therefore, the objective of the present study was not only to add comparable data on proptosis outcome after surgical treatment of SOM but also to enable comparison by individual patient data extraction and pooling from a systematic review of the literature leading to the largest comparable dataset on proptosis in patients suffering from SOMs.

METHODS

Patients

Between May 2009 and September 2019, 32 patients with SOM aged 18 years or older were surgically treated at our institution. Review of records was performed retrospectively after institutional review board approval had been obtained. Pertinent clinical information including age, sex, Karnofsky Performance Scale (KPS), tumor localization, tumor size, and presence of peritumoral edema, WHO grade referring to postoperative histological examination, extent of tumor resection according to the Simpson grading system, presence of preoperative visual symptoms, and presence and value of preoperative and postoperative proptosis were collected and entered into a computerized database (SPSS, version 25, IBM Corp., Armonk, NY). Furthermore, presence and value of preoperative and postoperative proptosis were independently analyzed by two authors (A-LP and PS). No disagreements were found. In addition, postoperatively worsened or newly diagnosed cranial nerve morbidity assessed at the 6-months follow-up examination as well as postoperative cerebrospinal fluid (CSF) leakage with insertion of a lumbar drainage system and/or secondary implantation of a ventriculoperitoneal shunt system as perioperative and postoperative complications was recorded.

Histopathological grading was performed according to the 2016 WHO criteria (6). All previous pathology reports underwent renewed review to confirm that diagnosis was in accordance to these requirements. Patients underwent standardized preoperative clinical, ophthalmological, computed tomography (CT), and magnetic resonance imaging (MRI) examinations. Clinical and imaging follow-up consisted of MRI scans 3 months after surgery as well as a yearly imaging for the following 5 years. Earlier clinical and imaging evaluation was advised in case of new or worsened neurological deficits as well as radiological signs of tumor recurrence or progression.

Preoperative and postoperative tumor-associated proptosis was measured by the EI as previously described by Scarone et al. (1). Therefore, a line between both anterior margins

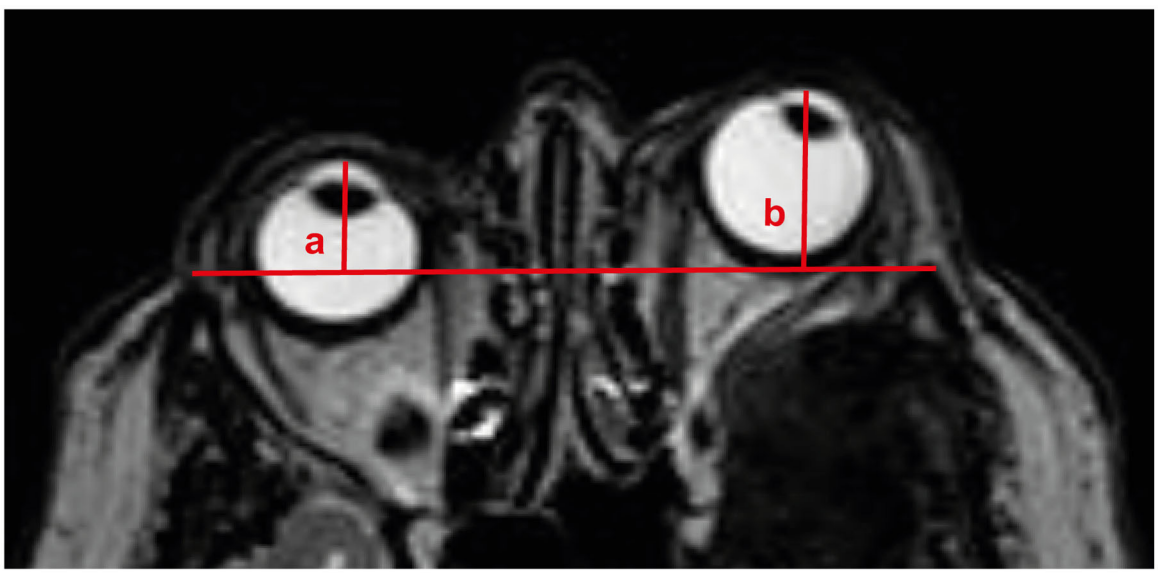


FIGURE 1 | Illustration of preoperative calculation of exophthalmos indices. The distance of the anterior limit of each eye globe to a line between both anterior margins of the frontal processes of the zygomas is measured. EI is calculated as the distance ratio between the pathological eye and the normal eye (b/a = 22.8 mm/15.3 mm = 1.5 for the presented case). EI, exophthalmos index.

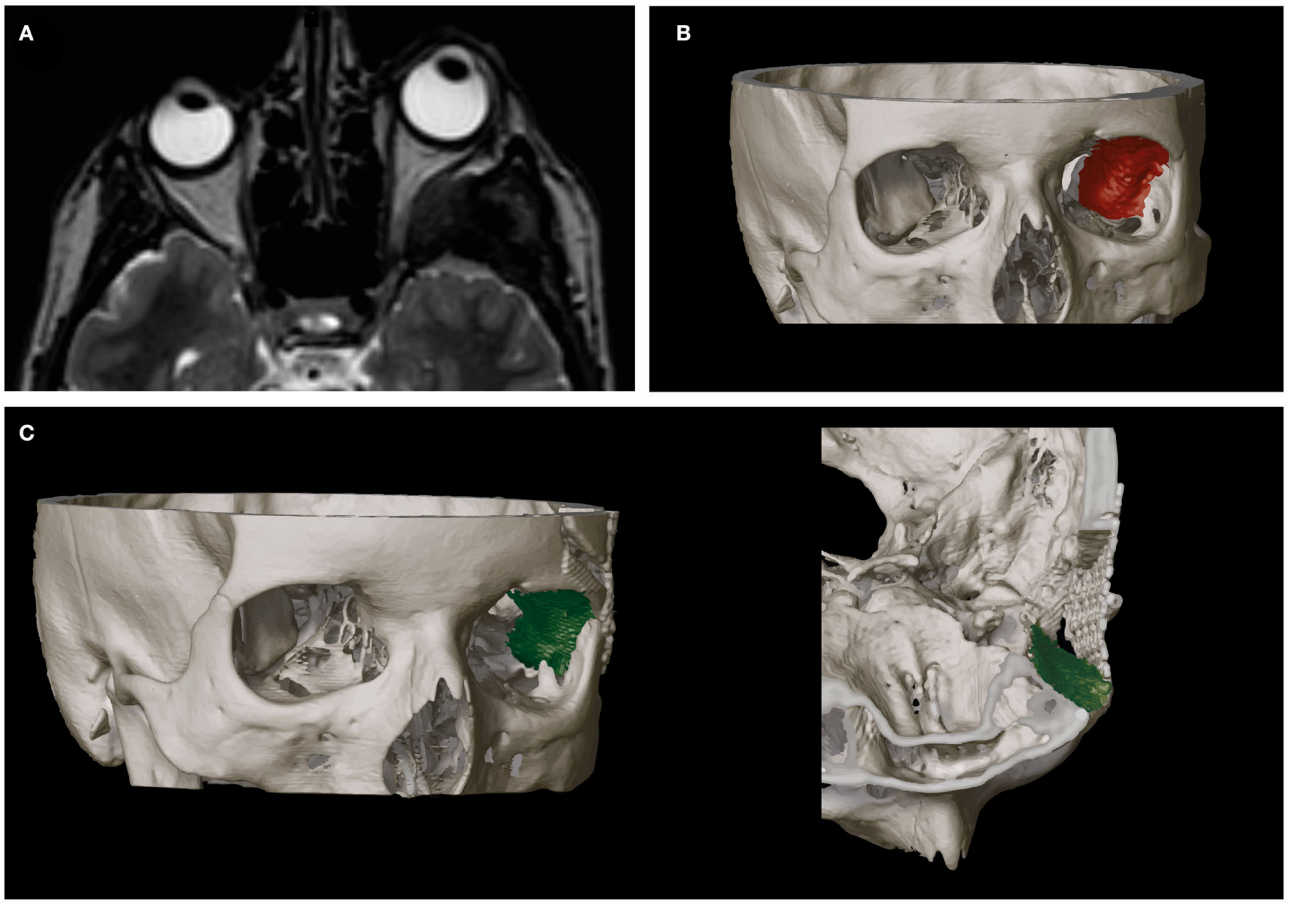


FIGURE 2 | Orbital reconstruction after removal of hyperostotic lateral orbital bone enables restoring of physiological intraorbital anatomy. Illustration of preoperative proptosis of the left eyeball **(A)** as a result of meningioma-induced lateral orbital wall hyperostosis (red) **(B)**. **(C)** Surgical reconstruction of the lateral orbital wall (green) yields removal of intraorbital space-occupying effects and restores intraorbital physiological topography (left, fronto-temporal view; right, cranial view).

of the frontal processes of the zygomas has to be drawn. Afterwards, the distance of the anterior limit of each eye globe to this line is measured, comparing the pathological eye with the unimpaired eye (**Figure 1**). Symmetric position of both ocular globes correlates to an EI of exactly 1.0, with EI $>$ 1.0 indicating proptosis. In order to reduce potential measurement inconsistency, cases of preoperative EI $<$ 1.1 were excluded from further analysis.

Surgical Approach and Orbital Reconstruction

The surgical approach consisted of frontolateral or pterional craniotomy with removal of the hyperostic bone of the lateral orbital wall. Depending on the bone infiltration caused by SOM, the orbital roof or the zygoma was partly removed. According to the treating neurosurgeon decision, an anterior clinoidectomy with unroofing of the optic canal was performed. Tumor extensions in the cavernous sinus were usually spared in order to obviate postoperative new neurological deficits. In cases of intraorbital tumor infiltration, resection was carried out with particular care for intraorbital anatomical structures.

Lateral and superior orbital walls were reconstructed to fit the anatomically normal structure for each patient using intraoperative navigation guidance. Orbital and sphenoid wing reconstruction was performed with titanium mesh in all patients (**Figure 2**).

Systematic Review

Search Methods

In order to gain a larger population, we performed a systematic review of the literature using the MEDLINE database (latest access February 2020). The following keywords were queried individually or in relevant combinations: "spheno-orbital meningioma," "exophthalmos," and "proptosis." Full-text versions were obtained from all studies that were independently reviewed and considered to be relevant by two authors (MS and A-LP). Any disagreement between the two authors was resolved in consensus meetings with the senior author (PS). References of relevant studies were searched for additional articles of interest.

Selection Criteria

We analyzed studies of patients suffering from SOM with tumor-associated proptosis as well as their references. Articles were

included when they analyzed and reported detailed individual data on preoperative and postoperative proptosis. Only studies using the EI to quantify tumor-associated proptosis were included in order to increase data comparability.

Anecdotal single case reports and case series with detailed individual data exclusively provided in a limited number of patients were excluded in order to reduce potential super-selection bias.

Data Collection and Extraction

We extracted data on patient characteristics, preoperative EI, presence of visual symptoms, surgical reconstruction technique, Simpson grade, WHO grade, postoperative EI, and postoperative visual outcome. Proptosis outcome was stratified by the reported clinical status at the last follow-up into favorable (difference between preoperative and postoperative EI > 0) vs. unfavorable (difference between preoperative and postoperative EI < 0). Data were independently extracted and verified by two authors (MS and A-LP). No disagreements were found.

Statistics

Data analyses were performed using the computer software package SPSS (version 25, IBM Corp., Armonk, NY). The D'Agostino–Pearson test was used to quantify deviations from normal distribution. In the case of $p < 0.05$, Wilcoxon matched-pairs signed rank test was performed. Results with $p < 0.05$ were considered statistically significant. Violin plots were programmed using R-software.

RESULTS

Present Series

Overall, 32 patients with SOM were treated surgically at our institution from May 2009 until September 2019; 25 of 32 patients (78%) suffered from tumor-associated proptosis with an EI > 1.1 and were therefore included in further analysis. Mean patient age was 58 ± 12 years. Simpson grade I resection was achieved in six patients (24%), Simpson grade II in 12 patients (48%), and Simpson grade III and IV resection of SOM in seven patients (28%) with tumor-associated proptosis. Histopathological assessment revealed WHO grade I tumors in 22 patients (88%), whereas three patients (12%) suffered from WHO grade II meningiomas. The median follow-up time from surgical treatment to last follow-up was 55 months. Tumor recurrence was present in four patients (16%) with one subject following Simpson grade II and III resections and two subjects following Simpson grade IV resections. Retreatment consisted

TABLE 1 | Patient characteristics in present series.

Case no.	Age (years), sex	Tumor WHO grade	Simpson grade	Cavernous sinus infiltration	Preoperative EI	Postoperative EI	Adjuvant RTX	Recurrence	FU (months)
1	53, M	I	II	Yes	1.16	1.05	No	No	23
2	52, M	II	II	No	1.25	1.04	No	No	104
3	60, F	I	II	No	1.28	1.15	No	No	89
4	51, F	I	IV	Yes	1.24	1.05	No	No	55
5	57, F	II	III	Yes	1.47	1.10	Yes	No	78
6	49, F	I	II	No	1.38	1.03	No	No	27
7	64, F	I	II	No	1.38	1.26	Yes	Yes	15
8	59, F	I	IV	Yes	1.49	1.15	No	No	12
9	66, F	I	II	No	1.17	1.03	No	No	7
10	73, F	I	I	No	1.32	1.06	No	No	107
11	78, F	I	I	No	1.37	1.25	No	No	102
12	48, F	I	I	No	1.68	1.16	No	No	99
13	39, F	I	I	Yes	1.29	1.09	No	No	99
14	29, F	I	IV	Yes	1.77	1.41	Yes	Yes	91
15	61, F	I	I	No	1.34	1.14	No	No	86
16	69, F	I	IV	No	1.77	1.39	No	Yes	82
17	79, F	I	II	No	1.20	1.11	No	No	80
18	50, F	I	II	No	1.22	1.18	No	No	77
19	69, M	I	II	No	1.31	1.19	No	No	53
20	57, F	I	I	No	1.40	1.18	No	No	53
21	52, F	I	II	No	1.34	1.13	No	No	49
22	67, F	I	II	No	1.21	1.08	No	No	38
23	56, F	I	IV	Yes	1.27	1.12	Yes	Yes	14
24	68, F	II	IV	Yes	1.68	1.23	No	No	6
25	42, F	I	II	Yes	1.24	1.10	No	No	26

WHO, World Health Organization; EI, exophthalmos index; RTX, radiotherapy; FU, follow-up; M, male; F, female.

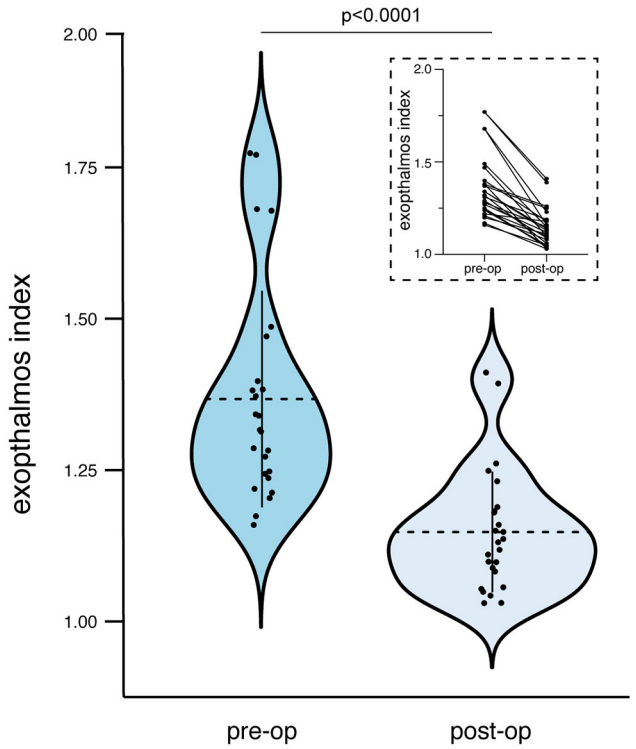


FIGURE 3 | Violin and before-after plots depicting resolution of proptosis following resection of spheno-orbital meningioma (present series). Violin plot shows mean and distribution of preoperative and postoperative EI, whereas before-after plot illustrates the difference between initial and follow-up EI for each patient individually. EI, exophthalmos index.

of adjuvant radiotherapy in four cases (16%). Further details on patient and tumor characteristics are given in **Table 1**. Postoperative new or worsened cranial nerve deficits examined 6 months after surgery were present in nine of 25 patients (36%) with SOM and tumor-associated proptosis. Thereby, cranial nerves II and III were the most affected cranial nerves accounting for three (12%) and six (24%) cases, respectively. Postoperative CSF leakage was present in two of 32 patients (6%) with secondary shunt dependency in one subject (3%).

Exophthalmos Index

Patients with tumor-associated proptosis presented in the current series with an initial mean EI of 1.37 ± 0.18. After surgical treatment, the postoperative mean EI in those patients after 6 months or at last follow-up was 1.15 ± 0.1. This results in a mean difference between initial and follow-up EI of 0.22 ± 0.12. Preoperative extent of proptosis was significantly distinct compared with the postoperative results after surgical treatment of SOM ($p < 0.0001$, CI 95% 0.17–0.27; **Figure 3**). Both Simpson grade I and II resections as an aggressive meningioma resection regime and Simpson grade III and IV resections as a rather meningioma mass reduction policy revealed a significant decrease of preoperative extent of proptosis [preoperative and postoperative mean EI of 1.52 (CI 95% 1.32–1.73) and 1.21 (CI 95% 1.08–1.34) for Simpson grades I and II, $p = 0.016$; respective values for Simpson grades II and IV were 1.31 (CI 95% 1.25–1.37) and 1.12 (CI 95% 1.09–1.16), $p < 0.0001$].

Search Result

The MEDLINE search yielded a total of 731 titles, of which 42 were considered relevant after filtering duplicates and application of our above-mentioned selection criteria. After review of the remaining articles, three studies reporting on a total of 78 patients met the inclusion criteria (**Figure 4**) (1, 2, 7). All included articles were classified as retrospective case series. Together with the current series of 25 patients with SOM and tumor-associated proptosis, there were a total of 103 patients included in the pooled dataset. Patient characteristics of the pooled data are detailed in **Table 2**.

Influence of Surgical Treatment on Proptosis

Overall, 100 of 103 patients (97%) achieved favorable proptosis outcome after surgical treatment of SOM. In detail, patients with SOM and tumor-associated proptosis in the pooled dataset presented with an initial mean EI of 1.52 ± 0.38. After surgical treatment, the postoperative mean EI in those patients after the last follow-up reported in the selected studies was 1.25 ± 0.28. This results in a mean difference between initial and last reported follow-up EI of 0.27 ± 0.26. Therefore, in the pooled data, preoperative extent of proptosis was significantly distinct as compared with the postoperative results after surgical treatment of SOM ($p < 0.0001$, CI 95% 0.18–0.4; **Table 2**).

DISCUSSION

Tumor-associated proptosis represents common concomitant impairment in patients with SOM. Despite cosmetic issues, certain impairment of functionality might result from tumor-associated proptosis (8). However, a rising number of reports stated that surgical treatment of SOM influences favorable outcome of tumor-associated proptosis in multiple fashion.

Reconstruction of the Orbit

Surgical reconstruction of the orbit in patients with SOM is still a controversially discussed topic. Heller et al. counteracted several considerations concerning the orbital wall reconstruction due to discussing the influence of the overall orbital volume after reconstruction (8). Heller et al. suggested three potential considerations with (a) smaller orbital reconstruction due to previous chronic compression and fat necrosis leading to a smaller orbital volume, (b) larger orbital reconstruction in order to prevent postoperative scar tissue to impair venous drainage from the orbita, and (c) orbital volume reconstruction estimated as anatomically normal for each patient (8). Furthermore, multiple techniques and materials for orbital reconstruction have been described previously (3, 4, 9).

In cases of absent orbital reconstruction, risk of postoperative development of pulsatile enophthalmos, meningoceles, diplopia, and extraocular muscle fibrosis leading to ophthalmoplegia should be often remembered (7, 10, 11). However, several groups reported their experience on improvement of tumor-associated

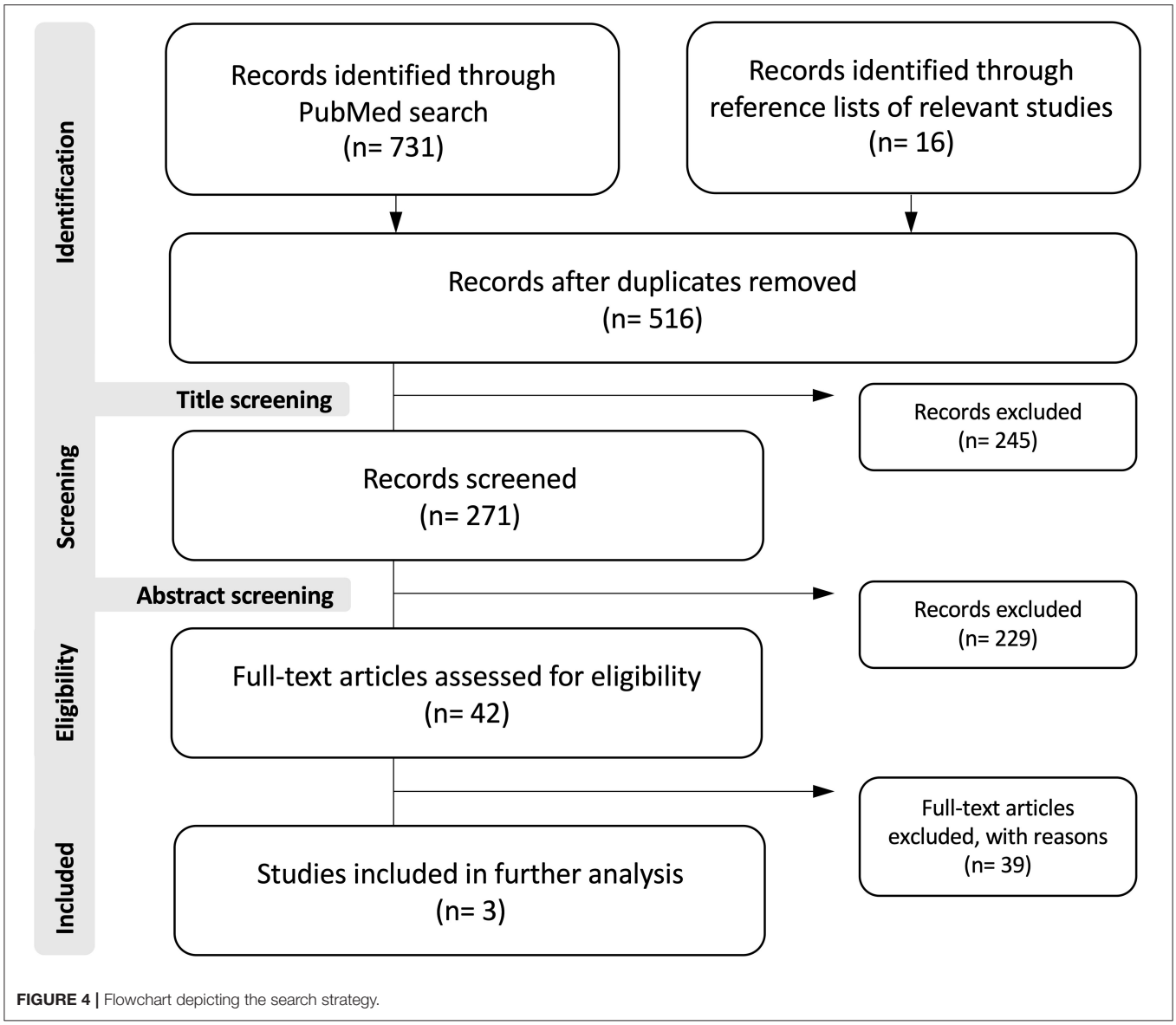


FIGURE 4 | Flowchart depicting the search strategy.

proptosis after no orbital reconstruction was performed after surgery leading to satisfactory cosmetic results, and they pointed out the above-mentioned complications must not necessarily result (7, 10).

In the present study, all patients underwent rigid individual orbital reconstruction of the lateral orbital wall using titanium mesh leading to favorable proptosis outcome.

Change in Surgical Strategy

Meanwhile, before controversial discussions of orbital reconstruction methods and needs, the surgical strategy in patients suffering from SOM itself was the subject of several arguments. Previously, aggressive tumor excisions including the resection of the dural tail providing the best tumor control rates were postulated. However, concerning the location of SOM and delicate structures of the orbital cone, radical resection might facilitate postoperative complications (1, 4). Furthermore, previous reports stated a high level of new cranial nerve morbidity after radical removal of frontal skull base meningiomas in previous decades (12–14). Ringel et al. reported 30% new cranial nerve deficits after surgical resection of SOM in a large series of patients treated from 1983 to 2006 (4). Therefore, a recent shift from aggressive surgical therapy toward a symptom-oriented surgery has witnessed symptom-oriented surgery in patients with SOM, mainly with focus on optic nerve decompression or treatment of proptosis (1, 5). The present series confirmed the rationale behind this paradigm shift by revealing profound reduction of preoperative EI in both case of aggressive Simpson grade I/II and Simpson grade III/IV resections as rather decompressive resection regimens.

The most recent studies disprove the assumption that only initial radical resection of SOM enhanced long-term tumor

TABLE 2 | Systematic review on proptosis outcome following spheno-orbital meningioma resection.

Authors and year	Patients included in further analysis	Mean preoperative EI ± SD	Mean postoperative EI ± SD	Patients with favorable proptosis outcome (%)
Scarone et al., 2009 (1)	30	1.88 ± 0.44	1.51 ± 0.37	29 (97)
Bowers et al., 2016 (2)	32	1.39 ± 0.28	1.13 ± 0.14	32 (100)
Freeman et al., 2017 (7)	16	1.33 ± 0.17	1.15 ± 0.13	14 (88)
present series, 2020	25	1.37 ± 0.18	1.15 ± 0.09	25 (100)
Total	103	1.52 ± 0.38	1.25 ± 0.28	100 (97)

EI, exophthalmos index; SD, standard deviation.

control in these patients (1, 4, 15). Long-term surveillance with constant follow-up consultation seems the widely accepted monitoring method in patients with SOM with repeated surgery when tumor recurrence causes cranial nerve deficits, such as visual symptoms (1, 11, 16).

Further, the symbiotic role of postoperative radiotherapy is evolving (17). In patients with higher WHO grading and/or necessity of rigorous tumor control, radiosurgical treatment after partial resection and surgical decompression of essential intracranial structures is increasingly advocated by several authors (15, 17). In the present series, successful orbital decompression indicated by sufficient decrease in preoperative EI was followed by postoperative radiotherapy in four patients with recurrent meningioma. Thus, with regard to adjuvant secondary treatment modalities, aggressive meningioma excisions in high-risk areas for increased postoperative morbidity such as the spheno-orbital region hardly seem to be justified with regard to an improvement in the rate of postoperative tumor recurrence.

Resolution of Proptosis After Surgical Treatment

Postoperative results of tumor-associated proptosis are inconsistently reported throughout the literature with mostly reporting on proptosis improvement in qualitative terms that do not entirely reflect the individual variability in ocular globe position (1, 2, 8). The number of studies investigating the influence of surgical treatment on correction of tumor-associated proptosis in a quantifiable fashion is limited (1, 2, 8). Therefore, Scarone et al. established the EI in 2009 (1). The EI is a simple tool producing reliable data that can be compared across different studies (8). Due to this previously mentioned comparability, we performed a systematic review of the literature, extracted individual patient data meeting our inclusion criteria, and gained the largest comparable patient dataset concerning resolution of tumor-associated proptosis after surgery for SOM. The results of our own present series are in line with those of the literature. The pooled data with a favorable proptosis outcome in 97% of the treated patient led to the assumption that surgical treatment of tumor-associated proptosis is promising. However, more studies are desirable, which present comparable data by the use of EI measurements for further and detailed comparison of patients with SOM regarding the different reconstruction and treatment strategies.

LIMITATIONS

The present study has several limitations. Acquisition of data was retrospective. Patients were not randomized but treated by the preference of the treating. However, the use of the EI as measuring instrument enables reliable and quantitative assessment of proptosis. The limited number of studies reporting data on EI and SOM nevertheless presented individual patient data, which allowed qualitative data pooling and therefore establishment of a large patient dataset for further analysis. However, the results of the present pooled dataset should engage further prospective study of SOM regarding surgical techniques as well as quantitative proptosis outcome.

CONCLUSIONS

The EI provides a comparable standard in evaluation of surgical outcome in patients with tumor-associated proptosis due to SOMs. The large dataset consisting of pooled individual patient data from the systematic review of the literature and the present case series supports the assumption that surgical treatment is highly effective in the treatment of tumor-associated proptosis in SOM.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics Committee at the University Hospital Bonn. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Conceptualization was performed by MS, PS, and UH. MS, A-LP, and PS performed the methodology and statistical analysis. Data collection was performed by A-LP, VB, and AH. Figures were provided by MS, A-LP, and PS. MS and PS wrote the original draft and supervised the study. Proof-reading was done by MS, A-LP, NS, ÁG, HV, EG, and PS.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Small Cerebellopontine Angle Meningioma—Surgical Experience of 162 Patients and Literature Review

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Objective: To retrospective analyze the clinical data of 162 patients with small cerebellopontine angle meningiomas. To compare with the nature of tumors, symptoms pre- and post-treatments, neurological deficit, and prognosis in literatures. To explore the surgical outcomes of small cerebellopontine angle meningiomas and summarize the surgical experience.

Methods: All of 162 patients with small cerebellopontine angle meningiomas underwent surgery between January 2010 and December 2019 in the neurosurgery department of the First Affiliated Hospital of Soochow University. This cohort of eight literatures reported about stereotactic radiotherapy of small cerebellopontine angle meningiomas between January 2010 and December 2019. All clinical data were obtained for analysis.

Results: Compared with stereotactic radiotherapy, surgical treatment for small cerebellopontine angle meningiomas lead to the better results in relieving symptoms and inhibiting tumor progression. Surgical treatment can obtain the exact pathological examination results to guide the further treatment.

Conclusions: Surgical treatment should be the first choice for small cerebellopontine angle meningiomas.

Keywords: small cerebellopontine angle meningioma, stereotactic radiotherapy, surgical treatment, symptom deterioration, tumor enlargement, further treatments

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INTRODUCTION

Cerebellopontine angle meningiomas account for 6–15% of the tumors in the cerebellopontine angle region (1). They are characterized by the deep tumor location, narrow surgical field, and proximity to the brainstem, multiple pairs of (V–XI) cranial nerves (2). At present, surgical treatment is the first choice for large cerebellopontine angle meningiomas, while small cerebellopontine angle meningiomas are always treated by stereotactic radiotherapy, pharmacotherapy and experimental therapy (3). In recent years, many studies have found that stereotactic radiotherapy had the limitations of low tumor control rate, post-treatment brain edema, and tissue adhesion, which hindered the further treatments (4). Therefore, more and more small cerebellopontine angle meningioma patients are turning to surgical treatment.

MATERIALS AND METHODS

Study Design

A retrospective analysis of small cerebellopontine angle meningioma patients was performed. These patients were operated on in the neurosurgery department of the First Affiliated Hospital of Soochow University between January 2010 and December 2019. These patients were classified as the surgery group. We also reviewed the literature on stereotactic radiotherapy of small cerebellopontine angle meningiomas from the past 10 years. The clinical data of patients in the literature were collected and analyzed, and these patients were classified as the radiotherapy group. We analyzed the differences between the two groups, including the nature of tumors, symptoms pre- and post-treatments, neurological deficits, and prognosis. Finally, we explored the surgical outcomes of small cerebellopontine angle meningiomas and summarized the surgical experience.

Inclusion Criteria

Diagnosis

To distinguish meningiomas from other cerebellopontine angle tumor, such as acoustic neuromas and gliomas, all the patients were diagnosed by both radiological and histopathological examination, including MRI, CT, PET, and SSTR2 ligands. Both the dural tail sign on MRI and no expansion of internal auditory canal on CT are the main differential points between cerebellopontine angle meningiomas and acoustic neuromas. To differentiate cerebellopontine angle meningiomas from gliomas and metastases, patients were conventionally tested by MR spectroscopy (5). In terms of histological aspects, immunohistochemical analysis was also conventionally tested, such as HE staining, Vimentin staining, EMA staining, Ki-67 and CD56.

Surgery Group

(1) The patients with small cerebellopontine angle meningioma were operated between January 2010 and December 2019, (2) tumor volume ≤ 8 cm^3, (3) no related treatment before surgery, (4) no other nervous system diseases, and (5) kept in touch during follow-up.

Radiotherapy Group

(1) The patients with small cerebellopontine angle meningioma were collected from the literature about stereotactic radiotherapy, which published between January 2010 and December 2019, (2) the included patients had complete pre- and post-treatment data, (3) no other nervous system diseases, and (4) kept in touch during follow-up.

Follow-up consisted of routinely visiting the patients and performing MRI or CT tests every 3–6 months for the first 3 years after treatment, and then visiting and testing every year.

Classification of Tumors

Based on the central site of dural attachment, cerebellopontine angle meningiomas were classified into three types (6): anterior tumors were those that originated from the tentorium cerebelli or the petrous bone dura anterior the internal auditory canal; middle tumors were those that originated from the dura mater in the internal auditory canal; posterior tumors were those that originated from the sigmoid and transverse sinuses or the petrous bone dura posterior the internal auditory canal (**Figure 1**).

Based on tumor pathology, cerebellopontine angle meningiomas were classified into three grades: WHO grade I (low recurrence and low invasive growth), WHO grade II (high recurrence and high invasive growth), and WHO grade III (strong recurrence and metastasize systemically).

Based on the grade of tumor resection, patients with cerebellopontine angle meningiomas were divided into five grades: Simpson grade I: total resection of the meningioma, dural attachment, and skull; Simpson grade II: total resection of the meningioma and electrocoagulation or laser treatment with dural attachment; Simpson grade III: total resection of meningiomas and no treatment with the dural attachment and skull; Simpson grade IV: partial resection of meningiomas; Simpson grade V: decompression and tumor biopsy.

Tumor progression and regression were defined as volume changes of more than 15% on radiological examination.

Surgical Program

All of the patients were using the suboccipital retrosigmoid approach. A suboccipital retrosigmoid straight incision of about 8–10 cm was made on the affected side. The long diameter of the oval bone window was 5 cm, and the short diameter was 3.5 cm. The bone window up to the transverse sinus, lateral to the mastoid root, exposed the angle between the sigmoid and transverse sinus. Cut the dura, stretched the cerebellum, opened up the cisterna magna, and released the cerebrospinal fluid. Finally, the cerebellopontine angle meningioma was completely resected, taking care to protect the petrous vein, the trigeminal nerve, and the abducens nerve. During the operation, electrophysiological monitoring was used to monitor the facial and acoustic nerves.

Statistical Analysis

All of the statistical analyses were performed with SPSS version 22.0. The parametric continuous variables were reported as mean $\pm$ standard deviation. The non-parametric variables were reported as the median with the range. Clinical outcomes and signs and symptoms were reported as three-category data (improvement or enlargement, no change, deterioration or diminution). The independent samples *t*-test was performed for two categories of data, and ANOVA was performed for three-category data. The chi-square test was performed to compare nominally distributed categorical variables. Logistic regression analysis was performed for multivariate analyses. *P*-values less than 0.05 were considered to be statistically significant.

RESULTS

Surgery Group

Participants

A total of 162 patients with small cerebellopontine angle meningioma were included, including 53 males and 109 females,

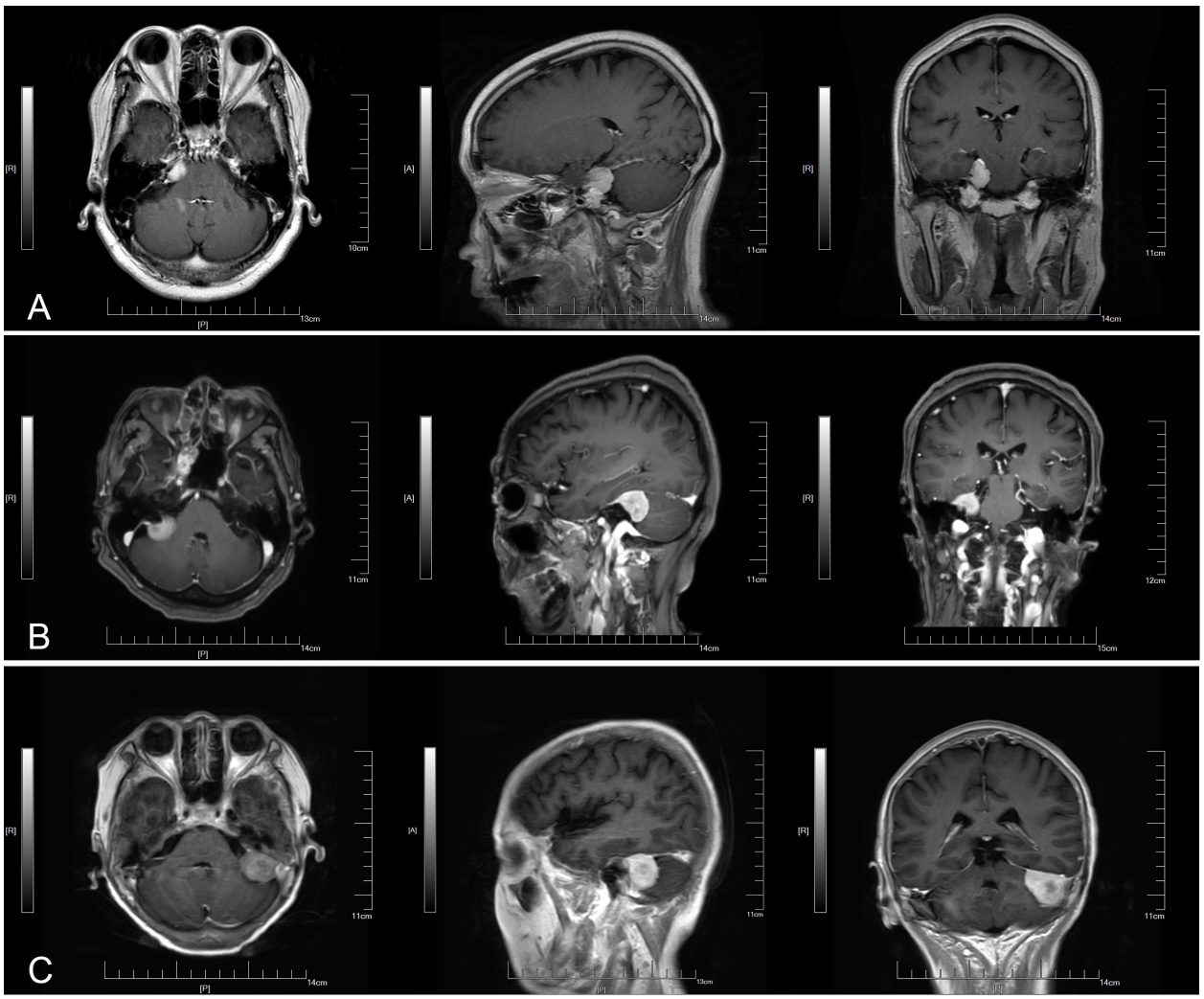


FIGURE 1 | Three types of small cerebellopontine angle meningiomas. **(A)** Anterior. **(B)** Middle. **(C)** Posterior.

with an average age of 54.85 years (21–89 years). The preoperative symptoms were headache and dizziness (96), hearing loss and tinnitus (48), facial sensation and paralysis (29), walking instability and ataxia (28), hoarseness, poor cough reflex (16). There were 77 patients with two or more symptoms and 64 patients without symptoms before diagnosis.

The Nature of the Tumors

The volume of tumors ranged from 1.042 to 8.161 cm^3, with an average of 4.710 cm^3; 72 patients had anterior tumors, 41 patients had middle tumors, and 49 patients had posterior tumors; 148 patients had WHO grade I tumors, and 14 patients had WHO grade II tumors.

Surgical Outcomes

There were 152 cases of Simpson grade I and 10 cases of Simpson grade II, 41 cases of post-operative symptom relief, 110 cases of no significant change, 11 cases of aggravation or new symptoms.

Radiotherapy Group

A total of 1644 patients with small cerebellopontine angle meningioma were included, including 335 males and 1309 females (**Table 1**).

Of the radiotherapy group, 971 patients (59.1%) had no significant change in symptoms after treatment, 546 patients (33.2%) showed an improvement in symptoms, and 127 patients (7.7%) showed a worsening of symptoms or developed new neurological symptoms.

There were 151 patients (9.2%) in the radiotherapy group with tumor recurrence during follow-up.

There were 54 patients (3.3%) received second stereotactic radiotherapy, and 62 patients (3.8%) underwent surgery during follow-up.

Symptomatic Outcomes

Of the surgery group, 102 patients (63.0%) had no significant change in symptoms after surgery, 49 patients (30.2%)

showed an improvement in symptoms, and 11 patients (6.8%) showed a worsening of symptoms or developed new neurological symptoms. There was no significant difference in the symptom deterioration rate between the surgery group and the radiotherapy group, with the exception of Andrew et al.'s study (**Table 2**). The symptom deterioration rate of Andrew et al. was significantly higher than that of the surgery group.

Radiologic Outcomes

There were 10 patients (6.2%) in the surgery group with tumor recurrence during follow-up. We found no significant difference in tumor enlargement rate between the surgery group and the radiotherapy group, with the exception of Robert et al. (**Table 3**). The tumor enlargement rate of Robert et al. was significantly higher than that of the surgery group.

Further Treatment

In the surgery group, there was one patient (0.6%) who underwent a second resection, and 12 patients (7.4%) received stereotactic radiotherapy during follow-up. We found no significant difference in the further treatment rate between the surgery group and the radiotherapy group, except for Kyung et al. and Andrew et al. (**Table 4**). The further treatment rate of Kyung et al. was significantly lower than that of the surgery group, while the further treatment rate of Andrew et al. was significantly higher than that of the surgery group.

In the surgery group, WHO grade II and Simpson grade II were risk factors of further treatment (**Table 5**).

DISCUSSION

The choice of surgery or stereotactic radiotherapy depends on the general situation of patients and the nature of tumors (7). Most of cerebellopontine angle meningiomas belong to benign tumors. The surgical effect of cerebellopontine angle meningiomas is always satisfied, and the rates of both post-operative symptom deterioration and tumor enlargement are lower than other nervous system tumors. However, the compression of

TABLE 1 | Characteristics of patients in literatures.

	Sex (M/F)	Age	Tumor volume	Symptomatic outcomes			Radiologic outcomes			Further treatment	
				No change	Improvement	Deterioration	No change	Diminution	Enlargement	Radiotherapy	Surgery
Kim et al. (13)	34/119	56.6 ± 7.4	2.5 (0.22–3.81)	57	92	4	91	53	9	1	1
Ge et al. (14)	23/107	54.5 (25–81)	3.68 (0.23–4.58)	83	40	7	86	37	7	4	3
Jahanbakhshi et al. (15)	18/75	52.2 (25–79)	6.0 (1.5–7.42)	36	46	11	38	52	3	3	6
Patibandla et al. (16)	28/92	61 (12–88)	4.0 (0.4–6.1)	85	28	7	21	86	13	2	2
Faramand et al. (17)	10/31	61 (39–83)	3.1 (0.3–7.1)	18	16	7	20	15	6	9	5
Sheehan et al. (18)	140/535	57.6 (12–89)	6.5 (0.15–8.14)	424	201	50	275	336	64	10	24
Starke et al. (19)	54/201	55 (19–85)	5.0 (0.3–5.5)	208	22	25	95	125	35	16	14
Ding et al. (20)	28/149	59.2 ± 12.18	3.6 (1.9–6.2)	60	101	16	81	82	14	9	7
Summary	335/1309	–	–	971	546	127	707	786	151	54	62

TABLE 2 | Symptom deterioration rate.

	Number	Symptom deterioration	λ^2 Value	*p* Value
Kim et al. (13)	153	4	3.025	0.082
Ge et al. (14)	130	7	0.246	0.620
Jahanbakhshi et al. (15)	93	11	1.902	0.168
Patibandla et al. (16)	120	7	0.106	0.745
Faramand et al. (17)	41	7	4.281	0.039*
Sheehan et al. (18)	675	50	0.074	0.786
Starke et al. (19)	255	25	1.141	0.286
Ding et al. (20	177	16	0.584	0.445
Surgery group	162	11	–	–

**Statistically significant ($p < 0.05$).*

TABLE 3 | Tumor enlargement rate.

	Number	Tumor enlargement	λ^2 Value	*p* Value
Kim et al. (13)	153	9	0.012	0.914
Ge et al. (14)	130	7	0.082	0.775
Jahanbakhshi et al. (15)	93	3	1.061	0.303
Patibandla et al. (16)	120	13	1.999	0.157
Faramand et al. (17)	41	6	3.226	0.073
Sheehan et al. (18)	675	59	1.139	0.286
Starke et al. (19)	255	35	5.870	0.015*
Ding et al. (20)	177	14	0.388	0.533
Surgery group	162	10	–	–

**Statistically significant ($p < 0.05$).*

TABLE 4 | Further treatment.

	Number	Further treatment	λ^2 Value	*p* Value
Kim et al. (13)	153	2	7.829	0.005*
Ge et al. (14)	130	7	0.788	0.375
Jahanbakhshi et al. (15)	93	9	0.205	0.651
Patibandla et al. (16)	120	4	2.678	0.102
Faramand et al. (17)	41	14	19.36	<0.0001*
Sheehan et al. (18)	675	34	2.200	0.139
Starke et al. (19)	255	30	1.498	0.221
Ding et al. (20)	177	16	0.111	0.739
Surgery group	162	13	–	–

**Statistically significant ($p < 0.05$).*

TABLE 5 | Risk factors of further treatments.

Risk factors	*p* Value	OR	95% CI
WHO II grade	0.045	2.504	0.108–58.24
Simpson II grade	0.001	20.34	0.829–49.90

the brain stem and cerebellum is a frequent occurrence of cerebellopontine angle meningiomas, especially in patients with large cerebellopontine angle meningiomas, the high intracranial pressure can lead to herniation and acute hydrocephalus. Either complete or partial resection can significantly reduce the risk of complications. Hence, surgery is the best choice for patients with large cerebellopontine angle meningiomas. For small cerebellopontine angle meningiomas, stereotactic radiotherapy, including Gamma Knife, cyber knife and other types of linear accelerator (8), is universally acknowledged as the first choice. With the development of medical treatment and the popularization of MRI, the early diagnosis of cerebellopontine angle meningioma in the small-volume or asymptomatic stage turns to possible. Early diagnosis and treatment greatly improve the prognosis of cerebellopontine angle meningioma, as well as bringing a confusion of choice between surgery and stereotactic radiotherapy for small cerebellopontine angle meningioma. In consideration of the edema and adhesion of brain tissue after stereotactic radiotherapy, which hindered the further surgery, more and more studies have supported early surgical treatments.

In terms of relieving pre-operative symptoms, the symptom deterioration rate in surgery group was similar to or even lower than the rate in radiotherapy group. Compared with stereotactic radiotherapy, surgical treatment can sometimes lead to better results in relieving pre-operative symptoms. Edema of peripheral brain tissue is a common side effect of stereotactic radiotherapy. Swelling of brain tissue will aggravate the tension and compression of nerves, which is the reason why the symptoms become worse after stereotactic radiotherapy. In order to reduce nerve injury and relieve symptom deterioration, operators need to carefully protect brain tissue, nerves, and blood vessels during the surgery. Compared with regular cerebellopontine angle meningiomas, surgical operation on small cerebellopontine angle meningiomas requires more protection for nerves and blood vessels, and neuroelectrophysiological monitoring during the whole surgery process is deemed essential, which contributes to the lower symptom deterioration rate in the surgery group. The most common clinical manifestation of small cerebellopontine angle meningiomas is functional defects of the facial and auditory nerves. Hence, protecting the facial and auditory nerves is a key point of surgery. Different types of cerebellopontine angle meningiomas will push the facial and auditory nerves to different positions (9). Thus, the first step of small cerebellopontine angle meningiomas surgery is locating the facial and auditory nerves. Anterior tumors generally push the facial and auditory nerves to the lateral or lateral inferior side. Posterior tumors generally push the facial and auditory nerves to the medial or medial inferior side. Middle tumors generally push the facial and auditory nerves vertically (**Figure 2**). Due to the compression of the tumor, the facial and auditory nerves are often elongated and become thin and discolored.

During the surgery, the operator needs to insist on sharp separation when separating the tumor from the facial and auditory nerves. The traction of the facial and auditory nerves and cerebellum should be minimized. The nutrient vessels around the facial and auditory nerves should be preserved as much as possible. Although the facial and auditory nerves are anatomically preserved after surgery, the loss of nerve function still exists in many patients, which may be result from the invasive growth of tumors, intraoperative traction, and heat conduction injury caused by electrocoagulation (10). Effective intraoperative neuroelectrophysiological monitoring can lessen the neuron injury by enabling the timely location of the facial and auditory nerves, thus increasing the rate of nerve function preservation.

In terms of inhibiting tumor progression, the tumor recurrence rate in the surgery group is similar to or even lower than the tumor enlargement rate in the radiotherapy group. Compared to stereotactic radiotherapy, surgical treatment can lead to the better results in inhibiting tumor progression. Stereotactic radiotherapy, mainly referring to Gamma Knife and cyber knife, suppresses tumor progression by killing tumor cells. The target of stereotactic radiotherapy is generally located in the center of tumors, and its dose decreases with the distance away from the center of tumors. Although peripheral dose enhancement technology has emerged in recent years, the

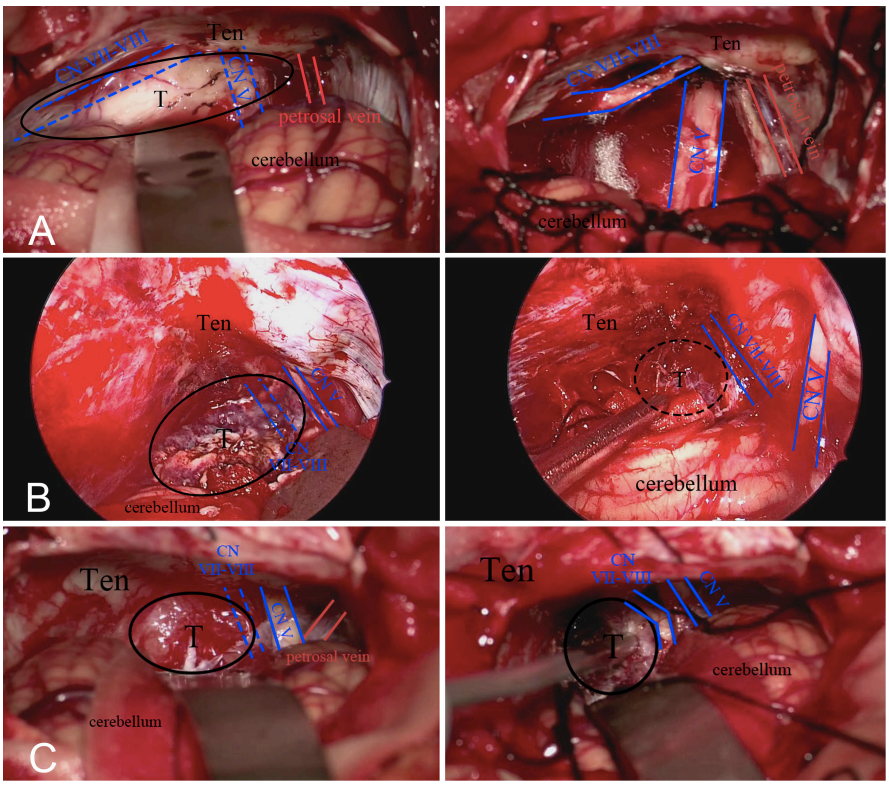


FIGURE 2 | (A) Anterior tumors push the facial and auditory nerve to the lateral side. **(B)** Middle tumors push nerve to the ventral aspect. **(C)** Posterior tumors push nerve to the medial inferior side.

problem of incomplete tumor boundary inactivation still exists, which also leads to the increase of the tumor enlargement rate in the radiotherapy group (11). For the surgical treatment of small cerebellopontine angle meningiomas, total resection of the tumor, dural attachment, and skull are key to preventing tumor recurrence. In the surgical principle, the operator needs to resect the dural attachment and skull after the tumor resection to achieve Simpson grade I. When the dural attachment and skull were resected incompletely, electrocoagulation is essential to reduce the possibility of tumor recurrence and achieve Simpson grade II. With the development of radiofrequency laser scalpels and other microinstruments, the surgical treatment of dural attachment and skull resection is becoming more and more standardized. The overall tumor resection rate of small cerebellopontine angle meningiomas is increasing, and the tumor recurrence rate is decreasing year by year.

Many radiotherapy studies have reported that the recurrence of small cerebellopontine angle meningiomas is connected with the pathology of the tumors. WHO grade II meningiomas are more likely to recur than WHO grade I meningiomas, which is related to the characteristic of high invasive growth. However, stereotactic radiotherapy cannot obtain the tumor tissue to examine the pathology of the tumor directly. Therefore, the grade of cerebellopontine angle meningiomas treated with radiotherapy is mostly inferred from imaging examination, which is uncertain. Contrary to stereotactic radiotherapy, surgery can directly obtain tumor tissue for pathological examination and guide further treatment through the exact pathological examination results. In the present study, WHO grade II and Simpson grade II were the risk factors of tumor recurrence after surgery. Therefore, patients with WHO grade II or Simpson grade II who undergo surgery need to receive further treatments at the early stage instead of waiting for the recurrence of tumors. This is also the reason why the recurrence rate in the surgery group was slightly lower than the tumor enlargement rate in the radiotherapy group.

In terms of further treatments, the further treatment rate in the surgery group was similar to or even lower than that reported in the radiotherapy group. Hence, compared with stereotactic radiotherapy, patients with surgical treatment might have a lower likelihood of further treatments. In Kyung et al.'s study, the subjects were asymptomatic patients with small cerebellopontine angle meningiomas. A lack of symptoms or relatively mild symptoms could significantly reduce the subjective desire of patients for treatment, which may be why the further treatment rate in Kyung et al. was lower than that reported in the surgery group. In the radiotherapy group, there was no significant difference between the number of patients who chose further radiotherapy and the number of patients who turned to surgery. In the surgery group, there was 1 patient (0.6%) who underwent a second resection, and 12 patients (7.4%) received stereotactic radiotherapy during follow-up. The reason for further radiotherapy for patients in the surgery group was

the high invasiveness of the tumor and the incomplete treatment of the dural attachment and skull (12). Similar to other meningiomas, stereotactic radiotherapy of small cerebellopontine angle meningiomas is more likely to be an auxiliary treatment for inhibiting tumor progression after surgery.

The surgical complications mainly included dysfunction of the facial and auditory nerves, trigeminal nerve, and posterior cranial nerves as well as hydrocephalus. Facial paralysis, facial numbness, and hearing loss can seriously affect the quality of life of patients after surgery. The symptoms of posterior cranial nerve damage, such as hoarseness, dysarthria, and weakened cough reflex, significantly affect the prognosis of patients after surgery. Because of the small size of the tumor, complications, such as hydrocephalus and intracerebral hemorrhage, are rare in patients with small cerebellopontine angle meningiomas.

CONCLUSION

Compared with stereotactic radiotherapy, surgical treatment for small cerebellopontine angle meningiomas can sometimes lead to better results in relieving pre-operative symptoms and inhibiting tumor progression. In terms of further treatments, compared with the uncertainty of stereotactic radiotherapy, surgical treatment can obtain exact pathological examination results to guide the further treatment. Similar to large tumors, surgical treatment should be the first choice for small cerebellopontine angle meningiomas, while stereotactic radiotherapy, pharmacotherapy and experimental therapy are more suitable as supplement to surgical treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Soochow University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW and GC designed the study. JB, PP, HY, WG, YL, ZY, and ZW performed the experiments and analyzed the data. JB wrote the manuscript. All the authors read and approved the manuscript. JB, PJ, and HY have contributed equally to this work. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Resection of Olfactory Groove Meningiomas Through Unilateral vs. Bilateral Approaches: A Systematic Review and Meta-Analysis

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Introduction: Consensus is limited regarding optimal transcranial approaches (TCAs) for the surgical resection of olfactory groove meningiomas (OGMs). This systematic review and meta-analysis aims to examine operative and peri-operative outcomes of unilateral compared to bilateral TCAs for OGMs.

Methods: Electronic databases were searched from inception until December 2019 for studies delineating TCAs for OGM patients. Patient demographics, pre-operative symptoms, surgical outcomes, and complications were evaluated and analyzed with a meta-analysis of proportions.

Results: A total of 27 observational case series comparing 554 unilateral vs. 451 bilateral TCA patients were eligible for review. The weighted pooled incidence of gross total resection is 94.6% (95% CI, 90.7–97.5%; $I^2 = 59.0\%$; $p = 0.001$) for unilateral and 90.9% (95% CI, 85.6–95.4%; $I^2 = 58.1\%$; $p = 0.003$) for bilateral cohorts. Similarly, the incidence of OGM recurrence is 2.6% (95% CI, 0.4–6.0%; $I^2 = 53.1\%$; $p = 0.012$) and 4.7% (95% CI, 1.4–9.2%; $I^2 = 55.3\%$; $p = 0.006$), respectively. Differences in oncologic outcomes were not found to be statistically significant ($p = 0.21$ and 0.35, respectively). Statistically significant differences in complication rates in bilateral vs. unilateral TCA cohorts include meningitis (1.0 vs. 0.0%; $p = 0.022$) and mortality (3.2 vs. 0.2%; $p = 0.007$).

Conclusions: While both cohorts have similar oncologic outcomes, bilateral TCA patients exhibit higher post-operative complication rates. This may be explained by underlying tumor characteristics necessitating more radical resection but may also indicate increased morbidity with bilateral approaches. However, evidence from more controlled, comparative studies is warranted to further support these findings.

Keywords: olfactory groove meningioma, transcranial approach, complications, meta- analysis, systematic review

INTRODUCTION

Olfactory groove meningiomas (OGMs) are arachnoid cell neoplasms of the frontoethmoidal suture and lamina cribrosa, accounting for 4.5–18% of intracranial meningiomas (1). Arising along the midline of the anterior fossa, OGMs frequently impinge on the frontal lobes through mass effect. Presenting symptoms vary but commonly begin with ipsilateral anosmia that is difficult to detect. As the growth enlarges, displacement of adjacent brain regions leads to headache, fatigue, seizures, and intracranial hypertension. Of note is that the compression of the optic chiasm may lead to visual acuity defects. Nevertheless, due to frontal lobe plasticity and their insidious growth, OGMs can grow substantially prior to symptom onset. Though histologically classified as benign tumors, OGMs can still have a detrimental effect on a patient's well-being and quality of life.

Traditionally, surgical resection of OGMs has been achieved through transcranial approaches (TCAs). These encompass a plethora of routes including subfrontal, subcranial, interhemispheric, pterional, etc. (2–5). While newer techniques, such as endoscopic endonasal approach (EEA), have been introduced, TCAs remain a core component of the armamentarium for large OGM management due to their variety, size, and difficulty of extensive endoscopic repair of the anterior skull base (6). However, few studies have compared outcomes and complications between different TCAs. In 2007, Nakamura et al. investigated the differences in outcome following bifrontal, unilateral, and pterional approaches on 82 patients (7). In the largest case series of its kind, Pallini et al. compared bifrontal, fronto-orbito-basal, and pterional approaches among 99 patients in 2015 (8). Though these were important observational studies, their insights are limited in scope as single-institution case series.

While multiple meta-analyses have compared EEA and TCA, none have been performed for specific TCAs. To our knowledge, this is the first study to perform a systematic review and meta-analysis of the literature examining unilateral vs. bilateral approaches for OGM resection. Understandably, there are certain analytical obstacles. Most studies investigating OGMs are case reports, and there are no randomized controlled trials (RCTs); direct comparative studies of TCAs are also scarce. The diversity of TCAs also introduces additional complexity. To bypass these issues, we propose categorizing TCAs into either bilateral or unilateral approaches to simplify moderator analysis and to have a sufficient number of studies per category. While this method can limit the analyses on each specific TCA, the meta-analytical insights regarding approach laterality may contribute a broader perspective to help guide debate on optimal OGM treatment.

METHODS

Search Strategy

This systematic review was conducted using Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations. Searches were performed on PubMed, SCOPUS, Embase, Web of Science, and Medline databases on all publications before December 2019. The literature was reviewed with the following MeSH terms in all permutations: "meningioma" AND "olfactory" AND "groove." The reference lists of articles were further examined to identify potentially relevant articles. All retrieved studies were independently reviewed by two investigators (AF and SS) and assessed according to inclusion and exclusion criteria.

Selection Criteria

Studies eligible for inclusion had patients undergoing OGM resection and reported post-operative complications and outcomes. Case studies, series with fewer than 10 OGM patients, indiscernible cohorts of surgical approaches and/or mixed pathologies, and studies with unclear outcomes or complications were excluded. Only English-language publications were screened. Abstracts, technical reports, cadaver studies, conference presentations, reviews, and editorials were also excluded.

Data Extraction and Appraisal

All data were extracted from the articles' tables, figures, and texts. Any estimate measures were based on original data and used validated statistical methodology (9–11). The investigators (AF and SS) independently reviewed and performed extraction on each retrieved article; discrepancies were resolved through discussion and consensus. The data extracted include patient demographics (e.g., sex and age), pre-operative symptoms (e.g., anosmia, vision defects, headache, seizure, etc.), surgical approach, tumor volume, resection outcome, post-operative visual outcome, complications [e.g., hydrocephalus, infection, cerebrospinal fluid (CSF) leak, etc.], mean follow-up, and recurrence rate. Study quality was appraised by two investigators (AF and SW) according to a critical review checklist of the Dutch Cochrane Center proposed by the Meta-analysis of Observational Studies in Epidemiology group.

Statistical Analysis

Meta-analysis of proportions was performed for pre-operative symptoms and post-operative complications. To stabilize the variance of observed proportions, a double-arcsine (Freeman–Tukey) transformation was applied. Random effects (RE) models estimated by the DerSimonian–Laird method were used to combine transformed proportions to incorporate heterogeneity. Pooled estimates were back-transformed. Heterogeneity was tested and quantified by Cochran Q and I^2 tests, respectively. Study effect sizes are weighted by the inverse of their variance. Analyses were performed using the metafor and meta packages for R version 3.6.3. Statistical significance is established at p-value <0.05. Assessment of potential publication bias is achieved through funnel plots, Begg rank correlation test, and Egger's test.

RESULTS

Literature Search Results

The search terminology yielded a total of 1,655 articles from various electronic databases and additional sources like reference lists. After duplicates were removed, 876 articles remained. Application of inclusion and exclusion criteria ultimately

TABLE 1 | Study characteristics.

References	Year	Transcranial approach category	Country	Design	Study period	Specific transcranial approach
Patel et al. (12)	2019	B	UK	Retrospective case series	2002–2016	Bifrontal transbasal, bifrontal interhemispheric
Xu et al. (13)	2019	B	China	Retrospective case series	2013–2017	Small extended bifrontal
Farooq et al. (14)	2018	B	Pakistan	Retrospective case series	N/A	Bicoronal, subfrontal without orbital osteotomies
Liu et al. (15)	2018	B	USA	Retrospective case series	2007–2016	Transbasal
Guduk et al. (2)	2017	U	Turkey	Retrospective case series	1987–2015	Pterional, unifrontal
Barzaghi et al. (16)	2017	B	Italy	Retrospective case series	2001–2014	Transfrontal-sinus-subcranial
Nanda et al. (17)	2016	B/U	USA	Retrospective case series	1990–2014	Bifrontal, fronto-orbito-basal, frontolateral, pterional
de Alemeida et al. (18)	2015	B	USA/Canada	Retrospective case series	2003–2012	Bifrontal
Pallini et al. (8)	2015	B/U	Italy	Retrospective case series	1984–2010	Bifrontal, fronto-orbito-basal, pterional
Mielke et al. (3)	2014	U	Germany	Retrospective case series	1990–2013	Anterior interhemispheric
Refaat et al. (19)	2014	B/U	Egypt	Retrospective case series	2012–2013	Bifrontal basal interhemispheric, bilateral subfrontal, frontotemporal, unilateral subfrontal
Bitter et al. (20)	2013	U	Germany	Retrospective case series	1991–2010	Pterional
Jang et al. (21)	2013	B/U	Korea	Retrospective case series	1993–2012	Bifrontal, frontolateral
Musluman et al. (22)	2012	U	Turkey	Retrospective case series	1996–2008	Unilateral subfrontal interhemispheric transfalcial
Tomasello et al. (23)	2011	U	Italy	Retrospective case series	1991–2007	Pterional
Pepper et al. (24)	2011	B	USA	Retrospective case series	1995–2009	Transglabellar/subcranial
El-Bahy et al. (25)	2009	U	Egypt	Retrospective case series	2003–2008	Frontolateral
Aguiar et al. (26)	2009	B/U	Brazil	Retrospective case series	1997–2007	Bifrontal, fronto-orbital, fronto-pterional
Romani et al. (4)	2009	U	Finland	Retrospective case series	1997–2008	Lateral supraorbital
Gazzeri et al. (27)	2008	B	Italy	Retrospective case series	1990–2004	Bifrontal
Colli et al. (28)	2007	B	Brazil	Retrospective case series	1988–2006	Bifrontal, bifrontal-bi-orbital
Nakamura et al. (7)	2007	B/U	Germany	Retrospective case series	1972–2002	Bifrontal, pterional, unilateral subfrontal
Spektor et al. (5)	2005	B/U	Israel	Retrospective case series	1990–2003	Bifrontal, fronto-orbital, pterional, subcranial, unilateral subfrontal
Paterniti et al. (29)	1999	U	Italy	Retrospective case series	1975–1996	Pterional
Turazzi et al. (30)	1999	U	Italy	Retrospective case series	1989–1996	Pterional
Tsikoudas et al. (31)	1999	B	UK	Retrospective case series	1976–1998	Bifrontal
Mayfrank et al. (32)	1996	U	Germany	Retrospective case series	N/A	Frontal interhemispheric

U, unilateral; B, bilateral.

identified 27 studies for further data extraction and meta-analysis (**Table 1**). These studies span from 2019 to 1996 and come from 13 countries. All studies were retrospective case series. A total of 24 studies exclusively reported on OGM, while three studies also included other neoplasms. The literature search process is diagrammed in **Figure 1**.

Demographics

Selected studies encompassed 1,005 subjects overall, with 554 and 451 receiving unilateral and bilateral approaches, respectively. Females are 65.3% of the subject population, with 64.8 and 66.1% receiving unilateral and bilateral approaches. The average age, weighted by study sample size, is 57.4 years in the unilateral cohort and 56.2 years in the bilateral cohort. Under unilateral, specific approaches include pterional/frontotemporal, unilateral subfrontal, interhemispheric, and lateral supraorbital. For bilateral, specific approaches include bifrontal, bifrontal variations (transbasal, interhemispheric, extended), subfrontal, subcranial, and fronto-orbito-basal. The weighted mean follow-up period for the unilateral cohort is 69.9 months and for the bilateral cohort is 74.0 months (**Table 2**).

Pre-operative Symptoms

The most common pre-operative symptoms in the unilateral and the bilateral cohorts are anosmia (54.1/48.5%) and behavioral anomalies (43.2/42.4%), respectively. The least common pre-operative symptoms are fatigue (3.8/3.4%) and seizures (11.2/15.3%) for unilateral and bilateral cohorts, respectively. Both visual abnormalities and headaches affect around a third of patients in both cohorts. All pre-operative symptom differences between cohorts are not statistically significant (**Table 2**).

Surgical Outcome

Weighted pooled incidence of gross total resection (GTR) for the unilateral and the bilateral cohorts are 94.6% (95% CI, 90.7–97.5%; $I^2 = 59.0\%$; $p = 0.001$) and 90.9% (95% CI, 85.6–95.4%;

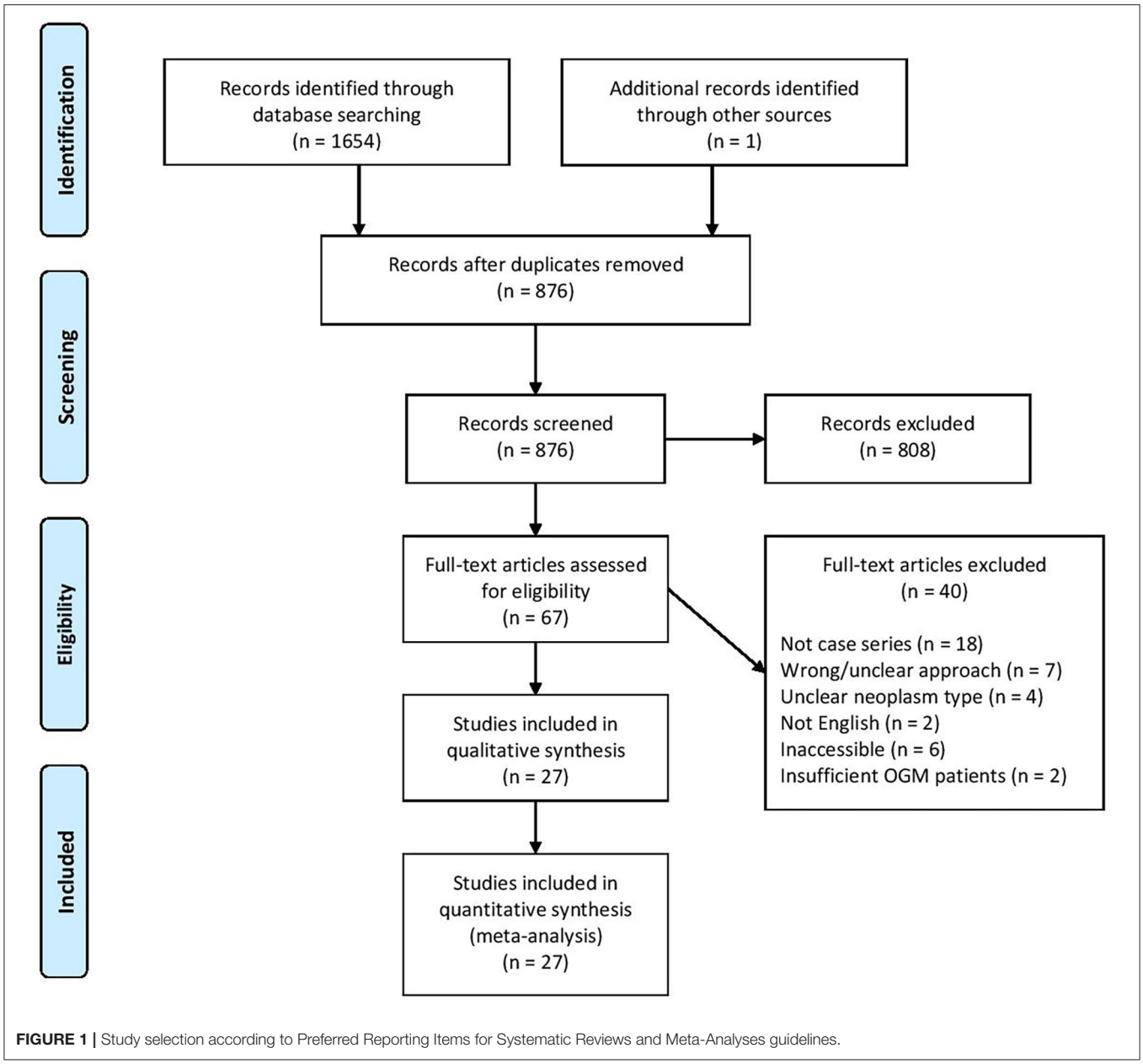


FIGURE 1 | Study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

$I^2 = 58.1\%$; $p = 0.003$), respectively. For OGM recurrence, weighted pooled incidence for the unilateral and the bilateral cohorts are 2.6% (95% CI, 0.4–6.0%; $I^2 = 53.1\%$; $p = 0.012$) and 4.7% (95% CI, 1.4–9.2%; $I^2 = 55.3\%$; $p = 0.006$), respectively. For improvement of vision, weighted pooled incidence for the unilateral and the bilateral cohorts are 55.9% (95% CI, 32.4–78.1%; $I^2 = 93.3\%$; $p < 0.001$) and 70.3% (95% CI, 38.2–94.6%; $I^2 = 94.2\%$; $p < 0.001$), respectively. Differences in GTR incidence, OGM recurrence, and vision improvement were not found to be statistically significant ($p = 0.210$, 0.351, and 0.442, respectively). The weighted pooled mean tumor volume for the unilateral and the bilateral cohorts are 57.4 and 71.8 cm^3, respectively. However, inconsistent tumor volume data (e.g., standard deviation and range) precluded a statistical comparison between these measurements (**Tables 3**–**5**).

Complications

For both unilateral and bilateral approaches, the most common complication is new-onset anosmia at 7.5% (95% CI, 0.4–19.8%; $I^2 = 94.1\%$; $p < 0.001$) and 9.4% (95% CI, 1.0–23.0%; $I^2 = 90.1\%$; $p < 0.001$), respectively. Similarly, for both approaches, the rarest reported complication is stroke, with 0.0% (95% CI, 0.0–0.4%; $I^2 = 0.0\%$; $p = 0.988$) and 0.0% (95% CI, 0.0–0.7%; $I^2 = 0.0\%$; $p = 0.823$), respectively.

For the majority of complications, weighted pooled incidence between unilateral and bilateral approaches were similar in

TABLE 2 | Demographics and pre-operative symptoms.

References	Transcranial approach category	Size (*n*)	Demographics		Mean follow-up (months)	Tumor volume (cm^3)	Pre-operative symptoms					
			Age	Females			Anosmia	Visual issues	Headache	Seizure	Behavioral abnormality	Fatigue
Patel et al. (12)	B	48	62	36	59	49	18	18	17	11	24	0
Xu et al. (13)	B	29	55	18	40	43	17	6	0	4	15	0
Farooq et al. (14)	B	19	51	18	60	113	11	15	15	0	13	0
Liu et al. (15)	B	15	52	10	14.5	92	0	4	3	2	2	0
Guduk et al. (2)	U	61	58	43	N/A	62	9	14	16	6	9	0
Barzaghi et al. (16)	B	21	54	12	87	51	11	8	0	3	8	0
Nanda et al. (17)	B/U	16/41	55/60	7/27	59.6	N/A	9/21	6/16	8/25	2/5	8/17	6/14
de Alemeida et al. (18)	B	10	50	8	N/A	36	N/A	N/A	N/A	N/A	N/A	N/A
Pallini et al. (8)*	B/U	81/18	57	52/12	103	67/70	59	46	38	19	35	0
Mielke et al. (3)	U	43	62	27	N/A	N/A	27	14	0	0	22	0
Refaat et al. (19)	B/U	8/6	54/47	6/5	N/A	134/69	4/3	4/3	6/5	0/1	2/2	0/0
Bitter et al. (20)	U	61	60	40	122	N/A	30	22	18	5	16	3
Jang et al. (21)	B/U	19/21	55/53	7/10	58	60.1/41.6	17/12	0/0	0/0	0/0	0/0	0/0
Musluman et al. (22)	U	42	59	24	52	N/A	19	23	37	10	28	0
Tomasello et al. (23)	U	18	59	12	93.5	23	18	13	13	2	18	0
Pepper et al. (24)	B	19	51	8	N/A	96	1	5	8	1	6	2
El-Bahy et al. (25)	U	18	49	10	31	34	13	5	18	3	8	0
Aguiar et al. (26)	B/U	7/14	55.5	15	50	41.6	21	8	12	5	4	0
Romani et al. (4)	U	66	57	38	45	54	38	22	11	14	33	0
Gazzeri et al. (27)	B	36	56	24	111	137	30	20	18	10	25	0
Colli et al. (28)	B	17	53	16	51	N/A	5	0	11	5	0	0
Nakamura et al. (7)*	B/U	46/36	58	63	63.4	61/38	48	20	26	16	59	0
Spektor et al. (5)*	B/U	47/34	55	58	89/71	48/47	47	22	41	9	21	0
Paterniti et al. (29)	U	20	49	15	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Turazzi et al. (30)	U	37	N/A	N/A	48	99	27	16	0	0	27	0
Tsikoudas et al. (31)	B	13	60	10	N/A	113	4	5	8	2	8	1
Mayfrank et al. (32)	U	18	N/A	13	N/A	18	11	4	0	1	10	0

**Not used in pre-operative symptom calculations because the values were not differentiated between approach categories.*

TABLE 3 | Surgical outcomes/complications (unilateral).

Surgical outcome	Weighted pooled estimate (%)	95% CI	*P*	I^2 (%)	Bias	
					Egger's	Begg's
GTR	94.6	90.7–97.5	0.001	59.0	0.271	0.363
Recurrence	2.6	0.04–6.0	0.012	53.1	0.710	0.427
Vision improvement	55.9	32.4–78.1	<0.001	93.3	0.982	0.615
Complication						
Hydrocephalus	1.3	0.1–3.3	0.042	41.5	0.182	0.317
Infection	1.2	0.0–2.9	0.192	23.1	0.335	0.415
Stroke	0.0	0.0–0.4	0.988	0.0	0.016	<0.001
Meningitis	0.0	0.0–0.3	0.997	0.0	0.084	0.003
Epilepsy	1.8	0.2–4.1	0.04	42.6	0.409	0.239
CSF leakage	2.7	0.3–6.7	0.006	51.1	0.336	0.147
New-onset anosmia	7.5	0.4–19.8	<0.001	94.1	0.698	0.124
Hemorrhage	0.9	0.0–2.2	0.889	0.0	0.582	0.785
Death	0.1	0.0–0.9	0.684	0.0	0.022	0.004

TABLE 4 | Surgical outcomes/complications (bilateral).

Surgical outcome	Weighted pooled estimate (%)	95% CI	*P*	I^2 (%)	Bias	
					Egger's	Begg's
Gross total resection	90.9	85.6–95.4	0.003	58.1	0.991	0.298
Recurrence	4.7	1.4–9.2	0.006	55.3	0.589	0.915
Vision improvement	70.3	38.2–94.6	<0.001	94.2	0.341	0.562
Complication						
Hydrocephalus	0.9	0.0–2.9	0.461	0.0	0.062	0.058
Infection	1.4	0.1–3.4	0.219	20.6	0.598	0.125
Stroke	0.0	0.0–0.7	0.823	0.0	0.002	<0.001
Meningitis	1.2	0.1–2.8	0.495	0.0	0.474	0.030
Epilepsy	1.6	0.3–3.5	0.662	0.0	0.328	0.104
CSF leakage	6.3	2.3–11.6	<0.001	76.1	0.037	0.019
New-onset anosmia	9.4	1.0–23.0	<0.001	90.1	0.090	0.052
Hemorrhage	1.9	0.2–4.8	0.037	42.6	0.301	0.470
Death	3.1	0.9–6.1	0.083	34.9	0.768	0.527

TABLE 5 | Surgical outcomes/complications (comparison).

Surgical outcome	*P*
Gross total resection	0.210
Recurrence	0.351
Vision improvement	0.442
Complication	
Hydrocephalus	0.727
Infection	0.851
Stroke	0.583
Meningitis	0.016
Epilepsy	0.858
CSF leakage	0.220
New-onset anosmia	0.810
Hemorrhage	0.150
Death	0.007

magnitude: hydrocephalus (1.3 vs. 0.9%; $p = 0.727$), infection (1.2 vs. 1.4%; $p = 0.851$), stroke (0.0 vs. 0.0%; $p = 0.583$), epilepsy (1.8 vs. 1.6%; $p = 0.858$), and new-onset anosmia (7.5 vs. 9.4%; $p = 0.810$). CSF leakage is notable as the pooled estimate from the bilateral approach is more than twice as large as that of the unilateral approach (6.3 vs. 2.7%), though this difference is not significant ($p = 0.220$). Incidence of hemorrhage following bilateral approach surgery was more than 50% greater than that following unilateral surgery (1.9 vs. 0.9%); however, this is also not significant ($p = 0.150$).

Among reported complications, only rates of meningitis and death were significantly different between cohorts (**Figures 2**, **3**). For meningitis, the weighted pooled incidence for bilateral approach is significantly greater than that for the unilateral approach (1.2 vs. 0.0%; $p = 0.016$). The bilateral approach's weighted pooled incidence of death is likewise significantly greater than that of the unilateral approach (3.1 vs. 0.1%; $p = 0.007$) (**Tables 3**–**5**).

Meta-Regression

Meta-regression for unilateral and bilateral approach cohorts was performed with covariates of study year, tumor volume, patient age, and study size. Tumor volume and age were significant modifiers (slope = 0.004, $p = 0.017$; slope = 0.02, $p = 0.007$) for the unilateral approach GTR in unilateral surgeries, with volumes and older age associated with a greater proportion of GTR. Both tumor volume and study year were significant modifiers (slope = −0.007, $p = 0.018$; slope = 0.08, $p = 0.001$) for vision improvement in the bilateral cohort, with larger volumes and new studies associated with worse and better vision improvement, respectively. In the bilateral cohort, larger sample size and older age were also linked to greater hydrocephalus incidence (slope = 0.003, $p = 0.024$; slope = 0.02, $p = 0.008$). For both CSF leakage and death, younger age was associated with greater rates of the respective complication (slope = −0.02, $p = 0.013$; slope = −0.02, $p = 0.014$) in the unilateral cohort. For both cohorts, tumor size was negatively correlated with patient age (unilateral/bilateral; slope = −0.99/−0.80), though this relationship was not significant ($p = 0.410$; $p = 0.756$, respectively). The remaining outcomes were unaffected by covariates (**Supplementary Material**).

Bias

Given the potential impact of publication bias on meta-analysis findings, funnel plot asymmetry analyses with both Egger's test and Begg's test were performed. Among unilateral approach findings, concern for publication bias was found for stroke and death by both Egger's and Begg's tests and for meningitis by Begg's test alone. With the trim-and-fill method, there are only minor changes to pooled incidence for stroke (0.0–>0.0%), meningitis (0.0–>0.0%), and death (0.2–>0.1%). For bilateral approach findings, concern for publication bias was found for stroke by both Egger's and Begg's tests, CSF leakage by Egger's test alone, and meningitis by Begg's test alone. With the trim-and-fill method again, changes to pooled incidence for

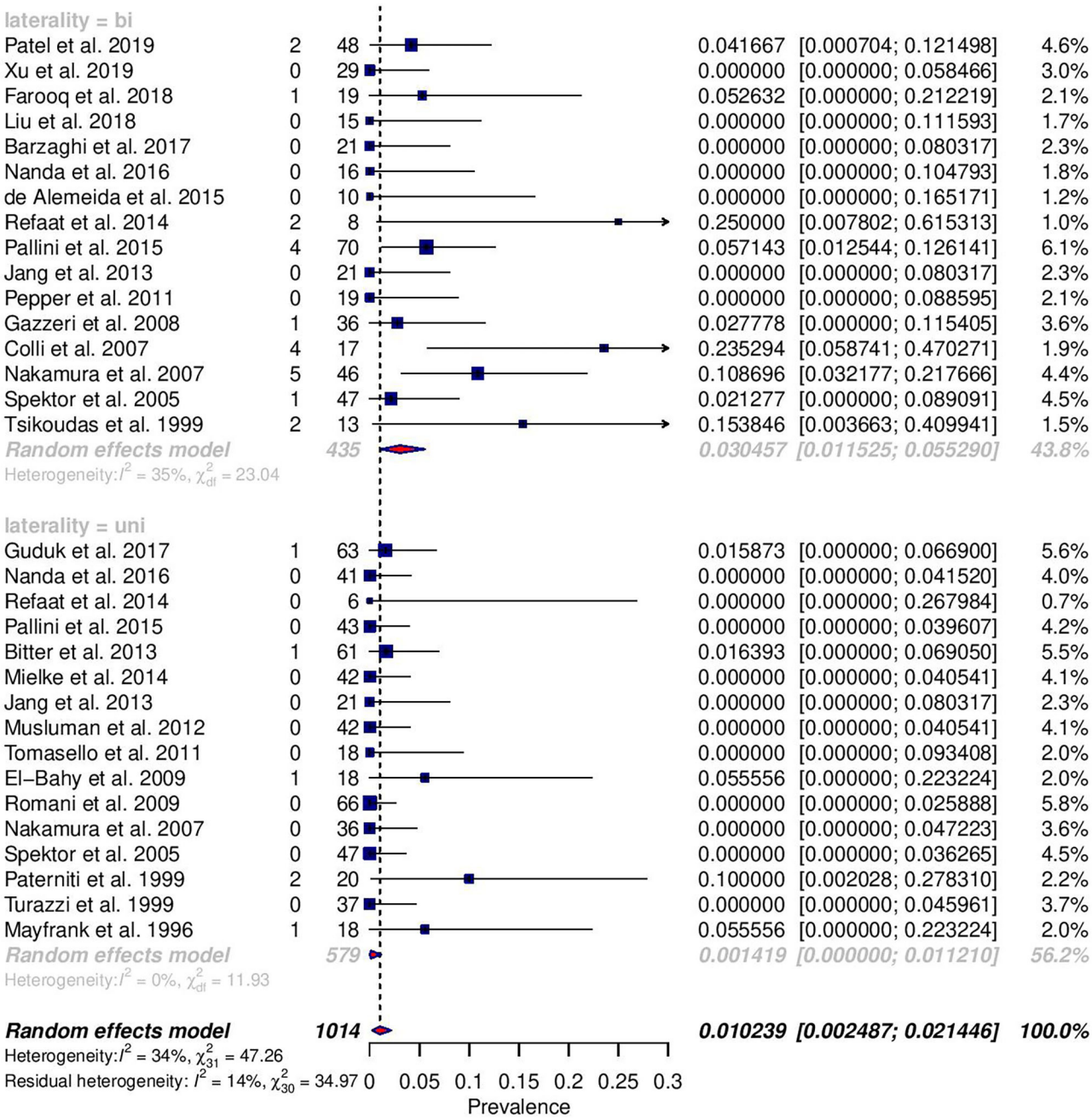


FIGURE 2 | Forest plots comparing the incidence of death between unilateral (uni) and bilateral (bi) approaches.

stroke (0.0–>0.0%), meningitis (1.0–>0.9%), and CSF leakage (6.3–>6.6%) are minor. Due to model constraints, significance testing was unavailable for the new estimated pooled incidence.

DISCUSSION

Transcranial resection of OGMs has a long history in neurosurgery. In fact, the first documented success of an intracranial meningioma surgery is an OGM removal with a unilateral approach in 1885 by Durante (1). While a plethora of different and modified approaches have since been developed, a unified consensus with regards to optimal approaches is still lacking. Over time, the strengths and the weakness of popular approaches have become well-characterized.

With broad exposure of the anterior cranial region, bilateral approaches facilitate the removal of hyperostosis from the

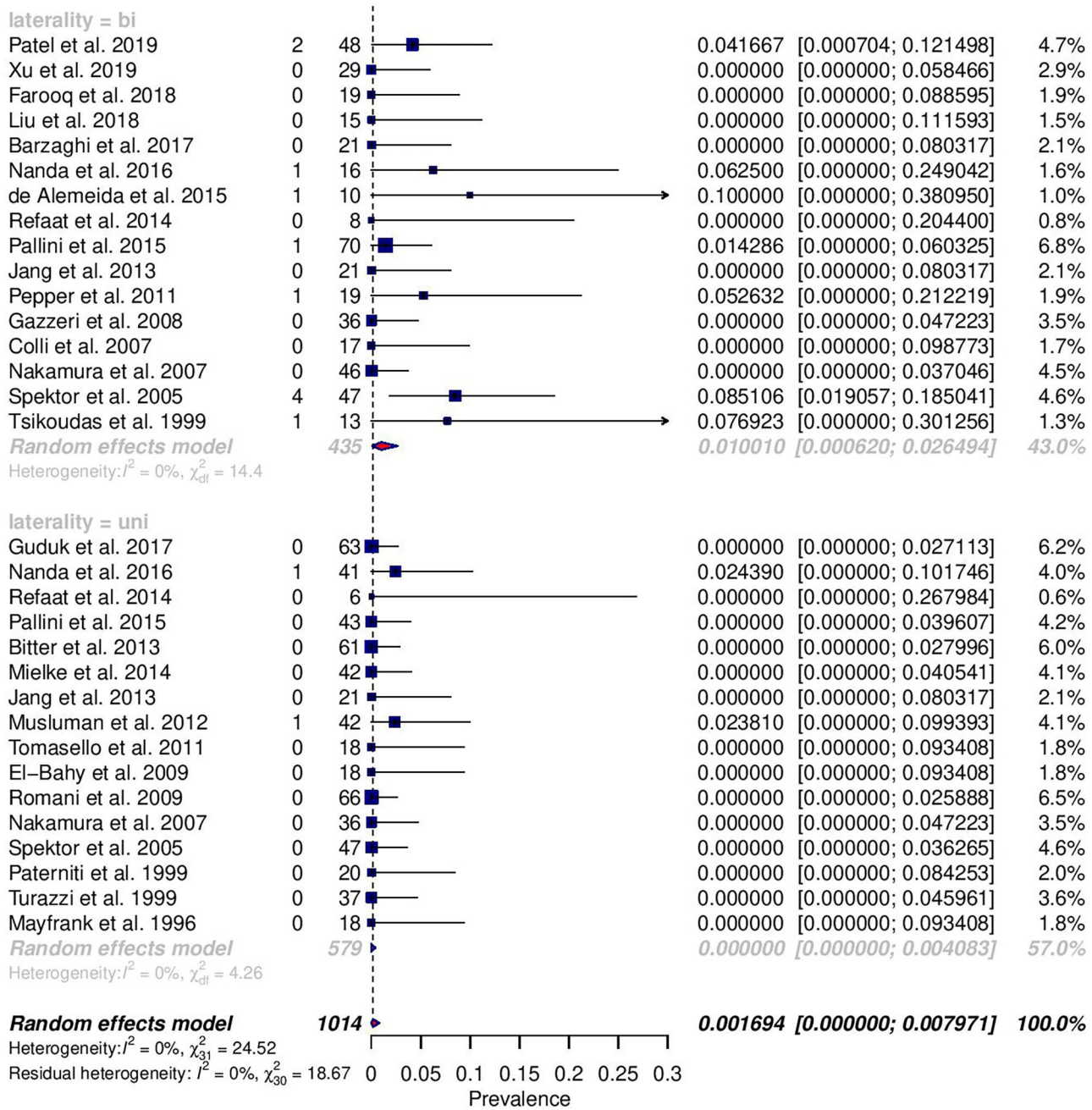


FIGURE 3 | Forest plots comparing the incidence of meningitis between unilateral (uni) and bilateral (bi) approaches.

cribriform area and radical tumor resection. However, it leads to late visualization of critical structures, such as the anterior cerebral/communicating arteries as well as the visual apparatus. In both subfrontal and subcranial approaches, the frontal sinuses often need to be opened, increasing the risk for post-operative CSF leakage. For the subfrontal approach, direct injury to the frontal lobes can occur via retraction for optimal visualization. However, perhaps even more significant, ligation and division of the superior sagittal sinus hinder venous drainage, furthering potential indirect insult to the frontal lobes *via* venous infarction.

Compared to bilateral approaches, the foremost advantage of unilateral approaches is the ease of approach. Only the ipsilateral frontal lobe is involved, and typically no division of the superior sagittal sinus is necessary. For the pterional approach

specifically, the frontal sinuses can be preserved. Visualization and control of the internal carotid artery and optic nerves can also occur earlier. The primary weaknesses of unilateral approaches are reduced access and minimized working angles. The contralateral side of the OGM will always be distant to the surgeon. Excessive manipulation of the frontal lobes may be necessary to properly visualize the tumor (5). The large size and the bilateral extension of many of these lesions would logically presume a wider exposure, and bilateral approach would be the most advantageous. However, it has been the authors' experience that, given the midline origin and the radial growth pattern of these lesions, especially with larger OGMs, the lesions have provided a more-than-adequate exposure and working aperture by pushing the frontal lobe(s) and other critical structures away (**Figures 4**, **5**).

Overall, the findings from this meta-analysis suggest that both approach categories have similar surgical resection outcomes. In terms of tumor resection, the pooled estimated rates of GTR are >90% for both unilateral and bilateral approaches, with no significant differences. In comparison to large, single-institution case series, comparable rates are seen. Nakamura et al. (7) reports GTR rates of 91.2 and 93.5% for unilateral (frontolateral) and bilateral (bifrontal) approaches in 76 patients. For their cohort of 99 patients, Pallini et al. (8) reports 84.8 and 81% of GTR with unilateral (pterional) and bilateral (bifrontal + fronto-orbito-basal) approaches. In terms of recurrence, the pooled estimated rates for bilateral approaches were greater than the rates for unilateral approaches, but the difference was insignificant. It is plausible that there is a tendency to choose bilateral approaches for certain tumors (e.g., with paranasal extension) that may have a propensity for recurrence, but further analysis is warranted. Thus, given the importance of achieving GTR as an outcome metric, both approach categories are similarly effective for OGM removal.

It is common knowledge that tumor volume is a key consideration for approach selection, with bilateral approaches providing more sizable operating fields for larger tumor removal. Though statistical analysis could not be performed, it was noted that the weighted pooled tumor volumes for the bilateral approaches were larger than the unilateral ones. Interestingly, tumor volume was negatively and positively correlated with GTR for bilateral and unilateral approaches, respectively; only the latter was found to be significant. While these trends appear conflicting, they may not be entirely relevant in practice. The estimated slopes for both approaches are both very minor in magnitude, suggesting that even large variations in volume would only correspond to trivial changes in GTR rates. In conjunction with the fact that both pooled GTR rates are very high, the contribution of tumor volume to GTR may be less vital. Indeed significant risk factors for subtotal meningioma resection were found to be symptomatic presentation and bone invasion, but not tumor volume (33). In the authors' experience, size has never been a limiting or deciding factor in the type of approach, and even extremely large tumors can be safely resected via a simple unilateral pterional approach (**Figures 4**, **5**).

The majority of patients of both categories of approaches had visual improvement. Though the difference was not significant, there was a trend of greater improvement in bilateral cohorts. A possible explanation is that bilateral approaches are able to achieve earlier tumor devascularization, facilitating dissection of the tumor away from the optic apparatus. It has been previously reported that the EEA has superior rates of vision improvements compared to TCAs. In particular, Kitano et al. (34) specifically report a significant improvement of visual acuity with EEA, but not for visual field defects compared to TCA. Though the EEA outcomes are outside the scope of this study, it is notable that vision improvement is not reported as a singular outcome. In our systematic review, the heterogeneity of reporting precluded such specificity in defining visual improvement. However, given the importance of vision to quality of life, future investigation on the relationship of specific approaches with post-operative visual function could provide important insights.

In terms of complications, bilateral and unilateral approaches have similarly low rates, of which most were found to be insignificant. This suggests that many of these complications were not consequences of the specific approach but likely inherent to undergoing craniotomy in general. Select complications were still found to be different between categories. Although a significant difference was not found, the bilateral category's pooled estimate of CSF leakage was markedly greater than the unilateral category's rate. As the bilateral opening of frontal sinuses is an inherent step of bilateral approaches, it is not unexpected to observe this trend. Additionally, of other possible contributing factors, orbital osteotomy, either unilateral or bilateral, is known to improve tumor exposure at the risk of increased CSF leakage (1). It may be worthwhile to further examine the utility of this trade-off given the procedure's association with CSF leakage, which is also linked to additional complications like headaches and meningitis.

Only the complication rates of meningitis and death were significantly different, and both were higher in the bilateral category. As such, the higher rates of CSF leakage in bilateral approaches may explain the higher rates of meningitis. Additionally, risk factors for post-craniotomy meningitis include longer duration of drain placement, longer length of surgery, and ICU admission—clinical parameters which are more likely to be associated with the larger involvement of bilateral approaches (35). Greater size and invasiveness of bilateral approaches are likewise likely primary contributors to greater mortality, subsequent to the development of post-operative brain edema (7, 8). Though not often reported, the specific causes of death are elucidating. Pulmonary embolism was seen in both unilateral and bilateral categories, suggesting that it is a non-specific consequence (7, 20, 27). However, given the fact that bilateral approaches are generally larger and involve more procedures, the increased duration of surgery would expose patients to higher risks of thromboembolism (36). Of the deceased patient who received a bilateral approach, Spektor et al. (5) describes CSF rhinorrhea leading to meningitis and death. Two of the deaths, also seen associated with bilateral approaches, reported in Nakamura et al. were caused by hemorrhage and edema (7). Notwithstanding these singular examples, they suggest how bilateral approaches can be riskier.

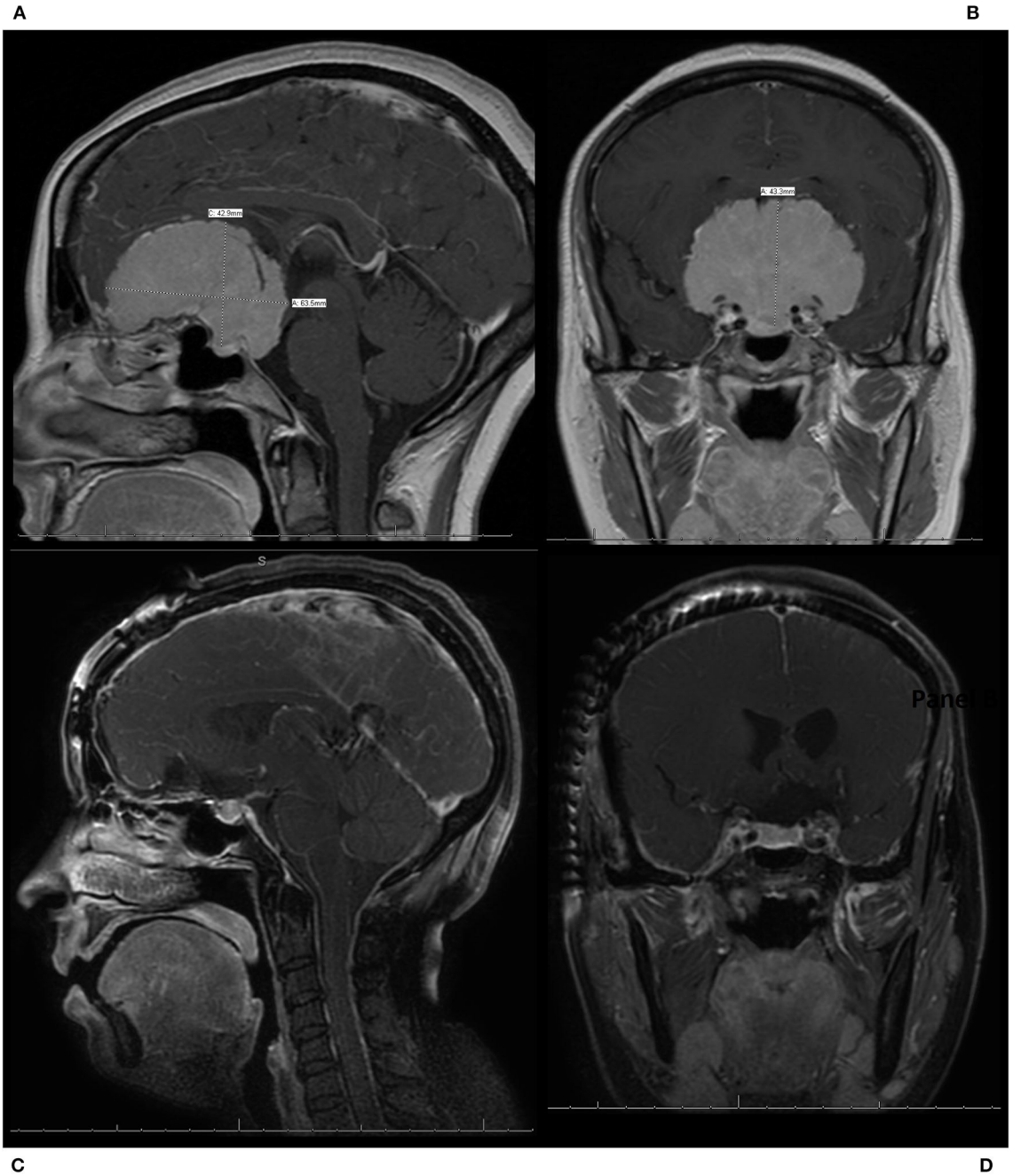


FIGURE 4 | A patient who presented with progressive vision loss and anosmia was found to have a 6.4 cm olfactory groove meningioma (OGM) encasing the bilateral internal carotid artery and its branches as well as the optic nerves bilaterally. The patient underwent a modified pterional craniotomy with extension past midline to expose the superior sagittal sinus for resection of the large WHO grade I OGM. The patient had an immediate improvement in vision post-operatively, with no new neurologic deficits, and was discharged home from the hospital on post-operative day 2. **(A)** Pre-operative sagittal T1 MRI with contrast, demonstrating a large 6.4 cm OGM with encasement of the anterior cerebral arteries and extension in the sella seen. **(B)** Pre-operative coronal T1 MRI with contrast, demonstrating a large OGM with encasement of the internal carotid artery (ICA) and the middle cerebral arteries as well as the optic nerves bilaterally. **(C)** Post-operative sagittal T1 MRI with contrast, demonstrating resection. **(D)** Post-operative coronal T1 MRI with contrast, demonstrating resection with preservation of the ICAs and decompression of the optic nerves.

Given their significance relative to other complications, death and meningitis may be occurring in a subpopulation of OGM patients with different tumor characteristics from the overall population. For instance, these patients could have had larger and more aggressive tumors, necessitating radical cranial base resection—a choice better suited for bilateral approaches but

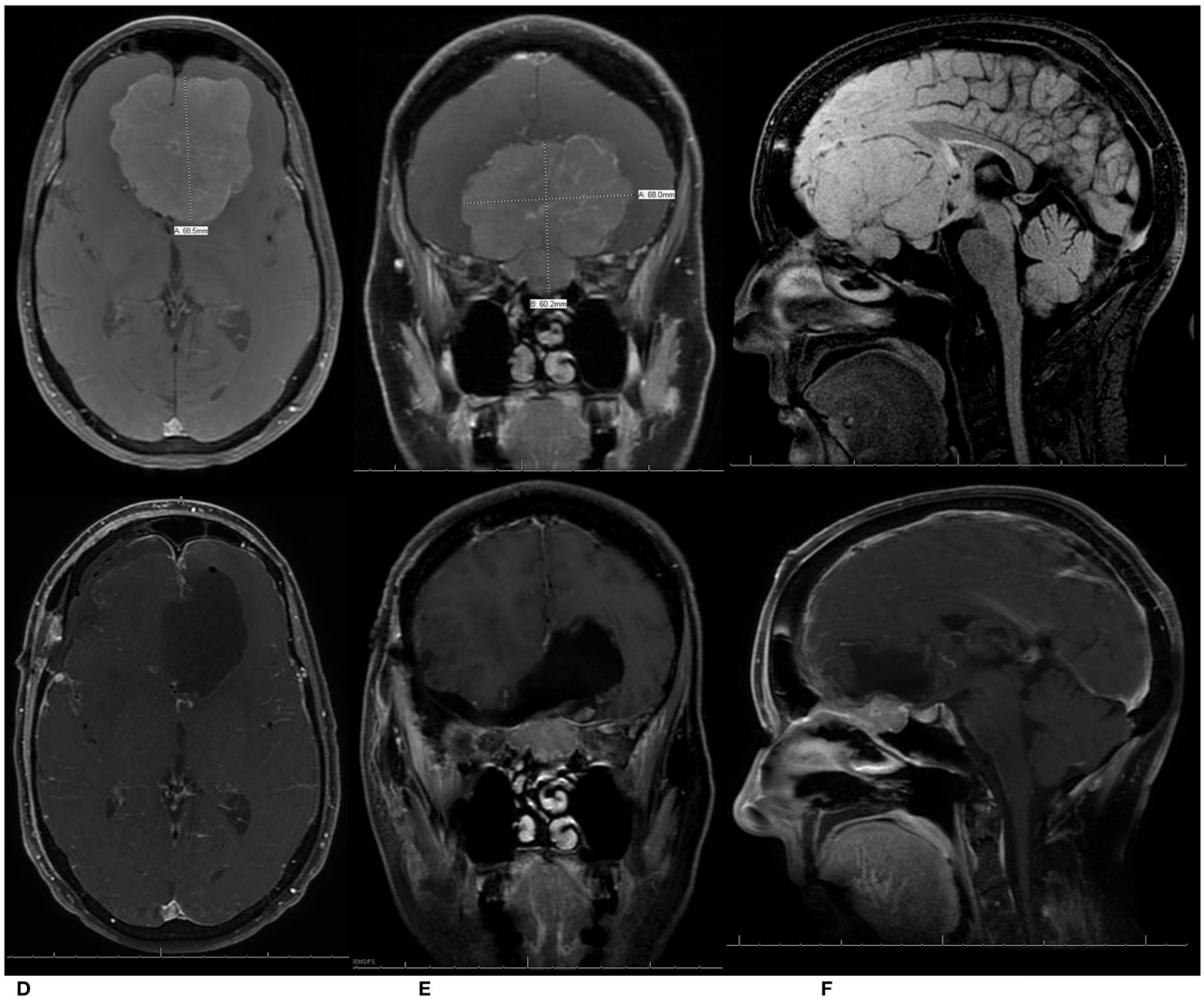


FIGURE 5 | A patient presented with progressive vision loss, anosmia, gait instability, and cognitive decline and was found to have a 6.8 cm olfactory groove meningioma (OGM) with expansion into the endonasal cavity. The internal carotid arteries and their branches were pushed posteriorly by the lesion. The patient underwent a pterional craniotomy for resection of the large WHO grade I OGM with a residual tumor left in the endonasal compartment. The patient had an immediate improvement in vision, with no new neurologic deficits, and was discharged home from the hospital on post-operative day 5. She also enjoyed recovery of taste/smell and gradual but full recovery of her cognition. **(A)** Pre-operative axial T1 MRI with contrast demonstrating a large 6.8-cm OGM with the anterior cerebral arteries (ACAs) pushed posteriorly. **(B)** Pre-operative coronal T1 MRI with contrast, demonstrating a large OGM with extension through the cribriform plate into the endonasal cavity. **(C)** Pre-operative sagittal T1 MRI without contrast, demonstrating a large OGM with endonasal extension and displacement of the ACAs posteriorly. **(D–F)** Post-operative axial, coronal, and sagittal T1 MRIs with contrast, respectively, demonstrating resection of the intracranial component of the large OGM, with preservation of the ACA vasculature and a residual meningioma left in the endonasal compartment to prevent the development of a cerebrospinal fluid leak.

one that increases the risk for CSF leaks. Pallini et al. (8) qualitatively comments on the larger size of these tumors in the patients who died. Another possible difference is age, which was found to negatively correlate with tumor size across the analyzed studies. Lu et al. (6) report a similar trend for patient age and anterior skull base meningiomas (e.g., olfactory groove and tuberculum sellae), and though our trend was not significant, this relationship may manifest more clearly as the literature grows.

LIMITATIONS

Although our study was conducted according to the PRISMA guidelines, there are a few limitations to this meta-analysis. Foremost, there are no RCTs and only minimal comparative studies of TCAs. This deficiency in the literature meant that the only available types of studies for meta-analysis were case series, which are relatively low in the hierarchy of evidence quality. Additionally, without direct comparisons

of TCA cohorts, odds ratios have not been calculated, and a meta-analysis of proportions was performed instead. To ameliorate these weaknesses, strict criteria for inclusion and exclusion were implemented and followed to maximize data quality. Furthermore, RE modeling was used for all analyses, given the heterogeneity and the variability in both studies (e.g., publication year, country, and duration) and clinical characteristics (e.g., surgeon experience and skill, post-operative management). While promising that our conclusions closely mirror the largest two OGM case series, this meta-analysis still needs to be interpreted with greater caution, given its source material.

Small sample sizes are another limitation for most of the included studies. Especially for rarer complications such as stroke, a limited cohort size may not be able to capture their true incidence. As a result, artificially low rates may be erroneously reported. There are also often varied levels of clarity in the reporting of outcomes and complications. Though analyzing multiple studies theoretically overcomes this noise and imprecision, it is still a potential error that could be eliminated by standardized assessments and measurements. Another issue is possible inconsistencies with clinical assessments, particularly for nuanced complications like anosmia. Out of 27 studies, only Jang et al. described an objective scale for olfactory evaluation. Discrepancies in assessment could hinder both the accuracy and the statistical significance of our findings. Finally, akin to reporting variability, selection bias for approach is a factor that is difficult to account for. Despite the general principles for choosing an approach, the lack of consensus-driven criteria explains its existence. As most of these concerns stem from working with case series, they can be overcome through higher-quality study types like RCTs or prospective cohort studies, being performed in the future, that utilize objective evaluations of patient complications.

CONCLUSION

Multiple TCAs are utilized for surgical resection of OGMs. Though a plethora of approaches exist, they may be simply categorized into unilateral or bilateral approaches. Through a systematic review and meta-analysis of proportions, it was found that, though comparable in many aspects of surgical outcomes and complications, bilateral approaches had a significantly higher risk of post-operative meningitis and death compared to unilateral ones. Though these insights need to be interpreted carefully, they suggest that unilateral approaches may be safer for the resection of OGMs. Given the presence of multiple comparative studies between EEA and TCA, the paucity of studies analyzing specific TCAs is unfortunate. This topic should be explored in greater depth with larger studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AF and SW authored the manuscript. AF, SW, and SS performed study selection and appraisal. MJ and AT provided analytical input and assistance with study. AP, AH, PR, and AE supervised the study. All authors agreed to submitted version of manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.560706/full#supplementary-material

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REVIEW
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Meningioma: A Review of Clinicopathological and Molecular Aspects

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Meningiomas are the most the common primary brain tumors in adults, representing approximately a third of all intracranial neoplasms. They classically are found to be more common in females, with the exception of higher grades that have a predilection for males, and patients of older age. Meningiomas can also be seen as a spectrum of inherited syndromes such as neurofibromatosis 2 as well as ionizing radiation. In general, the 5-year survival for a WHO grade I meningioma exceeds 80%; however, survival is greatly reduced in anaplastic meningiomas. The standard of care for meningiomas in a surgically-accessible location is gross total resection. Radiation therapy is generally saved for atypical, anaplastic, recurrent, and surgically inaccessible benign meningiomas with a total dose of ~60 Gy. However, the method of radiation, regimen and timing is still evolving and is an area of active research with ongoing clinical trials. While there are currently no good adjuvant chemotherapeutic agents available, recent advances in the genomic and epigenomic landscape of meningiomas are being explored for potential targeted therapy.

Keywords: meningioma, targeted treatment, molecular diagnosis, immunotherapy, neurosurgery, clinical trials, pathology, radiation therapy

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INTRODUCTION

Epidemiology

Meningiomas arise from arachnoid cap cells in the brain, and represent 37.6% of all primary brain tumors in adults, making them the most common type of intracranial tumor with an incidence of 8.83 per 100,000 in the most recent Central Brain Tumor Registry of the United States (1, 2). Conversely, they are equally rare in children and adolescents of both sexes (0.4%–4.6%) (3). The median age of diagnosis of meningioma is 65 years, likely due to the increasing incidence of meningiomas with age (2). Additionally, in the adult population, there is a marked female bias with a female:male ratio of 3:1 and increasing to 9:1 for spinal lesions (3). The rate of diagnosis of meningiomas has increased due to better imaging facilities and ageing populations with one survey showing a 3.9-fold increase in diagnosis of meningioma since 1943 (4). The calculated lifetime risk of developing meningioma without any associated factors is approximately 1% (3).

Clinical History

As with many of the lesions of the CNS, the symptoms correspond to the location of the mass. Meningiomas are slow growing and often not infiltrative in nature thus the symptoms tend to be insidious in onset. Common presentations include headaches secondary to increased intracranial pressure, focal neurological (cranial nerve) deficits, and seizures caused by mass effect and/or direct involvement by the tumor (5). A rare clinical syndrome, Foster Kennedy syndrome coined in 1911 by Dr. Robert Foster Kennedy, is characterized by ipsilateral optic atrophy, papilledema in contralateral eye, central scotoma in ipsilateral eye, and anosmia, secondary to a large olfactory meningioma (6). Large frontal meningiomas may also present with personality changes or altered mental status which can lead to a misdiagnosis of dementia or severe depression (5).

Natural History

Understanding the natural history of meningiomas is imperative for clinicians with a growing amount of incidental meningiomas now detected secondary to advanced imaging studies. As mentioned previously, meningiomas are generally slow growing lesions with a linear growth rate of 2–4 mm/year for asymptomatic meningiomas (7). In a retrospective study in which incidental meningiomas were followed by imaging, approximately a third of the tumors did not grow at all. However, of those that grew, nearly 25% grew exponentially, further underscoring the importance of surveillance imaging in untreated patients (8). The natural course of symptomatic larger lesions is deemed anecdotally to be a more aggressive growth pattern, but these lesions are rarely left untreated, and therefore, their true natural history remains ill-defined (9).

The estimated 10-year survival (overall 61.7%) for malignant meningiomas is very much dependent on age; 10-year relative survival is estimated to be around 76.8% for 20–44 year olds, while it is only 39.5% for patients age 75 years and older (2). Malignant meningioma of the spine has a higher 10-year relative survival of 73.4% when compared to the survival rate of 55.7% for intracranial tumors. Recurrence is a function of surgical resection (and/or radiation typically as adjuvant therapy in a subset), location and the histological grade of the meningioma (2), although location and surgical resection are somewhat interlinked. In terms of recurrence differences with grade, the five-year progression free survival (PFS) for a WHO grade I tumors is ~90% after gross total resection (GTR), Grade II are ~ 60%–90%, whereas grade III PFS after GTR is 28% (10, 11). These recurrences translate into meningioma-specific mortality in these patients, with 10-year overall survival rates of 53% for grade II patients and 0% for grade III patients, despite aggressive therapeutic efforts (12).

Etiology

Syndromes

Interestingly, in children and adolescents, meningiomas show a tendency for more aggressive subtypes. This may be secondary to their occurrence in several associated hereditary syndromes, such as Neurofibromatosis type 2 (NF-2) most commonly, but also less common causes such as Gorlin syndrome and Cowden syndrome (13).

Loss of heterozygosity and inactivating mutations in the *NF2* gene are seen in up to 60% of sporadic cases (14, 15). Germline mutations in the same gene lead to neurofibromatosis 2 (NF2), an autosomal disorder characterized by the occurrence of schwannomas, mengingiomas, and gliomas. The mutation often presents as a cytogenetically visible deletion of the long arm of chromosome 22 at q12, leading to decreased functional levels of the tumor suppressor gene, Merlin. More than half of patients with NF2 will demonstrate at least one meningioma in their lifetime, with initial diagnosis at the mean age of 30 (16, 17). The associated risk of the meningioma corresponds to the type of mutation seen. For example, a truncating mutation by frameshift tends to cause a greater tumor burden with early initial onset of meningioma. Most NF2 related meningiomas present as a fibrous or transitional phenotype, which are the most common histopathological subtypes of meningioma and are generally more aggressive than sporadic tumors (18, 19).

Gorlin syndrome or nevoid basal cell carcinoma syndrome is an uncommon autosomal dominant disease with an estimated prevalence varying from 1/57,000 to 1/256,000, and affecting males and females equally (20). Inactivation of the *PTCH1* gene located on chromosome 9q22.3-q31 is the hallmark of Gorlin syndrome. A second hit mutation of p53 often results in the formation of multiple BCC. *PTCH1* gene mutations lead to a hypersensitivity to radiation-induced tumorigenesis (21). Another missense mutation of the downstream factor, *SUFU* can be found rarely in families with hereditary multiple meningiomas (22). A natural history study from NIH speculated that patients affected by Gorlin syndrome have a 5% incidence of having a CT with radiological features suggestive of meningioma (23).

Cowden syndrome is an autosomal-dominant syndrome that predisposes the patient to developing benign and malignant cancers of a variety of organ systems, including breast, thyroid, uterus, and CNS. It is characterized by multiple hamartomas of ectodermal, mesodermal, and endodermal origin (24). Cytogenetically, it is associated with deletions on the chromosome 10 (PTEN) gene on 10q23.31 (25, 26). It shows a strong female dominance with an overall prevalence of one in 200,000 (27). The incidence of meningioma in patients with CS was 8.25% in a systematic meta-analysis (28).

Several hereditary conditions are associated with germline mutation of the SMARCB1 gene on 22q11.23, including schwannomatosis, rhabdoid tumor predisposition syndrome [atypical teratoid/rhabdoid tumor (AT/RT)], and Coffin-Siris syndrome.

Germline mutation of the *SMARCB1* gene on 22q11.23 causes several hereditary conditions, such as rhabdoid tumor predisposition syndrome (AT/RT) (29), schwannomatosis (30), and Coffin-Siris syndrome (31). Schwannomatosis is associated with a nontruncating mutation at the beginning of end of the SMARCB1 gene, presenting as a bening tumor disposition syndrome (32); 5% of patients with this syndrome will develop a meningioma. SMARCB1 is very closely associated to NF2 on

chromosome 22, and co-mutation of both genes has been seen with tumorigenesis of meningiomas (33). Germline mutations of *SMARCE1* gene on 17q21.2, with nearly all mutations being truncating characterized by loss of function mutations, was identified in families with multiple spinal meningiomas, and later alterations in *SMARCE1* were also found in individuals with intracranial and spinal clear cell meningiomas (34, 35).

BRCA1-associated protein 1 (BAP1) tumor predisposition syndrome (BAP1-TPDS) is associated with a germline mutation of the *BAP1* gene on 3p21.1. These individuals are vulnerable to a variety of neoplasms, including uveal and cutaneous melanomas, pleural and peritoneal mesotheliomas, renal cell carcinoma, and mesothelioma (36). Those affected develop meningiomas by the time they reach 50 years of age (37). Meningiomas in BAP1-TPDS tend to demonstrate rhabdoid morphology and show aggressive clinical behavior (36). BAP1 encodes a ubiquitin carboxyl-terminal hydrolase 1, which is involved in the regulation of chromatin modification as a part of the polycomb repressive complex (PRC), and response to DNA damage by interacting with a tumor suppressor, BRCA1 (36).

Other familial syndromes associated with meningiomas include Rubinstein-Taybi syndrome, Li-Fraumeni syndrome, Gardner syndrome, multiple endocrine neoplasia type 1, and Werner syndrome (**Table 1**).

Radiation

A primary modifiable risk factor for the development of meningioma is exposure to ionizing radiation, resulting in a six- to 10-fold increase in risk (38). For example, individuals who underwent low dose radiation (1-6 Gy) for the treatment of tinea capitis of the scalp were found to have a 2.3% lifetime risk over 35 years of developing one or more meningiomas (39). Likewise, a large study conducted by the USA Childhood Cancer Survivor Study (CCSS) reported on the incidence of secondary malignancy estimated to be 3.1% for meningioma alone, in which radiation exposure was identified as an independent risk factor, with a relative risk of 2.7 (40). In a meta-analysis, the mean intervals between primary cancer diagnosis (90% acute lymphoblastic leukemia (ALL) or brain tumor) and subsequent meningioma diagnosis were 10.7 to 23.1 years (41). Of note, these radiation induced meningioma have been found to have more atypical features with a high proliferation index resulting in a higher grade meningioma as well as being multifocal in nature (42). However, a review of survivorship data found that 5-year survival rates were similar to those with primary meningiomas (41, 42). Among the survivors of the atomic bomb in Hiroshima the incidence of meningiomas found on imaging in 5-year intervals since 1975 were 5.3, 7.3, 10.1, and 14.9 cases per 10 (5) population, respectively (43). Data from the Hiroshima Tumor Registry also showed that the incidence of meningioma was relative to the distance of radiation source, showing that individuals exposed within 1 km had three times higher risk than among those exposed 2 km away (43).

TABLE 1 | Familial syndromes associated with meningiomas.

Familial syndrome	Gene	Chromosome locus
Neurofibromatosis type 2	*NF2*	22q12
Familial schwannomatosis	*SMARCB1*	22q11.23
Multiple spinal meningiomas	*SMARCE1*	17q21.2
BAP1 tumor predisposition syndrome	*BAP1*	3p21.1
Gorlin syndrome (nevoid basal cell carcinoma syndrome)	*PTCH1*	9q22.3
	SUFU	10q24.32
Familial multiple meningiomas	*SUFU*	10q24.32
Rubinstein-Taybi syndrome	*CREBBP*	16p13.3
Cowden disease	*PTEN*	10q23.31
Li-Fraumeni syndrome	*TP53/ CHEK2*	17p13.1/22q12.1
Gardner syndrome	*APC*	5q21-22
Multiple endocrine neoplasia type 1	*MEN*	11q13
Werner syndrome	*LMNA*	1q21.1

Specific gene and chromosome locus are illustrated in the table.

Hormone Receptors

There has long been an association with hormone receptors expressed on meningiomas and their increased frequency among female patients, although the data has been highly variable. In a large scale study of ~500 meningiomas, 88% were progesterone receptor positive, 40% were positive for estrogen and 39% for androgen receptors. Estrogen and androgen receptors were significantly more common on lower grade (Grade I) meningiomas compared to higher grade lesions. In addition, estrogen-positive tumor samples showed a higher proliferation index than those that were estrogen-negative (44). However, a population-based, matched case-control study showed no significant associated between the risk of meningioma and the use of exogenous hormones (such as oral contraceptive use or hormone replacement therapy) (45).

Location

Meningiomas are thought to arise from meningothelial cells (arachnoid "cap" cells) and occur more frequently in areas where cap cells are most numerous. Cap cells are especially concentrated in the arachnoid granulations and are a common site of origin for meningiomas, especially along the dural venous sinuses where villi of arachnoid granulations are clustered. Additional sites of origin include the arachnoid associated with cranial nerves as they exit the cranial vault and even the choroid plexus (since the arachnoid participates in its formation, i.e., tela choroidea). Lesions in spinal locations constitute approximately 12% of all meningiomas. Of intracranial and juxtacranial meningiomas, the most to least common locations for occurrence of meningioma are: convexity (lateral hemisphere) (20%–34%); parasagittal (medial area of hemispheres) (18%–22%) (includes falcine meningiomas [5%], which account for lesions adjacent/involving the superior sagittal sinus or in some cases extending to both sides of sinus); sphenoid and middle cranial fossa (17%–25%); frontobasal (10%); posterior fossa (9%–15%), including the tentorium cerebelli (2%–4%), cerebellar convexity (5%), cerebellopontine angle (2%–4%), and clivus (< 1%); intraventricular (2%–5%) and orbital (<1%–2%) (**Table 2**) (46, 47). Recognizing potential atypical locations of these neoplasms is critical to ensure both proper diagnosis and treatment.

TABLE 2 | Frequency of meningioma depending upon location.

Location	Frequency
Convexity	20–34%
Parasagittal	18–22%
Falcine	5%
Sphenoid and middle cranial fossa	17–25%
Frontobasal	10%
Posterior fossa	9–15%
Tentorium cerebelli	2–4%
Cerebellar convexity	5%
Cerebellopontine angle	2–4%
Clivus	<1%
Intraventricular	2–5%
Orbital	<1–2%
Ectopic	<1%

Imaging Characteristics

The standard modality of radiological diagnosis of meningiomas is magnetic resonance imaging (MRI). However, in the cases in which a patient cannot undergo an MRI (e.g., pacemaker or other MRI incompatible device), a contrast-enhanced computed tomography (CT) may be utilized. Of meningiomas harbor regions of intralesional calcifications which can be observed, as well as bony changes, including hyperostosis resulting in a "beaten brass" appearance of the remodeled skull, this is particularly true of lesions along the sphenoid wings and convexity which can be more avidly seen on CT imaging. On MRI meningiomas may have the hallmark dural tail, and overall the lesion should have homogeneous enhancement and be well-circumscribed (**Figure 1**). Benign lesions additionally are isodense to surrounding gray matter on noncontract sequences. Nearly all meningiomas are extraaxial in nature and some may have CSF cleft adjacent to the meningioma. The majority of patients with meningiomas present with a solitary tumor, multiple meningiomas may be seen, particularly in NF2, however, multiple extra axial lesions could also be a result of metastatic disease (48).

Although the dural tail mentioned before is a hallmark of a meningioma—it is not pathognomonic and may also be observed with metastases or solitary fibrous tumor/hemangiopericytoma, but is frequently useful in distinguishing meningioma from other lesions (such as schwannoma) where it is absent (48). Infrequently peritumoral edema on T2 or FLAIR imaging may also be noted, in more aggressive meningiomas and in association with secretory and angiomatous histological phenotypes (12). Areas of central necrosis (hypointense T1, nonenhancing, cystic appearing) are not specific for malignant or higher grade meningiomas this finding can be seen on imaging in lower grade lesions as well (48). In fact, necrosis can commonly be seen after intravascular embolization of the meningiomas, which can be utilized and warranted in meningiomas that appear hypervascular pre-operatively to decrease blood loss. Lesions of the skull base may abut or encase the carotid or basilar arteries and their respective branches, and often an MR angiogram will be obtain to visualize these structures prior to any treatment. Likewise, MR Venograms are thus used for parafalcine meningiomas that are near or involving the superior sagittal sinus to determine if the lesion has direct invasion of the sinus, is causing sinus compression secondarily to mass effect, or has caused thrombosis of the sinus. Despite advancements in MR aiding in the diagnosing of meningiomas, it is not yet predictive of pathological grade or other measure of the aggressive nature of the lesion. Some have shown that there is an inverse correlation between the ADC and Ki-67 proliferation index values in meningiomas, and thus associate the ADC values of the low-grade and high-grade meningiomas (49). PET imaging technology is serving to circumvent the some of the issues with MRI to discern early recurrence versus treatment-related radiographic changes with utilization of a 68- Gallium-labeled somatostatin-receptor analogue (68-Ga-DOTATE) (50). Another PET imaging advancement has been the utilization of tryptophan metabolism *via* α-[(11)C]-methyl-L-tryptophan PET (AMT-PET), in which early studies has been shown that it may be able to delineate tumor grade among meningiomas and other primary brain tumors (51). However, in AMT-PET the (11) C labeled for visualization has a half-life of only 20 minutes (52). As with other primary brain tumors, MR spectroscopy (MRS) studies have features of increased choline peak combined with decreased N-acetyl aspartate and creatinine peaks in comparison with normal brain (53). A distinct alanine peak is a hallmark of meningiomas with variable sensitivity (54). The presence of alanine in meningiomas may be due to partial oxidation of glutamine (55) or conversion from an increased

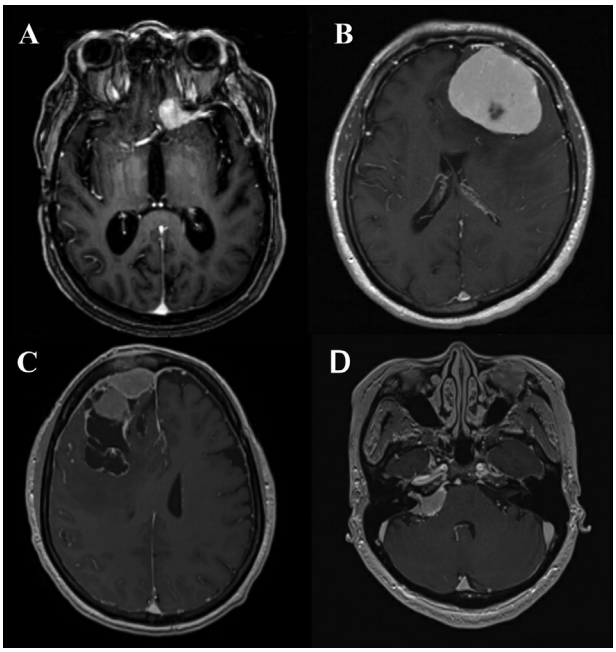


FIGURE 1 | **(A)** Axial T1-post contrast MRI demonstrating an anterior clinoid meningioma with a characteristic dural tail. **(B)** Axial T1-post contrast MRI demonstrating a convexity meningioma with dural tails. **(C)** Axial T1-post contrast MRI demonstrating a meningioma with irregular edges abutting the superior sagittal sinus. **(D)** Axial T1-post contrast MRI demonstrating cerebellopontine angle meningioma.

pool of pyruvate secondary to inhibitions of the enzyme pyruvate kinase by L-alanine (56). As with the other technologies listed the ability of MRS to determine to tumor grade is not well established; however, it has been shown that an elevated lactate more often seen in atypical meningioma. Likewise, the absolute concentrations of total alanine and creatine have been shown to be decreased in high-grade when compared with low-grade meningiomas, as was the ratio of glycine to alanine (57).

Pathology

Antoine Louis in 1774, a French surgeon, described a tumor-like meningioma and called it "fungus durae matris". However, it was Harvey Cushing an American neurosurgeon that was the first to use the term "meningioma" in 1922 (58, 59). Dr. Kepes's work on the tumor's biology, pathology and differential diagnoses has further helped advance this field (60). The histologic feature of a meningioma that is pathognomonic is "whorl" formation by meningothelial cells, which can mineralize to harbor "psammoma bodies" (concentric dystrophic calcifications). Additionally intranuclear cytoplasmic pseudoinclusions, which are cytoplasmic invaginations in the nuclei, nuclear clearing and nuclear grooves are often observed. Nonetheless, these features can be absent or often unassuming in a subset of meningiomas. Immunohistochemistry may be utilized for confirmation in such examples, with the most widely marker being epithelial membrane antigen (EMA). More recent studies have clearly shown that somatostatin receptor 2A (SST2A) is a superior immunostain target due to its higher sensitivity (61).

Meningiomas are heterogeneous in their histopathologic features. Currently, 15 variants exist that are classified into three histologic grades. The WHO grade I (benign) includes nine variants, and the most frequent are meningothelial (**Figure 2**), fibrous, and transitional variants. Psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic variants are also included in grade I. Atypical, chordoid, and clear cell variants are included in grade II, whereas anaplastic, papillary, and rhabdoid variants are included in grade III (**Table 3**).

Meningiomas are classified as grade II "atypical" tumors if the lesion contains 4 or more mitoses per 10 consecutive high-power fields (using a 40× objective) or brain invasion, latter defined as meningioma infiltration into the underlying brain parenchyma without an intervening layer of connective tissue (62). In prior WHO classifications, invasion was considered a staging feature rather than a grading feature; however, it is recognized in the new grading that the presence of brain invasion in a WHO grade I meningioma confers recurrence and mortality rates similar to those of a WHO grade II meningioma (63). If neither feature is present, at least three of the following five histologic criteria must be evident to arrive at a grade II diagnosis: spontaneous intratumoral necrosis; patternless pattern or sheeted architecture; prominent nucleoli; high cellularity; and small cell change (tumor cells with scant cytoplasm relative to nuclear size) (62).

It has been documented that a Ki67 proliferation index over 4% has also been correlated with increased recurrence risk, however, it is most commonly used as an adjunct to standard WHO grading, rather than as an independent indicator of grade (64). As mentioned elevated mitoses and invasion are both regarded as sufficient for grade II classification, however, multiple grade II features can usually occur within the same atypical meningioma, i.e., invasion plus increased mitoses, sheet-like growth pattern and areas of high cellularity with small cell changes.

The other two subtypes of grade II meningiomas, clear cell and chordoid, may not show additional findings like elevated mitotic activity, necrosis and invasion and are in need of additional datasets to clarify their prognostic implications. Larger meningiomas require microscopic examination of several blocks to ensure lack of atypical features as well as absence of specialize variants (12). Assessment of brain invasion may also be apparent only by histologic evaluation, most often following thorough lower power scanning the periphery of the meningioma; an immunostain for glial fibrillary acidic protein can additionally be used to confirm minuscule foci of brain-invasion (12).

Grade III or anaplastic meningiomas can often resemble high-grade sarcomas, carcinomas or melanomas. While they often display *atypical* features of grade II lesions, the mitotic threshold differs, i.e., presence of > 20+ mitoses per 10 consecutive high-power fields. Thus, all meningiomas with 4–19 mitoses are still within the grade II spectrum. Rhabdoid and papillary morphologic variants are also considered to be grade III (12). Of meningioma with documented WHO grade, 80.5% were WHO grade I, 17.7% were WHO grade II, and 1.7% were WHO grade III (2).

Genetics and Molecular Characteristics

The first genetic alteration found in association with meningiomas was observed by FISH in the deletion of Chromosome 22q, later determined to be the gene involved in NF2 on 22q12 (15, 65). The tumor suppressor, Merlin from 22q12 is inactivated in nearly two-thirds of meningiomas and is a member of the protein 4.1 superfamily of cytoskeleton linker proteins that includes erzin, radixin, and moesin (ERM) (14, 66, 67). Interestingly, *NF2* mutant meningiomas appear to have more histopathological findings of fibrous or transitional rather than some meningothelial histologic variants, likely due to lack of cytoskeleton linker resulting in a more mesenchymal phenotype (68, 69). Merlin is also involved in various developmental and survival signaling pathways with loss resulting in the dysregulation of cell proliferation, growth, and motility. Merlin enables Hippo-dependent YAP/TAZ destruction, restrains nuclear β-catenin activity in the WNT pathway, regulates TGF-β signaling activation, suppressor of mammalian target of the rapamycin (mTOR) pathway restricts activation of PGFR and EGFR, and controls the level of Notch receptor availability (70, 71). Therefore, it is not surprising that *NF2*-mutated meningiomas have been found to harbor more genetic alterations than the *NF2*-wildtype, despite both meningiomas within the same benign grade, which has continued the suggestion that a *NF2* mutation results in greater chromosomal instability overall (72).

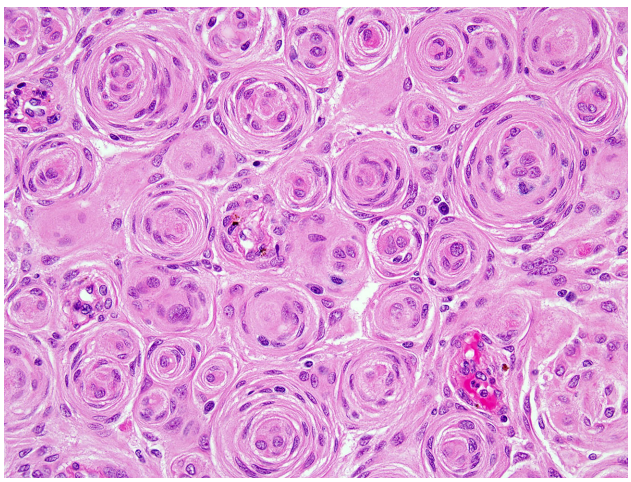


FIGURE 2 | H&E of meningothelial meningioma with prominent whorled architecture (400×; H&E, hematoxylin and eosin stain).

TABLE 3 | WHO Grade with their associated histopathological subtypes.

Grade	Histopathologic features
WHO Grade I	
	Meningothelial
	Fibrous (fibroblastic)
	Microcystic
	Transitional
	Psammomatous
	Angiomatous (includes hemangioblastic, angioblastic)
	Secretory subtypes
	Metaplastic
	Lymphoplasmacyte rich
WHO Grade II	
	Clear cell
	Choroid
	Atypical
WHO Grade III	
	Rhabdoid
	Papillary
	Anaplastic

Several studies have shown that a loss of 18q is associated higher WHO grade meningiomas and recurrence rates (73). The *DAL-1* (differentially expressed in adenocarcinoma of the lung) gene located at 18q has been purported to act as a potential tumor suppressor gene as a critical regulator of proliferation and apoptosis in meningiomas (74). Decreased expression of Dal-1 is also observed in up to 60%–76% of sporadic meningiomas, with loss of expression of either Dal-1 or merlin seen in 92% (75). The loss of merlin or Dal-1 are thought to be early events in the development or initiation of tumorigenesis in meningiomas (76). The loss of chromosome 10 has been found in a small study primarily in WHO Grade III but not in WHO Grade II specimens, suggesting that chromosome 10 loss may serve as a diagnostic and perhaps a prognostic marker (77).

Recent next-generation sequencing has elucidated a number of recurrent genetic alterations in *NF2*-nonmutated meningiomas which are driven by four mutually exclusive pathways: increased hedgehog signaling (through *SMO*, *SUFU* or *PRKAR1A* mutations); *TRAF7* (with either *KLF4* mutation or PI3K pathway activation); RNA polymerase II subunit A (*POLR2A*) mutations; and other (i.e., *AKT1)* mutations (68, 78). The majority of these mutations are usually found in WHO grade I meningiomas and also appear to not coexist with mutations in *NF2* (16). However, mutations in *TRAF7* can be present in isolation, though often they can co-occur with *KLF4*, *AKT1*, or *PIK3CA* mutations, whereas mutations in *SMO* and *POLR2A* are usually mutually exclusive (16, 79) Interestingly, the meningiomas arising from *SMO* and *AKT1-MTOR* aberrations often arise in the skull base (68). In contrast, meningiomas driven by the inactivation of *NF2* tend to localize primarily to the convexity (80). Likewise, there are associations between some mutations seen and with specific histopathologic variants of meningioma, for example *NF2* in fibroblastic and transitional meningiomas (68, 69), *KLF4* and *TRAF7* in secretory meningiomas (81), and *AKT1* mutations in grade I meningothelial meningiomas particularly of the base of the skull and spine (82). Mutations in BRAF V600E have been associated with rhabdoid meningiomas WHO grade III and recurrent meningiomas (83, 84). Alteration of the telomerase reverse transcriptase (*TERT*) promoter has been shown to be associated with an increased risk of recurrence (16, 85).

Growing evidence in the last two decades has shown that epigenetic modifications may have a pivotal function regarding tumorigenesis, progression and reoccurnce of meningiomas (**Table 4**) (86, 87). Moreover, several studies have propose methylation status of DNA within meningiomas may more accurately reflect the aggressiveness of the tumor and thus their anticipated recurrence rate compared with WHO grade of the lesion and/or extent of surgical excision (88–90). Numerous genes have been identified that are silenced by focal DNA hypermethylation in meningiomas include *TIMP3*, *TP73*, *MEG3*, *GSTP1*, several homeobox (*HOX*) family members (*HOXA7*, *HOXA9*, *HOXA10 HOXA6* and *HOXA9)*, *CDKN2A*, *WNK*, *TMEM30B*, and *MAL2* (91). In the case of hypermethylation of *TIMP3*, studies have shown that this methylation event inhibits matrix metalloproteinases and has been associated more aggressive and higher grade meningiomas (92, 93). Likewise, the inactivation of tumor suppressor gene, *TP73* by hypermethylation has been found in higher grade lesions and is thought to be associated with malignant transformation (94). Promoter methylation of *MEG3*, *GSTP1*, and *MAL2* has been shown to more commonly in higher grade meningiomas (92, 95, 96).

Various groups have subdivided meningiomas into distinct subsets based on the extent of the global DNA methylation profile, the have been various definitions but the results remained consistent which is the lesions within specific methylation classes (MCs) correlated particular mutations, histological variants, cytogenetic alterations and concluded that a DNA methylation-based classification system may provide a more accurate prognostication of clinical outcomes

TABLE 4 | Genes associated with meningiomas with corresponding chromosomal location and product (86).

Gene	Full name	Locus	Product
NF2	Neurofibromin 2	22q12.2	Merlin
TRAF7	TNF receptor-associated factor 7	16p13.3	TNF receptor-associated factor 7
KLF4	Kruppel-like factor 4	9p31	Kruppel-like factor 4
AKT1	v-Akt murine thymoma viral oncogene homolog 1	14q32.33	AKT1 kinase (serine/threonine protein kinase)
SMO	Smoothened, frizzled class receptor	7p32.1	Smoothened, G protein-coupled receptor
PIK3CA	Phosphadidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	3q26.32	Catalytic subunit of kinase, PI3K
POLR2A	RNA polymerase II subunit A	17p13.1	RNA polymerase II subunit A
BAP1	BRCA1-associated protein 1	3p21.1	Ubiquitin carboxyl-terminal hydrolase 1
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	22q11.23	Subunit of SWI/SNF complex
SMARCE1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1	17q21.2	Subunit of SWI/SNF complex
BRAF V600E	B-Raf proto-oncogene	7q34	Serine/threonine kinase
NOTCH2	Notch receptor 2	1p12	Notch2 (notch receptor family)
PTEN	Phosphatase and tensin homolog	10q23.31	Phosphatidylinositol-3,4,5-triphosphate 3-phosphatase
CDKN2A	Cyclin-dependent kinase inhibitor 2A	9p21.3	p16(INK4A), p14(ARF)
CDKN2B	Cyclin-dependent kinase inhibitor 2B	9p21.3	p15(INK4B)

(88–90). For example, one group has been shown that WHO grade I meningiomas with intermediate level of methylation status have a worse clinical outcome than the average outcome of WHO grade I meningiomas (89). Similarly a WHO grade II meningiomas with a benign methylation classification profile appear to have an improved overall survival than the average of WHO grade II meningiomas (89). Taken together, one study has developed a DNA methylation-based model for predicting the risk of early (5-year) recurrence of meningiomas which combines the methylation status, with extent of resection and WHO grade in the hopes of tailoring ongoing surveillance and therapy (90).

Modifications in histones known to result in remodeling key complexes on chromatin have been reported for various malignancies in the recent years. It has been reported that meningiomas with the loss of trimethylation of lysine 27 of histone H3 (H3K27me3) *via* immunohistochemistry was associated with lesion that had documented rapid progression (97). In a large molecular profiling study have reported overexpression of the histone cluster H1 family member C (*HIST1HIc*) genes (6p) to be associated with recurrent meningiomas (98). In addition *HIST1Hic* has been shown mediate chromatin transcription by blocking chromatin acetylation (99) and aid maintenance or establishment of specific DNA methylation patterns (100). In addition, nearly 10% of non-*NF2* meningiomas harbor loss of function mutations of *KDM5C* and *KDM6A*, encoding histone lysine-specific demethylases, resulting in alterations in histone function and epigenetic regulation in meningiomas (68). As discussed earlier mutations of two core subunits of the SWI/SNF complex, *SMARCB1* and *SMARCE1*, have been identified in familial syndromes at risk of developing meningiomas (101). However, within anaplastic meningiomas the PRC2 histone methyltransferase complex, an antagonist of SWI/SNF complex, is upregulated result in aggressive disease and stemness and epithelial-to-mesenchymal transition (102).

There is increasing evidence for the role of microRNAs (miRNAs) as a regulator of epigenetic mechanisms as well as in the initiation, progression, and recurrence of meningiomas (103). For instance, some studies have shown that miR-200a may act as a tumor suppressor and that the downregulation of miR-200a may promote the development of meningiomas, as miR-200a has been found to be downregulated in meningiomas (104). In higher grade meningiomas, it has been shown that the downregulation of miRNA-145 has also indirectly associated with the overexpression of the *COL5A1* gene (encoding collagen type V alpha) thus miRNA-145 may account for the aggressive and invasive nature of these higher grade gliomas (105). Likewise, the upregulation of miR-21 has been demonstrated among WHO grade II or III meningiomas to a greater extent than that found in WHO grade I meningiomas (106). In meningiomas with high rates of recurrence it has been sown that there is an upregulation of miR-190a and downregulation of miR-29c-3p and miR-219-5p (107). The expression of miRNA-224 has been shown to correlate with advanced pathological grade and has been suggested that its expression could be used to predict the overall survival and recurrence-free survival of patients (106, 108).

Treatment

Surgery

In an age of increased incidentally found meningiomas due to enhanced and improved imaging studies, when patients are asymptomatic, observation with routine surveillance imaging is an acceptable strategy. However, if the meningioma is growing and/or causing symptoms that could be related to the lesion, then maximal safe surgical resection is the standard of care. Nevertheless, the ability to achieve a GTR may be limited due to tumor location, involvement or invasion of nearby dural sinuses, arteries, cranial nerves and extent of brain invasion, especially in eloquent areas as well as patient specific factors affecting the safety of the procedure.

The surgical approach of meningiomas is dictated by the neuroanatomic location and surrounding structures. Convexity meningiomas are straightforward in their approach and often have GTRs. However, meningiomas in this location only account for about one sixth of meningiomas. Parasagittal meningiomas are more complex to resect and obtain a GTR as they often arise near the superficial sagittal sinus and can involve or invade this major intracranial draining sinus. In suspected cases of superficial sagittal sinus invasion, the surgical resection might not extend to remove that portion of the tumor due to an increased risk of air embolism, large blood loss and/or post-operative sinus thrombosis. Tumors of the skull base (sphenoid wing, olfactory groove, tuberculum sella, cerebellopontine angle or petroclival region) require more advanced surgical techniques and approaches to safely access the tumor without extensive brain retraction, injury to cranial nerve and vasculature. Advances in endoscopic technology and techniques have enabled the resection of skull bases meningiomas through an endoscopic endonasal approach that can be done alone or in combination with a traditional craniotomy, but risks associated with this location generally outweigh those in the convexity (109).

Several strategies might be leveraged pre- or intra-operatively for better outcomes. For example, coagulation and/or preoperative embolization could be employed to limit blood loss and to maintain good visualization throughout the procedure in hypervascular meningiomas. For meningiomas that are firm or calcified, a technique of debulking centrally or in piecemeal status through the resection can limit the need for retraction of the surrounding brain, cranial nerves, and corresponding vasculature. If the tumor forms a capsule in the arachnoid plane, performing the dissection while remaining in this plane can protect the pia of surrounding brain from injury. Similarly, cranial nerves and arteries may be enveloped or encased by skull base meningiomas, but the tumors rarely invade them and identification of the arachnoid plane can allow for safe dissection of the meningioma from normal structures. This technique of debulking, coagulation, and dissecting along the periphery are repeated until a GTR is achieved. As the adjacent dura is often involved with meningiomas, a dural graft is used in reconstruction. Additionally, the meningioma may invade adjacent bone of the skull. If involvement is limited, it may be possible to drill to the point of normal bone matrix; if there is more extensive involvement rendering the flap unsalvageable, the use of mesh or a cranial plating system instead should be considered. As mentioned, there are several factors that may preclude a GTR from occurring especially in skull base meningiomas (e.g., venous sinus involvement, arterial or cranial nerve envelopment and extensive involvement of the base of the skull). These circumstances may account at least in part for the improved survival of patients with convexity meningiomas over those with parasagittal and skull base meningiomas (110).

The extent of resection has been shown to be crucial to the rate of recurrence in the treatment of meningiomas. The extent of resection is defined by the Simpson grading system which is denoted by postoperative imaging as well as the assessment by the neurosurgeon during the procedure (**Table 5**) (111). A biopsy is a Simpson grade 5, subtotal resection of the meningioma is a grade 4, macroscopic resection without dural excision or coagulation is a Simpson grade 3, GTR with dural coagulation is a Simpson grade 2, and GTR including adjacent dura and bone is a Simpson grade 1 (111). Recurrence rates of Simpson grade I resection in a WHO grade I meningioma are low; they rise substantially with an increasing pathologic grade. In a retrospective study, 5 year recurrence rates after a Simpson grade I GTR in WHO grade I meningiomas are reported as 7%–23%, whereas the same resection in a WHO grade II results in a 50%–55% and in WHO grade III 72%–78% recurrence (9, 112). As the extent of resection decreases, there in an increase rate of recurrence (9, 113). However, the recurrence-free survival of Simpson grade 1–3 resection compared to Simpson grade 4 resection was more pronounced for tumors of the convexity than for parasagittal, parafalcine or skull base tumors as well as for meningiomas with high levels of proliferation (MIB-1 labeling index >3%) (114). Therefore, it is reasonable after a GTR of WHO grade I meningiomas to follow with routine surveillance imaging. However, in the case of a subtotal resection (Simpson grade 4–5) of WHO grade I meningioma, and generally all higher grade meningiomas comprised by WHO grade II and III, adjuvant treatment is necessary to delay or curtail recurrence.

TABLE 5 | Simpson grade for surgical resection of meningiomas.

Simpson Grade	Definition (extent of resection)
Grade I	Complete removal including resection of underlying bone and associated dura
Grade II	Complete removal and coagulation of dural attachment
Grade III	Complete removal without resection of dura or coagulation
Grade IV	Subtotal resection
Grade V	Simple decompression with or without biopsy

Radiation Therapy

Radiation therapy has been the primary treatment for growing meningiomas that are deemed nonsurgically resectable based on location and/or patient co-morbidities which preclude surgical resection. Additionally, radiation therapy is employed as an adjuvant therapy after surgical resection, for recurrence after a resection, and some consider an upfront treatment approach if subtotal resection or operative morbidity is likely. Treatment can be delivered as a single-fraction stereotactic radiation (SRS) or fractionated external beam radiotherapy (EBRT). There is a scarcity of prospective studies comparing these different radiation therapy delivery regimens (techniques, doses, etc.) and comparing a single regimen to surgical resection, and therefore, most of the data is based on retrospective studies. Likewise, evaluating different radiation modalities *via* an outcome measure of recurrence rates or meningioma volume are plagued with over simplification of diverse meningioma population, genetics and treatment specific toxicities.

Treatment of recurrent WHO grade I and radiographically defined (presumed grade I) meningiomas is typically with a total dose of 50–54 Gy with a clinical target volume (CTV) margin of

0–5 mm (115, 116). For more advanced, WHO grade II-III meningiomas, treatment is typically 59.4–60 Gy with a wider 10–20 mm gross tumor volume (GTC) to CTV anisotropic expansion while respecting anatomic barriers to tumor growth (116). For smaller tumors with a diameter of less than 3–4 cm and at least 2-mm separation from critical normal structures (such as optic nerves), single fraction SRS is a feasible option. EBRT has been utilized for some tumor locations in which a GTR may cause significant morbidity to the patient (116). For example, one series of patients with optic nerve sheath meningiomas had ~25% of patients treated with EBRT alone and they showed no failures and improved or stable vision in 86% at a median of 8.3 years of follow-up (117). Another series of ~100 patients with presumed WHO grade I skull base meningiomas received EBRT only (65%) or following STR (35%), and showed local control of 95% for all patients at a median follow-up of 5 years (118). Studies of particle therapy are limited, although there are phase I and phase II trials underway to look at the role of proton radiation in a variety of settings with meningiomas [UPCC 24309 (NCT01117844)] (119). As well as a combined phase I/II study (NCT02693990) is investigating proton therapy with dose escalation for atypical meningiomas that underwent STR and anaplastic meningiomas following surgical resection (116). Brachytherapy is infrequently used, with the largest cohort being 42 patients receiving I-125 permanent seed implant during resection of atypical or malignant meningiomas. Eight-five percent of patients had a history of prior radiation therapy with a median time to progression of 11.4 months and numerous complications including radiation necrosis, wound breakdown, wound infection, and pseudomeningocele (116, 120). Ongoing studies will be needed to determine its utilization in the treatment of meningiomas.

The toxicities of radiation are dependent on the technique and dosing of radiation therapy implemented. EBRT toxicities are location dependent but are known to include alopecia. Side of effects of SRS are primarily limited to fatigue which is often transient and abated with a steroid regimen (119). Late toxicities for cranial radiation therapy include endocrinopathies, cognitive effects, increased cerebrovascular events, and secondary neoplasm risks as mentioned earlier (121). While the rate of these complications is low, they warrant discussion with patients given that the tumors are frequently benign.

When considering radiation therapy as a primary modality, there are several factors to take into account. First, radiation therapy is not as effective at relieving mass effect or tumor-associated edema, neurological deficits, or symptoms. However, if a patient is a poor surgical candidate or has lesions that are inaccessible for safe resection, radiation therapy is frequently employed for mitigation of local tumor growth. Second, the use of radiation therapy upfront precludes surgical biopsy, preventing histological confirmation of tumor grade and molecular features. This decreases the opportunity for targeted therapy, as well as limits understanding of the natural history of the meningioma and the risk of recurrence.

Add into the recent controversy of radiation therapy not as an adjuvant treatment but primary treatment, a recent RANO working group performed a systematic literature review; WHO Grade I meningiomas when treated to 50–54 Gy in 27–30 fractions EBRT had control rates of 87%–100%. Likewise, WHO grade I meningiomas treated with 12–16 Gy SRS had 10-year control rates greater than 90%, but this was location specific as parasellar and skull base meningiomas had lower rates of control (69%–90%) (9). The PFS in meningiomas less than 35 mm was better with SRS (mean dose 17.7 Gy) compared with Simpson grade 2–5 resection, although not for Simpson grade I (122). As expected, for larger meningioma volumes, there is decreased control especially in single fraction SRS as well as increased (5%–23%) radiation-related complications (123). Therefore, some centers hypofractionated SRS (up to 5 fractions) treatments for larger volume tumors, typically for those tumors >10 mm (3) which has abated some of the complications (edema and radiation necrosis) as well as mitigate development of toxicity by allowing repair of normal tissues (9, 124). Local control rates in which hypofractionated SRS has been utilized grade I and II meningioma was reportedly 95 and 71%, respectively, with no acute toxicities (125, 126). However, more studies need to conducted to determine the role of hypofractionated SRS in comparison to EBRT for similar pathological grades and sizes. Interestingly, a small study of patients that underwent either SRS or EBRT suggested that necrosis may be a negative predictor of radiation response regardless of radiation timing or modality (127).

For the majority of the cases, radiation therapy is adjuvant after surgical resection to decrease recurrence rates. In retrospective studies the addition of EBRT (to 59.4 Gy) demonstrated only 20% recurrence at 6 years versus 65% without radiation therapy following surgery (128). However, there is no consensus on the dosage and/or the timing of adjuvant radiation for high grade aggressive meningiomas. A recent cooperative group trial NRG/RTOG 0539 (NCT00895622) grouped patients into three risk categories in a nonrandomized fashion based on tumor grade and resection status. Patients with newly diagnosed grade I tumors following either gross total (Simpson grade 1–3) resection or subtotal (Simpson grade 4–5) resection were identified as being low-risk. This group showed a recurrence-free survival of 86% based on preliminary data. These findings support withholding adjuvant radiation for gross totally resected grade I tumors (129).

The National Comprehensive Cancer Network (NCCN) provides guidelines for the use of radiation therapy in the management of meningiomas, with most recommendations having Level 2A evidence (130). Radiation therapy should be considered for small (<30 mm) asymptomatic meningiomas at presentation if grade II and subtotally resected or grade III regardless of resection volume, and in grade I tumors when sub-totally resected if there is a ”potential” symptom. Radiation therapy should be pursued for large (>30 mm) asymptomatic tumors if grade III and considered if WHO grade II or incompletely resected grade I. For all asymptomatic meningiomas, observation alone (with serial imaging) is also an acceptable option. For symptomatic meningiomas at initial presentation, radiation therapy is recommended following surgery for any grade III and should be considered for any grade II tumors or large (>30 mm) incompletely resected grade I tumors. For surgically inaccessible tumors or surgically contraindicated patients, radiation treatment alone is also

recommended. Upon recurrence, surgery (if accessible) followed by radiation treatment or re- radiation treatment, or radiation treatment alone (if inaccessible) is recommended (130). Of note, these guidelines do not take into account tumor location, patient age, or any molecular pathologic markers.

Systemic Treatment

As with radiation treatment there is a paucity of large and/or randomized trials to determine the efficaciousness of systemic therapy for the management of meningiomas. Thus, the NCCN recommends the use of only three classes of medical therapy: α-IFN, somatostatin receptor agonists and vascular endothelial growth factor (VEGF) inhibitors for the treatment of meningioma (130, 131). The guidelines by European Association of Neuro-Oncology (EANO) consider the use of systemic pharmacotherapy to be experimental with Level C evidence and thus do not recommend any specific agents or class of therapeutics for the management of meningiomas (**Table 6**) (132).

The utilization of IFN-α in the treatment of recurrent WHO grade I and in higher grade meningioma has shown some promise with PFS at 6 months of 54% and 17%, respectively (133, 134). However, these were small studies and IFN-α was moderately toxic, additional studies will need to performed to determine it efficacy.

However, there are more encouraging results with the use with antiangiogenic agents targeting VEGF. Sunitinib, a small molecule inhibitor of VEGF signaling was used in a Phase II trial of 36 patients with grade II/III refractory meningioma had a PFS at 6 months of 42%, however, had a high toxicity profile (60% with severe adverse events) (135). Bevacizumab, anti-VEGF monoclonal antibody, has been shown to have a PFS at 6 months of 87%, 77%, and 46% in recurrent grade I, II, and III tumors, respectively (136). A Phase II prospective trial of bevacizumab is ongoing (NCT01125046) for recurrent or progressive meningiomas.

Pasireotide, an alternative somatostatin analog, was utilized in a Phase II trial in recurrent meningioma that failed prior surgical or radiation treatment, although it only had a PFS at 6 months of 17% in the high grade (WHO grade II/III) cohort and 50% in the WHO grade I cohort and was well tolerated (137)). A recent retrospective chart review study, found that the use of sandostatin (octreotide) was especially effective in prolonging PFS at 6 month in estrogen negative progesterone positive tumors to 87.8% while patients with estrogen negative progesterone negative meningiomas had PFS at 6 months of 62.5% (138). However, in a trial of nine high grade meningioma patients treated with octreotide and in a larger trial of pasireotide, no radiographic response was observed and no significant benefit in PFS was detected (139).

Very much like gliomas, meningiomas often demonstrate immune evasion with T cell exhaustion resulting in decreased levels of PD-1$^+$ T cells. However, trials of the inhibitory PD-L1 antibody-based therapies, prembrolizumab (NCT03016091, NCT03279692), nivolumab alone (NCT02648997), or nivolumab with hypofractionated SRS in combination with or without ipilumumab (CTLA4 inhibitor NCT03604978) and avelumab (in combination with proton radiotherapy, NCT03267836) are ongoing (12, 139). A recent case report demonstrated a remarkable response to nivolumab in a patient with recurrent, treatment-refractory meningioma and homozygous deletion of the DNA mismatch repair gene, MSH2 (140). Application of agents targeting the mTOR-pathway is currently being examined in trials with everolimus (NCT01880749 and NCT01419639) and vistusertib (AZD2014, NCT03071874, and NCT02831257). Everolimus is also being studied in combination with the somatostatin receptor analog octreotide (CAVOREM, NCT02333565) in recurrent meningioma (**Table 7**) (12, 139).

TABLE 6 | Recommendations for the management of meningiomas of WHO grades I–III.

Histology, degree of resection	Recommendations for the therapeutic management
WHO grade I, gross total resection	Observation
WHO grade I, subtotal or partial resection	Observation or sterotactic radiosurgery/ fractionated radiosurgery
WHO grade II, gross total resection	Observation or fractionated radiosurgery
WHO grade II, subtotal or partial resection	Fractionated radiosurgery
WHO grade III	Fractionated radiosurgery, experimental chemotherapy or peptide receptor radionuclide therapy

TABLE 7 | Active recruiting of clinical trials for treatment of meningioma, updated and modified from Al-Rashed (139).

Drug (Trade Name)	Target	ClinicalTrials.gov Identifier
Immunotherapies		
Pembrolizumab (Keytruda)	PD-1	NCT03279692 NCT03016091
Avelumab and Hypofractionated Proton Radiation Therapy	PD-1	NCT03267836
Nivolumab (Opdivo) with or without Ipilimumab (Yervoy)	PD-1	NCT03604978
Nivolumab (Opdivo)	PD-1	NCT03173950
Targeted small molecules		
Vistusertib (AZD2014)	mTORC1/ mTORC2	NCT03071874
Alpelisib (Piqray) and Trametinib (Mekinist)	PI3K/MEK	NCT03631953
Ribociclib	cyclin D1/ CDK4 & CDK6	NCT02933736
Brigatinib (Alunbrig)	NF2	NCT04374305
Selumetinib	NF2	NCT03095248
Abemaciclib	CDK4/6	NCT03220646
Peptide receptor radionuclide therapy (PRRT)		
177Lu-DOTATATE (Lutathera)	SSR	NCT03971461 NCT04082520
Somatostatin receptor (SSTR)		
SOM230C	pasireotide LAR	NCT00859040
Tumor Treating Field		
NovoTTF-110A (Optune) and Bevacizumab (Avastin)	N/A	NCT02847559

CONCLUSION

While meningiomas are a benign tumor, they nonetheless cause significant impact to patients and can challenge clinicians with their ongoing surveillance and management. Surgical resection remains the gold standard when GTR can be achieved. In cases where maximal resection cannot be obtained safely, inoperable cases, residual tumor remains, and/or the tumor is an aggressive high-grade lesion, adjuvant therapy is required. As reviewed, there are drawbacks to many of these adjuvant therapies and few systemic therapies have been approved or shown to be efficacious. Ongoing research and clinical trials will be needed to address these treatment gaps.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REVIEW
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The Current State of Radiomics for Meningiomas: Promises and Challenges

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Meningiomas are the most common primary tumors of the central nervous system. Given the fact that the majority of meningiomas are benign, the preoperative risk stratification and treatment strategy decision-making highly rely on the conventional subjective radiologic evaluation. However, this traditional diagnostic and treatment modality may not be effective in patients with aggressive-growing tumors or symptomatic patients with potential risk of recurrence after surgical resection or radiotherapy, as this passive "wait and see" strategy could miss the optimal opportunity of intervention. Radiomics, a new rising discipline, translates high-dimensional image information into abundant mathematical data by multiple computational algorithms. It provides an objective and quantitative approach to interpret the imaging data, rather than the subjective and qualitative interpretation from relatively limited human visual observation. In fact, the enormous amount of information generated by radiomics analyses provides radiological to histopathological tumor information, which are visually imperceptible, and offers technological basis to its applications amid diagnosis, treatment, and prognosis. Here, we review the latest advancements of radiomics and its applications in the prediction of the pathological grade, pathological subtype, recurrence possibility, and differential diagnosis of meningiomas, and the potential and challenges in general clinical applications. In this review, we highlight the generalization of shared radiomic features among different studies and compare different performances of popular algorithms. At last, we discuss several possible aspects of challenges and future directions in the development of radiomic applications in meningiomas.

Keywords: meningioma, radiomics, medical imaging, diagnosis, deep learning

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INTRODUCTION

Meningiomas are the most common primary central nervous system (CNS) tumors, composing up to 36.4% of all CNS tumors, with an incidence of 7.86/100000 (1). The majority of meningiomas are benign (2), while only 1% are malignant (1) but with increased morbidity and mortality rates (3). According to the 2016 edition of the WHO classification of CNS tumors, meningiomas are considered as heterogeneous tumors that can be divided into three grades and 15 different

pathological subtypes (4). Moreover, meningiomas may present also an intratumoral heterogeneity, such as different degrees of growing patterns, vascularization, necrosis, infiltration, etc., in the same tumor. The transformation from low-grade to high-grade meningiomas is a rare event that can happen as consequences of this intratumoral heterogeneity (5). These intertumoral and intratumoral heterogeneities can explain the different outcomes after resection of meningiomas. Thus, better understanding of the actual biological behavior of these tumors preoperatively could benefit the risk stratification and decision-making process. For example, the "wait and see" modality with a longer imaging follow-up period would be an ideal and cost-effective option in small, stable and benign meningiomas (6). On the other hand, early surgical resection should be recommended in patients with meningiomas which are small in size, but active in growing, or malignant in genotyping.

Nowadays, medical imaging plays a fundamental role in the process of preoperative and differential diagnosis in the CNS tumors such as meningiomas (7). Modern imaging technology, as 3T MRI, provides sufficient high-quality information of the lesions, such as post contrast T1-weighted images can highlight enhancing regions within the tumor because of the leakage of contrast agent from the intravascular lumen into the tumor through a disrupted blood-brain barrier (8), or the integrated use of fluid-attenuated inversion-recovery sequences and T2-weighted images to delineate a more precise boundary between edema and the solid tumor (9). Nevertheless, these data are commonly reported by the radiologist in a descriptive, qualitative, and subjective way. As a dural-based lesion, meningiomas can be misdiagnosed, especially when the radiologists are not familiar with the differential diagnosis of other dural-based lesions. For example, the "dural tail sign" on enhanced T1-weighted sequences, a characteristic imaging sign often regarded as the representative of meningiomas (10), can also be positive in other diseases including sarcoidosis (11), lymphoma (12), metastases (13–15) and other lesions (16, 17). Also, some imaging features, such as the peritumoral edema and morphological irregularity of the meningioma, which may suggest an aggressive pattern, have not been validated yet (18, 19).

Recently, some promising progresses in the preoperative diagnosis have emerged in the field of oncology, as well as in meningiomas. In this scenario, radiomics analysis refers to different methods that "decode" the quantitative features of medical images across different types of tumors. The primary intention of this technique is to identify, from radiological images, several quantitative characteristics of the tumor, so they can be used to improve the understanding of the pathology and biology of the lesion. This data are also sought to predict clinical outcomes, such as patients' survival and responses to therapy (7). The features commonly included in this type of analysis are: volume, shape, intensity (MRI signal) and other texture features, referring to pixel intensities, their distribution pattern, and their interrelationships (20). Nowadays, the radiomics analysis has been used for various types of cancer including lung cancer (21–23) and prostate cancer (24–26). Yet, only few studies reported on radiomics analysis of meningiomas. This analysis can help in preoperative diagnosis by adding new information, such as the growth rate of an incidental meningioma, guiding the differential diagnosis of tumors with dural implantation, predicting tumors' recurrence, and subsequently tailoring the treatment strategies. In this study, we discuss the latest application of radiomics analysis for meningiomas and the potential clinical implications of its integration in preoperative diagnosis.

OVERVIEW OF THE WORKFLOW OF RADIOMICS

Generally, the procedure of radiomics can be divided into four main steps (7, 27, 28): image acquisition, segmentation, feature extraction, and statistical analysis/model (**Figure 1**), but each step is somewhat different across various studies for different purposes (29).

Image Acquisition

Image acquisition is the first step of the radiomics workflow, including acquisition and reconstruction of the image data (29). Acquiring image data refers to collecting raw data with full annotations of multiple imaging parameters, such as repetition time, echo time and field of view in the MRI images, tube voltage and tube current in the CT images, etc., which can be extracted from the image software (28). Image reconstruction is the process of transforming the raw non-image-formative data into the image format by various algorithms. Because the variations in the imaging scanners, modalities, sequences, parameters, and reconstruction algorithms are likely to impact on the results of the final analysis, it is necessary to provide quantitative imaging with error bars or standardizing the original image data to improve the homogeneity (29).

Segmentation

The second step contains identification and segmentation of the region of interest (ROI), either manually, automatically or semi-automatically. In clinical settings, meningiomas are usually manually delineated by experienced radiologists. Given the fact that many other types of tumor do not have distinct borders and their inside heterogeneity, the accompanying inter-user variability is an inevitable issue. There are several strategies to minimize the variability, the common one is the segmentation tools (28). The rational choice of segmentation software and double-check with vision manually can not only optimize the result but also raise the efficiency of workflow, especially when a radiologist handles hundreds of cases at the same time. Other approaches such as application of an algorithm (30) or segmenting a fixed-size ROI (31) also work in certain scenarios.

Feature Extraction

Feature extraction is to decode the high-dimension image data and output them quantitatively (29). In the present, the patterns of feature extraction can be simply classified into with or without

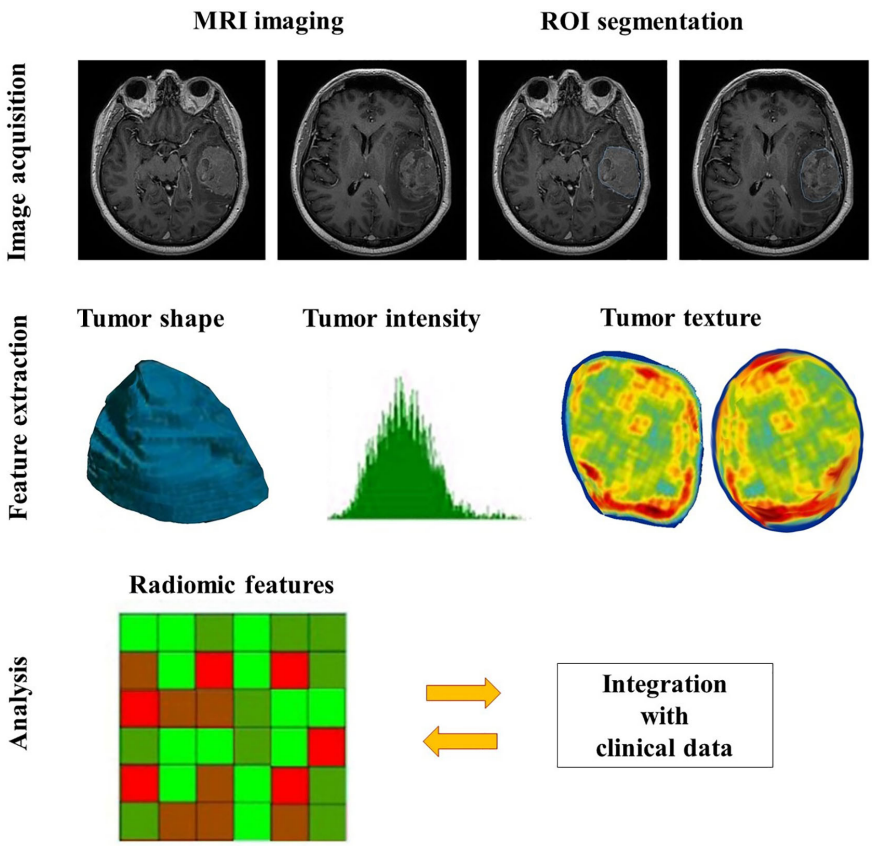


FIGURE 1 | The general workflow of radiomics in meningiomas includes image acquisition, ROI segmentation, feature extraction and analysis.

human orders (7). The conventional way needs specialized algorithms under human instructions. While the newer mode can nearly complete the rest of the whole task automatically and independently from human aids, which is based on the deep learning radiomics (DLR), such as convolutional neural networks (CNNs). Moreover, the number of extracted features within the CNNs is several orders of magnitude greater than the conventional methods (7), but it is necessary to reduce the feature dimensions to avoid overfitting (29). Besides, feature extraction, selection, and classification can occur across different layers in the same CNN (7).

Features in radiomics are divided into two groups, semantic and agnostic. Semantic features indicate the radiology lexicons which are commonly used to intuitively describe the lesion, such as size, location, and shape. Conversely, agnostic features are mathematically-extracted quantitative descriptors, which aim to highlight the lesion heterogeneity (29). Agnostic features can be subdivided into three categories, which are first-, second-, and higher-order. First-order statistics depict the distribution of values of individual voxels without any concerns of the spatial relationships, mostly based on the histogram, such as skewness and kurtosis. Second-order statistics describe statistical interrelationships between voxels with similar (or dissimilar) contrast values, termed as "texture" features. Higher-order statistical features are repetitive or nonrepetitive patterns filtered through specific grids on the image, for example, Laplacian transforms, Minkowski functionals, etc. (29).

Statistical Analysis/Modeling

In the final step, the selected features can be used for many different analyses, and they are mostly incorporated into predictive models to provide improved risk stratification (28). Model construction is the process of developing integration of a set of analysis methods, involving with clustering features and assigning these features with different values according to the predefined information content. Those analysis approaches include artificial intelligence, machine learning, and statistical methods. An ideal model can not only handle the extracted features adequately, but also is able to accommodate sparse data, for instance, genomic profiles (29). The more covariates it can handle, the more specific meaning of a model can be.

However, it would be rather difficult for an inexperienced user to make a choice among multiple algorithms for model building. This situation promotes the implementations of multiple-modelling methodology in a single study, although it may not be necessary (32). The fundamental principle of selecting an algorithm is the reproducibility of the whole process (32), which could be enhanced by a set of measures: (I) evaluate the feature

reproducibility; (II) conduct the cross-correlation analysis; (III) contain clinically significant variables (volume included); (IV) warrant sufficient observation rates (at least 10–15 per feature); (V) provide an external validation cohort; (VI) interpret radiomic features of no physical (or biological) meaning with prudency (33).

CURRENT APPLICATION OF RADIOMICS IN MENINGIOMAS

Most studies using radiomic analysis in meningioma were based on the MRI, ranging from a single to multiple imaging sequences. Indeed, the MRI can provide a superior anatomical delineation (e.g. spatial location) of the intracranial structures and characterize the predominance of different physiopathological processes, due to the different sensitivity of tumor physiology in various MRI imaging sequences (8). In general, the application of radiomics in meningioma can be roughly divided into two aspects: grade prediction and other applications (**Table 1**). The workflow of treating meningiomas may alter based on these radiomic findings (**Figure 2**).

Predicting Pathological Grade of Meningiomas

Tumor grade is a prerequisite to assess the necessity of a subsequent treatment of meningiomas. Currently, this kind of information, regarding the tumor grade, is available only after histopathologic inspection on tumor samples deriving from invasive biopsy or surgery (46). To achieve non-invasive pathological grading, the burgeoning development of radiomics has brought a new dawn in the preoperative grading prediction.

In the initial stages of radiomics analysis experimentation, multiple studies have explored the feasibility of various radiomic features in the prediction of pathological grade of meningiomas. The results showed that both conventional radiomic features, including the shape, histogram, texture, gray-level run length matrix, wavelet transform, and other higher-order statistics (19, 34–38, 40), and the DLR features (39) could predict the tumor grades. Yan et al. have identified two textural features based on the run length matrix and two shape-based features significantly related with the WHO grade II meningiomas; Similarly, in terms of the low grade meningiomas (WHO grade I), one textural feature based on run length matrix and one shape-based feature were selected (35). Zhu et al. have utilized up to 39 novel DLR features to distinguish high grade meningiomas (WHO grade II or III) from low grade ones (39). More detailed information of radiomic features applied in grade prediction and other aspects are summarized in **Table 2**.

Notably, there are several common radiomic features across different studies regardless of their nonidentical nomenclatures (47). One radiomic feature is the sphericity, evaluating how a tumor is morphologically similar to a sphere (19, 36, 39), or spherical disproportion, rating the deviation of a lesion's morphology from a sphere of the similar volume (34, 40). There were 5 studies explicitly demonstrating that high-grade meningiomas tend to have less sphericity than low grade meningiomas, in another word, high-grade meningiomas show more spherical disproportion than low grade ones (19, 34, 36, 39, 40). Moreover, one of these studies found that low sphericity was also associated with local recurrence and less favorable overall survival (19), which may imply that early intervention and shortening observation are warranted in meningiomas of low sphericity. The non-uniformity of the gray level or the run length matrix is another important radiomic feature, which is sensitive in reflecting the heterogeneity within the contoured area (34, 35, 38–40), such as the positive capsular enhancement, indistinguishable tumoral border, and heterogeneous tumor enhancement (46, 48). Because the fluctuance of parameters from second or higher order statistics revealed irregular changes in the gray pixels in aggressive meningiomas due to the intratumoral nonuniform structure tissue (49). Furthermore, it seems that diversified combinations of these features, such as a combination of radiomic features from different feature categories, multiple imaging sequences, heterogenous raw data or combined with qualitative imaging features or clinical data, could improve the performance of the classification models even if those improvements may not always be significant (19, 34, 37, 39).

In addition to radiomic features, the algorithm used in modeling is another critical factor affecting the performance of prediction (50). Since there has been no standardized guidance of algorithms selection yet, the selection usually depends on the preference and experience of analysts (32). At present, the classification methods presently applied for grade prediction include the random forest (RF) (19, 34, 37, 40), logistic regression (LR) (35, 36), naïve Bayes (NB) (35), support vector machine (SVM) (35, 37, 38, 40), eXtreme gradient boosting (XGBOOST) (37), multilayer perceptron (MLP) (37), and linear discriminant analysis (LDA) (38, 39) (**Table 3**). Among these various algorithms, numerically, the best performance of prediction was achieved in a tree-based classification algorithm, XGBOOST, which based on a combination of features derived from multiple MRI sequences and yielded a high AUC of 0.97, a sensitivity of 1.0 and a specificity of 0.97 (37). While the most widely used algorithms are the RF and SVM, the RF is an ensemble method that calculates multiple decision tree-based classifiers containing several identically distributed random independent vectors (37, 51), whereas the SVM is a non-linear classifier that iteratively constructs a hyperplane or high-dimensional feature space consisting of a series of hyperplanes that separates different classes (52, 53). There have been two studies comparing different performances of the RF and SVM, Hamerla et al. have built four different classification models, including the RF, XGBOOST, SVM, and MLP, based on same radiomic features; Their results demonstrated both RF and SVM had same AUC of 0.93 (37). However, in the study of Park et al., the SVM have shown to have a better predicting performance with an AUC of 0.86 comparing to 0.84 in the RF (40). Whereas it was contradictory in the prognosis prediction superiority between the RF and SVM in a study of lung cancer (54). Actually, the RF has a number of advantages, such as its totally

TABLE 1 | Summary of previous reported application of radiomics in meningiomas.

Research groups	Sample Size	Modality	Aim	Segmentation	Features	Feature Selection	Statistical Analysis	Result	Conclusion
Coroller et al. (34)	175	TICE	Grading	Manual	Intensity, Histogram, Texture, Wavelet, LoG	PCA FA	RF	Validation: AUC = 0.78, P = <0.0001. Radiomic classifier could significantly predict meningioma grade.	Demonstrated the ability to discriminate between WHO grade I from grade II/III, which was ready for clinical application.
Yan et al. (35)	131	T1WI+C, T2WI, FLAIR	Grading	Manual	Histogram, Gradient, RLM, CM, Wavelet transform, Autoregressive model	CfsSubset-Eval evaluator in the data mining software Wek	LR, NB, SVM	Training: AUC = 0.87, P = <0.0001. The SVM classifier built on all six representative radiomic features achieved the best performance, with a sensitivity, specificity, diagnostic accuracy of 0.86, 0.87, 0.87, respectively.	Demonstrated that a SVM classifier based on texture and shape features was able to satisfactorily predict meningioma grade before surgery.
Laukamp et al. (36)	71	T1WI, T2WI, T1-CE, FLAIR, DWI/ ADC	Grading	Semiautomatic	Shape, Texture	RF	Multivariate logistic regression analysis	AUC = 0.91, P = <0.001. A radiomic classifier built on the combination of the features was able to differentiate grade I and grade II meningiomas.	Demonstrated the ability to discriminate between WHO grade I from grade II, and a classifier built on the combined features had the best performance.
Hamerla et al. (37)	138	T1WI, T2WI, T1-CE, Sub, FLAIR, ADC,	Grading	Semiautomatic	Shape, Histogram, Texture, A set of high-order statistical features	Mann-Whitney U test	RF, XGBOOST, SVM, MLP	Validation: AUC = 0.97, sensitivity = 1.0, specificity = 0.97 The best classifier was XGBoost consisting of the combination of ADC, ADC of the peritumoral edema, T1, T1c, Sub and FLAIR-derived features.	Demonstrated the ability to classify meningiomas between WHO grade I and grade II/III despite the heterogeneity of raw imaging data from different centers by the method of machine learning.
Chen et al. (38)	150	TIWI, T1CE	Grading	Manual	Histogram, Shape, Texture, High-order features	Distance correlation, LASSO, GBDT	LDA, SVM	Validation: Accuracy=0.756, Kappa value=0.603. The Lasso + LDA model represented the highest diagnostic performances than SVM-based models.	Demonstrated that machine learning algorithms with texture features extracted from T1C images could preoperatively classify meningioma grades.
Zhu et al. (39)	118	T1CE	Grading	Manual	Deep learning features	RF, SBS	LDA	Primary: AUC = 0.891, P = <0.001. Validation: AUC = 0.811, P = <0.001. DLR features could function as effective grade predictor, and their performance was better than the hand-crafted features.	Demonstrated that a DLR model was able to discriminate between WHO grade I from grade II/III, and its capacity was stronger than HCR model.
Park et al. (40)	136	TICE, ADC, FA	Grading, Subtyping	Semiautomatic	Histogram, Texture	Recursive feature elimination	SVM, RF	Validation: AUC = 0.86, accuracy=0.897, sensitivity = 0.75, specificity = 0.935. The machine learning classifiers showed different performances according to the machine learning algorithms and the best classifier was SVM. Diverse texture parameters distinguished significantly between fibroblastic and non-fibroblastic subtypes.	Demonstrated that machine learning classifiers based on radiomic features derived from T1C images, ADC, and FA maps were able to differentiate meningioma grades.

(Continued)

TABLE 1 | Continued

Research groups	Sample Size	Modality	Aim	Segmentation	Features	Feature Selection	Statistical Analysis	Result	Conclusion
Morin et al. (19)	303	T1WI, T2WI, FLAIR, DWI/ ADC, SPGR-T1CE	Grading, Local failure (LF), Overall survival (OS)	Manual	Shape, Histogram, Intensity, Texture, Wavelet filters	Supervised false-positive avoidance methodology	RF	ADC hypointensity (HR 5.56, 95% CI 2.01–16.7, P = .002) was corelated with WHO grade II/III meningioma, and low sphericity was associated both with increased LF (HR 2.0, 95% CI 1.1–3.5, P = .02) and worse OS (HR 2.94, 95% CI 1.47–5.56, P = .002).	Demonstrated that preoperative radiologic and radiomic features were able to predict tumor grade, LF, and OS in patients with meningioma.
Niu et al. (41)	241	CE-T1WI	Subtyping	Manual	Histogram, Texture, Form factor, GLCM, RLM	Spearman correlation analysis, t test analysis	LDA	Training: Accuracy=100%; Validation: Accuracy=94.2%. Both training model and validation method built on radiomic features showed high accuracy in the differentiation of meningothelial, fibrous and transitional subtypes.	Demonstrated that radiomics features and the combined statistical analysis were able to distinguish different meningioma subtypes preoperatively with satisfactory performance.
Li et al. (42)	67	T2-FLAIR, DWI, T1WI+C	Differential	Manual	Gray-level histogram, CM, RLM, Autoregressive model, Wavelet transform	'Boruta' Package in R software	SVM	Training: AUC=0.90. The performance of classifier based on the enhanced T1WI was significantly higher than that of T2-FLAIR-based or DWI-based classifiers in the differentiation between malignant hemangiopericytoma and angiomatous meningioma.	Demonstrated that SVM built on texture features extracted from T1C was capable of differentiating malignant hemangiopericytoma from angiomatous meningioma preoperatively.
Zhang et al. (43)	60	T2WI, DWI/ ADC, T1C	Relapse Prediction	Automatic	Histogram, GLCM	RF	A binary decision tree	Training: Accuracy=0.90. The accuracy of radiomic model for prediction of P/R was higher than ADC values. The three most significant features contained in the final radiomics model were T1 max probability, T1 cluster shade, and ADC correlation.	Demonstrated that the radiomics approach was able to provide objective and important clinical information preoperatively for the cure of skull base meningiomas.
Tian et al. (44)	127	CE-TIWI T2WI	Differential	Manual	Histogram, GLCM	Mann–Whitney U test with the Benjamini–Hochberg method	Binary logistic regression analysis	Training: AUC=0.776, P = <0.001 The radiomic model built on the integrated quantitative parameters showed the best performance in differentiating craniopharyngioma from meningioma. These texture features were also significantly correlated with cystic alteration, which could be considered as diagnostic independent predictors.	Demonstrated that texture features could be used to distinguish craniopharyngioma from meningioma. The radiomic features were correlated with qualitative MR images features.
Zhang et al. (45)	1,728	T1C T2WI	Brain invasion	Manual	Shape, Histogram, Texture	LASSO	SVM	Training: AUC=0.857,。 Radiomics features were significantly correlated with brain invasion.	Demonstrated that the clinicoradiomic model was able to predict brain invasion in meningioma.

LoG, Laplacian of Gaussian; PCA, principal component analysis; FA, factor analysis; RF, random forest; AUC, area under the curve; CM, co-occurrence matrix; LR, logistic regression; NB, naive Bayes; SVM, support vector machine; Sub, Subtraction maps; LASSO, least absolute shrinkage and selection operator; SBS, sequential backward selection; LDA, linear discriminant analysis; CNN, convolutional neural networks; MC, multicentric; XGBOOST, eXtreme gradient boosting; MLP, multilayer perceptron; GBDT, gradient boosting decision tree; GLCM, gray-level co-occurrence matrix; RLM, run length matrix; P/R, progression/recurrence.

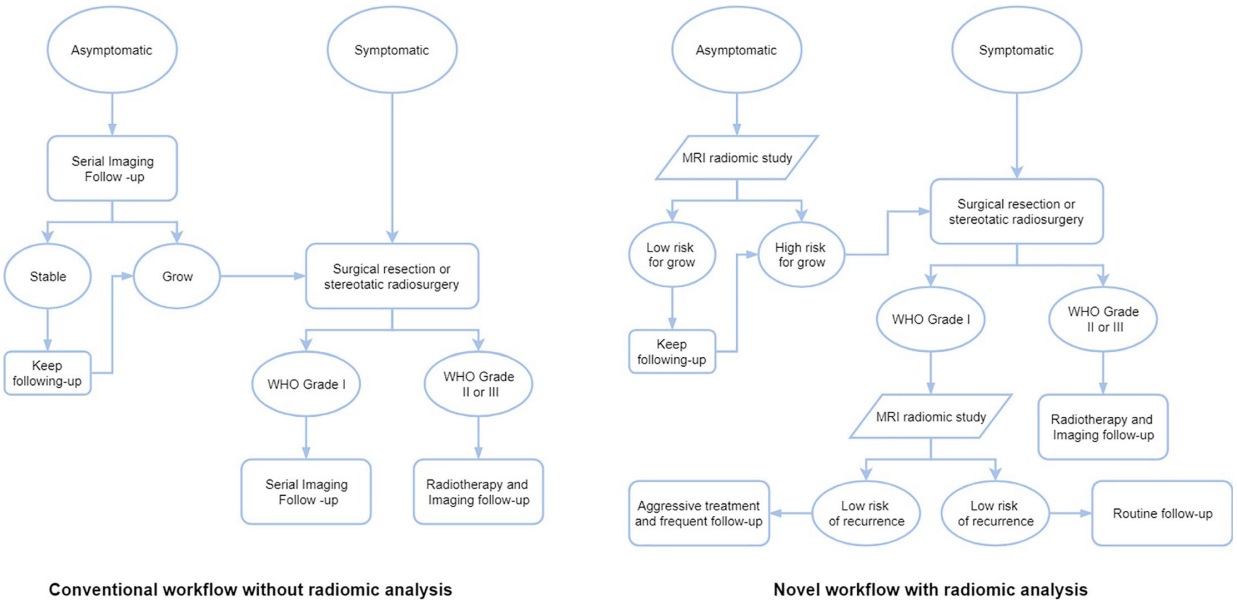


FIGURE 2 | The workflows of different treatment strategies of meningiomas without or with radiomic analysis.

TABLE 2 | Summary of most useful set of radiomic features applied in grade prediction and other aspects.

Type	Application	Morphology	Histogram	Texture	Deep learning
Grade	High	T1C_SD (34), T1C_GeoFv (35), T1C_GeoW4 (35), Roundness-of-FLAIR-shape (36)	T1C_HILAE (34), T1C_LILAE (34), T1C/ADC/FA_entropy (40)	T1C_RLN (34), T1C_Horzl_RLNonUni (35), T1C_S(2,2)SumOfSqs (35), Cluster-shades-of-FLAIR/T1CE-grey-level (36), DWI-ADC-grey-level-variability (36), FLAIR/T1CE-grey-level-energy (36), T1C/ADC/FA_dissimilarity (40), T1C/ADC/FA_RLN (40)	DLR from CNN (39)
	Low	T1C_GeoW5b (35), T1C_ Sphericity (19, 39)		T1C_WavEnHL_s-3 (35), T1C_ LGLRE (39) T1C_GLevNonU	
Differentiation	AM and HPC (42) MNG and CPG (44)		T1C_Skewness, T2_Skewness	T1C_GLCM-Contrast	
Recurrence (43)				T1C_GLCM_T1 maximum probability, T1C_GLCM_T1 cluster shade, ADC_GLCM_ADC correlation	
Brain invasion (45)		T1C_original_shape_maximum 2D diameter slice, T1C_original_shape_maximum 3D diameter		T2_lbp-3D-m2_glrlm_short run high grey level emphasis	

T1C_, contrast-enhanced T1-MRI; HILAE, High Intensity Large Area Emphasis; LILAE, Low Intensity Large Area Emphasis; SD, Spherical Disproportion; RLN, Run Length Non-uniformity; Horzl_RLNonUni, run length nonuniformity" with θ being 0°; S(2,2)SumOfSqs, "sum of squares" with θ being 45° and d being 2; GeoFv, vertical Feret's diameter; GeoW4, GeoU1/GeoUw; GeoU1, the profile specific perimeter; GeoUw, the convex perimeter; DLR, deep learning features; CNN, convolutional neural networks; LGLRE, a sparse distribution of low gray-level values; GlevNonU, the grey-level nonuniformity; AM, angiomatous meningioma; HPC, haemangiopericytoma; MNG, meningioma; CPG, craniopharyngioma; GLCM, Grey-level co-occurrence matrix. For more explanations of these radiomic features please refer to each respective reference.

non-parametric property, so that it can be used given the existence of collinearities among features (55). Furthermore, overfitting is less of a concern compared with other machine-learning methods (51). Therefore, all these characteristics make RF especially suitable for high-dimensional data analyses as radiomics, where it is impractical to strictly control all features (56).

Besides, there was also a comparison study between the SVM and LDA, in which Chen et al. had shown that a LDA-based model displayed an AUC of 0.934 in predicting the WHO grade I

TABLE 3 | Summary of commonly used algorithms along with their performance metrics.

Algorithm	Description	Performance metrics
Random forest	An ensemble method that calculates multiple decision tree-based classifiers containing several identically distributed random independent vectors.	AUC=0.93 Sensitivity=0.90 Specificity=0.97 (37)
Support vector machine	A non-linear classifier that iteratively constructs a hyperplane or high-dimensional feature space consisting of a series of hyperplanes that separates different classes.	AUC=0.93 Sensitivity=0.95 Specificity=0.94 (37)
eXtreme gradient boosting	A tree-based classification algorithm where an ensemble of decision trees is built.	AUC=0.97 Sensitivity=1.00 Specificity=0.97 (37)
Multilayer perceptron	A feed-forward deep artificial neural network.	AUC=0.88 Sensitivity=0.95 Specificity=0.87 (37)
Linear discriminate analysis	A linear classifier, consisting of the shape of the decision boundary of straight line in the first case and straight line in second.	AUC=0.934 Accuracy= 0.756 (38)
Logistic regression	A kind of multiple regression method to analyze the relationship between a binary outcome or categorical outcome and multiple influencing factors.	AUC=0.85 Accuracy=0.89 Sensitivity=0.67 Specificity=0.94 (35)
Naive Bayes	Acyclic directed graphs, in which each node of the graph represents a variable and each arc is a direct probabilistic relationship between the variables.	AUC=0.91 Accuracy=0.89 Sensitivity=0.76 Specificity=0.92 (35)
Convolutional neural network	Deep learning networks comprising hundreds of self-learning units had advantages in quantifying the prognostic features that could not be manually defined.	AUC=0.811 Sensitivity=0.769 Specificity=0.898 (39)

meningiomas higher than that of 0.845 in a SVM-based model (38). Both of them are regarded as the top pattern recognition technology, functioning obeying to two different working principles (57). Whereas in the non-linear attribute of the SVM, the LDA is a linear classifier which means the shape of the decision boundary of LDA is a straight line, or a plane different from that of curved lines, or a surface in SVM (57). Additionally, when comparing the classification algorithms, their comparison also contained the selection method, and their results indicated that the modeling algorithms may weigh more than that used in feature selection processes in the aspect of increasing the diagnostic performances (38). As for the LR and NB, it is imperative to pay attention to their inherent limitations, including the independence assumption to features of the LR and the request for feature discretization in the NB (32). The novel machine learning method, MLP, which had also been utilized in modeling, though not the best, exhibited a predicting performance of 0.88 (37). Moreover, another deep learning method, convolutional neural network has been implemented in the process of feature extraction; Instead of modeling, it provided a better predictive performance than the hand-crafted features (39).

Other Applications in Meningiomas

Radiomics analysis has also shown to be predictive in other aspects of meningiomas, like subtypes identification, differential diagnosis, recurrence prediction and brain invasion. Niu et al. have extracted 385 radiomic features from the T1C images of 241 patients and built a Fisher discriminant analysis model which successfully distinguished subtypes of meningothelial, fibrous, and transitional meningiomas yielding a perfect accuracy of 100% with an as high accuracy of the validation model as 94.2% (41). Another study also reported that there were significant differences in various texture features derived from the T1C, ADC, and FA parameters between the fibroblastic and nonfibroblastic pathological subtypes, without establishing a radiomic model (40).

Regarding the differential diagnosis, a study has constructed three SVM classifiers based on texture features respectively derived from the T2-FLAIR, DWI and enhanced T1WI sequences to compare their capacities in differentiating malignant hemangiopericytomas from angiomatous meningiomas. Their results indicated that the enhanced T1WI-based classifier (AUC = 0.90) had significantly better performance than the T2-FLAIR-based and DWI-based classifiers (42). Specifically, a recent study has selected three independent imaging predictors, including skewness, contrast on the contrast-enhanced images, and skewness derived from the T2WI to distinguish craniopharyngiomas and meningiomas, and the binary logistic regression model built on the three integrated radiomic features achieved an AUC of 0.776. Moreover, it was also discovered that these texture features were significantly related with the cystic alteration which was found as the only independent diagnostic predictor in qualitative imaging features in their research (44).

Regarding the relapse prediction, a study has extracted 99 radiomic features from the T2WI, DWI, and T1C and has filtered the three most significant parameters as the T1 max probability, T1 cluster shade, and ADC correlation in predicting the recurrence of skull base meningiomas. The accuracy of predicting recurrence in their binary decision tree model, which was founded on these three features, was 0.90 higher than that of the other model based on ADC values (43). Besides, there was a study with a relatively large multi-institution sample size, composed of 303 patients revealed that the low sphericity was associated with not only the increased local recurrence but also worse overall survival; The integrated RF model combining radiomic, radiologic, and clinical features showed an AUC of 0.75 and 0.78 in predicting local recurrence and overall survival, respectively (19).

More recently, a multicenter study has shown that radiomic features have the potential of preoperatively predicting brain invasion in meningioma (45). They have built a SVM model derived from the T1C and T2 MRI sequences and yielded an AUC of 0.819. What's more, the clinicoradiomic model integrating radiomic features and sex information exhibited the best predictive performance (AUC=0.857).

LIMITATIONS OF RADIOMICS ANALYSIS FOR MENINGIOMAS

As radiomics is still in its initial phase of application in meningiomas, there are still many drawbacks to overcome in its whole process. Currently, most radiomics studies in meningiomas were designed as unicentric and retrospective studies which can lead to selection bias (19, 36–40, 42, 43, 58). Another prominent issue is the lack of high-quality raw data, which manifested mainly as the significant heterogeneity of patient cohorts or imaging data and small sample sizes (28, 29). A wide variety in the overall staging of patients may be a confounding factor since staging itself is usually of prognostic significance (28). The heterogeneity of the original data can introduce changes that may be not due to the underlying biological effects (29). Small sample sizes can increase both statistical error rates and the risk of overfitting (28). There is not only a lack of original data, also an insufficient utilization, as quite many studies only used a portion of the imaging data; For example, in some study, only the enhancing sequences were selected rather than all sequences of MRI (40), or features were extracted from a series of consecutive slices instead of all slices (39).

Beyond these limitations in designing and imaging acquisition, there are some considerable problems in the rest of the procedure, especially in the segmentation process (29). To date, most meningiomas radiomics studies have based on manual segmentation, which can lead to greater inter-observer variations. Although the assistance of segmentation software or DLR can reduce the difference, whether the timely update of these assistive tools can be achieved is another challenge. Besides, the time cost of manual delineation is also an important consideration especially when an operator is facing hundreds of patients simultaneously (7). The conventional manual feature extraction relies on predefined algorithms designated for specific imaging characteristics. As different extraction techniques and software were chosen, different results of features were generated which apparently could lead to bias in the results (7, 59). All these changes can impact on the reproducibility of the features, which unfortunately, directly determines the generalization of the research conclusion (7, 28). Consequently, with the advanced imaging modalities continuously emerging, the need of autonomic learning algorithms with the capacity of handling integrated multiparametric imaging data is increasingly urgent (60). Likewise, at the final stage of the radiomics workflow, the requirement for constantly improved models is also increasing. Lots of studies have to face the problems from over-simple correlation analyses, such as contradictory conclusions of similar situations from different researchers or the risk of overfitting or underfitting (7), the insufficient interpretation of the data, and the lack of machine learning or other advanced statistical analysis methods (38, 43).

Above all, all the variations in the aforementioned steps call for the standardization or the guideline of the detailed implementation procedure of the radiomics workflow in different situations. In the meantime, the boundary of data sharing among different institutions is still vague, and it is necessary to establish and improve relevant laws and regulations.

FUTURE PERSPECTIVES OF RADIOMICS ANALYSIS FOR MENINGIOMA

As the capability and potential of radiomics are increasingly revealed, many different aspects still merit future developments.

Curation of Big Data

The curation of big data plays a prerequisite role in the efficacy and efficiency of radiomics. Generally, from a biopsychosocial view, big data related to radiomics should not only include imaging data but also involve demographics and social networks. This seemingly insignificant information reflects the compliance of meningioma patients under surveillance having a prognostic value, which should be taken into consideration during the model building, especially in meningiomas suspicious of malignancy. Furthermore, radiomics has shown its application in the prediction of genomics, proteomics or other biology–omics. The integration of those different datasets also places requirements of curation. Specifically, the annotations of imaging data currently often do not use a standard lexicon, this hinders efficient utilization of data (29). Also, given the fact that the majority of present radiomics studies are retrospective, prospectively collected imaging data is in urgent need. This situation requires radiologists and clinicians to actively participate in the beginning period of data gathering rather than merely in later analysis.

DLR Analysis

DLR analysis has shown its powerful advantages compared to the conventional radiomics demonstrating as automatic operation, full exploitation of data, free of manual variance, low labor-consuming, etc. However, there is still a range of gaps for the DLR to overcome. The DLR eagers to embrace big datasets equipped with millions of images for the requirement of training, because the high-quality training data is directly related with better performance of the DLR (61). The cost of the computational infrastructure of the DLR is another bottleneck that appeals to data scientists to contribute more efforts (62). Interestingly, on one hand, scientists put great expectations on the future of the DLR, on the other hand, they have not completely understood how deep learning works yet, namely as the fear of 'black box' (63). In a word, DLR is a double-edged sword which enlightens us with its intelligence except for careful trust.

Comprehensive Interdisciplinary Cooperation

The development of radiomics owes to the devotion of both clinical and technical investigators. This new discipline shows a continuous progression, together with a mutual competition between those two sides of the research. Indeed, conventionally separated, these two aspects of research are used to analyze

problems from their own perspective, overcoming the benefits of the other. This condition may explain the existence of simple correlations between imaging features and clinical significance, regardless of methodological disadvantages, or the pursuit of novel methodology while neglecting the clinical significance (7). Indeed, the thrive of radiomics does not only rely on balancing the interdisciplinary contradiction, it also demands the expansion of the collaboration, including the introduction of data source, enhancement in data sharing, renewing, and accessibility.

CONCLUSION

Radiomics analysis for meningiomas is a promising new area of research based on the development of computational advances. The current correlation is mainly between the imaging phenotypes and meningioma grades. With overcoming limitations in the process of the radiomics analysis, there will be a vast expansion of its applications in meningiomas, varying from risk stratification, to precise diagnosis, prognosis, and therapy.

AUTHOR CONTRIBUTIONS

Conception or design of the work: HG and TX. Drafting the paper: HG, XuZ, and PR. Revising it critically for important intellectual content: XiZ and TX. Provide approval for publication of the content. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Long Non-Coding RNA MEG3 Modifies Cell-Cycle, Migration, Invasion, and Proliferation Through AKAP12 by Sponging miR-29c in Meningioma Cells

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Meningioma (MEN) is a common central nervous system disease. Accumulating evidence indicated that long non-coding RNA maternally expressed gene 3 (MEG3) participated in the progression of MEN. However, the potential mechanisms of MEG3 in altering the aggressive phenotypes of MEN need further exploration. Levels of MEG3, microRNA (miR)-29c, and A-kinase anchor protein 12 (AKAP12) were determined using quantitative real-time Polymerase Chain Reaction (qRT-PCR) assay. Dual-luciferase reporter and RNA immunoprecipitation (RIP) assays were performed to verify the relationship between miR-29c and MEG3 or AKAP12. The protein level of AKAP12 was detected by western blot. Moreover, cell-cycle arrest, migration, invasion, and proliferation were assessed by flow cytometry, wound healing, transwell assays, and CCK-8 assay, respectively. Levels of MEG3 and AKAP12 were downregulated, while miR-29c was effectively increased in MEN tissues and cell line. Mechanically, MEG3 was a sponge of miR-29c to regulate the expression of AKAP12. Functionally, increase of MEG3 diminished cell-cycle, migration, invasion, and proliferation in MEN cells, and reintroduction of miR-29c could eliminate these effects. In addition, AKAP12 depletion overturned the inhibitory effects of miR-29c absence on cell-cycle, migration, invasion, and proliferation *in vitro*. Also, AKAP12 was co-regulated by MEG3/miR-29c axis. MEG3 mediated the aggressive behaviors of MEN cells via miR-29c/AKAP12 axis, supporting that MEG3 served as a promising biomarker for the diagnosis and treatment of human MEN.

Keywords: MEG3, miR-29c, AKAP12, meningioma, LncRNA

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INTRODUCTION

Meningioma (MEN) belongs to the central nervous system disease with 30–40% morbidity (1). MEN is classified according to the classification of the World Health Organization (WHO). MEN is regarded as a type of general neoplasm that derived from the meningeal coverings of the brain or spinal cord. Although most of MEN is classified as benign tumors in qualitative classification (2, 3), the malignant MEN usually occurs with rapid growth and metastasis (4). Currently, continuous studies have achieved development on diagnosis and therapy for MEN, but the occurrence and recurrence of MEN is still pessimistic due to the ambiguous pathogenesis (5). Hence, it is important to discover the effective therapeutic strategies for MEN via understanding the pathogenesis and progression of MEN.

Among the transcriptome, the largest portion of gene is non-coding RNAs (ncRNAs). Also, long non-coding RNAs (lncRNAs) with over 200 nucleotides in length constitute the partial members of ncRNAs (6). Emerging evidence implied the extensive function of lncRNAs on the onset and development of diverse tumors, such as cell proliferation, metastasis, and recrudesce (7–9). Moreover, various lncRNAs were identified and confirmed to modify the pathological processes of MEN. Maternally expressed gene 3 (MEG3) is a well-known lncRNA, and it is commonly considered to be a tumor suppressor (10). For example, MEG3 impeded tumor growth of cervical carcinoma cells via promoting cell-cycle arrest and apoptosis (11). Furthermore, MEG3 was also associated with MEN, and it can constrain the tumorigenesis of MEN (12). Thus, we attracted more attention on the biological role of MEG3 in MEN progression.

Recently, microRNAs (miRNAs) are a type of post-transcriptional mediator that play the master roles in the modulation of gene expression (13). Moreover, miRNAs were demonstrated to be involved in cell-cycle arrest, apoptosis, and other physiological progressions (14). Multiple researches reported that miRNAs played key roles in healthy individuals and several cancers (15). Consequently, miRNAs are intensely considered as the biomarkers of diagnosis and prognosis in cancers (16). To be specific, miR-29c served as a tumor suppressor in nasopharyngeal carcinoma by targeting TIAM1 to suppress cell metastasis (17). Nevertheless, miR-29c-3p was validated to be upregulated in MEN tissues, implying that miR-29c restrained the development of MEN (18). In this study, we aimed to explore whether miR-29c could interact with MEG3 to regulate the pathogenesis and tumorigenesis of MEN. In addition, miRNAs exerted their functions via binding to the 3'-untranslated regions (3'UTRs) of targets (19). A-kinase anchor protein 12 (AKAP12) was confirmed to be closely implicated in MEN (20). In this paper, we determined the expression profiles of MEG3, miR-29c, and AKAP12 in MEN, and the work pathway among them was also expounded.

MATERIALS AND METHODS

Clinical Specimens and Cell Culture

A total of 32 cases of human MEN tissues and 5 cases of normal meninges samples were collected from The First Affiliated Hospital of Fujian Medical University. The clinicopathologic features of MEN patients were presented in **Table 1**. All the available specimens were immediately stored at -80°C. Moreover, all written informed consents were gained from every participator before surgery, and this research was approved by the Ethics Committee of The First Affiliated Hospital of Fujian Medical University.

Malignant meningioma cell lines (IOMM-Lee and CH157-MN) were obtained from the Chinese Academy of Medical Sciences (Beijing, China). In this assay, the meningioma cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Carlsbad, CA, USA), supplemented with 10% fetal bovine serum (FBS; Gibco), and cultured in a humidified incubator containing 5% CO_2 at 37°C.

Vector and Oligonucleotide Transfection

Small interfering RNA (siRNA) targeting MEG3 (si-MEG3, 5'-GGAUGGCACUUGACCUAGA-3'), siRNA targeting AKAP12 (si-AKAP12, 5'-AGGUUAGUCACGCCAAGAA-3'), and the siRNA control (si-con) were purchased from Ribobio (Guangzhou, China). Also, the overexpression vector of MEG3 (MEG3) and its blank control (pcDNA) were obtained from Ribobio. All the oligonucleotides, including miR-29c mimic (miR-29c), miR-29c inhibitor (anti-miR-29c), and their relative controls (miR-con and anti-miR-con), were purchased from GenePharma (Shanghai, China). Transient transfection was carried out using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) as per the manuals.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) Assay

Total RNA was harvested and extracted from clinical tissues and meningioma cell lines using Trizol reagent (Invitrogen) in accordance with the user's guidebook. RNA was reversely transcribed into complementary DNA (cDNA) using PrimeScript RT Reagent Kit (TaKaRa, Dalian, China). Next, SYBR Premix Ex Taq (TaKaRa) was employed to perform qRT-PCR assay via mixture with equal cDNA, primers, and RNA-free water. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH; for MEG3 and AKAP12) and U6 (for miR-29c) acted as the endogenous

TABLE 1 | Clinicopathological variables and MEG3 level in meningioma.

Clinicopathologic features	Relative MEG3 level		P value
	Low (%)	High (%)	
Age(years)			>0.05
≥55	10 (55.6)	8 (44.4)	
<55	8 (57.1)	6 (42.9)	
Gender			>0.05
Male	6 (50.0)	6 (50.0)	
Female	12 (60.0)	8 (40.0)	
Tumor side			>0.05
Right	13 (65.0)	7 (35.0)	
Left	5 (41.7)	7 (58.3)	
Tumor location			>0.05
Frontal and/or temporal lobes	14 (60.9)	9 (39.1)	
Other	4 (44.4)	5 (55.6)	

controls, and the relative level was assessed via the $2^{-\Delta\Delta Ct}$ method. The primers were provided by Sangon Biotech (Shanghai, China):

MEG3 (Forward: 5'-CTGCCCATCTACACCTCACG-3', Reverse: 5'-CTCTCCGCCGTCTGCGCTAGGGGCT-3'); miR-29c (Forward: 5'-GCCTAGCACCATTTGAAATCG-3', Reverse: 5'-GTGCAGGGTCCGAGGT-3'); AKAP12 (Forward: 5'-GGAATTCGATGGGCGCCGGGAGCTCCAC-3', Reverse: 5'-CCGCTCGAGGTCATCTTCGTTGGCCCCTG-3'); GAPDH (Forward: 5'-ACTCCTCCACCTTTGACGC-3', Reverse: 5'-GCTGTAGCCAAATTCGTTGTC-3'); U6 (Forward: 5'-CTCGCTTCGGCAGCACA-3', Reverse: 5'-AACGCTTCACGAATTTGCGT-3').

Bioinformatics Analysis

LncBase V2.0 was used to predict the potential binding sites between MEG3 and miR-29c. StarBase showed that there were binding sites between miR-29c and AKAP12.

Dual-Luciferase Reporter Assay

The sequences of MEG3 and 3'UTR of AKAP12 containing the binding sites of miR-29c were amplified and cloned into psiCHECK-2 vector (Promega, Madison, WI, USA), named as MEG3-WT and AKAP12-WT. The putative common fragments were replaced as indicated (MEG3-MUT and AKAP12-MUT) to mutant the predictive binding sites of MEG3 and AKAP12. IOMM-Lee and CH157-MN cells were seeded into a 24-well plate. Then, cells were co-transfected with the above-formed reporters and miR-29c or miR-con when cells reached ~70% confluence. The fluorescence intensities of the reporters were identified by the Dual-Luciferase Reporter Assay System (Promega) at 48 h post-transfection.

RNA Immunoprecipitation (RIP) Assay

Magna RIP Kit (Millipore, Bedford, MA, USA) was used to analyze the relationship between miR-29c and MEG3 or AKAP12. First, IOMM-Lee and CH157-MN cells were lysed by the RIP lysis buffer, and then the lysate was incubated with the relative magnetic beads that conjugated with human anti-Argonaute2 (Ago2; Abcam, Cambridge, MA, USA) antibody or matched control antibody (IgG; Abcam). QRT-PCR was used to assess levels of MEG3, miR-29c, and AKAP12.

Flow Cytometry Assay

MEN cells were re-suspended and fixed with 70% ethanol (ice-cold) for at least 1 h. Then, cells were re-suspended in HBSS (Hank's balanced salt solution) supplemented with 50 μg/mL Propidium Iodide (PI; Sigma, St. Louis, MO, USA) and RNase A (Thermo Fisher Scientific, Rockford, IL, USA) and incubated for 1 h at room temperature without light. The ability of cell-cycle arrest was assessed using flow cytometry (FACS Calibur; BD Biosciences, San Jose, CA, USA).

Wound Healing Assay

For wound healing assay, cells were plated into the 6-well plates, and a 200 μL pipette tip was employed to generate an artificial wound at 12 h post-inoculation. Then, the cells were incubated for 48 h, and the wound closure was observed and photographed. The migrated distance of the cell coverage across the initial wound was deemed to represent the migration rate.

Transwell Assay

Cell invasion assay was performed using the transwell chamber (8 μm, Corning Costar, Corning, NY, USA). Briefly, the upper chamber was pro-coated with Matrigel (Corning Costar). Then, the transfected MEN cells (5×10^4) were re-suspended with serum-free media and added into the upper transwell chamber. Meanwhile, to the lower chamber was added 600 μL complete medium. After incubation for 48 h, the non-invasion cells were erased, and the invaded cells were stained with 0.1% crystal violet (Sigma). The stain condition was photographed and quantitated via counting five random fields.

Cell counting Kit-8 (CCK-8) Assay

The proliferation ability of MEN cells was assessed by CCK-8 assay. Seeded into each well were 5×10^3 cells in 200 uL cell suspension of the 96-well plates. Then, cells were treated with 10 μL CCK-8 solution (Dojindo, Tokyo, Japan) and the absorbance was detected at 450 nm using Multiskan Go spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA).

Western Blot Assay

As previously described (21), total proteins were isolated from MEN tissues and cells by RIPA lysis buffer (Beyotime, Shanghai, China). Next, sodium dodecyl sulfate-polyacrylamide gel (12%) was used to separate equal proteins, and the isolated proteins were transferred onto the nitrocellulose membrane (Millipore) and incubated with corresponding primary antibodies (Abcam): anti-AKAP12 (1:6000, ab9698) and β-actin (1:6000, ab8226). After incubation overnight at 4℃, the membrane was covered by the diluted secondary antibody for 40 min at room temperature. Then, the complex signals were visualized with enhanced chemiluminescence reagent (Millipore) and film exposure.

Statistical Analysis

The data from the three independent assays were exhibited as mean ± standard deviation (SD). Difference comparison was analyzed using one-way analysis of variance (ANOVA; for three or more groups) or Student's two-tailed *t*-test (for two-group), and Tukey test was selected as the post-hoc test for ANOVA. Pearson correlation analysis used to analyze the expression correlations among MEG3, miR-29c, and AKAP12. A *P*-value less than 0.05 was considered to be statistical significance.

RESULTS

MEG3 Was Low-Expressed, While Mir-29c Was Upregulated in MEN Tissues

The expression of MEG3 was determined in MEN specimens. Compared with normal control, a low level of MEG3 was

observed in MEN tissues (**Figure 1A**). In addition, relative operating characteristic curves (ROC) analysis was carried out, and the area under the ROC curves (AUC; 0.85) showed that MEG3 might be a potential marker in MEN progression (**Figure 1B**). Moreover, miR-29c was increased in MEN tissues (**Figure 1C**). Similarly, the ROC curves implied the apparent isolation between MEN and match healthy donators, with an AUC of 0.875 for miR-29c (**Figure 1D**). From all subjects, we displayed that miR-29c was inversely correlated with MEG3 in clinical MEN tissues (**Figure 1E**). Collectively, MEG3 and miR-29c acted as strict factors in the process of MEN.

MEG3 Was a Sponge of miR-29c

According to the opposite expression between MEG3 and miR-29c, we speculated that MEG3 could regulate miR-29c. As described in **Figure 2A**, lncBase V2.0 predicted that there were the binding sites between MEG3 and miR-29c. Then, dual-luciferase reporter assay and RIP assay were performed to verify the interrelation between them. We found that the luciferase activity of MEG3-WT reporter was remarkably decreased (about 70%) in miR-29c-transfected IOMM-Lee and CH157-MN cells, whereas miR-29c had no statistical impact on the luciferase activity of mutant reporter (**Figures 2B, C**). As shown in **Figures 2D, E**, the levels of MEG3 and miR-29c were augmented in the Ago2-treated group. Next, MEG3 or si-MEG3 was transfected into IOMM-Lee and CH157-MN cells, respectively. QRT-PCR analysis exhibited that MEG3 passively regulated miR-29c in the two MEN cells (**Figures 2F, G**). All the results demonstrated that MEG3 served as the upstream of miR-29c in MEN cells.

The Repressive Impact of MEG3 Increase on Cell-Cycle, Migration, Invasion, and Proliferation Was Overturned by miR-29c Upregulation in MEN Cells

Given the molecular mechanism between miR-29c and MEG3, we investigated the biological function of them in MEN cells. First, MEG3 alone or combined with miR-29c was transfected into IOMM-Lee and CH157-MN cells. As depicted in **Figures 3A, B**, MEG3 increase could impede the level of miR-29c in the two MEN cells, and reintroduction with miR-29c could overturn this effect. The triggered ability of cell-cycle arrest resulted from MEG3 augment was distinctly hindered via co-transfection with MEG

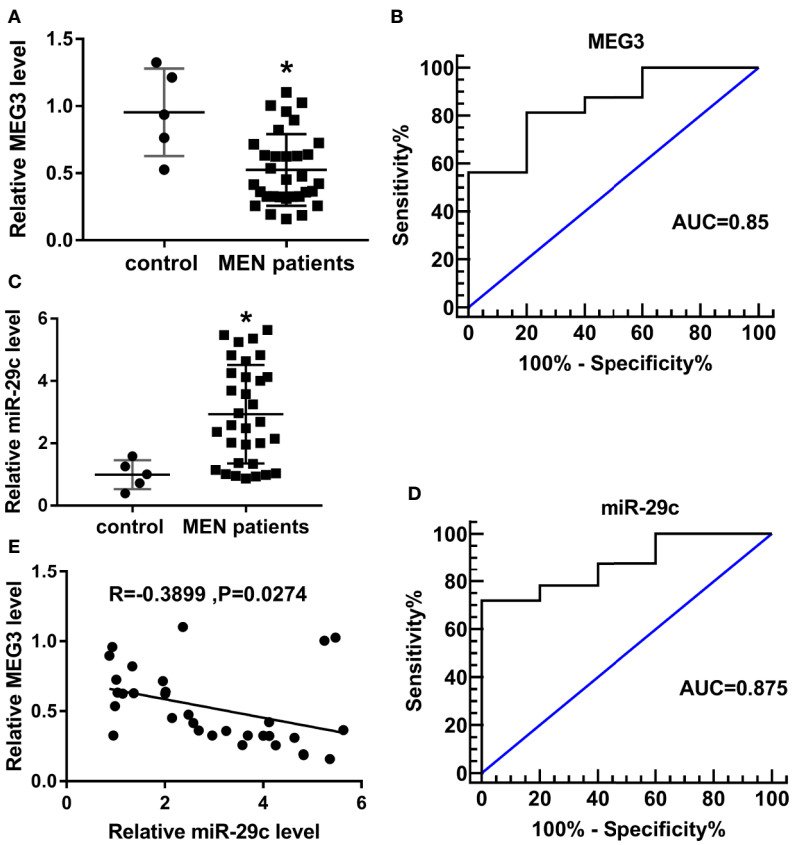


FIGURE 1 | MEG3 was low-expressed, while miR-29c was upregulated in MEN tissues. **(A, C)** Relative levels of **(A)** MEG3 and **(C)** miR-29c in MEN tissues compared with normal control. **(B, D)** ROC curve about **(B)** MEG3 and **(D)** miR-29c in which MEN samples compared with matched control. **(E)** The correlation between miR-29c and MEG3 in MEN samples. *P<0.05.

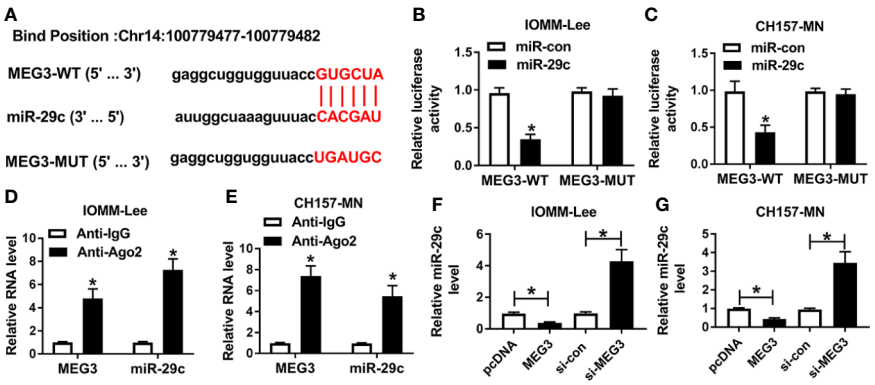


FIGURE 2 | MEG3 was a sponge of miR-29c. **(A)** The predictive common fragments between MEG3 and miR-29c. **(B, C)** The luciferase activities of MEG3-WT and MEG3-MUT reporters in IOMM-Lee and CH157-MN cells with miR-29c or miR-con transfection. **(D, E)** RIP analysis for the relationship between miR-29c and MEG3. **(F, G)** Relative level of miR-29c in the two MEN cells under MEG3 or si-MEG3 introduction. *P<0.05.

and miR-29c in the two MEN cells (**Figures 3C, D**). Moreover, cell migration was assessed using wound healing assay, and the results determined that miR-29c supplement relieved the inhibitory effect of MEG3 on cell migration *in vitro* (**Figures 3E, F**). Also, cell invasion was restrained as a result of MEG3 increase, which was regained by miR-29c supplement in IOMM-Lee and CH157-MN cells (**Figures 3G, H**). MEG3 overexpression inhibited cell proliferation, which was reversed by miR-29c upregulation (**Figure 3I**). In brief, MEG3 regulated cell-cycle arrest, migration, invasion, and proliferation via miR-29c in MEN cells.

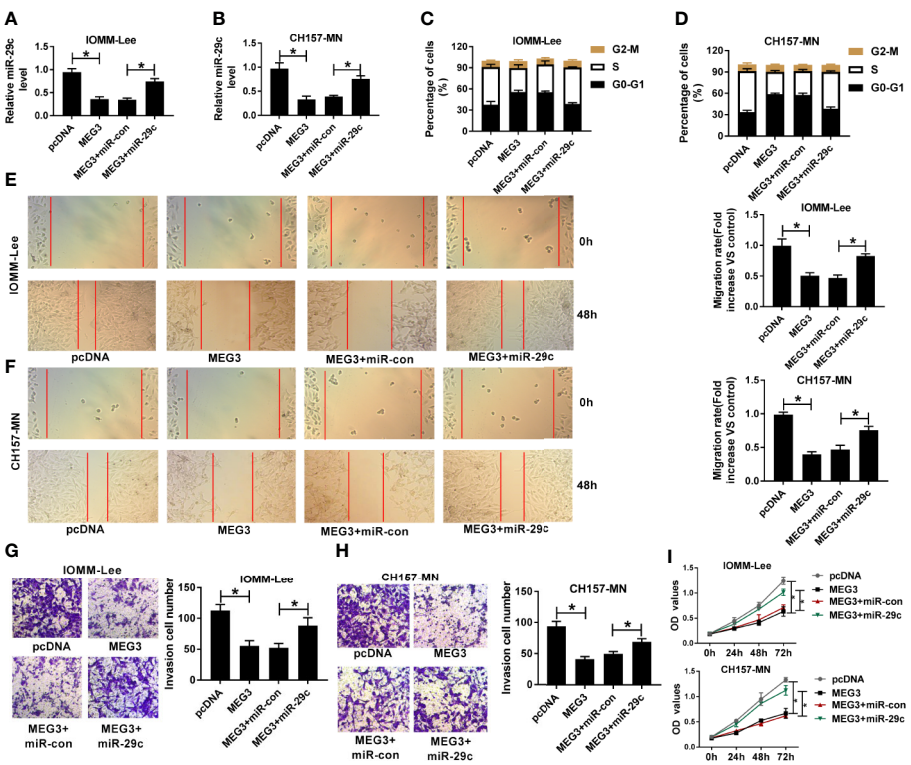


FIGURE 3 | The repressive impact of MEG3 increase on cell-cycle, migration, invasion, and proliferation was overturned by miR-29c upregulation in MEN cells. **(A-I)** IOMM-Lee and CH157-MN cells were transfected with pcDNA, MEG3, MEG3+miR-con, or MEG3+miR-29c, respectively. **(A, B)** Relative level of miR-29c in MEN cells with MEG3 and miR-29c introduction. **(C, D)** Flow cytometry analysis for cell-cycle arrest in the two MEN cells. **(E, F)** Wound healing analysis for the influence of MEG3 or miR-29c increase on cell migration *in vitro*. **(G, H)** The capacity of cell invasion in IOMM-Lee and CH157-MN cells with MEG3 and miR-29c supplement. **(I)** Cell proliferation was detected by CCK-8 assay. *P<0.05.

MiR-29c Directly Targeted AKAP12

In view of the foregoing introduction, we attempted to seek the potential targets of miR-29c. After prediction with starBase software, we found that miR-29c possessed complementary sequence with AKAP12 (**Figure 4A**). Results from dual-luciferase reporter analysis showed that the luciferase activity of AKAP12-WT reporter was significantly diminished by miR-29c, but miR-29c had no statistical effect on changing luciferase activity of the mutant reporter system in IOMM-Lee and CH157-MN cells (**Figures 4B, C**). Levels of miR-29c and AKAP12 were notably upregulated in Ago2-treated IOMM-Lee and CH157-MN cells (**Figures 4D, E**). As shown in **Figures 4F, G**, miR-29c could inversely regulate the level of AKAP12 at the aspect of protein expression. Overall, we could conclude that AKAP12 acted as the downstream of miR-29c.

The Absence of AKAP12 Reversed The Reductive Effect Of Mir-29c Inhibitor n Cell-Cycle, Migration, Invasion, and Proliferation *In Vitro*

Considering the molecular mechanism between miR-29c and AKAP12, we further researched the functional roles of them. First, anti-miR-29c alone or along with si-AKAP12 was introduced into IOMM-Lee and CH157-MN cells. AKAP12 silencing could abrogated miR-29c inhibitor-mediated promoting effect on the level of AKAP12 *in vitro* (**Figures 5A, B**). Then, functional assays were carried out, and flow cytometry analysis illustrated that cell-cycle arrest was reinforced as a result of miR-29c inhibition, and such promoting effect was abolished via simultaneous deficiency of AKAP12 in IOMM-Lee and CH157-MN cells (**Figures 5C, D**). Moreover, reintroduction with si-AKAP12 could eliminate the reductive impact of miR-29c inhibitor on cell migration and invasion in the two MEN cells (**Figures 5E–H**). Furthermore, AKAP12 knockdown could abolish the inhibition effect of miR-29c inhibitor on cell proliferation (**Figures 5I, J**). Namely, miR-29c modified cell behaviors, including cell-cycle arrest, migration, invasion, and proliferation via targeting AKAP12 in MEN progression.

AKAP12 Was Co-Regulated by MEG3 and miR-29c

As mentioned above, we were devoted to exploring the regulatory mechanism systematically. As described in **Figure 6A**, an inverse correlation between miR-29c and AKAP12 was observed in clinical MEN tissues. On the contrary, AKAP12 was positively associated with MEG3 in MEN samples (**Figure 6B**). Then, MEG3 alone or combined with miR-29c was transfected into IOMM-Lee and CH157-MN cells, and the high level of AKAP12, caused by MEG3 increase, was apparently decreased after co-transfection with miR-29c and MEG3 in the two MEN cells (**Figure 6C**). Similarly, the declined level of AKAP12 induced by si-MEG3 was restored by anti-miR-29c (**Figure 6D**). Collectively, AKAP12 was co-regulated by MEG3 and miR-29c in the process of MEN.

DISCUSSION

The interaction between lncRNAs and human cancers has been generally illustrated by increasing researches, suggesting the critical functions on epigenetic modulation of human phenotypes (8, 9, 22). MEN, especially malignant MEN (high-grade), is characterized by migrated and invasive capacity. Therefore, the underlying role of lncRNAs in MEN process is complex and ambiguous, but attractive. And there are still other possible transformations of MEN from benign to malignancy.

As previously described, lncRNAs were believed to participate in multiple human diseases, including cardiovascular, endocrine system disease, and tumors (23, 24). For example, LINC00341

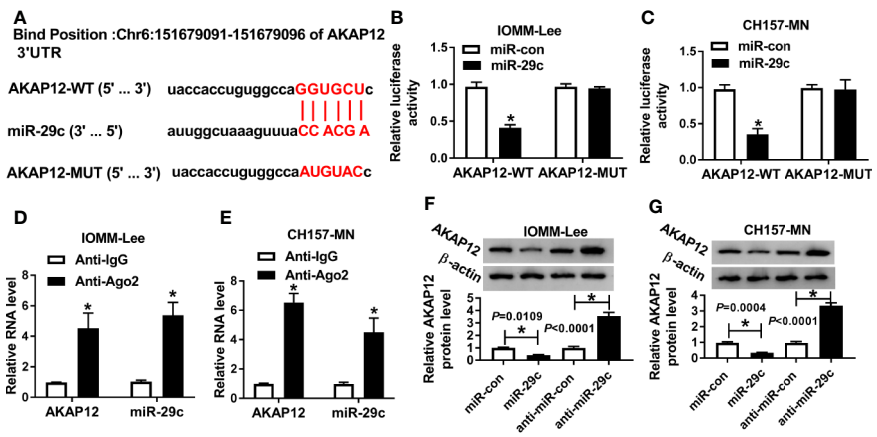


FIGURE 4 | MiR-29c directly targeted AKAP12. **(A)** The binding sites between miR-29c and AKAP12. **(B, C)** Dual-luciferase reporter analysis for the interrelation between miR-29c and AKAP12. **(D, E)** Relative levels of miR-29c and AKAP12 in Ago2 or IgG-combined precipitates. **(F, G)** The role of miR-29c mimic or inhibitor in altering the protein level of mature AKAP12 in IOMM-Lee and CH157-MN cells. *P<0.05.

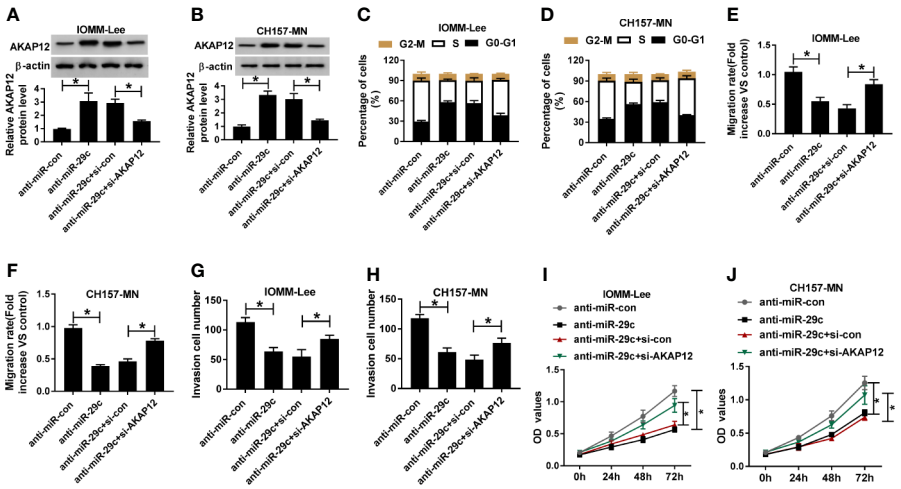


FIGURE 5 | The absence of AKAP12 reversed the reductive effect of miR-29c inhibitor on cell-cycle, migration, invasion, and proliferation *in vitro*. **(A–J)** The anti-miR-con, anti-miR-29c, anti-miR-29c+si-con, or anti-miR-29c+si-AKAP12 was introduced into IOMM-Lee and CH157-MN cells, respectively. **(A, B)** Relative level of AKAP12 in selected MEN cells. **(C, D)** The effect of miR-29c or AKAP12 decrease on the alteration of cell-cycle arrest *in vitro*. **(E, F)** The ability of cell migration in anti-miR-29c or anti-miR-29c+si-AKAP12-transfected MEN cells. **(G, H)** Transwell analysis for the change of cell invasion in IOMM-Lee and CH157-MN cells with anti-miR-29c or anti-miR-29c+si-AKAP12 introduction. **(I, J)** Cell proliferation in MEN cells was determined by CCK-8 assay. *P<0.05.

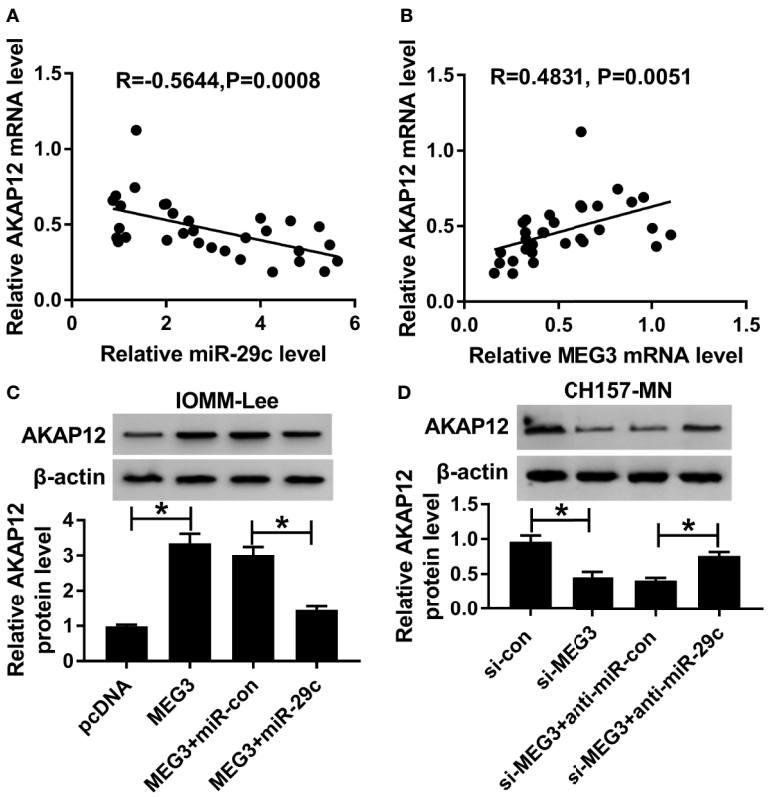


FIGURE 6 | AKAP12 was co-regulated by MEG3 and miR-29c. **(A, B)** The correlation between AKAP12 and **(A)** miR-29c or **(B)** MEG3 in clinical MEN tissues. **(C, D)** PcDNA, MEG3, MEG3+miR-con, or MEG3+miR-29c was transfected into IOMM-Lee and CH157-MN cells, respectively. Relative level of AKAP12 in treated MEN cells. *P<0.05.

reinforced cell proliferation and migration of vascular smooth muscle cells by targeting miR-214 (25). The tumor growth and metastasis of MEN were modulated by the LINC00460/miR-539 axis *in vitro* (26). MEN is a type of brain disease with a large proportion as benign. However, the occurrence of the rapid invasion capacity becomes a serious barrier for human health. In consideration of the critical function of lncRNAs in tumorigenesis and pathogenesis, we attempted to discover the influence of unique lncRNA in the progression and initiation of MEN. In the present research, we determined that MEG3 was expressed at a low level in clinical MEN specimens and cell lines (IOMM-Lee and CH157-MN) with respect to the matched controls, indicating the possible tumor-suppressive role of MEG3 in aggressive phenotypes. A previous report manifested that MEG3 could retard aggressive behaviors, including cell proliferation, migration, and invasion by sponging miR-19a in glioma cells (22). Currently, the supplement of MEG3 acted as a tumor suppressor, showing as the blockage of cell-cycle, migration, invasion, and proliferation in MEN cells. Moreover, the incidence of cell migration *in vivo* is related to mostly Grade II (atypical) and Grade III (malignant) meningioma (27). Our results provided that MEG3 could regulate cell migration in MEN cells, indicating a potential biomarker for the treatment of MEN.

Until now, the well-known pattern of lncRNAs mediating the carcinogenesis is the competing endogenous RNA (ceRNA) of miRNAs. Especially, lncRNAs served as the sponge of miRNAs to separate the abundance of target miRNAs (28–30). According to the above description, we tried to expose the partial work pathway of MEG3 in MEN. We found that miR-29c was a potential target of MEG3. In the present investigation, an evident high expression of miR-29c was observed in MEN tissues and cell lines in comparison with matched controls. Previous research implied that miR-29c-3p regulated the pathogenesis of MEN by mediating pentraxin 3 (PTX3) (18). In addition, miR-29c acted as cancer-associated miRNA and could modulate the tumorigenesis of multiple human carcinomas. For instance, miR-29c deletion was tightly implicated in poor prognosis in laryngeal squamous cell carcinoma (31). Also, another report presented that miR-29c retarded cell migration and invasion by inactivating cyclin-dependent kinase 6 (CDK6) in gastric cancer (32). Currently, the interrelation between MEG3 and miR-29c was illustrated by means of the dual-luciferase reporter and RIP assays. Also, an inverse correlation between miR-29c and MEG3 was determined. Subsequently, functional assays were conducted to explore the biological role of miR-29c in affecting the process of MEN *in vitro*. Furthermore, the reductive impact of MEG3 increase on cell-cycle, migration, invasion, and proliferation was eliminated after co-transfection with miR-29c mimic in IOMM-Lee and CH157-MN cells. Moreover, ROC analysis indicated that MEG and miR-29c might be the biomarkers for the diagnosis of MEN.

Accruing findings have disclosed that miRNAs exerted their function by repressing the expression or transcription of special mRNAs (33). Consequently, finding the underlying targets might serve as a novel insight for genetic therapy. As predicted by starBase software, AKAP12 possessed some binding sites of miR-29c. AKAP12 was regarded to be strictly connected with several human cancers (34). A previous research expounded that the absence of AKAP12 caused the augment of cell proliferation and metastasis and conferred an anaplastic profile in MEN cells (20). Consistently, we agreed that AKAP12 suppressed the aggressive phenotypes of MEN cells. In the current study, we proved that miR-29c negatively regulated AKAP12 expression. Indeed, the inhibition of miR-29c declined cell-cycle and mobility of MEN cells, and such repressive influence of anti-miR-29c could be abolished via co-transfection with si-AKAP12 *in vitro*. Apart from that, AKAP12 was co-modulated by miR-29c and MEG3 in the two MEN cells.

In general, this present study revealed that MEG3 was down-regulated in MEN tissues and cells, serving as a tumor-suppressive lncRNA in MEN malignancy. MEG3 declined the expression of AKAP12 by targeting miR-29c to block cell-cycle, migration, invasion, and proliferation *in vitro* and might supply a novel biomarker for the treatment of MEN.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by This study was approved by The First Affiliated Hospital of Fujian Medical University Ethics Committee. Informed consents were obtained from the parents or their guardians in accordance with the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CD, XY, and JX performed and designed experiments, analyzed, and interpreted data, and wrote the manuscript. DK, ZH, XB, DW, HG, and GZ performed the experiments. JG, DK, and XW contributed to discussions and reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Gene Expression Signatures Identify Biologically Homogenous Subgroups of Grade 2 Meningiomas

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Introduction: Meningiomas are the most common brain tumor, with prevalence of approximately 3%. Histological grading has a major role in determining treatment choice and predicting outcome. While indolent grade 1 and aggressive grade 3 meningiomas exhibit relatively homogeneous clinical behavior, grade 2 meningiomas are far more heterogeneous, making outcome prediction challenging. We hypothesized two subgroups of grade 2 meningiomas which biologically resemble either World Health Organization (WHO) grade 1 or WHO grade 3. Our aim was to establish gene expression signatures that separate grade 2 meningiomas into two homogeneous subgroups: a more indolent subtype genetically resembling grade 1 and a more aggressive subtype resembling grade 3.

Methods: We carried out an observational meta-analysis on 212 meningiomas from six distinct studies retrieved from the open-access platform *Gene Expression Omnibus.* Microarray data was analyzed with systems-level gene co-expression network analysis. Fuzzy C-means clustering was employed to reclassify 34 of the 46 grade 2 meningiomas (74%) into a benign "grade 1-like" (13/46), and malignant "grade 3-like" (21/46) subgroup based on transcriptomic profiles. We verified shared biology between matching subgroups based on meta-gene expression and recurrence rates. These results were validated further using an independent RNA-seq dataset with 160 meningiomas, with similar results.

Results: Recurrence rates of "grade 1-like" and "grade 3- like" tumors were 0 and 75%, respectively, statistically similar to recurrence rates of grade 1 (17%) and 3 (85%). We also found overlapping biological processes of new subgroups with their adjacent grades 1 and 3.

Conclusion: These results underpin molecular signatures as complements to histological grading systems. They may help reshape prediction, follow-up planning, treatment decisions and recruitment protocols for future and ongoing clinical trials.

Keywords: meningioma, transcriptomics, gene expression networks, bioinformatics, marker discovery

BACKGROUND

Meningiomas are the most common adult brain tumor, carrying an overall prevalence of approximately 3% in the population (1, 2). Histopathologic analysis is the mainstay of diagnosis and, together with the extent of surgical resection, is a key determinant of outcome and treatment planning (3, 4). According to World Health Organization (WHO) grading, the majority of meningiomas (almost 70%) constitute grade 1, of which about two thirds are cured with surgical excision alone (4) and 15–20% recur within 5 years of diagnosis (5–8). Grade 3 meningiomas, by contrast, are rare and aggressive with a 5 year recurrence rate of approximately 90% (4). These extremes of histological grades have relatively homogenous clinical behavior, yet grade 2 histopathologic variants, which constitute 20–30% of all meningiomas, represent a biological intermediate. Predicting the clinical course and treatment response for these tumors is particularly challenging (9) given their heterogeneous biology, and the 5-year recurrence rate of grade 2 meningiomas is approximately 50% (10–12). This uncertainty is corroborated by regular revisions in WHO definitions (13), overlapping molecular signatures with adjacent grades (14, 15) and open questions about the benefits of chemotherapy (9, 16) and adjuvant radiation (17–19) for these tumors. Defining subgroups of grade 2 meningiomas with homogenous biological and clinical properties may be critical to successfully resolving these questions, thereby improving prognostication and treatment for patients.

Molecular markers have been successfully implemented in heterogenous diseases like glioblastoma (20) and medulloblastoma (21) to identify subgroups with shared biology and clinical outcome. Several studies have also examined markers for meningioma biology (14, 22, 23). These previous findings suggest that some grade 2 meningiomas share features with grade 1s while others more closely resemble grade 3s based on clinical behavior and genetic features such as somatic mutations, copy number variants (15, 24, 25), methylation status (14), and genome wide expression profiles (22, 26). Most research on gene expression in meningioma, however, focuses on single-gene analytics. This is not optimized for the low and additive molecular signals which frequently underlie complex and heterogeneous diseases. Systems biology approaches such as co-expression networks (27, 28), on the other hand, are able to provide a higher resolution of these complex genetic processes (27, 29–31).

In this study we hypothesize that grade 2 meningiomas can be segregated into homogeneous subgroups that either resemble indolent grade 1 tumors or aggressive grade 3s. Our aim was to establish gene expression signatures using co-expression networks to identify homogenous subgroups of grade 2 meningiomas.

MATERIALS AND METHODS

This study is an observational analysis of open-source data from the repository *Gene Expression Omnibus* (GEO) (32) and therefore does not require IRB review. All studies with human meningioma microarray data annotated with WHO grade were included in the analysis, which yielded six studies. Another study using RNA-seq transcriptomics constituted an external validation cohort (**Table 1**). All studies included in our meta-analysis were published after the 2007 edition of WHO grading for meningiomas, suggesting this classification was implemented in these studies. For each study, the data was backgrounded corrected, quantile normalized, and log-2 transformed using the *Affy* (33) and *Limma* (34) R (The R Project) packages for Affymetrix and Illumina/RNA-seq platforms, respectively. After selecting only the genes which were common to the six microarray studies, the studies were merged, scaled to a global mean and standard deviation of 0 and 1, respectively (35), and batch-corrected using *ComBat,* a well-established empirical Bayes approach (36). The same approach was used to batch-correct the RNA-seq study, which had been divided into "Discovery" and "Validation" cohorts. The resultant data matrices were used during all subsequent analysis.

Differential gene expression analysis was used to compare grades 1 and 3 meningiomas. In log2-transformed space, the fold change (FC) was computed by subtracting the mean expressions of each gene in grade 1 tumors from the corresponding mean expressions in grade 3 tumors. Genes with absolute log2-transformed FC ≥ 1.5 and $p \leq 0.0001$ were considered significant.

We used the well-established "Weighted Gene Correlation Network Analysis" (WGCNA) to detect "modules" (clusters) of strongly co-expressed genes (29). Per these previously described techniques, we first computed an "adjacency matrix" using soft-thresholded Pearson correlations between each gene pair. This was converted into a biologically-inspired topological overlap map (TOM), wherein pairwise gene similarities are derived from comparing their connectivity profiles (37). Hierarchical clustering converted the TOM into a dendrogram, and a subsequent "dynamic" tree-cut (38) served to identify gene modules. These modules were annotated the annotation platform *Enrichr* (39), an open-source bioinformatics resource. Additionally, representative module "meta-genes" for each sample were computed as the first principal component of their constituent genes' expression values. The utility of this approach was verified in our dataset by demonstrating that higher principle components capture a very small proportion of the overall variance (**Supplementary Figure S1A**) and showing that neither study batch nor sex cluster along the first principle component (**Supplementary Figures S1B,C**). This eliminates the possibility of batch effect or sex being drivers of our "meta-gene" values and confounding results. Differences in the expression levels of these "meta-gene" between grades was tested with a Mann–Whitney test, with a $p \leq 0.05$ considered significant.

In order to better understand the heterogeneity of grade 2 meningiomas, we began by identifying genetic signatures able to best distinguish grades 1 and 3 alone. Fuzzy C-means (FCM) clustering was applied to the set of all patients in our study and the resultant separation of grades 1 and 3 was established with

TABLE 1 | Study demographics.

GEO entry	Platform	*N*	Mean age (SD)	*N* male (%)	WHO grade (*n*)			N recurrence (%)	Median F/U[1] (95% CI)	Median TTR[2] (95% CI)
					I	II	III			
GSE100534	GPL6244	8	N/A	3 (37.5)	6	1	1	N/A	N/A	N/A
GSE77259	GPL6244	14	54.1 (10.1)	4 (28.6)	10	4	0	N/A	N/A	N/A
GSE54934	GPL6244	22	N/A	N/A	20	2	0	N/A	N/A	N/A
GSE43290	GPL96	47	61.7 (15.0)	13 (27.7)	33	12	2	8 (17.0)	4.7 (3.7–5.7)	5.8 (3.6–8.0)
GSE16581	GPL570	68	63.2 (14.7)	25 (36.8)	43	19	6	13 (56.5)	4.7 (4.1–5.3)[3]	N/A
GSE74385	GPL10558	53	N/A	N/A	17	8	28	22 (48.9)	N/A[4]	N/A
Overall[5]		212	61.7 (14.6)	45 (32.8)	129	46	37	43 (37.4)	4.7 (4.3–5.4)	N/A
GSE136661	Illumina HiSeq400	145	58.0 (13.5)	52 (35.9)	116	29	0	22 (15.1)	N/A[6]	N/A

[1]Follow-up (years). [2]Time to recurrence (years). [3]Time to survival (time until death or end of study). [4]Follow-up at least 3 years for non-recurrent tumors, though specific times are not available. [5]Of available data. [6]Follow-up reported as 0–91 months (up to 7.6 years) with a median of 28 months (2.3 years), though specific times are not available.

a sigmoidal cost function that is balanced for differences in the prevalence of both grades:

$$C = \frac{1}{N_1}\sum_{i\in S_1}\left(\frac{1}{1+\ e^{-\alpha(P_i\ -0.5)}}\right) + \frac{1}{N_3}\sum_{j\in S_3}\left(\frac{1}{1+\ e^{-\alpha(0.5-P_j)}}\right)$$

In the above equation, N_1 and N_3 are the number of grade 1 and grade 3 tumors, respectively; S_1 and S_3 are the sets of grade 1 and grade 3 tumors, respectively; P_k is the FCM clustering-derived probability of patient k being in the grade 3-enriched cluster; and α is a tunable hyperparameter. We used a two centroid model wherein cluster polarity was established by comparing the ratio of grade 3 to grade 1 tumors at both ends of the probability distribution (hard-thresholding at 80% probabilities).

Single genes and module "meta-genes" which were significantly different between grade 1 and grade 3 tumors served as input variables. Backward elimination and forward selection were used for feature selection with model performance measured using the above cost function. Hyperparameter (α) values of 1, 5, 10, and 100 tested for all models. Once the separation of grades 1 and 3 was optimized, the probability distribution of grade 2 meningiomas within the same output was investigated. Grade 2 meningiomas with a probability ≥80% of being in the grade 1-enriched cluster were defined as "grade 1-like," and those with a probability ≥80% of being in the grade 3-enriched cluster were defined as "grade 3-like."

We first compared the recurrence rates of "grade 1-like" and "grade 3-like" meningiomas, and compared each to the rates of grade 1 and grade 3 tumors. Notably, only 115 of the 212 patients in our cohort have annotated recurrence, though all had recurrence labels in the RNA-seq validation cohort. To investigate the degree of biological overlap between "grade 1-like" and grade 1 meningiomas, and similarly between "grade 3-like" and grade 3 meningiomas, we used the correlation between their module "meta-gene" expression levels. In addition, we compared the biological separation between the newly described subtypes of grade 2 meningiomas to the separation of grades 1 and 3 by correlating their differential module expression levels.

All computational work relied on the open-source computational platform R (40) (The R Project), including packages *WGCNA* (29), *ppclust* (41), *Affy* (33), *Limma* (34), and *SVA* (42).

Statistical Methods

Transcriptomic expression levels were analyzed using the two-sample *t*-test and Mann–Whitney U test. Recurrence rates were compared with a Chi-square test. Notably, since only a subset of samples had recurrence annotated, recurrence analysis was only performed on this subset of patients.

RESULTS

Participants, Descriptive, and Outcome Data

Please refer to **Table 1** for details of our study cohort. In brief, we included six microarray series [GSE100534 (43), GSE77259 (44), GSE54934 (45), GSE43290 (46), GSE16581 (47), GSE74385 (48)] with a combined 212 patients and one RNA-seq series [GSE136661 (49)] with 145 patients. The distribution of histopathologic subtypes are illustrated in **Supplementary Figure S2**. We identify two subgroups of grade 2 meningiomas with significantly different recurrence rates among those with available data (75% in the aggressive subgroup and 0% in the indolent subgroup, $p < 0.005$). These recurrence rates are similar to the recurrence rates of grades 3 and 1, respectively, suggesting clinical utility in this reclassification. A more detailed outline of our results can be found below.

Main Results

We firstly established the gene expression profile that differentiates grade 1 from grade 3 meningiomas. Differential gene expression showed four up-regulated and two down-regulated genes ($\log_2$ fold change ≥1.5, $p \leq 0.0001$) summarized in **Figure 1A** and **Supplementary Table S1**.

We created another signature to distinguish grade 1 from grade 3 meningiomas using gene co-expression networks. This yielded 29 co-expressed gene modules (**Figure 1B**), of which 15 had median meta-gene expression levels that differed

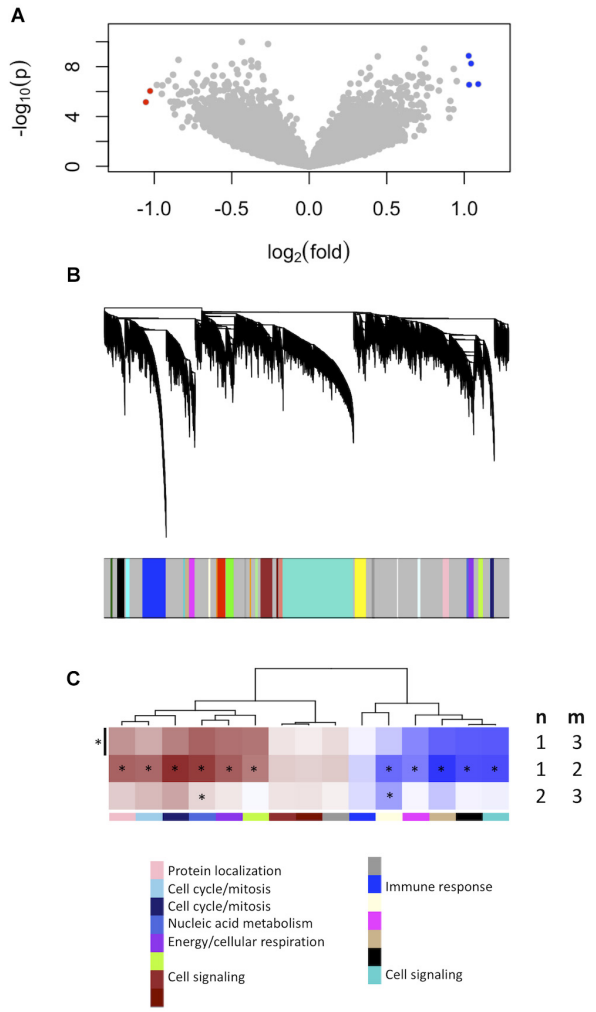


FIGURE 1 | Gene expression signatures associated with meningioma grade. **(A)** Differential gene expression between grades 3 and 1 meningiomas reveal four upregulated and two downregulated genes in grade 3 tumors [| $\log_2$(fold change)| $\geq$ 1.5, $p < 0.0001$] highlighted with blue and red dots, respectively. **(B)** Gene co-expression networks analysis. Dendrogram of genes based on the topological overlap map, with the 29 gene modules represented by colors in the bar below. Gray represents unclassified genes. **(C)** Plot of median module meta-gene expression differences between grades ("m" versus "n"). Only modules with significantly different expression between grades 1 and 3 are included (Mann–Whitney $p < 0.05$). Red indicates modules which are upregulated in grade (m), and darker shades indicate larger effect sizes. Notably, 11/15 modules are significantly different between grades 1 and 2 while 2/15 are also significantly different between grades 2 and 3. *$p < 0.05$ (Mann–Whitney).

significantly between grades 1 and 3 (Mann–Whitney $p < 0.05$, **Figure 1C**). A subset of these 15 were also significant between grades 1 and 2 and/or between grades 2 and 3 tumors, suggesting the intermediate biology of grade 2 meningiomas.

To find a genetic signature that best differentiates grades 1 and 3 tumors, we used two-centroid soft clustering and evaluated the resultant distribution of patients with a balanced sigmoidal cost function (with a lower cost being indicative of greater average separation). An iterative feature selection approach was conducted using single genes and gene modules which were differentially expressed between grades 1 from 3. Notably, modules (represented by their meta-gene expression) consistently yielded better performance (lower cost) than single genes (**Figure 2A**). The lowest cost was achieved with two modules as inputs; one of which contained 61 genes which map predominantly to purine biosynthesis and the other consisted of 121 genes which map strongly to mRNA splicing. Gene lists for both of these modules can be found in the supplemental content. We then used this signature to reclassify grade 2 meningiomas. Importantly, this signature was derived without the clustering model having any input from grade 2 meningiomas during training. Using 80% membership probability as a cutoff, we reclassified 34 of 46 grade 2 meningiomas (74%) into a "grade 1-like" (13/46) and "grade 3-like" (21/46) subgroup of grade 2 meningiomas (**Figure 2B**). A small group of 12 grade 2 meningiomas did not fall into either "grade 1-like" or "grade 3-like" groups and may therefore represent a true biological intermediate. The histopathologic subtype was annotated for 7/13 "grade 1-like" tumors (six atypical, one transitional with brain invasion) and 7/21 "grade 3-like" tumors (six atypical, one atypical with brain invasion). Of the 12 unclassified grade 2 meningiomas, 2 were atypical, 1 was meningothelial with brain invasion, and 9 were not annotated. Recurrence rates were available for only a subset of cases (30/46) and were significantly higher in "grade 3-like" (9/12) compared to "grade 1-like" (0/8) subgroups ($p < 0.005$). Concordantly, there was no significant difference in recurrence rates between grade 1 and "grade 1-like" groups (10/59 versus 0/8) nor between grade 3 and "grade 3-like" groups (22/26 versus 9/12). Of the 12 unclassified grade 2 meningiomas 2 recurred, 8 had no documented recurrence and 2 had unknown recurrence status. Comparatively, we reclassified 20 of 29 grade 2 meningiomas in the RNA-seq validation cohort (69%) using the same gene signatures and thresholding (6 "grade 1-like" and 14 "grade 3-like") (**Figure 3**). The recurrence rates of "grade 3-like" and "grade 1-like" were 1/6 (17%) and 7/14 (50%), respectively. However, the numbers were too small to achieve statistical significance.

Next, we verified the molecular identity of the newly detected subgroups of grade 2 meningiomas. Using a systematic comparison based on median module expression levels (**Figure 4**), we found concordance between the biology of our newly identified grade 2 subtypes with their adjacent grade (**Figure 4A**). Differential analysis also suggested that the overall biological separation between the newly described subgroups is similar to the separation between grades 1 and 3 in module space. These findings further lend to the validity of dividing grade 2 meningiomas into biologically homogenous subgroups which parallel existing grades.

DISCUSSION

Key Results

Our study focuses on the most heterogenous group of meningiomas: WHO grade 2. We were able to identify subgroups

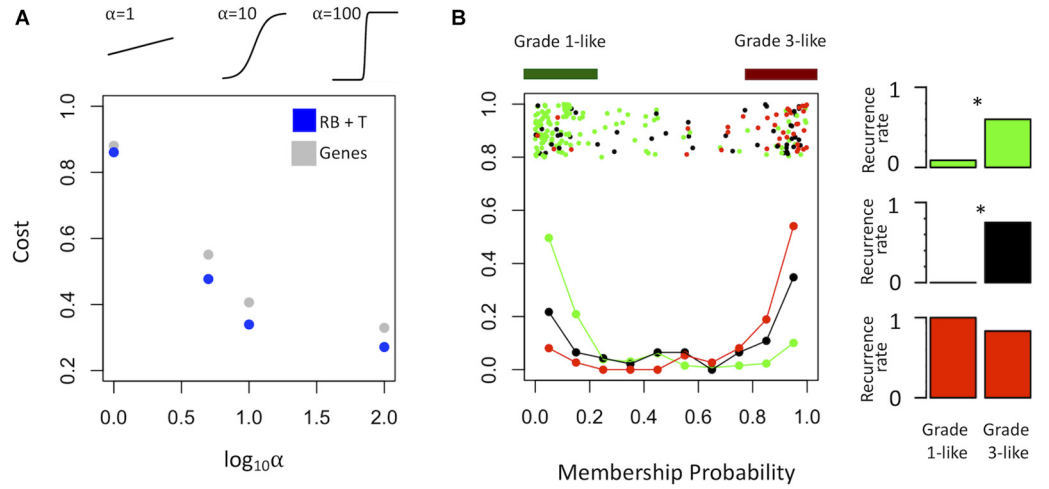


FIGURE 2 | Optimized soft clustering reveals two subgroups of grade 2 meningiomas. **(A)** Cost of multiple input configurations: "royal blue" (RB) and "tan" (T) modules in blue and optimized differentially expressed genes in gray. Top inset depicts shape of sigmoid function with varied alphas. **(B)** Summary graph of fuzzy C-means clustering best performing inputs (RB + T). The *x*-axis represents the probability of being in the grade-3 enriched cluster and *y*-axis represents the proportion of patients in each bin of 10%. Line graph component represents normalized frequency distribution of each histological grade (green = grade 1, black = grade 2, red = grade 3). Top jitter plot represents individual patients. Dark green and red bars above represent the 20 and 80% thresholding into grade 1-like and grade 3-like subgroups of grade 2 meningiomas. Recurrence rates are plotted on the right by grade (green, black, red) and subgroup ("grade 1-like" and "grade 3-like"). *Chi-square $p < 0.05$.

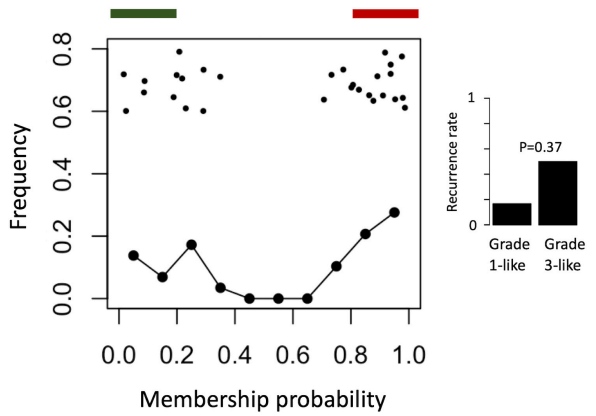


FIGURE 3 | Validation of meningioma reclassification using RNA-seq data. Summary graph of fuzzy C-means clustering best performing inputs on the microarray data (modules RB + T). The *x*-axis represents the probability of being in the grade-3 enriched cluster and *y*-axis represents the proportion of patients in each bin of 10%. Line graph component represents normalized frequency distribution of each histological grade (green = grade 1, black = grade 2, red = grade 3). Top jitter plot represents individual patients. Dark green and red bars above represent the 20 and 80% thresholding into grade 1-like and grade 3-like subgroups of grade 2 meningiomas. Recurrence rates are plotted on the right by grade and subgroup ("grade 1-like" and "grade 3-like"). Notably, recurrence data is not available for the grade 3 meningiomas in this cohort.

with greater homogeneity compared to preceding studies, with 0 and 73% recurrence rates for grade 1-like and grade 3-like grade 2 subgroups, respectively. We found that gene expression signatures derived using co-expression networks outperform the limited number of genes derived using conventional differential gene expression. Validating this microarray-based classifier with RNA-seq data, we found recurrence rates of 17 and 50% for the same reclassified groups, though the number of samples was insufficient to achieve statistical significance. These findings demonstrate the conceptual advantages of system-based approaches like co-expression networks over conventional techniques like differential gene expression and/or clustering.

Gene Modules

Interestingly, the modules found to be most predictive of recurrence map to very broad and non-specific molecular functions (RNA splicing and nucleotide synthesis). While this makes the traditional identification of targetable pathways difficult, these domains have been shown to be reliably affected in cancer. Furthermore, they may be targetable with agents such as small molecule splicing modulators and drugs such as rapamycin, respectively (50, 51). We therefore propose further investigation into these sub-disciplines of oncology within the context of meningioma, though these findings remain preliminary and are peripheral to our main findings.

Limitations

Though our study achieves its purpose, there are a number of limitations which must be considered. Firstly, only a subset of samples have recurrence and follow-up times documented, which may influence generalizability. Furthermore, while a meta-analysis of six independent case-series minimizes bias, there may still be a degree of selection bias as one study is particularly enriched in high grade tumors and the RNA-seq data lacks grade 3 tumors entirely (**Table 1**). We also acknowledge that the year

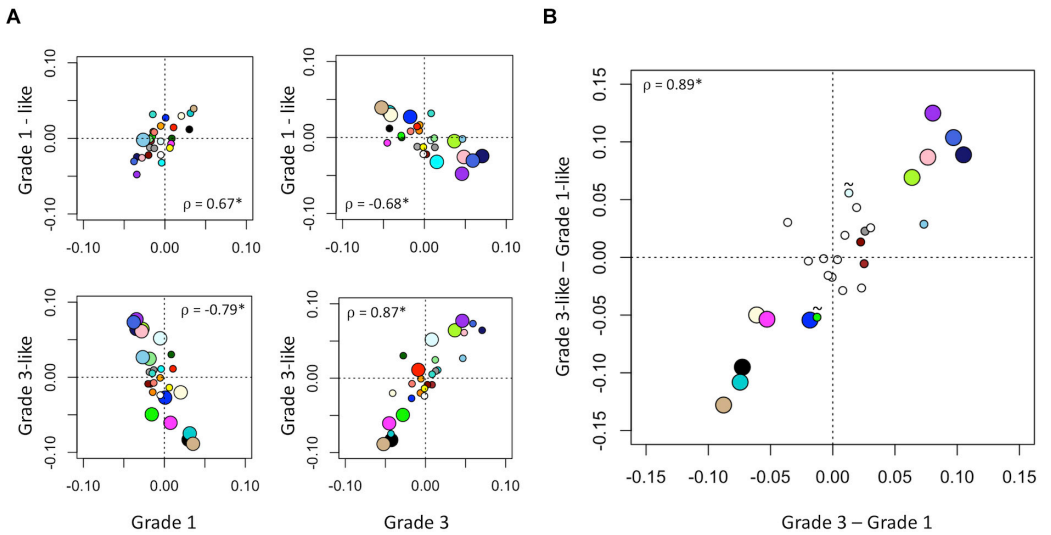


FIGURE 4 | Molecular identity of newly described grade 2 meningioma subgroups. **(A)** Scatter plot of median module meta-gene expression (unitless). Larger circles indicate Mann–Whitney $p < 0.05$. Colors correspond to previously identified modules in **Figure 1B**. ρ = Pearson coefficient, $^*p < 0.05$. Note the positive correlation between the modules of grade 1 and "grade 1-like" and grade 3 and "grade 3-like" subtypes. **(B)** Scatter plots of genetic separation between grade 2 subtypes as histological grades. The *x*-axis represents the difference in median module expression between grades 3 and 1, while the *y*-axis represents the difference in median module expression between "grade 3-like" and "grade 1-like." Large circles represent modules which are significantly different in both comparisons and empty circles indicate modules which are not significantly different in either. Of the remainder, 4/6 are significantly different between grades 3 and 1 only and 2/6 is significantly different between "grade 3-like" and "grade 1-like" (∼).

of WHO grading is not annotated in the data used. However, we consider the grading system used to classify meningiomas in these studies to be post WHO 2007 given that all data were deposited well after 2007. This classification incorporate the updated criteria of the WHO 2000 edition (at least 4 mitoses in 10 high powered fields or 3 of the following criteria: increased cellularity, high nuclear-to-cytoplasm ratios, prominent nucleoli, uninterrupted pattern-less or sheet-like growth, or necrosis) (13). Introduction of these criteria caused a surge in diagnostic rates for grade 2 meningiomas followed by a plateau (13). Importantly, further modifications of the WHO criteria are unlikely to result in increased reporting for grade 2 meningiomas (52), and so the prevalence of meningioma grades in our study is consistent and parallels current practice. Additionally, the objective of this paper is to subdivide grade 2-labeled meningiomas into homogeneous subgroups based on transcriptomics alone, independent of WHO grade, which we have done despite inconsistencies in grade 2 criteria. Finally, our cohort is highly heterogeneous, with patients from geographically diverse centers with potentially different surgical practices and a mixture of microarray and RNA-sequencing platforms. Similarly, a stratification based on relevant mutations in meningioma was not possible due to a lack of sufficient annotation for such an analysis. Nevertheless, we show reclassification of grade 2 meningiomas which is corroborated by the recurrence rates and biological mechanisms which align with the adjacent grade tumor.

Interpretation

The highly heterogeneous clinical behavior of grade 2 meningiomas suggests that histological criteria do not adequately capture it is biology, thus motivating the segregation into more homogeneous subgroups. So far, molecular profiling of meningiomas has largely taken a monogenetic approach to marker discovery for aggressive phenotypes (22). This has been fruitful in identifying recurrence mutations (15) and transcripts (22) linked to oncogenic cascades in meningiomas. However, these approaches rely on differential gene expression to identify relevant molecular mechanisms and thereby remains limited in its ability to resolve small additive signal often relevant in tumor biology. The use of gene co-expression networks helps to address this limitation. Additionally, a majority of studies on meningioma genetics use histopathological grade as the outcome measure (15), which does not capture disease biology for the case of grade 2 meningiomas. Epigenetic studies using conventional clustering have analyzed heterogeneity of meningiomas across all grades (14) proposing new benign, intermediate and malignant methylation subclasses. "Intermediate" meningiomas are quoted a 20% chance of disease-free survival, which is clinically more useful than the outcome prediction yielded by histology (50%). We believe this study adds to this developing literature surrounding meningioma classification.

Generalizability

The generalizability of our study is augmented by its design as a meta-analysis, though its purpose is one of hypothesis generation for subsequent, confirmatory studies. Our results therefore require prospective verification and could ultimately help guide molecular diagnostics and prognostics in grade 2 meningiomas. This may ultimately inform recruitment protocols for future and ongoing clinical trials, which are currently limited

by the uncertainty of clinical outcomes in grade 2 meningiomas (18). The approach in this study lend to the utility of complex molecular signatures in augmenting histological diagnosis and resolving other heterogeneous and challenging diseases.

CONCLUSION

Our findings help resolve the heterogeneity of grade 2 meningiomas by deconvolving them into subgroups which are more homogenous than are proposed in prior studies. These subgroups may help predict clinical course, thus allowing for customized follow-up planning to manage resource intense investigations such serial imaging while optimizing patient care.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.ncbi.nlm.nih.gov/geo/; accession GSE100534, GSE77259, GSE54934, GSE43290, GSE16581, GSE74385, and GSE136661.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ZZ conceived the study. ZZ, AL, and AS carried out the analysis. ZZ and AL prepared the figures, wrote the manuscript. MC, ZZ, and AL revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.541928/full#supplementary-material

FIGURE S1 | Validating meta-genes as representations of module gene expression. **(A)** The proportion of variance explained by each principle component (PC) in the "tan" (left) and "royal blue" (right) modules. In both cases, the first principle component explains considerably greater variance than any higher PC. **(B,C)** Scatter plot of patients by first and second PCs, with colors representing batch and sex, respectively. The "tan" module is depicted on the left and the "royal blue" module on the right. Only patients with annotated sex are included in **(C)**. Notably, there is no clustering of batch and/or sex evident along the first (or second) PC.

FIGURE S2 | Distribution of histopathologic subtypes in the microarray cohort, by individual study. Top bar represents WHO grade (green = 1, black = 2, red = 3). NOS, not otherwise specified.

TABLE S1 | Differentially regulated genes between grades 1 and 3.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prognostic Model That Predicts Benefits of Adjuvant Radiotherapy in Patients With High Grade Meningioma

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Objective: Adjuvant radiotherapy is the main treatment modality for high grade meningioma after surgical resection; however, recurrence and survival outcomes vary. The aim of this study was to create a new "prognostic score" that allows personalized recommendations for post-operative adjuvant radiotherapy in patients with high grade meningioma.

Methods: Clinical data were collected from 115 patients with high grade meningioma treated with surgical resection and adjuvant radiotherapy. A prognostic model was built based on the hazards ratios of independent prognostic factors yielded by multivariate cox proportional analysis. Calibration and discrimination of the prognostic score was evaluated using good of fit test and Harrel's C index, respectively.

Results: A total of 115 high grade meningioma patients (72 atypical and 43 anaplastic meningiomas) were enrolled. Three factors were independently associated with progression-free survival (PFS): extent of resection (GTR vs. STR), recurrent status (*de novo* vs. recurrent), and Ki-67 labeling index (<5% vs. ≥ 5%). The respective β-coefficients were used to generate the "prognostic score". The cohort was divided into low-risk and high-risk groups based on the median prognostic score. Good of fit test showed strong calibration (P = 0.7133) and Harrel's C index 0.766 indicated a strong discrimination capability of the prognostic score. The Harrel's C index for OS was 0.60.

Conclusions: Our prognostic model using three basic clinical parameters robustly separated high grade meningioma patients who benefit vs. do not benefit from adjuvant radiotherapy. External validation of our model is warranted to help improve patient selection suitable for adjuvant radiotherapy.

Keywords: high grade meningioma, prognostic model, radiation, prognosis, atypical meningioma, anaplastic meningioma

INTRODUCTION

Meningioma is one of the most common primary neoplasms arising in the central nervous system (CNS), accounting for about 36.4% of all CNS tumors (1). It has been classified into three grades and fifteen histological subtypes according to the World Health Organization (WHO) 2016 meningioma grading criterion (2). While most of them are benign and slow-growing tumors, higher tumor histological grade is significantly associated with more malignant phenotypes and worse patient outcome, regarding both recurrence and premature mortality. WHO Grade II meningioma was defined by 4–19 mitoses per 10 hpf, brain invasion or presence of the histological features associated with atypia. WHO Grade III meningiomas have a mitotic index higher than 20 per 10 hpf (2). Among high grade meningiomas, atypical (grade II) and anaplastic meningioma (grade III) represent the most common two subtypes. Studies report 5-year survival rates ranging from 78% to 91% and 35% to 79% for atypical and anaplastic meningioma, respectively (3–13).

Although efforts have been made through a dearth of treatment options and biological targets, surgery remains the mainstream treatment strategy (14, 15). Radiation followed by surgical resection is usually recommended for high grade meningioma due to the high rate of recurrence. However, Despite post-operative radiation therapy tumor recurrence or progression is not uncommon, suggesting that adjuvant radiation is only effective in a subset of the patients (9, 16–22). Therefore, patients with high grade meningioma must be appropriately stratified to select patients who are more likely to benefit from adjuvant radiotherapy.

We here propose a novel and simple evaluation score based on basic pre and post-operative clinical information to predict and assess the efficacy of adjuvant radiation therapy regarding both tumor recurrence and overall survival. This scoring model provides us with a clinically applicable tool that assists with personalized treatment recommendations and enables predictions of treatment outcomes in these heterogeneous patients.

PATIENTS AND METHODS

Study Cohort

During the period between January 2003 and December 2008, a total of 115 patients underwent surgical resection of high grade meningioma (atypical and anaplastic) and received post-operative radiation therapy at the Department of Neurosurgery, Huashan Hospital, Fudan University, providing the study cohort for model development and detailed analysis. Patients demographics including age at admission, gender, preoperative Karnofsky performance scale (KPS), tumor location, tumor histological grade, extent of surgical resection, and outcome data were collected and analyzed. The pathological results of all the 115 patients were rechecked and confirmed by two experienced neuro-pathologists (Hong Chen and Yin Wang) according to the 2016 WHO CNS tumor grading criterion. WHO grade II and III meningiomas diagnosed as rarer pathological variants were not included. Meningioma surgical resection was evaluated based on post-operative enhanced T1-weighted MRI and surgical records according to the Simpson grading criterion, and were classified to gross total resection (GTR, Simpson grades I–III) and subtotal resection (STR, Simpson grades IV–V) subgroups. Tumor location was divided into "skull base" and "non-skull base" locations. Follow-up was conducted routinely according to the guidelines of Huashan Neurosurgical Center. Tumor progression was identified as tumor enlargement compared to previous images at the operative location via post-operative MRI. Progression-free survival (PFS) and OS were defined as time since surgical resection to tumor progression or to death as a result of any cause or censored at the date of the last follow-up. Written informed consent was obtained from all patients involved in our study. This clinical study was approved by the Human Subjects Institutional Review Board at Huashan Hospital, Fudan University (KY-2017-09).

Postoperative Radiotherapy

All patients received post-operative radiotherapy within 2 to 4 weeks after the surgery. Either conventional external beam radiotherapy or Gamma knife was applied. The selection of the type of radiation therapy was based on radiation oncologists' decision as well as patients' preference. The planning protocol for radiation therapy was delineated according to the treatment protocol of Huashan Radiation center. For traditional external beam radiation therapy, 2.0 Gy daily fractions with 1- to 2-cm clinical target volume (CTV) and 3- to 5-mm planning target volume (PTV) was applied with the mean total dose 48.9 ± 5.1 Gy (range 32–66 Gy). For Gamma-knife treatment protocol, the prescription dose was 14.0 Gy at 50% and 28.0 Gy at 100%.

Statistics

Based on previous studies and our own experiences which reported association between clinical indices and outcome of high grade meningioma, we put forth the primary hypothesis that a constellation of clinical and treatment parameters is associated with the efficacy of radiation on patients with high grade meningioma and that a prognostic score based on a weighted model of these parameters will assist decision making whether or not to apply radiation to these high grade meningioma patients. PFS was used as the primary endpoint for model development since tumor recurrence was the most clinically relevant. In addition, the model was validated for its predictability of OS as well. We turned continuous factors such as age and Ki-67 index into dichotomies according to suggestions proposed by P Royston et al. (23). The model development approach was in kept with Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines.

Model Building

Univariate Cox-proportional hazards regression model was initially used to identify prognostic factors for tumor

Abbreviations: PFS, progression-free survival; OS, overall survival; CNS, central nervous system; WHO, World Health Organization; KPS, karnofsky performance score; GTR, gross total resection; STR, subtotal resection; CTV, clinical target volume; ER, estrogen receptor.

recurrence. Clinical factors considered for prognostic analysis included: age (<60 years vs. ≥60 years), gender (female vs. male), WHO grade (grade II vs. grade III), treatment status (newly diagnosed vs. recurrent), Simpson resection grade (GTR vs. STR), and Ki-67 index (<5% vs. ≥5%). Factors with a *P* value less than 0.05 in the univariate Cox regression model were further included in multivariate Cox proportional hazards regression model for building the prognostic score by using a backward elimination procedure. Non-significant factors ($P \geq 0.05$ in the multivariable Cox-proportional hazards regression model) were removed from the model with a stepwise procedure. The model fitting was evaluated by using the Akaike information criterion (AIC) and the model with the smallest AIC was selected as the final prognostic score (23). The predictive ability of the model was evaluated by its discrimination and calibration. The discriminative ability was examined with Harrell c-statistics, while calibration was assessed through Hosmer-Lemeshow goodness of fit test as well as comparing the observed and predicted survival rate at 18, 24, 30, 36, 48, 60, and 72 months.

The regression coefficient for each independent prognostic factor was computed from the equation [$\beta = \ln(HR)$], in which HR is the hazards ratio in the multivariate Cox regression model. The prognostic score was calculated for each patient by the sum of the individual scores. The cohort was dichotomized into low-risk and high-risk subgroups according to the median prognostic score of the whole cohort to predict patients that did not benefit from adjuvant radiotherapy.

Statistical analysis was performed using software STATA 13.3 for windows (StataCorp, College Station, TX). Clinical data such as medians were summarized with descriptive analysis. Categorical variables were compared with either Pearson chi-square test or Fisher's exact test. Student t test (data with normal distribution) or Mann-Whitney U test (data with skewed distribution) was used for continuous variables. Survival curves were estimated by Kaplan-Meier method. $P < 0.05$ was considered significantly different.

RESULTS

Baseline Characteristics

A total of 115 patients with high grade meningioma treated with surgical resection followed by adjuvant radiotherapy at the Neurosurgical center of Huashan Hospital, Fudan University met the inclusion criterion. Among them, 72 (62.6%) were atypical and 43 (37.4%) were anaplastic meningioma. The median age of these patients was 48.05 ± 12.31 years (range: 19–81 years). 59 patients (51.3%) were females. The median of preoperative KPS was 80 (range: 20–100). The most common location in our series was convexity (n = 52, 45.2%), followed by falcine/parasagittal (n = 38, 26.1%) and skull base (n = 25, 21.7%). GTR was achieved in 91 cases (79.1%) and the rest of the patients (n = 24, 20.9%) underwent subtotal resection. Thirty patients (26.1%) had a previous history of surgical meningioma resection, and they were diagnosed as recurrent meningioma. Demographic characteristics are summarized in **Table 1**.

Follow-Up and Outcome

The median follow-up was 51.8 months (range: 3 to 142 months). Median PFS was 70 months for all patients, with 3-, 5-, and 7-year recurrence free rate being 80.7%, 68.5%, and 57.9%, respectively. For atypical meningioma, median PFS was 71 months, with 3-, 5-, and 7-year recurrence free rate being 86.2%, 77.2%, and 64.8%, respectively. And for anaplastic meningioma, median PFS was 55 months, with 3-, 5-, and 7-year recurrence free rate being 71.8%, 54.0%, and 46.9%, respectively. Median OS for all patients was 77 months, with 3-, 5-, and 7-year survival rate being 85.2%, 78.1%, and 67.6%, respectively. When grouped by tumor grade, median OS was 81 months for atypical meningioma, with 3-, 5-, and 7-year survival rate being 87.5%, 84.7% and 78.4%, respectively. Median OS for anaplastic meningioma was 66 months, with 3-, 5-, and 7-year survival rate being 81.4%, 66.9%, and 47.8%, respectively. There existed a significant difference in both PFS (P = 0.026) and OS (P = 0.009) between grade II and grade III tumors (**Figure 1**).

Univariate and Multivariable Progression-Free Survival

Clinical factors listed in **Table 2** were firstly tested for their association with PFS using the Cox proportional hazards model; significant prognostic factors for PFS on univariate analysis were histological grade (HR, 1.96; 95% CI, 1.09 to 3.57; P = 0.026), recurrent status (HR, 1.90; 95% CI, 1.3 to 2.77; P = .001), tumor resection grade (HR, 4.01; 95% CI, 2.19 to 7.34; P = 0.000), Ki-67 labeling index (HR, 2.01; 95% CI, 1.10 to 3.65; P = 0.022),

TABLE 1 | Baseline characteristics of patients in our cohort.

Characteristics	Overall, No. (%)
Age, years	48.05 ± 12.31
<60	81 (70.4%)
≥60	34 (29.6%)
Gender	
Male	56 (48.7%)
Female	59 (51.3%)
WHO grade	
Grade II (atypical)	72 (62.6%)
Grade III (anaplastic)	43 (37.4%)
Tumor location	
Skull base	25 (21.7%)
Non-skull base	90 (78.3%)
Recurrent status	
De novo	85 (73.9%)
Recurrent	30 (26.1%)
Extent of tumor resection	
GTR	91 (79.1%)
STR	24 (20.9%)
Preoperative KPS score	
<80	40 (34.8%)
≥80	75 (65.2%)
Recurrent status	
Primary	85 (73.9%)
Recurrent	30 (26.1%)
Ki-67 labeling index	
<5	64 (55.7%)
≥5	51 (44.3%)

KPS, karnofsky performance score; GTR, gross total resection; STR, sub-total resection.

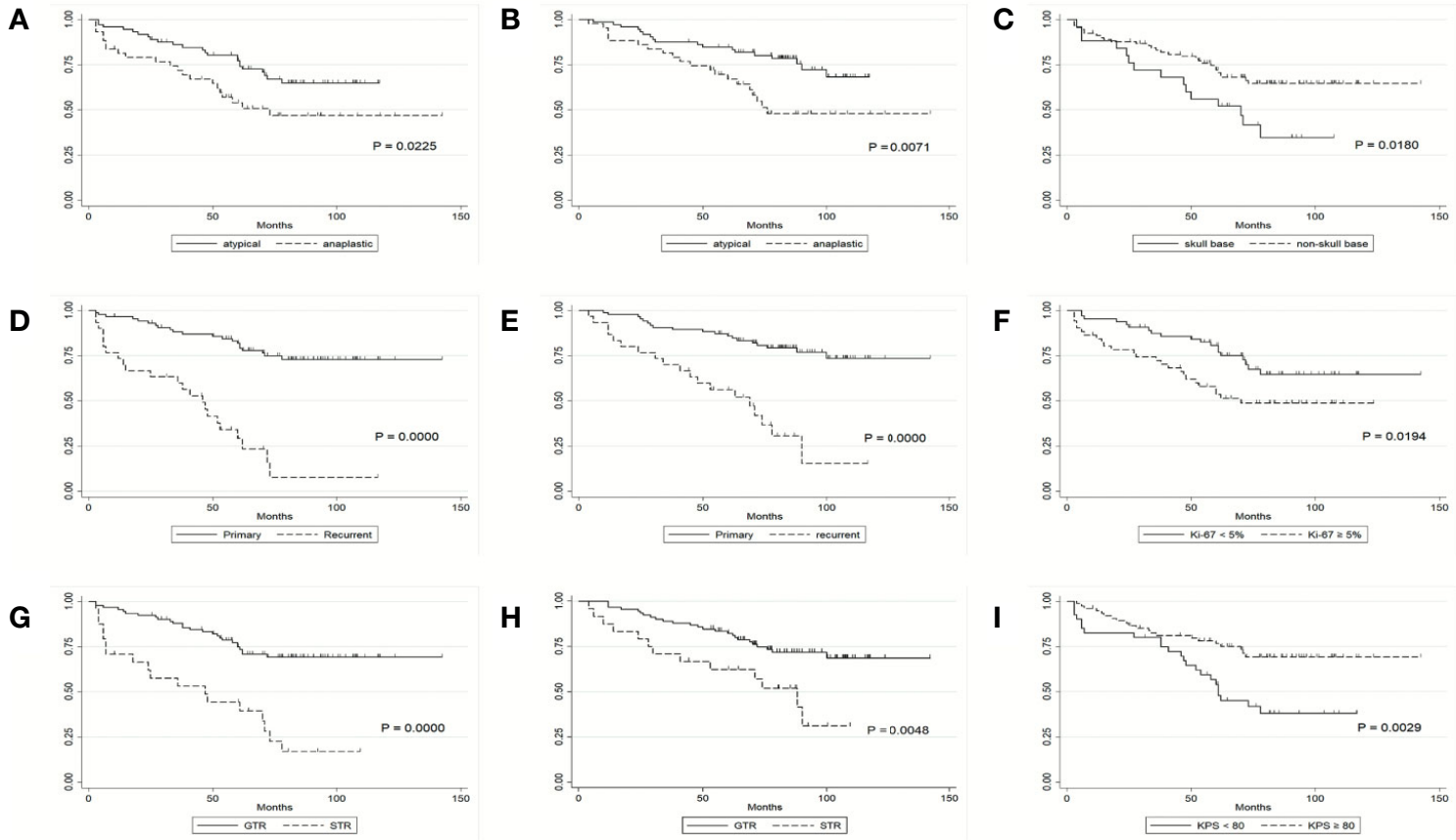


FIGURE 1 | Kaplan-Meier survival curves. **(A)** PFS of patients by histological grade. **(B)** OS of patients by histological grade. **(C)** PFS of patients by tumor location. **(D)** PFS of patients by tumor recurrence status. **(E)** OS of patients by tumor recurrence status. **(F)** PFS of patients by Ki-67 labeling index. **(G)** PFS of patients by extent of tumor resection. **(H)** OS of patients by extent of tumor resection. **(I)** PFS of patients by KPS score.

TABLE 2 | Univariate and Multivariate Analysis of Prognostic Factors in high grade meningioma patients rerated with adjuvant radiotherapy.

Variable	Univariate Analysis				Multivariate Analysis			
	PFS		OS		PFS		OS	
	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR(95% CI)
Age (<60/≥60)	0.515	0.809 (0.428–1.531)	0.552	0.812 (0.409–1.613)				
WHO grade (grade II/III)	0.026*	1.968 (1.086–3.566)	0.009*	2.347 (1.237–4.454)			0.010*	2.452 (1.234 - 4.871)
Gender (female/male)	0.522	1.215 (0.669–2.207)	0.632	0.856 (0.453–1.618)				
Preoperative KPS (<80/≥80)	0.004*	0.418 (0.231–0.757)	0.059	0.541 (0.286–1.024)				
Extent of resection (GTR/STR)	0.000*	4.011 (2.191–7.343)	0.007*	2.538 (1.296–4.971)	0.000*	3.322 (1.744–6.330)		
Location (skull base/non-skull base)	0.021*	0.480 (0.257–0.895)	0.326	0.696 (0.338–1.434)			0.046*	0.454 (0.208 - 0.987)
Ki-67 index (<5%/≥5%)	0.022*	2.006 (1.104–3.646)	0.339	1.365 (0.722–2.579)	0.009*	2.302 (1.235–4.293)		
De novo (no/yes)	0.000*	6.145 (3.313–11.401)	0.000*	4.670 (2.430–8.972)	0.000*	4.809 (2.484–9.312)	0.000*	4.607 (2.374 - 8.944)

*KPS, karnofsky performance score; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; GTR, gross total resection; STR, sub-total resection; *p < 0.05 considered statistically significant.*

preoperative KPS (HR, 0.42; 95% CI, 0.23 to 0.76; P = 0.004) and tumor location (HR, 0.48; 95% CI, 0.26 to 0.90; P = 0.021) (**Figure 1** and **Table 2**). These factors were further included in the multivariable Cox proportional model. We found that extent of tumor resection (HR, 3.32; 95% CI, 1.74 to 6.33; P = 0.000), Ki-67 labeling index (HR, 2.30; 95% CI, 1.23 to 4.29; P = 0.009) and tumor recurrent status (HR, 4.81; 95% CI, 2.48 to 9.31; P = 0.000) were independent predictors of PFS (**Table 2**).

Construction of the Prognostic Model

The model containing these three factors (i.e., extent of resection, Ki-67 labeling index and recurrent status) yielded the smallest AIC number, thus were included in the final model. We then constructed the "prognostic score" by weighing these three independent prognostic factors based on the β-coefficient of the respective $\log_{10}$ (HR). The Harrell's C index of this scoring system was 0.766 (95% CI, 0.692 to 0.839), indicating a strong discriminative ability of the model. In addition, the Hosmer-Lemeshow goodness of fit test also showed a strong calibration of this model (P = 0.7133). The score of the smallest β-coefficient was assigned as 1 and that of the other two factors was accordingly assigned based on the respective β-coefficient. As a result, the score for STR was 1, it was 1.5 for higher Ki-67 labeling index, and the score was 2 for recurrent tumor. The prognostic score for each patient was then calculated based on the sum of weighed numbers of the factors: The prognostic score = 1* [STR = 1 or GTR = 0] + 1.5 * [Ki-67 LI ≥5 = 1 or Ki-67 LI < 5 = 0] + 2 * [recurrent tumor =1 or *de novo* tumor = 0] (**Table 3**).

Predicting PFS

The median prognostic score in our cohort was 1.5 (range: 0–4.5). The score was dichotomized into the low risk and high risk subgroups based on the median cutoff point (i.e., 50th percentile score) of all patients. Fifty-one patients were in the low-risk group and 64 patients were in the high-risk group. The median PFS for the low- and high-risk group was 72 months (range: 20 to 142) and 57 months (range: 1 to 90), respectively, and the difference was significant between the two groups (HR, 2.01; 95% CI, 1.10 to 3.65; P = 0.001, log-rank test) (**Figure 2A**). The Harrell's C index for this median cutoff point was 0.647 (95% CI, 0.581–0.710). To further validate the predictive accuracy of our prognostic score for PFS in patients with high grade meningioma, the predicted and observed PFS rates at 18, 24, 30, 36, 48, 60, and 72 months of low and high risk subgroups were compared and illustrated in **Figure 3A**. The predicted PFS was closely matched to the corresponding observed probability at these time points.

TABLE 3 | Constructed Prognostic score to predict progression-free survival in high grade meningioma patients with adjuvant radiotherapy.

Covariate	β [β = log (HR)]	Score
Extent of resection	1.57	2 * (0/1; GTR = 0, STR = 1)
Ki-67 index	1.19	1.5 * (0/1; <5% = 0, ≥5% = 1)
Recurrent status	0.83	1 * (0/1; primary = 0, recurrent = 1)
Total computed score and risk stratification		
Low risk		<1.5
High risk		≥1.5

HR, hazard ratio.

Validation of Prognostic Score for OS

The factors that were associated with OS in univariate Cox proportional analysis were histological grade (HR, 2.35; 95% CI, 1.24 to 4.45; P = 0.009), recurrent status (HR, 4.67; 95% CI, 2.43 to 8.97; P = 0.000), and tumor resection grade (HR, 2.54; 95% CI, 1.30 to 4.97; P = 0.007) (**Table 2**). Ki-67 labeling index was not significant (HR, 1.36; 95% CI, 0.72 to 2.58; P = 0.339). In multivariate analysis, the independent factors for OS were tumor recurrent status (HR, 4.61; 95% CI, 2.37 to 8.94; P = 0.000), and tumor grade (HR, 2.45; 95% CI, 1.23 to 4.87; P = 0.010).

Given that the independent factors for OS overlapped with those for PFS, we hypothesized that our prognostic score built with PFS could also serve as a predictor for OS. The median OS in the low- and high-risk groups was 80 months (range: 25–142 months) and 71 months (range: 4–123 months), respectively (**Figure 2B**). The Harrell's C index of this prognostic score for OS was 0.676 (95% CI, 0.586 to 0.768), indicating a strong discriminative ability of the model. Hosmer-Lemeshow goodness of fit test also showed a strong calibration of this model for predicting OS (P = 0.2657).

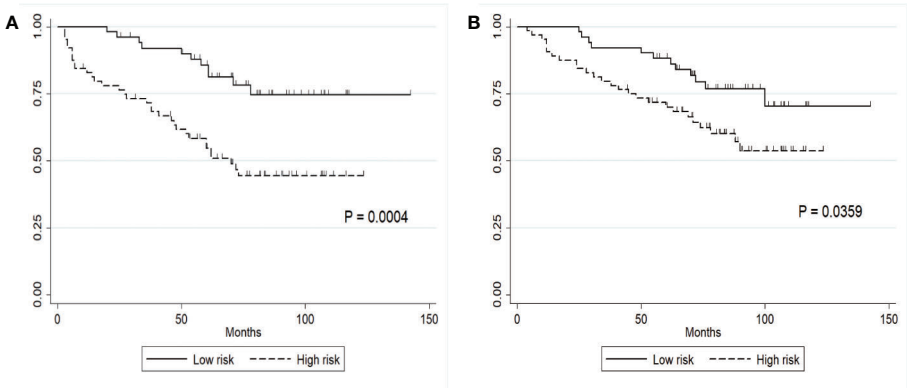
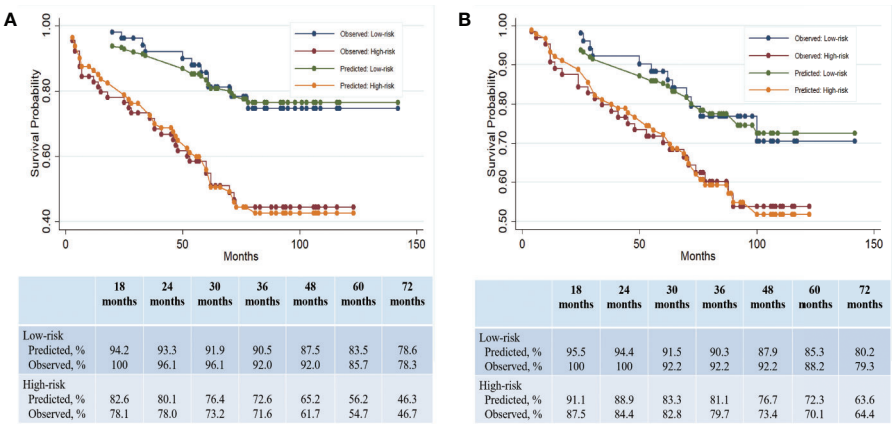


FIGURE 2 | Clinical stratification of PFS and OS on the basis of a constructed prognostic score. **(A)** PFS in the low- and high-risk subgroups defined by a cutoff of 1.5; the cutoff score was the median score in the whole cohort. **(B)** OS in the low- and high-risk subgroups.



	18 months	24 months	30 months	36 months	48 months	60 months	72 months
Low-risk							
Predicted, %	94.2	93.3	91.9	90.5	87.5	83.5	78.6
Observed, %	100	96.1	96.1	92.0	92.0	85.7	78.3
High-risk							
Predicted, %	82.6	80.1	76.4	72.6	65.2	56.2	46.3
Observed, %	78.1	78.0	73.2	71.6	61.7	54.7	46.7

	18 months	24 months	30 months	36 months	48 months	60 months	72 months
Low-risk							
Predicted, %	95.5	94.4	91.5	90.3	87.9	85.3	80.2
Observed, %	100	100	92.2	92.2	92.2	88.2	79.3
High-risk							
Predicted, %	91.1	88.9	83.3	81.1	76.7	72.3	63.6
Observed, %	87.5	84.4	82.8	79.7	73.4	70.1	64.4

FIGURE 3 | Clinical predication of PFS and OS on the basis of a constructed prognostic score. **(A)** Predicted and observed PFS rates in the low- and high-risk subgroups. **(B)** Predicted and observed OS rates in the low- and high-risk subgroups.

The OS difference between low- and high groups was significant (HR, 2.05; 95% CI, 1.03 to 4.06; P = 0.04). The Harrell's C index for this median cutoff point was 0.60 (95%CI, 0.52–0.67). The prognostic score was further evaluated for its calibration by plotting the predicted OS at the mentioned time points, which was also quite close to the observed survival probability at these time points (**Figure 3B**). These results confirmed the strong predictability of our prognostic score for both PFS and OS.

DISCUSSION

In patients with high grade meningioma after surgical resection, adjuvant radiotherapy is usually recommended to improve PFS and OS. Radiation has been shown to provide significant disease control and longer survival for high grade meningiomas that did not undergo radical resection (5, 8, 9, 24). Based on current reports, the 5-year recurrence free survival rate after adjuvant radiotherapy for grade II meningioma ranges from 48% to 68%, while in grade III meningioma, it drops to 8%–61%, which is quite consistent with our results (16, 17, 20, 25–28). Our series showed a 5-year recurrence free survival rate of 77.2% for atypical and 54.0% for anaplastic meningioma. Although adjuvant radiotherapy is generally thought to be effective for patients with high grade meningioma, grade I evidence is still lacking (29). In addition, a significant proportional of patients do not gain outcomes benefits from adjuvant radiation. Thus, a reliable method of identifying individuals who are more likely to benefit from adjuvant radiotherapy should help select patients with high grade meningioma appropriate for post-operative radiation therapy and avoid overtreatment in unfavorable patients. In our study, patients with the most representative two subtypes of high grade meningioma (atypical and anaplastic) were enrolled for survival analysis. We present a new

prognosis scoring system that is based on optimized selection of conventional clinical parameters and is valid in predicting both PFS and OS. Because of the typically long natural history of meningioma, tumor recurrence is clinically relevant, and PFS is the preferred primary clinical endpoint over OS.

In the present study, we evaluated a variety of clinical factors of high grade meningioma treated with adjuvant radiation therapy and identified those that are of prognostic significance. Prognostic factors reported to be predictive of worse survival in high grade meningioma include skull base location, higher tumor grade and less radical resection (4, 5, 7, 8, 30). Some studies reported that lower pre-operative KPS, higher Ki-67 labeling index, tumor recurrent status and estrogen receptor (ER) are also associated with poorer survival (9, 10). However, for patients who received adjuvant radiotherapy, studies about the prognostic factors are limited. Here, we identified that recurrent tumor, higher Ki-67 labeling index, Simpson resection grade, skull base location, preoperative KPS and higher histological grade were associated with worse recurrence free survival. However only tumor recurrent status (*de novo* vs. recurrent), Ki-67 labeling index (<5 vs. ≥5) and Simpson resection scale (GTR vs. STR) were with independent prognostic significance, thus were incorporated to calculate the weighted prognostic score. Ki-67 labeling index is a well-known proliferative indictor in tumors, which is reported to be associated with higher tumor grade and more malignant phenotypes. Our previous study of 87 patients with grade III meningioma also showed significant association of the Ki-67 index with PFS or OS (9). Abry E et al. reviewed a total of 53 publications and found that Ki-67 labeling index can be used as a useful predictor of tumor recurrence in high grade meningioma as well, which was in agreement with our analysis (31).

Since Simpson grade was first asserted in evaluating the extent of resection in 1957, subsequent studies consistently showed that more radical resection was associated with lower rate of recurrence and longer survival. In our previous study of grade III meningioma, more radical resection was associated with longer PFS (9). However, the role of Simpson resection grade in outcomes remains undetermined for patients who receive adjuvant radiotherapy. Recently, Kim D et al. reported that Simpson resection grade was not associated with recurrence risk in their analysis of 76 patients with high grade meningioma treated with adjuvant radiotherapy after surgical resection (10). In contrast, in our cohort, Simpson resection grade was associated with both PFS and OS and served as an independent prognostic factor for PFS. The difference between Kim et al. and us may be caused by factors such as neurosurgeon's estimate of the degree of resection and use of early postoperative MRI.

Consistent with with our study, several studies have underlined the longer survival in *de novo* high grade meningiomas compared to secondary or recurrent tumors (12, 32, 33). In our previous series of grade III meningioma, we have demonstrated that recurrent tumor, especially those with malignant transformation, tended to have worse outcome (9). Peyre et al. analyzed a series of 57 anaplastic meningioma and suggested different histo-molecular prognostic factors for *de novo* and recurrent tumors, including *TERT* mutation (34), which was further validated by that secondary meningioma had a higher proportion of *TERT* promoter mutation and is associated with significantly worse outcome (35, 36).

Our prognostic model divided the cohort into low-risk and high-risk groups, which had contrasting prognoses regarding both PFS and OS. Since all these three factors are obtained either immediately or days after surgical resection in routine clinical practice, our prognostic score enables clinical stratification and treatment recommendation (radiation vs. no radiation).

Limitations

Our study is a single institution, retrospective analysis. In order to gain a long-term follow-up result, only patients treated between 2003 and 2008 were enrolled, which limited the sample size. The significance of this study could be reinforced by analyzing a separate validation cohort.

Conclusions

To the best of our knowledge, this is the first prognostic model for risk stratification in patients with high grade meningioma who were treated with adjuvant radiotherapy. Our prognostic score is robust in predicting both PFS and OS of these individuals and therefore serves as a treatment decision making tool for both neurosurgeons and patients. Our work demonstrates that adjuvant radiation therapy can be a suitable approach for low risk groups but may not be appropriate for some high risk patients. Future work is warranted to adjust our model to improve prediction accuracy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from all patients involved in our study. This clinical study was approved by the Human Subjects Institutional Review Board at Huashan Hospital, Fudan University (KY-2017-09).

AUTHOR CONTRIBUTIONS

Study concepts: DW, SS, LH, and YG. Study design: DW. Data acquisition: DW, LH, HZ, JD, and SS. Quality control of data and algorithms: HC and HZ. Data analysis and interpretation: LH, DW, HW, and QX. Statistical analysis: LH, DW, and HW. Manuscript preparation: DW, SS, and LH. Manuscript editing: LH, HW, and QX. Manuscript review: HW, YG, and QX. All authors contributed to the article and approved the submitted version.

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REVIEW
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Review of Atypical and Anaplastic Meningiomas: Classification, Molecular Biology, and Management

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Although the majority of meningiomas are slow-growing and benign, atypical and anaplastic meningiomas behave aggressively with a penchant for recurrence. Standard of care includes surgical resection followed by adjuvant radiation in anaplastic and partially resected atypical meningiomas; however, the role of adjuvant radiation for incompletely resected atypical meningiomas remains debated. Despite maximum treatment, atypical, and anaplastic meningiomas have a strong proclivity for recurrence. Accumulating mutations over time, recurrent tumors behave more aggressively and often become refractory or no longer amenable to further surgical resection or radiation. Chemotherapy and other medical therapies are available as salvage treatment once standard options are exhausted; however, efficacy of these agents remains limited. This review discusses the risk factors, classification, and molecular biology of meningiomas as well as the current management strategies, novel therapeutic approaches, and future directions for managing atypical and anaplastic meningiomas.

Keywords: atypical meningioma, anaplastic meningioma, high grade meningiomas (HGMs), WHO grade II meningioma, WHO grade III meningioma

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INTRODUCTION

Harvey Cushing, in his 1922 publication, suggested the term *meningioma* to describe tumors arising from the pachymeningeal coverings of the brain and spinal cord, and he hypothesized these lesions arose from the arachnoid cap cells (1–3). Meningiomas are the most common primary intracranial tumors with an incidence of 2.3–8.3 in 100,000 (4–9). Although most meningiomas are benign (80%) and slow-growing, atypical (15–20%) and anaplastic (1–3%) meningiomas are more aggressive with a proclivity for recurrence, worse clinical outcomes, and higher disease-specific mortality (7, 10–13). Ideal management of higher grade meningiomas remains debated, specifically concerning use of adjuvant radiation in patients following complete resection of atypical meningiomas. Furthermore, recurrent meningiomas often become refractory to standard surgical and radiation therapies, which makes management challenging. Chemotherapy and other systemic medical therapies are reserved as salvage therapies in these patients; however, they have shown limited success with a few medical treatments demonstrating marginal clinical benefit. Accurate risk stratification and tumor classification are critical in identifying patients at risk for recurrence and tailoring subsequent management. Furthermore, advancements in understanding the pathophysiology and molecular genetics of meningiomas is critical for improving risk stratification, predicting prognosis and recurrence, and designing novel treatments for these patients (14–16). In this review, we will discuss the risk factors, classification, molecular biology, and current management strategies as well as novel therapeutic approaches and future directions for managing patients with atypical and anaplastic meningiomas.

RISK FACTORS

Age, male sex, and prior cranial ionizing radiation are risk factors for high grade meningiomas. The incidence of meningiomas increases with age, peaking around the 6th and 7th decades, but high grade meningiomas have a lower median age of diagnosis than benign meningiomas. Whereas benign meningiomas have a much higher incidence in females, atypical and anaplastic meningiomas occur almost twice as often in males (17, 18). Approximately 70–80% of meningiomas express progesterone receptors, and to a lesser extent, estrogen receptors, which corroborates the theory of a hormonal component to growth and provides an explanation for the higher incidence in females. High levels of progesterone receptors are associated with favorable prognosis, whereas meningiomas with loss or absence of progesterone receptors tend to be more aggressive with increased rates of recurrence (9, 19–22).

Meningiomas are very rare in children, but those with a history of cranial ionizing radiation are reported to have a 6–10 times increased relative risk of developing a meningioma with an elevated risk of atypical or anaplastic features (23). The strongest increase in incidence of meningioma occurrence has been identified after craniospinal radiation for the treatment of childhood acute lymphoblastic leukemia (ALL) and in individuals who received low dose radiation for the treatment of cranial tinea capitis (24). In atomic bomb survivors a significant dose related increase in intracranial tumors, including meningiomas (25). The association of ionizing radiation to meningioma development has been clearly established in individuals who received low dose radiation to the head for the treatment of tinea capitis (26). Cranial radiation on the order of 1–2 Gy significantly increased the risk of meningioma and glioma with the highest relative risk of development of nerve sheath tumors. One common theme among all the reports of secondary meningiomas is that the tumor typically occurred several decades after the radiation exposure.

Atypical and anaplastic meningiomas occur more frequently over the cerebral convexities than at the skull base. Additionally, when these high grade meningiomas occur at the skull base, they have lower recurrence rates and better overall prognosis than similar tumors found over the convexities (27, 28).

There are several inherited genetic syndromes that predispose patients to developing a meningioma. Neurofibromatosis 2 (NF2) is the most common and well-known. The neurofibromin 2 gene, also known as merlin, is located on chromosome 22q, and deletion or any other mutation at this site is associated with meningioma development (29). Other syndromes associated with meningiomas include multiple endocrine neoplasia (MEN) type 1 and von Hippel-Lindau (30).

CLASSIFICATION

The WHO grading system classifies meningiomas into grade I (benign), grade II (atypical), and grade III (anaplastic) based on histopathological features associated with tumor aggressiveness and tendency for recurrence (10, 11). The 1993 WHO classification was the first effort of the WHO to organize meningiomas by tumor grade, but there was criticism over this edition due to vague criteria, which led to high interobserver variability in reporting tumor grade. Since the 2000 edition, the WHO classification system has remained largely unchanged with the exception of brain invasion, as these newer editions have more objective criteria with less variation in classifying tumors among physicians. In the 2000 WHO classification, brain invasion was not a criterion for grade II or grade III meningiomas; however, later studies have shown brain invasion to be associated with aggressive behavior and increased risk of recurrence. The 2007 WHO classification was therefore revised to include brain invasion as an independent criterion for grade II (atypical) meningiomas (10). Since this change, the proportion of atypical meningiomas has increased from ∼7 to 15–20% (13, 31, 32). In the most recently published 2016 WHO classification, there were no further modifications to grading criteria (11). Criteria for grade II and grade III meningiomas across the different WHO editions are shown (**Table 1**).

Currently, Grade II (atypical) meningiomas are characterized by increased mitoses (4–19 mitotic figures per 10 high power microscope fields), brain invasion, or presence of three of the following five histologic features: hypercellularity, small cells with high nuclear to cellular ratio, prominent nucleoli, patternless sheet-like growth, and spontaneous or geographic foci of necrosis (**Figures 1A–E**). The clear cell and chordoid subtypes are also considered atypical (10, 11, 33). Grade III (anaplastic) meningiomas exhibit histologic features of overt malignancy, including high mitotic activity (20 or more mitotic figures per 10 high power microscope fields), frank anaplasia with focal, or diffuse loss of meningothelial differentiation, and their cytology often resembles carcinoma, sarcoma, or melanoma (**Figures 2A–E**). The rhabdoid and papillary subtypes are also classified as anaplastic (10, 11, 33). Metastases are not common with meningiomas, but they can occur.

The WHO classification is an important prognostic tool, but it has several limitations. First, despite revisions, the grading criteria remain somewhat vague, and studies have demonstrated inter-observer differences in applying these criteria. Additionally, the WHO grading system is based solely on histologic criteria, and unlike many other CNS tumors, objective molecular and genetic data is not used in classification of meningiomas. Furthermore, there is substantial within grade variation among tumors with studies reporting indolent behavior with no recurrence in up to 71 and 50% of atypical and anaplastic meningiomas, respectively (34–36). Thus, the WHO classification is inadequate for entirely predicting tumor aggressiveness, recurrence, and prognosis, and alternative methods are required for more adequate risk stratification (37).

In addition to the aforementioned WHO criteria, the mouse intestinal bacteria 1 (MIB-1) proliferation index is a histopathological biomarker that is associated with higher recurrence rates in meningiomas (38). A higher MIB-1 index is associated with worse prognosis with one study reporting MIB-1 indices of 1.9, 4.5, and 11.7% in benign, atypical, and anaplastic meningiomas, respectively (39–41). Studies have shown that the MIB-1 proliferation index is a more sensitive proliferation marker than mitotic rate. The MIB-proliferation index has been most commonly used as an adjunct to WHO criteria, and it

TABLE 1 | WHO classifications for Grade II and Grade III meningiomas by year.

Year of Classification	WHO Grade II	WHO Grade III
1993	Several of the following • Frequent mitoses • Hypercellularity • Small cells with high nuclear to cell ratio • Prominent nucleoli • Small cells with high nuclear to cell ratio	Histological features of frank malignancy far in excess of the abnormalities noted in atypical meningiomas
2000	Mitotic rate 4–19 per 10 HPF OR Three or more of the following • Hypercellularity • Small cells with high nuclear to cell ratio • Prominent nucleoli • Patternless sheet-like growth • Spontaneous or geographic foci of necrosis	High mitotic rate >20 per 10 HPF OR Frank anaplasia with loss of meningothelial differentiation, often resembling carcinoma, sarcoma, or melanoma
2007/2016	Mitotic rate 4–19 per 10 HPF OR Brain invasion OR Three or more of the following • Hypercellularity • Small cells with high nuclear to cell ratio • Prominent nucleoli • Patternless sheet-like growth • Spontaneous or geographic foci of necrosis OR Histologic subtypes: Clear cell and choroid	High mitotic rate >20 per 10 HPF OR Frank anaplasia with loss of meningothelial differentiation, often resembling carcinoma, sarcoma, or melanoma OR Histologic subtypes: Papillary and rhabdoid

**HPF: High-power field.*

is particularly useful in borderline cases for determining tumor grade and prognosis (42, 43).

MOLECULAR BIOLOGY

Advancements in understanding the pathophysiology and molecular biology of meningiomas is critical for improving risk stratification, predicting prognosis and recurrence, and designing novel treatments for these patients. As molecular analyses of meningiomas continue to evolve, several cytogenetic, genomic, epigenetic, and expression alterations associated with tumor aggressiveness and proclivity for recurrence have been identified as potential biomarkers to enhance diagnosis and risk stratification as well as serve as sites to target new therapies.

Cytogenetics and Genomics

Genomic instability is associated with tumor aggressiveness, and karyotype abnormalities are observed in progressively increasing frequency as a meningioma becomes more aggressive. Several cytogenetic abnormalities have been identified in meningiomas. As mentioned briefly above, the most common cytogenetic aberration observed in meningiomas is deletion or loss of genetic loci containing the neurofibromin 2 (NF2) gene on chromosome 22q. This alteration occurs in 40–60% of meningiomas. This gene encodes a tumor suppressor protein, merlin, involved in regulating activation of the mTOR pathway. Presence of this mutation is predictive of higher risk of recurrence. Meningiomas with NF2 mutations have a proclivity for the cerebral hemispheres (44).

Loss of genetic loci at chromosome 1p is the second most common aberration, and this is oftentimes seen in association with chromosome 22q mutations. Mutation of genetic loci within the Telomerase Reverse Transcriptase (TERT) promotor segment is observed in 6% of meningiomas, but this mutation occurs almost exclusively with concurrent chromosome 22q alterations, and the addition of a TERT promotor mutation is predictive of increased tumor aggressiveness and likelihood of recurrence. Other, less common, cytogenetic abnormalities associated with tumor aggressiveness and recurrence include loss at 6q, 9p, 10p, 10q, 14q, and 18q and gain at 17q and 20q (45–47).

Whereas these abnormalities are rare in benign meningiomas, they are observed frequently in atypical and anaplastic meningiomas (48, 49). Thus, accumulation of genetic aberrations increases progressively with higher tumor grade, and increasing frequency of cytogenetic alterations is associated with higher rates of recurrence and shorter progression free survival times (50, 51). Furthermore, evidence in ongoing research suggests that genetic profiles may vary by meningioma location (52).

Epigenetics

Through whole genome analysis, global DNA methylation profiling has demonstrated higher levels of methylation are associated with increased tumor aggressiveness and risk of recurrence. DNA methylation is an epigenetic change hypothesized to contribute to genomic instability by silencing genes involved with DNA repair and control of cell cycling. Evidence suggests methylation status may predict tumor behavior more accurately than the current WHO classification, and DNA methylation status has been proposed as an alternate classification system for meningiomas (16). However, DNA methylation profiling is costly, which may limit its utility.

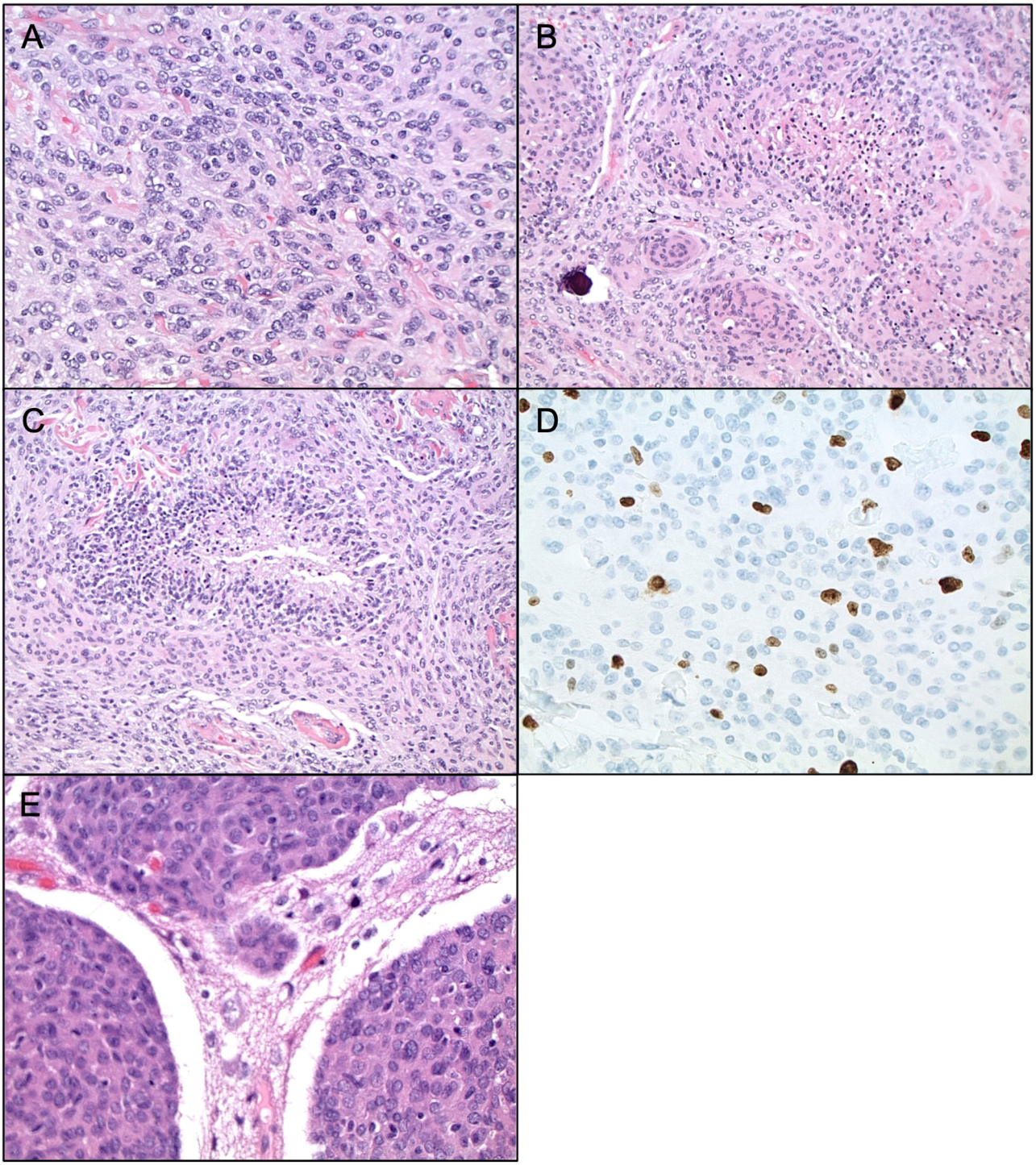


FIGURE 1 | Histopathology of Atypical Meningiomas. Atypical meningioma (WHO grade II). **(A)** H&E staining, ×400 magnification, demonstrating cell sheeting. **(B)** H&E staining, ×200 magnification, demonstrating whorls, and early focus of degeneration. **(C)** H&E staining, ×200 magnification, demonstrating necrosis. **(D)** Ki67 staining, ×400 magnification, demonstrating proliferation indices. **(E)** H&E staining, ×400 magnification, demonstrating brain invasion.

Recent studies have begun to investigate epigenetic modification on the level of histones with particular focus on H3K27 trimethylation (H3K27me3). Using immunohistochemistry, one study found that meningiomas absent of H3K27me3 staining were associated with significantly higher risk of progression. Furthermore, H3K27me3-negative

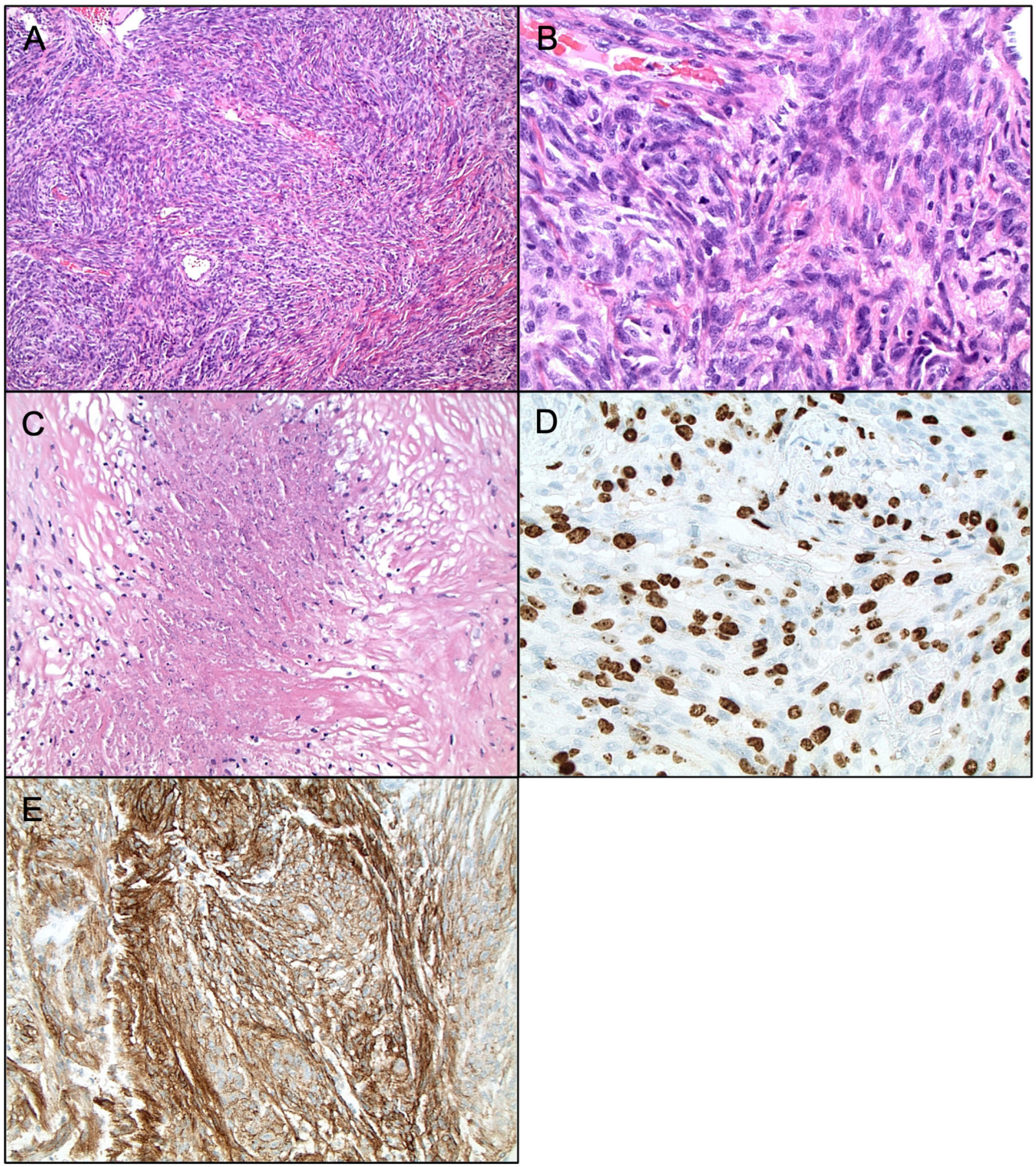


FIGURE 2 | Histopathology of Anaplastic Meningiomas. Anaplastic meningioma (WHO grade III). **(A)** H&E staining, ×200 magnification. **(B)** H&E staining, ×400 magnification, demonstrating mitoses >20 per high powerfield. **(C)** H&E staining, ×200 magnification, demonstrating frank necrosis. **(D)** Ki67 staining, ×400 magnification, demonstrating proliferation indices. **(E)** EMA staining, ×200 magnification.

meningiomas were associated with DNA methylation patterns observed in more aggressive meningiomas, and there was a proportionally higher percentage of NF2 mutations among H3K27me3-negative meningiomas. This study found that H3K27me3 may play a role in risk stratification, especially in meningiomas at the border of WHO I and II; however, it is less useful in grade III meningiomas (53).

Protein Expression

Alterations in protein expressions are seen in meningiomas. Several growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF), and their associated receptors are overexpressed in meningiomas, which stimulates tumor growth and progression in such tumors. Hormonal dysregulation occurs frequently in meningiomas. Absence of progesterone receptors is associated with increased tumor aggressiveness and recurrence, and overexpression of estrogen, somatostatin, and prolactin receptors are associated with increased proliferative activity of meningiomas (19, 54). Many of these growth factors and hormones are also overexpressed in other tumors and are the target of several new targeted therapies.

Another more recently discovered that inactivation of the breast cancer (BRCA)1-associated protein-1 tumor suppressor gene (BAP1) is found within a subgroup of rhabdoid meningiomas and may be assessed with immunohistochemistry. Loss of expression is associated with shorter time to recurrence and worse prognosis. Interestingly, a subgroup of patients with loss of expression of BAP1 have associated BRCA1 germline mutations, suggesting that patients with this mutation are also at increased risk of rhabdoid meningiomas (55).

Immunotherapy

Meningiomas and their associated microenvironment are associated with a local immune response, and analysis of immune cell infiltrate has revealed potential biomarkers and targets for immunotherapy (56). Following encouraging results in other tumors, immune checkpoint inhibitors are being explored for treatment of meningiomas (57). Under physiologic conditions, immune checkpoints modulate the immune response and prevent autoimmunity; however, meningiomas and other tumors also utilize these checkpoints to evade immune system detection and create an immunosuppressed microenvironment (57). Programmed-death 1 (PD-1) and its ligand, (PD-L1), function as part of the immune checkpoint pathway that regulates T cell lymphocytes, and its expression in meningiomas is correlated with higher tumor grade and aggressiveness (56, 58, 59). Currently, several trials of PD-1 and PD-L1 antibody-mediated inhibition in meningiomas are underway (57).

SURGICAL RESECTION

The primary treatment for atypical and anaplastic meningiomas is surgical resection. Small, asymptomatic meningiomas that are presumably benign may be monitored or treated with radiation, but these meningiomas are out of the scope of this paper. In 1957, Donald Simpson described this strong association between extent of recurrence (60). He classified extent of resection into five categories (**Table 2**). Generally, Simpson Grades I–III are considered gross total resection (GTR), and Simpson Grades IV–V constitute subtotal resection (13, 34, 61, 62). Recently, a sixth category, Grade 0, has been proposed in which there is complete tumor removal plus an additional 2–3cm from tumor insertion site with good results (63).

TABLE 2 | Simpson grading for extent of meningioma resection.

Simpson Grade	Description
Grade 0	Complete tumor removal, plus removal of an additional 2–3 cm from the tumor insertion site
Grade I	Complete tumor removal, including any dural attachments or abnormal bone
Grade II	Complete tumor removal with coagulation of dural attachment
Grade III	Complete tumor removal without resection or coagulation of its dural attachment
Grade IV	Partial tumor removal
Grade V	Biopsy only

Simpson grading remains the standard method for describing surgical resection, and it is determined by the neurosurgeon's assessment and, more recently, postoperative imaging. The extent of resection is the most important modifiable predictor of local control and progression free survival, independent of tumor grade and other prognostic factors (30, 60, 64). Thus, the goal of surgery, when feasible, is GTR; however, tumor location, involvement of nearby neurovascular structures, or brain invasion may limit the extent of resection, in which case maximum safe resection is appropriate.

Prognosis is strongly related to the histopathological grade and extent of resection. Recurrence is utilized to describe patients whose meningioma returns despite complete surgical resection. Although there is no consensus on definition, progression refers to growth of residual tumor in patients with incompletely resected tumors. Furthermore, progression is also applied for meningiomas that transform from a lower to a higher-grade tumor. Following complete resection, the 5-year recurrence rate is 29–58% for atypical and 72–94% for anaplastic meningiomas (12, 30, 64) The 5-year risk of progression for incompletely resected meningiomas is as high as 83–100% (30, 65) Specifically, the 5-year survival rates are 78–91% and 41–65% for atypical and anaplastic meningiomas, respectively, and the 10-years survival rates decrease to 53% in atypical and 0% in anaplastic (34, 61, 65–67).

Multiple factors, including neurosurgeon preference, tumor size and location, extent of dural attachment, and relationship to surrounding neurovascular structures influence surgical approach. Ideally, the approach is wide enough to expose enough of the meningioma, its dural attachment, and surrounding structures to allow disruption of blood supply while simultaneously minimizing brain retraction and manipulation of critical structures to reduce procedure-related morbidity (68).

Over the past several decades, considerable advancements in surgical technologies, including the operating microscope, improved neuroimaging, image-guided neuronavigation systems, intraoperative neurophysiological monitoring, ultrasonic aspiration devise, and endovascular embolization techniques, have revolutionized modern neurosurgery improving the safety of surgery (69, 70). Introduced in the 1970s, the modern operating microscope and refinement of microsurgical

technique significantly enhanced the neurosurgeons ability to carefully dissect meningiomas (71, 72). Furthermore, in the late 1980s, new technology with spatially accurate neuroimaging, computer-assisted imaging systems, and three dimensional digitizers allowed integration in image space with operative space and led to development of more modern, frameless stereotactic image-guided navigation (69). Typically, unless contraindicated, contrast-enhanced CT or MRI imaging is used, but these images can be fused with additional studies, such as PET or functional MRI, to improve visualization of structures of interest (73). With contemporary neuronavigation systems, neurosurgeons are able to preoperatively plan surgeries and explore alternate approaches. Furthermore, using multiplanar imaging, neuronavigation provides real-time intraoperative guidance and data regarding the location and orientation of surgical instruments in relation to nearby structures (69, 70, 74).

Ultrasonic aspiration devices are another valuable tool for resecting meningiomas, especially larger ones. These devices are used to internally debulk meningiomas, which helps avoid damage to adjacent brain and other neurovascular structures during tumor dissection. Furthermore, through tissue selection, the ultrasonic transducer spares vital surrounding neurovascular structures (75–77).

Moreover, as endovascular techniques advance, preoperative embolization has been increasingly used to facilitate meningioma resection and decrease intraoperative blood loss, especially in select patients with giant convexity meningiomas or petroclival meningiomas in which the feeding arteries may be less accessible during surgery. A systematic review of preoperative embolization for meningiomas by Shah et al. (78), reported that liquid embolic agents were preferable to particle agents as liquid agents demonstrated deeper penetration into the tumor vessels and had a smaller risk of hemorrhage.

In addition to enhanced safety, these innovations improve tumor access, debulking, and extent of resection, especially in meningiomas that were once considered unresectable or partially resectable (52). Furthermore, these technologies are associated with decreased blood loss, reduced operative times, fewer complications, and, accordingly, shorter ICU and overall hospital length of stays (73, 74, 79, 80). Moreover, many neurosurgeons report an enhanced appreciation of anatomy and increased perception of safety (74, 80). Most importantly, however, technology does not replace the neurosurgeon's knowledge and skills, and it is critical for neurosurgeons to be aware of limitations and potential for error, especially regarding neuronavigation systems.

RADIATION

Radiation is an effective and generally well-tolerated treatment for meningiomas. Based on evidence in the literature, adjuvant radiation is usually recommended for atypical meningiomas following incomplete resection, for anaplastic meningiomas regardless of the extent of resection, and for recurrent meningiomas (81–86). However, in patients with completely resected atypical meningiomas, the role of adjuvant radiosurgery remains undefined, and there remains considerable debate regarding optimal management of these patients with treatment decisions varying based upon physician preference (5, 31, 34, 64, 85, 87–89). Advocates argue that adjuvant radiation reduces the risk of recurrence, increases time to recurrence and tumor burden in those who develop recurrence, and improves disease-specific survival (34, 61, 64, 84, 85, 88–92). Opponents, however, argue that adjuvant radiation does not reduce risk of recurrence, and the costs and potential harm associated with possibly unnecessary radiation outweighs any benefits (32, 64, 65, 81, 93).

Regarding the literature, there is a paucity of high-quality evidence regarding adjuvant radiation for patients with completely resected atypical meningiomas. The majority of studies are small retrospective with low power and inconsistent results. Although several of these studies reported lower recurrence rates with adjuvant radiation, many were unable to demonstrate statistical significance (31, 34, 64, 85, 89). Other studies, however, showed no difference in recurrence rates with adjuvant radiation vs. actively monitoring (17, 31, 62, 81, 94). Few studies report long term follow up of 10 years of more, but some evidence suggests the benefits of adjuvant radiation may be more significant in the long term as median recurrence rates for atypical meningiomas are longer than anaplastic meningiomas (95, 96). The main findings regarding efficacy of post-surgery adjuvant radiation were summarized in **Table 3**.

Although the specifics vary depending on organ system and some of the criteria are somewhat vague, radiation-induced toxicities are generally graded from 1 to 5: grade I is mild symptoms, grade II is moderate symptoms, grade 3 is severe symptoms, grade 4 is life-threating symptoms, and grade 5 is death from radiation-induced symptoms. These grades are referenced to describe outcomes in some of the below studies.

A meta-analysis of 14 retrospective studies by Hasan et al. (84) comparing GTR alone vs. GTR plus adjuvant radiotherapy (RT) in patients with atypical meningioma reported significantly higher 5 year recurrence rates in those receiving GTR alone compared with those also receiving radiation therapy (33 vs. 15%; $p = 0.005$). Of the patients who experienced recurrence, recurrence occurred an average of 8 months later in those treated with radiation (39.5 vs. 31.5 months; $p = 0.014$). In the five studies reporting survival rates, there were similar 5-year overall survival rates in those with GTR vs. GTR plus RT (89.7 vs. 89.4%; $p = 0.95$). Radiation-induced toxicities occurred in <10% of patients with severe toxicities reported in <10%, which included radiation necrosis, visual impairment, and cognitive dysfunction. No life-threatening radiation-induced toxicities were reported. Results support that the benefits of adjuvant radiation may outweigh the risks; however, the authors caution that due to the small number of retrospective studies available for their meta-analysis, no clear recommendations can be made (84).

Another meta-analysis by Graffeo et al. (64) with seven studies plus data from the author's institution comparing GTR alone vs. GTR plus RT in patients with atypical meningioma found a trend toward lower 5 year recurrence rates in patients treated with radiation; however, this did not reach statistical significance (12 vs. 19%; $p = 0.2$). Additionally, in the five studies with survival data, there was a trend toward improved

TABLE 3 | Summary of the main studies regarding efficacy of adjunctive radiotherapy in atypical (Grade II) meningiomas.

Author	Study type	WHO	Patients number	ART Regimen	Outcome of ART vs no ART
Mair et al. (31)	Retrospective	2000	114 patients ($n = 84$ no ART; $n = 30$ ART)	Average dose of 51.8 Gy in 28 fractions over 6 weeks	ART did not reduce overall tumor recurrence following first-time surgery. Significant benefit was evident if excluded the patients who had undergone postoperative stereotactic radiosurgery for a tumor remnant (and no radiotherapy) from analysis.
Aghi et al. (34)	Retrospective	2004	108 ($n = 70$ no ART; $n = 38$ ART, of which 8 received ART after initial GTR; 30 with recurrent tumor)	8 patients after CRT, received fractionated stereotactic radiotherapy at an average dose of 60.2 Gy in 1.5–1.8-Gy fractions. In 30 patients with recurrent tumors, 14 received fractionated stereotactic radiotherapy at mean dose of 55 Gy and 16 received single-fraction stereotactic radiosurgery at mean marginal dose of 18.0 Gy	None of these 8 patients experienced tumor recurrence, but there was no statistical difference in recurrence between irradiated and nonirradiated patient. Most recurrences occurred within 5 years after resection. One-third of patients with recurrence died of their disease despite irradiation or chemotherapy at the time of recurrence.
Graffeo et al. (64)	Retrospective with meta-analysis with additional 9 retrospective studies	2016	69 patients ($n = 61$ no ART; $n = 8$ ART)	A median dose of 5,400 cGy over median 30 fractions	Overall recurrence at time of last follow-up was 25% after observation and 38% after RT, with median times to recurrence of 176 and 101 months, respectively. At 5 years, PFS was 79% after observation and 88% after RT; however, OS was 89% after observation and 83% after RT. Thus, preemptive ART has no significant advantage on either recurrence or survival.
Hasan et al. (84)	Meta-analysis. Including 14 retrospective studies	Not specified	757 patients ($n = 549$ no ART; $n = 208$ ART)	A median dose of 54 Gy	The crude recurrence rate was twice as high in GTR than GTR with ART (33.7 vs. 15%, $P = 0.005$). The 1-year local control rate was 90% for GTR and 97% for GTR with A RT (OR = 3.36, $P = 0.11$). The median 5-year local control rate was 62% for GTR and 73% for GTR with ART, respectively (OR = 1.71, $P = 0.06$). The 5-year overall survival for each group was 90%, which was not were not significantly different (OR = 0.97, $P = 0.95$). Radiation-related toxicity was <10%, at a median follow-up of 42 months.
Park et al. (85)	Retrospective	2000/ 2007	83 patients ($n = 56$ no ART, $n = 27$ ART)	A median dose of 61.2 Gy over 7 weeks with photon	ART led to lower local tumor progression.

(Continued)

TABLE 3 | Continued

Author	Study type	WHO	Patients number	ART Regimen	Outcome of ART vs no ART
Komotar et al. (89)	Retrospective	Not specified	45 patients ($n = 32$ no ART; $n = 13$ ART)	A median dose of 59.4 Gy in daily fractions of 180 or 200 cGy and completed over a median of 6 weeks	There were no recurrences in 12 (92.3%) of 13 ART patients. No other factors were significantly associated with recurrence in univariate or multivariate analyses.
Stessin et al. (94)	Retrospective	2000	657 patients ($n = 413$ no ART; $n = 244$ ART)	Not specified	Patients with Grade III disease were 41.9% more likely to receive ART than that of Grade II meningioma, 36.7% more likely to receive it after subtotal resection (95% CI 0.58–3.26). Controlling for grade, extent of resection, size and anatomical location of the tumor, year of diagnosis, race, age, and sex, ART did not have a survival benefit (HR 1.492; 95% CI 0.827–2.692)
Jo et al. (96)	Retrospective	2000	35 patients ($n = 13$ no ART; $n = 21$ ART)	Not specified	The median interval to recurrence was 17 months (range = 5–46 months) for the patients who underwent surgery alone, and 39 months (range = 13–97 months) for the patients in ART group. ART following initial incomplete surgical resection was crucial for long-term management.
Jenkinson et al. (97)	Prospective	2000	190 patients will be enrolled (comparing no ART vs. ART)	60 Gy in 30 fractions over 6 weeks.	Results not reported yet

ART, Adjunctive Radiotherapy; GTR, Gross total resection.

overall survival in patients treated with radiation; however, this also did not reach statistical significance (96 vs. 87%; $p = 0.4$). Radiation-induced toxicities occurred in <10% of patients, and they reported only 1 life-threatening toxicity (85). Similar to Hasan et al., the results support that benefits of adjuvant radiation may outweigh risk, but due to the small number of retrospective studies available for analysis, these authors also reported that no definitive recommendations can be made.

A recent phase II trial (RTOG 0539), investigated outcomes of recurrent grade I and completely resected grade II meningiomas treated with adjuvant RT using a standard dose of 54 Gy. They observed at 93.8% PFS at 3 years, which was significantly higher than historical controls ($p = 0.003$). They also described a 4.1% recurrence rate and 96% overall survival rate at 3 years with low rates of radiation-induced toxicities (97). Another phase II trial (EORTC 22042–26042), evaluated atypical meningiomas following complete resection treated with adjuvant radiotherapy using a high-dose of 60 Gy. They reported a 90% PFS at 3 years and a 96.4% survival rate over the same time period (98). These phase II studies are the first prospective studies to report a benefit to RT for atypical meningiomas following complete resection.

Currently, there is an international, multicenter, randomized control phase III randomized control trial (ROAM-EORTC 1308) comparing adjuvant RT with active monitoring in patients with atypical meningioma follow gross total resection. Patients randomized to the radiosurgery arm will receive 60 Gy in 30 fractions over 6 weeks. This will be the first randomized control trial comparing these two management approaches for patients with atypical meningiomas. Hopefully, the results of this study will clarify the controversy regarding adjuvant radiotherapy in these patients and guide clinical decision making (97).

Additionally, the optimal radiation dose also remains undefined. Historically, radiation doses ranging from 50 to 60 Gy administered in 1.8–2.0 Gy fractions to the tumor bed and any residual tumor with a margin ranging from 0.5 to 2.0 cm (64, 84). Atypical meningiomas are usually treated with a median of 54 Gy and anaplastic meningioma treated with high doses with a median of 60 Gy (99). Although doses from 50 to 70 Gy have been used, there is evidence from several retrospective studies suggesting that higher doses may improve patient outcomes (34, 65, 88, 93, 100, 101). Recurrent meningiomas may even be treated with higher doses at ranges of 65–70 Gy (13).

Due to advancements in radiation technique, several new options have emerged for delivery of radiation to meningioma. In addition to conventional fractionated photon radiotherapy, these modalities include stereotactic radiosurgery (SRS), fractionated stereotactic conformal radiotherapy (FSRS), intensity modulated photon radiation therapy (IMRT), and particle therapies with protons or carbon ions. These methods and the evidence for their use in treating meningiomas are described below (**Table 4**).

Stereotactic Radiosurgery (SRS) and Fractionated Stereotactic Radiosurgery (FSRS)

SRS delivers a single high dose of precisely targeted radiation. It has been increasingly utilized over time due to its high rates of local tumor control, improved dose conformity with better dose conformity and sparing surrounding normal tissue from extraneous radiation, and convenience of being delivered in a single fraction (102–105). It is generally used in atypical and anaplastic meningiomas with residual or recurrent disease. Treatment doses typically range from 12 to 20 Gy (67, 81, 90, 91, 106–108). However, one study of SRS for recurrent atypical and anaplastic meningiomas reported worse tumor control with doses <20 vs. 20 Gy with PFS at 5 years of 29 and 63%, respectively (106). In addition to lower radiation dose, other factors associated with increased recurrence and overall worse outcomes following SRS are larger tumor volumes and suboptimal coverage (67, 81, 90, 91, 106–108).

However, several retrospective studies have described SRS to be associated with high rates of symptomatic perilesional edema ranging from 2.5 to 50%. Risk factors associated with developing perilesional edema include prior radiation treatment, larger tumor volume, higher tumor grade, and parasagittal location (103–105). Thus, due to this risk of edema, there has been more interest in treating meningiomas with FSRS instead.

FSRT delivers several fractions of higher radiation doses while maintaining stereotactic precision. Several retrospective studies of FSRS have described delivery of radiation doses of 15–35 Gy over 3–6 fractions in meningiomas with similar local tumor control and slightly lower rates of perilesional edema ranging from 2.7 to 26% compared with SRS (103, 105, 109–112). One study reported that rates of perilesional edema rose as radiation dose per fraction increased with rates of 2.7, 8.8, and 11.9% with fractions of 6 Gy or less, 7–14 Gy, and 15 Gy or higher, respectively (105). However, most authors agree that larger, prospective trials should be conducted to better evaluate this modality.

Intensity-Modulated Photon Radiotherapy (IMRT)

IMRT is an advanced form of radiotherapy that delivers a conformal isodose of photons to the target. Computer controlled linear accelerators allows radiation dose to more precisely conform to the three-dimensional volume of the tumor by modulating the intensity of the radiation beam delivered to the tumor. Furthermore, this precise delivery allows IMRT to use higher radiation doses targeted to the tumor while minimizing radiation exposure to the surrounding normal brain structures.

A phase II trial of IMRT administered radiation doses ranging from 54 to 60 Gy in 30 fractions for treatment of incompletely resected atypical meningiomas, anaplastic meningiomas regardless of extent of resection, and recurrent meningiomas. The authors reported an overall 3-year PFS of 59% and overall survival of 79%. With the exception of one grade 5 radiation-induced toxicity of necrosis, the other acute and late toxicities were limited to grade 1–3. The authors concluded that overall IMRT was safe and effective in atypical, anaplastic, and recurrent meningiomas, and this therapy deserves further study in these patients (113).

TABLE 4 | Summary of radiation treatments types.

	RT	SRS	SRT	IMRT	PBT	CIRT
Radiation type	Photon	Photon	Photon	Photon	Proton beam	Ion beam
Total Dose	50–70 Gy	12–20 Gy	15–35 Gy	54–60 Gy	45–66 Gye	30–48 Gy
Fractions	∼30	1	3–6	∼30	15–30	10–16
Dose/fraction	1.8–2 Gy	12–20 Gy	Variable; over 3–6 fractions	1.8–2.0 Gy	1.8–3 Gye	∼3 Gye
Pros	Well-studied; accessibility	Stereotactic precision; Single treatment	Stereotactic precision; higher doses than SRS	Precise targeting; conformal dose	Lower toxicity; better dose distribution	Lower toxicity; better dose distribution
Cons	Higher toxicity	Higher risk of edema	Needs further study	Needs further study	Higher cost; accessibility	Higher cost, accessibility
Indications	Primary;** residual; recurrent	Residual; recurrent	Residual; recurrent	Primary;** residual; recurrent	Primary;** residual; recurrent	Primary;** residual; recurrent

CIRT, Carbon ion radiotherapy; PBT, Proton beam therapy; IMRT, Intensity modulated photon therapy; RT, Radiotherapy; SRS, Stereotactic radiosurgery; SRT, Stereotactic radiotherapy.
***Primary refers to primary tumor following surgical resection.*

Particle Radiation Therapies

Unlike conventional photon radiation, particle therapy uses protons or carbon ions to deliver radiation. Compared with photons, protons and carbon ions are more homogeneous and have better dose conformity, allowing more precise delivery of higher radiation doses to tumor cells while limiting radiation to surrounding healthy brain structures. Several studies have reported less radiation-induced toxicity with particle therapy than with photon radiation. Most studies describe predominantly skin irritation and alopecia with minimal to no acute or late severe toxicity (114–118). Re-irradiation with photons is challenging due to the surrounding healthy tissue's limited tolerance to more radiation; however, particle therapy has been described as safe and effective for re-irradiation in recurrent or progressive meningiomas (114). Disadvantages to both proton and carbon ion therapies are limited availability and higher cost than photon radiation therapies. Several studies have been conducted to explore whether the benefits of these therapies outweigh the increased expense of these therapies, but results have been variable (114, 119).

A study comparing proton beam therapy (PBT) alone (56 GyE in 1.8–2 GyE daily fractions), IMRT (50 in 2 Gy daily fractions) with carbon ion radiotherapy (CIRT) boost (18 with 3 Gy daily fractions), IMRT (median 56 in 1.8–2 Gy daily fractions), and fractionated SRT (56 in 1.8–2 Gy daily fractions) found tumor shrinkage and local control at 1 and 2 years follow up was independent of radiation modality. Instead, tumor grade and extent of resection appeared to be the determining factors of tumor shrinkage and local control (115).

Another study comparing PBT with IMRT for atypical, anaplastic, and recurrent meningiomas reported similar dose conformity to the tumor volume but observed significantly less extraneous radiation exposure to surrounding structures with PBT. Thus, higher radiation doses were prescribed for PBT (66 in 2.2 Gy fractions) than for IMRT (54 in 1.8 Gy fractions) with fewer radiation induced tumors. Thus, the authors reported that higher radiation doses allowable with PBT may improve local tumor control and reduce radiation-induced toxicities (120).

In a recent systematic review of ion therapies in atypical and anaplastic meningiomas, PBT and CIRT demonstrated higher rates of PFS compared with conventional photon radiation. Comparing ion therapies, PBT had superior PFS compared with CIRT (121). However, another study reported that CIRT has better dose conformity to tumor volume with reduced extraneous radiation exposure to surrounding brain structures than both PBT and IMRT (117). In a phase I/II trial of CIRT (18 Gy) boost with either FSRT or IMRT (54 Gy) for atypical and anaplastic meningiomas, addition of CIRT appeared to be well tolerated and potentially beneficial to these patients. The authors conclude, however, that a larger prospective trial is needed to corroborate these findings (116).

CHEMOTHERAPY AND OTHER MEDICAL THERAPIES

Chemotherapy and other systemic therapies have demonstrated limited clinical efficacy in treating meningiomas (122). Although marginal, interferon-alpha, somatostatin receptor antagonists, and VEGF receptor inhibitors are the only FDA-approved agents providing any benefit to these patients. Currently, these options are used for salvage therapy for meningiomas recurrence or progression following surgery and radiation that have become refractory or no longer amenable to these standard treatment options.

Several chemotherapeutic agents have been studied for meningioma with minimal clinical efficacy. Hydroxyurea has been studied in many other cancers, and it is one of the most studied chemotherapeutic agents in meningioma. In preclinical trials, hydroxyurea reduced meningioma growth (123, 124), however, it has failed to provide similar results in clinical trials and other human studies (125–127). Other chemotherapeutic agents, including temozolomide, irinotecan, and combination

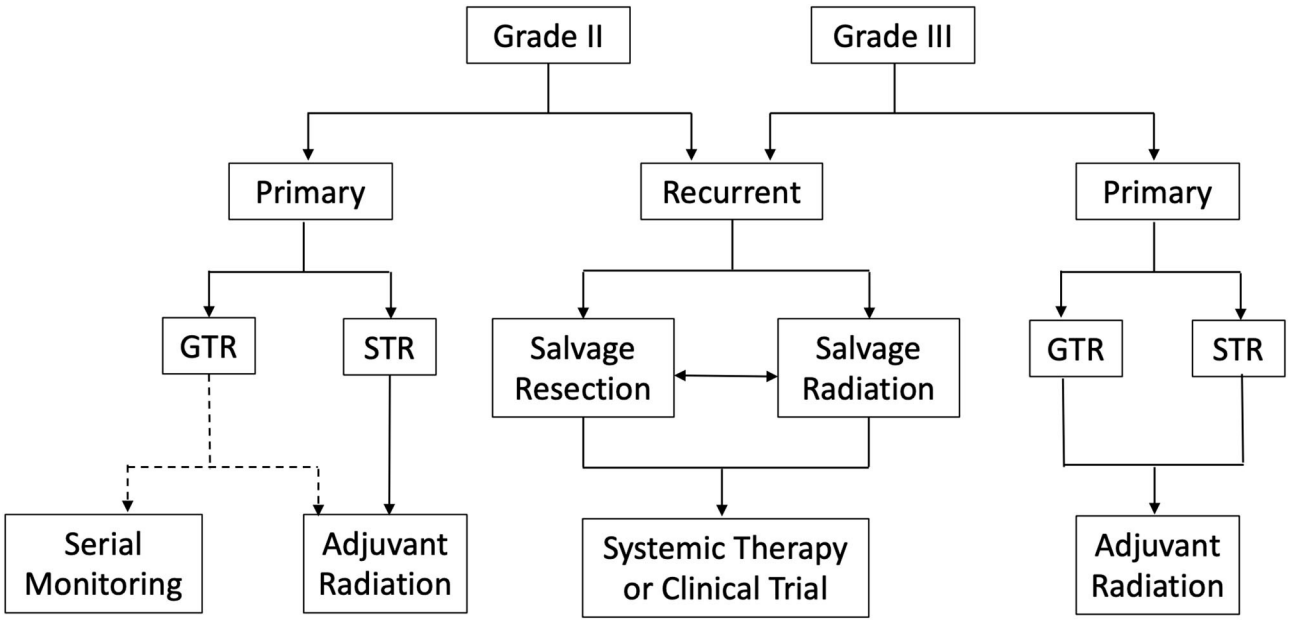


FIGURE 3 | Summary of management strategies for atypical and anaplastic meningiomas. *GTR, Gross total resection; STR, Subtotal resection; Dotted line represents lack of consensus regarding serial monitoring vs. adjuvant radiation following complete resection of WHO grade II meningioma.

therapy with cyclophosphamide, Adriamycin, and vincristine, have not shown benefit in treating meningiomas (128–130).

Interferon-alpha is an immunomodulating agent demonstrating slight therapeutic benefit in recurrent meningiomas not amenable to resection. Several studies demonstrated stabilization of tumor growth, and a phase II study of recurrent meningiomas reported a slight improvement in PFS at 12 weeks without improvement in overall survival rates (131–133).

As mentioned above, overexpression of somatostatin receptors is associated with more aggressive tumors and higher recurrence rates. Thus, several somatostatin receptor inhibitors have been studied in recurrent meningiomas with questionable therapeutic effects. In one study using a long-acting inhibitor sandostatin, the authors observed a slight improvement in PFS and overall survival at 6 months (134), but other phase II clinical trials using sandostatin, octreotide, or other somatostatin receptor inhibitors have demonstrated minimal efficacy and not reported similar results (135, 136). Other hormone receptor inhibitors, including antiestrogen and antiprogesterone agents, have not demonstrated clinical benefits (137–142).

Similar to other neoplasms, meningiomas often overexpress VEGF, PDGF, EGF, and other growth factor receptors. Overexpression is hypothesized to promote tumor growth. Thus, a variety of therapies using monoclonal antibodies or small molecule kinase inhibitors targeting one or more of these receptors have been studied in recurrent meningiomas. Unfortunately, studies using these targeted therapies alone or in combination have demonstrated limited or no success in treatment of meningioma (143–149).

Several studies using bevacizumab, a monoclonal antibody against the VEGF receptor, have reported mild improvement in PFS in patients with recurrent meningiomas (150–152). Despite slight benefit, the overall clinical efficacy remains poor with one systematic review of bevacizumab in recurrent meningioma reporting median PFS of 15.3 months in recurrent atypical and 3.7 months in anaplastic meningiomas (150). A phase II trial of bevacizumab plus everolimus (an mTOR inhibitor) reported PFS similar to prior studies of bevacizumab alone (148).

Sunitinib is a small molecule kinase inhibitor that targets both VEGF receptor and PDGF receptor. In phase II clinical trials of sunitinib for recurrent and progressive atypical and anaplastic meningiomas, there was a PFS of 42% at 6 months, which was an improvement from reported natural history PFS of 5–30% at 6 months. Toxicity, however, was a concern with 60% of patients experiencing a severe or life-threatening event. The authors recommend that sunitinib warrants further investigation with a larger, randomized trial to better characterize the efficacy of sunitinib in this population of patients (143).

Erlotinib and gefitinib are both small molecule kinase inhibitors of EGF receptor that have been studied in phase II trials for recurrent meningioma. Although these therapies were well tolerated, they did not improve PFS or overall survival of these patients (144). Similarly, in a phase II trial of imatinib, a small molecule kinase inhibitor of PDGF receptor, in recurrent meningioma, the therapy was well tolerated, but did not prolong PFS in these patients (149).

DISCUSSION

Atypical and anaplastic meningiomas remain challenging to treat. Currently, the standard of care is maximum safe resection followed by adjuvant radiation for grade III and incompletely resected grade II meningiomas. However, controversy surrounds

the role of adjuvant radiation for completely resected grade II meningiomas (**Figure 3**). Advocates argue adjuvant radiation reduces recurrence and lengthens progression free survival in those who recur; conversely, opponents contend adjuvant radiation does not reduce recurrence and introduces further costs and potential harm from possibly unnecessary radiation. Moreover, the literature offers inconsistent and ultimately inconclusive data. However, as mentioned above, ROAM-EORTC 1308 is a phase III randomized clinical trial investigating adjuvant RT vs. active monitoring in patients with atypical meningioma following gross total resection. Hopefully, the results of this study will clarify this controversy and provide insight into clinical decision making (97).

Despite maximum treatment, atypical and anaplastic meningiomas have a strong proclivity for recurrence. Accumulating mutations over time, recurrent tumors behave more aggressively and often become refractory or no longer amenable to further surgical resection or radiation. Chemotherapy and other medical therapies are available as salvage treatment once standard options are exhausted; however, efficacy of these agents remains limited. Furthermore, accurate risk stratification remains an obstacle. Across all grades, meningiomas exhibit a spectrum of aggressive behavior only partially predicted by histological criteria alone. Clinically, this translates into difficulty predicting prognosis and determining the optimal management approach.

Despite these challenges, however, advances in oncologic research and technology provide hope by uncovering new and informative genetic mutations, aberrant signaling pathways, and protein biomarkers associated with tumor behavior and recurrence risk. Understanding the pathophysiology and molecular biology of meningiomas is critical in more adequately predicting prognosis, discovering novel therapeutic approaches, and tailoring treatment to individual patients and the biology of their meningiomas.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prognostic Significance of Preoperative Neutrophil-to-Lymphocyte Ratio in Patients With Meningiomas

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Background: Meningiomas are the most common benign intracranial tumors. However, even WHO grade I meningiomas occasionally show local tumor recurrence. Prognostic factors for meningiomas have not been fully established. Neutrophil-to-lymphocyte ratio (NLR) has been reported as a prognostic factor for several solid tumors. The prognostic value of NLR in meningiomas has been analyzed in few studies.

Materials and Methods: This retrospective study included 160 patients who underwent surgery for meningiomas between October 2010 and September 2017. We analyzed the associations between patients' clinical data (sex, age, primary/recurrent, WHO grade, extent of removal, tumor location, peritumoral brain edema, and preoperative laboratory data) and clinical outcomes, including recurrence and progression-free survival (PFS).

Results: Forty-four meningiomas recurred within the follow-up period of 3.8 years. WHO grade II, III, subtotal removal, history of recurrence, Ki-67 labeling index ≥3.0, and preoperative NLR value ≥2.6 were significantly associated with shorter PFS ($P < 0.001$, < 0.001, 0.002, < 0.001, and 0.015, respectively). Furthermore, NLR ≥ 2.6 was also significantly associated with shorter PFS in a subgroup analysis of WHO grade I meningiomas ($P = 0.003$). In univariate and multivariate analyses, NLR ≥2.6 remained as a significant predictive factor for shorter PFS in patients with meningioma ($P = 0.014$).

Conclusions: NLR may be a cost-effective and novel preoperatively usable biomarker in patients with meningiomas.

Keywords: meningioma, neutrophil-to-lymphocyte ratio, World Health Organization grade I, recurrence, progression-free survival

INTRODUCTION

Meningioma is the most common primary brain tumor, accounting for 37.6% of all brain tumors (1). Approximately 80% of meningiomas are classified as WHO grade I (1). However, even benign WHO grade I meningiomas occasionally show rapid growth and may recur after total removal (2). The biological characteristics of meningioma have not been fully elucidated. The identification of prognostic biomarkers is warranted to optimize the treatment strategies.

To date, various prognostic factors for meningiomas have been described in previous studies, and among those factors, the most reliable clinical factors have been WHO grade and the extent of removal (EOR) (3, 4). Ki-67 labeling index (Ki-67 LI), which is frequently used to predict the prognosis of malignant tumors (5), has been reported to be useful in predicting meningioma recurrence (6, 7). However, other studies have not shown a significant correlation between Ki-67 LI and poor prognosis (8, 9). These factors are based on postoperative information; however, no preoperative prognostic factors have been established.

Recently, hematological inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) have been reported to be poor prognostic indicators for various solid tumors (10–12). However, the significance of NLR in patients with meningiomas has not been analyzed extensively (13, 14). Furthermore, the association between peripheral and intratumoral inflammatory markers has not been analyzed in meningiomas ever.

Here, we investigated the prognostic significance of hematological inflammatory markers, including NLR, LMR, and PLR, in patients with meningiomas, and discussed the role of the inflammatory response in the tumor microenvironment.

MATERIALS AND METHODS

Study Population and Clinical Data

We retrospectively analyzed data from patients who underwent surgery for meningiomas (WHO grade I–III) at our institute between October 2010 and September 2017. This study was approved by the Institutional Review Board (Reference number: 20050002), and written consent was obtained from all patients.

The exclusion criteria of this study were as follows: 1) patient aged < 18 years (n = 1); 2) patients who received steroids before preoperative laboratory test (n = 12); 3) patients with incomplete medical records (n = 20); 4) patients with neurofibromatosis type 2 (n = 2); 5) patients with a known history of whole-brain radiation therapy before surgery (n =2).

Clinical data including age at surgery, sex, primary/recurrent, WHO grade, EOR, tumor location, and peritumoral brain edema (PTBE) were obtained from hospital and electronic medical charts. The Simpson grading scale was used to evaluate the EOR (15). The EOR was categorized as gross total removal (GTR) (Simpson grade I–III) or subtotal removal (STR) (Simpson grade IV and V), as described previously (16). Surgical data were retrieved from operative reports and the removal rate was validated with routine postoperative head CT at 7 days after the operation. Gadolinium-enhanced T1-weighted MRI was used to evaluate the tumor location. Skull base location was defined as described previously (17). PTBE was evaluated on preoperative T2-weighted images or fluid-attenuated inversion recovery images (18).

Postoperative MRI was performed every 6–12 months. Tumor recurrence was defined as follows: 1) for patients with GTR, the appearance of new lesions at the prior surgical site and 2) for patients with STR, residual tumor growth (> 2 mm/year) (19).

Progression-free survival (PFS) was calculated from the date of surgery to the date of either tumor recurrence or death from meningioma. For patients with no confirmed recurrence, PFS was calculated from the date of surgery to the date of the last follow-up MRI.

Laboratory Data

Routine preoperative laboratory test data were used for analysis. The absolute neutrophil, lymphocyte, monocyte, and platelet counts were collected. Subsequently, we calculated the following parameters; NLR (absolute neutrophil count divided by absolute lymphocyte count) (10), LMR (absolute lymphocyte count divided by absolute monocyte count) (13, 20), and PLR (absolute platelet count divided by absolute lymphocyte count) (13). Neutrophilia was defined as the absolute neutrophil count ≥ 7.5 x 10^9/L, and lymphocytopenia as the absolute lymphocyte count < 1.5 x 10^9/L, as reported previously (21).

Histopathological Analysis

For histopathological analysis, we used paired (primary and recurrent) samples (26 tumors) obtained from 13 patients. None of the 13 patients had received chemotherapy or radiation therapy before tumor recurrence. The intratumoral neutrophils were assessed with their characteristic morphology using hematoxylin and eosin staining. Immunohistochemical staining was performed on 4-μm-thick sections of formalin-fixed paraffin-embedded tissues. The following steps were performed as described previously (22, 23). The primary antibodies were anti-Ki-67 antibody (1:200, M7240, Agilent DAKO, Santa Clara, CA, USA), anti-CD4 antibody (1:250, 1F6, Nichirei Biosciences, Inc., Tokyo, Japan), anti-CD8 antibody (1:200, ab17147, Abcam, Cambridge, UK), and anti-CD163 antibody (1:500, ab87099, Abcam). The primary antibodies were detected using the appropriate secondary antibodies (ImmPRESS Detection Systems, Vectorlabs, Burlingame, CA, USA). Diaminobenzidine was used for color development, and the products were visualized and photographed under a light microscope (Biorevo BZ-9000, Keyence Corporation, Osaka, Japan).

Immunohistochemical expression was assessed by two neurosurgeons and one neuropathologist who were blind to clinical information. Ki-67 LI was recorded as the percentage of tumor cells with positive nuclear staining at ×20 magnification. The cell counts were performed in regions of maximum immunoreactivity. For the assessment of neutrophils,

and CD4, CD8, and CD163 + cells, the stained tissue sections were screened at ×4 magnification, and five hot spots were selected, as described previously (22, 23). The cells were counted manually at ×40 magnification. The mean numbers of neutrophils and positive cells per field were calculated.

Statistical Analyses

We used GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) to perform statistical analyses. Receiver operating characteristic (ROC) curves were constructed to determine the optimal cut-off values of NLR, LMR, and PLR (based on Youden's index) to predict the recurrence of meningioma after surgery. Subsequently, each variable was analyzed as a dichotomous variable, according to the optimal cut-off value. Ki-67 LI was dichotomized at 3.0, as reported previously (6, 24). Continuous variables were expressed as means±standard deviations. The chi-squared test was used to compare categorical variables, and the Mann-Whitney U test was used to compare continuous variables. PFS was estimated using the Kaplan-Meier method and log-rank analysis was used to compare survival curves between different subgroups. Cox's proportional hazards method was used to investigate the influence of variables on PFS in univariate and multivariate analyses. A P value of < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 160 patients (39 male and 121 female) with complete preoperative laboratory data available were included in this study (**Table 1**). The median follow-up period was 3.8 years (range: 0–8.9 years). The median age at operation was 61 years (range: 28–84 years). Twenty-seven patients (16.9%) were recurrent cases. There were 144 WHO grade I (90.0%), 14 grade II (8.8%), and two grade III (1.2%) meningiomas. GTR was achieved in 117 cases (73.1%). The histological subtypes of meningiomas are shown in **Supplementary Table 1**. One hundred and eight patients (67.5%) had skull base meningiomas; the other 52 (32.5%) had non-skull base meningiomas. PTBE was observed in 72 patients (45.0%). Forty-four meningiomas recurred within the follow-up period [32 WHO grade I (22.2%), 10 grade II (71.4%), and two grade III (100%) meningiomas]. Among WHO grade I meningiomas, meningothelial and transitional subtypes exhibited a higher frequency of recurrence (25.4% and 28.1%, respectively).

Laboratory Data

Preoperative laboratory data are shown in **Table 2**. Preoperative neutrophilia was observed in only one patient. Preoperative lymphopenia was observed in 48 patients (30%). The ROC curve showed NLR cut-off value of 2.6 as a predictive marker of tumor recurrence, with a sensitivity 34.1% and specificity 81.9%. The area under the curve was 0.55 (**Supplementary Figure 1**). Similarly, the optimal cut-off values for LMR and PLR were 5.3, and 140, respectively (**Supplementary Figure 1**).

TABLE 1 | Baseline characteristics (N = 160).

Clinical feature	All cases	Baseline NLR		*P*-value
		< 2.6	≥ 2.6	
		No. (%)	No. (%)	
Patient number	160	124 (77.5)	36 (22.5)	
Age (means±SD)		60.1±12.2	57.1±14.3	0.26
Sex				0.92
Male	39	30 (76.9)	9 (23.1)	
Female	121	94 (77.7)	27 (22.3)	
Tumor status				0.97
Primary	133	103 (77.4)	30 (22.6)	
Recurrent	27	21 (77.8)	6 (22.2)	
WHO grade				0.70
Grade I	144	111 (77.1)	33 (22.9)	
Grade II and III	16	13 (81.3)	3 (18.7)	
Extent of removal				0.47
Gross total removal	117	89 (76.1)	28 (23.9)	
Subtotal removal	43	35 (81.4)	8 (18.6)	
Location				0.013
Skull base	108	90 (83.3)	18 (16.7)	
Non-skull base	52	34 (65.4)	18 (34.6)	
Peritumoral brain edema (PTBE)				0.068
With PTBE	72	51 (70.8)	21 (29.2)	
Without PTBE	88	73 (83.0)	15 (17.0)	

NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation; WHO, World Health Organization; PTBE, peritumoral brain edema.

TABLE 2 | Preoperative laboratory data and hematological inflammatory markers.

Marker	Mean±SD
Neutrophil count (×10^9/L)	3.53±1.26
Lymphocyte count (×10^9/L)	1.78±0.55
NLR (Neutrophil-to-lymphocyte ratio)	2.14±1.03
LMR (Lymphocyte-to-monocyte ratio)	6.33±2.29
PLR (Platelet-to-lymphocyte ratio)	148.38±61.59

SD, standard deviation.

As shown in **Table 1**, the preoperative NLR did not differ with regard to age, sex, WHO grade, EOR, and PTBE. NLR ≥ 2.6 were significantly more common for non-skull base meningiomas than for skull base meningiomas.

Kaplan-Meier Analysis

Kaplan-Meier analysis showed that both WHO grade and EOR were correlated with shorter PFS (P < 0.001 for each). A history of recurrence and PTBE were also correlated with shorter PFS (P = 0.002 and 0.009, respectively). When we dichotomized NLR and Ki-67 LI at 2.6 and 3.0, both were predictive of shorter PFS (P = 0.015 and < 0.001, respectively; **Figure 1**). No other clinical factors were associated with shorter PFS.

Univariate and Multivariate Analyses

To investigate the influence of variables on PFS, we performed univariate analysis with Cox's proportional hazards model for age (≥ 60 versus < 60 years), sex, primary/recurrent, WHO grade (I versus II and III), EOR (GTR versus STR), tumor location (skull base versus non-skull base), PTBE (with PTBE versus without PTBE), absolute neutrophil count (continuous variable), lymphocytopenia (present versus not present), NLR (≥ 2.6 versus

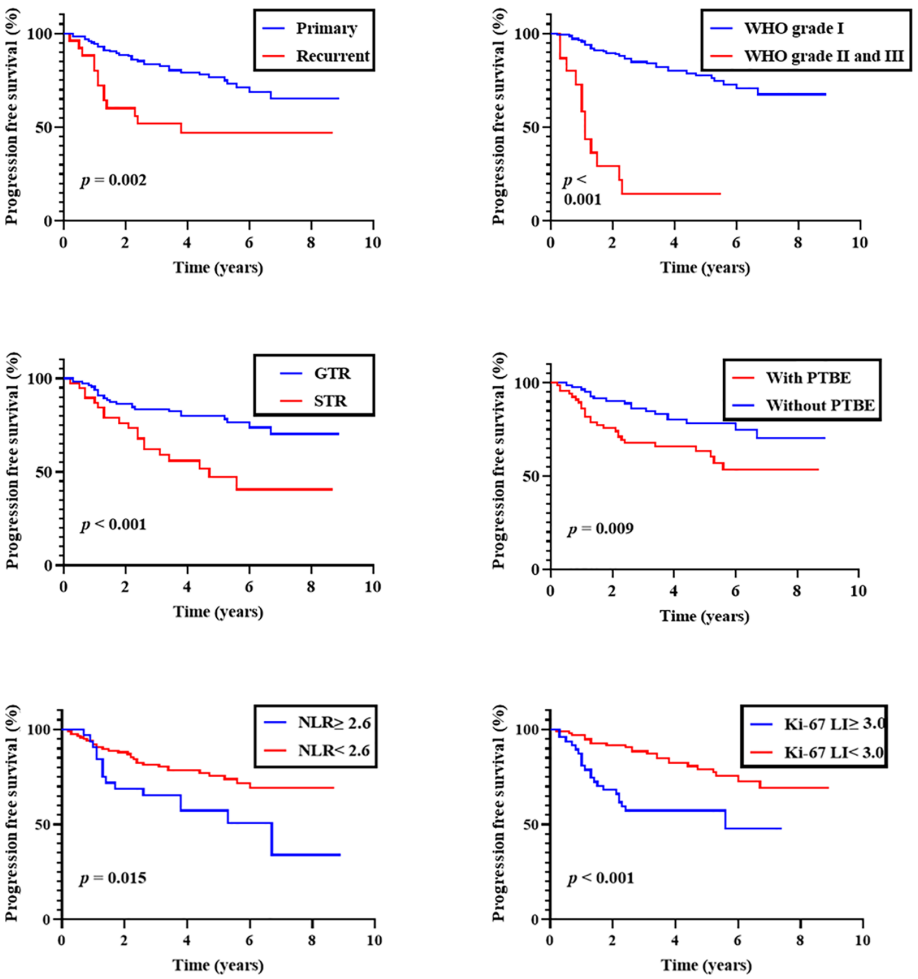


FIGURE 1 | Progression-free survival of overall patients. Kaplan-Meier curves of progression-free survival stratified by primary/recurrent, WHO grade, the extent of removal, peritumoral brain edema (PTBE), preoperative neutrophil-to-lymphocyte ratio (NLR; cut-off 2.6), and Ki-67 labeling index (Ki-67 LI; cut-off 3.0).

< 2.6), LMR (≤ 5.3 versus > 5.3), PLR (≥ 140 versus < 140), and Ki-67 LI (≥ 3.0 versus < 3.0; **Table 3**). Among these variables, a history of recurrence, WHO grade (II and III), EOR (STR), PTBE (with PTBE), NLR (≥ 2.6), LMR (≤ 5.3), and Ki-67 LI (≥ 3.0) were associated with shorter PFS and were included in the subsequent multivariate analysis [history of recurrence, hazards ratio (HR) = 2.64, 95% confidence interval (CI) = 1.38–5.06, P = 0.003; WHO grade, HR = 8.87, 95% CI = 4.42–17.80, P < 0.001; EOR, HR = 2.69, 95% CI = 1.48–4.91, P = 0.001; PTBE, HR = 2.18, 95% CI = 1.19–3.98, P = 0.011; NLR, HR = 2.13, 95% CI = 1.14–3.98, P = 0.018; LMR, HR = 2.39, 95% CI = 1.32–4.32, P = 0.004; Ki-67 LI, HR = 2.84, 95% CI = 1.55–5.21, P < 0.001].

Multivariate analysis showed that a history of recurrence, WHO grade (II and III), EOR (STR), and NLR (≥ 2.6) were independent predictors of poor prognosis (history of recurrence, HR = 2.07, 95% CI = 1.02–4.23, P = 0.045; WHO grade, HR = 10.01, 95% CI = 3.71–27.03, P < 0.001; EOR, HR = 4.44, 95% CI = 2.27–8.67, P < 0.001; NLR, HR = 2.29, 95% CI = 1.13–4.64, P = 0.022) (**Table 3**).

Subgroup Analysis

An additional subgroup analysis was performed after stratifying cases by the primary/recurrent, WHO grade (I, II, and III), EOR (GTR and STR), tumor location (skull base and non-skull base), and PTBE (with and without PTBE) (**Figure 2**). In a subgroup of primary meningiomas, EOR (GTR), tumor location (SB), and PTBE (without PTBE), both preoperative NLR (≥ 2.6) and Ki-67 LI were significantly associated with shorter PFS (NLR, P = 0.029, 0.004, 0.013, and 0.034, respectively; Ki-67 LI, P = 0.005, < 0.001, < 0.001, and 0.008, respectively). However, in a subgroup of WHO grade I meningiomas, only preoperative NLR (≥ 2.6) was significantly associated with shorter PFS (NLR, P = 0.003; Ki-67 LI, P = 0.17). In a subgroup of recurrent meningiomas, NLR (≥ 2.6) was not significantly associated with shorter PFS (P = 0.32). In each subgroup, ROC curves were constructed to determine the optimal NLR cut-off value to predict recurrence with sensitivity and specificity (**Supplementary Table 2**).

TABLE 3 | Univariate and multivariate analysis.

Variables	Univariate			Multivariate		
	P-value	HR	95%CI	*P*-value	HR	95%CI
Age (≥ 60)	0.55	0.83	0.46–1.51			
Sex (Male)	0.097	1.73	0.91–3.31			
Tumor status (Recurrent)	**0.003**	**2.64**	**1.38–5.06**	**0.045**	**2.07**	**1.02–4.23**
WHO grade (Grade II and III)	**<0.001**	**8.87**	**4.42–17.80**	**<0.001**	**10.01**	**3.71–27.03**
Removal rate (Subtotal removal)	**0.001**	**2.69**	**1.48–4.91**	**<0.001**	**4.44**	**2.27–8.67**
Location (Non-skull base)	0.21	1.47	0.80–2.71			
Peritumoral brain edema (With PTBE)	**0.011**	**2.18**	**1.19–3.98**	0.55	1.23	0.63–2.42
Preoperative Neutrophil count*	0.20	1.00	0.9999–1.0003			
Preoperative Lymphocytopenia	0.16	1.54	0.84–2.82			
Preoperative NLR (≥ 2.6)	**0.018**	**2.13**	**1.14–3.98**	**0.022**	**2.29**	**1.13–4.64**
Preoperative LMR (≤ 5.3)	**0.004**	**2.39**	**1.32–4.32**	0.10	1.74	0.89–3.38
Preoperative PLR (≥ 140)	0.060	1.79	0.97–3.28			
Ki-67 LI (≥ 3.0)	**<0.001**	2.84	1.55–5.21	0.27	1.55	0.71–3.37

HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; PTBE, peritumoral brain edema; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; Ki-67 LI, Ki-67 labeling index.
Bold font indicates statistical significance (P < 0.05).
**Continuous variable.*

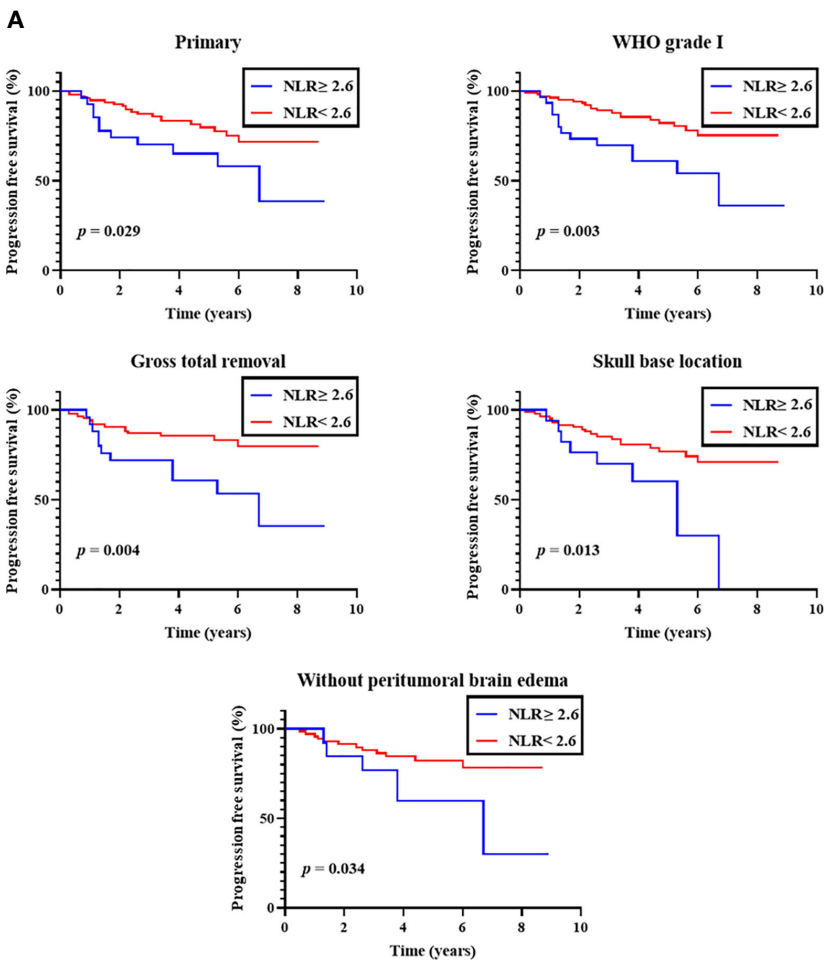


FIGURE 2 | Continued

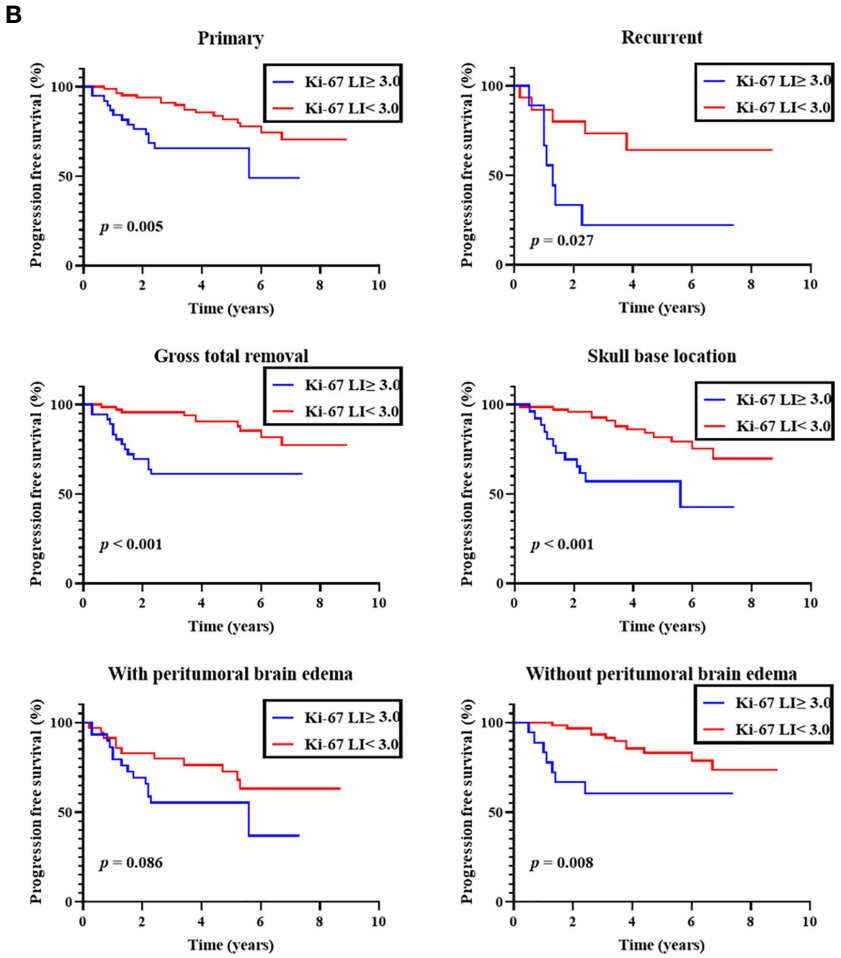


FIGURE 2 | Subgroup analyses of progression-free survival. Kaplan-Meier curves of progression-free survival. **(A)** Subgroup analysis of preoperative neutrophil-tolymphocyte ratio (NLR; cut-off 2.6) **(B)** Subgroup analysis of Ki-67 labeling index (Ki-67 LI; cut-off 3.0).

Immunohistochemical Analyses

To evaluate the association between peripheral NLR and intratumoral inflammatory markers, we analyzed neutrophils and CD8, CD4, and CD163+ cells from paired primary and recurrent tumor specimens. Elevated peripheral NLR was not correlated with the number of intratumoral neutrophils or CD8, CD4, or CD163+ cells in meningioma (**Supplementary Figures 2A, B**). The numbers of CD4 and CD163+ cells tended to be higher in recurrent meningiomas than in primary meningiomas (P = 0.057 and 0.084, respectively) (**Supplementary Figure 2C**).

DISCUSSION

Although meningiomas are typically benign intracranial tumors, the recurrence rates of WHO grade I, II, and III meningiomas have been reported as 7.2%, 29.6%, and 72%, respectively (25, 26). Therefore, prognostic factors are essential for personalized postoperative therapeutic interventions. The prognostic factors reported most frequently were the EOR and WHO grade (3). However, preoperative prognostic factors have not been fully established.

NLR has been reported to be a useful prognostic factor for brain tumors, such as gliomas and brain metastases (**Supplementary Table 3**) (27–40). However, analyses of the prognostic significance of NLR in benign brain tumors have been limited (41–43). For meningiomas, Liang et al. demonstrated that high leukocyte count and low LMR were independent predictive factors of high-grade meningiomas (13). In our study, we also investigated the preoperative NLR, LMR, and PLR in patients with meningioma. In multivariate analysis, NLR ≥ 2.6 remained an independent prognostic factor for shorter PFS. According to literature review, the median cut-off value of NLR is 4 (range: 2.5–7), which is relatively higher than the cut-off value in our study (**Supplementary Table 3**). This may be associated with the difference between benign and malignant tumors. Further analyses with benign tumors are needed.

Although a substantial number of WHO grade I meningiomas recur (24, 25), few prognostic factors have been established (4). In

our study, a subgroup analysis demonstrated that NLR ≥ 2.6 was also significantly associated with shorter PFS in patients with WHO grade I meningiomas. Ki-67 LI has been reported to be useful in predicting meningioma recurrence (6, 7) and is frequently used in a clinical setting. However, Roser et al. reported that there was no statistically significant correlation between Ki-67 LI and recurrence-free survival in patients with WHO grade I meningioma (8), which was compatible with our results. Therefore, NLR may be a novel prognostic factor for WHO grade I meningiomas in addition to all grades of meningiomas. NLR can be obtained with preoperative laboratory tests, which allows us to select patients who require adjuvant therapy.

The reason why higher NLR is associated with poor prognosis remains unclear because few studies have been conducted to evaluate the relationship between peripheral blood and the tumor microenvironment (29, 44). Tumor-infiltrating lymphocytes and tumor-associated macrophages have been reported to be associated with the poor prognosis of meningioma (45, 46). Our study also revealed that the numbers of CD4+ lymphocytes and CD163+ macrophages tended to be higher in recurrent meningiomas than in primary tumors. However, we did not find a significant correlation between peripheral NLR and infiltration by these inflammatory cells. In addition, a previous study reported that NLR does not necessarily correlate with WHO grade (14). Further analysis is needed to confirm the biological role and involvement of peripheral NLR.

Besides the retrospective study design, several limitations of our study should be mentioned. First, the data were too limited to evaluate patient-reported outcomes beyond the window of overall survival because most patients were still alive. Further long-term investigative follow-up is needed. Second, we excluded factors that could affect laboratory tests, such as steroid use before laboratory tests. Third, patient backgrounds may differ from that of the reference which included only the gross total removal cases (25) because our institution performs a large number of skull base surgeries. Fourth, a rare subtype of meningioma (e.g., lymphoplasmacyte-rich meningioma) was not included in the present study. Another limitation was the paucity of the number of paired tumor tissues. A larger number of the paired samples must be studied to confirm our findings.

CONCLUSION

We investigated the prognostic significance of preoperative hematological inflammatory markers in patients with meningioma. Preoperative NLR ≥ 2.6 was significantly associated with poor prognosis in WHO grade I meningiomas in addition to all grades of meningiomas. NLR can be obtained easily and cost-effectively from routine preoperative laboratory tests and thus represents a novel prognostic factor for meningiomas.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Keio University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YK and KY conceived the study design. YK, KK, and YM were responsible for data collection. NT, YK, and RT conducted histological analysis. YK and RT organized database and were responsible for statistical calculations and drafted the article. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.592470/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prophylactic AEDs Treatment for Patients With Supratentorial Meningioma Does Not Reduce the Rate of Perioperative Seizures: A Retrospective Single-Center Cohort Study

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Meningiomas, the most common brain tumor, inevitably require surgical treatment. However, the efficacy of prophylactic antiepileptic drugs (AEDs), in reducing the frequency of new-onset seizures during the perioperative period remains controversial. To further clarify if prophylactic antiepileptic drug treatment for patients with meningioma had value, we reviewed the medical records of 186 supratentorial meningioma patients who were operated at our hospital between 2016 and 2018. SPSS 24.0 software was used for statistical analysis. The results of univariate analysis showed that factors including age, sex, the course of the disease (years), maximum cross-sectional area of the tumor, location of the tumor, multiple or single tumors, adjacent to the cortex, peritumoral brain edema, World Health Organization classification, and peritumoral adhesion were not associated with perioperative seizures (P >0.05). Furthermore, the results of multivariate analysis revealed hydrocephalus (OR 4.87 P = 0.05) and non-skull base location (OR 1.88 P = 0.04) were significant risk factors for perioperative in-hospital seizures. Prophylactic valproic acid treatment did not contribute to the alleviation of perioperative seizures (OR 1.76 P = 0.04). However, Multivariate logistic regression analyses excluding the patients

with seizures before operation confirmed prophylactic valproic acid treatment did not reduce the frequency of seizures during the perioperative period (OR 1.84 P = 0.04). Taken together, the data suggest that prophylactic valproic acid treatment for patients with supratentorial meningioma does not reduce the rate of perioperative seizures.

Keywords: seizure, operation, prophylactic treatment, antiepileptic drugs, supratentorial meningioma, non-skull base location

INTRODUCTION

Meningiomas are very common tumors in the brain and account for approximately 36.4% of all brain tumors (1). Almost 90% of meningiomas are benign (1). The World Health Organization (WHO) classifies meningiomas as grades I, II, and III according to the characteristics of the histopathology (2). Computed tomography (CT) scan or magnetic resonance imaging (MRI) scan are usually used to confirm the initial diagnosis of meningioma (3). The incidence of meningioma increases with age (1).

Patients with meningiomas show a variety of different clinical symptoms, which is mainly due to the location of the meningioma in the brain (4, 5). Focal neurological deficits often occur because the meningioma affects the blood vessels or brain tissue (6). Seizures are a common symptom of meningiomas. Reports indicated that the incidence of preoperative epilepsy in meningiomas ranges from 15–39% (6–10).

The vast majority of patients receive surgical resection treatment (11); however, some patients have apparent seizures after surgery. Reily et al. (12) showed that the incidence of postoperative seizures was approximately 30% (12). In order to reduce the risk of seizures, some surgeons have utilized prophylactic AEDs (13). However, whether AEDs can help reduce perioperative seizures remains controversial.

Islim et al. published the review in 2017 (14). The data were collected from between January 1990 and November 2016. The conclusion showed the prophylactic valproic acid treatment could reduce the rate of perioperative seizures. They performed a retrospective cohort study in 2018 (15), and also got the same conclusion. Between 2017 and 2020, additional published articles were retrospective cohort studies (16–19). The results showed prophylactic AEDs treatment did not decrease the incidence of postoperative seizures of supratentorial meningioma. In order to further clarify if AEDs reduced the incidence of postoperative seizures, we collected the data of patients who underwent meningioma resections during the past 2 years in our hospital and performed a retrospective study.

METHODS

Study Design

Our study was a retrospective study. All patients received surgical treatment in Affiliated hospital of Guizhou Medical University (Guizhou, China). Our project was approved by the Ethics Committee of Affiliated Hospital of Guizhou Medical University. Because our study was a retrospective cohort study, informed consent was not needed.

First, we collected all the risk factors that might affect the occurrence of postoperative seizures. Seizures during the perioperative period were recorded. We were primarily interested in the incidence of seizures during the perioperative period, when prophylactic AEDs are administered.

Second, we performed univariate analysis to observe which indicators might have an impact on the occurrence of perioperative seizures. Then, we used multivariate analysis to determine which factors might contribute to the occurrence of perioperative seizures.

Third, we excluded patients who had seizures before surgery. We then used univariate analysis and multivariate analysis to explore whether prophylactic AEDs decreased the incidence of perioperative seizures.

Patients and Data Collection

All patients came from the Department of Neurosurgery of the Affiliated Hospital of Guizhou Medical University, were diagnosed with meningioma, and underwent meningioma surgery between 2016 and 2018. All were older than 18 years of age. Of the 252 registered cases, 186 (73.8%) were deemed eligible, and 66 (26.2%) were excluded from the analysis. Specifically, 10 patients could not be followed-up, 54 patients were diagnosed with subtentorial meningioma, and two patients had loss of important data (**Figure 1**).

We collected the all the data related with the meningioma, including: age (years) at operation, sex, seizures before operation, the course of the disease (years), maximum cross-sectional area of the tumor (cm^2), location of the tumor, multiple or single tumors, adjacent to the cortex, peritumoral brain edema, hydrocephalus, WHO classification, peritumoral adhesion, and use of AEDs in the perioperative period (20).

Prophylactic AED Treatment During the Perioperative Period

Prophylactic AED treatment, in this case valproic acid, at 0.4 g added physiological saline (40 ml) to prevent seizures by continuous venous pump at 4 ml/h (3 days before surgical operation and 7 days after surgical operation). If the patients received valproic acid by oral administration before the operation, oral intake of valproic acid was ceased and switched to an intravenous pump. If the patients have taken

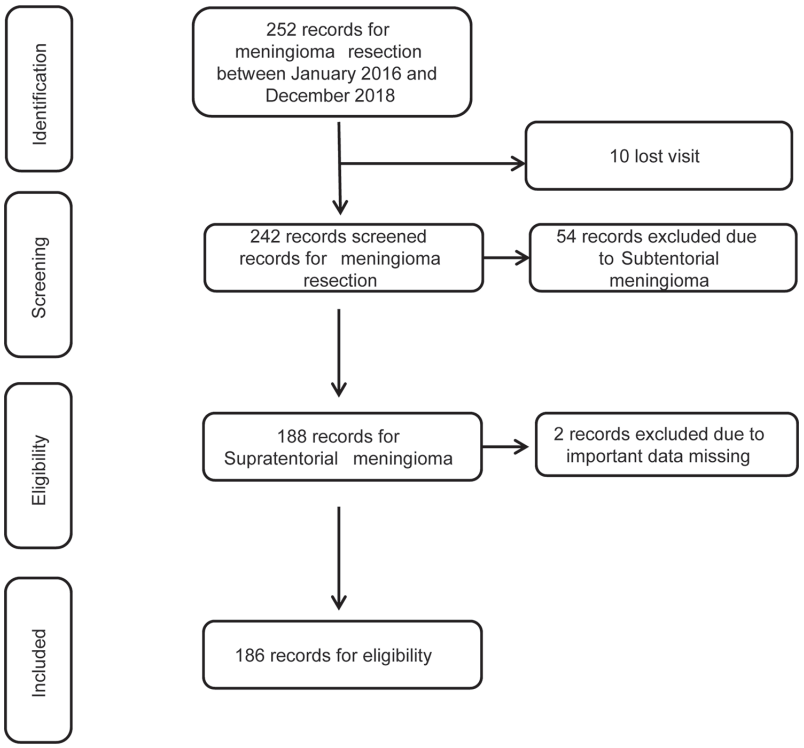


FIGURE 1 | Flow chart of patients.

other AEDs before operation, the patients would continue to use this drug.

Data Grouping

Age (years) at surgery was categorized into two groups: ≥60-years-old and <60-years-old; course of disease (years) was divided three groups: <1 year, 1–5 years, and >5 years; maximum cross-sectional area of the tumor was categorized two groups: >15.0 cm^2 and ≤15.0 cm^2; location of the tumor was divided two groups: skull base location and non-skull base location; and WHO classification was divided into three groups: WHO grades I, II, and III according to the WHO classification of 2010 (12). Finally, according to whether AEDs were used or not and the number of AEDs, the patients were divided three groups: the no AEDs group, the prophylactic valproic acid treatment group, and the multiple AED treatment group (seizures before operation).

Outcome of Postoperative Meningioma

On the 15th day after surgery, we recorded the patient's seizures within 14 days. Fasting blood was also drawn for routine blood samples and liver and kidney function.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (normal distribution) or median (quartile; skewed distribution). Categorical variables were expressed in frequency or as a percentage. The chi-square tests (categorical variables) were used to determine any statistical differences between proportions of the groups. First, we performed a baseline characteristic of all patients to obtain an overview of the distribution of the data. A two-tailed chi-square test was then performed. P values less than 0.05 (two-sided) were considered statistically significant. Second, we performed univariate logistic regression analysis to assess the impacts of the determined variables on the occurrences of early postoperative seizures, including variables with odds ratios (ORs) with 95% confidence indexes (Cis). Third, multivariate logistic regression analyses were performed. All the meaningful factors were included. SPSS 24.0 for Windows (IBM, Armonk, New York, USA) was used for statistical analyses.

RESULTS

A total of 186 patients with meningioma were included in this study. All patients were categorized two groups according to seizure after operation. Detailed information is provided in **Table 1**. There were no statistically significant differences in age, sex, the course of the disease, maximum cross-sectional area of the tumor, seizures before surgery, location of the tumor, multiple tumors, adjacent to the cortex, peritumoral brain edema, WHO classification, or

TABLE 1 | Baseline characteristics of participants.

Variable	Seizure after operation		P value
	Yes	No	
Age (years) at operation			0.526
≥60	10/54	44/54	
<60	30/132	102/132	
Gender			0.638
male	10/52	42/52	
female	30/134	104/134	
Seizure before operation			0.090
Yes	12/38	26/38	
No	28/148	120/148	
The course of disease(years)			0.983
<1	31/146	115/146	
1–5	6/27	21/27	
>5	3/13	10/13	
Maximum cross-sectional area			0.579
≤15	23/114	91/114	
>15	17/72	55/72	
Location of tumor			0.032
non-skull base location	34/142	108/142	
skull base location	6/44	36/44	
Multiple tumor			0.502
Yes	3/10	7/10	
No	37/176	139/176	
Adjacent to the cortex			0.150
Yes	27/107	80/107	
No	13/79	66/79	
Peritumoral brain edema			0.149
Yes	27/108	81/108	
No	13/78	65/78	
Hydrocephalus			0.003
yes	7/13	6/13	
No	33/173	140/173	
WHO classification			0.245
I level	35/171	136/171	
II/III level	5/15	10/15	
Peritumoral adhesion			0.774
Yes	27/122	95/122	
No	13/64	51/64	
AEDs			0.021
no	7/80	73/80	
Prophylactic treatment	24/68	44/68	
Treatment for seizure attack before operation	9/38	29/38	

peritumoral adhesion between two groups (P >0.05). However, the results showed the patients with hydrocephalus, non-skull base location and were more prone to perioperative seizures (P <0.05). We also found that prophylactic AED treatment did not lower the rates of perioperative seizures (P <0.05).

Study Population for a Univariate Logistic Regression Analysis

The results of univariate analysis are shown in **Figure 2** and showed that factors including age, sex, the course of the disease, maximum cross-sectional area of the tumor, seizures before surgery, location of the tumor, multiple tumors, adjacent to the cortex, peritumoral brain edema, WHO classification, and peritumoral adhesion were not associated with seizures after operation. Furthermore, we found prophylactic valproic acid treatment did not contribute to alleviation of seizures (P >0.05). Again, hydrocephalus and non-skull base location to the tumor likely contributed to perioperative seizure attack (P <0.05).

Study Population for Multivariate Logistic Regression Analysis

The results of multivariate analysis are shown in **Table 2**. Age, sex, tumor location, hydrocephalus, and prophylactic valproic acid treatment were included. The results showed that there were no statistically significant differences in age, sex. Hydrocephalus (OR 4.87 P = 0.05) and non-skull base location (OR 1.88 P = 0.04) were significant risk factors for perioperative in-hospital seizures. We found incidence of epileptic seizure in the no prophylactic AEDs group were lower than that in the prophylactic AEDs group (OR 1.76 P = 0.04).

Study Population Excluding the Patients With Seizures Before Operation

We again performed analyses of baseline characteristics of patient data but excluded patients with seizures before operation. Detailed information is provided in **Table 3**. The results showed that there was no statistically significant differences in age, sex, the course of the disease, maximum cross-sectional area of the tumor, seizures before operation, location of the tumor, multiple tumors, adjacent to the cortex, peritumoral brain edema, WHO classification, or peritumoral adhesion (P >0.05). We found patients with hydrocephalus were more prone to occur perioperative seizures compared with patients without hydrocephalus (P <0.05). We confirmed that patients with non-skull base location to the tumor were more prone to perioperative seizures and that prophylactic AED treatment had no effect on the rate of seizures (P <0.05).

Study Population Excluding Patients With Seizures Before Operation for a Univariate Logistic Regression Analysis

The results of univariate analysis are shown in **Figure 3** and showed that age, sex, course of the disease, sectional area, tumor side, multiple tumors, location adjacent to the cortex, brain edema around the tumor, WHO classification and peripheral adhesion were not associated with perioperative seizures (P >0.05). We further confirmed that prophylactic valproic acid treatment did not reduce perioperative seizures (P <0.05). Hydrocephalus and non-skull base location to the tumor likely contributed to seizures (P <0.05).

Study Population Excluding Patients With Seizures Before Operation for Multivariate Logistic Regression Analysis

The results of multivariate analysis are shown in **Table 4**. Age, sex, abundant blood supply, hydrocephalus and prophylactic valproic acid treatment were included in the analysis. Age, sex

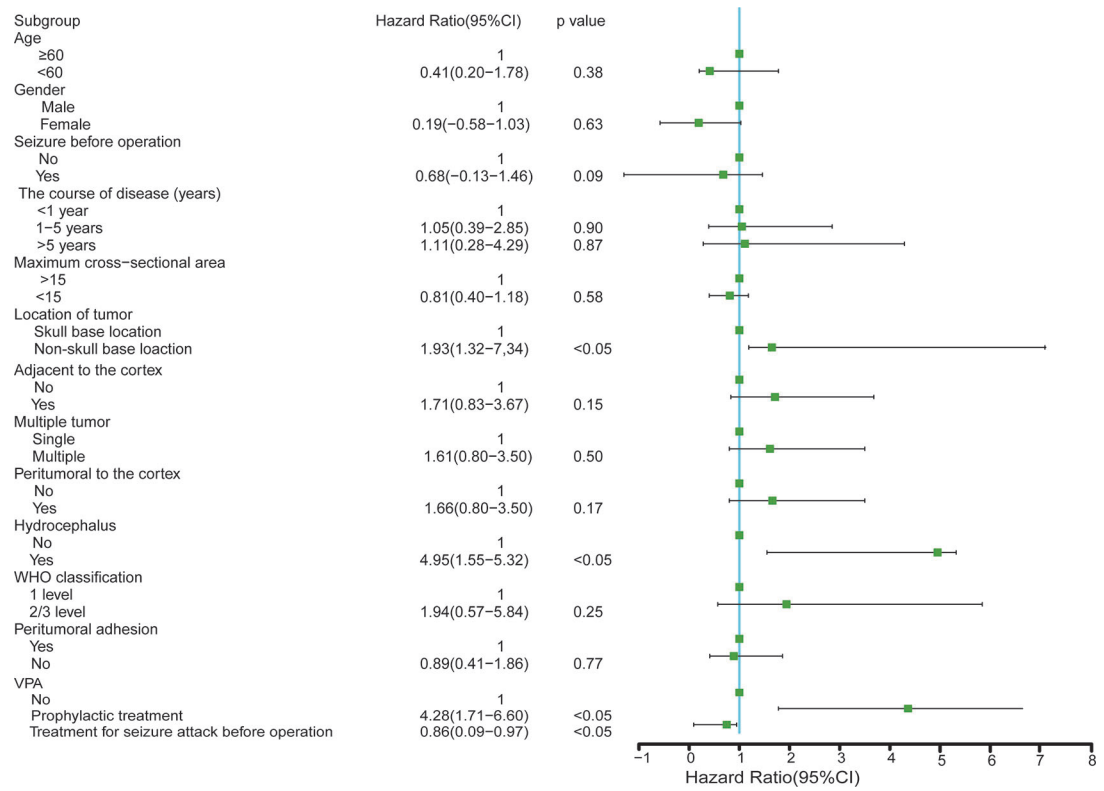


FIGURE 2 | Study population for a univariate logistic regression analyses.

TABLE 2 | Multivariate logistic regression analysis of study population.

	HR	CI 95%	P value
Age			
≥60	Reference		
<60	0.86	0.24–6.35	0.48
Gender			
Male	Reference		
Female	1.02	0.45–4.23	0.54
Hydrocephalus			
No	Reference		
Yes	4.87	1.34–13.56	0.05
Location of tumor			
skull base location	Reference		
non-skull base location	1.88	1.43–11.34	0.04
AEDs			
No	Reference		
Prophylactic treatment	1.76	1.52–9.56	0.04
Treatment for seizure attack before operation	1.21	0.37–8.15	0.43

were not associated with perioperative seizures (P >0.05). Hydrocephalus and non-skull base location to the tumor likely contributed to seizures. We further confirmed that prophylactic valproic acid treatment did not reduce perioperative seizures (OR 1.84 P = 0.04).

Side Effect of Drug at 15 Days

Hepatorenal function was performed at 15 days post-surgery. There were three patients with mild increases of transaminase in liver function; all recovered after treatment.

DISCUSSION

Meningiomas, the most common type of brain tumor, are usually effectively treated surgically. However, perioperative seizures are a recurrent problem. Some surgeons choose to control epilepsy by prophylactic AEDs. In the neurosurgery department of our hospital, prophylactic AEDs have been given to patients with meningioma, although the efficacy of prophylactic AEDs in reducing the frequency of new-onset seizures in the perioperative period remains controversial (10). To further clarify if prophylactic AED treatment for patients with meningioma reduces the occurrence of seizures, we performed a retrospective study. The results showed patients with hydrocephalus and abundant blood supply were more prone to postoperative seizures. Importantly, we found that prophylactic AED treatment did not reduce the rate of postoperative seizures.

Intraoperative hemorrhage is more complicated for patients with abundant blood supply. Some of them with cerebral cortex

TABLE 3 | Baseline characteristics of participants excluding the patients with seizure attack before operation.

Variable	Seizure after operation		P value
	Yes	No	
Age (years) at operation			0.600
≥60	7/43	36/43	
<60	21/105	84/105	
Gender			0.257
male	5/39	34/39	
female	23/109	86/109	
The course of disease(years)			0.028
<1 year	22/118	96/118	
1–5years	4/20	16/20	
>5 years	2/10	8/10	
Maximum cross-sectional area			0.384
≤15	15/90	75/90	
>15	13/58	45/58	
Location of tumor			0.045
non-skull base location	33/108	75/108	
skull base location	6/40	34/40	
Multiple tumor			0.504
Yes	2/7	5/7	
No	26/141	115/141	
Adjacent to the cortex			0.756
Yes	17/86	69/86	
No	11/62	51/62	
Peritumoral brain edema			0.645
yes	15/86	71/86	
no	10/62	52/62	
Hydrocephalus			0.002
yes	6/11	5/11	
No	22/137	115/137	
WHO classification			0.575
I level	25/136	111/136	
II/III level	3/12	9/12	
Peritumoral adhesion			0.440
yes	17/99	82/99	
no	11/49	38/49	
AEDs			0.001
no	7/80	73/80	
Prophylactic AED treatment	21/68	47/68	

contusion, even local hematoma formation, postoperative edema may be the main cause of seizure. As reported in the literature, postoperative complications can lead to seizures (21). Hydrocephalus is one of the causes of epilepsy. Previous studies have shown the stimulation of hydrocephalus to neurons may lead to neuronal discharge (22). Although the operation has relieved cortical compression, the brain tissue edema around the lesion and a large amount of exudation may cause seizure attack (23). Neuronal discharge will gradually decrease with the reduction of brain edema and absorption of exudation. Patients with non-skull base locations of meningioma seem to be more vulnerable to seizure attack. The main reason is more involved with the epileptogenic neocortical gray matter than those located at the skull base (21).

A report in 2011 analyzed the data of patients who underwent supratentorial meningioma resection from 1979 to 2010 (24). The authors found there were no significant differences between the incidence of early seizures and prophylactic AED therapy in patients undergoing supratentorial meningioma resection. Another study in the same year reported 180 patients with no preoperative history of seizures who underwent resection of a convexity meningioma. The patients received antiepileptic prophylaxis for 7 continuous days postsurgery. The rates of clinically evident seizures in the first 3–4 weeks after surgery were compared and indicated that routine use of prophylactic antiepileptics could prevent seizures in patients undergoing surgery for a convexity meningioma (25). Two studies in the same year reported different results.

In 2016, a meta-analysis of data collected from January 1980 to September 2014 was conducted and indicated that routine use of prophylactic anticonvulsants in patients without seizures was unnecessary (10). Islim et al. published the review in 2017 (14). The data were collected from between January 1990 and November 2016. The conclusion showed the prophylactic valproic acid treatment could reduce the rate of perioperative seizures. They performed a retrospective cohort study in 2018 (15), with the same conclusion. However, more studies showed the opposite conclusion (16–19). Routine use of prophylactic anticonvulsants in patients without seizures was unnecessary.

In our study, 186 cases were analyzed retrospectively. Patients received antiepileptic prophylaxis for 7 continuous days postsurgery. The results showed that incidence of perioperative seizures did not decrease. In order to exclude the effect of seizures before operation, we analyzed 148 patients with no preoperative history of seizures who underwent meningioma resection. The results showed there were no significant differences between the incidence of early seizures and prophylactic AED therapy. We think prophylactic use of AEDs had no effect on the rate of seizures for several reasons. First, meningiomas are relatively benign, mostly with intact borderlines. The operation was helpful to remove the tumor completely without damaging the surrounding brain tissue. Therefore, the possibility of seizures attack after operation was relatively low. The review written by Islim AI, et al. showed the results that early post-operative seizures occurred in 2.6% of patients (20 of 766) in the AED cohort. In the no-AED cohort of 377 patients, early post-operative seizures occurred in 2.7% of patients (10 of 377) (14). Second, there are many reasons leading to seizure attack after meningioma resection. Seizure attack could be reduced if the relevant factors were controlled. Third, sodium valproate is a common drug for controlling the seizure. However, more adverse effects were found.

Certainly, our study had some limitations. First, the sample size was not large enough to make multivariate logistic regression analyses for all the factors. Therefore, we made univariate logistic regression analyses, and screened for the meaningful factors. Then, we performed multivariate logistic regression analysis. Second, our study was a retrospective study, not a randomized controlled trial. It is difficult to balance all factors between the observation group and control group (for example, see **Table 1**). We should therefore perform univariate logistic regression analysis and multivariate logistic regression analysis to correct our data. Our study was a retrospective study, we did not collect more detailed data, such as brain infiltration, subdural

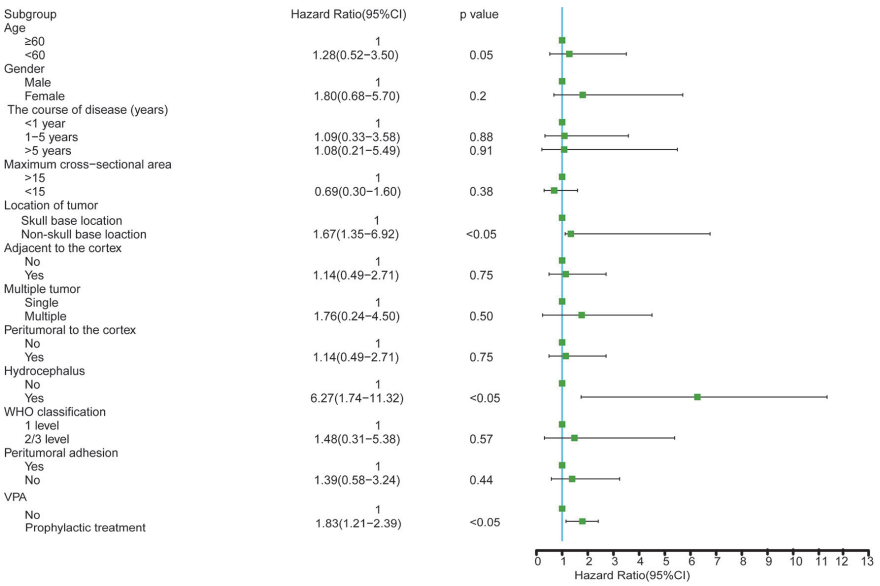


FIGURE 3 | Study population excluding the patients with seizure attack before operation for a univariate logistic regression analyses.

TABLE 4 | Multivariate logistic regression analysis of study population excluding the patients with seizure attack before operation.

	HR	CI95%	P value
Age			
≥60	Reference		
<60	1.32	0.52–5.16	0.48
Gender			
Male	Reference		
Female	1.78	0.67–6.78	0.65
Hydrocephalus			
No	Reference		
Yes	5.12	1.45–9.56	0.04
Location of tumor			
skull base location	Reference		
non-skull base location	2.34	1.23–6.95	0.03
AEDs			
No	Reference		
Prophylactic treatment	1.84	1.35–5.21	0.04

hemorrhage, or any venous injury surgery. Third, we just confirmed that sodium valproate as prophylactic medication did not contribute to alleviation of perioperative seizures.

Taken together, we believe that prophylactic valproic acid treatment did not contribute to alleviation of perioperative seizures. We think randomized controlled trials should be a better way to study this problem.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Affiliated Hospital of Guizhou Medical University. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

MY and Z-CX contributed to the drafting of the manuscript. Y-RC and M-YZ contributed to analysis and interpretation of the data. M-WW and LY contributed the collection of data. Z-HF and X-TM contributed to the conception and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Meningiomas in Premenopausal Women: Role of the Hormone Related Conditions

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Background: Several epidemiological and pathological findings suggest that the female sex hormones may influence the development of meningiomas. However, the role of pregnancy, oral contraceptives, and fertilization therapies is still controversial.

Methods: From the surgical series of 354 patients with meningiomas operated between 2006 and 2019, the group of 72 premenopausal women was separately considered. The tumor location, WHO grade, Ki67-labeling index (LI), progesterone receptor (PR) expression, and histological types were studied in premenopausal women with and without hormone-related conditions were compared.

Results: In this premenopausal group, 24 patients had hormone-related conditions, including use of oral contraceptives in 16, intrauterine fertilization in one, pregnancy in three, and tumors of the female reproductive system in four. The group of patients with hormone-related conditions, as compared to that with no hormone related conditions, showed slightly lower median age (38 *versus* 43 years) and no significant difference of meningioma location WHO grade, Ki 67-Li, PR expression and histological type. The clinical onset during pregnancy in three patients and tumor growth during contraceptive progesterone therapy in two others were evidenced.

Conclusion: The biological behavior of meningiomas and their pathological findings, including PR expression, are not correlated with the different hormone related conditions in premenopausal female patients. Contraceptives and fertilization therapies, mainly with progesterone, should be avoided in patients with meningiomas.

Keywords: meningioma, progesterone receptor expression, pregnancy, oral contraceptives, fertilization therapies

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INTRODUCTION

Meningiomas are mostly benign tumors which arise from meningothelial cells of the arachnoid membrane; their incidence is about two fold higher in women than in men (1).

Several epidemiological and pathological findings other than the higher female incidence may suggest that sex hormones may play a role in the development of these tumors. These include the

frequent presence of progesterone and estrogen receptors in the meningioma tissue (2–7), the possible association with tumors of the female system (8–10), the documented changes of the meningioma biology during the menstrual cycle and pregnancy (11–13), the sometimes reported regression after delivery (14), the *in vitro* proliferation of meningioma cell lines in culture after exposure of estrogen and progesterone (15, 16). Besides, the incidence and risk of meningioma in patients with sex hormone-related conditions and during the exogenous use of sex hormones for contraceptive therapies have been investigated in several studies (16–22).

In this monoinstitutional study we have investigated the epidemiological and pathological findings of premenopausal women with meningioma and the effects of the sex hormone-related conditions in this age group.

MATERIALS AND METHODS

Patient Population and Study Design

Three hundred fifty-four patients with primary intracranial and spinal meningiomas who underwent surgery at the neurosurgical clinic of the "Federico II" University of Naples between January 2006 and April 2019 were retrospectively reviewed. Cases of recurrent meningiomas and those with insufficient data were excluded. From the overall series, 72 female patients where the diagnosis of meningioma was made in the premenopausal age period were selected for the study. These 72 patients were classified in two groups: group A with sex hormone-related conditions at the meningioma diagnosis and group B with no hormone-related conditions.

Ethical approval for this human study was not required according to local and or national legislation.

Analyzed Factors

The factors analyzed in the study include meningioma location, WHO grade, progesterone receptor (PR) expression, Ki67-MIB1, recurrence rate. The sex hormone-related conditions, which were analyzed in the premenopausal group, include exogenous hormone contraceptive therapies, pregnancy at the meningioma diagnosis, hormone-related extraneural tumors, and fertilization therapies.

The tumor location was defined from the review of the MR images and the surgical descriptions. Four groups were identified: group 1 or medial skull base including olfactory groove, ethmoidal–sphenoidal planum, tuberculum sellae, parasellar, clival-petroclival, and foramen magnum meningiomas; group 2 or lateral skull base, including the middle and lateral sphenoid wing and temporal fossa meningiomas and those of the petrous bone and occipital fossa; group 3 or non-skull base, including convexity, parasagittal or falx meningiomas, those of the tentorium, cerebellar convexity, and pineal region, and those of the lateral ventricles; group 4, including spinal meningiomas.

Abbreviation: Ki67-LI, Ki67 Labelling Index; PR, Progesterone Receptor; ER, Estrogen Receptor; MRI, Magnetic Resonance Images.

The surgical specimens were reviewed independently by two pathologists (MC and EG). The WHO grade was defined according to the 2007 WHO classification (23). The immunohistochemical studies were performed to evaluate the Ki67-MIB1 and the PR expression. The specimens were fixed in neutral buffered 10% formalin, embedded in paraffin and cut into sections of 5 mm thickness.

The expression of PR was determined in all specimens with monoclonal antibody against the progesterone (DAKO 1:400, overnight incubation). The quantitative evaluation was expressed as percentage for positive nuclei among 100 cells, for a total of 500 cells. The following score was used: 1. absent or low (L) (<15%); 2. moderately low (ML) (16–50%); 3. moderately high (MH) (51–79%); 4. high (H) (≥80%) (**Figure 1**).

The expression of Ki67-MIB1 was evaluated in all specimens by using the monoclonal antibody MIB1 Immunotech® (DAKO system, dilution 1:1,000, overnight incubation). The streptavidin–biotin system and the diaminobenzidine (DAB) were used for antigen detection and visualization. A specimen of breast carcinoma was used as a positive control. Ki67-LI count was performed by eye counting, taking the average on five adjacent representative fields of neoplastic cells in a hot spot area. The values of Ki67-LI were classified into two groups: group I ≤4%; group II >4%.

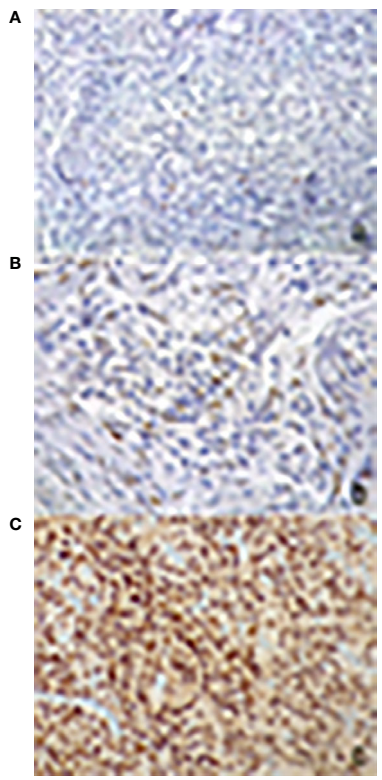


FIGURE 1 | Immunohistochemical evaluation of progesterone receptor antibody expression: nuclear signal respectively in less than 1% **(A)**, in 15% **(B)** and in 95% **(C)** of neoplastic cells (200× magnification).

The histological types of WHO grade I meningiomas were classified as: meningothelial, transitional, fibroblastic, psammomatous, microcystic, secretory, chordoid.

Statistical Analysis

The meningioma location, WHO grade, Ki67-MIB1, PR expression and histological subtype were analyzed in all patients and stratified in the two groups, of patients with and without sex hormone-related conditions.

The data were analyzed by one-way ANOVA test or Fisher's exact test, and p-value was correlated. A p value ≤0.05 was considered statistically significant. All tests were two-sided and carried out with Graph Prism 5 software (Graph Pad Software, La Jalla. CA. USA).

RESULTS

Epidemiological and Pathological Data

The 72 female patients where the meningioma was diagnosed in the premenopausal age period account for 20% of the overall series of 354 meningiomas and 27.5% of the 262 female patients at all ages. Twenty-four patients (39.3%) were in group A with sex hormone-related conditions at the meningioma diagnosis and 48 (66.7%) in group B with no hormone-related conditions. The epidemiological and pathological data are summarized in **Table 1**. The patient age ranged from 19 to 52 years (median age 42 years), with no significant difference between groups A and B (38 *vs* 43 years, p = 0.81). According to the location (**Table 1**) 18 meningiomas (25%) were medial skull base, 11 (15%) lateral skull base, 40 (56%) non-skull base and three (4%) spinal. Fifty-five tumors (77%) were WHO grade I and 17 (23%) WHO grade II. The Ki-67Li was ≤4% in 43 patients (60%) and >4% in 29 (40%). The PR expression was <15% of the tumor cells in 10 cases (14%), between 16 and 50% in 17 (28%), between 51 and 79% in nine (13%) and ≥80% in 36 (50%). The more frequent histological subtypes of WHO I meningiomas were transitional (49%), fibroblastic (27%), and meningothelial (11%), whereas others were infrequent. The differences of tumor location, WHO grade, Ki67Li, PR expression, and histological subtype between group A and group B were not statistically significant (**Table 1**).

Sex Hormone-Related Conditions

Twenty-four premenopausal women had associated sex hormone-related conditions at meningioma diagnosis. These include use of oral contraceptives in 16, assisted fertilization in one, pregnancy in three and hormone-related tumors of the sex female system in four (**Table 2**). Among the 16 patients with oral contraceptives (progesterone–estrogen), nine currently use the therapy at the meningioma diagnosis, and

TABLE 2 | Sex hormone-related conditions at meningioma diagnosis (24 patients).

•oral contraceptives	16 (67%)
•current use	9
•previous use (1 to 2 years previously)	7
•pregnancy	3 (12.5%)
•hormone-related tumors	4 (16.5%)
•breast cancer	2
•ovarian cyst	1
•ovarian adenoma	1
•artificial fertilization	1 (4%)

TABLE 1 | Epidemiological and pathological data on premenopausal women with and without hormone-related conditions.

Covariates	Overall premenopausal A + B (72 pts)	Group A (24 pts)	Group B (48 pts)	Statistical significance P value
Median age	42 y	38 y	43 y	0.081
Meningioma location				
- Median skull base	18 (25%)	8 (33%)	10 (21%)	
- Lateral skull base	11 (15%)	4 (17%)	7 (15%)	
- Non-skull base	40 (56%)	12 (50%)	28 (58%)	
- Spinal	3 (4%)	-	3 (6%)	
WHO grade				
- I	55 (77%)	17 (70%)	38 (79%)	
- II	17 (23%)	7 (30%)	10 (21%)	
Ki67Li				
- ≤4%	43 (60%)	16 (67%)	27 (56%)	
- >4%	29 (40%)	8 (33%)	21 (44%)	
Progesterone receptor expression				
- <15%	10 (14%)	5 (21%)	5 (10%)	
- 16–15%	17 (23%)	6 (25%)	11 (23%)	
- 51–79%	9 (13%)	2 (8%)	7 (15%)	
- ≥80%	36 (50%)	11 (46%)	25 (52%)	
Histological type (WHO I)				
- Meningothelial	6 (11%)	2 (12%)	4 (10.5%)	
- Transitional	27 (49%)	10 (58%)	17 (45%)	
- Fibroblastic	15 (27%)	4 (24%)	11 (29%)	
- Psammomatosus	4 (7%)	1 (6%)	3 (8%)	
- Microcystic	1 (2%)	-	1 (2.5%)	
- Secretory	1 (2%)	-	1 (2.5%)	
- Chordoid	1 (2%)	-	1 (2.5%)	

seven had used it up to 1 to 2 years before the diagnosis. Another patient, a 35-year-old woman with tuberculum sellae meningioma (**Figure 2**), presented visual deficit during the treatment of artificial *in vitro* fertilization and with human chorionic gonadotropin.

Four patients had an associated tumor of the female system diagnosed and treated within 3 years before the meningioma diagnosis; these included ovarian cyst in one case, ovarian adenoma in another, and breast carcinoma in two.

Thirty-nine (54%) among the 72 patients (14 in group A and 25 in group B) experienced one or more previous pregnancies 3 or more years before the meningioma diagnosis. In these patients the previous pregnancy was not considered as hormone-related condition because the pregnancy-related hormonal effects were not present at the meningioma diagnosis. Thus, the correlation between pregnancy and meningioma occurrence and growth was difficult to be defined.

In three women, the onset of the clinical symptoms occurred during pregnancy, between the 26th and 30th gestational weeks (**Table 3**). The tumor location was in all three cases on the midline skull base (ethmoidal–sphenoidal planum in two and tuberculum sellae in one); the tumor size was very large in two cases (6.5 and 7 cm) (**Figures 3**, **4**). A rapid decrease of the visual function was the presenting symptom in all three cases, with intracranial hypertension in one. Surgery for meningioma resection was performed 2 and 7 days after the delivery in two patients, whereas another decided to delay the operation. The tumor resection was complete (Simpson 2) (24). All three meningiomas were WHO grade I with high PR expression (≥80%) and Ki67-LI ≤4%. All three patients were symptom-free with no recurrence 18 months to 3 years after surgery.

Two patients with known meningioma experienced tumor growth during contraceptive therapy with progesterone alone in a close MRI follow-up before surgery. The tumor location was parasagittal in one and tentorial in another; both had low PR values (30 and 1%).

Eight patients of the group of 72 premenopausal women experienced tumor recurrence (11%). It occurred in four cases

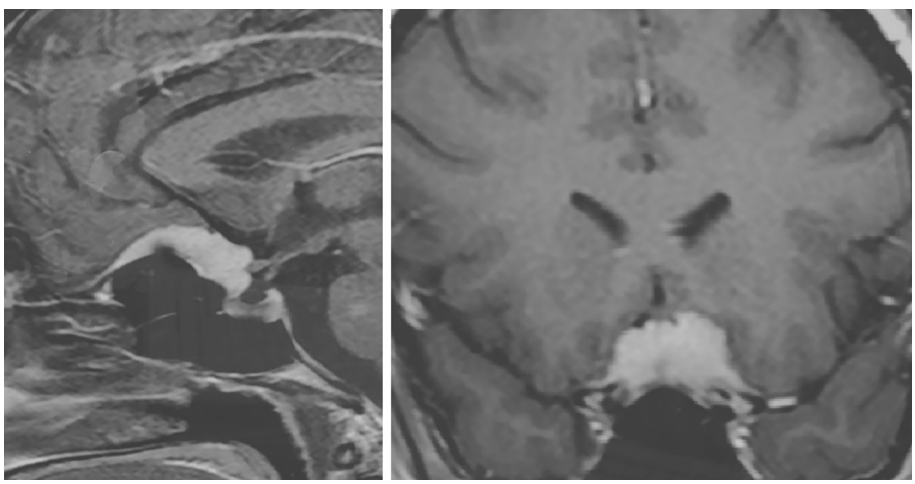


FIGURE 2 | Post-contrast cranial MRI of 35-year-old female with tuberculum sellae meningioma presenting sudden onset of visual deficit during artificial *in vitro* fertilization treatment on the therapy with human chorionic gonadotrophin.

TABLE 3 | Data of three patients with meningiomas presenting during pregnancy.

N. of cases	Age	Gestational age at onset (weeks)	Neurological symptoms	Delivery	Interval time between delivery and craniotomy	Meningioma location and size	Entity of resection	Pathology	Outcome
1.	37 y	26	intracranial hypertension sopor visual loss	cesarian delivery (32 wks)	2 days	ethmoidal–sphenoidal planum (6.5 cm)	complete (Simpson 2)	WHO I, transitional Ki67 3% PR 90%	cured at 6 y
2.	30 y	30	bilateral visual loss	spontaneous delivery (at term)	6 months	ethmoidal–sphenoidal planum (7 cm)	complete (Simpson 2) two stages	WHO I, transitional Ki67 3% PR 90%	cured at 26 mos
3.	28 y	28	bilateral visual loss	spontaneous delivery (at term)	7 days	tuberculum sellae (3 cm)	complete (Simpson 2)	WHO I, transitional Ki67 3% PR 80%	cured at 8 y

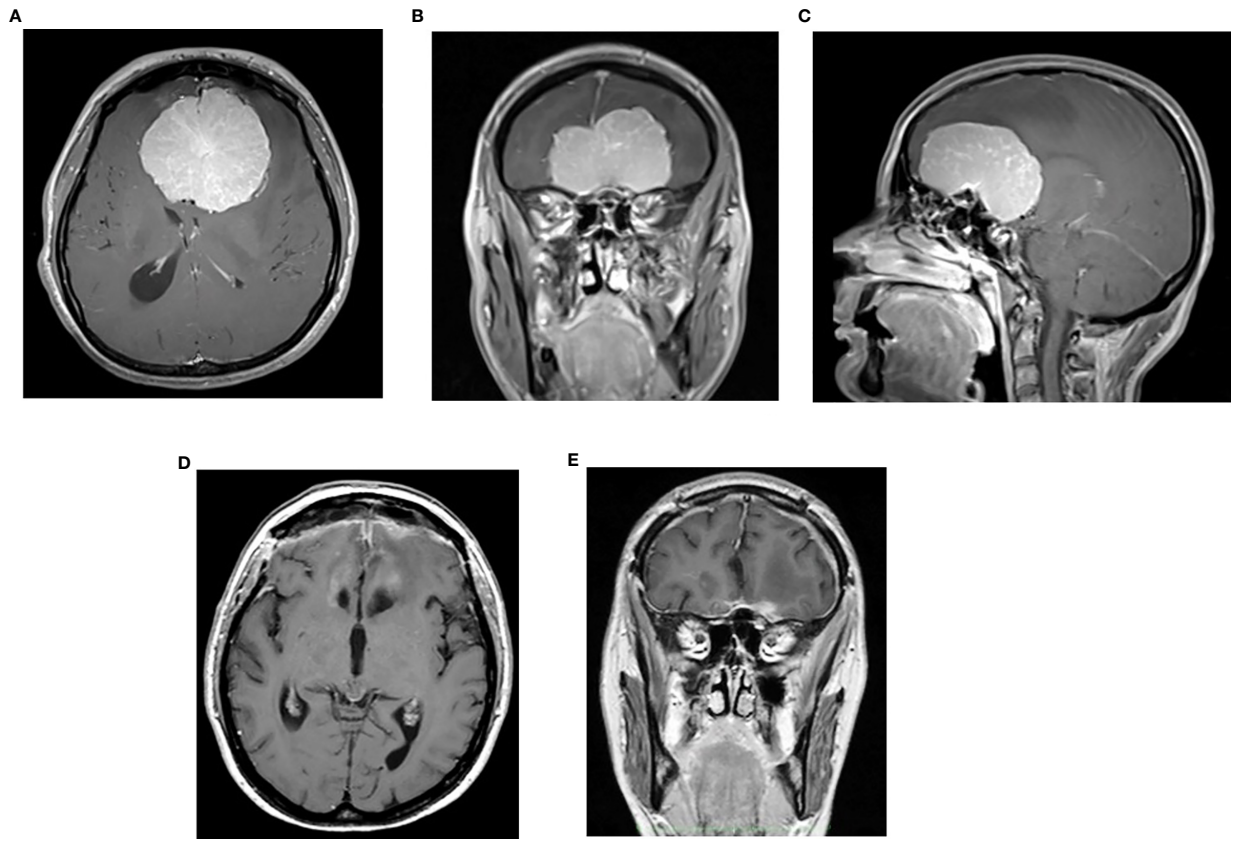


FIGURE 3 | Preoperative post contrast MRI, axial **(A)**, coronal **(B)** and sagittal **(C)** sequences of 37-year-old female with large ethmoidal–sphenoidal planum meningioma presenting with visual loss and intracranial hypertension syndrome at 26th week of pregnancy; postoperative post-contrast axial **(D)** and coronal **(E)** sequences.

(one WHO II and three WHO I) among 24 of group 1A with sex hormone-related conditions (16%) and in four cases (three WHO grade II and one WHO I) among 48 of group 1B with no hormone-related conditions (8%).

DISCUSSION

Meningiomas occur more frequently in postmenopausal women than in premenopausal ones, with a ratio of about 3:1 in our series. This difference is likely due to hormonal differences between the two age groups.

The role of the menopause as a risk factor for meningioma is cited in several studies, which provide controversial results. Some of them report a two to fivefolds higher risk (18, 25–28) or a moderately higher risk (29, 30) in postmenopausal women, whereas no association was found in others (31, 32). The occurrence of meningiomas in premenopausal women may involve some epidemiological and pathological aspects and may be influenced by coexisting hormone-related conditions, such as pregnancy and contraceptive and fertilization therapies.

We will discuss these conditions and the clinical significance of the correlated basic research studies.

Meningioma Location and Pathological Findings

This study first discusses the location and pathological and immunohistochemical findings of meningiomas in premenopausal women.

No significant difference of tumor location was evidenced between premenopausal patients with and without hormone-related conditions. Although we have demonstrated in a previous study that medial skull base meningiomas have higher PR expression than lateral skull base and non-skull base ones (33), this finding is not correlated with the hormonal status.

We did not find significant differences for WHO grade, Ki 67-MIB1, and PR expression in premenopausal women, according to the presence of hormone-related conditions.

These data confirm that the biological behavior of meningiomas and their PR expression are not correlated with the different hormonal status of the female patients.

Pregnancy

The relationship between pregnancy and meningiomas is a discussed problem in the neurosurgical practice. The risk of

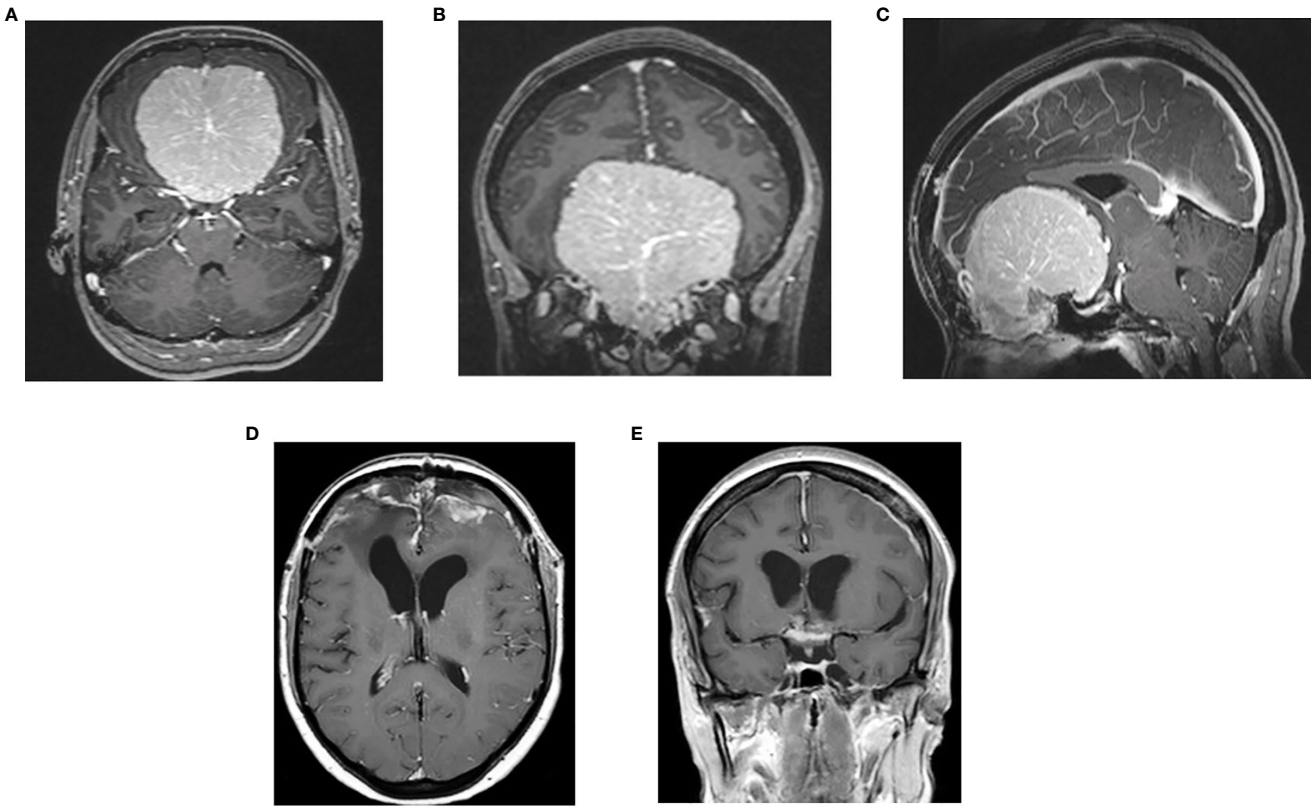


FIGURE 4 | Preoperative post-contrast MRI, axial **(A)**, coronal **(B)** and sagittal **(C)** sequences of 30- year-old female with giant meningioma of spheno-ethmoidal planum presenting with bilateral visual deficit at 30th week of pregnancy; postoperative postcontrast axial **(D)** and coronal **(E)** sequences: complete tumor removal.

meningioma in female patients with one or more previous pregnancies does not seem to be increased (25–27, 30, 32, 34–37).

The onset of neurological symptoms of a known or a still undiagnosed meningioma during pregnancy (more often at the second or third trimester) or at delivery is a rare event which has been reported in 150 cases, as confirmed by several literature reviews (13, 38, 39).

Pregnancy-related meningiomas, when compared to those in the general population, are more frequently supratentorial (95%) and located in the medial skull base (68%); they are more often large (40% >5cm) and present in more than half of the cases with often rapid decrease of the visual function. Most reported cases are WHO grade I (75%), with mean Ki67-LI <4% and mean PR expression of 90%. The three cases of our series agree with these features.

Thus, pregnancy-related meningiomas exhibit more favorable pathological findings suggesting a better prognosis. The often reported sudden onset and rapid progression of clinical symptoms at the second or third trimester may depend on several factors, including increase of size, peritumoral edema, increase of the vascular supply to the tumor and probably pituitary-related hormone changes (13).

The rapid visual deterioration and sudden intracranial hypertension from a large meningioma, as in case one of our series, is a dangerous event at risk of visual deficit. The meningioma resection sudden after delivery is the best option, if possible. However, if necessary, an urgent craniotomy may be decided after the 27th week, or the delivery may be anticipated to allow the craniotomy.

Oral Contraceptives

The use of hormone-based contraceptives is widely diffuse in young women. The risk of meningioma correlated to contraceptive use has been discussed in several studies of the last 20 years (16–18, 20, 22, 26–28, 30, 32, 36, 37, 39). These provide controversial results, depending on several factors, such as type of contraceptive drugs, current or past use, and duration of the treatment.

The studies including patients using progesterone-only contraceptives (17, 18, 22) have shown increased risk of meningioma in those taking therapy for more than 5 years (17) and in those with PR positive meningiomas (18), and increased risk of recurrence and decrease of the progression free-survival (22). Two patients of our series who currently used progesterone-based contraceptives experienced tumor progression before surgical resection.

In the studies including patients who used estrogen-only or estrogen–progesterone contraceptives, those who currently used them showed increased risk of meningioma than those who had used them in the past (26, 27, 36, 39); besides, an increased

meningioma risk was also evidenced for contraceptive use for more than 5 years (26, 27, 31).

The relationship between oral contraceptive use and hormone status of meningiomas is still unclear. Among the 16 patients of our series who used contraceptive therapy the PR expression of the meningioma was ≥80% in eight and <50% in eight, with no statistically significant difference. Korhonen et al. (18) report slightly higher risk for tumors expressing ER than for PR; on the other hand, Horland et al. (22) did not find significant differences. Custer et al. (26) showed increased risk of meningioma with low PR expression during contraceptive therapy. The two patients of our series showing increased tumor growth before surgery had low PR expression (30 and 1%). This agrees with the known more aggressive tumor biology in cases with low PR expression (40).

The experiences of our and other studies suggest avoiding contraceptive therapy, mainly with progesterone, in patients with meningioma.

Fertility Therapies

The fertility treatments include a variety of methods: pharmacological ovarian stimulation, intrauterine insemination, *in vitro* fertilization, injection of human chorionic gonadotropin. One patient of our series with tuberculum sellae meningioma developed visual symptoms during the artificial insemination and treatment with chorionic gonadotropin.

The relationship between fertility treatment and meningiomas has scarcely been discussed. In the study of Korhonen et al. (18) the fertility treatments did not influence the risk of meningioma. Three single case reports describe meningiomas diagnosed in women with history of fertilization (41–43). In the study of Shahin et al. (44), the group of female patients with meningioma and history of fertility treatment had significantly younger age and higher rate of multiple non-skull base meningiomas as compared to the group with no fertility treatment. The development of meningiomas, even multiple, was reported in patients exposed to high-dose progesterone therapy (45, 46). All these data suggest that fertility treatments may influence the meningioma tumorigenesis. However, further studies are needed to better define this relationship.

CONCLUSION

The pathological findings, biological behavior, and PR expression of meningiomas are not correlated with the hormone status and hormone-related conditions of the female patients. Pregnancy may be responsible for the sudden clinical onset of intracranial meningiomas because of the hormone-related tumor changes. Contraceptive and fertilization therapies, mainly with progesterone, should be avoided in patients with known meningiomas because of the risk of symptom occurrence and tumor progression.

Characteristics of the Study

Strengths

This study discusses a scarcely focused aspect of meningiomas concerning their occurrence in premenopausal women and the differences between those with and without hormone-related conditions.

Limitations

This study is retrospective. Data on the hormonal substitution among postmenopausal women are lacking.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Malignant Progression Contributes to the Failure of Combination Therapy for Atypical Meningiomas

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Objective: To investigate the independent risk factors for recurrence in intracranial atypical meningiomas (AMs) treated with gross total resection (GTR) and early external beam radiotherapy (EBRT).

Methods: Clinical, radiological, and pathological data of intracranial AMs treated with GTR-plus-early-EBRT between January 2008 and July 2016 were reviewed. Immunohistochemical staining for Ki-67 was performed. Kaplan–Meier curves and univariate and multivariate Cox proportional hazards regression analyses were used to explore independent predictors of tumor recurrence. Chi square test was performed to compare variables between subgroups.

Results: Forty-six patients with intracranial AMs underwent GTR and early EBRT. Ten (21.7%) recurred and three (6.5%) died during a median follow-up of 76.00 months. Univariate and multivariate Cox analyses revealed that malignant progression (MP) ($P = 0.009$) was the only independent predictor for recurrence, while Ki-67 was of minor value in this aspect ($P = 0.362$). MP-AMs had a significantly higher recurrence rate ($P = 0.008$), a higher proportion of irregularly shaped tumors ($P = 0.013$) and significantly lower preoperative Karnofsky Performance Scale (KPS) scores ($P = 0.040$) than primary (Pri) AMs. No significant difference in Ki-67 expression was detected between these subgroups ($P = 0.713$).

Conclusions: MP was significantly correlated with an increased incidence of recurrence in GTR-plus-early-EBRT-treated intracranial AMs. Significantly higher frequencies of tumor relapse and irregularly shaped tumors and lower preoperative KPS scores were

observed in MP-AMs compared with Pri-AMs. Ki-67 expression is of minor value in predicting tumor recurrence or distinguishing tumor origins in AMs.

Keywords: malignant progression, Ki-67, atypical meningioma, gross-total resection, external beam radiotherapy

INTRODUCTION

Meningiomas are the most common primary intracranial tumors (1). Among the three World Health Organization (WHO) grades of meningiomas, WHO grade II meningiomas are further classified into three subtypes: AMs, chordoid meningiomas, and clear cell meningiomas (2). Their reported incidence increased as the WHO classification was updated, ranging from 19 to 35.5% of all meningiomas in the literature (3–5). They exhibit a higher recurrence rate (up to 30%) and an unfavorable survival outcome than benign meningiomas (BMs, WHO grade I) (4). Treatment approaches for malignant meningiomas (MMs, WHO grade III) were referenced to improve this unsatisfactory prognosis (6). Surgical resection is the primary treatment, and the extent of resection is considered the most important factor for predicting recurrence and survival (7, 8). Previous studies have also demonstrated that adjuvant radiotherapy significantly improves progression-free survival (PFS) and overall survival (OS) after subtotal resection (STR) of AMs (9). However, its efficiency in those following GTR remains heavily debated (10) and has consequently led to non-uniform clinical decision-making across institutions (6). Confounding effects of different subtypes of WHO grade II meningiomas (11–14), different radiation methods (15, 16), timing of radiation (17–19), *etc.*, in previous studies may have contributed to this uncertainty and complicated the exploration of possible prognostic factors. Therefore, these effects were eliminated in the present study to target the precise reasons for the recurrence of GTR-plus-early-EBRT-treated intracranial AMs.

MATERIALS AND METHODS

Inclusion Criteria and Clinical Data Collection

Medical records and radiologic data of intracranial AM patients who underwent operations in the Department of Neurosurgery, Beijing Tian Tan Hospital, Capital Medical University from January 2008 to July 2016 were reviewed. All pathology slides were centrally reviewed and graded based on the 2016 revision of the WHO classification of tumors of the central nervous system (20) (independently by two neuropathologists blinded to clinical history, and a senior neuropathologist made the judgment if there was a discrepancy). Patients who underwent GTR as well as adjuvant EBRT at their initial pathological diagnosis of AM were included. The following exclusion criteria were adopted to explore prognostic factors more objectively: 1) pathological diagnosis of chordoid or clear cell meningioma; 2) received any other form of radiotherapy; 3) without explicit documentation of an EBRT plan; 4) lack of timely adjuvant EBRT [which was defined as within 6 months postoperatively in the literature (17)] or EBRT was postponed/terminated early; and 5) diagnosis of neurofibromatosis.

Data of the included patients were compiled from medical records, imaging, and pathological tests, and other records provided by the patients themselves. Follow-ups were performed by postoperative outpatient visits. The extent of resection was based on both the surgeon's impression during surgery and our review of the first postoperative magnetic resonance imaging (MRI) scans. GTR was defined as Simpson grades I–II. AMs were stratified into the Pri group and the MP group based on tumor origins. MP-AMs refer to AMs who were pathologically diagnosed as BMs in previous surgeries and/or histopathologically confirmed to transform into MMs in subsequent surgeries. Others without any documentation of progression were considered as Pri-AMs. Tumor location was divided into the skull base group (including sphenoidal ridge, petroclival, foramen magnum, middle fossa, olfactory groove and orbital meningiomas) and the non-skull base group (including convexity, parasagittal, falx, cerebellar convexity, lateral ventricular and tentorial meningiomas). Tumor shape was classified as either irregular or regular based on the presence or absence of lobulation at the tumor–brain interface (mushroom-shaped tumors were included in the irregularly shaped group). PFS was defined as the period between the onset of surgery prior to EBRT and the observation of imaging-verified disease progression. OS was defined as the period from the date of surgery prior to EBRT to death or the last follow-up.

Pathological Examination

All AM samples were obtained during the surgery right before EBRT and were formalin-fixed and paraffin-embedded (FFPE) postoperatively. Hematoxylin and eosin (HE) staining and immunohistochemical staining for Ki-67 (the primary Ki-67 antibody was obtained from Abcam, Cambridge, Massachusetts, USA) were performed.

Statistical Analysis

The baseline patient characteristics are summarized as percentages for categorical variables and as the mean ± standard deviation for continuous variables. Univariate and multivariate Cox proportional hazards regression analyses were used to assess correlations between various factors and recurrence. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Kaplan–Meier curves were generated to graphically display the associations between

Abbreviations: AM, atypical meningioma; BM, benign meningioma; CI, confidence interval; EBRT, external beam radiotherapy; FFPE, formalin-fixed and paraffin-embedded; GTR, gross total resection; HE, hematoxylin and eosin; HR, hazard ratio; KPS, Karnofsky Performance Scale; MM, malignant meningioma; MP, malignant progression; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; Pri, primary; STR, subtotal resection; IR, ionizing radiation.

variables and PFS. Chi square test was performed to compare variables between different subgroups. All P values are two-sided, and significance was defined using a threshold of 0.05. Statistical analyses were performed with SPSS Statistics software (version 19.0; IBM Corporation, Armonk, NY, USA). The hospital ethics committee approved this study, and all patients provided written consent.

RESULTS

Patient Demographics and Tumor Characteristics

A total of 46 intracranial AM patients met the aforementioned criteria, including 25 (54.3%) males and 21 (45.7%) females. The male-to-female ratio was 1.19:1. The mean age at the first presentation of AM was 49.67 ± 13.15 years (range, 20–77 years). The median surgery-radiation interval was six weeks (range, 2–21 weeks). The median radiation dose of EBRT was 60 Gy (range, 50–63 Gy; delivered to the tumor bed in 1.8- to 2.0-Gy fractions). Ten patients (21.7%) experienced tumor relapse and three patients (6.5%) died before the last follow-up (May 2020). All these three fatalities were due to meningiomas. The median follow-up duration was 76.00 months (range, 48–144 months). The median PFS was 73.50 months (range, 21–144 months). 16 (34.8%) AMs experienced MP. All of these 16 patients progressed from BMs before the combination therapy, and one of them experienced another transformation (from AM to MM) during the follow-up (**Table 1**).

Univariate and Multivariate Analyses Associated With Tumor Recurrence

The univariate Cox analysis showed that the PFS of GTR-plus-early-EBRT-treated AM patients was significantly influenced by MP (P = 0.012). A high radiation dose (≥60.0 Gy), a Simpson grade II resection and a skull base location were not significant prognostic factors for PFS. Since Ki-67 has been widely correlated with cell proliferation and the degree of malignancy of meningeal tumors (21, 22), both MP and Ki-67 were incorporated in the multivariate analysis. The multivariate Cox analysis revealed that only MP was an independent predictor of tumor recurrence in GTR-plus-early-EBRT-treated AMs (P = 0.009) (**Table 2**, **Figure 1**). Regarding OS, three patients died during the follow-up, all of whom experienced MP prior. However, this event number was too small to be used for further exploration of the prognostic factors of OS.

Comparison Between Primary-Atypical Meningiomas and Malignant Progression-Atypical Meningiomas

The characteristics of Pri-AMs and MP-AMs were compared. The recurrence rate (P = 0.008) and the proportion of irregularly shaped tumors were significantly higher in MP-AMs than in Pri-AMs (P = 0.013), while the preoperative KPS score was significantly lower in MP-AMs than in Pri-AMs (P = 0.040). No significant differences in the radiation dose, surgery-radiation interval or Ki-67 expression level were detected between the groups (**Table 3**).

DISCUSSION

In the present study, MP was the only independent risk factor for tumor recurrence in GTR-plus-early-EBRT-treated AMs (**Table 2**). MP-AMs accounted for 34.8% (16/46) of the current series (**Table 1**). Except for their higher tendency of recurrence as compared with Pri-AMs, their lower preoperative KPS score and higher proportion of irregular-shaped tumors were also presented (**Table 3**). In addition, three patients died during follow-up, all of whom were MP-AM patients (**Table 1**).

Malignant Progression Meningiomas

High Proportions of Malignant Progression in Recurrent Meningiomas and Non-Benign Meningiomas

The clinical value of MP has been underestimated due to its low incidence in the entire meningiomas (0.16 to 2%) (23, 24). However, MP-meningiomas account for a large proportion of recurrent meningiomas and non-benign meningiomas. 14 to 28.5% of recurrent BMs transform into atypical or malignant lesions (25–27), and this rate rises to approximately 26 to 33% in recurrent AMs (25, 27, 28). MP-meningiomas have been reported as high a proportion as 38% of AMs and 70% of MMs (29). In the present cohort, 34.8% (16/46) of AMs progressed from BMs (**Table 1**), consistent with previous literature; 43.8% (7/16) of MP-AMs recurred, which was significantly higher than that of Pri-AMs (10%, 3/30) (p = 0.008) (**Table 3**); and among these recurrent AMs, MP-AMs accounted for up to 70% (7/10). Due to our strict criteria, the current high proportions of MP-AMs failed to reflect the situations when GTR and/or early EBRT were not achieved. Nevertheless, these high frequencies of MP-meningiomas in recurrent meningiomas and non-benign meningiomas reflect the poor efficacy of the existing therapies on MP-meningiomas. Therefore, MP of meningiomas is of value and should be considered in the prognostic analyses.

Unsatisfactory Therapeutical Efficacy in Malignant Progression Meningiomas

A prognostic benefit associated with Pri-meningiomas has been previously reported in the literature. Krayenbühl et al. demonstrated a statistically significant decrease in the survival time of MP-AMs (average, 1.95 years; range, 1.02–15.95 years) as compared with Pri-AMs (average, 5.36 years; range, 0.07–7.71 years), and they postulated that this difference was caused by the increased technical difficulty of GTR in reoperations and the more aggressive behavior of MP-AMs (29). Moliterno et al. exhibited an OS advantage in patients with Pri-MMs independent of the extent of resection (medium OS: Pri-MM, 3.0 years; MP-MM, 2.4 years), though this finding was prohibited from reaching statistical significance in their multivariate analysis by their small sample size (30). An OS disadvantage in MP-AM patients can also be observed in the present study since three patients died during follow-up and they were all MP-AM patients. Likewise, further analyses were also limited by the small event number, which may be due to the strict criteria applied.

TABLE 1 | Baseline characteristics of 46 combination-therapy-treated intracranial AM patients.

Characteristic	Total (n = 46)	Pri-AM (n = 30)	MP-AM (n = 16)
Tumor origin, n (%)	46 (100.0)	30 (65.2)	16 (34.8)
Age (years)			
Median (range)	53 (20–77)	53.50 (24–77)	47 (20–65)
Mean ± SD	49.67 ± 13.15	51.13 ± 12.58	46.94 ± 14.17
Gender, n (%)			
Female	21 (45.7)	13 (43.3)	8 (50.0)
Male	25 (54.3)	17 (56.7)	8 (50.0)
Tumor location, n (%)			
Non-skull base	33 (71.7)	22 (73.3)	11 (68.8)
Convexity	11	7	4
Parasagittal	5	3	2
Falx	7	6	1
Cerebellar convexity	3	2	1
Lateral ventricular	4	1	3
Tentorial	3	3	0
Skull-base	13 (28.3)	8 (26.7)	5 (31.3)
Sphenoidal ridge	5	3	2
Petroclival	4	2	2
Foramen magnum	1	1	0
Middle fossa	1	1	0
Olfactory groove	1	1	0
Orbital	1	0	1
Max tumor diameter (mm)			
Median (range)	50 (12–100)	50.50 (24–79)	45.50 (12–100)
Mean ± SD	51.15 ± 18.02	52.20 ± 15.48	49.19 ± 22.46
Preoperative KPS			
Median (range)	80 (60–100)	90 (60–100)	80 (60–90)
Mean ± SD	82.61 ± 8.80	84.33 ± 8.58	79.38 ± 8.54
Postoperative KPS			
Median (range)	90 (70–100)	90 (70–100)	80 (70–90)
Mean ± SD	85.43 ± 7.52	86.33 ± 8.09	83.75 ± 6.19
Intraoperative blood loss (ml)			
Median (range)	400 (100–4,000)	400 (100–4,000)	350 (200–1,000)
Mean ± SD	638.04 ± 723.43	755.00 ± 859.57	418.75 ± 250.92
GTR + early EBRT, n (%)	46 (100.0)	30 (100.0)	16 (100.0)
Simpson grading, n (%)			
Grade I	37(80.4)	26 (86.7)	11 (68.8)
Grade II	9(19.6)	4 (13.3)	5 (31.3)
Surgery-radiation interval (weeks)			
Median (range)	6 (2–21)	5.50 (2–21)	6 (2–15)
Mean ± SD	6.67 ± 4.08	6.40 ± 4.22	7.19 ± 3.89
Radiation dose (Gy)			
Median (range)	60 (50–63)	60 (50–63)	60 (50–63)
Mean ± SD	57.97 ± 4.09	58.13 ± 4.09	57.69 ± 4.22
PFS (months)			
Median (range)	73.50 (21–144)	81.00 (21–144)	63.00 (21–112)
Mean ± SD	76.02 ± 28.27	82.80 ± 26.80	63.31 ± 27.28
Follow-up (months)			
Median (range)	76.00 (48-144)	81.00 (54-144)	72.50 (48-112)
Mean ± SD	81.89 ± 22.75	84.73 ± 24.36	76.56 ± 18.97
Recurrence, n (%)	10 (21.7)	3 (10.0)	7 (43.8)
Frequency of recurrence			
Median (range)	0 (0-3)	0 (0-1)	0 (0-3)
Mean ± SD	0.26 ± 0.61	0.07 ± 0.25	0.63 ± 0.89
Frequency of operation before MP			
Median (range)	— —	— —	1 (1-3)
Mean ± SD	— —	— —	1.31 ± 0.60
Pathways of MP, n (%)			
Benign to Atypical	— —	— —	15 (93.8)
Benign to Atypical to malignant	— —	— —	1 (6.7)
Death, n (%)	3 (6.5)	0 (0.0)	3 (18.8)

AM, atypical meningioma; EBRT, external beam radiotherapy; GTR, gross total resection; KPS, Karnofsky performance score; MP, malignant progression; PFS, progression-free survival; Pri, primary; SD, standard deviation.

TABLE 2 | Univariate and multivariable Cox regression predicting tumor recurrence in 46 combination-therapy-treated intracranial AM patients.

Variables	Univariate		Multivariate	
	HR(95%CI)	p	HR(95%CI)	p
Age ≥ 50 years	0.354(0.091–1.371)	0.133		
Male	0.844(0.244–2.926)	0.789		
MP-AM	5.676(1.454–22.167)	0.012*	6.354(1.571–25.697)	0.009*
Preoperative KPS ≥ 90	1.300(0.374–4.522)	0.679		
Postoperative KPS ≥ 90	0.870(0.245–3.086)	0.829		
Skull base group	1.109(0.286–4.304)	0.881		
Max tumor diameter ≥ 50.0 mm	0.848(0.245–2.933)	0.795		
Heterogeneous contrast enhancement	1.371(0.387–4.865)	0.625		
Cystic tumor	22.923(0.001–5.917 × 10^5)	0.546		
Hemorrhage or necrosis	22.923(0.001–5.917 × 10^5)	0.546		
Intratumoral calcification	21.143(0.000–3.650 × 10^8)	0.720		
Nerves/vessels involved	1.628(0.420–6.320)	0.481		
Irregular-shaped	1.107(0.319–3.836)	0.873		
Ill-defined margins	1.523(0.323–7.187)	0.595		
Peritumoral edema	0.971(0.249–3.784)	0.967		
Midline shift	0.953(0.274–3.310)	0.940		
Compressed ventricles	0.474(0.060–3.745)	0.479		
Cerebral hernia	1.320(0.278–6.262)	0.727		
Empty sella	1.143(0.296–4.423)	0.846		
Larger intraoperative blood loss	2.221(0.570–8.648)	0.250		
Simpson grade II	1.070(0.227–5.040)	0.932		
Surgery-radiation interval ≥ 6 weeks	0.869(0.251–3.003)	0.824		
Radiation dose ≥ 60.0 Gy	0.583(0.164–2.069)	0.404		
Ki-67 ≥ 5%	1.340(0.377–4.771)	0.651	1.849(0.493–6.930)	0.362

AM, atypical meningioma; CI, confidence interval, HR, hazard ratio; KPS, Karnofsky performance score; MP, malignent progression.
**P value < 0.05 indicates statistical significance.*

Meanwhile, MP was a significant independent predictive factor for tumor recurrence in combination-therapy-treated AMs (**Table 2**). These findings underscore the value and advantages of exploring an effective identification method of MP-meningiomas.

Even after administration of the combination therapy described herein, the recurrence risk of MP-AMs was still high (43.8%), which may question the necessity of adjuvant radiotherapy (**Table 1**). It has been demonstrated that ionizing radiation (IR) can enhance cellular invasion and induce malignant transformation in several cancer cells (including breast, lung, and liver cancer and glioma cells) (31–36). Our previous study confirmed that the invasiveness of IOMM-Lee meningioma cells can also be promoted by IR (37). In the context of the unsatisfactory efficacy of combination therapy in MP-AMs and the shortage of effective IR-induced MP-meningioma models (38), whether radiotherapy improves the prognosis of MP-AMs or stimulates them to undergo MP and recur requires further investigation.

Identification of Malignant Progression Meningiomas

At present, the clinical method of identifying MP meningiomas is based on the comparison between former and present pathologic diagnoses. However, for initial treatment, the effectiveness of this method is restricted. Continuous efforts have been made to identify MP-meningiomas cytogenetically and clinically. Accumulated evidences indicated that meningiomas can be classified into two distinct subtypes based on their origins: Pri- and MP-meningiomas (29, 30, 39). Meningiomas with different progression statuses possess variant molecular bases and display distinct clinical characteristics and behaviors (29, 30).

① Cytogenetical Differences Between Primary and Malignant Progression Meningiomas

A stepwise clonal evolution model was initially used to explain the MP in meningiomas (40), which states that the malignancy of meningiomas progresses as genetic alterations accumulate (41–44). That is, more aggressive meningiomas tend to present with more complex karyotypes (41). However, this model was proposed based on cytogenetic alterations in large groups of patients with different grades of tumors (39). It is more of a reflection of the difference between WHO grades than a reflection of the difference between prior- and post-status of MP. Moreover, complex karyotypes have been detected in BMs by Perry et al. (45). Based on an analysis of the biological and genetic findings in specimens of successive histological grades of each MP meningioma, a predetermined-progression notion was developed by Al-Mefty and his colleagues (39). They documented that the presence of complex karyotypes in benign tumors preceded the histopathological manifestation of malignancy, which raised the possibility that these tumors were intrinsically malignant and destined to progress. The clonal evolution model states that lower-grade tumors possess lower karyotype complexity, while the predetermined-progression notion states that complex karyotypes already exist in lower-grade statuses of MP-meningiomas. Hence, there is a possibility that, in meningiomas of a same grade, those with higher

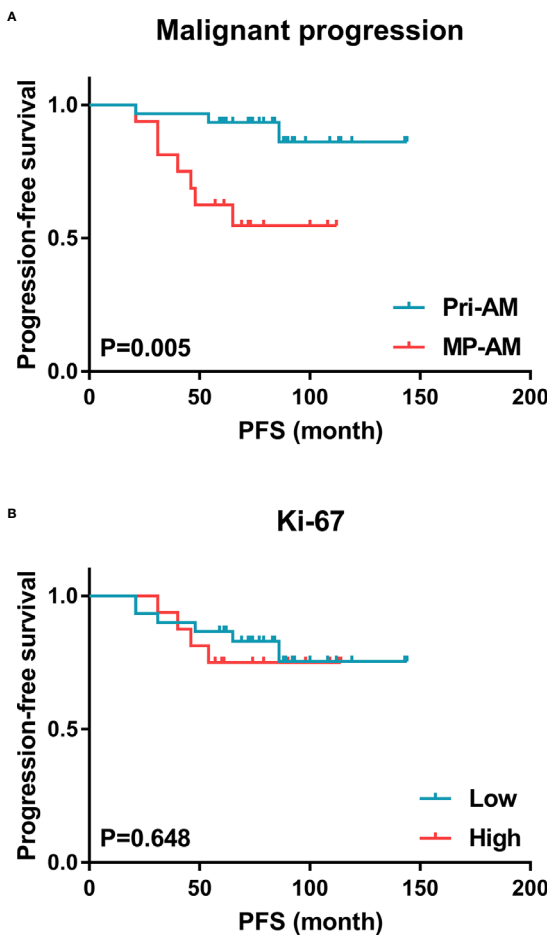


FIGURE 1 | Kaplan–Meier estimates of PFS for combination-therapy-treated AM patients. **(A)** Malignant progression was a significant predictor of tumor recurrence in GTR-plus-early-EBRT-treated AMs, while **(B)** the Ki-67 expression level was of minor value in this respect (AM, atypical meningioma; PFS, progression-free survival).

karyotype complexity may indicate that they are MP-meningiomas, otherwise they are may be Pri-meningiomas. As the only cytogenetic comparison of Pri- and MP-meningiomas to date, Krayenbühl et al. described higher frequencies of combined cytogenetic changes (chromosomes 1, 14 and 22) and monosomy of chromosomes 10 and 18 in MP-AMs and MP-MMs than in their Pri counterparts, respectively (29). Therefore, the Pri- and MP-meningiomas of a same grade may be distinguished by their karyotype differences.

② Clinical Differences Between Primary and Malignant Progression Meningiomas

The distribution of locations of Pri- and MP-meningiomas has been reported diversely. Based on a research with a high percentage of skull base meningiomas (61.1%, 22/36), Krayenbühl et al. reported that primary grade II-III meningiomas were predominately located in the cranial base (73.7%, 14/19), whereas progressed grade II–III meningiomas displayed a similar distribution in the skull base (47.1%) and non-skull base (52.9%) regions (29). In Moliterno's study of MMs, the majority of tumors were located along the convexity/parasagittal areas (73.0%, 27/37). In their study, the majority of MP-MMs were located in the skull-base/posterior fossa (57%, 8/14), while Pri-MMs were discovered almost exclusively in the convexity/parasagittal regions (91%, 21/23) (30). In the present study, in which non-skull base AMs accounted for 71.7% of the cohort, a non-skull base predominance in AMs was observed regardless of the progression status (Pri-AMs: 73.3%; MP-AMs: 68.8%) (**Table 3**).

In addition, Moliterno et al. also detected a slight female predominance in Pri-MMs, and all of the Pri-MMs with metastatic lesions in their series were located along the convexity/parasagittal area (30). In the present study, patients with MP-AMs had lower preoperative KPS scores than those with Pri-AMs, which might be due to their higher frequency of previous surgeries, and the tumors were more likely to be irregular-shaped, which might be attributed to differences in the growth velocity of different regions of the tumor (46) (**Table 3**).

Minor Value of Ki-67 in the Recurrence Prediction and Origin Identification of Atypical Meningomas

Minor Value of Ki-67 in Predicting Recurrence of Gross Total Resection-Plus-Early-External Beam Radiotherapy-Treated Atypical Meningiomas

Ki-67 has been widely used in studies of the proliferative potential of meningiomas (22). A recent meta-analysis by Liu et al. indicated a significant adverse prognostic value of a high Ki-67 expression level in the prognosis of meningiomas, and 4% was recommended as the appropriate cutoff value (47). Of their 43 included studies (comprising 5012 patients), only seven specifically targeted WHO grade II meningiomas and evaluated the prognostic value of Ki-67 expression in tumor recurrence (11–14, 48–50). Each of these seven studies met at least two of the following situations: 1) inclusion of chordoid and/or clear cell meningiomas; 2) with/without postoperative radiotherapy and/or different radiotherapy modalities; and 3) diverse Ki-67 cutoff values. Based on a relatively short follow-up (1–50 months; median: 10 months), Siegers et al. stated that differences in Ki-67 expression could not be observed between three recurring and 49 non-recurring meningiomas (51). Defining non-recurring meningiomas as those without recurrence at least 8 years postoperatively, Maj-Lis Møller and Otto Brændstrup detected no significant differences in the Ki-67 labeling index between recurring and non-recurring meningiomas, when either totally and subtotally resected tumors were studied or when only radically resected tumors were studied (52). Likewise, our present results suggest that the Ki-67 expression level cannot be used as a predictor of recurrence in GTR-plus-early-adjuvant-EBRT-treated AMs. The possible reasons may be as follows. First, tumor recurrence is not dependent solely on the proliferative status of cells, especially for tumors that have undergone radical GTR. Second, the mitotic index, a

TABLE 3 | Clinical characteristics of different origins of 46 combination-therapy-treated intracranial AMs.

Variable, n (%)	Overall	Tumor origin		
		Pri-AM (n = 30)	MP-AM (n = 16)	P
Age				0.292
<50 years	21(45.7)	12 (40.0)	9 (56.3)	
≥50 years	25(54.3)	18 (60.0)	7 (43.8)	
Gender				0.665
Female	21 (45.7)	13 (43.3)	8 (50.0)	
Male	25 (54.3)	17 (56.7)	8 (50.0)	
Preoperative KPS				0.040*
<90	25(54.3)	13 (43.3)	12 (75.0)	
≥90	21(45.7)	17 (56.7)	4 (25.0)	
Postoperative KPS				0.082
<90	18(39.1)	9 (30.0)	9 (56.3)	
≥90	28(60.9)	21 (70.0)	7 (43.8)	
Tumor location				1.000†
Non-skull-base	33 (71.7)	22 (73.3)	11 (68.8)	
Skull-base	13 (28.3)	8 (26.7)	5 (31.3)	
Max tumor diameter				0.292
<50.0 mm	21(45.7)	12(40.0)	9(56.3)	
≥50.0 mm	25(54.3)	18(60.0)	7(43.8)	
Contrast enhancement				0.421
Homogeneous	15(32.6)	11(36.7)	4(25.0)	
Heterogeneous	31(67.4)	19(63.3)	12(75.0)	
Cystic component				0.496†
Absent	43(93.5)	27(90.0)	16(100.0)	
Present	3(6.5)	3(10.0)	0(0.0)	
Hemorrhage or necrosis				1.000†
Absent	43(93.5)	28(93.3)	15(93.8)	
Present	3(6.5)	2(6.7)	1(6.3)	
Intratumoral calcification				1.000†
Absent	45(97.8)	29(96.7)	16(100.0)	
Present	1(2.2)	1(3.3)	0(0.0)	
Nerves/vessels involvement				0.869
Uninvolved	18 (39.1)	12 (40.0)	6 (37.5)	
Involved	28 (60.9)	18 (60.0)	10 (62.5)	
Shape of tumor				0.013*
Regular	23 (50.0)	19 (63.3)	4 (25.0)	
Irregular	23 (50.0)	11 (36.7)	12 (75.0)	
Tumor margins				0.635†
Well-defined	34 (73.9)	21 (70.0)	13 (81.3)	
Ill-defined	12 (26.1)	9 (30.0)	3 (18.8)	
Peritumoral edema				1.000†
Absent	14 (30.4)	9 (30.0)	5 (31.3)	
Present	32 (69.6)	21 (70.0)	11 (68.8)	
Midline shift				0.686
Absent	24 (52.2)	15 (50.0)	9 (56.3)	
Present	22 (47.8)	15 (50.0)	7 (43.8)	
Compressed ventricles				0.558†
Absent	8 (17.4)	4 (13.3)	4 (25.0)	
Present	38 (82.6)	26 (86.7)	12 (75.0)	
Cerebral hernia				0.813†
Absent	35 (76.1)	22 (73.3)	13 (81.3)	
Present	11 (23.9)	8 (26.7)	3 (18.8)	
Empty sella				0.066
Absent	31 (67.4)	23 (76.7)	8 (50.0)	
Present	15 (32.6)	7 (23.3)	8 (50.0)	
Intraoperative blood loss				0.829
<400 ml	22 (47.8)	14 (46.7)	8 (50.0)	
≥400 ml	24 (52.2)	16 (53.3)	8 (50.0)	
Simpson grading				0.285†
Grade I	37(80.4)	26 (86.7)	11 (68.8)	
Grade II	9(19.6)	4 (13.3)	5 (31.3)	
Surgery-radiation interval				0.418
<6 weeks	21 (45.7)	15 (50.0)	6 (37.5)	
≥6 weeks	25 (54.3)	15 (50.0)	10 (62.5)	
Radiation dose				1.000†
<60.0 Gy	14 (30.4)	9 (30.0)	5 (31.3)	
≥60.0 Gy	32 (69.6)	21 (70.0)	11 (68.8)	
Ki-67				0.713
<5%	30(65.2)	19 (63.3)	11 (68.8)	
≥5%	16(34.8)	11 (36.7)	5 (31.3)	
Recurrence				0.008*
Absent	36(78.3)	27 (90.0)	9 (56.3)	
Present	10(21.7)	3 (10.0)	7 (43.8)	

AM, atypical meningioma; KPS, Karnofsky performance score; MP, malignant progression; Pri, primary.

**P value <0.05 indicates statistical significance.*

†Correction for continuity.

proliferation marker, has been utilized as a standard in the WHO classification of meningiomas (49, 53). Therefore, the difference in tumor cell proliferation ability among meningiomas of the same grade is not as obvious as that among meningiomas of different grades. The expression of Ki-67, another proliferation marker, is also associated with cell proliferation (54). Its labeling index determines the growth fraction of tumors in percentages and is widely used to estimate tumor prognoses. The Ki-67 expression level fluctuates throughout the cell cycle, peaks in mitosis (M phase) but is absent in the resting phase (G_0 phase) (55, 56). Consequently, the correlation between the peak expression level of Ki-67 in mitosis and the mitotic index leads to a minor difference in Ki-67 expression among meningiomas of the same WHO grade. Third, the abovementioned differential expression of Ki-67 among phases is also related to its role in estimating radioresistance (49). It has been substantiated that meningiomas with a higher Ki-67 labeling index may be more susceptible to adjuvant radiotherapy (49). In the present study, all the samples were obtained before IR, and all the patients received EBRT postoperatively. Hence, it is possible that some of these AMs with higher Ki-67 expression might present higher radiosensitivity to EBRT and obtain better prognoses thereafter. To a certain extent, these aforementioned points might restrict Ki-67's ability to predict tumor recurrence in GTR-plus-early-adjuvant-EBRT-treated AMs.

Minor Value of Ki-67 in the Origin Identification of Atypical Meningiomas

The positive correlation between the Ki-67 expression level and the degree of malignancy of meningeal tumors has also been reported (21), yet this conclusion was derived mostly from studies including multiple grades of meningiomas. In a study of meningiomas with the same WHO grade yet different origins, Krayenbühl and colleagues explored a statistically significant increase in the number of MP-AM patients with high

proliferative indices (a Ki-67 index greater than 5% was considered high) compared with Pri-AM patients. However, it should be noted that only 20 patient samples were stained for Ki-67. Maj-Lis Møller and Otto Brændstrup detected no differences between the Ki-67 labeling index of BMs that recurred as BMs, WHO grade II meningiomas or MMs. In other words, the expression level of Ki-67 cannot be used to judge whether a BM will experience MP. Similarly, it cannot be used to determine whether an AM is primary or malignant progressed based on our results (**Table 3**). According to Al-Mefty's theory, some lower-grade meningiomas that harbor complex genetic aberrations are predetermined to histopathological progression to malignancy. They also stated that proliferation indices denoted something that was already occurring in the tumor cells more than they predicted the tumor's potential behavior. That is to say, MP in meningiomas is a predestined but gradually manifested process. The proliferation index at one certain point in time cannot fully reflect the pre- or post-MP state of these cells. This may explain the current inability to determine the genesis of AMs by the expression level of Ki-67.

LIMITATIONS

Potential limitations of this study should be taken into consideration. First, selection bias is inevitable due to the single-center-based retrospective design and the selection of GTR-plus-early-EBRT-treated AMs as the research object. Second, the present rigorous criteria restricted the sample size and the statistical power, and the small event number of death further restricted the exploration of the prognostic factors for OS in GTR-plus-early-EBRT-treated AMs and its difference between Pri-AMs and MP-AMs. Third, the present identification method of MP in meningiomas was based on the comparison between former and present pathologic diagnoses. Hence, there still exist uncertainties that some Pri-AMs in the present study may arise from BMs before any surgery or progress to MMs in the future even though the shortest follow-up period in the current cohort exceeded the reported mean period for MP-AM progression to MM (39.8 months) (57).

CONCLUSIONS

MP is the only independent predictor of tumor recurrence in GTR-plus-early-EBRT-treated AMs. Satisfactory efficacy was not achieved in MP-AMs even after radical combination therapy. Significant higher frequencies of tumor relapse and irregularly shaped tumors as well as lower preoperative KPS scores were observed in MP-AMs than in Pri-AMs. The Ki-67 expression level is of minor value in predicting tumor recurrence or distinguishing tumor origins in AMs. More accurate and effective methods to distinguish MP-AMs from Pri-AMs are required. Further comparisons between MP-AMs with or without adjuvant radiotherapy after GTR, and the construction of effective IR-induced MP-meningioma models will be helpful to assess the necessity of radiotherapy in preventing the recurrence of MP-AMs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials; further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Beijing Tian Tan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors conceptualized and made the experimental design. QZ, ZWe, MN, DL, and KW acquired the data. QZ, ZWe, MN, DL, and KW analyzed and interpreted the data. QZ drafted the article. All authors critically revised the article. WJ, JZ, and LW provided administrative/technical/material support. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Effectiveness of Postoperative Adjuvant Radiotherapy in Atypical Meningioma Patients After Gross Total Resection: A Meta-Analysis Study

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Background: It still remains unclear whether patients with atypical meningioma (AM) could benefit from postoperative adjuvant radiotherapy (PORT) after gross-total resection (GTR).

Objective: Exploring the effectiveness of PORT on AM patients after GTR.

Methods: Literatures on PubMed, Embase, Web of science, and Scopus databases published between January 2000 and January 2019 were searched. After the selection based on the certain exclusion criteria, the Newcastle-Ottawa evaluation scale was used to evaluate the quality of the included literatures. Finally, a meta-analysis was conducted to analyze the effectiveness of PORT on local control (LC), progression-free survival (PFS) and overall survival (OS) in atypical meningioma patients after GTR.

Results: A total of 17 articles with 2,008 AM patients were included in the meta-analysis. The 5-year LC, 5-year PFS, and 5-year OS rates were 82.2, 84.1, and 79.0%, respectively, for AM patients receiving PORT after GTR, and they were 71.0, 71.9, and 81.5%, respectively, for those not receiving PORT after GTR. PORT could significantly improve 5-year LC rate (OR [95% CI] = 2.59 [1.40–4.81], $P = 0.002$) and 5-year PFS rate (OR [95% CI] = 1.99 [1.35–2.95], $P = 0.001$), but did not significantly improve 5-year OS rate (OR [95% CI] = 1.07 [0.60–1.91], $P = 0.828$).

Conclusion: PORT could improve the 5-year LC rate and 5-year PFS rate in AM patients after GTR. AM patients might benefit from PORT after GTR.

Keywords: atypical meningioma, radiotherapy, gross-total resection, surgery, prognosis

INTRODUCTION

Meningiomas are the most common primary intracranial tumors with an incidence rate of about 8 per 100,000 population, accounting for approximately 37% of all central nervous system tumors (1). According to WHO 2016 classification, it can be divided into WHO grades I–III (2).

Compared to benign meningiomas (WHO grade I), atypical meningiomas (WHO grade II) have a more aggressive behavior, a higher risk of recurrence (seven to eight times increased in 5 years) and a higher mortality (3–5). Therefore, it is particularly important to find out the factors which could significantly influence the prognosis of AM patients. The common consensus is that postoperative adjuvant radiotherapy (PORT) is generally recommended for meningioma patients underwent subtotal resection (STR). Whether AM patients need PORT after GTR depends on the grade of meningiomas (6). After GTR, follow-up observation is generally recommended for benign meningioma patients, while adjuvant radiotherapy is routinely recommended for malignant meningioma patients (WHO grade III) (6). But there is still a controversy for atypical meningioma (AM) patients because of the unclear effectiveness of PORT. Several studies with small sample sizes have been performed to investigate the effect of PORT in AM patients after GTR, but obtained contradictory results (7–25). A recent study based on the National Cancer Database found that PORT and GTR were both associated with improved survival for AM patients (26). Whereas our recent study based on the Surveillance, Epidemiology, and End Results database found that PORT might not prolong the overall survival (OS) in AM patients undergoing GTR (27).

Hasan et al. published a meta-analysis concerning the efficacy of PORT after GTR on AM patients in 2014 (28). That study showed that for the enrolled 757 patients, PORT significantly reduced the risk of recurrence and increased the local control rate for 5 years, but did not reduce the overall mortality (28). However, the articles included in this meta-analysis were published between 1993 and 2013. Besides, they did not analyze the impact of PORT on progression-free survival (PFS), which is also an important prognostic indicator. With the great modifications in the 2000 WHO classification criteria for meningioma and a large number of articles focused on the prognosis of AM patients after GTR in recent years, it is necessary to summarize them again. The aim of this study was to systematically review and meta-analyze the effectiveness of PORT in AM patients after GTR.

MATERIALS AND METHODS

Literature Search and Study Selection

A systematic review of the literatures on the relationship between PORT and the prognosis of AM patients after GTR between January 2000 and January 2019 in the Pubmed, Embase, Web of science, and Scopus databases was performed. The search of published articles was undertaken using the following terms: "gross total resection," "atypical meningioma" or "grade II meningioma" and "radiotherapy."

The excluding criteria are listed as below: (1) research subjects were not well defined, such as AM patients including benign meningioma patients or malignant meningioma patients, and GTR patients including STR patients; (2) the efficacy of PORT after GTR on AM patients was not compared; (3) AM was defined according to the WHO classification criteria before the year 2000; (4) the 5-year prognostic data were not available; (5) non-English literatures or literatures of systematic reviews, case reports, observational studies; (6) database-based researches.

Data Extraction and Quality Assessment

Two investigators extracted data from the relevant articles independently. If the opinions or data were inconsistent, they would discuss until consensus were reached. Extracted data should include: name, year of publication, the type of study, WHO classification criteria, the number of cases, age, gender, the grade of meningioma, degree of surgical resection, PORT, and the treatment endpoint. GTR was defined as Simpson grade I-III in this study.

Newcastle-Ottawa Scale (NOS) literature quality assessment scale and revised standards were used to assess quality of included articles. The evaluation scales were based on the following three indicators: patient selection, study comparability, and research outcome. The score was 9 points in total, the article with 6 points or more was considered as high-quality.

Statistical Analysis

The patients were divided into two groups, patients received GTR plus PORT and patients received GTR without PORT. Because of the cumulative survival rates, we performed a meta-analysis by converting that to the assumed cumulative number of survivors. Odds ratios (ORs) with 95% confidence interval (CI) were utilized to evaluate the difference in 5-year local control (LC) rate, 5-year PFS rate, and 5-year OS rate between the two groups. Heterogeneity of pooled results was assessed using Cochrane's Q test and I^2 measurement. $P > 0.10$ or $I^2 < 50\%$ indicated that the heterogeneity was not significant, and then a fixed-effects model was used. Otherwise, a random effect model was used. Sensitivity analysis was conducted to evaluate the validity and reliability of present meta-analysis. Begg's funnel plot and Egger's test were used to evaluate the publication bias risk. All statistical analyses were performed using STATA version 15.1 (STATA Corporation, College Station, TX, USA), and all P values were two sides.

RESULTS

Study Characteristics

According to the above search strategy, 273 articles were initially screened. The detailed screening process was shown in **Figure 1**. By carefully reading the literature titles and abstracts, and excluding the literature of which types or contents did not

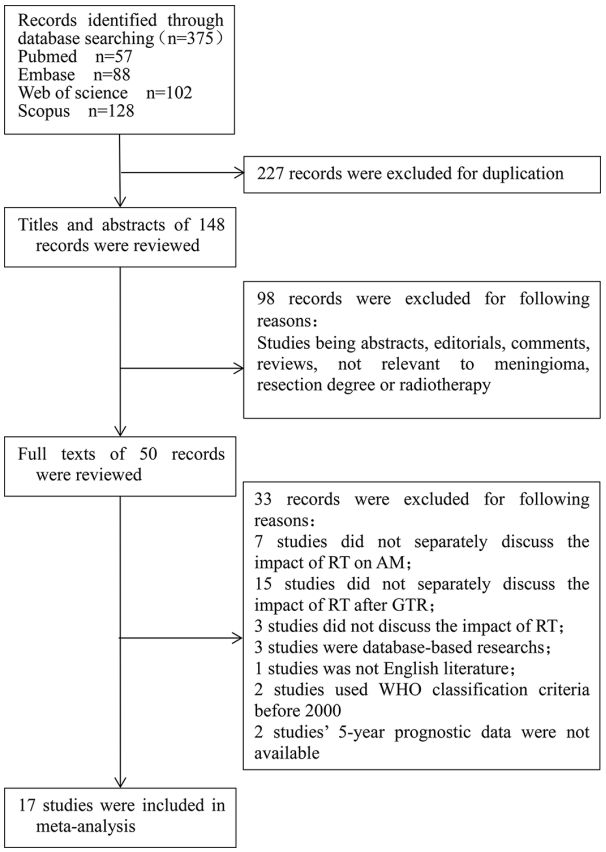


FIGURE 1 | Flow chart of study selection procedure.

meet research topics, 50 articles were initially included. By reading the full text, 33 articles were excluded according to the excluding criteria. Finally, a total of 17 articles were included in this meta-analysis.

The basic characteristics of the final included studies were shown in **Table 1**. The data included the author, the year of publication, the country, the year of treatment, the WHO classification standard, the type of study, the sample data, and the survival rate. A total of 2,008 AM patients were included in the 17 articles. Among them, 1,492 patients did not receive PORT after GTR and 369 patients received PORT after GTR.

According to the NOS literature quality evaluation scale and revised standards, the included literatures were evaluated. As shown in **Table 1**, the quality of the literatures was generally high (6–9 points).

Effectiveness of Postoperative Adjuvant Radiotherapy on 5-Year Progression-Free Survival

Twelve articles reported the effect of PORT on 5-year PFS in AM patients after GTR. One of the articles suggested that PORT significantly improved 5-year PFS (14), but 11 articles found that PORT had no significant relationship with 5-year PFS. Integrating the above literature data for analysis, 662 AM patients did not receive PORT after GTR, and 276 patients received PORT after GTR. There was no significant difference in heterogeneity analysis (I^2 = 42.6%, P = 0.058). The 5-year PFS was 84.1% in the patients receiving PORT and 71.9% for those not. The meta-analysis showed that PORT could significantly improve 5-year PFS in AM patients after GTR (OR [95% Cl] = 1.99 [1.35–2.95], P = 0.001) (**Figure 2A**). **Figure 2B** indicated that there was no significant publication bias (P = 0.075). The sensitive analysis was performed by removing studies one by one, and the removal of any individual study did not affect its overall trend, indicating that the results of this meta-analysis were stable and reliable (**Figure 2C**).

Effectiveness of Postoperative Adjuvant Radiotherapy on 5-Year Overall Survival

Five articles reported the effect of PORT on 5-year OS in AM patients after GTR. None of them found that PORT could significantly improve 5-year OS. Among them, 353 AM patients did not receive PORT after GTR, and 114 patients received PORT after GTR. There was no significant difference in heterogeneity analysis (I^2 = 0%, P = 0.931). The 5-year OS was 79.0% in the patients receiving PORT and 81.5% in those not. The meta-analysis showed that PORT had no significant relationship with 5-year OS (OR [95% Cl] = 1.07 [0.60–1.91], P = 0.828) (**Figure 3A**). **Figure 3B** indicated that there was no significant publication bias (P = 0.142). The sensitive analysis was performed by removing studies one by one, and the removal of any individual study did not affect its overall trend, indicating that the results of this meta-analysis were stable and reliable (**Figure 3C**).

Effectiveness of Postoperative Adjuvant Radiotherapy on 5-Year Local Control

Six articles reported the effect of PORT on 5-year LC in AM patients after GTR. Heterogeneity analysis found significant differences between two groups. Begg's funnel plot and Egger's test showed that there was a clear publication bias in an article (**Figures 4A, B**). The sensitive analysis was performed by removing studies one by one, and the Charles Champeaux's was significantly heterogeneous, so it was excluded. Remaining articles had no heterogeneity (I^2 = 0%, P = 0.460) (**Figure 5B**). The 5-year LC was 82.2% in the patients receiving PORT and 71.0% for those not. The meta-analysis showed that PORT could significantly improve 5-year LC (OR [95% Cl] = 2.59 [1.40–4.81], P = 0.002) (**Figure 5A**). There was no significant publication bias (P = 0.142) and the results were stable and reliable (**Figure 5C**).

DISCUSSION

At present, optimal postoperative management for AM patients after GTR remains a great deal of controversy. The NCCN Guideline recommends radiotherapy in several situations (29), but there is no conclusion on whether radiotherapy is needed for AM patients after GTR. In the current study, we found that PORT could improve the 5-year LC rate and 5-year PFS rate in

TABLE 1 | Characteristics of studies for association between PORT and survival.

Author/year of publication/country	Year of treatment	WHO classification criteria	Type of study	No. of case	Sex(male/female)	Age (year)	Follow-up time (month)	GTRdefinition	No. of GTR	No. of PORT	Indicator	NOS
Manish K. Aghi/2009/USA (8)	1993–2004	2000	Retrospective cohort study	108	48/69	55 (19–82)	39 (1–168)	Simpson grade I resection	80	8	OR、5-year LC	8/9
Kyungil Jo/2010/Korea (9)	1997–2008	2000	Retrospective cohort study	35	18/17	56 (15–80)	40 (6–97)	Simpson grade I resection	32	19	OR、5-year LC	7/9
Kangmin D. Lee/2013/USA (10)	1999–2009	2007	Retrospective cohort study	90	34/56	56.9 (22–83)	48.7 (12–108)	Simpson grade I–III resection	71	17	OR、5-year PFS	8/9
Sam Q. Sun/2014/USA (11)	1993–2012	2007	Retrospective cohort study	151	63/88	54 (8.8–86.2)	45 (6–232)	Simpson grade I–III resection	151	39	OR、5 year LC+PFS	8/9
Michael D. Jenkinson/2016/UK (12)	2001–2010	2000/2007	Retrospective cohort study	133	68/65	62 (22–86)	57.4 (0.1–152.2)	Simpson grade I–III resection	113	32	OR、5-year PFS+OS	8/9
Christopher S. Graffeo/2017/USA (13)	1988–2011	2016	Retrospective cohort study	69	25/44	61 (27–91)	74	Simpson grade I–III resection + no residue in image	69	8	OR、5-year PFS+OS	7/9
Shakir I. Shakir/2018/Canada (14)	1992–2013	2007	Retrospective cohort study	70	32/38	62 (32–87)	69 (5.2–273.5)	Simpson grade I–III resection	40	12	OR、5-year PFS	8/9
Salah Hammouche/2014/UK (15)	1996–2009	2007	Retrospective cohort study	79	43/36	58 ± 13.6	50 (1–172)	Simpson grade I resection	34	9	OR、5-year PFS	7/9
Hae Jin Park/2013/USA (16)	1997–2011	2000/2007	Retrospective cohort study	83	33/50	52 (24–78)	43 (6.2–160.0)	Simpson grade I–II resection	55	17	5-year PFS	7/9
Richard Mair/2011/UK (17)	2001–2010	2000	Retrospective cohort study	114	55/59	57 (17–85)	NR	Simpson grade I–II resection	66	15	5-year PFS	7/9
Ming Zhi/2018/USA (18)	2002–2012	2000/2007	Retrospective cohort study	149	74/75	64 (18–91)	74.2(0.5–182.2)	Simpson grade I–III resection	98	26	OR、5-year PFS+OS	8/9
Ammoren Dohma/2017/USA (19)	1993–2014	2007	Retrospective cohort study	115	45/70	63.6 ± 14.7	NR	Simpson grade I–III resection	78	41	5-year OS	6/9
Karol P. Budohoski/2018/UK (20)	2007–2014	2016	Retrospective cohort study	220	98/122	61(50–68)	NR	Simpson grade I–III resection	143	35	OR	6/9
Hannah Yoon/2015/USA (21)	2000–2010	2000	Retrospective cohort study	158	72/86	58 (19–90)	NR	Simpson grade I–III resection	109	7	5-year OS	7/9
Yu-Chi Wang/2014/China (22)	2001–2009	2007	Retrospective cohort study	28	13/15	56.8 (23–85)	57.4 (16–144)	Simpson grade I–III resection + no residue in image	14	3	5-year PFS	8/9
Charles Champeaux/2016/UK (23)	2000–2015	2000/2007	Retrospective cohort study	178	81/97	57 (44.7–68.8)	43.2 (18–74.4)	Simpson grade I–III resection	127	24	5-year LC	8/9
Douglas A. Hardesty/2013/USA (24)	1992–2011	2007	Retrospective cohort study	228	97/131	62(2–94)	52	Simpson grade I–III resection	149	72	5-year PFS	7/9

OR, overall number of recurrence.

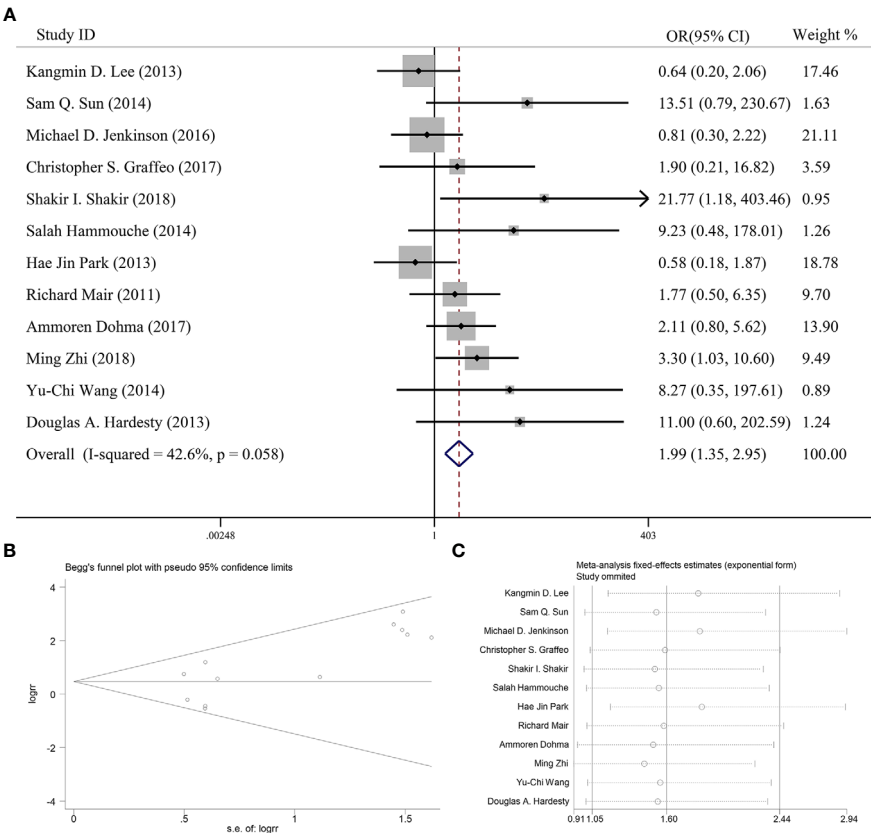


FIGURE 2 | **(A)** Forest plot for the relationships between PORT and 5-year PFS. **(B)** Begg's funnel plots of publication bias for meta-analysis of PORT. **(C)** Sensitivity analysis for meta-analysis of PORT.

AM patients after GTR, indicating that AM patients might benefit from PORT after GTR.

PORT plays an important role in post-operative management of AM patients. It was showed that patients without PORT after STR had worse PFS (16). Recently, Chenyang Wang et al. (30) found that PORT could significantly improve OS in AM patients who underwent STR (30), which was consistent with our previous finding (27). Currently, PORT has been routinely recommended for AM patients who underwent STR (6, 31).

However, it is contentiously debated whether AM patients can benefit from PORT after GTR. In recent years, a large number of studies have been conducted to find out whether PORT has an effect on the prognosis of AMs after GTR, but lead to contradictory conclusions. Recently, Shakir et al. performed a single-center retrospective study and reported that PORT could improve the 5-year PFS rate in AM patients after GTR (14). However, many studies revealed the ineffectiveness of PORT on AMs after GTR, although most of them showed that PORT had a trend to improve the 5-year PFS rate (11, 13, 15, 17–19, 22, 24). The non-significant differences may due to the relatively small sample sizes of these studies. Therefore, we performed this meta-analysis with a total of 2,008 AMs enrolled to overcome this limitation. The results showed that PORT could significantly improve 5-year PFS rate and 5-year LC, indicating that AMs can benefit from PORT after GTR.

A previous meta-analysis by Hasan et al., including 14 retrospective studies reported from 1984 to 2012, found that PORT for AM patients might decrease risk for relapse (28). However, the WHO classification standard for meningiomas was greatly modified in 2000. Therefore, the literatures enrolled in the current study were all using 2000 WHO classification criteria or later, and the literatures using WHO classification criteria before 2000 or without identified WHO classification criteria were all excluded. In some degree, our study might reduce sample selection bias. Therefore, we considered it was meaningful to conduct this meta-analysis to show that AM patients could benefit from PORT after GTR, which was in line with that previous meta-analysis.

As reported in the previous literatures, many types of radiotherapy, such as conventional radiotherapy, single-fraction stereotactic radiosurgery, fractionated stereotactic radiotherapy, three-dimensional conformal radiotherapy and intensity modulated radiotherapy, have been conducted in AM patients after GTR (8, 16, 18, 24). However, most of the enrolled articles did not compare the differences in the treating effect among different radiotherapy methods. At present, it still remains

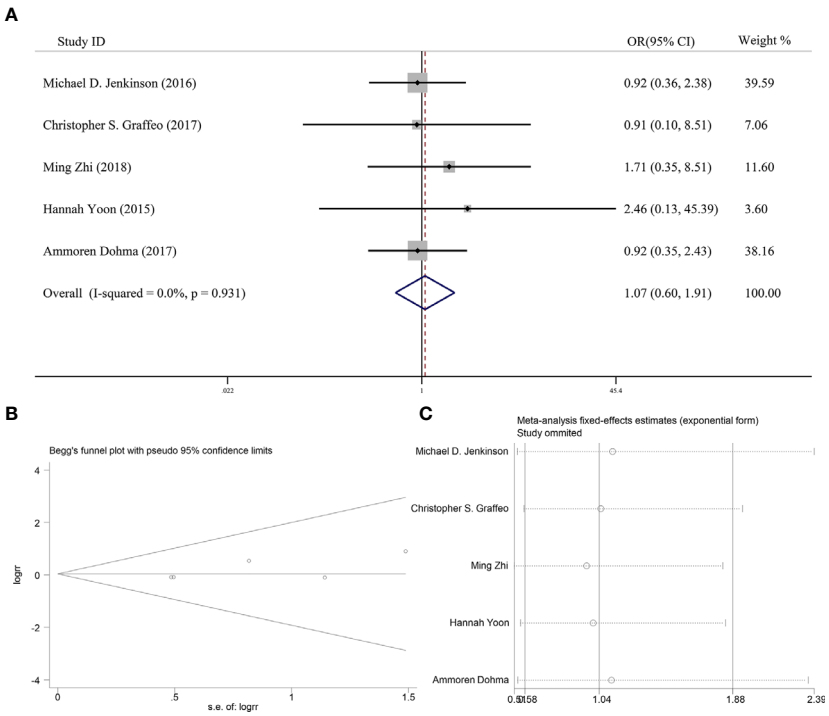


FIGURE 3 | **(A)** Forest plot for the relationships between PORT and 5-year OS. **(B)** Begg's funnel plots of publication bias for meta-analysis of PORT. **(C)** Sensitivity analysis for meta-analysis of PORT.

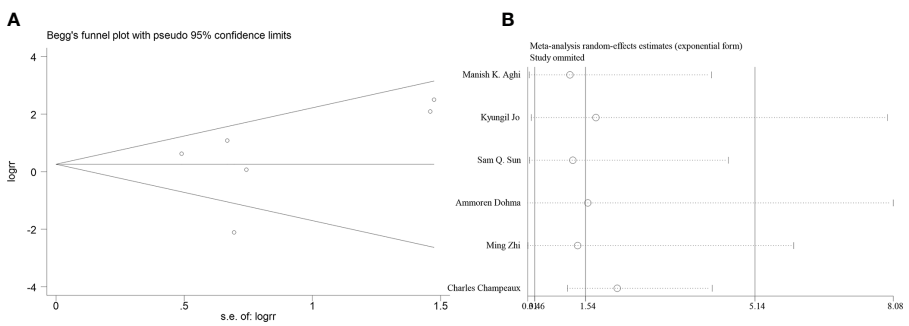


FIGURE 4 | **(A)** Begg's funnel plots of publication bias for meta-analysis of PORT on 5-year LC before excluding. **(B)** Sensitivity analysis for meta-analysis of PORT.

unclear which type of radiotherapy is preferred for AM patients after GTR. Further studies are needed to investigate the effect of different types of PORT, which might guide the selection of PORT type for radiotherapist.

Our study also has several limitations. First, all enrolled articles are retrospective single-center studies (8–24), and inherent limitations exist in this kind of studies, such as selection bias. Second, the WHO classification criteria (13) and the definition of GTR (8, 9, 15–17) are somewhat different among the articles which may also lead to bias. Third, in the current meta-analysis, we could not perform multivariable analysis including other factors, such as MIB-1 index, location, brain edema, and several molecular markers, which might also influence tumor behavior and recurrence rate. Forth, we chose 5-year PFS, LC, and OS as the prognostic indicators, because most of previous studies did not reported the rates of PFS, LC, and OS with a longer time. The non-significant effect of PORT on OS in our study might due to the short follow-up time. Thus, a longer window than 5 years might be more effective at teasing out potential advantages of PORT on OS. Further studies with a longer follow-up time are warrant. Thus, further multi-center prospective studies of a large sample size with a panel of these markers and longer follow-up time are needed to confirm our findings. Currently, two phase-III clinical trials, ROAM-EORTC

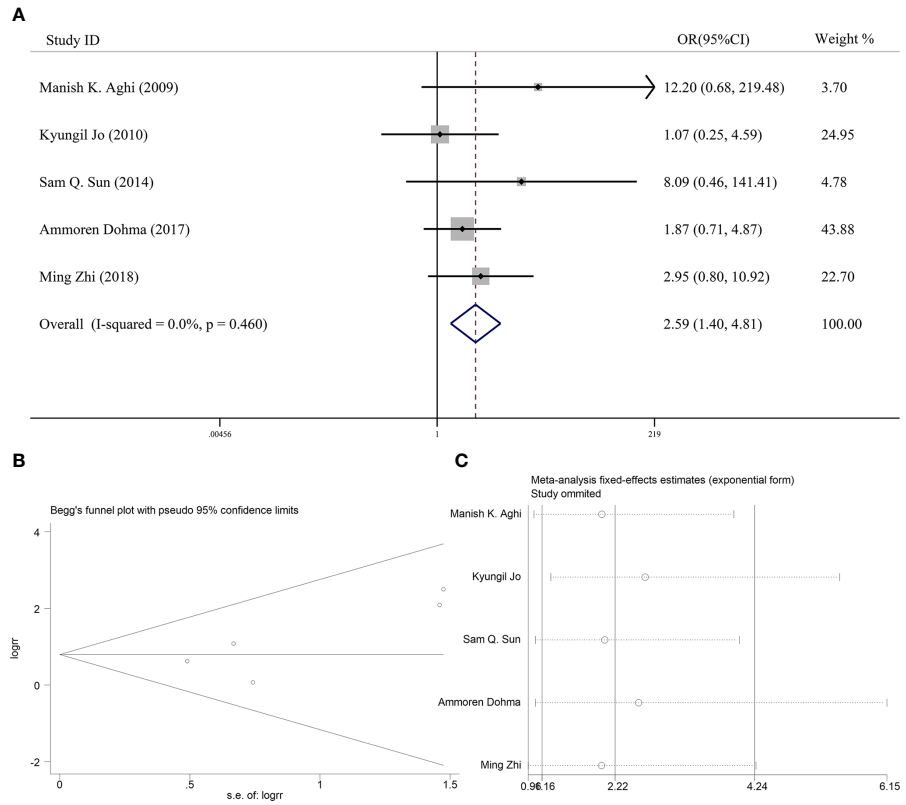


FIGURE 5 | **(A)** Forest plot for the relationships between PORT and 5-year LC after excluding. **(B)** Begg's funnel plots of publication bias for meta-analysis of PORT. **(C)** Sensitivity analysis for meta-analysis of PORT.

1308 and NRG-BN003, are now ongoing to investigate whether AM patients can benefit from PORT after GTR.

CONCLUSION

This meta-analysis showed that PORT could significantly improve 5-year LC and 5-year PFS in AM patients after GTR, indicating that AM patients may benefit from PORT after GTR. The results from two ongoing phase-III clinical trials (ROAM-EORTC 1308 and NRG-BN003) will further help to address the controversy about the effectiveness of PORT in atypical meningioma patients after GTR.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Clear Cell Meningioma in the Central Nervous System: Analysis of Surveillance, Epidemiology, and End Results Database

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Background: Clear cell meningioma (CCM) is a rare subtype of meningioma, accounting for approximately 0.2% of all meningiomas. The present study aimed to analyze the epidemiology and outcome of CCMs using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Patients diagnosed with central nervous system CCM between 2004 and 2016 were identified from the SEER database. Descriptive analyses were performed to evaluate the distribution of patients and tumor-related characteristics. The survival analysis was performed using Kaplan-Meier curves. The Cox proportional hazards model was used for the univariate and multivariate analyses.

Results: The age-adjusted incidence rate was 0.032 per 1,000,000 person-years. The median age was 52 years. Most of the CCMs were intracranial CCMs that were larger than 3 cm. The overall cumulative survival rates at 1, 3, and 5 years were 97.6, 93.2, and 86.9%, respectively. The log-rank test and Cox proportional hazards regression analysis revealed that age at diagnosis and primary site of the tumor were independent prognostic factors.

Conclusion: CCM is an extremely rare entity with a favorable survival rate. CCMs usually affect patients during the fourth to fifth decades of life. Patients diagnosed at 21–60 years old and patients with spinal CCMs have a better prognosis.

Keywords: CNS disease, SEER Program, survival, epidemiology, clear cell meningioma

INTRODUCTION

Clear cell meningioma (CCM) is an exceedingly rare variant of meningioma characterized by sheets of round or polygonal cells with a clear and glycogen-rich cytoplasm, and prominent perivascular and interstitial collagen. CCMs predominantly affect children and young adults (1). Furthermore, CCM has been recognized by the World Health Organization as a Grade II neoplasm, and aggressive clinical course and occasional cerebrospinal fluid metastasis have been widely reported (1, 2). The existing literature on CCM is limited to case reports and small case series. Due to the

rarity of CCMs, the epidemiological and clinical characteristics of CCMs have not been fully understood. The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute collects data on tumor diagnoses (including the primary site and tumor morphology), treatment, and survival for approximately 34.6% of the United States (US) population (3). The present study aimed to analyze the epidemiology and outcome of CCMs using the SEER database.

METHODS

Data Extraction

The SEER database is available to the public for research purposes, and no ethics committee approval or informed consent is required. The age-adjusted incidence rates (directly standardized to the 2000 US standard million population) between 2004 and 2016 were calculated using the SEER 18 database (November 2019 submission) (4). The detailed patient demographic data and clinical profiles were obtained from the SEER 18 Regs Custom Data (November 2018 submission) (5). The diagnosis of "central nervous system clear cell meningioma" was defined using the International Classification of Diseases for Oncology 3 (ICD-O-3) code 9538/0 and 9538/1, and the site was set as "brain and other nervous system." Since the SEER program has identified benign and borderline tumors of the central nervous system since 2004, the time span of the diagnosis was set as 2004–2016. Only the patients diagnosed with positive histology according to the code "Diagnostic Confirmation" were included in the population analysis. Additionally, only the patients with active follow-up according to the code "Type of follow-up expected" were included for the survival analysis. All data were obtained using the SEER*Stat 8.3.6 software. Statistical analyses were performed using the SPSS Statistics 26.0 software (IBM Corporation, Armonk, NY, USA).

Population Analysis

The demographic and clinical variables included gender (male or female), age (0–20, 21–40, 41–60, or >60 years old), race (white, black, or others), primary tumor site (cerebral meninges, spinal meninges, or not clarified), behavior code ICD-O-3 (benign or borderline malignancy), tumor size (≤3 cm, >3 cm, or unknown), radiation (yes or no/unknown), and the extent of the surgical resection. The investigators categorized the surgical procedure codes into three groups, as previously described (6, 7): no surgery (code 00), partial resection (20, 21, 22, 30, and 40), and gross total resection (code 55). Descriptive analyses were conducted to evaluate the distribution of patients and tumor-related characteristics. The age distribution of the patients at diagnosis was described using a histogram.

Survival Analysis

The Kaplan-Meier curve analysis was performed to estimate the overall survival (OS), and the intergroup differences were assessed using log-rank tests. All variables with a significant result in the univariate Cox proportional hazard regression analysis were included in the following multivariate analysis. The hazard ratios (HR) and 95% confidence intervals (CIs) were estimated to identify the independent prognostic factors associated with OS in patients with CCM. A *P*-value of ≤0.05 was considered statistically significant.

RESULTS

Population Analysis

The age-adjusted incidence rate was 0.031 per 1,000,000 person-years between 2004 and 2016. The annual age-adjusted incidence rate was 0.024 per 1,000,000 person-years in 2004, which increased to 0.040 per 1,000,000 person-years in 2016 (**Figure 1**). The age-adjusted incidence rate for male is 0.027 per 1,000,000 person-years. Compared to male counterpart, the rate for female is 0.036 per 1,000,000 person-years, and the rate ratio and 95% CI is 1.3195 (1.0613–1.6437). A total of 363 cases of CCM in the central nervous system were identified between 2004 and 2016. There were 358 cases diagnosed with positive histology in the population analysis. The demographic and clinical characteristics of these patients are summarized in **Table 1**. There were 208 female patients (58.1%) and 150 male patients (41.9%), yielding a female-to-male ratio of 1.4:1.0. The average age was 50.77 ± 17.648 years (median, 52 years; range, 3–88 years). Among all these patients, 41.9% of these patients (n = 150) were within 41–60 years old, and 74.9% of these patients were white (*n* = 268). CCMs most commonly affect patients during the fourth to sixth decades of life (**Figure 2A**). When the female and male patients were analyzed separately, we found that CCMs usually occur during the fourth to fifth decades of life in female patients (**Figure 2B**) and during the fifth to sixth decades of life in male patients (**Figure 2C**). Most of the tumors were borderline malignancy (n = 350, 97.8%). The primary tumor site was available for 326 patients. The tumor arose from the cerebral meninges in 285 patients (87.4%), and from the spinal meninges in 41 patients (12.6%). The tumor size was available in 272 patients, and the tumor size was larger than 3 cm in 207 patients (76.1%). Surgical resection was performed for 342 (95.5%) patients. Among these patients, partial resection was achieved in 271 patients (75.7%), and gross total resection was achieved in 71 patients (19.8%). Radiation therapy was performed for 101 (28.2%) patients. At the time of data collection, 304 (84.9%) patients were alive and 54 (15.1%) were deceased.

Survival Analysis

The overall cumulative survival rates at 1, 3, and 5 years were 97.6, 93.2, and 86.9%, respectively. The OS of the whole cohort was presented as a Kaplan-Meier curve in **Figure 3A**. The log-rank tests indicated that age at diagnosis (**Figure 3B**) and primary tumor site (**Figure 3C**) were the potential risk factors for OS. The univariate analyses revealed that patients diagnosed at 21–60 years old and patients with spinal tumors had a more favorable prognosis. The codes of age at diagnosis and primary site were included in the multivariate analysis. The multivariate

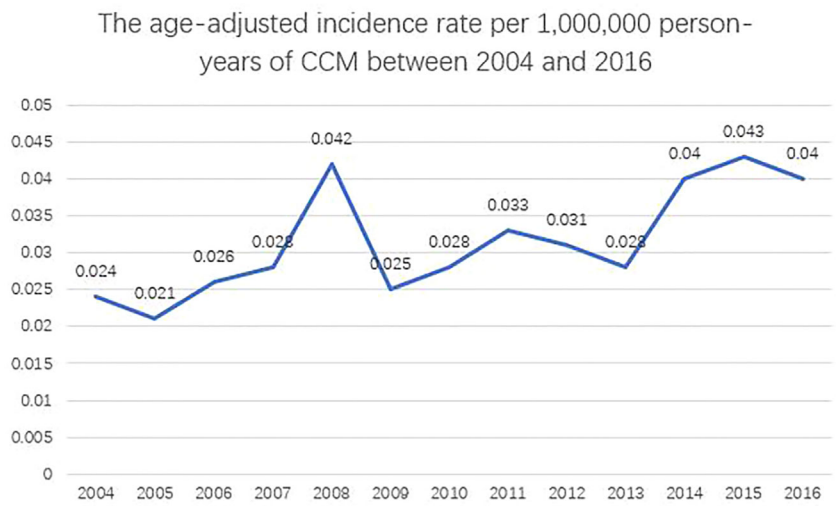


FIGURE 1 | The age-adjusted incidence rates of the central nervous system clear cell meningioma between 2004 and 2016.

Cox proportional hazards regression analysis revealed that age at diagnosis (21–60 years old) was an independent factor for predicting a favorable prognosis. And the patients with spinal CCMs had better prognosis than those with intracranial CCMs. The statistical results are summarized in **Table 2**.

DISCUSSION

CCM was first reported by Harkin et al. (8), and the electron microscopic examination of spinal meningioma demonstrated broad zones with large amianthoid collagen fibers in the tumor. CCM was previously classified as Grade I, according to the World Health Organization (WHO) Classification of Central Nervous System Tumors (2). However, due to its high recurrence rate and aggressive clinical course, CCM was later prompted to Grade II (9). According to existing literatures (10, 11), CCM represents as one of the rarest subtypes that occupies approximately 0.2–0.8% of all meningiomas, and the present evidence is limited to single case reports or small case series. Although some gene mutations have been reported to be associated with CCM, such as the neurofibromatosis gene (*NF-2*) (11, 12) and *SMARCE1* (13–15), the definitive etiology of CCM remains unclear.

Zhang et al. reviewed all the reported cases of intracranial CCMs (16) and spinal CCMs (17), and they found a significant female predilection in spinal CCMs. The female-to-male ratio was 1.4:1.0 in the present study, which is consistent with previous reports (11, 18). Louis *et al.* proposed that CCMs are more likely to affect young patients, including children and young adults (1). According to Zhang's review, 42.9% of patients with spinal CCMs were younger than 18 years old (17), and the mean age at surgery was 24 and 32 years old for spinal and intracranial CCMs, respectively (16, 17). However, the predilection for the young population was not remarkable in some reports (18). In the present cohort, the mean age was 50.77 ± 17.648 years old (median age: 52 years old), most of the patients were diagnosed

TABLE 1 | Demographic and clinical characteristics of patients with CCM.

Variables	Number	%
Sex (n = 358)		
Female	208	58.1
Male	150	41.9
Age at diagnosis (years; n = 358)		
Mean ± SD	50.77 ± 17.648	
Median	52	
Range	3–88	
0–20	21	5.9
21–40	75	20.9
41–60	150	41.9
>60	112	31.3
Primary Site (n = 326)		
Cerebral meninges	285	87.4
Spinal meninges	41	12.6
Race (n = 358)		
White	268	74.9
Black	52	14.5
Others	38	10.6
Behavior code ICD-O-3 (n = 358)		
Benign	8	2.2
Borderline malignancy	350	97.8
Tumor Size (n = 272)		
≤3cm	65	23.9
>3cm	207	76.1
Extent of resection (n = 358)		
No resection	16	4.5
partial resection (PR)	271	75.7
gross total resection (GTR)	71	19.8
Radiation (n = 358)		
Yes	101	28.2
None/Unknown	257	71.8
Vital status (n = 358)		
Alive	304	84.9
Dead	54	15.1

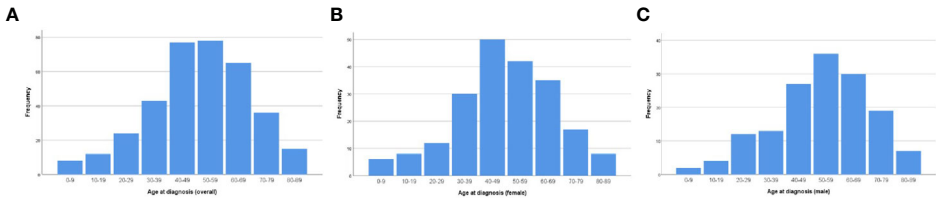


FIGURE 2 | Age distribution of the patients at diagnosis: **(A)** for the whole cohort; **(B)** for female patients; **(C)** for male patients.

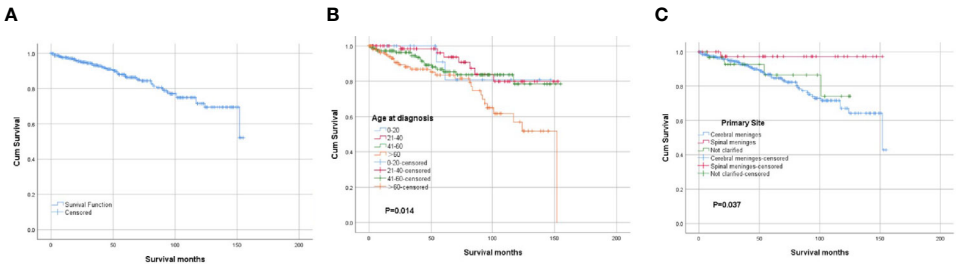


FIGURE 3 | Kaplan-Meier survival analysis: **(A)** The overall survival for the whole cohort. **(B)** The survival analysis of patients classified based on the age at diagnosis. **(C)** The survival analysis of patients classified based on the primary tumor site.

TABLE 2 | The results of the log-rank test, and univariate and multivariate Cox regression analysis.

Variable	Log-Rank Test	Univariate Analysis		Multivariate Analysis	
	P value	HR (95% CI)	P value	HR (95% CI)	P value
Sex	0.658				
Female		Reference			
Male		1.132 (0.653–1.963)	0.658		
Age at diagnosis (years)	0.014				
0–20		0.385 (0.091–1.623)	0.193	0.688 (0.159–2.979)	0.617
21–40		0.335 (0.145–0.773)	0.010	0.370 (0.160–0.855)	0.02
41–60		0.485 (0.263–0.895)	0.021	0.505 (0.273–0.933)	0.029
>60		Reference		Reference	
Primary Site	0.037				
Cerebral meninges		Reference		Reference	
Spinal meninges		0.117 (0.016–0.852)	0.034	0.132 (0.018–0.988)	0.049
Not clarified		0.790 (0.284–2.196)	0.652	0.707 (0.253–1.973)	0.508
Race	0.866				
White		Reference			
Black		0.802 (0.357–1.802)	0.593		
Others/Unknown		0.982 (0.387–2.490)	0.969		
Behavior code	0.212				
Benign		Reference			
Borderline malignancy		22.325 (0.013–37245.571)	0.412		
Tumor Size	0.104				
≤3cm		Reference			
>3cm		2.449 (0.957–6.267)	0.062		
Unknown		1.625 (0.578–4.572)	0.357		
Extent of resection	0.229				
No resection		Reference			
PR		2.308 (0.314–16.979)	0.412		
GTR		3.413 (0.460–25.345)	0.230		
Radiation	0.831				
None/Unknown		Reference			
Yes		0.934 (0.497–1.755)	0.832		

at 41–60 years old and the proportion of patients younger than 20 years old was only 5.9%. This result is consistent with the findings reported by Cahill *et al.*, in which the mean age at diagnosis of patients with nonmalignant intracranial meningioma was 62 ± 16 years old (19).

CCMs predominantly occur at the cerebellopontine angle and spine, especially in the cauda equina region (1). In the present SEER database, the primary site of meningioma is classified as cerebral meninges or spinal meninges. Thus, it is difficult to analyze the definitive location of CCMs. Noteworthily, spinal CCMs constituted 12.6% of all CCMs in the present study, which is similar to a previous report on CCMs (11), and much higher than the proportion of spinal counterparts in other meningioma subtypes (20).

In the present study, most of the tumors were larger than 3 cm. Furthermore, 95.5% of these tumors were surgically resected, and 28.2% of the patients chose radiation therapy. The prognosis of spinal CCMs was better than that of cerebral CCMs. According to previous reviews (16, 17), the 5-year progression-free survival was 47% for patients with spinal CCM and 37% for patients with cerebral CCM. In the present cohort, the OS rate of patients with CCM at 1, 3, and 5 years after diagnosis was better than that in a previous report (11), and similar to that for patients with nonmalignant meningiomas (19). The extent of surgical resection and radiology therapy were not significantly correlated to the OS. Tao et al. (11) retrospectively reviewed 56 cases of CCMs, and found that the extent of resection was associated with the progression-free survival, but not with the OS (11). Another study that involved 36 cases of CCM also reported similar results (21). Since the prognosis of CCMs is generally favorable, and the OS of CCMs is much better than that of gliomas and other central nervous system malignant tumors, the progression-free survival should be a more valuable indicator for evaluating the prognosis. Unfortunately, the progression-free survival was not documented in the SEER database. According to previous reports, total resection was still the first choice of treatment (21), and the role of adjuvant radiotherapy in CCM remains controversial (10, 21). On the other hand, chemotherapy does not appear to have a significant role in the management of CCM (21).

There were several limitations in the present study. First, some valuable parameters were not available in the SEER database, such as the detailed information on the recurrence and quality of life. This information may be more important for patients with borderline or benign tumors. Second, the present study was retrospective in nature. Hence, some inherent biases may exist. However, to the best of our knowledge, this is the largest series of CCM, to date.

CONCLUSION

CCM is an exceedingly rare entity with a relatively favorable prognosis. CCMs usually affect patients during the fourth to sixth decades of life. Patients diagnosed at 21–60 years old and patients with spinal CCMs have a better prognosis.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/data/.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GZ and YX designed the research. YW, XQ, ML, XL, and YY performed the work and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Postoperative Long-Term Independence Among the Elderly With Meningiomas: Function Evolution, Determinant Identification, and Prediction Model Development

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Background: Maintenance of postoperative long-term independence has value for older adults who undergo surgical procedures. However, independence has barely caught attention for the elderly with meningiomas. Preventing postoperative long-term independence decline in this population necessitates the identification of the factors related to this outcome and minimizing their implications. Therefore, we assessed the independence evolution and identified potential determinants and population.

Materials and Methods: From 2010 to 2016, elderly meningioma patients (≥65 years old) undergoing operation at Beijing Tiantan Hospital were included in our study. The primary outcome was 3-year (*i.e.*, long-term) postoperative independence measured by Karnofsky performance scale (KPS) score. We used univariate and multivariate analyses to determine the risk factors for postoperative long-term independence, and nomogram was established.

Results: A total of 470 patients were included eligibly. The distribution in each KPS was significantly different before and 3 years after resection ($P < 0.001$). Especially in patients with preoperative KPS 80 and 70, only 17.5 and 17.3% of the patients kept the same KPS after 3 years, and the remaining patients experienced significant polarization. The most common remaining symptom cluster correlated with postoperative long-term independence included fatigue (R = –0.795), memory impairment (R = –0.512), motor dysfunction (R = –0.636) and communication deficits (R = –0.501). Independent risk factors for postoperative long-term non-independence included: advanced age (70–74 *vs.* 65–69 OR: 2.631; 95% CI: 1.545–4.481 and ≥75 *vs.* 65–69 OR: 3.833; 95% CI: 1.667–8.812), recurrent meningioma (OR: 7.791; 95% CI: 3.202–18.954), location in the skull base (OR: 2.683; 95% CI: 1.383–5.205), tumor maximal diameter >6 cm (OR: 3.089; 95% CI: 1.471–6.488), nerves involved (OR: 3.144; 95% CI: 1.585–6.235), high risk of WHO grade and biological behavior (OR: 2.294; 95% CI: 1.193–4.408), recurrence during follow-up (OR: 10.296; 95% CI: 3.253–32.585), lower preoperative KPS (OR: 0.964; 95%

CI: 0.938–0.991) and decreased KPS on discharge (OR: 0.967; 95% CI: 0.951–0.984) ($P < 0.05$). The discrimination and calibration of the nomogram revealed good predictive ability (C-index: 0.810).

Conclusion: Elderly meningioma patients might present significant polarization trend in maintaining long-term independence after surgery. Our findings will be helpful for guiding surgical management for the elderly with meningioma and provide proposals for early functional rehabilitation.

Keywords: independence, meningioma, the elderly, functional evolution, prediction model

INTRODUCTION

Meningiomas are the most common primary intracranial tumor, with rising incidence in patients aged 65 years and older (1). The majority of meningiomas are benign and are considered surgically cured once tumor resection is complete (2). Therefore, measures of treatment success in such patients have appropriately shifted to more patient-centered metrics (3), including postoperative quality of life (QoL). Up to 35% of meningiomas are biologically aggressive or surgically inaccessible and have significant risk of recurrence, resulting in a second brain injury and a clinical course of repetitive debilitating treatments (4). Hence the postoperative long-term QoL of these patients should be paid more attention. However, the QoL after surgical resection of tumor in meningioma achieved inconsistent results. The majority of meningioma patients were reported to have improved QoL after surgical resection of tumors (5–7). However, the recent largest prospective longitudinal study of long-term Health-Related Quality of Life (HRQoL) outcomes in meningioma patients found that meningioma patients have sustained clinically significant impairments in global HRQoL after tumor resection (3). As we have known, elderly people are vulnerable to poorer outcomes because of a decrease in physiological reserve and in the ability to deal with stressors due to a systemic decline in health (8). Therefore, the risk/benefit ratio for neurosurgical treatment increase with age (9, 10). However, until now, few studies have investigated the QoL after tumor resection in elderly meningioma patients. Fried et al. reported physical deterioration as part of attenuated QoL was listed as one of the four outcomes that older adults considered as unacceptable results after surgical treatment (11). More recently, in a qualitative study published by Lindsey M. and colleagues, the need to measure long-term independence in the elderly after surgery remains vital due to more than 20% rate of functional decline at 30 days (12). Investigators have acknowledged that long-term maintenance of independence has recently been considered to be the preferred outcomes in older surgical patients in clinical trials (13–15), while, in patients with brain tumors, long-term independence is more likely to reflect better postoperative cognition and less neurological deficits (12, 16–18). Nevertheless, postoperative long-term independence in the elderly with meningioma has barely caught attention.

In this retrospective study, we investigated the incidence of postoperative long-term independence, explored the suspected risk factors that may contribute to the risk of loss of independence after tumor resection in elderly meningioma patients, and developed the risk model for predicting the postoperative long-term non-independence.

MATERIALS AND METHODS

Participants

This was a single-center retrospective cohort study that was conducted in the Department of Neurosurgery at Beijing Tiantan Hospital, Capital Medical University, Beijing, China, from January 2010 to December 2016. Ethical approval was obtained from the Ethics Committee of Beijing Tiantan Hospital, and this study was conducted in accordance with the principles of the declaration of Helsinki.

Elderly patients who were aged 65 or older, pathologically diagnosed with meningiomas and underwent surgical resection of tumor from January 2010 to December 2016 were included. The exclusion criteria were as follows: (i) patients with other brain or spine lesions; (ii) patients with neurofibromatosis type 1 or 2; (iii) concurrence with other malignancies or death from other lethal diseases in hospital or discharge; (iv) concurrence with other diseases affecting postoperative long-term functions after discharge; (v) loss of follow-up data. **Supplementary Figure 1** shows the study flowchart.

Data Collection

Baseline and clinical data were extracted from hospital electronic medical records (details in **Supplementary Table 1**). Radiology features were evaluated from neuroimaging data by two neuroradiologists who had over 10 years of experience. The World Health Organization (WHO) grade and biological behavior of tumors according to 2016 WHO classification of Tumors of the Central Nervous System (4) were determined based on the pathological reports by two experienced neuropathologists (**Supplementary Table 2**). The extent of resection was extracted from surgical reports which were categorized as gross total resection (GTR) or subtotal resection (STR), according to the Simpson grade (Simpson I–III for GTR, Simpson IV–V for STR) and the postoperative neuroimaging evaluation (2). The tumor shape was defined as regular or irregular, *e.g.*, in terms of mushroom-like growth. Tumor recurrence was defined as an appearance of new contrast-enhancing lesions on MRI after surgery. Lastly, Symptom-

related function deficits were collected and categorized as none, mild, moderate, and severe status, and the definition and detailed information are described in **Supplementary Table 3**. Moreover, all Karnofsky performance scale (KPS) scores of individuals were measured before surgery, on discharge, and in postoperative long-term periods.

KPS score has become a standard assessment tool of comprehensive function performance widely used by clinicians and researchers in the neuro-oncology field (19, 20), which is defined in terms of the ability to carry out daily activities for patients. The KPS consists of 11 categorical ratings in increments of 10 that range from 0 (dead) to 100 (normal, no complications; no evidence of disease) (20). KPS from 100 to 0 represents the decreased function outcomes in turn. Furthermore, KPS ranging from 100 to 80, 70 to 50 and 40 to 0 represent independent, partial independent, and dependent daily activities, respectively (21). The cutoff value for KPS was set to 70 based on independence and non-independence (*i.e.*, dichotomized as >70 and ≤70) (21, 22).

Follow-Up

As previously reported in published literature, a large proportion of patients showed spontaneously improved function over the first 1 to 2 years after surgical resection of the meningioma (7), which might suggest the possibility that existing function deficits would begin to improve 3 years later remains slim. Therefore, the follow-up endpoint was defined as 3 years after discharge (*i.e.*, long-term independence). To estimate postoperative long-term functional outcomes more accurately, details about the functional outcomes and daily activities including remaining symptoms which refer to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Brain Neoplasm 20 (QLQ-BN20) (23, 24), objective KPS and comprehensive satisfaction for the patients' life condition using modified Common Toxicity Criteria (CTC) (10, 25) were recorded. The patients were followed up for 3 months, 1, 2 and 3 years in our institution after discharge, and follow-up was carried out by telephone or E-mail thereafter. The follow-up was completed and the postoperative long-term KPS was subjectively conducted by three experienced neurosurgeons (**Supplementary Figure 2**). The median follow-up of the present cohorts was 68 months with an interquartile range (IQR): 41 to 104 months.

Statistical Analysis

Evaluation of Function Outcome

Kruskal–Wallis H test was calculated in the population distribution rate of each KPS before surgery and 3 years after surgery. The differences between preoperative KPS and postoperative long-term KPS were depicted based on each level of preoperative KPS. We further described the population distribution frequency of postoperative long-term function conversion using composite column-diagram and heat map. The remaining symptoms related to postoperative long-term function outcomes were shown by proportion and displayed in different levels of KPS (100–80, 70–50 and ≤40). Spearman correlations between symptoms and KPS were performed to determine a pivotal symptoms' cluster affecting postoperative long-term independence ($R \geq |\pm 0.5|$ means significantly strong correlation). Furthermore, the Kaplan–Meier curves regarding recurrence related to postoperative long-term independence were illustrated with the log-rank test.

Comparison of Clinical Features

Demographic and clinical data were generalized by mean ± SD or median and IQR for continuous variables and counts with proportions for categorical features. Association between function outcomes (postoperative long-term independence or non-independence) and variables of interest was tested with a Chi-square, Fisher's exact test or Mann–Whitney U test, as necessary. A correlated matrix was used to estimate all explanatory variables for collinearity, and plausible interaction terms were tested with a variance inflation factor (VIF). The multivariate analysis was performed by Logistic regression model. Potential-risk estimators with P value <0.05 in the univariate Logistic regression analysis or based on clinical importance, scientific knowledge and predictors identified in previously published articles (7, 10, 26–29), among all variables, were tested in the multivariate model. Backward stepwise selection with the Akaike information criterion (AIC) was used to identify variables for the multivariable Logistic regression model and Odd ratios (ORs) were presented with their 95% confidence intervals (CIs).

Model Development and Performance Evaluation

To conduct early postoperative consultation, creating a simple-to-use function evaluation score that could be utilized by clinicians to predict the possibilities of postoperative long-term non-independence in elderly meningioma remains of importance. We generated a nomogram using each weighted covariate derived from the fitted multivariate Logistic regression model except for the variable of recurrence during follow-up due to its unpredictability. The C-index was graphically illustrated to compute the area under the curve (AUC) for the model, and Hosmer–Lemeshow goodness-of-fit was performed. The calibration of the model was performed graphically, which as the main approach was implemented to evaluate consistency between the predicted probability values and actual probability values. And scattered points on the 45-degree diagonal reference line of the graphical indicated stable calibration. Statistical analysis and nomogram construction and validation were performed by R v3.6.3. All tests were two-sided with a statistically significant P value <0.05.

RESULTS

Patient Features

The clinical histories of 549 elderly individuals admitted to our institution between 2010 and 2016 were reviewed. A total of 470 patients met the inclusion criteria. **Supplementary Figure 1** shows ineligible patients' details. There were 138 males and 332 females (ratio: 1:2.4) with a mean age of 68.79 years (range: 65–79). There were 175 (37.2%) patients with postoperative long-term KPS ≤70, 32 (6.8%) patients with

recurrence, and 29 (6.0%) with mortality during follow-up. Additionally, recurrence presented in follow-up commonly combined with long-term KPS ≤70 ($P < 0.001$) (**Supplementary Figure 3**). Baseline details were summarized in **Supplementary Table 4**.

Postoperative Long-Term Independence

Compared with preoperative values, the human distribution of postoperative long-term KPS were significantly different, with 1.5 *vs.* 4.0%, 47.0 *vs.* 25.3%, 14.3 *vs.* 43.8, 13.2 *vs.* 22.1%, and 24.1 *vs.* 4.7%, respectively (H = 13.550, $P < 0.001$) (**Figure 1A**). Furthermore, our results showed that the proportion of KPS 90 and ≤60 increased 21.7 and 19.4% after 3 years, respectively, and the proportion of KPS 80 and 70 decreased 29.5 and 8.9% after 3 years, respectively (**Figure 1B**). To explore the postoperative long-term conversion of each KPS (**Figure 1C**) and transform-based distribution (**Figure 1D**), we found that 31.6% of patients with preoperative KPS 100 kept the same KPS after 3 years, and the KPS of all the remaining patients had decreased, but 52.6% of patients only slightly decreased to KPS 90 (**Figure 1D**). Among patients with preoperative KPS 90 and ≤60, 67.2 and 63.6% stay with unchanged KPS after 3 years, and all the remaining declined and improved to the extent across the board, respectively (**Figures 1C, D**). Most notably, we found that in patients with preoperative KPS 80, only 17.5% of the elderly maintained the same KPS 3 years after surgery, and the remaining emerged with distinct polarization trend that 45.6% of patients experienced better postoperative long-term independence while 36.9% as worse (**Figures 1C, D**). A similar phenomenon that only 17.3% of the elderly preserved the KPS unchanged 3 years after surgery, but 82.7% of elderly individuals experienced polarization trend in postoperative long-term independence recovery (49.1% patients experienced better independence while 33.6% as worse) was investigated when elderly patients harbored preoperative KPS 70 (**Figures 1C, D**).

Postoperative Long-Term Remaining Symptoms

To evaluate the correlation between remaining symptoms and long-term independence after surgery, **Figure 2A** showed 28.5% of elderly patients were recorded as asymptomatic status in a follow-up but 71.5% with symptoms where the top three of the highest frequent deficits were fatigue (32.3%), memory impairment (30.6%), and motor dysfunction (26.4%). In terms of severity of symptoms, the majority of symptoms were experienced as moderate or severe and less often as mild when elderly patients harbored postoperative long-term KPS 70–50 or ≤40 (**Figure 2B**). We further found that the quantity of symptoms was significantly increased following the attenuated long-term KPS after surgical procedure (**Figure 2B**). Additionally, a graphical representation of the Spearman correlations between remaining symptoms and postoperative long-term KPS was presented in **Figure 2C**. One pivotal symptomatic cluster including fatigue (R = −0.795), memory impairment (R = −0.512), motor dysfunction (R = −0.636)

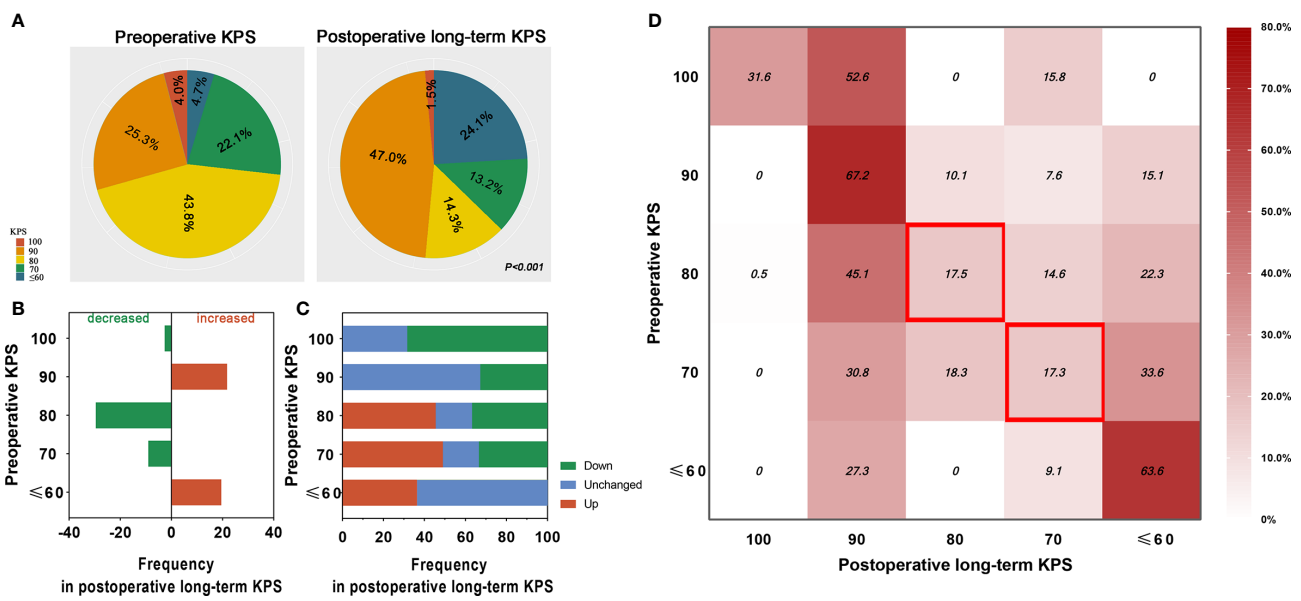


FIGURE 1 | Comparison and distribution of elderly meningioma population between preoperative KPS and postoperative long-term KPS. **(A)** Distribution of elderly meningioma patients before and 3 years after surgery in different levels of KPS ($P < 0.001$). The red, orange, yellow, green, and blue colors represent KPS 100, 90, 80, 70 and ≤ 60, respectively. **(B)** Difference of elderly meningioma patients' distribution before and 3 years after surgery in different gradients of preoperative KPS. The green and red columns represent decreased and increased rate of the elderly population. **(C)** Ability to the conversion of postoperative long-term KPS in elderly with meningiomas. Red, blue, and green columns represent the rate of better, unchanged, and worse conversion, respectively. **(D)** Distribution of elderly meningioma population of each postoperative long-term KPS in different gradients of preoperative KPS. Contents in the red blank box emphasize only less than 20% of elderly patients with preoperative KPS 80 or 70 maintain unchanged KPS 3 years after resection.

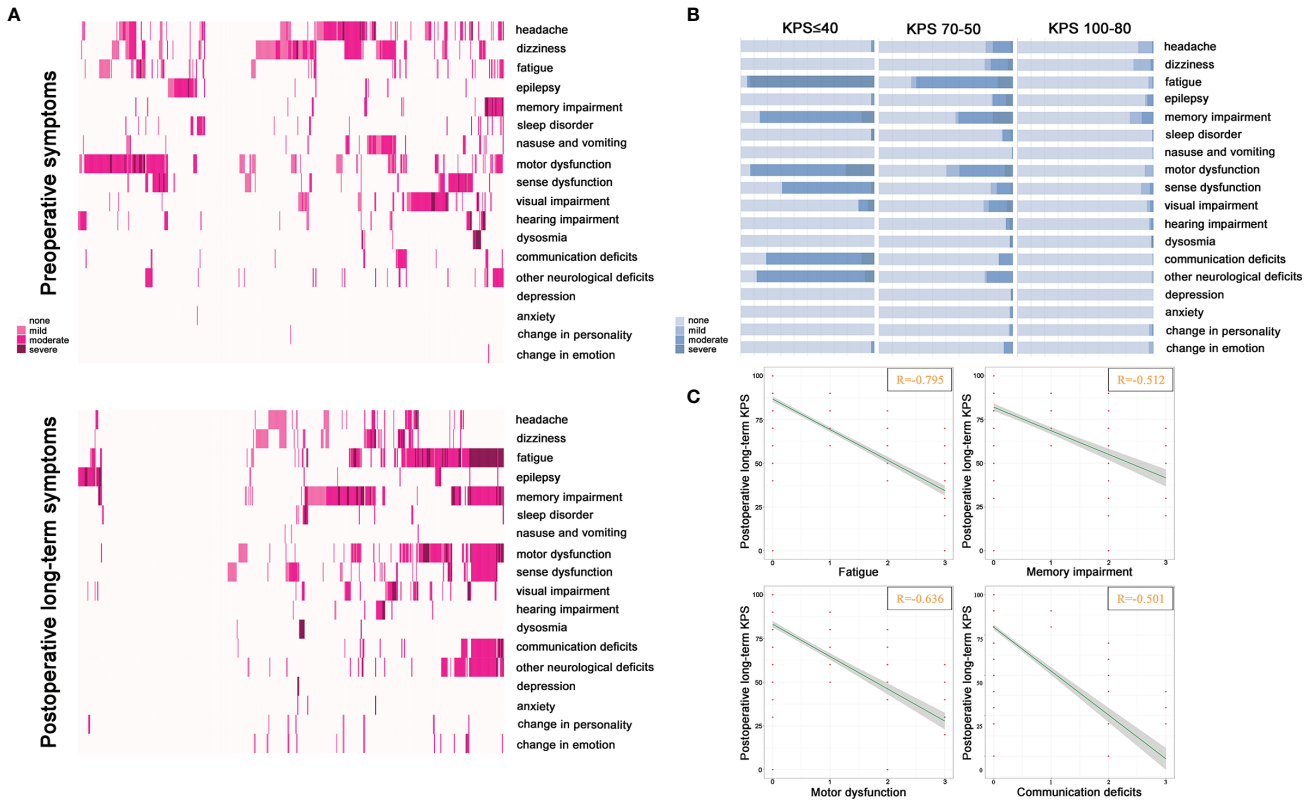


FIGURE 2 | Distribution of symptoms and correlation with KPS. **(A)** The description of preoperative symptoms and postoperative long-term remaining symptoms. The color of the block from light pink to dark pink represents none, mild, moderate, and severe. **(B)** Correlation between severity and quantity of each symptom and different levels of postoperative long-term KPS. The color from light blue to dark blue represents none to severe. **(C)** Correlations between severity of remaining symptoms and postoperative long-term KPS. Significantly correlated symptoms include fatigue (R = −0.795), memory impairment (R = −0.512), motor dysfunction (R = −0.636) and communication deficit (R = −0.501) ($P < 0.001$).

and communication deficits (R = −0.501) was confirmed as adverse events significantly associated with attenuated long-term independence.

Comparison of Clinical Characteristics Between Postoperative Long-Term Independent and Non-Independent Cohorts

The proportions of patients with advanced age at surgery, recurrent meningioma, presenting symptoms, attenuated preoperative KPS, preoperative comorbidities, tumor located in the skull base, tumor maximal diameter > 6cm, irregular tumor shape, tumor involved nerves, medical/surgical complications, high risk of WHO grade and biological behavior, attenuated KPS on discharge, radiotherapy after surgery and recurrence during follow-up were higher in the postoperative long-term non-independent cohort ($P < 0.05$), while that of those with GTR was lower ($P < 0.05$) (**Table 1**). However, the frequency of tumor in the right or left hemisphere and single or multiple lesions was found to be comparable between the two cohorts. Furthermore, we found a tendency that the presence of tumor involved motor cortex was prevalent in postoperative long-term non-independent cohorts, but this difference was not statistically significant ($P = 0.084$).

Univariate and Multivariate Logistic Regression Analysis in Postoperative Long-Term Non-Independence

We selected 15 candidates fitting both the clinical and statistical criteria of $P < 0.05$ into a multivariate Logistic regression analysis. These candidate predictors included older age at surgery, presenting symptoms, attenuated preoperative KPS, preoperative comorbidities, recurrent meningioma, different tumor locations, tumor maximal diameter >6cm, nerves involved, irregular tumor shape, high risk of WHO grade and biological behavior, STR, medical/surgical complications, attenuated KPS on discharge, radiotherapy after surgery and recurrence during follow-up (**Table 2**).

Subsequent multivariate analysis of variables indicated that older age (70–74 *vs* 65–69 OR: 2.631; 95% CI: 1.545–4.481 and ≥75 *vs* 65–69 OR: 3.833; 95% CI: 1.667–8.812), recurrent meningioma (OR: 7.791; 95% CI: 3.202–18.954), tumor location in the falx/sagittal sinus (OR:2.346; 95% CI:1.179–4.667),

TABLE 1 | Univariate comparison between both cohorts.

	Long-term independent status N (%)		*P* value
	Yes N = 295 (62.8)	**No N = 175 (37.2)**	
Gender N(%)			
Female	217(73.6)	115(65.7)	0.071
Male	78(26.4)	60(34.3)	
Age at surgery, years			0.000*
65–69	218(73.9)	98(56.0)	
70–74	59(20.0)	54(30.9)	
≥75	18(6.1)	23(13.1)	
Presenting symptoms[a] N(%)			0.001*
Yes	255(86.4)	168(96.0)	
No	40(13.6)	7(4.0)	
Preoperative comorbidities N(%)			0.043*
Yes	152(51.5)	107(61.1)	
No	143(48.5)	68(38.9)	
Preoperative γ-knife N(%)			0.500
Yes	7(2.4)	6(3.4)	
No	288(97.6)	169(96.6)	
Recurrent meningioma N(%)			0.000***
Yes	9(3.1)	38(21.7)	
No	286(96.9)	137(78.3)	
Other surgery history N(%)			0.916
Yes	111(37.6)	65(37.1)	
No	184(62.4)	110(62.9)	
Smoking N(%)			0.584
Yes	29(9.8)	20(11.4)	
No	266(90.2)	155(88.6)	
Drinking N(%)			0.430
Yes	18(6.1)	14(8.0)	
No	277(93.9)	161(92.0)	
Tumor side N(%)			0.080
Left/Right side	257(87.1)	142(81.1)	
midline	38(12.9)	33(18.9)	
Multiple lesions N(%)			0.847
Yes	14(4.7)	9(5.1)	
No	281(95.3)	166(94.9)	
Location N(%)			0.015*
convexity	91(30.8)	33(18.9)	
Falx/sagittal sinus	61(20.7)	47(26.9)	
Tentorium	32(10.8)	12(6.9)	
Skull base	106(35.9)	80(45.7)	
intraventricular	5(1.7)	3(1.7)	
Motor cortex involved N(%)			0.084
Yes	44(14.9)	37(21.1)	
No	251(85.1)	138(78.9)	
Maximal diameter, cm			0.000***
≤6	277(93.9)	143(81.7)	
>6	18(6.1)	32(18.3)	
Tumor shape N(%)			0.005*
Regular	257(87.1)	135(77.1)	
Irregular	38(12.9)	40(22.9)	
Nerves involved N(%)			0.003*
Yes	30(10.2)	35(20.0)	
No	265(89.8)	140(80.0)	
WHO grade and biological behavior N(%)			0.000***
Low risk of recurrence and aggressive behavior	269(91.2)	122(69.7)	
High risk of recurrence and aggressive behavior	26(8.8)	53(30.3)	
Resection extent N(%)			0.000***
GTR	269(91.2)	136(77.7)	
STR	26(8.8)	39(22.3)	
Any medical/surgical complications N(%)			0.007*
Yes	60(20.3)	55(31.4)	
No	235(79.7)	120(68.6)	
Radiotherapy after surgery N(%)			0.004*
Yes	7(2.4)	14(8.0)	
No	288(97.6)	161(92.0)	
Long-term antiepileptic drug therapy			0.142
Yes	10(3.4)	11(6.3)	
No	285(96.6)	164(93.7)	
Recurrence during follow-up			0.000***
Yes	5(1.7)	27(15.4)	
No	290(98.3)	148(84.6)	
Preoperative KPS median (IQR)	80(80,90)	80(70,80)	0.000***
KPS on discharge median (IQR)	90(80,90)	80(70,90)	0.000***
Postoperative long-term KPS median (IQR)	90(90,90)	60(50,70)	0.000***

[a]*Presenting symptoms refer to* ***Supplementary Table 3****.*

P < 0.05;*P < 0.001.*

tentorium (OR:1.455; 95% CI: 0.564–3.754), skull base (OR: 2.683; 95% CI: 1.383–5.205) and intraventricular (OR: 4.465; 95% CI: 0.836–23.857), tumor maximal diameter >6 cm (OR: 3.089; 95% CI: 1.471–6.488), nerves involved (OR: 3.144; 95% CI: 1.585–6.235), high risk of WHO grade and biological behavior (OR: 2.294; 95% CI: 1.193–4.408), lower preoperative KPS (OR: 0.964; 95% CI: 0.938–0.991), lower KPS on discharge (OR: 0.967; 95% CI: 0.951–0.984) and recurrence during follow-up (OR: 10.296; 95% CI: 3.253–32.585) were independent risk factors for postoperative long-term non-independence following elderly meningioma resection (**Table 2**).

Individualized Prediction Nomogram and Model Performance

An easy-to-use scoring assessment to predict postoperative long-term functional outcomes remains of importance when elderly patients underwent discharge. Therefore, established risk predictors besides the variable of recurrence during follow-up incorporated into multivariate Logistic regression analysis were selected to configure a nomogram (**Figure 3**) (**Supplementary Table 5**). The discriminative ability of the model using the C-index was 0.810 (**Figure 4A**) without collinearity (VIF = 1.052–1.175). **Figure 4B** displays the calibration plot of the model, indicating a good fit between observed and predicted values. The Hosmer–Lemeshow goodness-of-fit test yielded a non-significant statistic ($\chi 2$ = 6.081, P = 0.638), which suggested that there was no departure from the perfect fit.

TABLE 2 | Logistic regression showing the association of variables with postoperative long-term non-independent status.

	Univariable	*P* value	Multivariable	*P* value
	OR(95%CI)		OR(95%CI)	
Gender (male/female)	1.452(0.968–2.177)	0.072		
Age at surgery, years				
65–69	1	0.000***	1	0.000***
70–74	2.036(1.312–3.159)	0.002*	2.631(1.545–4.481)	0.000***
≥75	2.842(1.467–5.506)	0.002*	3.833(1.667–8.812)	0.002*
Presenting symptoms (yes/no)	3.765(1.648–8.602)	0.002*	1.865(0.667–5.214)	0.235
Preoperative comorbidities (yes/no)	1.480(1.012–2.165)	0.043*	1.405(0.877–2.250)	0.157
Preoperative γ-knife (yes/no)	1.461(0.483–4.418)	0.502		
Recurrent meningioma (yes/no)	8.814(4.145–18.745)	0.000***	7.791(3.202–18.954)	0.000***
Other surgery history (yes/no)	0.980(0.665–1.442)	0.916		
Smoking (yes/no)	1.184(0.648–2.163)	0.584		
Drinking (yes/no)	1.338(0.648–2.763)	0.431		
Tumor side (left or right side/midline)	0.636(0.382–1.059)	0.082		
Multiple lesions (yes/no)	1.088(0.461–2.569)	0.847		
Location				
Convexity	1	0.016*	1	0.022*
Falx/sagittal sinus	2.125(1.225–3.685)	0.007*	2.346(1.179–4.667)	0.015*
Tentorium	1.034(0.477–2.242)	0.932	1.455(0.564–3.754)	0.437
Skull base	2.081(1.271–3.407)	0.004*	2.683(1.383–5.205)	0.004*
Intraventricular	1.655(0.374–7.310)	0.507	4.465(0.836–23.857)	0.080
Motor cortex involved (yes/no)	1.529(0.943–2.482)	0.085		
Maximal diameter, cm (>6/≤6)	3.444(1.868–6.349)	0.000***	3.089(1.471–6.488)	0.003*
Tumor shape (irregular/regular)	2.004(1.227–3.272)	0.005*	1.387(0.728–2.646)	0.319
Nerves involved (yes/no)	2.208(1.301–3.748)	0.003*	3.144(1.585–6.235)	0.001*
WHO grade and biological behavior (High risk/Low risk)	4.495(2.684–7.528)	0.000***	2.294(1.193–4.408)	0.013*
Resection extent (STR/GTR)	2.967(1.734–5.078)	0.000***	1.477(0.763–2.858)	0.247
Any medical/surgical complications (yes/no)	1.795(1.171–2.751)	0.007*	1.568(0.911–2.698)	0.105
Radiotherapy after surgery (yes/no)	3.578(1.415–9.045)	0.007*	0.503(0.158–1.603)	0.245
Long-term antiepileptic drug therapy (yes/no)	1.912(0.795–4.598)	0.148		
Recurrence during follow-up (yes/no)	10.581(3.993–28.040)	0.000***	10.296(3.253–32.585)	0.000***
Preoperative KPS	0.937(0.916–0.958)	0.000***	0.964(0.938–0.991)	0.009*
KPS on discharge	0.961(0.945–0.977)	0.000***	0.967(0.951–0.984)	0.000***

*$P < 0.05$; ***$P < 0.001$.

DISCUSSION

Meningiomas are the common primary intracranial tumor, and the majority are benign and can be surgically cured through complete tumor resection (2). With an aging global population, the incidence of meningiomas in patients aged 65 years and older has also steadily increased (1). Given the increased risk of adverse outcomes among older patients after a surgical procedure and oncologic curability, measures of treatment success have appropriately shifted to more patient-centered metrics, including postoperative long-term maintenance of independence in meningioma patients. Our study demonstrated the postoperative long-term independence status varied considerably across meningioma patients, especially patients with preoperative KPS equal to 80 and 70 have obvious polarization trends in postoperative long-term independence. Then, similar to what has been reported in a previous study about glioma (30), we have found that fatigue, memory impairment, motor dysfunction, and communication deficits were consistently highly correlated with long-term loss of independence in elderly meningioma patients. Finally, we identified several independent risk factors to develop and internally validate a prediction model for postoperative long-term loss of independence in the elderly with meningioma.

So far, this is the largest reported study of postoperative long-term independence in elderly meningioma patients. In this study, we report the long-term independent status of 470 meningioma patients treated with surgical resection. The KPS is a validated and widely used function evaluation scale to assess performance status in clinical practice region (31). In several recent studies, functional independence is defined by a KPS >70 (17, 22). Assessing evolution over of the KPS is important because functional independence is a key factor for QoL and is emerging as an important endpoint in clinical trials (13–15, 32). Although the HRQoL scale could obtain multi-dimensional details of function deficits, the complex assessment process and high training demand might limit the use of both clinicians and patients (3, 33). Therefore, in the present study, we used the KPS score to evaluate postoperative long-term independence status in elderly patients with meningioma. Our results demonstrated that almost half of elderly meningioma patients have improved long-term independent status after surgical resection of tumors, while a proportion of patients might have worse non-independent status. This is the first time that we considered postoperative

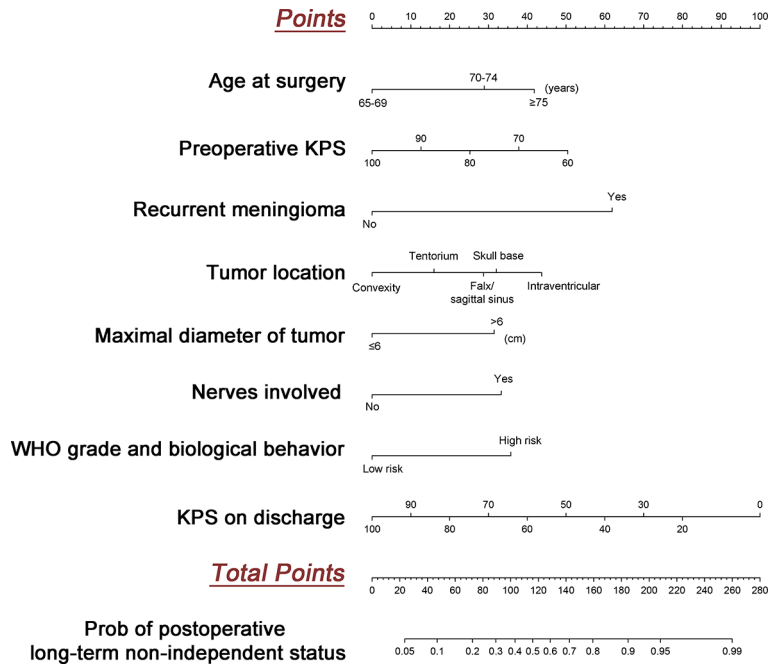


FIGURE 3 | Development of the predicted model. The nomogram to predict postoperative long-term non-independent status in the elderly with meningioma is created based on eight risk factors incorporated into multivariate logistic regression. For instance, a patient with age of 70, preoperative KPS at 80, primary tumor, maximal diameter at 4 cm, location in the skull base, nerves involved, low risk WHO grade and biological behavior, and KPS on discharge at 80 would have a total of 140.5 points (29 points for age at 70, 25 points for preoperative KPS at 80, 0 point for the primary tumor, 0 point for maximal diameter at 4cm, 32.5 points for location in the skull base, 34 points for nerves involved, 0 points for low risk WHO grade and biological behavior, and 20 points for KPS on discharge at 80), for a predicted postoperative long term non-independent status of 68%.

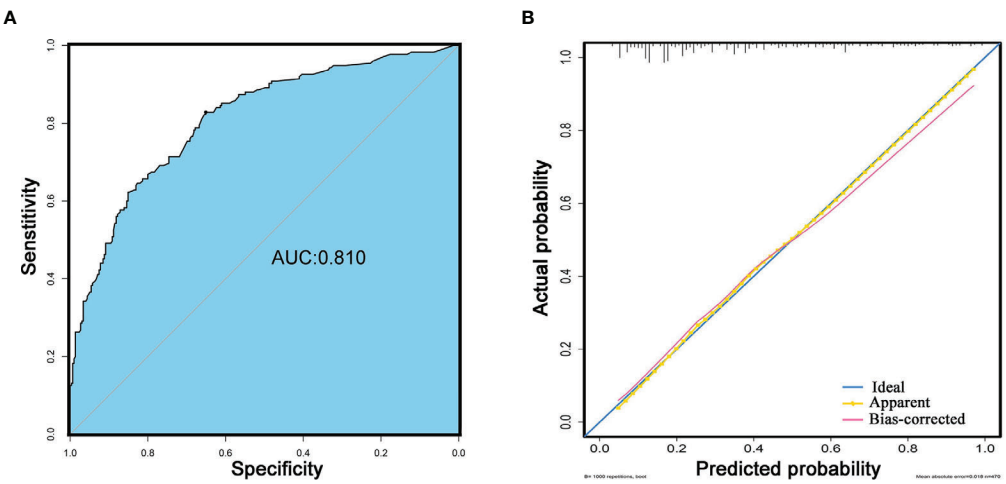


FIGURE 4 | Performance of the model. **(A)** The discriminative ability for the prediction of postoperative long-term non-independent status in the elderly with meningioma. Blue background represents the area of AUC (C-index: 0.810). **(B)** Calibration curves of model. The blue line represents the ideal fit. The yellow line represents apparent model-predicted probabilities and the pink line represents bias-corrected estimates with 1000-fold bootstrapping.

long-term independence in elderly meningioma patients that comprehensively presents a polarization trend. Through further analyzing the change of KPS scores before and after surgery, we found that there were slightly decreased postoperative long-term KPS scores in more than half of patients with perfect preoperative independent status (KPS scores of 100), but the degree of decline had little impact on independence. Whereas, the majority of elderly meningioma patients with preoperative

KPS of 90 or ≤60 would keep the same independent status even undergoing surgery. This could mean that in elderly meningioma patients with better or worse preoperative functional status, tumor resection would provide very little space for improvement or deterioration of function. Most notably, though, among elderly meningioma patients with preoperative KPS of 70 or 80, only less than 20% of patients preserved the original independence status, while the remaining patients showed obvious polarization trend and were evenly split between improvement and deterioration of postoperative long-term independence. This finding is a little bit different from previous studies that reported worse prognostic outcomes after resection in meningioma were closely associated with preoperative KPS less than 70 (26, 34). The heterogeneity of aging physiology and surgical attack may be an underlying cause of our findings. Therefore, for elderly meningioma patients with preoperative KPS of 70 or 80, a comprehensive strategy involving screening for predisposing factors of postoperative non-independence and early prevention of modifiable factors should be established in this population.

In order to preserve and improve the postoperative long-term independence in elderly meningioma patients, we further explored the risk factors to facilitate early recognition of high-risk population and early prevention of modifiable factors. Until now, few studies have investigated independent risk factors of postoperative long-term QoL, also including long-term independence in meningioma patients. Unsurprisingly, several independent risk factors that have previously been associated with functional deficits, recurrence, and death in meningioma patients, including poor performance before operation and on discharge, advanced age, large tumor diameter and high risk of grade and biological behavior were also found to increase the elderly meningioma patients' susceptibilities to long-term non-independent status (9, 10, 26, 27, 29). In addition, we also confirmed that tumor located in the skull base was an independent risk factor for long-term non-independent status in our population. Previous studies suggested that brain tumors located in the cerebellopontine angle and anterior clinoidal might affect postoperative functional status and QoL, perhaps because they were always adjacent to important nerves and vessels (26). Besides, Hischam Bassiouni et al. reported that approximately one-third of patients with meningioma involved visual nerve could achieve improved functional outcomes after excision, but the majority remained unchangeable and even worsened (35). We found a similar phenomenon that a close correlation between postoperative long-term non-independent status and tumor involved nerves in our cohort. Furthermore, our results showed that recurrent tumor before surgery and tumor recurrence in follow-up were the most significant risk factors for postoperative long-term non-independence with the top two highest weight in the present study. Recurrence of meningioma not only brings a second attack to the brain but could also mean more malignant biological behavior. Therefore, although meningiomas are mostly benign tumors, postoperative follow-up cannot be ignored. Some variables including presenting symptoms, preoperative comorbidities, tumor shape, extent of resection, medical/surgical complications and radiotherapy after surgery in our study had high significance in univariate analysis but were not selected into the final multivariable analysis, which means there may be some indirect association between these variables and independent predictors. More research studies are still needed for these variables. Finally, in order to identify high-risk patients for postoperative long-term non-independence and early implementation of proactive multifactorial interventions, we developed and internally validated a prediction model for postoperative long-term non-independence in elderly meningioma patients. We need to draw up the early systemic rehabilitation plan for the high-risk population on discharge, so we did not incorporate the factor of recurrence during follow-up into our model. Our prediction model consists of eight risk factors that are readily available on discharge and has a high predictive value. However, the optimal cut-off point of the model and the most effective preventive interventions for our population need to be studied shortly.

Our study also has several limitations. First, this was a single-center study and the model developed was only internally validated and not externally verified. Therefore, our finding might be limited for widely generalizing in other regions and races. Second, due to the retrospective nature of this project, not all information, mainly including long-term independence trajectory for older adults with meningiomas was available in our study, and some certain biases should be generated inevitably. Third, collection and record of symptoms were referred to QLQ-BN20 questionnaires. Owing to some common symptoms in patients with brain tumors, such as cognitive decline, emotion deficits and hearing impairments were not included in QLQ-BN20 questionnaires (3). We added some extra symptoms by patients' complaints and psychiatric diagnosis. While, some symptoms in QLQ-BN20, such as diarrhea or appetite loss, were not reported in our study because few presented during the follow-up. Therefore, a specific meningioma symptom assessment may be urgently needed in future studies. Fourth, HRQoL scales are widely used in the assessment of QoL of patients with tumors because they could obtain multi-dimensional details of functional deficits. Functional independence is a key factor for QoL and also the primary outcome in the present study. Therefore we used KPS as an assessment tool of independent status. Several previous studies reported the close association between KPS and HRQoL or cognition (16, 32, 33) but KPS might not be sensitive enough to cognition impairment (20). This is also the most important limitation in our study.

CONCLUSIONS

In this study, maintenance of postoperative long-term independence appeared to be a polarization trend, especially in patients with preoperative KPS equal to 80 and 70. The remaining symptom clusters including fatigue, memory impairment, motor dysfunction and communication deficits were highly correlated with non-independence 3 years after surgery, and strategies targeting these domains from an early

point in treatment may offer the optimal approach for maximizing postoperative long-term independence in these population. Furthermore, identifying the potential risk predictors and developing the prediction model might also help to draw up the early rehabilitation plan for patients with high risk of long-term loss of independence.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GZ, ZJ, and HL conceptualized and designed the study. HL, HH, XZ, XR, YC, and DS collected the data. GZ, HL, and HH analyzed and interpreted the data. HL and HH drafted the article. GZ, ZJ, SL, YW, HL, HH, and XZ critically revised the article. GZ, ZJ, and SL supervised the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.639259/full#supplementary-material

Supplementary Figure 1 | Consort chart showing the selection path for patients to be included this study.

Supplementary Figure 2 | Consort chart showing the process of follow-up.

Supplementary Figure 3 | Kaplan–Meier curves of recurrence after surgery for the elderly who underwent long-term independence and non-independence after meningioma resection.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Progesterone Receptor Expression in Meningiomas: Pathological and Prognostic Implications

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Background: The progesterone receptor (PR) is variably expressed in most meningiomas and was found to have prognostic significance. However, the correlation with patient age, tumor location, time to recurrence, and pattern of regrowth has scarcely been discussed.

Methods: A surgical series of 300 patients with meningiomas is reviewed. The PR expression was classified as: 0. absent; 1. low (<15%); 2. moderately low (16–50%); 3. moderately high (51–79%); 4. high (≥80%). The PR values were correlated with the patient age and sex, meningioma location, WHO grade, Ki-67 MIB1, recurrence rate, pattern of recurrence (local-peripheral *versus* multicentric diffuse), and time to recurrence.

Results: The PR expression has shown lower rate of high expression in the elderly group ($p = 0.032$) and no sex difference (including premenopausal *versus* postmenopausal women), higher expression in medial skull base and spinal *versus* other locations ($p = 0.0036$), inverse correlation with WHO grade and Ki67-MIB1 ($p < 0.0001$). Meningiomas which recurred showed at initial surgery higher rates of low or moderately low PR expression than the non-recurrent ones ($p = 0.0004$), whereas the pattern of regrowth was not significant. Higher rates of PR values ≥80% were found in cases with time to recurrence >5 years ($p = 0.036$).

Conclusion: The higher PR expression in medial skull base meningiomas, the significant correlation with the time to recurrence, the lack of difference of PR expression between premenopausal and postmenopausal women and between local-peripheral *versus* multicentric-diffuse recurrences are the most relevant unreported findings of this study. The rate of PR expression must be included in the routine pathological diagnosis of meningiomas because of its prognostic significance.

Keywords: meningioma, progesterone receptor, WHO grade, proliferation index Ki 67 MIB1, meningioma recurrence

INTRODUCTION

The presence of sex steroid hormone receptors in meningiomas is known since about 40 years (1, 2).

Some clinical evidence suggests that sex steroids play a role in the growth of meningiomas; these include the clear female predominance (female/male ratio 2:1), the reported rapid growth during pregnancy (3, 4), and women who receive oral contraceptives or hormone replacement therapy (5, 6). The progesterone receptor (PR) expression is found in variable and often very high rate meningiomas (39 to 88%) in some studies (7–9), whereas the estrogen receptor (ER) expression is lower than 10% and often undetectable. The PR expression was found to be correlated with the WHO grade and recurrence in ours (10) and other studies (11–14), with low expression associated with WHO grade II and recurrence. On the other hand, other factors, including patient age, intracranial tumor location, spinal meningiomas, time to recurrence, and patterns of regrowth, have scarcely been discussed.

This study reviews a surgical series of meningiomas and discusses the pathological correlation and prognostic significance of the PR expression.

MATERIALS AND METHODS

Patient Population

Three hundred fifty-two patients who underwent neurosurgery for intracranial and spinal tumors diagnosed as meningiomas at the neurosurgical clinic of the "Federico II" University of Naples between 2006 and 2016 were reviewed. Two children with neurofibromatosis, five patients with post-irradiation meningiomas, and forty-two patients with recurrences were excluded. Thus, 300 consecutive patients with primary intracranial or spinal meningiomas were included in the study. Besides, the 42 patients with recurrence observed in this period and 33 observed between 2000 and 2006 were included in a recurrence group for a total of 75 patients, all with recurrent intracranial meningiomas.

An ethics committee approval was not required according to local and national legislation.

Analyzed Factors

The factors analyzed in the study included patient age and sex, meningioma location, WHO grade, PR expression, Ki67 MIB-1, recurrence rate, regrowth or recurrence pattern, and time to recurrence.

According to the patient age, two main groups were identified: group I or elderly ≥70 years old and group II <70 years. For the sex evaluation, the female patients were divided in two groups: A, premenopausal and B, postmenopausal. The tumor location was defined from the review of the magnetic resonance (MR) images and the surgical descriptions. Four groups were identified: group 1 or medial skull base included olfactory groove, ethmoidal-sphenoidal planum, tuberculum sellae, parasellar, clival-petroclival, and foramen magnum meningiomas; group 2 or lateral skull base included middle and lateral sphenoid wing and temporal fossa meningiomas and those of the petrous bone and occipital fossa; group 3 or non-skull base included convexity, parasagittal or falx meningiomas, and those of the tentorium, cerebellar convexity, pineal region and lateral ventricle; group 4 included spinal meningiomas.

The surgical specimens were reviewed independently by two pathologists (MC and EG) who were unaware of the clinical data. The WHO grade was defined according to the 2007 WHO classification (15), which was used at the observation period. The immunohistochemical studies were performed to evaluate the Ki67 MIB-1 and the PR expression. The specimens were fixed in neutral buffered 10% formalin, embedded in paraffin, and cut into sections of 5 mm thickness.

The expression of PR was determined in all specimens with monoclonal antibody against the progesterone (DAKO, Italy 1:400, overnight incubation). The quantitative evaluation was expressed as percentage for positive nuclei among 100 cells, for a total of 500 cells. The percentage of PR positivity was determined by a semiquantitative scoring scale with respect to staining intensity, according to the recommendations for immunohistochemistry of hormonal receptors (16) and slightly modified.

The PR expression was graded as follows: 0. absence of positive nuclei; 1. low (<15%); 2. moderately low (16–50%); 3. moderately high (51–79%); 4. high (≥80%) (**Figure 1**).

The expression of Ki67 MIB-1 was evaluated in all specimens by using the monoclonal antibody MIB-1 Immunotech® (DAKO system, dilution 1:1,000, overnight incubation). The streptavidin–biotin system and the diaminobenzidine (DAB) were used for antigen detection and visualization. A specimen of breast carcinoma was used as a positive control. Ki67-LI count was performed by eye counting, taking the average on five adjacent representative fields of neoplastic cells in a hot spot area. The values of Ki67-LI were classified into two groups: group I ≤4%; group II >4%.

The histological types of WHO grade I meningiomas were classified as: meningothelial, transitional, fibroblastic, psammomatous, microcystic, secretory, and chordoid.

The 75 patients with tumor recurrence were classified into two groups: group I (50 cases) with local-peripheral recurrence, in which the recurrence occurred at the previous dural site or at the surrounding dura mater (within 2 cm); group II (25 cases) with multicentric-diffuse recurrence (at variable distance from the initial dural site). The data of these two groups have been compared with those of 100 consecutive patients operated between 2006 and 2010, who did not experience recurrence 9 years or more after the initial surgery.

The analyzed variables included patient age and sex, meningioma location, Simpson grade of surgical resection, PR expression, WHO grade, Ki67 Li.

The patient age was considered as median values; the data stratification between patients ≤70 years and those >70 years was avoided in the analysis of the recurrences because of very different life expectancies and length of the follow-up between the two groups.

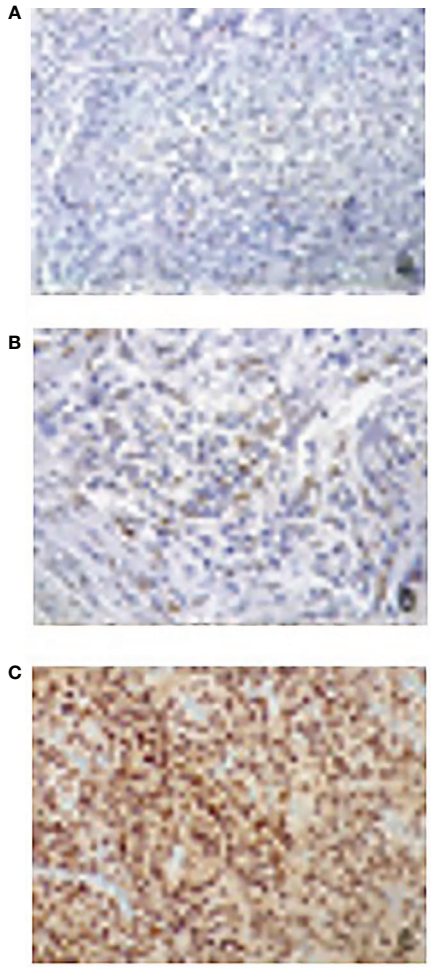


FIGURE 1 | Immunohistochemical evaluation of progesterone receptor antibody expression: nuclear signal respectively in less than 1% **(A)**, in 15% **(B)** and in 95% **(C)** of neoplastic cells (×200 magnification).

In the overall group of 75 patients with recurrence, the PR expression was correlated to the recurrence time (≤5 years *versus* >5 years). Finally, the values of PR expression at the initial surgery were compared to those at the first recurrence.

Statistical Analysis

The values of PR expression were carefully analyzed and stratified in all cases according to the patient age and sex, tumor location, WHO grade, Ki67-LI, overall recurrence rate, and pattern of recurrence (local and peripheral *versus* multicentric and diffuse). The data were analyzed by one-way ANOVA test or Fisher's exact test, and p-value was calculated. A p-value ≤0.05 was considered statistically significant. The group of 75 patients with recurrence was studied for PR expression, MIB-1 index, WHO grade, and tumor location, by a multivariate non-parametric statistical tests of hypotheses (Pearson linear correlation test, Spearman R test, Mann–Whitney U test). A Kaplan–Meier test was also performed for the time to recurrence.

RESULTS

In the overall series of 300 patients with meningioma at first diagnosis, the PR expression was low (0–15%) in 54 (18%), moderately low (16–50%) in 68 (23%), moderately high in 60 (20%) and high (≥80%) in 118 (39%). No cases with complete absence of positive nuclei were found. The data of the PR expression according to the analyzed factors are as follows.

Patient Age and Sex

The patients were 223 women (74%) and 77 men (26%); their age was <70 years in 225 (75%) and ≥70 years in 75 (25%). The distribution of the PR expression in the age groups (**Table 1**) has shown lower rate of cases with expression ≥80% in the elderly group (p = 0.032). According to the patient sex, no significant difference was evidenced between females and males (**Table 2**). In the female group, 69 (30%) premenopausal and 154 (70%)

TABLE 1 | PR expression and patient age.

PR expression	N. cases	Group 1 (≥70 years) 75 pts	Group 2 (<70 years) 225 pts	Statistical significance group 1 *vs.* group 2
L (0–15%)	54	20 *(27%)*	34 *(15%)*	p = 0.99
ML (16–50%)	68	20 *(27%)*	48 *(22%)*	p = 0.81
MH (51–79%)	60	12 *(16%)*	48 *(21%)*	p = 0.17
H (≥80%)	118	23 *(30%)*	95 *(42%)*	**p = 0.032**

Statistically significant values have been reported in bold.

TABLE 2 | PR expression and patient sex.

PR expression	N. cases	Group 1 Females	Group 1A premenopausal women	Group 1B postmenopausal women	Group 2 Males	Statistical significance group 1 *vs.* group 2	Statistical significance group 1A *vs.* group 1B
L (0–15%)	54	41 (18%)	10 (14%)	31 (20%)	13 (17%)	p = 0.55	p = 0.23
ML (16–50%)	68	47 (21%)	16 (23%)	31 (20%)	21 (27%)	p = 0.20	p = 0.63
MH (51–79%)	60	43 (20%)	17 (25%)	26 (17%)	17 (22%)	p = 0.39	p = 0.81
H (≥80%)	118	92 (41%)	26 (38%)	66 (43%)	26 (34%)	p = 0.86	p = 0.24
	300	223	69	154	77		

postmenopausal women were considered separately; the distribution of the PR expression in these last two groups was not significantly different (**Table 2**).

PR Expression and Meningioma Location

The meningioma location was at the medial skull base in 72 patients (24%) and at the lateral skull base in 39 (13%); 161 (54%) were non-skull base and 28 (9%) were in the spinal canal. The distribution of the different locations within the four groups is summarized in **Table 3**.

Medial skull base and spinal meningiomas showed significantly higher rate of cases with high PR expression and lower rate of cases with low expression than the lateral skull base and non-skull base meningiomas (p = 0.0036) (**Table 4**).

PR Expression, WHO Grade, Ki67 MIB-1 and Histological Type

Atypical WHO grade II meningiomas have shown significantly lower rate (18%) of cases with high (≥80%) PR expression; on the other hand, benign WHO grade I tumors mainly showed high PR expression (82% of the examined cases). This correlation was statistically significant (p < 0.0001) (**Table 5**).

The correlation between PR expression and Ki67 MIB 1 has provided significant differences. Cases with Ki67 LI >4% showed significantly lower rate of high (≥80%) PR expression (p = 0.0001) and higher rates of low (p = 0.04) or moderately low (p = 0.017) expression (**Table 5**). Thus, the study confirms an inverse correlation of the PR expression with both the WHO grade and Ki67 MIB-1.

The most frequent histological type of WHO I meningiomas was transitional (43%) followed by fibroblastic (22%) and meningothelial (15%). Tumors of meningothelial and psammomatous types showed slightly higher rates of high PR expression (76 and 77% respectively) than transitional (63%) and fibroblastic (52%), but with no statistical significance (**Table 6**).

PR Expression and Recurrence

The results of the clinical and pathological variables at the initial surgery were compared between the groups of patients with and without recurrence The data are summarized in **Table 7**. The 75 patients with recurrence were 48 (64%) women and 27 (36%) men, with a median age of 55 years at initial diagnosis. The male rate was higher than in the group with no recurrence (25%) but with no significance. No differences of the median values of patient age and sex were evidenced. The analysis of the meningioma location has shown lower rate of medial skull base (13 *versus* 29%) and spinal meningiomas (0 *versus* 8%) and higher rate of lateral skull base meningiomas (31 *versus* 13%) in group I (recurrence). According to the extent of surgical resection, the recurrence groups, as expected, showed significantly lower number of Simpson grade I resection (33 *versus* 61%) and higher rate of grade III resections (27 *versus* 10%) than the no recurrence group. Meningiomas which recurred showed at initial examination higher rate of low and moderately low PR expression (69 *versus* 37%) and significantly lower rate of cases with high PR expression (12 *versus* 43%) (p = 0.0004) than the non-recurrent meningiomas. On the other hand, there were no significant differences between cases with local-peripheral *versus* multicentric-diffuse recurrences (p = 0.5). These data agree with the significantly higher rate of atypical forms (p > 0.00001) and of those with Ki67-LI >4% (p = 0.003) in meningiomas which recurred, as compared to the non-recurrent ones (**Table 7**).

The multivariate non-parametric statistical tests confirm strong correlation between PR expression ≥80%, low WHO grade, and low expression (≤4%) of Ki 67-Li. The WHO grade is the most efficient variable to predict recurrence. The high PR expression (≥80%) is a single efficient predictive factor (p = 0.017).

TABLE 3 | Meningioma location.

Location	No. of cases
Medial skull base	
- Olfactory groove, planum ethmoidale-sphenoidale	33
- Tuberculum sellae	18
- Parasellar (anterior clinoid and optic canal)	16
- Clivus, petroclival, foramen magnum	5
- Total	72 (24%)
Lateral skull base	
- Middle and lateral sphenoid wings, temporal fossa	14
- Spheno-orbital	16
- Petrous bone, occipital fossa	9
- Total	39 (13%)
Non-skull base	
- Cerebral convexity, parasagittal, falx	137
- Tentorial, cerebellar convexity, pineal	19
- Lateral ventricles	5
- Total	161 (54%)
Spinal	28 (9%)
Total	300

TABLE 4 | PR expression and meningioma location.

		PR expression						
Meningioma location	**N. cases**	**L (0–15%)**		**ML (16–50%)**		**MH (51–79%)**	**H (≥80%)**	**Statistical significance**
Medial skull base	72	5 (7%)	13	(18%)	12	(16.5%)	42 (58.5%)	
Lateral skull base	39	6 (15.5%)	9	(23%)	10	(25.5%)	14 (36%)	Lateral skull base and non-skull base
Non-skull base	161	39 (24%)	39	(24%)	31	(19.5%)	52 (32.5%)	*vs.*
Spinal	28	4 (14%)	7	(25%)	7	(25%)	10 (36%)	medial skull base and spinal
Total	300	54 (18%)	68	(23%)	60	(20%)	118 (39%)	**p=0.0036**

Statistically significant values have been reported in bold.

TABLE 5 | PR expression, WHO grade and Ki67/MIB1.

PR expression	N. cases	WHO grade		Statistical significance	Ki 67/MIB1		Statistical significance
		I	II		≤4%	>4%	
L (0–15%)	54	24 *(47%)*	30 *(53%)*	p = 0.30	23 *(42%)*	31 *(58%)*	**p = 0.04**
ML (16–50%)	68	32 *(49%)*	36 *(51%)*	p = 0.40	28 *(41%)*	40 *(59%)*	**p = 0.017**
MH (51–79%)	60	41 *(69%)*	19 *(31%)*	p = 0.99	35 *(58%)*	25 *(42%)*	**p = 0.014**
H (≥80%)	118	97 *(82%)*	21 *(18%)*	**p < 0.0001**	100 *(85%)*	18 *(15%)*	**p < 0.0001**
	300	194 *(65%)*	106 *(35%)*		186 *(62%)*	114 *(38%)*	

Statistically significant values have been reported in bold.

TABLE 6 | PR expression and histological type of 194 WHO grade I meningiomas.

PR expression	Meningothelial	Transitional	Fibroblastic	Psammomatous	Microcystic	Secretory	Chordoid
L (0–15%)	3 (10%)	3 (3%)	9 (22%)	2 (9%)	2 (22%)	–	-
ML (16–50%)	1 (4%)	14 (17%)	8 (19%)	2 (9%)	2 (22%)	–	2 (50%)
MH (51–79%)	3 (10%)	14 (17%)	3 (7%)	1 (5%)	1 (11%)	–	-
H (≥80%)	22 (76%)	52 (63%)	22 (52%)	17 (77%)	4 (45%)	5 (100%)	2 (50%)
Total (194)	29 (15%)	83 (43%)	42 (22%)	22 (11%)	9 (5%)	5 (2%)	4 (2%)
Statistical significance	p = 0.08	p = 0.5	p = 0.09	p = 0.096	p = 0.15		

TABLE 7 | PR expression, WHO grade, Ki67/MIB1 at initial surgery and recurrence.

Covariates	Group 1 overall recurrence (75 pts)	Group 1A Local-peripheral recurrences (50 pts)	Group 1B Multicentric diffuse recurrences (25 pts)	Group 2 No recurrence (100 pts)	Statistical significance group 1 vs. 2	Statistical significance group 1A vs. 1B
PR expression						
L (0–15%)	22 *(29%)*	14 *(28%)*	8 *(32%)*	13 *(13%)*	p = 0.99	p = 0.35
ML (16–50%)	30 *(40%)*	18 *(36%)*	12 *(48%)*	24 *(24%)*	p = 0.98	p = 0.15
MH (51–79%)	14 *(19%)*	12 *(24%)*	2 *(8%)*	20 *(20%)*	p = 0.4	p = 0.95
H (≥80%)	9 *(12%)*	6 *(12%)*	3 *(12%)*	43 *(43%)*	**p = 0.0004**	p = 0.5
WHO grade						
I	23 *(30%)*	18 *(36%)*	5 *(20%)*	72 *(100%)*	**p = 0.000001**	p = 0.07
II	52 *(70%)*	32 *(64%)*	20 *(80%)*	28 *(28%)*	**p = 0.00001**	p = 0.07
KI67/MIB1						
≤4%	27 *(36%)*	22 *(44%)*	5 *(20%)*	62 *(62%)*	**p = 0.003**	p = 0.07
>4%	48 *(64%)*	28 *(56%)*	20 *(80%)*	38 *(38%)*	**p = 0.003**	p = 0.07

Statistically significant values have been reported in bold.

The PR expression at initial surgery was significantly correlated with the recurrence time, with higher rate of patients (23 *versus* 8%) with high PR values ≥80% in the group with recurrence time >5 years (p = 0.036) (**Table 8** and **Figure 2**).

Finally, the PR values of the surgical specimens at recurrence, as compared with those at initial surgery, had the same score (almost unchanged) in 42 cases (56%) and at a lower score in 33 (44%). This finding is associated with rather similar behavior of the Ki67 MIB-1, showing 44 cases (59%) with

TABLE 8 | PR expression and time to recurrence (75 pts).

PR expression	Time to recurrence		Statistical significance	Statistical significance groups L+ML vs MH+H
	≤5 years	>5 years		
L (0–15%)	17 (32%)	5 (23%)	p = 0.78	**p = 0.009**
ML (16–50%)	24 (45%)	6 (27%)	p = 0.92	
MH (51–79%)	8 (15%)	6 (27%)	p = 0.11	**p = 0.0096**
H (≥80%)	4 (8%)	5 (23%)	**p = 0.036**	

Statistically significant values have been reported in bold.

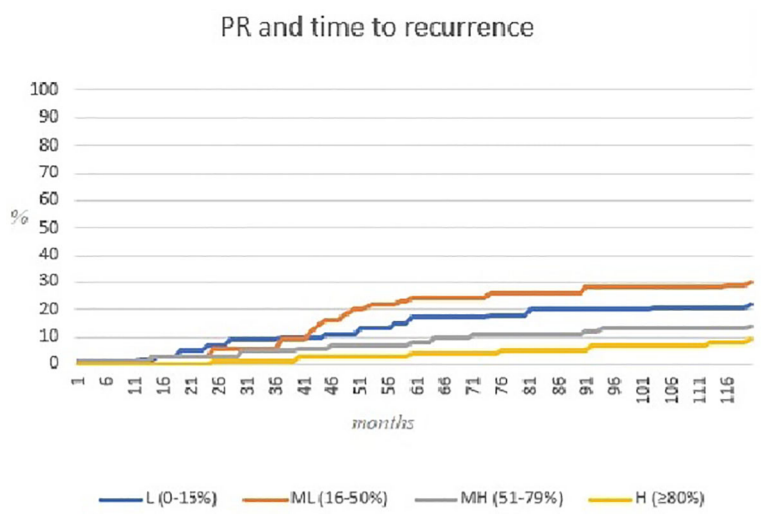


FIGURE 2 | Kaplan–Meier curve representing relation between PR expression and time to recurrence.

increased values, from ≤4 to >4%, and 31 (41%) with values in the same subgroup, both at initial surgery and recurrence.

DISCUSSION

The possible pathological and prognostic implications of the PR expression in meningiomas have been discussed in several studies. However, the role of several factors is still controversial. **Table 9** summarizes the results of 30 studies from the literature that focused on the epidemiological, pathological, and prognostic role of the PR expression in meningiomas (8, 10–14, 17–40).

Definition of the Progesterone Receptor Expression

The score and cut-off values of PR expression have variably been considered in the reviewed reports. Many studies (11, 13, 17, 21, 26, 31, 39) only report negative or positive expression. Others consider as positive only those cases with strong staining in >10% or moderate staining in >50% (12, 34, 37). Two studies (16, 32) used stratification only for cases with positivity in <50% of the cells, whereas cases with >50% positive cells are considered as a unique group. Only three studies (14, 30, 35) have stratified all cases with different positivity, but the employed cut-off values are different. We have used the semiquantitative scoring scale recommended by the Group for Evaluation of Prognostic Factors using Immunohistochemistry, published in 1999 (16); we have only modified the cut-off of the lower expression (15% instead of 10%). We agree that the definition of negative and positive expression is not sufficient. The stratification of the data must be made for all cases with different positivity. In fact, our study shows significant correlation of PR expression with the WHO grade and recurrence only for cases with high PR expression (>80%).

Progesterone Receptor Expression and Patient Age and Sex

The PR expression of meningiomas in the different age groups is scarcely focused in the literature. Two recent reviews of reported studies on elderly patients do not include data on the PR expression (41, 42). We have found significantly higher rate of PR expression ≥80% in patients aged <70 years ($p = 0.032$), whereas lower PR values are not correlated. Our results agree with those of Wolfsberger et al. (25); on the other hand, Roser et al. (43) as well as others (8, 17, 18, 21, 22, 26, 28) did not find significant differences between younger and older patients. The discrepancy between our and these studies is likely due to the lesser stratification of the PR values.

The significant correlation between PR expression and patient sex was evidenced in four reviewed studies (17, 19, 28, 34). Others report slightly higher rate of expression in females (14, 22) or in males (25) but with no statistical significance or no relevant sex difference (12, 18, 20–22, 24–26, 32, 40), as in our series. All have considered the overall female group without no relation to the age and the sex female function. We did not find significant differences of PR expression between premenopausal and postmenopausal women. This confirms that the PR expression of meningiomas does not reflect the patient hormonal status.

Progesterone Receptor Expression and Meningioma Location

Seven reviewed studies (12, 17, 18, 22, 24, 25, 40) did not find significant correlation between PR status and tumor location.

TABLE 9 | Data of 30 reviewed studies on the progesterone receptor expression in meningiomas.

Authors/year	N° of cases	Correlation of PR expression with epidemiological and pathological findings and recurrence							
		Age	Sex	Location	WHO grade	Ki67 MIB1	Mitotic index	Histological type	Recurrence
Magdelenat et al., 1982 (17)	42	n.s.	p = 0.05	n.s.	-	-	-	n.s.	-
Markwalder et al., 1983 (18)	34	n.s.	n.s	n.s.	–	–	n.s	++meningothelial	–
Nagashima et al., 1995 (19)	39	-	p < 0.02	-	p < 0.001	p < 0.05	-	-	-
Hsu et al., 1997 (8)	70	n.s.	–	–	p < 0.001	–	p < 0.0001	n.s	–
Fewings et al., 2000 (11)	62	-	-	-	b.m.	-	-	-	p = 0.013
Perry et al., 2000 (20)	175	–	n.s.	–	p < 0.001	–	–	n.s	–
Das et al., 2002 (21)	90	n.s.	n.s.	-	b.m.	-	-	-	n.s.
Gursan et al., 2002 (22)	110	n.s.	n.s.	n.s.	–	p < 0.05	–	–	–
Strik et al., 2002 (23)	30	-	-	-	b.m.	n.s.	-	-	OR 3.533
Konstantinidou et al., 2003 (24)	51	–	n.s	n.s	p = 0.036	p = 0.041	p = 0.009	++meningothelial p = 0.04	–
Roser et al., 2004 (12)	588	n.s.	n.s	n.s.	p < 0.0001	p < 0.001	-	p < 0.0001	p < 0.0005
Wolfsberger et al., 2004 (25)	82	p=0.05	n.s.	n.s.	n.s.	–	–	++meningothelial p = 0.032	–
Kohronen et al., 2006 (26)	443	n.s.	n.s.	-	n.s.	-	-	-	n.s.
Omulecka et al., 2006 (27)	64	–	–	–	s	–	–	p < 0.05	–
Pravdenkova et al., 2006 (13)	239	-	-	-	p < 0.00009	-	-	-	p = 0.002
Maiuri et al., 2007 (10)	100	–	–	–	–	–	–	–	p < 0.0001
Taghipour et al., 2007 (28)	51	n.s.	p < 0.021	-	s	-	-	-	-
Metellus et al., 2008 (29)	120	–	–	–	–	–	–	–	p = 0.0025
Takey et al., 2008 (30)	57	-	-	-	p = 0.0419	n.s.	-	n.s.	-
Guevara et al., 2010 (31)	42	–	–	–	–	–	–	–	n.s
Kandemir et al., 2010 (32)	53	-	n.s.	-	n.s.	n.s.	-	n.s.	-
Karya et al., 2010 (33)	59	–	–	–	b.m.	–	–	–	n.s.
Shayanfar et al., 2010 (34)	78	-	p < 0.05	-	p < 0.0001	p < 0.0001	-	-	-
Abdelzaher et al., 2011 (14)	60	–	–	–	b.m.	–	–	–	p = 0.028
Tao et al., 2012 (35)	102	-	-	-	-	-	-	-	n.s.
Iplikcioglu et al., 2014 (36)	48	–	–	–	p = 0.01	n.s.	p = 0.002	–	n.s
Mukhopadhyay et al. 2017 (37)	90	-	-	-	p < 0.001	-	-	-	-
Kuroi et al., 2018 (38)	161	–	–	+skull base p=0.00009	–	–	–	–	–
Carvalho et al., 2020 (39)	96	-	-	-	b.m.	n.s.	-	-	n.s.
Portet et al., 2020 (40)	90	–	n.s.	n.s.	n.s.	–	–	n.s.	–
Present study	300	p = 0.032	n.s.	lateral s.b and non-s.b. *VS* medial s.b. and spinal p=0.0036	p < 0.0001	p < 0.0001	-	n.s.	p = 0.0004

n.s., not significant; not studied; s.b., skull base; b.m., only benign WHO grade I meningiomas included; s.g, referred as significant but with no statistical data.

However, they consider the overall locations in a unique group. In several studies, as discussed in our recent report (35), the meningioma location was found to be correlated with the WHO grade and Ki67 MIB-1 in several studies which report significantly higher rates of WHO II grades and higher values of Ki67 LI in non-skull base meningiomas.

Only Kuroi et al. (38) reported significantly higher rate of positive PR expression in skull base meningiomas as compared

to the non-skull base ones. In our series we have first studied the PR expression of medial skull base and lateral skull base meningiomas as distinct groups; our data show that medial skull base meningiomas have significantly higher rate of cases with higher PR expression and significantly lower rate of cases with low expression than lateral skull base ones.

The higher PR expression of medial skull base and spinal meningiomas, together with the lower values of Ki76-LI (44), may suggest an embryological explanation. Two studies (45, 46) have stated that the meninges around the brain stem develop from the cephalic mesoderm and those of the spinal canal from the somatic mesoderm, whereas the telencephalic meninges develop from the neural crest. This may explain the different PR expression levels and pathological features according to the meningioma location.

These different pathological features have some clinical significance. The skull base meningiomas may have different clinical behavior and recurrence rates. The medial skull base group includes locations, such as olfactory groove, tuberculum sellae, and foramen magnum, with more often slow course and lower recurrence rates (0 to 15%) (47, 48); on the other hand, the recurrence rates are higher for lateral skull base meningiomas (35–40%) (49, 50). This agrees with the different PR expression levels of such locations.

Progesterone Receptor Expression and Pathological Findings

The correlation between PR expression and pathological findings of meningiomas has largely been discussed, but the reported results are controversial. Among the 30 reviewed studies (**Table 9**), six only included benign WHO grade I meningiomas (11, 14, 21, 23, 33, 39); thus the significance of the WHO grade was not possible. Among the 24 studies including all WHO grades, the correlation between PR expression and WHO grade was studied in 16; 12 found significantly higher rate of cases with high PR expression in benign WHO I tumors and low expression in atypical WHO II ones (8, 12, 13, 19, 20, 24, 27, 28, 30, 34, 36, 37) (**Table 9**). The correlation between PR expression and Ki67 MIB-1 was studied in 10 reviewed series; 5 (12, 19, 22, 24, 34) found significantly lower PR expression in meningiomas with higher Ki67-Li; on the other hand, others (23, 30, 33, 36, 39) did not find significant differences.

The mitotic index was studied in four reports; three of them (8, 24, 36) found significant inverse correlation with the PR expression.

In a recent report (51), we studied the expression of p40, a shorter form of the p53 homolog gene p63, in a series of WHO I and II meningiomas; it was found to be significantly associated with Ki67 LI and recurrence and inversely correlated with the PR expression. All these data confirm that the decrease or loss of the PR expression is associated with histological and biological progression of meningiomas.

The histological subtypes of WHO I meningiomas were studied in 11 reviewed reports; 5 of them (12, 18, 24, 25, 27) have found significantly higher PR expression in the meningothelial ones, with no significant correlations with the other subtypes. In our study the difference of PR expression between the histological subtypes is not significant.

Presurgical information of the PR status of meningiomas, as for other pathological parameters, has recently been obtained with diffusion weighted imaging of magnetic resonance through histogram profiling of apparent diffusion coefficient (ACD) volumes. Skewness and entropy of the ACD are significantly associated with PR expression and Ki 67 LI values (52).

Progesterone Receptor Expression and Recurrence

Intracranial meningiomas are estimated to recur in 10 to 32% of the cases at 10 years (53–55). Fourteen reviewed studies focused on PR expression and recurrence of meningiomas; seven have found significant inverse correlation, with high recurrence rates in meningiomas with low PR expression at initial surgery (10–14, 23, 29). On the other hand, other studies (21, 26, 31, 33, 35, 36, 39) did not find significant results. Like our previous report (10), the present study confirms the inverse correlation between PR values and recurrence ($p = 0.0004$); the high PR expression (≥80%) is a single efficient predictive factor ($p = 0.017$).

The meningioma location may influence the recurrence rate. As discussed in our recent report (44), the medial skull base group includes locations, such as tuberculum sellae and olfactory groove meningiomas, at low recurrence rate; on the other hand, the lateral skull base group includes spheno-orbital meningiomas with dural and bone invasion and higher recurrence rate. This different distribution reflects the different possibilities of achieving resections of Simpson grades I and II.

The present study does not include recurrent spinal meningiomas (only one case in the observation period). Spinal meningiomas very rarely show diffuse growth (56) and are known to recur less frequently than intracranial ones, with reported rates ranging from 0 to 18% (57). Two reports (58, 59) have focused on the PR expression in spinal meningiomas and have found variable positivity in high rate of cases. In a recent study (57) we have first investigated the PR expression in recurrent *versus* non-recurrent tumors, and we did not find significant correlation, with high values in both groups. These data confirm that, differently from intracranial meningiomas, the PR expression is not a predictive factor for spinal meningiomas.

Intracranial meningiomas more often recur at the initial dural site or at the contiguous dural region; however, some patients show multicentric and diffuse recurrences, distant from the initial site, likely from undetected microscopic tumor nodules in distant regions. The reviewed studies which correlate PR expression and recurrence include the overall recurrent tumors, without considering the regrowth pattern. The present study first investigated the PR expression at initial surgery in patients who later experienced local-peripheral *versus* multicentric-diffuse recurrences; we did not find statistically significant differences of PR expression, although the values of Ki67 LI are significantly higher in meningiomas with multicentric and diffuse recurrences. This finding has not previously been reported.

CONCLUSION

The higher PR expression in medial skull base meningiomas, the significant correlation with the recurrence time, the lack of difference of PR expression between premenopausal and postmenopausal women and between local-peripheral *versus* multicentric-diffuse recurrences are the main findings of this study.

The immunohistochemical evaluation of the PR expression must be included in the routine histological study of meningiomas, together with the WHO grade and Ki67 LI. Percentages of the expression must be provided, whereas the definition of positive or negative expression is not sufficient.

The well-defined correlation of the PR status with the WHO grade, Ki67 LI, and recurrence is of prognostic significance. For atypical WHO grade II intracranial meningiomas, the low PR expression is a further risk factor of recurrence with the Ki67 LI. For WHO grade I meningiomas, even without high Ki67-LI, the low values of PR expression must suggest a closer follow-up. However, further biomolecular studies will contribute to stratify the group of patients with low PR expression and those at different recurrence risks.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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