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Methods in surgical oncology

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Methods in surgical oncology

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Early enteral vs. oral nutrition after Whipple procedure: Study protocol for a multicentric randomized controlled trial (NUTRIWHI trial)

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Background: Malnutrition has been shown to be a risk factor for postoperative complications after pancreatoduodenectomy (PD). In addition, patients needing a PD, such as patients with pancreatic cancer or chronic pancreatitis, often are malnourished. The best route of postoperative nutrition after PD remains unknown. The aim of this randomized controlled trial is to evaluate if early postoperative enteral nutrition can decrease complications after PD compared to oral nutrition.

Methods: This multicenter, open-label, randomized controlled trial will include 128 patients undergoing PD with a nutritional risk screening $\geq$3. Patients will be randomized 1:1 using variable block randomization stratified by center to receive either early enteral nutrition (intervention group) or oral nutrition (control group) after PD. Patients in the intervention group will receive enteral nutrition since the first night of the operation (250 ml/12 h), and enteral nutrition will be increased daily if tolerated until 1000 ml/12 h. The primary outcome will be the Comprehensive Complication Index (CCI) at 90 days after PD.

Discussion: This study with its multicentric and randomized design will permit to establish if early postoperative enteral nutrition after PD improves postoperative outcomes compared to oral nutrition in malnourished patients.

Clinical trial registration: https://clinicaltrials.gov/(NCT05042882)
Registration date: September 2021.

KEYWORDS

pancreas cancer, pancreatoduodenectomy, malnutrition, complications, morbidity

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers in humans (more than 47'000 estimated deaths in 2020 in the United States) (1). It is predicted to become the second most common cause of cancer deaths in the United States by 2030 (2). The mean costs in 2015 were estimated to be $79'800 per patient with PDAC and $164'100 for each resection (3). The observed overall 3-year survival after diagnosis is 6% (4, 5). Surgery remains the only potentially curative strategy when combined with adjuvant or neoadjuvant chemotherapy. However, resection of the pancreatic head remains a difficult surgical procedure with high morbidity (40-60%) (6, 7). Recently, the concept of Enhanced Recovery After Surgery (ERAS) has contributed to reduce overall morbidity, length of hospital stay and costs by implementing multimodal measures influencing the pre-, intra- and postoperative periods (8–12).

Patients suffering from pancreatic tumors as well as patients with chronic pancreatitis often present with cachexia or at least with a certain level of malnutrition (13). This situation is difficult to correct preoperatively. Nutritional therapy should therefore be started early during the postoperative course to prevent further malnutrition, as the latter is an important risk factor to develop complications (14–16). In addition, surgery disrupts the digestive tract, leading to postoperative indigestion and malabsorption (17). Postoperative nutritional supports, including early enteral nutrition (EEN) and parenteral nutrition (PN), have been shown to be effective in improving clinical outcomes after major abdominal surgery (14).

Malnutrition is still poorly defined. Many definitions have been proposed based on criteria that vary between medical history, biometric and biological data. Currently, the European Society for Parenteral and Enteral Nutrition (ESPEN) recommends the Nutritional Risk Score (NRS) as a screening tool, even if it has not been prospectively validated (18, 19). Several studies have proven its reliability to identify patients at nutritional risk who will benefit from perioperative nutritional support (15, 20). Patients with NRS ≥3 are considered to be exposed to higher incidence and severity of postoperative complications.

Recent randomized clinical trials and meta-analyses have shown that EEN could shorten length of stay, reduce postoperative infections and mortality and improve cost-effectiveness when compared to PN in gastrointestinal cancer surgery (21–24). Specifically after pancreatoduodenectomy (PD), EEN has been shown in one study to reduce early and late complications, infections, and readmission rates (25). Another retrospective study showed no differences with respect to time to resumption of normal oral intake, morbidity and mortality when comparing EEN *via* nasojejunal tube or jejunostomy tube and parenteral nutrition (26). However, a recent multicentric randomized controlled trial that compared nasojejunal EEN to PN after PD showed that EEN was associated with an increase of overall postoperative complications (27). One major drawback of this study is that it did not compare EEN to the recognized standard which is oral feeding and not PN (28). Another systematic review compared the outcomes of 5 feeding routes after PD (oral diet, enteral nutrition *via* either a nasojejunal, gastrojejunostomy tube or jejunostomy tube, and PN) and reported no evidence to support routine enteral or parenteral feeding after PD (29).

The study of EEN and its impact in terms of morbidity require the use of a validated tool. Most studies fail to provide information about the severity of complications and inform only on the most severe event, ignoring events of lesser severity (30). The Comprehensive Complication Index (CCI) was created to summarize all postoperative complications and is more sensitive than existing morbidity endpoints (31).

The primary objective of the study is to assess the impact of EEN through a jejunal tube placed intraoperatively on postoperative morbidity after PD, according to the CCI. Secondary objectives are to assess the impact of EEN on major postoperative complications, according to Clavien classification, specific complications, length of stay, readmission rates, reoperations, quality of life (QoL), metabolic stress and nutritional response after PD.

Materials and methods

Hypothesis and primary/secondary objectives

The hypothesis is that EEN after PD might decrease the postoperative complications compared to oral nutrition as patients undergoing PD often are malnourished. The primary objective is to assess the impact of EEN on postoperative morbidity after PD, according to the CCI, in patients at nutritional risk with a NRS ≥3.

The secondary objective is to evaluate the impact of EEN on major postoperative complications, according to Clavien classification (defined as ≥3a), specific complications, length of stay, readmission rates, reoperations, QoL, metabolic stress and nutritional response after PD in patients at nutritional risk with a NRS ≥3.

Primary and secondary endpoints

The primary endpoint measuring postoperative morbidity will be assessed using the CCI at 90 postoperative days.

Secondary endpoints are the following:

- Most severe postoperative complications (≥3a) will be measured using the Clavien classification within 90 postoperative days.
- Specific complications of PD will be recorded:
  - Surgical site infections (SSI), further divided into 'superficial', 'deep' and 'organ-space' according to the specific anatomic involvement and the Centers for Disease Prevention definition (32).
  - Postoperative pancreatic fistulas (POPF) are classified into three grades, A, B and C, according to the consensus of the International Study Group for Pancreatic Surgery (ISGPS) (33).
  - Delayed gastric emptying (DGE), which is classified into three grades, A, B and C, according to the consensus of the ISGPS (34).
  - Postoperative pancreatic hemorrhage (PPH), which is also classified into three grades, A, B and C, according to the consensus of the ISGPS (35).
  - Biliary fistula (no standard definition)
  - Gastrojejunal anastomosis fistula (no standard definition)
  - Pancreatitis (no standard definition)

- Length of stay will be measured from operative day until discharge.
- Readmissions will be counted until postoperative day 90.
- Reoperations
- Patients' QoL will be assessed by the EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 questionnaire (36). This questionnaire will be filled 4 times: at preoperative consultation or admission, at patient's discharge, between the 4th and 6th postoperative week and on POD 90 (via phone call).
- The subjective tolerance of EEN will be assessed daily during the first 7 postoperative days, using a visual analogue scale (0: perfect tolerance to 10: no tolerance). Objective tolerance will be assessed by the amount of EEN as a percentage (tolerated/total amount of EEN required).
- Time required (in days) to reach respectively 50% and 100% of the daily caloric targets required (30 kcal/kg/day if BMI <30 kg/m2 and 25 kcal/kg/day if BMI ≥30 kg/m2, protein target: 1.5 g/kg/day).
- Metabolic response to EEN will be assessed with biological measurements preoperatively and twice weekly (currently already measured, according to our PD care map):
  - C-Reactive Protein (CRP) and procalcitonin
  - Simple blood count, coagulation
  - Electrolytes: sodium, potassium, calcium, magnesium, phosphate
  - Creatinine, urea, blood glucose, liver and pancreatic function tests, prealbumin, albumin, triglycerides

- Various malabsorption due to PD surgery: measurements will be made twice, once before surgery and once between the 4th and 6th postoperative week during the follow-up visit. As PD might induce duodenal and pancreatic insufficiencies postoperatively due to the resection of the duodenum and the pancreatic head, it is presently unknown if EEN might influence these insufficiencies by improving the overall nutritional state and the mucosal trophic status of the small bowels.
  - Duodenal insufficiency: folate, magnesium, calcium, iron, ferritin, transferrin saturation
  - Exocrine pancreatic insufficiency: malabsorption of fat-soluble vitamins: vitamin D (with calcium/phosphate balance and parathormone) and vitamin E
  - Endocrine pancreatic insufficiency: due to risk of developing a secondary diabetes, HbA1c (glycated hemoglobin) will be measured.

- Body measure using bioelectrical impedance analysis (BIA) and muscle strength using handgrip will be measured preoperatively, on discharge day, and on the first follow-up visit. BIA will calculate the percentage of body fat and muscle mass using 2 or 4 electrodes on the wrists/fingers and ankles to measure the impedance. Handgrip will be measured in both hands (best of 3 attempts).
- Resting energy expenditure will be measured bedside by the dietician on POD 5 using indirect calorimetry.

Indirect calorimetry will measure respiratory gas exchange using a canopy hood or a face mask.

Each of these endpoints will be measured in the study (EEN) and control (oral nutrition) groups.

Study design

This study is an open-label, multicentric, international two-arm, randomized controlled trial.

Study intervention

After PD, patients will be randomized to receive either EEN or oral nutrition. Patients included in the EEN arm will receive, in addition to oral nutrition based on the current care maps, enteral nutrition according to the following scheme that was established in accordance with nutritionists:

- Six hours after the operation, a low flow enteral feeding will be initiated (21 ml/h, 250 ml/12h), and based on a Isosource® Energy Fibre solution (or similar product, 400 kcal).
- If the tolerance is subjectively good, with a visual analogue scale ≤4/10, the flow will be increased on first postoperative day (POD), at the flow of 42 ml/h (500 ml/12h from 8 pm to 8 am, 800 kcal).
- On POD 2: increased flow to 62.5 ml/h (750 ml/12h, 1200 kcal)
- On POD 3: increased flow to 83.5 ml/h (1000 ml/12h, 1600 kcal)

If the tolerance is not satisfactory (5/10 and 6/10), the current flow will be maintained 24 hours more. It will be decreased to previous stage if tolerance is >6/10 or put on hold for 6 hours in case of persisting digestive symptoms (severe nausea, vomiting, severe bloating or severe diarrhea) despite diminution of the nutrition flow, and increased the next day if tolerated until the maximum of 1000 ml/12h.

The diet will be infused over 12 hours with a pump and controlled flow rate. EEN will be continued until oral food intake will have reached more than 50% of nutritional requirements. Daily nutritional requirements will be defined as 30 kcal/kg if BMI <30 kg/m2 and 25 kcal/kg if BMI ≥30 kg/m2 (protein target: 1.5 g/kg/day). The oral intake will be assessed by the dietitian.

If a patient in the EEN group loses or displaces its nasojejunal tube (vomiting, accidental removal), a new probe will be replaced under endoscopic control by the gastroenterologist through the gastrojejunal anastomosis. If this happens a second time, another attempt to put the nasojejunal tube will not be made (the patient will remain in the study). In the same previous scenario (nasojejunal tube expulsion), and if the patient suffers from DGE, a nasogastric tube will be installed at the same time.

In the enteral nutrition group, if the patient suffers from DGE and the nasojejunal tube is in place, a nasogastric suction tube will be installed in addition, and enteral feeding will be continued. Parenteral nutrition will be used to complete, if necessary, the missing caloric needs. In the control group (without jejunal tube), in case of DGE, a nasogastric suction tube will be installed (the patient will remain in the study) and parenteral nutrition will be started.

The use of parenteral feeding will be standardized similarly in both groups. A parenteral nutrition will be initiated if the caloric intake is <50% of caloric requirements for 24 hours and from POD 3. Parenteral nutrition will be continued until the total caloric intake without the parenteral nutrition reaches >50% of daily caloric needs and until no more nasogastric tube will be in place.

Inclusion and exclusion criteria, justification of study population

Participants fulfilling all the following inclusion criteria are eligible for the study:

- Patient scheduled for elective open PD.
- Patient ≥18 years old.
- Patient at nutritional risk, i.e., with NRS ≥3.

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Patient not able to give informed consent as documented by signature of consent form (e.g., vulnerable patients).
- Enteral feeding already initiated preoperatively.
- Inability to follow the procedures of the study, e.g., due to language problems, psychological disorders (i.e., eating disorders and bipolar disorders), or dementia.

The total number of included patients will be 128 (64 in each group). The choice of the patient population is justified by the fact the patients undergoing PD often are malnourished (cachexia due to cancer or chronic pancreatitis) and are at nutritional risk postoperatively due to the important stress response induced by this major abdominal surgery. As malnutrition is a risk factor for complications, EEN might reduce the morbidity burden after PD.

Recruitment, screening and informed consent procedure

The study will be proposed to any patient planned for a PD meeting inclusion criteria. The study will be presented to the patients during the first preoperative consultation by the investigators at the hospital. Expected benefits (fewer postoperative complications) and potential disadvantages as well as risks (poor tolerance of the nasojejunal tube, nausea, vomiting, diarrhea, tube obstruction, bronchial inhalation) will be explained. An information sheet will be given to the patient during the preoperative consultation. The patient will have the opportunity to ask questions.

A time of reflection will be given (at least 24 hours). The consent form will therefore be obtained at last the day before the intervention.

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorized individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

The consent form will be signed and dated by the investigator or his designee at the same time as the participant signs. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records. The informed consent process will be documented in the patient file and any discrepancy to the process described in this protocol will be explained.

Study procedures

Given the rate of annual procedures, a recruitment of about 60% of eligible patients, and based on the experience of two randomized studies successfully completed in the CHUV Visceral Surgery Department (NCT00508300, NCT00512213), the planned overall study duration is three years including the recruitment period and follow-up. For patients the study duration will be from enrolment until POD 90, date of last follow-up phone call. The expected hospitalization duration for each patient will be approximately 14 days, which is the current mean hospital stay after PD in our department.

Eligibility of the patients will be confirmed on the day before the operation (day -1). Then, patients will be randomized before the operation (day -1) or on operation day in either the control arm or the experimental one (EEN).

Standardized surgical procedure in all eligible patients: In terms of surgical details, all patients will receive a prophylactic dose of antibiotics (cefuroxime) 30 minutes before incision and first have exploratory laparotomy followed by conventional or pylorus-preserving PD. Pancreaticojejunostomy will be performed. The technique of the pancreaticojejunal anastomosis will be left to the surgeon choice. End-to-side hepaticojejunostomy will be performed with single-layer interrupted sutures. A gastrojejunostomy on an omega loop will finally be constructed approximately 70 cm distally to the ligament of Treitz. One or two perianastomotic drains will be placed.

Specific study procedure: At the end of surgery (after the three anastomoses are finished but before closure of the abdomen) and in the EEN study group only, a polyurethane single or double lumen feeding nasojejunal tube (Freka®) 8F will be inserted by the anesthesiologist and placed under direct palpation and visual control by the surgeon, 30 cm distally to the gastrojejunostomy into the alimentary limb (jejunum). The tube will be attached according to current practice to the nose wing with a tape. The patient will therefore be under general anesthesia during tube insertion and no x-ray control will be needed. An accepted alternative to nasojejunal tube will be to place a surgical gastrojejunal tube at the end of the operation.

Postoperatively, patients will receive standardized perioperative care according to the ERAS protocol in both arms.

From a nutritional point of view, this includes:

- The day before surgery: 2 carbohydrate drinks of 200 ml
- The operative day: 2 carbohydrate drinks of 200 ml up to 2 hours preoperatively, then postoperative free drinks
- On postoperative day (POD) 1: broths, creams, yogurts, drinks ≥2l
- On POD 2: light diet, drinks ≥2l
- On POD 3: normal diet (half serving)
- On POD 4: normal diet (full serving)

From POD 1, patients of both groups will receive two oral nutritional supplements (Resource® Ultra XS 125 ml, 280 kcal, 18 grams of proteins or analogous products) until discharge. In terms of intravenous infusions, a parenteral crystalloid solution will be used (Ringer-Lactate): 1000 ml during operative day and on POD 1, 500 ml during POD 2 and 3, then 250 ml, if necessary, until POD 8 (minimum for maintenance of the central venous line). Anti-nausea agents (ondansetron 4 mg 3x/j and mephameson 4 mg 1x/j) as well as laxatives (magnesium hydroxyde 4.5 g 2x/j) will be used daily for 3 days, then on demand. Prokinetic agent (metoclopramide 10 mg 3x/j) will be used on demand. An anti-acid (esomeprazole 40 mg 1x/j) will be introduced for the duration of the hospitalization. Digestive enzymes will be prescribed from the first postoperative day (Creon 40'000 UI 3x/j). The dose of digestive enzymes will be adapted based on the quantity of oral food that the patient will eat.

In terms of mobilization, patients will be stimulated by nurses/physiotherapists according to the following plan:

- Operative day: just get up from bed
- On POD 1: walk once during the day, spend ≥6h out of bed (3 x 2h)
- On POD 2 to discharge: walk twice during the day, spend ≥ 8h out of bed (4 x 2h)

In our current practice, no suction gastric tube is routinely left in place after the operation, but this choice will be left to the surgeon and recorded in the electronical case report form.

A standard nutrition protocol for the EEN intervention group will be prescribed as established in accordance with the nutritionists. Patients randomized into the oral nutrition group will receive the current postoperative management and receive from POD 1 an oral nutrition that will be gradually increased if tolerated until a normal diet (see above).

Several blood tests will be performed during the postoperative period. A timeline summary table of all study visits, relevant procedures, and samplings is shown in Table 1 (schedule of assessments).

Demographic disparities or differences in patient characteristics could be a source of bias. To reduce this risk, we decided to undertake a randomization of the participants. Moreover, heterogeneity in general management between centers might be a source of bias. Randomization will be stratified by center to decrease the risk of center bias.

Withdrawal and discontinuation

Patients will be withdrawn from the study if they leave the operation room with only a suction nasogastric tube in place or in case of withdrawal of informed consent, non-compliance to the study protocol, or due to safety concerns. Participants will

TABLE 1 Schedule of assessments.

Study periods	Screening	Entry	Intervention			Discharge	Follow-up	
Visits	1	2		Daily		3	4	5
Days	Preoperative	-1	0	1-7	Hospitalization	14^	30-45	90
Patient information and informed consent	x*	x*						
Patient eligibility confirmation		x						
Demographics	x	x						
Randomization		x						
Standard surgery (not study procedure)			x					
Nasojejunal tube (EEN group)			x***					
Physical examination	x	x		Daily		x	x	
Vital signs	x	x		Daily		x	x	
Metabolic tests ¥		x			2x/week			
Nutrition tests Ω		x					x	
Body measures°		x				x	x	
Indirect calorimetry				on POD 5				
EORTC QLQ-C30	x**	x**				x	x	x
Subjective tolerance (VAS 0-10)				x				
Complications - CCI						x	x	x
Complications - Clavien						x	x	x
LOS						x		
Readmissions								x

Demographics include the measure of serum CA 19-9 at admission in case of pancreatic cancer.
EEN, early enteral nutrition; EORTC, European Organisation for Research and Treatment of Cancer; VAS, Visual Analog Scale; CCI, Comprehensive Complication Index; LOS, length of stay; POD, postoperative day.
¥Metabolic tests: CRP, procalcitonin, simple blood count, coagulation tests, electrolytes (sodium, potassium, calcium, magnesium, phosphate), creatinine, urea, blood glucose, liver and pancreatic function tests, prealbumin, albumin, triglycerides.
ΩNutrition tests: folate, magnesium, iron, ferritin, transferrin saturation, vitamin D, calcium, phosphate and parathormone, vitamin E, HbA1c (glycated hemoglobin).
°Body measures: lean body mass using bioelectrical impedance analysis and strength using handgrip.
*Filled either during screening visit or at hospital admission.
**The preoperative EORTC questionnaire will be filled during screening visit or on hospital entry day. In total, four questionnaires will be filled. The last one on postoperative day 90 will be filled by the study nurse who will perform the phone call.
***At the end of surgery and in the EEN study group only: polyurethane single or double lumen feeding nasojejunal tube (Freka®) 8F or surgically-placed gastrojejunal tube.
^Discharge on day 14: current mean hospital stay.

not be replaced and considered as dropouts. Study data already collected on a participant until the time of withdrawal will still be used for analysis in a coded manner. No further data will be collected however from that time onwards.

Assessment

The CCI will be assessed on postoperative day 90. All complications that occurred during the 90 days after PD will be included for each patient in the CCI. The CCI is a global index of postoperative morbidity that includes all the complications that a patient present and is based on the Clavien classification. The CCI is graded from 0 (no complication) to 100 (death) by using an algorithm available online (https://www.assessurgery.com/about_cci-calculator).

Follow-up

Follow-ups will be performed 4 weeks after hospital discharge with physical consultations and on POD 90 with phone calls.

Statistical analysis and sample size calculation

A statistician was involved in the study design and estimate of the sample size. A statistician will realize the statistical analyses once all data will have been collected.

Null hypothesis H0: EEN has no effect on postoperative complications (CCI) in the population (and therefore the observed effect is entirely due to chance): p2 = p1.

Scientific hypothesis H1: EEN has an effect on postoperative morbidity (CCI) in the population (and therefore the observed effect is not entirely due to chance): p2 > p1.

According to a previous randomized trial including a series of PD and assessing a realimentation process (enteral *vs*. parenteral), the mean CCI was impacted of about 30% (32.8 *vs*. 24.2) (27). Another study reported a mean CCI of 38 after PD (37).

Based on the above results, we hypothesize that ENN will reduce by 30% a mean CCI of 35 (+/- 20) of the oral nutrition group. We will therefore expect a mean CCI for the treatment group (EEN) of 24.5 (SD 20). In this superiority study, for a power of 80% and a significance level of p-value ≤0.05 (two-sided alpha), we will therefore need 57 patients per group according to the sample size calculation. Nevertheless, we will increase the sample size to a total of 128 patients to take into account 10% of drop-out (e.g., due to discomfort associated with the tube or nasojejunal tube displacement) at 90 days (primary endpoint evaluation). We will therefore need to enroll 64 patients per group in the trial.

The study will be closed once the required 128 patients will be included. No interim analysis will be performed.

Normality of distribution will be determined by the Kolmogorov-Smirnov test and quantile-quantile plots of dependent variables for all continuous variables.

We will use a Student's *t*-test to evaluate if the primary outcome (CCI) can significantly be reduced by EEN compared to the control group (comparison of mean CCI hypothesizing a normal distribution) if the normality of distribution is confirmed. On the contrary if normality is not satisfied a Mann-Whitney *U* test will be used. For the analysis of all secondary endpoints, we will also use *t*-tests (or Mann-Whitney *U* tests if distribution is not normal) or chi-square tests based on the variable types. Regarding the questionnaires filled 4 times during the study, tests specific to repetitive ordinal measures will be used.

The primary analysis will be based on the intention-to-treat method and not per protocol. We will perform an intention-to-treat analysis so that all patients being intended to treat will be analyzed in the statistics independently. All patients will therefore be analyzed according to the group in which they were initially randomized. The intention-to-treat population (full analysis set) will be defined as the groups of patients who were randomized to have enteral nutrition (intervention group) or oral nutrition (control group). The inclusion in the enteral or oral groups will be defined at the moment of randomization, not taking into account if the patients finally received the specific postoperative nutrition based on the study protocol. As a sensitivity analysis, we will perform a per protocol analysis. The per protocol analysis will permit to assess the effect of enteral nutrition if correctly received as mentioned in the study protocol.

Blocked randomization will be done using a computerized algorithm *via* REDCap by a research coordinator the day before surgery. The proportion of "study" (EEN) and "control" (oral nutrition) subjects will be 1:1 (mix of variable block sizes of 4, 6, and 8 patients, randomly selected). Before surgery, only the responsible surgeon will know the allocation group. Postoperatively, the inclusion in the different groups will be known by the caregiver team and the patient, as it is not possible to blind the intervention (nasojejunal tube). The investigators, the outcome adjudicators, and the data analysts will be blinded (allocation concealment).

The statistical package used for analysis will be SPSS version 26 (IBM Corp., Armonk, NY, USA).

Handling of missing data and drop-outs

In case of missing data among variables other than endpoints (adjustment variables, >5% of expected data) we will consider the use of the multiple imputation technique. This process will be performed multiple times (e.g., 10-20 times) to combine multiple data sets to produce one final data sets replacing the missing data (38). A 10% drop-out was considered in the sample size calculation.

Discussion

Anticipated results

The hypothesis of this study is that EEN through a jejunal feeding tube will permit to provide to patients the required calories after PD more rapidly and will decrease the number and severity of postoperative complications after PD. The authors anticipate a decrease of the CCI on POD 90 by 30% in the EEN group compared to patients with oral nutrition.

Overall ethical considerations

The study design (randomized controlled trial) will permit to have a good internal validity of the study. Moreover, the CCI used as main outcome is a validated index of general postoperative morbidity and it enables to encompass all complications that a patient may present. The inclusion of several centers internationally will increase the generalizability of the results (external validity). The complication rate after PD remains high (around 60%) and malnutrition has been established as a risk factor of postoperative complication. An intervention that could improve the nutritional status of the patients may lead to a decrease of morbidity after PD.

If the results are favorable, this study will permit to establish an EEN protocol to improve patient outcomes after PD. Patients undergoing PD could rapidly benefit of this management, and EEN could become the new standard of care for the perioperative nutrition management after PD. The results of this study could be implemented and translated into daily clinical practice promptly.

The need for research in this field is clearly present, as the issue of postoperative nutrition after PD is not resolved and does not reach a consensus among pancreatic surgeons. The numerous presentations, debates in congresses, and our recently published survey on that subject attest and highlight the absence of consensus and lack of solid data (39).

The results of this study would go beyond the only scientific interest, as they will directly impact patients undergoing pancreas surgery. As pancreas cancer incidence is projected to grow in the upcoming years, pancreas surgery number will correlatively increase. Ultimately, in the current era of growing health expenditures and need for cost containment, if EEN allows decreasing complications and length of stay, it could also decrease the overall costs for each patient hospitalization for PD, which could have important positive repercussions on the health care system.

Particular attention will be paid to the process of randomization to ensure a sound methodology. An overall fair balance for the study participant will be maintained.

Risk-benefit assessment

There are potential adverse events associated with nasojejunal tube and enteral nutrition: poor tolerance, nausea, vomiting, diarrhea, tube obstruction, or bronchial inhalation. Nursing teams are trained to use the equipment and will perform the same care as usual: position verification, flushing, nasal fixation, nasal eschar surveillance. With these measures, the risk of adverse events associated with the study is judged to be low. In addition, the intraoperative positioning of the tube in the efferent alimentary loop should minimize these risks.

From the investigators' perspective, we hypothesize that the EEN intervention will be a benefit for patients included in the study group. Benefits of EEN could be a decrease of postoperative complications and a shorter length of stay. Nevertheless, the control group cannot be considered disadvantaged as the current recommended nutrition management after PD is oral nutrition. It is also possible that the participation to the study will not bring any benefits.

Conclusion

This study will bring new insights on the impact of enteral nutrition on postoperative complications after PD in malnourished patients compared to oral nutrition.

Data availability statement

The original data will be included in the future articles and supplementary materials. Further inquiries can be directed to the corresponding author.

Ethics statement

This study involving human participants was reviewed and approved by the Ethics commission of Vaud, Lausanne, Switzerland (Commission cantonale d'éthique de la recherche sur l'être humain, CER-VD). The patients/participants will provide their written informed consent to participate in this study.

Author contributions

G-RJ, DM, and MS designed the study. G-RJ drafted the manuscript. All authors contributed to the manuscript. All authors reviewed and approved the final 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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Incidence of bifid pancreatic duct in pancreaticoduodenectomy and its impact on clinically relevant postoperative pancreatic fistula

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Objectives: This study aimed to examine the incidence of bifid pancreatic duct (BPD) in pancreaticoduodenectomy (PD) and clarify its impact on clinically relevant postoperative pancreatic fistula (CR-POPF).

Background: Until now, all the literature about BPD during PD are published as case reports, and the incidence of BPD in PD and its impact on CR-POPF remain unknown.

Results: A total of 438 consecutive PDs were divided into two groups: the former year group and the latter year group. The former year group included 215 consecutive PDs, while the latter year group included 223. In the latter year group, we found 16 BPDs during PD (O-BPD); the incidence of O-BPD is 7.17%. Of them, there were eight patients who had BPD in the preoperative imaging (I-BPD). All the I-BPDs are O-BPDs; which means that 50% of O-BPDs were a single pancreatic duct in the preoperative imaging (I-SPD). There were 17 I-BPDs in the 438 consecutive PDs; the incidence of I-BPD is 3.88%. In the former year group, the rate of severe complications of I-BPD and I-SPD is 77.78% and 27.18%, respectively (p = 0.003); the rate of CR-POPF of I-BPD is higher than I-SPD, 55.56% vs. 27.18%, but there were no statistically significant differences. In the latter year group, the rate of severe complications of O-BPD and O-SPD is 50% and 18.36%, and the rate of CR-POPF of O-BPD and O-SPD is 37.5% and 22.22%, respectively; both of them have statistically significant differences, and the p-value is 0.003 and 0.006, respectively. In the subgroup analysis, both the rate of severe complications and the rate of CR-POPF of I-BPD were higher than O-BPD, 77.78% vs. 50%, and 55.56% vs. 37.5%, but there were no statistically significant differences in both of them; the p-value is 0.174

and 0.434, respectively. Univariate and multivariate analyses showed that BPD was an independent risk factor of CR-POPF.

Conclusions: The incidence of O-BPD in PD is 7.17%, 50% of O-BPDs were I-SPD, and the incidence of I-BPD is 3.88%. BPD is an independent risk factor of CR-POPF. The suture closure method may be a simple, safe, and effective method in dealing with BPD in PD.

KEYWORDS

bifid pancreatic duct, morbidity, pancreaticoduodenectomy, CR-POPF, nomogram

Introduction

Pancreaticoduodenectomy (PD) represents the standard surgical procedure for neoplasms of the pancreatic head and periampullary region. It involves the removal of the pancreatic head, duodenum, gallbladder, and common bile duct, with or without the removal of the gastric antrum; after resection, pancreaticojejunostomy (PJ), cholangiojejunostomy, and gastrojejunostomy must be performed. The most common complications after PD are delayed gastric emptying (DGE), pancreatic fistulae, hemorrhage, chyle leaks, endocrine and exocrine pancreatic insufficiency, and surgical site infections (1). The mortality rate of PD is about 2%–5%; the two most frequent causes of death were a leak from an anastomosis with sepsis/multiple organ system failure and bleeding. Clinically relevant postoperative pancreatic fistula (CR-POPF) occurs in up to 20% of patients and is typically associated with an increased hospital stay, cost, and reintervention rates. It is one of the most important initiating factors of severe complications and even death after PD (2).

The validated Fistula Risk Score (FRS) by Callery et al. (3) is the most cited and best used POPF prediction model. The FRS consists of gland texture, pancreatic duct diameter, intraoperative blood loss, and definitive pathology. The alternative Fistula Risk Score for PD (a-FRS) by Mungroop et al. (4) was based on pancreatic texture, duct diameter, and body mass index (BMI), without blood loss and pathology, and was successfully validated for both the 2005 and 2016 POPF definition. Kantor et al. (5) derived a modified Fistula Risk Score (mFRS) for preoperative risk stratification in patients undergoing PD, which included five predictors: sex, BMI, preoperative total bilirubin, pancreatic ductal diameter, and gland texture.

Except for the above risk factors, Shukla et al. (6) believed that the anatomy of the main pancreatic duct plays an important role in determining the outcomes of pancreatic anastomoses, and an investigation to identify its correlation is necessary. Bifid pancreatic duct (BPD) represents a relatively rare anatomical variation of the pancreatic ductal system, presenting a major bifurcation in the main pancreatic duct along its length. Halpert et al. (7) first reported a patient with bifid pancreas in 1990, diagnosed by ERCP. Steger et al. (8) investigated the anatomy of the pancreatic duct in 25 human cadaveric pancreas with a focus on the corpus area, and they found that in addition to the main and accessory pancreatic duct in the head, an additional BPD was observed within the pancreas corpus in 16% of the cases. Since then, there were some case reports about the BPD during PD (9–13). On 20 March 2015, we found two pancreatic duct orifices in the remnant of the pancreas during PD for the first time, and the BPD anatomy was confirmed *via* intraoperative probing, direct visualization of the ductal orifices, and dissecting the resected specimen postoperatively. As mentioned above, all the literature about the BPD during PD are case reports now; we do not know the incidence of BPD in PD, and the relationship between BPD and CR-POPF. This study aims to address these points.

Patients and methods

Patients and study design

Between 20 March 2015 and 19 March 2016, 223 consecutive PDs were performed by a single surgeon in the Department of Hepatobiliary and Pancreatic Surgery (HBP Surgery) of Changhai Hospital Affiliated with the Naval Military Medical University. After transecting the pancreas, we inspected the cut surface of the residual dorsal pancreas carefully; if there are two pancreatic duct orifices in the remnant of the pancreatic body, and both of the two pancreatic ducts are more than 2 mm in diameter, we confirmed the BPD *via* intraoperative probing, direct visualization of the ductal orifices intraoperatively, and dissecting the resected specimen postoperatively (Figure 1).

In the former year (between 20 March 2014 and 19 March 2015), we did not pay attention to BPD, and all the 215 consecutive PDs performed by the same surgeon were treated

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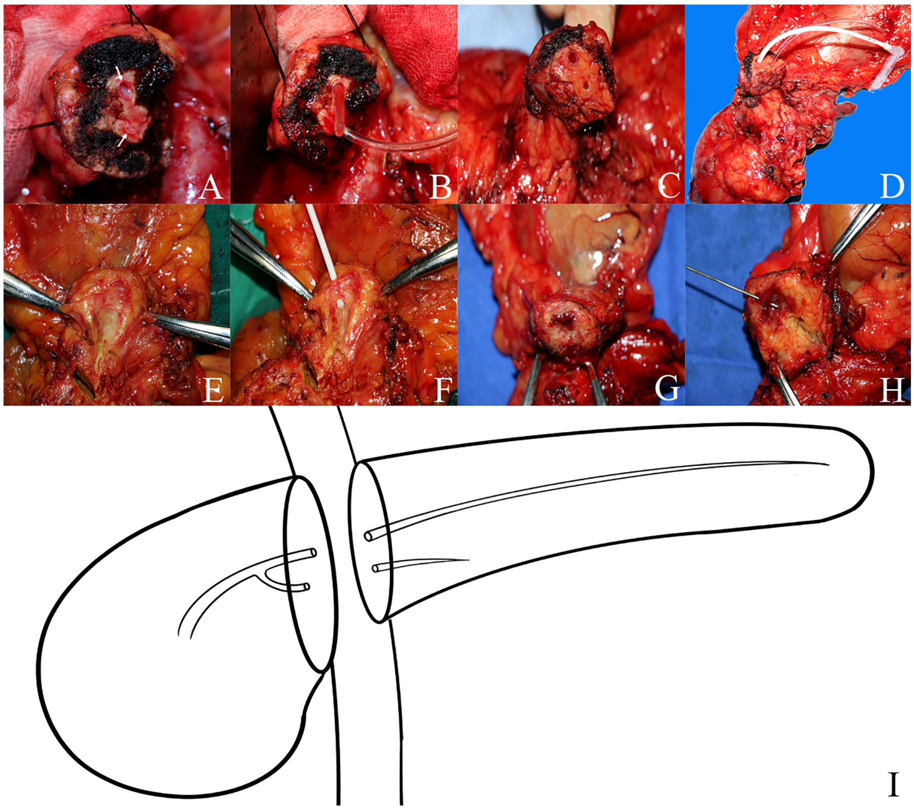

FIGURE 1
The anatomy of bifid pancreatic duct **(A–D)** Two pancreatic duct orifices in the remnant pancreas body during pancreaticoduodenectomy and the bifid pancreatic duct anatomy were confirmed *via* intraoperative probing and direct visualization of the ductal orifices. **(E–H)** The bifid pancreatic duct anatomy was confirmed by dissecting the resected specimen postoperatively; the bifid pancreatic duct in the body of the pancreas joins at the pancreatic head and drains through the major papilla. **(I)** Diagram of the anatomy of bifid pancreatic duct.

as a single pancreatic duct (SPD). The preoperative imaging data of the two groups of patients were reviewed retrospectively, and all the patients were divided into four subgroups: imaging single pancreatic duct (I-SPD), imaging bifid pancreatic duct (I-BPD), operative single pancreatic duct (O-SPD), and operative bifid pancreatic duct (O-BPD). In I-BPD, the bifurcation and the joints of the two pancreatic ducts must be seen in the preoperative imaging.

Pancreaticoduodenectomy and pancreatojejunostomy

The PD operation consists of an en bloc removal of the pancreatic head, the duodenum, the common bile duct, the gall bladder, and the distal portion of the stomach together with the adjacent lymph nodes. Pylorus-preserving pancreaticoduodenectomy (PPPD) leaves the functional pylorus at the gastric outlet. Because the neck of the pancreas is a vascular watershed between celiac and superior mesenteric arterial systems, the transection plane was 1.5–2.0 cm to the left of the neck of the pancreas (14, 15) in this study. In the O-BPD group, we sutured and ligated the small pancreatic duct with silk thread (suture closure method), and the large pancreatic duct was anastomosed with the jejunum by the double-layer continuous suturing PJ method (16) with 5-0 and 3-0 Prolene, respectively.

Data collection and definition of postoperative complications

Demographic, histopathologic, and perioperative data of all the patients in the 2 years were collected comprehensively from the electronic medical record. The staging was based on the American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017). The diagnosis of postoperative pancreatic fistulas (POPFs), postpancreatectomy hemorrhage (PPH), and delayed gastric emptying (DGE) was according to the International Study Group of Pancreatic

Surgery (ISGPS) definition, POPF-ISGPS (2016) (17), PPH-ISGPS (2007) (18), and DGE-ISGPS (2007) (19), respectively. The assessment of postoperative complications was according to the Clavien–Dindo classification (2004) (20).

Statistical method

Continuous variables were reported as median (interquartile range), and were compared using Mann–Whitney *U* test. Categorical variables were presented as whole numbers, and proportions and were compared by the χ^2 test or Fisher's exact test when appropriate. The cutoff value of certain parameters was determined using the receiver operating characteristic curve. Logistic regression analyses were applied in univariate and multivariate risk factor analysis, then a nomogram was established for predicting CR-POPF according to the results of multivariate risk factor analysis. The nomogram was validated *via* concordance index analysis, receiver operating characteristic curve, and calibration plot. Statistical analyses were conducted using GraphPad Prism 9, SPSS 24.0 software, and R software version 4.1.2. All the statistical significance levels were two-sided, with *p*-values less than 0.05.

Results

Clinicopathological features

In this study, there were 438 consecutive PDs performed by the same surgeon, and they were divided into two groups: the former year group (between 20 March 2014 and 19 March 2015) and the latter year group (between 20 March 2015 and 19 March 2016). Of them, the former year group included 215 consecutive PDs, while the latter year group included 223. The main clinicopathological characteristics and postoperative complications of the two groups are shown in Table 1. There were no statistically significant differences in baseline characteristics among the two groups except that the postoperative complication is fewer in the latter year group compared with the former year group using the Clavien–Dindo classification (p = 0.036).

The incidence of bifid pancreatic duct in pancreaticoduodenectomy

In the latter year group, we found 16 BPDs during PD (O-BPD); thus, the incidence of O-BPD is 7.18% (16/223). Of them, there were eight patients who had BPD in the preoperative imaging (I-BPD). All the I-BPDs are O-BPDs; it means that 50% of O-BPDs were SPD in the preoperative imaging (I-SPD). There were 17 BPDs in the 438 consecutive PDs in the preoperative imaging (I-BPD); thus, the incidence of I-BPD is 3.88% (17/438) in this study (Figure 2).

The effect of bifid pancreatic duct on postoperative complications in PD

There were no statistically significant differences in preoperative baseline characteristics among the two groups, including the rate of CR-POPF (p = 0.227). In the former year group, the rate of severe complications (Clavien–Dindo classification ≥ IIIa) of I-BPD and I-SPD is 77.78% (7/9) and 27.18% (56/206), respectively (p = 0.003); the rate of CR-POPF of I-BPD is higher than I-SPD, 55.56% (5/9) vs. 27.18% (56/206), but there were no statistically significant differences (p = 0.122). In the latter year group, the rate of severe complications of O-BPD and O-SPD is 50% (8/16) and 18.36% (38/207), and the rate of CR-POPF of O-BPD and O-SPD is 37.5% (6/16) and 22.22% (46/207), respectively; both of them have statistically significant differences, and the *p*-value is 0.003 and 0.006, respectively. In the subgroup analysis, both the rate of severe complications and the rate of CR-POPF of I-BPD were higher than O-BPD, 77.78% (7/9) vs. 50% (8/16), and 55.56% (5/9) vs. 37.5% (6/16), but there were no statistically significant differences in both of them; the *p*-value is 0.174 and 0.434, respectively. The effect of BPD on postoperative complications in PD is shown in Table 2.

Univariate and multivariate analyses of the factors associated with CR-POPF

The perioperatively obtained variables, include age, gender, hypertension, cardiovascular disease, smoking history, history of alcoholism, history of pancreatitis, history of abdominal surgery, BMI, TNM stage, pathology, blood type, NYHA score, ASA score, NNIS score, APACHE score, intraoperative bleeding, intraoperative blood transfusion, and indexes of blood or serum tests, were subjected to univariate and multivariate analyses. Our results showed that BPD (hazard ratio [HR] 2.396, 95% confidence interval [CI] 1.054–5.433), pancreatic duct diameter <0.2 cm (3.515, 2.041–6.054), tumor diameter ≤2 cm (3.31, 2.021–5.423), ASA score (1.914, 1.186–3.089), pathology except for pancreatic cancer and pancreatitis (4.371, 2.691–7.101), and BMI ≥ 23 (2.808, 1.809–4.359) were independent risk factors of CR-POPF (Table 3).

Construction and validation of nomogram

As listed in Table 3, BPD, pancreatic duct diameter <0.2 cm, tumor diameter ≤2 cm, ASA score, pathology except for pancreatic cancer and pancreatitis, and BMI ≥ 23 were selected in the construction of nomogram predicting CR-POPF (Figure 3). The concordance index was 0.795, and the area under the curve (AUC) was 0.790 according to the receiver operating characteristic (ROC) curve (Figure 4). The

TABLE 1 Clinicopathological characteristics and postoperative complications.

Variable	Period		*p*-value	CR-POPF		*p*-value
	First year (n = 215)	Second year (n = 223)		Absent (n = 325)	Present (n = 113)	
Bifid pancreatic duct			0.178			0.032
Absent	206	207		311	102	
Present	9	16		14	11	
Gender			0.920			0.139
Female	82	83		129	36	
Male	133	140		196	77	
Age (years)			0.322			0.979
Male	60	52		83	29	
Female	155	171		242	84	
Smoking history			0.113			0.080
Absent	171	163		241	93	
Present	44	60		84	20	
History of alcoholism			0.293			0.405
Absent	188	202		287	103	
Present	27	21		38	10	
History of pancreatitis			0.525			0.609
Absent	195	207		297	105	
Present	20	16		28	8	
BMI			0.200			0.000
≤23.0	134	125		214	46	
≤23.0	81	97		111	67	
TNM stage			0.867			0.777
I-II	178	178		263	93	
III-IV	13	15		20	8	
Pathology			0.183			0.000
Other	102	113		137	188	
Pancreatic cancer and pancreatitis	121	102		86	27	
Postoperative blood transfusion		0.925			0.002	
Absent	165	173		263	75	
Present	50	50		62	38	
High-grade antibiotic			0.327			0.000
Absent	140	156		287	9	
Present	75	67		38	104	
Intestinal fistula			NA			NA
Absent	215	223		325	113	
Present	0	0		0	0	
Chylous fistula			0.714			0.067
Absent	213	219		323	109	
Present	2	4		2	4	
Surgical site infection			0.058			0.000
Absent	134	159		288	5	
Present	81	64		37	108	
Pulmonary infection			0.466			0.000
Absent	209	220		324	105	
Present	6	3		1	8	

(Continued)

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TABLE 1 Continued

Variable	Period		*p*-value	CR-POPF		*p*-value
	First year (*n* = 215)	Second year (*n* = 223)		Absent (*n* = 325)	Present (*n* = 113)	
AP			1.000			0.005
Absent	211	219		323	107	
Present	4	4		2	6	
T-tube placement			0.423			0.238
Absent	204	216		309	111	
Present	11	7		16	2	
Clavien–Dindo Classification		0.036			0.000	
1, 2	152	177		284	50	
3a, 3b, 4a, 4b, 5	63	46		41	63	
CR-POPF			0.227			NA
0	154	171				
1	61	52				
Blood type			0.573			0.813
O	73	67		107	33	
A	24	23		36	11	
B	57	56		81	32	
AB	61	77		101	37	
Postoperative abdominal hemorrhage		0.783			0.004	
Absent	177	180		274	83	
Level B	33	39		48	24	
Level C	5	4		3	6	
Gastrointestinal hemorrhage		0.090			0.000	
Absent	208	205		315	98	
Level B	5	14		8	11	
Level C	2	4		2	4	
DGE classification			0.399			0.003
0+A	182	195		289	88	
B+C	33	28		36	25	
NYHA score			0.102			0.173
1	117	125		182	60	
2	93	97		138	52	
3	5	0		5	0	
4	0	1		0	1	
ASA score			0.208			0.025
1	6	9		14	1	
2	164	181		261	84	
3	45	33		50	28	
NNIS score			0.597			0.279
0	126	140		195	71	
1	86	79		123	42	
2	3	4		7	0	
Rehospitalization			0.500			0.384
Absent	188	189		283	94	
Present	27	34		42	19	
Tumor diameter	3.08 ± 1.45	3.00 ± 1.43	0.568	3.17 ± 1.40	2.64 ± 1.50	0.001
Pancreatic duct diameter	0.50 ± 0.25	0.47 ± 0.27	0.156	0.52 ± 0.25	0.39 ± 0.26	0.000

(Continued)

TABLE 1 Continued

Variable	Period		*p*-value	CR-POPF		*p*-value
	First year (*n* = 215)	Second year (*n* = 223)		Absent (*n* = 325)	Present (*n* = 113)	
Intraoperative bleeding	569.07 ± 419.04	487.22 ± 337.46	0.183	538.77 ± 403.23	494.69 ± 309.76	0.329
Total bilirubin	103.39 ± 117.86	95.99 ± 103.08	0.364	104.02 ± 108.07	86.9 ± 117.12	0.077
Direct bilirubin	75.72 ± 91.33	67.66 ± 79.4	0.806	74.42 ± 82.79	63.54 ± 92.88	0.178
Albumin	39.48 ± 3.04	39.98 ± 3.84	0.185	39.74 ± 3.56	39.7 ± 3.22	0.581
Alkaline phosphatase	279.98 ± 234.7	305.7 ± 289.1	0.777	594.31 ± 706.89	493.27 ± 735.88	0.107
Gamma-glutamyl transpeptidase	512.64 ± 579.8	624.34 ± 824.24	0.676	12.7 ± 0.97	12.48 ± 0.84	0.088
Hemoglobin	126.02 ± 16.41	125.5 ± 16.3	0.542	124.74 ± 15.37	128.69 ± 18.6	0.005
Platelet	235.56 ± 84.24	232.94 ± 88.06	0.843	230.91 ± 87.44	243.74 ± 81.8	0.056
C-reactive protein	17.52 ± 23.52	13.99 ± 19.32	0.669	14.37 ± 20.65	21.47 ± 25.13	0.295
CA199	163.83 ± 239.78	148.68 ± 215.16	0.615	174.94 ± 236.18	101.8 ± 189.09	0.001
Carcinoembryonic antigen	4.99 ± 5.62	7.86 ± 24.04	0.627	6.54 ± 16.45	6.36 ± 21.81	0.068
Alpha fetoprotein	23.59 ± 167.85	24.87 ± 183.51	0.598	18.35 ± 153.01	41.37 ± 229.96	0.047
CA153	14.89 ± 24.41	11.12 ± 5.07	0.441	13.55 ± 19.42	10.76 ± 4.74	0.198
CA724	3.23 ± 4.31	5.62 ± 21.61	0.160	5.12 ± 19.04	3 ± 2.97	0.736
Hospitalization days	13.93 ± 10.27	12.18 ± 8.88	0.661	10.43 ± 5.77	20.57 ± 13.72	0.000

$p < 0.05$ by Continuity Correction χ^2 test for count data and $p < 0.05$ by Mann–Whitney U test for continuous data.
CR-POPF, Clinically relevant postoperative pancreatic fistula.
PD, Pancreaticoduodenectomy.
PPPD, Pylorus-preserving pancreaticoduodenectomy.
PV/SMV, Portal Vein/Superior Mesenteric Vein.
NYHA, New York Heart Association classification.
ASA, American Society of Anesthesiologists.
APACHE, Acute Physiology And Chronic Health Evaluation scoring system.
NNIS, National Nosocomial Infections Surveillance risk index.
DGE, Delayed gastric emptying.

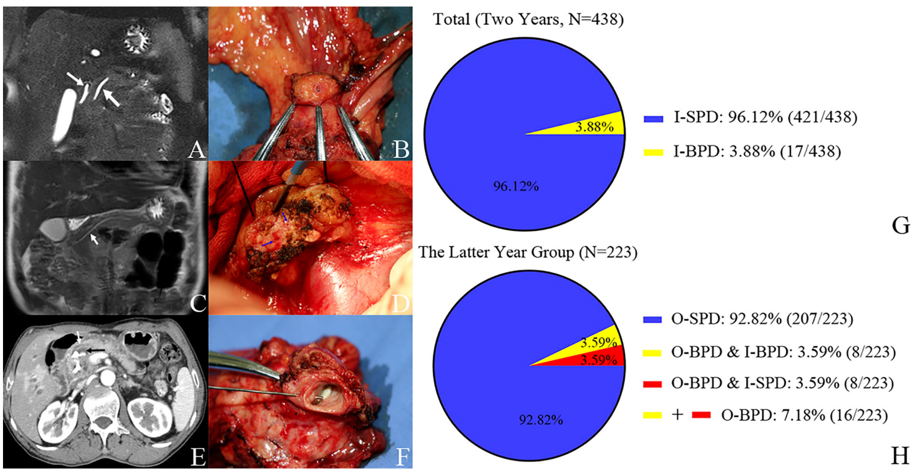

FIGURE 2
Pancreatic duct in preoperative imaging and operation and the incidence of bifid pancreatic duct. Case 1. **(A)** I-SPD vs. **(B)** O-SPD. **(A)** I-SPD: common bile duct (left arrow) and main pancreatic duct (right arrow) in preoperative imaging. **(B)** O-SPD: one pancreatic duct orifice in the remnant of pancreas. Case 2. **(C)** I-SPD vs. **(D)** O-BPD. **(C)** I-SPD: main pancreatic duct (arrow) in preoperative imaging. **(D)** O-BPD: bifid pancreatic duct (two green arrows) in pancreaticoduodenectomy. Case 3. **(E)** I-BPD vs. **(F)** O-BPD. **(E)** I-BPD: bifid pancreatic duct (white arrow and black arrow) in preoperative imaging. **(F)** O-BPD: bifid pancreatic duct in resected specimen; the bifid pancreatic duct in the body of the pancreas joins at the pancreatic head (probe in the small pancreatic duct). **(G, H)** Incidence of bifid pancreatic duct in preoperative imaging and operation. I-SPD, imaging single pancreatic duct; O-SPD, operative single pancreatic duct; I-BPD, imaging bifid pancreatic duct; O-BPD, operative bifid pancreatic duct.

TABLE 2 Bifid pancreatic duct and postoperative complications.

Variable	Severe complications		p-value	CR-POPF		p-value
	Absent	Present		Absent	Present	
Bifid pancreatic duct			<0.001			0.032
Absent (n = 413)	319	94		311	102	
Present (n = 25)	10	15		14	11	
The former year I-BPD			0.003			0.122
Absent (n = 206)	150	56		150	56	
Present (n = 9)	2	7		4	5	
The latter year O-BPD			0.003			0.006
Absent (n = 207)	169	38		161	46	
Present (n = 16)	8	8		10	6	
I-BPD and O-BPD			0.174			0.434
The former year I-BPD (n = 9)	2	7		4	5	
The latter year O-BPD (n = 16)	8	8		10	6	

$p < 0.05$ by Continuity Correction χ^2 test for count data.
Severe complications: complications of level 3, level 4, and level 5 according to Clavien–Dindo classification.

TABLE 3 Univariate and multivariate factor analysis.

Variable	Univariate				Multivariate			
	p	HR	Lower limit	Upper limit	p	HR	Lower limit	Upper limit
Bifid pancreatic duct, present: absent	0.037	2.396	1.054	5.443	0.000	7.115	2.590	19.548
Pancreatic duct diameter, <0.2:≧0.2	0.000	3.515	2.041	6.054	0.013	2.328	1.192	4.548
Tumor diameter, ≤2:>2	0.000	3.310	2.021	5.423	0.000	3.090	1.706	5.597
ASA score, 3:2:1	0.008	1.914	1.186	3.089	0.000	3.339	1.827	6.103
Pathology, other: Pancreatic cancer and pancreatitis	0.000	4.371	2.691	7.101	0.000	3.522	1.926	6.440
BMI, ≥23:<23	0.000	2.808	1.809	4.359	0.000	2.834	1.648	4.875

$p < 0.05$ by Logistic regression model.
Cutoff value of tumor diameter was calculated by ROC curve.

concordance index is a measure of the predictive accuracy of the model being tested, which ranges from 0.5 (completely random prediction) to 1 (perfect prediction). The apparent incidence of CR-POPF, the ideal incidence, and the bias-corrected incidence were shown as different lines in a calibration plot (Figure 5). The bias-corrected (also known as overfitting-corrected or optimism-corrected) line is produced using a bootstrap approach to estimate predicted and observed values based on a nonparametric smoother applied to a sequence of predicted values. These three lines were closely aligned, demonstrating good calibration.

Discussion

On 20 March 2015, we found BPD in the remnant pancreatic body during PD for the first time, and the BPD anatomy was confirmed *via* intraoperative probing, direct visualization of the ductal orifices, and dissecting of the resected specimen postoperatively. BPD represents a relatively rare anatomical variation of the pancreatic ductal system, presenting a major bifurcation in the main pancreatic duct along its length; it is different from the main pancreatic duct (Wirsung duct) and accessory pancreatic duct (Santorini duct) in the head of the pancreas (Figure 1). Steger et al. (8) investigated the anatomy of the pancreatic duct in 25 human cadaveric pancreas with a focus on the corpus area, and they found BPD within the pancreas corpus in 16% of the cases (Figure 6). There are also some case reports about the BPD during PD (9–13), and since all the literature about BPD are published as case reports, the incidence of BPD in PD remains unclear. In this study, we defined BPD as the diameter of both pancreatic ducts larger than 2 mm.

In this study, during PD, the incidence of O-BPD is 7.17% (16/223), and 50% of O-BPDs were SPD in the preoperative imaging (I-SPD); thus, during PD, a careful intraoperative inspection of the cut surface of the residual dorsal pancreas is

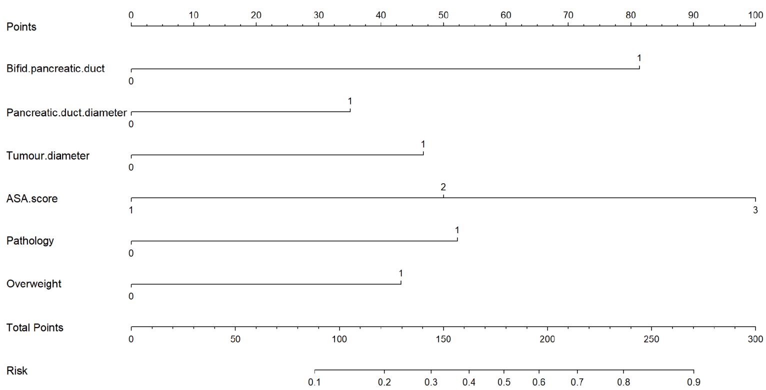

FIGURE 3
A novel nomogram for predicting CR-POPF of patients who underwent pancreaticoduodenectomy. The nomogram is used by adding up the points identified on the points scale for each variable. According to the sum of these points projected on the bottom scales, the nomogram can provide the incidence of CR-POPF for an individual patient. CR-POPF, clinically relevant postoperative pancreatic fistula.

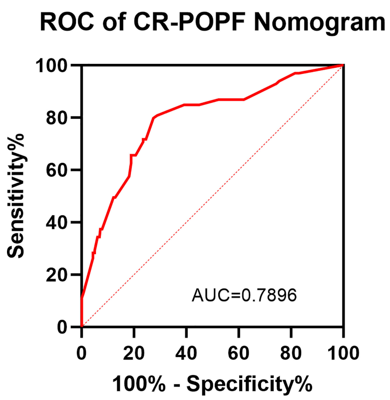

FIGURE 4
ROC of the CR-POPF nomogram. A receiver operating characteristic (ROC) curve was conducted for assessing the model. The area under the ROC curve is 0.7896.

needed to identify the presence of BPD even in I-SPD patients. There were 17 BPDs in the 438 consecutive PDs in the preoperative imaging (I-BPD); thus, the incidence of I-BPD is 3.88% (17/438). Obstruction of the pancreatic duct and transecting the pancreas at the left of the pancreatic neck may increase the incidence of BPD in PD (8).

There are two pancreatic duct orifices in the remnant pancreatic body in patients with BPD during PD; in this study, we found that both the rate of severe complications and the rate of CR-POPF of BPD were higher than SPD, and both the rate of severe complications and the rate of CR-POPF of I-BPD in the former year (untreated) were higher than O-BPD (treated with the suture closure method), suggesting that we must deal with the BPD in PD. Yoshida et al. (9) and Vasiliadis et al. (10) reported one case of double duct-to-mucosa PJ for BPD following PD. On the other hand, Ball et al. (11) and Shim et al. (12) sutured and ligated the small BPD, and the large pancreatic duct was anastomosed with the jejunum using a standard duct-to-mucosa PJ. Recently, Ishida et al. (13) presented a novel technique named the "two-in-one" method in a case of PD for BPD; they anastomosed one jejunal hole to a double pancreatic duct. In this study, we sutured and ligated the small pancreatic duct with silk thread (suture closure method) in O-BPD patients, and the large pancreatic duct was anastomosed with the jejunum by double-layer continuous suturing PJ (16) with 5-0 and 3-0 Prolene, respectively (Figure 7). By using the suture closure method, both the rate of severe complications and the rate of CR-POPF decreased, suggesting that the suture closure method may be a simple, safe, and effective method in dealing with BPD in PD. Different from duct-to-mucosa PJ, invagination PJ is performed by invagination of 1–2 cm of the proximal end of the pancreatic stump into the jejunum (21); thus, invagination PJ may be superior to duct-to-mucosa PJ in patients with BPD.

In the study of the anatomy of the pancreatic duct in the human cadaveric pancreas, fewer transversely cut side branches were observed within the plane of the portal vein as compared to the resection planes 2–4 cm beneath (8), suggesting that it is appropriate to transect the pancreas within the plane of the portal vein when it does not affect the radical PD.

When the transection plane of the pancreas is obscured by burning or bleeding during PD, intraoperative ultrasonography (IOUS) was useful in identifying the exact location of the BPD. Ohkubo et al. (22) used the IOUS and IOUS-guided pancreatography to clarify the exact location of BPD during PD; the transection line was set on the proximal side of the pancreatic duct bifurcation, which helped prevent the inadvertent suture of the second pancreatic duct or leave the second duct without

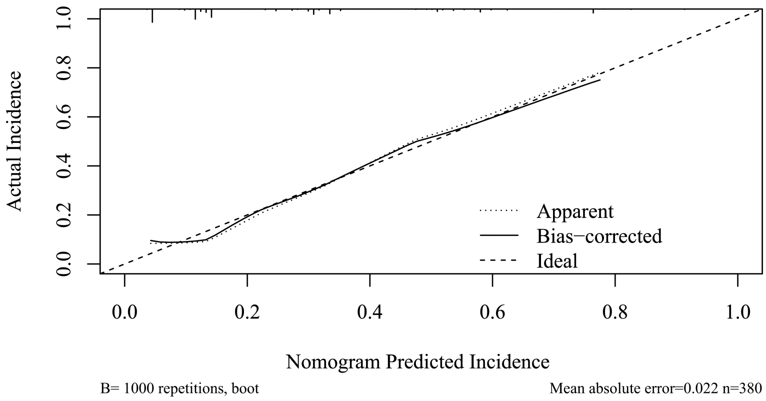

FIGURE 5
Calibration plot of the nomogram. Calibration plot of the nomogram predicting CR-POPF. The *x*-axis represents the nomogram-predicted survival, and the actual survival is plotted on the *y*-axis. The apparent incidence of CR-POPF, the ideal incidence, and the bias-corrected incidence were shown as different lines. CR-POPF, clinically relevant postoperative pancreatic fistula.

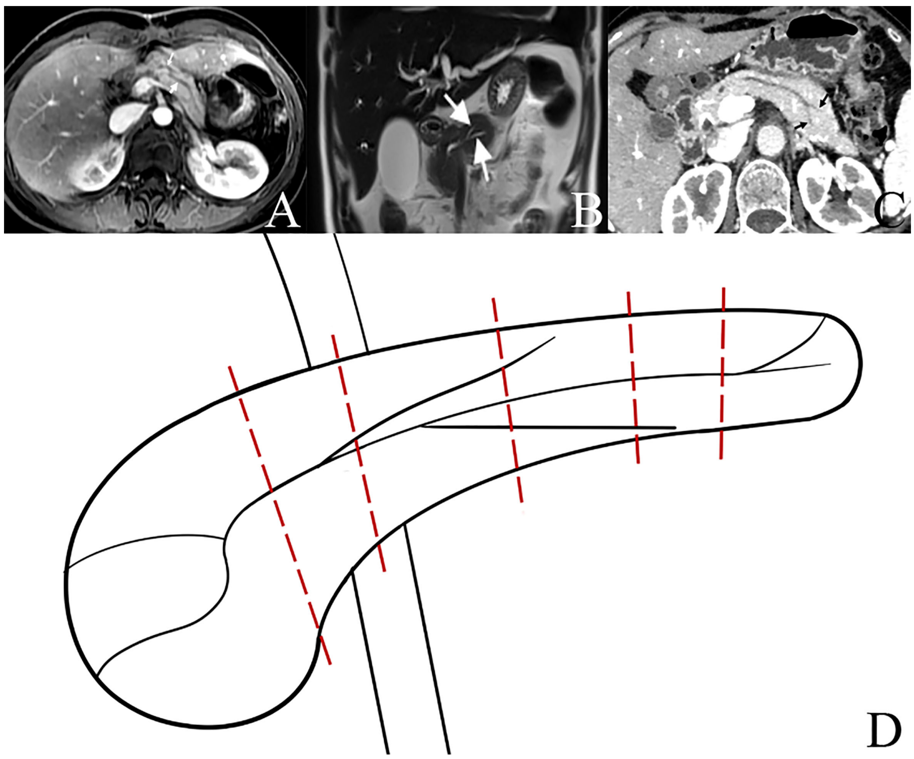

FIGURE 6
Bifid pancreatic duct at the neck, body, and tail of pancreas. **(A)** Bifid pancreatic duct (two white arrows) at the neck of pancreas. **(B)** Bifid pancreatic duct (two white arrows) at the body of pancreas. **(C)** Bifid pancreatic duct (two black arrows) at the tail of pancreas. **(D)** Diagram of bifid pancreatic duct at different locations of pancreas; different pancreatic transections result in different numbers of pancreatic duct orifices in the remnant of pancreas during operation.

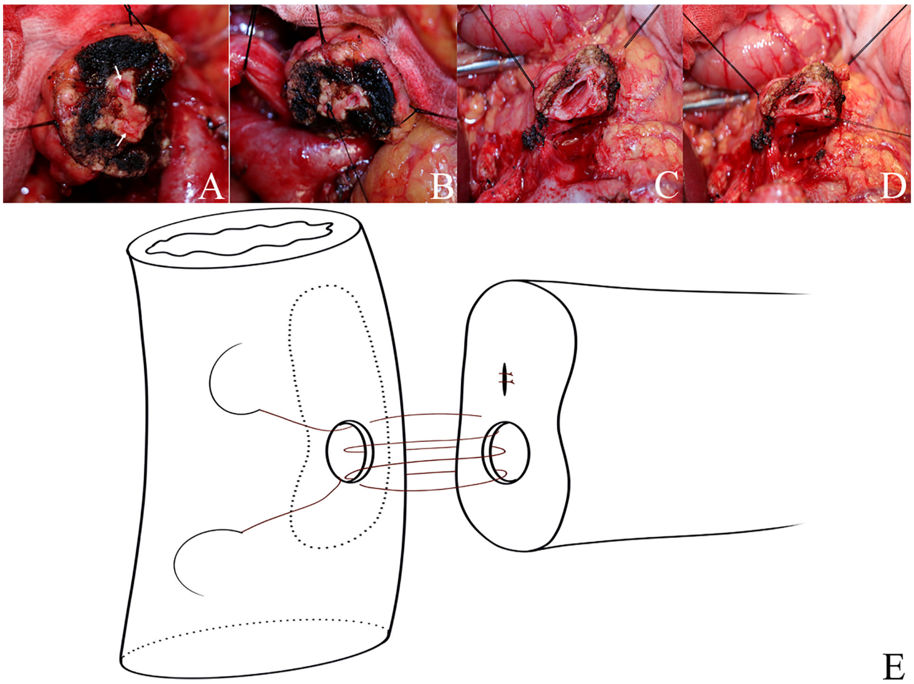

FIGURE 7
Suture closure method and double-layer continuous suturing pancreaticojejunostomy. **(A–D)** Suture closure method (suture and ligate the small pancreatic duct with silk thread). **(E)** The large pancreatic duct was anastomosed with the small intestine by double-layer continuous suturing pancreaticojejunostomy with 5-0 and 3-0 Prolene, respectively.

anastomosis, which may result in CR-POPF and severe complications. By using IOUS to confirm the exact location of the pancreatic duct bifurcation as well as the tumor extension, Tajima et al. (23) performed a distal pancreatectomy, instead of a middle pancreatectomy, with a cutting line at the downstream pancreas to the duct bifurcation point, which resulted in a favorable outcome without any postoperative complications. It suggests that IOUS-guided pancreatography should be recommended to confirm the relationship between the transection line of the pancreas and the duct bifurcation point when performing PD if BPD is suspected.

Postoperative pancreatic fistula (POPF) is one of the most threatening complications after PD. POPF occurs in up to 20% of patients and is typically associated with an increased hospital stay, cost, reintervention rates, and mortality. Different factors may predict POPF, including gland texture, pancreatic duct diameter, intraoperative blood loss, definitive pathology, BMI, sex, and preoperative total bilirubin (3–5). Except for the above risk factors, the anatomy of the main pancreatic duct plays an important role in determining the outcomes of pancreatic anastomoses (6). BPD represents a relatively rare anatomical variation of the pancreatic ductal system, presenting a major bifurcation in the main pancreatic duct along its length. Our results showed that BPD, pancreatic duct diameter <0.2 cm, tumor diameter ≤2 cm, ASA score, pathology except for pancreatic cancer and pancreatitis, and BMI ≥ 23 were independent risk factors of CR-POPF.

Nonetheless, our study has some limitations. First, this study is a single-center retrospective study; a selection bias may be suggested by the retrospective nature. Second, BPD in the former year group was not intraoperatively investigated and estimation of I-BPD is difficult even after reviewing MR imaging, and as the incidence of BPD is low, and the sample size of this study was not large enough, we put the I-BPD cases from the former year group together with the O-BPD from the latter year group in the univariate and multivariate analyses. Third, as mentioned above, because the incidence of BPD is low, and the sample size of this study was not large enough, we have not performed a propensity matching score (PSM) study. Fourth, BPD should be treated during PJ; in this article, because we only used the suture closure method, we do not know the result of other methods [such as double duct-to-mucosa PJ (9, 10) and the two-in-one method (13)]; hence, a large-sample-size, multicenter, and randomized controlled trial needs to be performed in the future.

In conclusion, in this study, the incidence of O-BPD is 7.18% during PD, 50% of O-BPDs were SPD in the preoperative imaging (I-SPD), and the incidence of I-BPD is 3.88%. BPD is an independent risk factor of CR-POPF after PD, and the suture closure method may be a simple and safe method in dealing with BPD, with a potential reduction of CR-POPF rate, although the effectiveness still needs to be proven in further clinical research.

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

This study was reviewed and approved by the Ethics Committee of Changhai hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Contributions: (I)†contribute equally; (II)Conception and design: GJ, X-GH, and GL. (III) Administrative support: GJ, X-GH, and GL. (IV) Provision of study patients: GJ, LO, ZS, K-LZ, WJ. (V) Collection and assembly of data: LO, HH, GN. (VI) Data analysis and interpretation: All authors; (VII) Manuscript writing: LO. 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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Case report: Treatment of intraductal papillary mucinous neoplasms located in middle-segment pancreas with end-to-end anastomosis reconstruction after laparoscopic central pancreatectomy surgery through a pigtail-tube-stent placement of the pancreatic duct

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Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is one type of pancreatic cystic neoplasm. IPMNs can be classified into three types: main duct-IPMN (MD-IPMN), branch duct-IPMN (BD-IPMN), and mixed type-IPMN (MT-IPMN). It is universally accepted by most surgeons that patients who suffered from MD-IPMN with a high risk of malignant transformation should undergo surgical resection. However, a consensus on the best surgical strategy for MD-IPMN located in the pancreatic neck has still eluded the surgical community worldwide. Recently, one patient suffering from this condition in our Minimally Invasive Pancreas Center underwent a successful surgical procedure. In this case report, we performed a laparoscopic central pancreatectomy for this patient. During this surgical procedure, we used a method of end-to-end anastomosis reconstruction through a pigtail-tube-stent placement of the pancreatic duct. Before the construction of the remnant *pancreas*, the surgical margins of the frozen section should be negative. After surgery, the outcome of this case was satisfactory. No complications such as postoperative hemorrhage, abdominal infection, pancreatitis, delayed gastric emptying, and clinically relevant postoperative pancreatic fistula occurred, which demonstrated that this surgical strategy could achieve a good clinical therapeutic effect for the pancreatic neck MD-IPMN. The result of postoperative routine pathology confirmed the diagnosis of MD-IPMN. The pathological features also showed that there was a high degree of hyperplasia in the local epithelium, which indicated the necessity of surgical treatment.

KEYWORDS
intraductal papillary mucinous neoplasm (IPMN), laparoscopic, pancreatectomy, anastomosis, case report

Introduction

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a mucinous tumor involving the main or branching pancreatic duct. It was first reported in the late 1970s. With improvements in radiographic and endoscopic imaging techniques, IPMN represents approximately 1% of all pancreatic neoplasms (1, 2). IPMNs are divided into three types: main duct-IPMN (MD-IPMN), branch duct-IPMN (BD-IPMN), and mixed type-IPMN (MT-IPMN) based on imaging studies and/or histology (3). Because MD-IPMN has a higher risk (36%–100%) of malignant transformation than the others (4, 5), it is common practice to completely remove the lesion. However, devising appropriate surgical strategies for patients with pancreatic IPMNs is still a challenge (2). For example, there are diverse clinical protocols to completely remove the tumor located in the pancreatic neck and achieve a negative margin, such as pancreaticoduodenectomy (PD), distal pancreatectomy (DP), and central pancreatectomy (CP). According to the Fukuoka guidelines, DP is preferred because it is technically easier to resect additional pancreatic tissue to achieve a negative margin (3). CP has the advantage of preserving the pancreatic parenchyma, thus reducing the occurrence of postoperative endocrine and exocrine insufficiency (6). Besides, the operating procedure of CP is relitavey uncomplicated, compared to PD. Nevertheless, CP has a higher rate of postoperative pancreatic fistula (POPF), which is the main reason for CP not being routinely used in eligible patients (7). Due to improvements in minimally invasive surgery, CP has also been implemented by using the laparoscopic and robotic approaches in recent years (8–10). At present, the reported pancreatic continuous reconstruction after surgery whether in a laparoscopic or robotic operation is done through pancreaticogastrostomy and pancreaticojejunostomy, except in the research reported by Rong et al. (11–13). They first used end-to-end anastomosis after CP through the robotic method. But the mature and safe technique of pancreatic end-to-end anastomosis has not been uniformly used. In this report, we used a method of end-to-end anastomosis reconstruction after laparoscopic central pancreatectomy (LCP) surgery through a pigtail-tube-stent placement of the pancreatic duct and achieved a good therapeutic effect.

Cases and methods

(1) Case history summary

(a) A female, 62 years old, was admitted for the treatment of the pancreatic space-occupying lesion found by color ultrasound.

(b) Main concerns and symptoms of the patient: The patient had no obvious signs and symptoms, and the pancreatic space-occupying lesion was found only by color ultrasound. There had been no previous intervention or treatment for the disease.

(c) Medical history: Denial of history of diabetes, hypertension, history of infectious diseases, and genetic diseases, denial of history of trauma, surgery, and history of allergies to drugs, food, and other contacts. Family history: Both parents of the patient are alive, and they have one son and another daughter. They are all healthy, without the same disease as the patient, and have no genetic-related disease.

(d) Physical examination and blood drawing tests (including tumor markers such as CA199 and CEA) showed no obvious abnormalities.

(e) Imaging examination: One cystic lesion of the pancreatic neck (2.7 cm × 1.8 cm in size) (**Figure 1A**), with a significantly dilated pancreatic duct (the diameter is greater than or equal to 10 mm) (**Figure 1B**), was found by magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), throwing

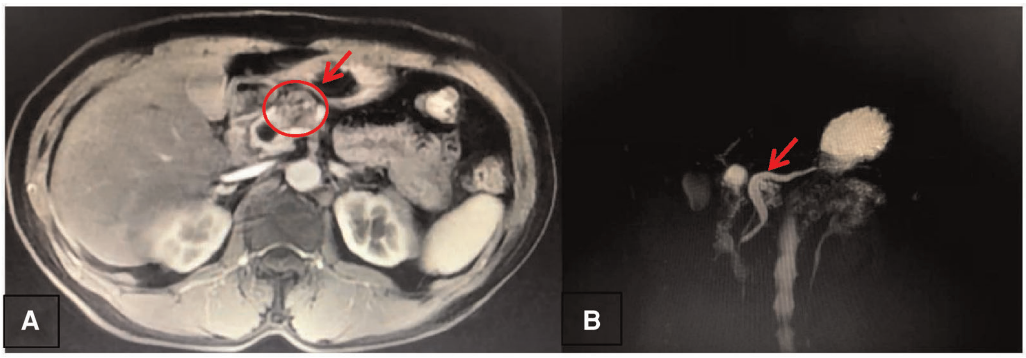

FIGURE 1
A: Magnetic resonance imaging. B: Magnetic resonance cholangiopancreatography..

open the possibility of pancreatic IPMN (not excluding other lesions).

(f) EUS-FNA: Pathological histology suggested a benign lesion.

(2) Preoperative diagnosis: MD-IPMN of the pancreatic neck

(3) Surgical method: LCP (end-to-end pancreatic anastomosis)

(a) The reason we chose LCP (end-to-end pancreatic anastomosis) for this case pertained to two aspects: One was that CP can reserve a higher volume of the remanent *pancreas* compared with DP or PD and the end-to-end anastomosis maintained the original continuity of the intestinal tract, which is also in line with the concept of protecting organ function. The other was that laparoscopic surgery may better reflect the concept of minimally invasive medicine.

(b) Operational procedure:

Artificial pneumoperitoneum was established by using the layout of “5 trocar-puncture” (**Figure 2A**). Exploration of the organs in the abdominal and pelvic cavity showed that they were not abnormal. Then, the gastrocolic omentum was opened to reveal the pancreas, and the tumor was found in the neck of the pancreas. Therefore, it was decided to carry out middle pancreatic resection.

The first process was surgical resection (**Figure 2B**): The lower margins of the pancreas were separated at 1 cm from the right side of the tumor. Then, the gaps between the pancreas and the veins including the superior mesenteric vein and the splenic vein should be separated carefully so that the tunnel behind the pancreas could be opened. The middle pancreas and the main pancreatic duct were cut off from the left and right sides of the tumor with an ultrasonic knife when the cutting lines were marked by suturing a traction line on the “A” and “B” tangent plane (**Figure 2C**). The routinely intraoperative frozen pathology of the removal specimen showed that the pancreatic tumor belonged to the benign lesions and no tumor or tissue infiltration of the high-grade atypia hyperplasia (HGD) was observed at the trans-section margins of the pancreatic parenchyma and duct.

The second was the pancreatic reconstruction process (**Figure 3**): Due to the significantly dilated pancreatic duct and thin pancreatic tissue, in this case, the end-to-end pancreatic anastomosis could be performed analogous to an intestinal anastomosis. The posterior walls of the pancreas and pancreatic duct of the two ends that might be considered the posterior layer of the intestinal anastomosis were continuously sutured with a 4–0 prolene line (**Figure 4A**). Similarly, the anterior wall of the pancreas and pancreatic duct of the two ends that might also be considered the anterior layer of the intestinal anastomosis was repaired by interrupted 4.0 prolene sutures (**Figure 4B**). Before the suture of the anterior layer began, we designed a pigtail tube to be placed in the pancreatic duct. One end of this tube was placed in the remanent pancreas and the other end was placed through the duodenal papilla into the duodenum (**Figures 4C,D**). To avoid stent-tube displacement, one end of the stent tube was sutured and fixed at the end-to-end anastomosis of the pancreas and the curled end would catch the duodenal papilla when the inner core of the stent tube was taken out (**Figure 5**).

Finally, two drain tubes were placed near the pancreatic wound. Intraoperative bleeding was 20 ml, and the operative time was 140 min.

(4) Postoperative outcome:

(a) On the 3rd postoperative day (POD3), the patient had an anal exhaust, so the gastric tube was removed and the fluid diet could be taken out.

(b) On POD7, the abdominal computed tomography (CT) (**Figure 6A**) was reviewed and it showed no significant

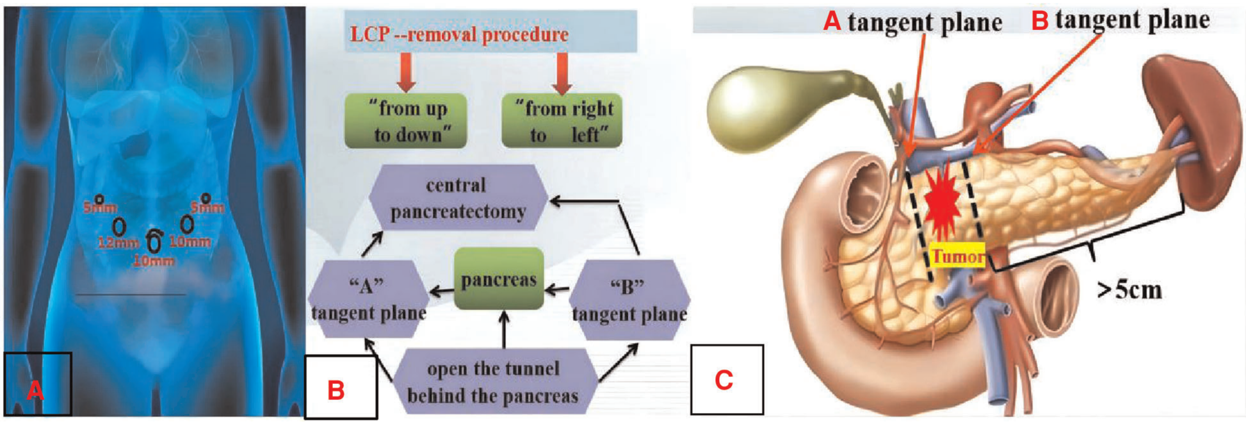

FIGURE 2
Preoperative design. A: Layout of “5 trocar-puncture”. B: LCP-removal procedure. C: Schematic diagram of CP pancreatic margin.

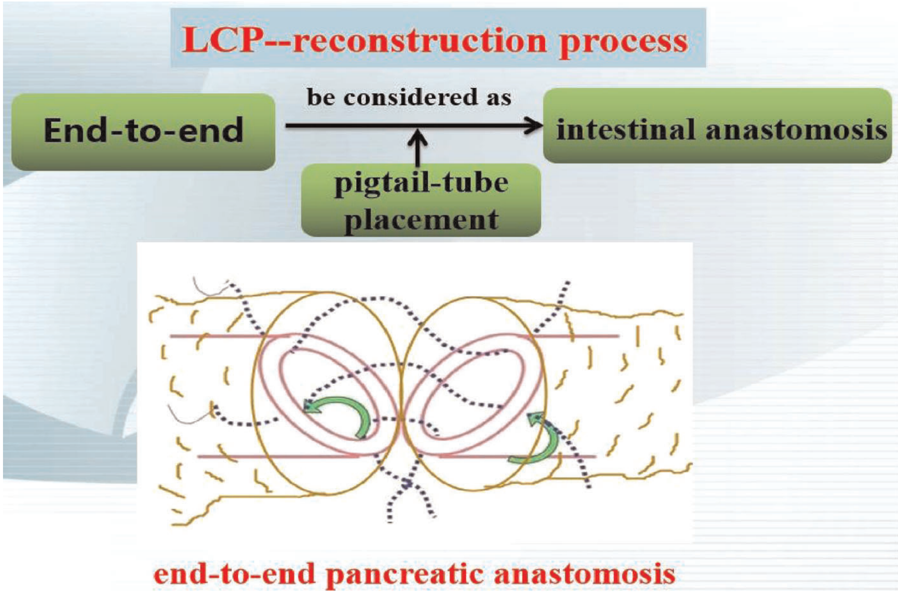

FIGURE 3
Pancreatic reconstruction process.

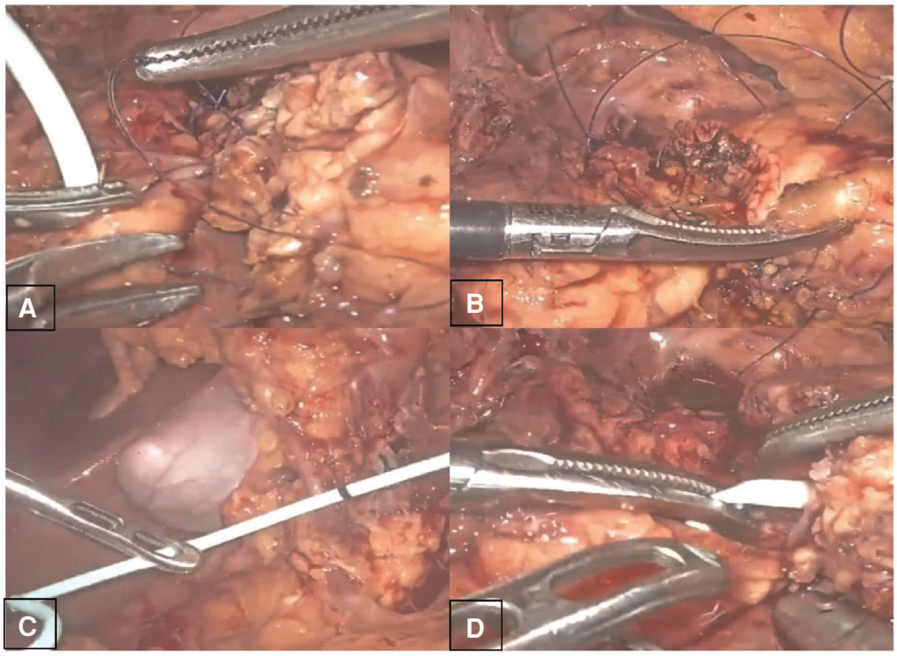

FIGURE 4
Laparoscopic central pancreatectomy (involving A, B, C, D four steps).

seroperitoneum, so the abdominal drainage tubes were removed.

(c) On POD12, the patient recovered and was discharged from the hospital.

(d) On POD1, 3, 5, and 7, the ascitic amylase (Figure 7A) and the volume (Figure 7B) of the two abdominal drainage tubes and the blood results such as C reactive protein (CRP), white blood cell (WBC) count, procalcitonin (PCT), hemoglobin (HGB), and serum amylase (AMS) were tested (Tables 1, 2). The results showed that clinically relevant postoperative pancreatic fistula (cr-POPF) did not occur, although there was a biochemical leak (according to the 2016 ISGPS definition and grading). In addition, other complications such as postoperative hemorrhage (POH), abdominal infection, pancreatitis, and delayed gastric emptying (DGE) did not occur.

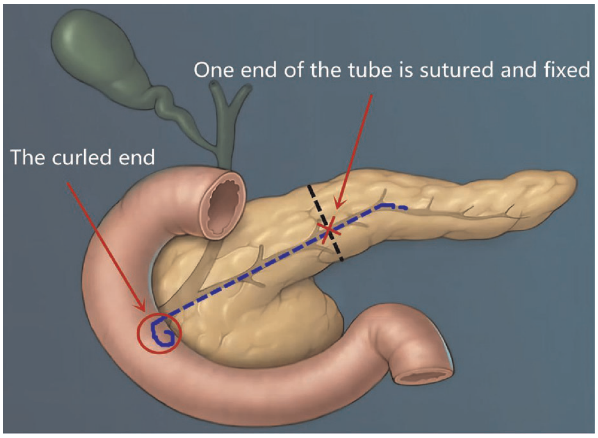

FIGURE 5
The pigtail position.

(e) Postoperative pathological images (Figure 6B) showed that the lesion tissue matched the preoperative imaging diagnosis of IPMN. At the same time, HGD was found in the local epithelial tissue.

(5) Postoperative follow-up.

The patient was followed up to this day. On 1 and 6 months after the operation, the patient visited the hospital for a physical examination and blood tests for tumor markers and also for a CT scan review. The outcomes displayed that there were no recurrence signs.

Discussion

Because the pancreatic cystic lesion was accompanied by a significantly dilated pancreatic duct (main pancreatic duct (MPD) diameter ≥ 10 mm), MD-IPMN should be considered for diagnosis in this case. Regardless of the diverse claims on the diameter of the MPD and the size of the cystic lesion, almost all guidelines such as AGA, ACR, and European

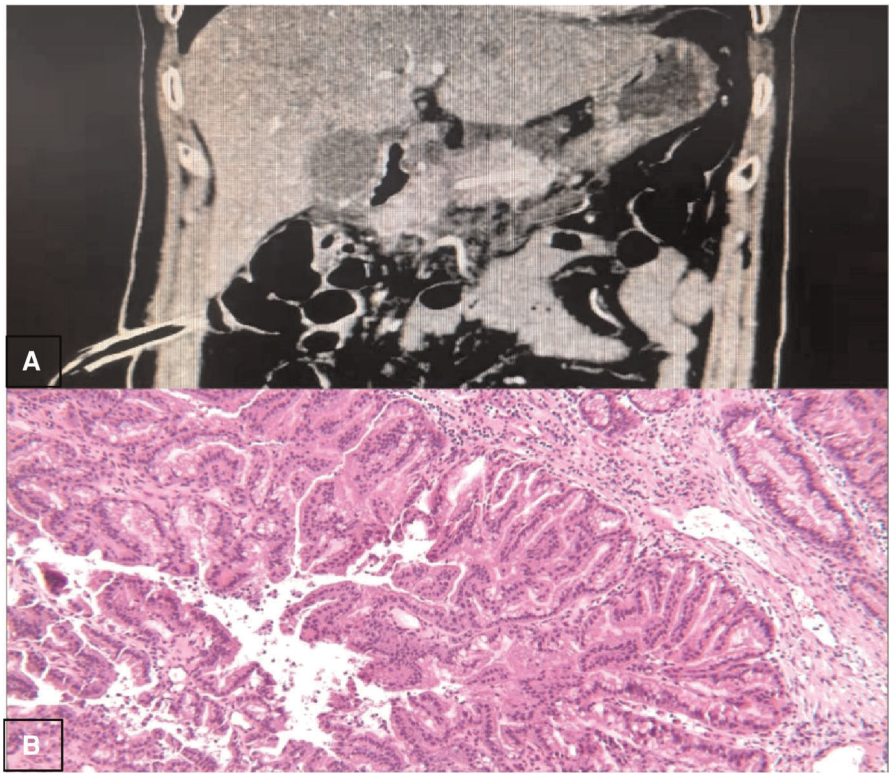

FIGURE 6
Postoperative outcome: CT and pathological images. A: CT images, B: pathological images.

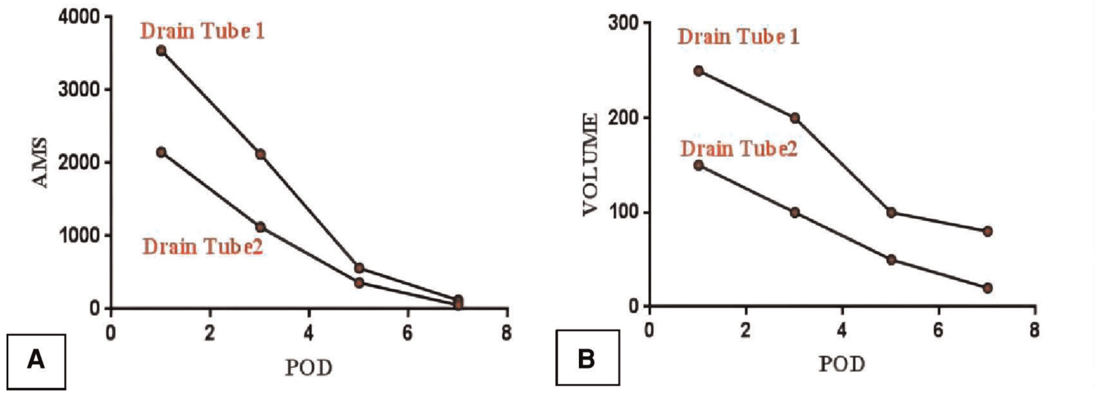

FIGURE 7
Postoperative outcome: the amylase (A) and volume of abdominal drainage tubes (B).

TABLE 1 The amylase and volume of abdominal drainage tubes.

	Drain tube 1		Drain tube 2	
	AMS (U/L)	Volume (ml)	AMS (U/L)	Volume (ml)
POD1	3,545	250	2,150	150
POD3	2,125	200	1,125	100
POD5	560	100	360	50
POD7	120	80	56	20

POD, postoperative day.

TABLE 2 The blood results.

	CRP (mg/L)	WBC ($\times 10^9$/l)	PCT (ng/ml)	Serum AMS (U/dl)	HGB (g/L)
POD1	15.6	16.5	2.5	105	112
POD3	7.1	9.8	0.25	123	110
POD5	2.5	8.6	0.13	43	113
POD7	1.3	7.6	0.18	52	125

POD, postoperative day; PCT, procalcitonin.

guidelines suggest that surgery is recommended for MD-IPMN with high-risk stigmata (14). Due to the above reasons, we took surgical treatment measures for this case. After surgical resection, postoperative pathological images showed that the lesion tissue matched the preoperative imaging diagnosis of IPMN and HGD was found in the local epithelial tissue, which confirmed the necessity of the surgical treatment.

In addition, it is still a controversial topic how to choose reasonable methods for the resection range and appropriate surgical approaches for IPMN of the pancreatic neck. For instance, PD, DP, and CP can yield a negative margin for a benign or low-grade malignant tumor of the middle pancreas. Because of the complexity and difficulty of PD, DP and CP have become the mainstream surgical methods. Compared with DP, CP is more difficult to perform and has a higher rate of cr-POPF, which could result in higher mortality (15). Thus, many surgeons may choose DP when confronting this disease. However, CP has the advantage of reserving a large number of pancreatic tissues, which could prevent postoperative endocrine and exocrine insufficiency. Therefore, the question of how to improve the technique of CP has attracted increasing attention from researchers. Most reported studies about anastomosis reconstruction after CP are pancreaticogastrostomy or Roux-en-Y pancreaticojejunostomy (12). Reconstruction of pancreatic end-to-end anastomosis is rarely used for CP, and only some authors have reported this method in an open or robotic operation (11, 16–19), which shows that the anastomotic technique is far from mature. For example, in the study of Rong et al. (19), the group of end-to-end pancreatic anastomosis had a higher incidence of cr-POPF (69.2% vs. 36.4%, $p = 0.009$) and more overall complications than the group of pancreaticojejunostomy. Also, pancreatitis and abdominal infection, which were a result of the relatively serious complications of pancreatic operation, also occurred. Furthermore, this end-to-end pancreatic anastomosis after CP has not yet been used for laparoscopic surgery. This is because it is harder to perform than open or robotic surgery. Therefore, it is very important to improve and simplify this technique to reduce the rate of cr-POPF in laparoscopic surgery.

In this case report, we first applied the approach of end-to-end anastomosis reconstruction to laparoscopic surgery through a pigtail-tube-stent placement of the pancreatic duct. After the surgery, the patient did not develop the symptoms of infection including fever, abdominal distension, and abdominal pain. Besides, the blood results of the patient such as CRP, white blood cell count, and PCT downed to the normal level on POD3, and the serum amylase and hemoglobin remained at normal levels after the operation. The above results showed that POH, DGE, abdominal infection, and pancreatitis did not occur. At the same time, cr-POPF did not occur, although there was a biochemical leak. From the postoperative outcome of this patient, it can be seen that we have achieved a good clinical therapeutic effect by this approach. We think this might be due to the following aspects: (1) As to simplifying the end-to-end anastomotic method after LCP, we treated the walls of the dilated pancreatic duct and the thin pancreatic tissue as the two layers of the anastomosis in this case. The above design made the end-to-end anastomosis easier under laparoscopic conditions and also firmer. (2) As to lowering the incidence rate of cr-POPF after LCP, we drew on our experience from the study of Huscher et al. (20) and devised the following way: One end of a pigtail tube was placed in the remanent pancreatic duct, while the other end was placed through the duodenal papilla into the duodenum. This design might prove more effective for sufficient drainage of pancreatic fluid into the intestinal lumen so as to reduce pancreatic leakage. Moreover, being similar to the lock design, we fixed two ends of the pig tube at the pancreas and the duodenal papilla. In theory, it would be more favorable to avoid cr-POPF than simple stent tube drainage.

Conclusion

In summary, the method of LCP with end-to-end anastomosis reconstruction after surgery through a pigtail-tube-stent placement of pancreatic duct is feasible, as testified by the fact that the patient in this case report recovered well and cr-POPF did not occur. However, additional evidence will be needed to conclude that the proposed technique effectively reduces cr-POPF and has satisfactory clinical efficacy.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Affiliated Hospital of Guangdong Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

The specific contributions made by the authors GL and ML to the submitted manuscript relate to the conception and design of the study, participating operation, acquisition of clinical data, data analysis or interpretation, and drafting of the manuscript. The authors XT, JL, GZ, and JZ contributed to the study in terms of participating operation, acquisition of clinical data, and data analysis. All authors contributed to the article and approved the submitted version.

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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Imaging and pathological comparison of inflammatory pseudotumor-like follicular dendritic cell sarcoma of the spleen: A case report and literature review

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Background: Inflammatory pseudotumor-like follicular dendritic cell sarcoma (IPT-like FDCS) is a rare subtype of follicular dendritic cell sarcoma (FDCS) that is mainly located in the liver and spleen (1). Splenic IPT-like FDCS is a rare low-grade malignancy with non-specific clinical manifestations and laboratory findings. Herein, we reported the pathological and imaging features of a case with splenic IPT-like FDCS.
Case presentation: A 57-year-old woman was found to have a mass in the spleen during a physical examination and was hospitalized for further treatment. Her laboratory results were within the normal range. Unenhanced and contrast-enhanced computed tomography scans of the whole abdomen showed a round mass in the spleen, with a diameter of about 5 cm. After further examination with enhanced MRI, a provisional diagnosis of splenic hemangioma or splenic hamartoma was made. The patient underwent splenectomy, and the pathological diagnosis was splenic IPT-like FDCS. No tumor recurrence or metastasis was found during the 1-year follow-up after the operation.
Conclusions: Herein, we reported a case of splenic IPT-like FDCS. Although the clinical examination and laboratory examination lack specificity, the imaging of this case showed that the lesion was a solid mass with progressive enhancement, and the central scar showed the characteristics of delayed enhancement, which facilitated the diagnosis.

KEYWORDS

spleen tumor, follicular dendritic cell sarcoma, tomography, x-ray computed, magnetic resonance imaging

Background

Inflammatory pseudotumor (IPT)-like follicular dendritic cell sarcoma (FDCS) is a rare low-grade malignancy that occurs most often in the liver or spleen (1). The pathogenesis and causes remain unclear, but EBV infection is considered one of the most important etiologies of this tumor (2), as almost all cases are EBER positive.

Despite its slow growth and low malignancy, the recurrence rate is approximately 10% (3). Due to histomorphological similarity, this tumor is often confused with inflammatory myofibroblastic tumors, such as benign reactive IPT and inflammatory myofibroblastic tumors (4–6). Due to the lack of imaging and clinical characteristics, preoperative diagnosis is difficult and mainly relies on the pathological diagnosis. Herein, we described the imaging characteristics and comparative pathological analysis of a case of splenic IPT-like FDCS.

Case description

The patient was a 57-year-old female who underwent physical examination seven days ago at the Department of Radiology, Beilun People's Hospital, Ningbo, Zhejiang Province. The ultrasonographic findings were as follows: Inhomogeneous hypoechoic mass with calcification in the spleen, hemangioma requiring excision, and further examination was recommended (**Figure 1D**). The patient was hospitalized for further treatment. The patient was healthy in the past, and the spleen was not palpable under the ribs on physical examination. The patient's biochemical indexes and liver and kidney function electrolyte indexes were within the normal range. Routine blood, urine, and fecal tests were also within normal ranges. Blood tumor markers CEA, CA-199, CA-125, and AFP were all normal, and coagulation function, electrocardiogram and chest x-ray were normal.

Plain and contrast-enhanced CT scans of the spleen showed local enlargement of the spleen, with a type of circular isodensity and punctate calcifications (**Figure 1**). The lesions in the arterial and venous phases showed progressive enhancement, with a CT value of about 40 HU on the plain scan, and a CT value of about 84 HU in the enhanced part of the venous phase. Conventional and contrast-enhanced magnetic resonance imaging (MRI) scans of the spleen showed localized enlargement of the spleen with abnormal intracellular signal and well-defined lesions (**Figure 2**). T2-weighted imaging (T2WI) scans showed that most of the lesions were slightly low-intensity shadows, with strip-shaped high-low mixed signal shadows, while T1-weighted imaging (T1WI) showed that most of the lesions were iso-intensity shadows, with slightly high signal shadows in local areas. Diffusion-weighted imaging (DWI) showed hypointense shadows with stripes of lower signal shadows inside. The lesions showed obvious enhancement in arterial and venous phases, with strip-like unenhanced areas inside and internal strip-like enhancement in the delayed scan and the remaining areas showed isointensity shadows.

Splenectomy was performed after the examination. The spleen was completely removed by surgery after the diagnosis of the splenic tumor by rapid pathology. A splenectomy specimen was obtained. A gray tumor with a diameter of about 5 cm was observed in the spleen section. HE-stained tumor cells were fascicular, swirled, oval cells, with no mitoses, with scattered lymphocyte infiltration. Immunohistochemistry showed CD21 (+), CD23 (+), CD35 (+), BCL-2 (−), Bcl-6 (−), CD10 (−), CD138 (−), CD15 (−), CD20 (−), CD3 (−), CD30 (−), CD43 (−), CD45RO (−), CD5 (−), CD79α (−), Cyclin D1 (−), Ki67 (~20% +), Kappa (−), Lambda (−), MUM-1(−), PAX-5 (−), CKpan (−), CD31 (−), CD34 (−), β-Catenin (−), CD68 (partial +), Desmin (−), S-100 (−) and ALK(1A4) (−). In situ hybridization showed EBER positive (**Figure 3**). The final pathological diagnosis was inflammatory pseudotumoral splenic follicular dendritic cell sarcoma. The patient recovered well after surgery. No tumor recurrence was found during the 1-year follow-up.

Discussion

Follicular dendritic cell sarcoma (FDCS) was first reported by Monda et al. in 1986 (7). FDCS is a rare low-grade malignant tumor that mainly occurs in the lymph nodes and occasionally in the liver and spleen. The morphology of FDCS is similar to that of inflammatory pseudotumor but different from classic FDCS. IPT-like FDCS was first reported in 2001 by CHEUK et al. (8). Its histopathology is different from classical FDCS and is closely related to EBV infection. Studies have shown that EBER-positive tumor cells were found by *in situ* hybridization in almost all cases (1). It is extremely rare, with a higher incidence in women than in men (9), and there are generally no specific clinical symptoms. The final diagnosis of this disease depends on pathological examination. The pathological results of the patient in this report showed that the tumor cells were fascicled and swirled, the cells were oval, and no mitoses were seen. There were scattered lymphocytes and plasma cells infiltrating the inflammatory background. These findings were consistent with a previous report (10) for IPT-like FDCS-specific behavior (11–14). Histologically, IPT-like FDCS is similar to inflammatory pseudotumor, which can easily lead to misdiagnosis. However, based on the immunohistochemistry of this case, the positive expression of follicular dendritic cell (FDC) markers CD21, CD23, and CD35 can be correlated with that of inflammatory pseudotumor. At the same time, *in situ* hybridization of EBER (+) and inflammatory cells are helpful to distinguish IPT-like FDCS from other FDCS subtypes (15–17).

Spleen IPT-like FDCS imaging findings are rarely reported (18). The majority of reported lesions are solitary, round, solid, or cystic-solid, with clear borders and occasional punctate calcifications. CT-enhanced lesions were mildly enhanced in the arterial phase, further enhanced in the venous phase, and showed continuous enhancement (19), which is consistent with the findings of the case presented herein. Bui reported the presence of a central stellate area in

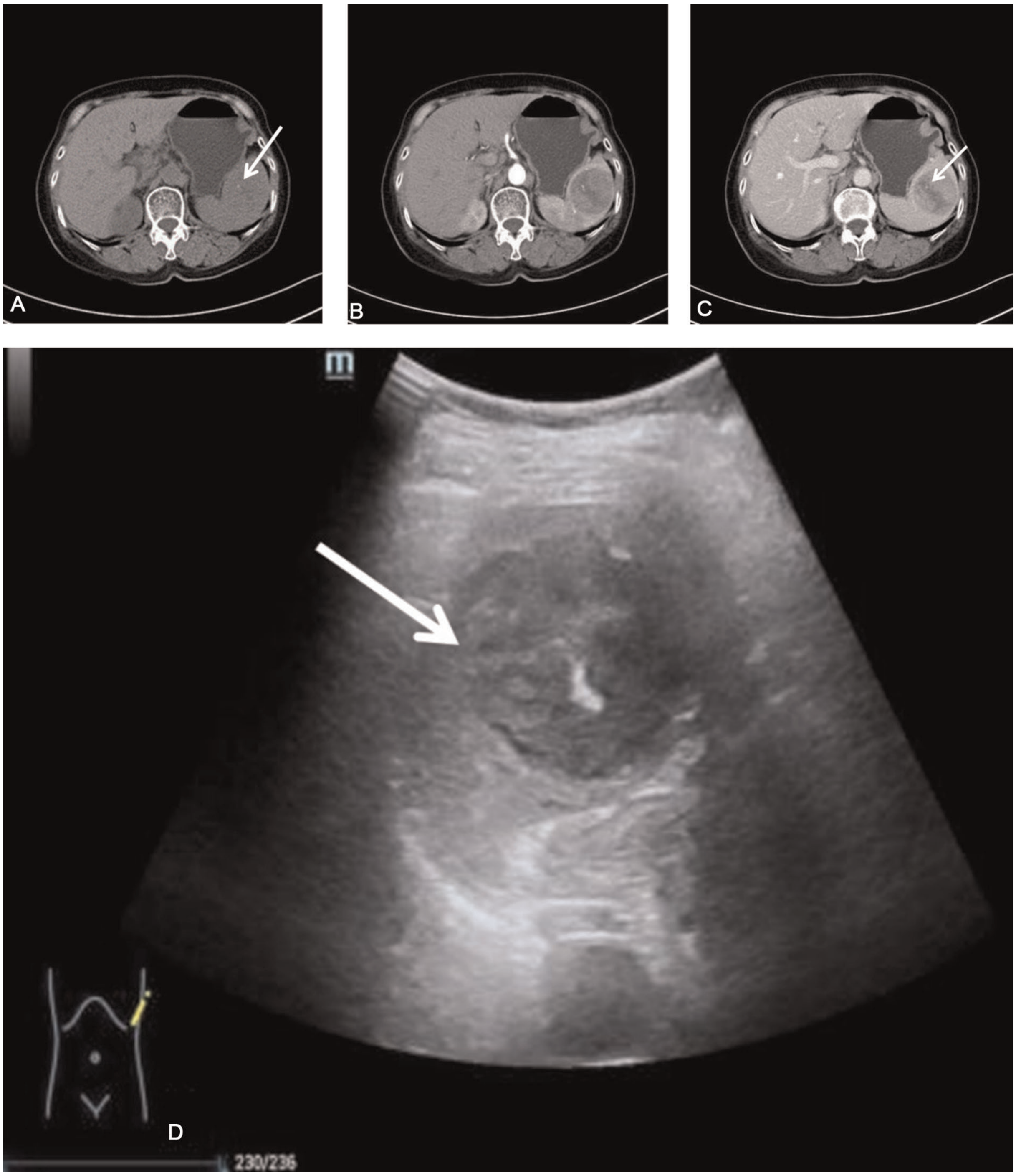

FIGURE 1
The patient's splenic CT scan. (A) Plain CT scan showed that the spleen was a round mass shadow in the parenchyma, with punctate calcifications (white arrows). The normal parenchyma was poorly demarcated. (B,C) Contrast-enhanced CT showed that the tumor enhancement was weaker than that of the normal spleen, with clear borders, and a strip-like cleft-like non-enhanced area (white arrow). (D) B-ultrasound showed a heterogeneous low echo in the spleen, with a spot-like strong echo (white arrow). CT, Computed Tomography.

the lesion showing low signal intensity on T1 and T2-weighted MRI due to fibrosis and varying degrees of necrosis (18), unlike in our case, where intralesional fibrous scar tissue and thickened blood vessels were seen, which is the pathological basis for delayed enhancement on T2WI in enhanced MRI. This is a characteristic image that has not been previously reported. Our case showed different enhancements. The early enhancement was weaker than the spleen, a clear demarcation

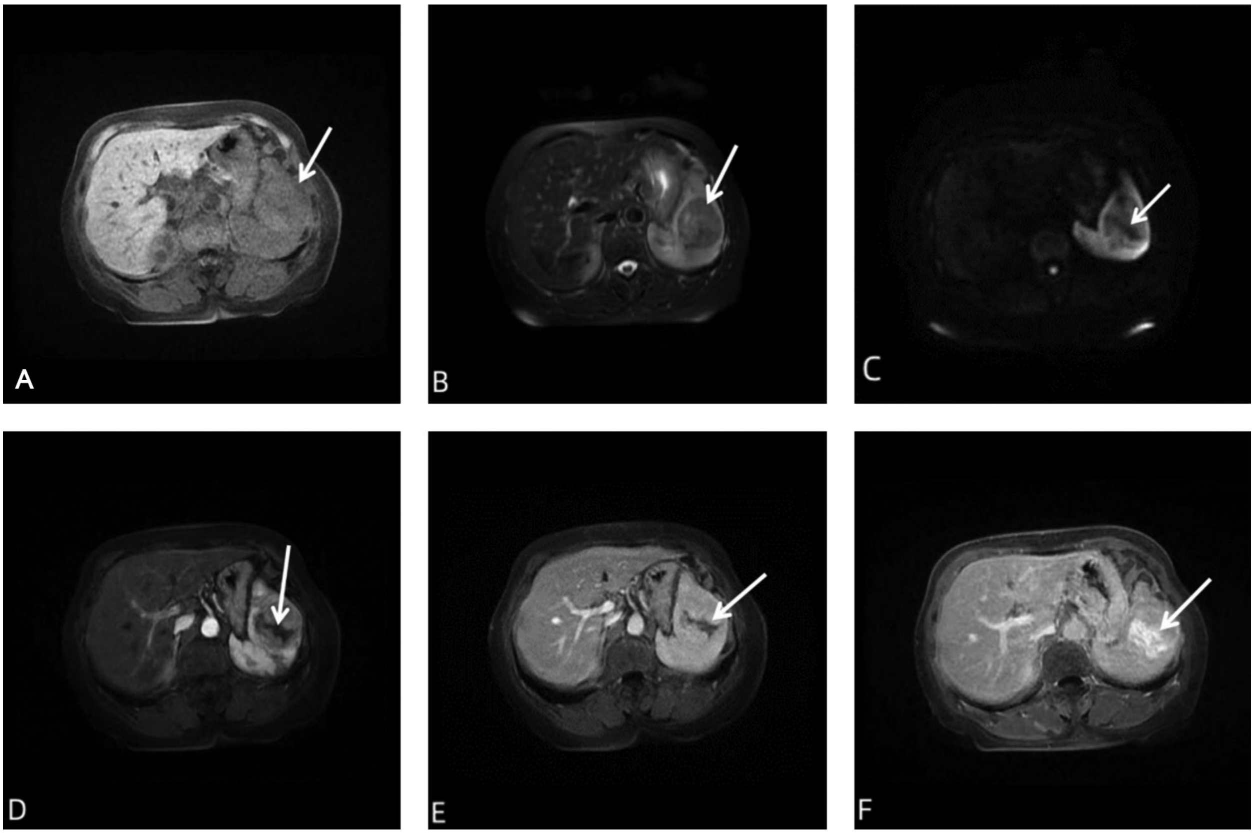

FIGURE 2
MRI of the patient's spleen. (A) Conventional spleen MRI scan showed a type of round mass in the spleen (white arrows). Most of the lesions on T1WI showed isointensity shadows, and localized slightly high signal shadows. (B) Most of the lesions on T2WI showed slightly low signal shadows, with strip-shaped high and low mixed signal shadows (white arrows). (C) In the DWI sequence, the overall signal was low, and lower signal shadow was seen inside (white arrow). (D–F) Contrast-enhanced MRI showed obvious enhancement in the arterial and venous phases of the lesion, with strip-like unenhanced and enhanced areas inside (white arrows) in delayed scan, and isointensity shadows in the remaining areas. DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging.

and the local capsule could be seen; the T2WI scan showed that most of the lesions were slightly low-signal shadows, with strip-shaped high-low mixed signal shadows inside. The high and low signals were caused by fibrous scars and vascular components, while DWI showed low signal shadows, with strip-shaped lower signal shadows inside, and fibrous scars explain the existence of low signal. Therefore, this case report described obvious characteristic manifestations. The lesions were round and solid, with delayed enhancement, and the enhancement degree was higher than that of the surrounding normal spleen parenchyma. The characteristic is called delayed enhancement of scars. The enhanced MRI scan should be delayed for at least three minutes to show the enhancement characteristics. The CT enhancement was not seen because the scanning time was not reached, and it was mistaken for cystic degeneration. The enhancement mode is the newly discovered important sign of this disease, which is helpful for future imaging diagnoses.

Based on the data published to date, splenectomy is the treatment of choice if the tumor is confined to the spleen. There is less recurrence or metastasis after surgery. Adjuvant therapy is not required (20). The patient in this report underwent complete tumor resection and was followed up for one year after surgery. The patient is currently healthy, with no tumor recurrence or metastasis.

Differentiation of spleen IPT-like FDCS from other splenic tumors is necessary (21). 1. Spleen inflammatory myofibroblastic tumor is also called inflammatory pseudotumor phase identification. Because inflammatory pseudotumor is composed of spindle cells and inflammatory cells, it lacks blood supply, with delayed enhancement performance, but it is always lower than that of the normal spleen. Parenchymal enhancement (22), imaging differences with splenic IPT-like FDCS. 2. Sclerosing hemangiomatous nodular transformation is a rare non-neoplastic vascular disease of the spleen. Concentric enhancement and spoke sign

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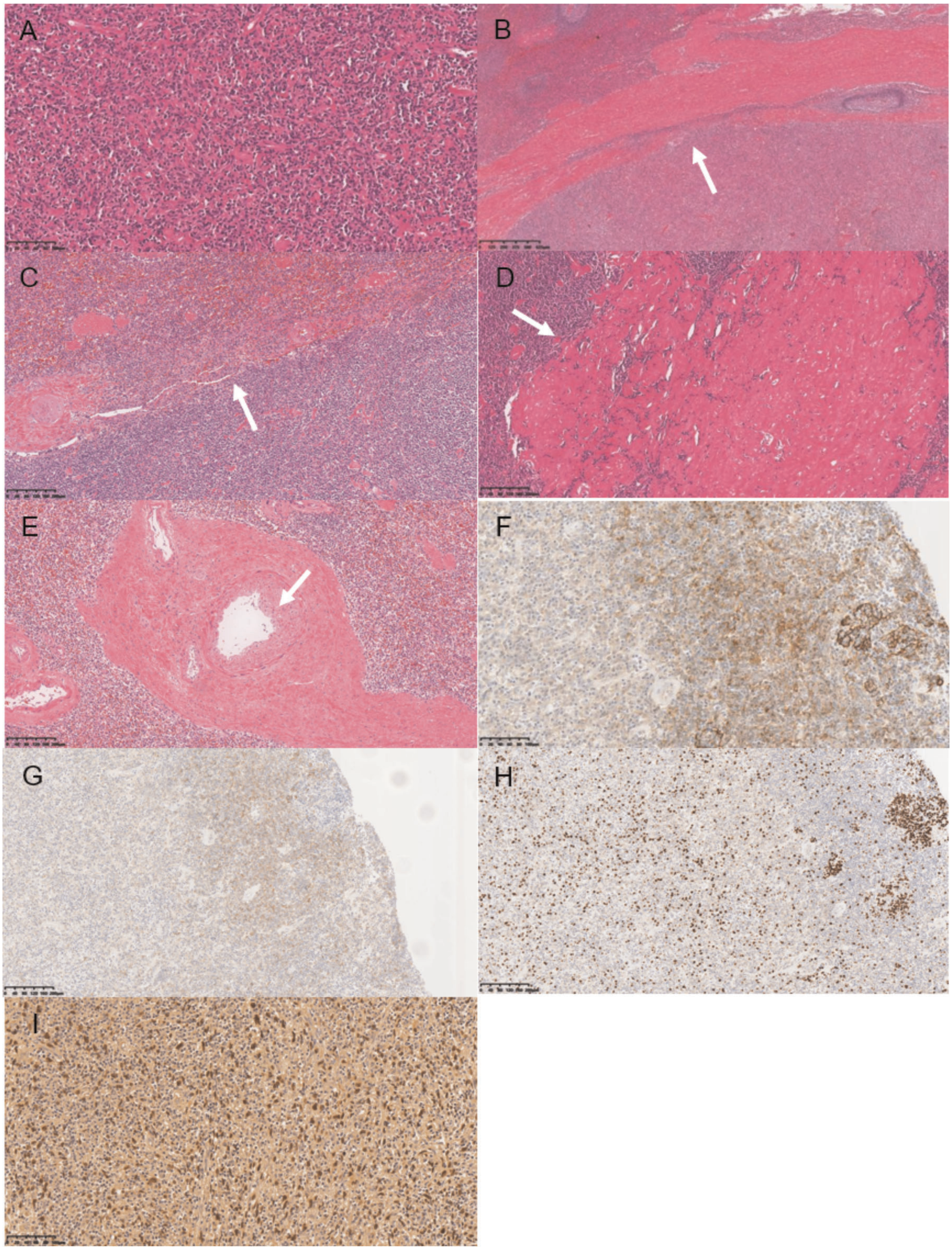

FIGURE 3
(A) The tumor cells were arranged in bundles and spirals, and the cells were oval. No mitoses were seen. There were scattered lymphocytes and plasma cells infiltrating HE-200. (B) Fibrous capsule (white arrow) HE-100 was visible at the tumor margin. (C) The tumor showed poorly defined borders and no capsule (white arrow) HE-100. (D) Intratumoral scar tissue (white arrow). (E) Thick blood vessels (white arrows) HE-100 were seen in the scar. (F) Tumor cells were positive for CD21 HE-21. (G) Tumor cells were positive for CD23 HE-100. (H) Tumor cells expressed 20%–30% Ki-67 HE-100. (I) Positive EBER expression was seen in tumor cells for HE-200.

are considered to be characteristic features of SANT, while the central part of the lesion is delayed without enhancement (23), which can be differentiated from IPT-like FDCS. 3. Given that the splenic hamartoma is a solid mass with clear boundary, isointensity on T1WI and hyperintensity on T2WI, with heterogeneous enhancement in the early stage, and a similar signal compared to the surrounding spleen parenchyma in the later stage, it is not difficult to distinguish from IPT-like FDCS (21). 4. Spleen angiosarcoma must be considered because of the dismal prognosis of the disease. The CT manifestations of angiosarcoma are heterogeneous low-density shadows with unclear borders and round or oval shapes; most of them are solitary lesions, and a few can be multiple. Because the lesions are prone to hemorrhage, cystic areas are prone to form, and the enhanced scan looks like a hemangioma. It is enhanced from the edge of the lesion first, and then the contrast gradually fills to the center. MRI shows uneven low signal on T1WI, uneven high signal on T2WI, and high signal intensity on DWI. The enhancement is the same as CT appearance. Because it is a malignant tumor, there are metastases. Once intrahepatic metastases are found, the diagnosis of angiosarcoma is not difficult (24).

Conclusion

IPT-like FDCS in the spleen is very rare, the clinical manifestations lack specificity, and no characteristic imaging signs were found in all previous reports. However, this study found that the tumor had delayed enhancement of scars, and the appearance of this characteristic manifestation was helpful for preoperative diagnosis. However, the final diagnosis should be made based on a pathological immunohistochemical examination.

Contribution to the field statement

Follicular dendritic cell sarcoma (FDCS) is a rare lymphoid hematopoietic tumor of unknown etiology. It is composed of spindle-shaped and oval cells, mixed with a large number of inflammatory cells, and the typical fascicular and spiral arrangement is rare, similar to inflammatory pseudotumor, so it is described as inflammatory pseudotumor-like follicular dendritic sarcoma(IPT-like FDCS), a low-grade malignancy, which has been shown to be associated with EBV, pathologically characterized by positive expression of immune markers including CD21, CD35, and CD23, which is rare and involves the spleen The reports on the imaging manifestations of IPT-like FDCS are all case reports. Due to the lack of specific clinical manifestations, preoperative diagnosis often leads to misdiagnosis. Reviewing the literature and imaging reports that the disease lacks imaging characteristics, we provide this case, which is confirmed by pathology as spleen IPT-like. FDCS, through the patient's clinical, imaging and pathological data, summarizes the imaging features and compares them with the pathology, and finds a new characteristic imaging sign, that is, the characteristic of scar enhancement in the lesions in the delayed MRI enhanced scan. At the same time, we found that the pathology There are fibrous and vascular structures inside the lesion. Through our case report, the accuracy of preoperative diagnosis of this disease can be improved for future clinical work.

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.

Ethics statement

Written informed consent was obtained retrospectively from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

FC and PX carried out the studies, participated in collecting data, and drafted the manuscript. JL participated in the comparative analysis of imaging and pathology. All authors contributed to the article and approved the submitted version.

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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Application of the natural orifice specimen extraction surgery I-type E method combined with 3D laparoscopy in sphincter-preserving surgery of low rectal cancer

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Purpose: Analysis of the clinical efficacy of the application of the NOSES I-type E method combined with 3D laparoscopy in sphincter-preserving surgery of low rectal cancer.

Method: A retrospective analysis of 109 patients who underwent laparoscopic low rectal cancer surgery for anus preservation without preventive stoma admitted to the Department of Colorectal Surgery in Shanxi Provincial Cancer Hospital between January 2017 and May 2019. The 109 cases comprised 52 cases treated with the NOSES I-type E method (NOSES I-type E group) and 57 cases treated with the Dixon method (Dixon group). In the NOSES I-type E group, 25cases underwent 3D laparoscopic surgery (group A) and 27 cases underwent 2D laparoscopic surgery (group B). The general clinical data, perioperative indicators, three-day postoperative pain score, postoperative pathological conditions, complications, return visit to assess the 1-year postoperative anal function, 3-year local recurrence and distant metastasis, and survival were compared among the groups.

Result: The distance between the tumor and the anal verge was significantly different between NOSES I-type E group and the Dixon group ($P < 0.05$), while there was no significant difference between group A and group B ($P > 0.05$). The exhaust time, eating time, drainage tube removal time, hospitalization costs, hospitalization time, and the number of days of analgesic administration were significantly different between NOSES I-type E group and the Dixon group ($P < 0.05$), while group A had no significant difference compared to group B ($P > 0.05$). There were significant differences in difficulty urinating between group A and B ($P < 0.05$), while there was no significant difference between NOSES I-type E group and the Dixon group ($P > 0.05$). Anastomotic leakage in NOSES I-type E group were significantly lower than those in the Dixon group ($P < 0.05$), while there was no significant difference between group A compared to group B ($P > 0.05$). Anal stenosis, rectal Prolapse and colon retraction in NOSES I-type E group were significantly higher than those in Dixon group ($P < 0.05$), there was no significant difference between group A compared to group B ($P > 0.05$). Anastomotic bleeding in Dixon group occurred in higher frequency than in NOSES I-type E group ($P < 0.05$). The pain scores of patients in NOSES I-type E group in the first three days after operation were significantly lower than those in Dixon group ($P < 0.05$),while there was no significant difference between group A and group B ($P > 0.05$). There were no significant differences in postoperative pathology, 1-year postoperative anal function score, 3-year recurrence rate and overall survival rate among the groups ($P > 0.05$).

Conclusion: The NOSES I-type E method is a safe and effective sphincter-preserving operation for low rectal cancer and its combination with 3D laparoscopy may have better neurological protection which is worth of clinical application.

KEYWORDS

NOSES I-type E method, 3D laparoscopy, low rectal cancer, sphincter-preserving, surgery

Introduction

Rectal cancer is a common malignant tumor type of the digestive system and its morbidity and mortality is increasing. Low rectal cancer (less than or equal to 7 cm from the anal verge) accounts for about 60%–75% of all rectal cancers (1). It has always been a difficult and hot topic in clinical work to pay attention to preserving the anus and its function while pursuing a good survival rate for those patients. The technologies that have added great value to achieve this goal are laparoscopic and minimally invasive surgery technology (2). In recent years, 3D laparoscopy has been widely used in rectal cancer surgery. It combines the advantages of a clearer anatomy, a more precise neuroprotection and a strong depth with that of a three-dimensional sense and meanwhile has been accepted by the majority of colorectal surgeons as a useful tool. Therefore, its application in colorectal surgery has become increasingly popular.

For low rectal cancer anus preserving surgery, laparoscopy-assisted anterior rectal resection (Dixon) has achieved good results. Specimen collection through a natural orifice combines natural orifice endoscopic surgery and laparoscopic surgery. In recent years, the application of NOSES surgery has become increasingly accepted by colorectal surgeons (3). NOSES I techniques are divided into A, B, C, D, and E methods, of which the E subtype is the main surgical method for low rectal cancer in NOSES surgery (4). Nevertheless, the NOSES I-type E method, which combines laparoscopy with the modified Bacon method, as a sphincter-preserving surgical method for low rectal cancer, its indications, complications, anal function, and prognosis is still controversially discussed (5). However, major points of the NOSES surgery debate still seem to be total tumor resection and sterility (6). Moreover, its procedure is complex and difficult and thus, still needs to be continuously improved (7). Therefore, its comparison with the laparoscopic-assisted combined anterior rectal resection with sphincter-preserving surgery for low rectal cancer is one of the foci of clinical work.

As one of the largest colorectal cancer diagnosis and treatment center in China, the center has implemented the NOSES I type-E method to preserve the anus in patients with low rectal cancer since 2016 and has accumulated a considerable amount of data. However, there were rare reports on the application value of the NOSES I-type E method combined with 3D laparoscopy in sphincter-preserving surgery for low rectal cancer. To explore this issue, this study retrospectively analyzed a total of 109 patients who underwent low rectal cancer surgery using the NOSES I-type E method or the Dixon method in Shanxi Provincial Cancer Hospital in the time between January 2017 and May 2019 with anus-preserving surgery were divided into NOSES I-type E group and Dixon group according to the operation method, NOSES I-type E group further divided into 3D laparoscopy (group A) and 2D laparoscopy (group B). The clinical efficacy of the groups is expected to provide a basis for the clinical development of the NOSES I-type E method in combination with 3D laparoscopy to implement a sphincter preservation method for low rectal cancer with a higher probability of therapy success.

Materials and methods

General information

A retrospective analysis of 109 patients with laparoscopic low rectal cancer sphincter - preserving surgery without preventive stoma admitted to the Department of Colorectal Surgery in Shanxi Provincial Cancer Hospital between January 2017 and May 2019. Collected patient data included general as well as perioperative data, postoperative complications, postoperative pathological results, postoperative pain score, postoperative follow-up anal function, recurrence, and survival. According to the operation method, they were divided into the following groups: NOSES I-type E group and Dixon group according to the operation method, NOSES I-type E group further divided into 3D laparoscopy (group A) and 2D laparoscopy (group B).

Inclusion criteria: (1) Single low rectal cancer (≤7 cm distance from the anal verge) was diagnosed by preoperative digital rectal examination, colonoscopy, pathology, etc (8), and pathologically confirmed as rectal cancer; (2) Displaying stage T1-T3, judged by MR or CT with no distant metastasis; (3)

All those who needed neoadjuvant therapy received neoadjuvant therapy; (4) No history of rectal anal canal disease and the tumor was not specific to the distal rectum enteritis or radiation enteritis; (5) Function well before surgery; (6) No prophylactic leakage was performed.

Exclusion criteria: (1) Preoperative or intraoperative evaluation of the tumor with a distance of greater than 7 cm from the anal verge; (2) Abnormal function of the internal and external anal sphincter before operation was excluded; (3) Malignant diseases of other systems; severe cerebrovascular disease, severe cardiopulmonary, liver and kidney dysfunction, coagulation dysfunction; (4) Abdominal and pelvic implants or distant metastases were found before or during surgery; (5) Incomplete clinical data; (6) Unable to cooperate with treatment procedures.

Observation indicators

(1) General information: gender, age, BMI, distance from tumor to anal verge, tumor stage; (2) Perioperative indicators: operation time, intraoperative blood loss, hospitalization costs, exhaust time, eating time, catheterization time, hospital stay time, drainage tube removal time, days of analgesia; (3) Postoperative complications: anastomotic leakage, anal stenosis, rectal prolapse, colon retraction, dysuria, anastomotic bleeding, incision infection, pelvic infection, ureteral injury, incisional hernia. (4) The Visual Analogue Scale (VAS) scale was used to evaluate the degree of pain 3 days after the operation, with 0 points indicating no pain, 10 points indicating severe pain (9); (5) Postoperative pathological examination: general score type, histological type, differentiation type, T stage, N stage, specimen length, total lymph node number, distance between the lower edge of the tumor and the distal resection edge, the number of positive cases at the circumferential resection edge, the long diameter of the tumor, the width and thickness of the tumor; (6) Wexner score to evaluate anal function at 12 months after operation, which includes 5 items, each item is evaluated with 0–4 points, the total score is 0–20 points and the higher the score, the worse the anal function. 0 represents normal, Scores below 10 indicate good bowel control, 10 and above indicate incontinence, and 20 indicates complete incontinence (10); (7) 3-year local recurrence rate and distant metastasis rate; (8) 3-year survival rate. This study was approved by the Medical Ethics Committee of Shanxi Provincial Cancer Hospital (approval number: 202108), exempting informed consent.

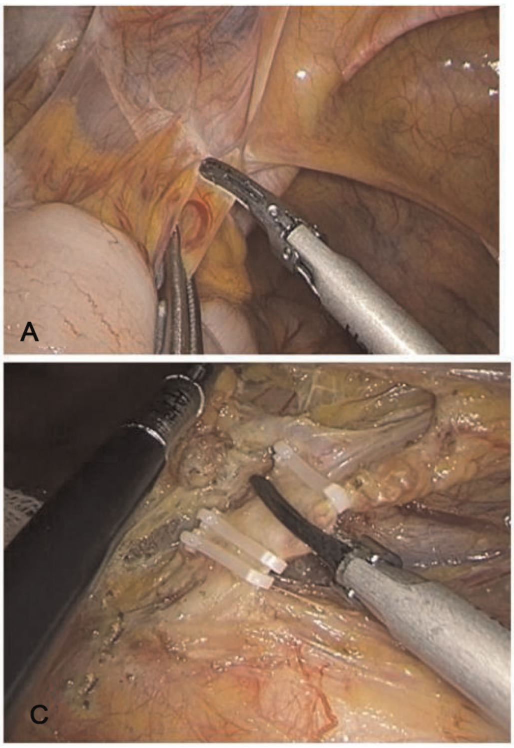

FIGURE 1
3D or 2D laparoscopy to complete the abdominal cavity operation, (A) Separation of the lateral physiological adhesions; (B) The peritoneum was incised at the level of the sacral promontory; (C) Disconnection of the inferior mesenteric vessels; (D) Dissociation to the level of the upper edge of the levator ani.

Surgical method

The operation followed the standard of complete total rectal mesentery resection and third-station lymph node dissection (11). The operation process mainly included: establishment of pneumoperitoneum (14 mmHg) (1 mmHg = 0.133 kPa) by the five-hole method, for which the incision was made on the front of the sacral promontory. The peritoneum, after dissecting the root of the inferior mesenteric artery, was clipped and cut off at a distance of 1 cm from the root and the inferior mesenteric vein was treated in the same way. From the back of the rectum to the plane of the coccyx tip, then free the sides and front to the level of the upper edge of the levator ani muscle. After completion of the above operations, specimen removal and bowel reconstruction were performed (**Figures 1A–D**).

For the 3D or 2D laparoscopic NOSES I-type E method group the procedure was as follows: the anus was abducted with sutures, a purse-string suture 1 cm below the tumor and the anal canal mucosa was stripped above the white line or the intestinal wall was opened near the dentate line and freed upwards, retaining the internal anal sphincter and dragging the free intestinal segment down from the anus. The bowel was cut at 7–10 cm above the tumor, and 3–5 cm of bowel was left outside the anus. The surrounding sutures were fixed with 3–4 stitches, the pelvic cavity was flushed, and a drainage tube was indwelled. Stage II anoplasty was performed 14 days later (**Figures 2A–F**).

For the 3D or 2D laparoscopic traditional Dixon group the surgery procedure was as follows: the bowel is closed with a cutting and closure device 2 cm from the lower end of the tumor, a longitudinal incision of about 5 cm is made 5 cm below the umbilicus, an incision dilator is inserted, and the proximal rectum is taken out with oval forceps, the bowel canal was transected 7 cm from the upper boundary of the tumor, the stapler base was placed, ligated in the knot groove and returned to the pelvis and the incision was closed layer by layer. The abdominal cavity was flushed with 1500 ml of normal saline under laparoscopy and no bleeding was detected (**Figures 3A,B**).

Statistical methods

The data were processed by using SPSS 22.0. The count data were described by frequency and percentage and the comparison between groups was evaluated by a X^2 or a Fisher's exact probability test; measurement data were described by mean ± standard deviation ($x \pm s$). A t-test or one-way analysis of variance test was used for data analysis between groups; Mann-Whitney U test was used for nonparametric data; $P < 0.05$ indicated that the difference was statistically significantly different.

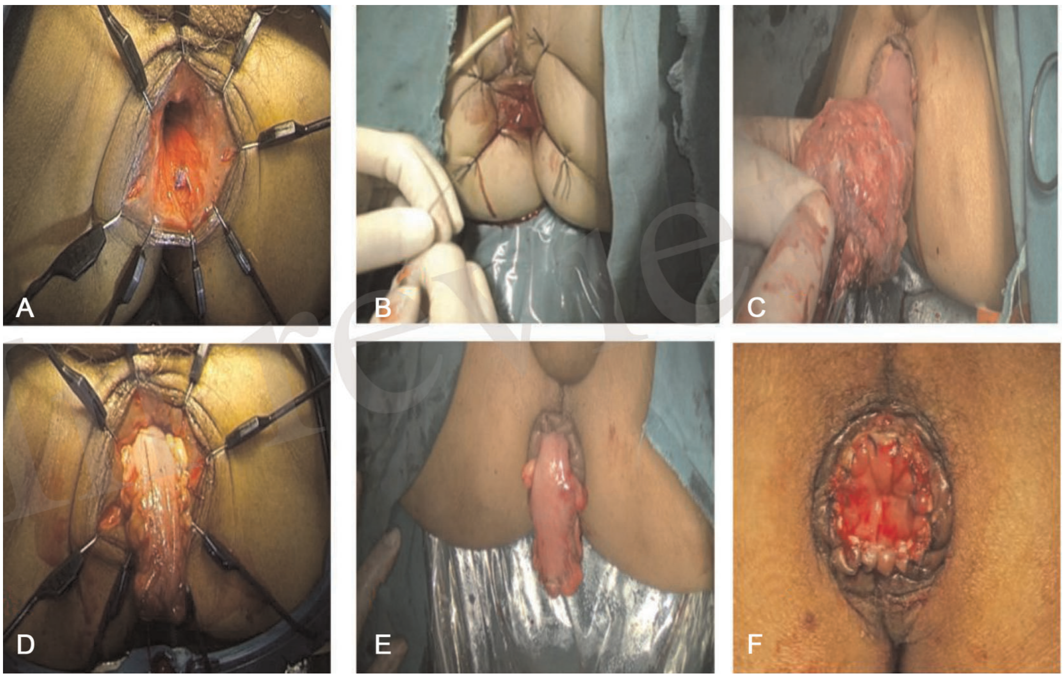

FIGURE 2
3D or 2D laparoscopic NOSES I-type E method to preserve the anus, (A) Full exposition of the anus; (B) Suturing the purse at the lower edge of the tumor; (C) Pulling out the rectum through the anus; (D) Removal of the specimen; (E) 5 cm of bowel was left outside the anus and fixed with suture; (F) Picture of 14 days after anus formation.

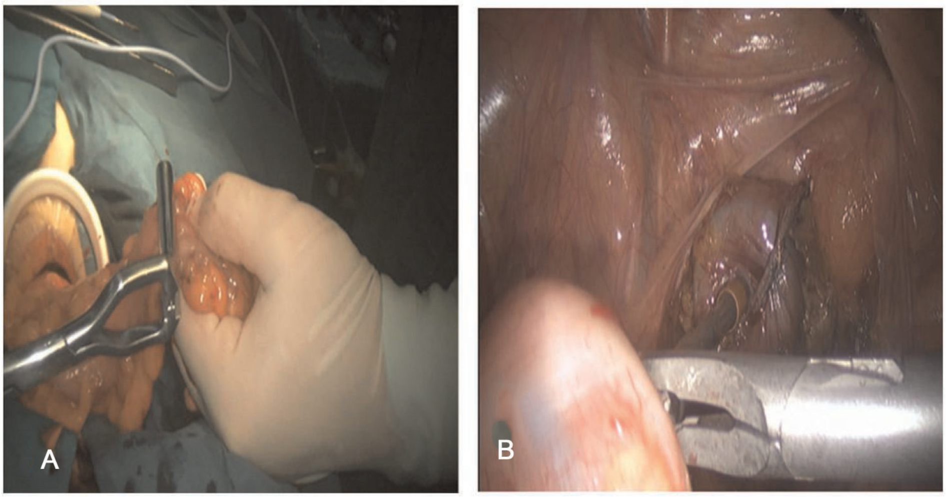

FIGURE 3
3D or 2D laparoscopic assisted Dixon method to preserve the anus, (A) The assisted abdominal wall incision to remove the specimen; (B) The colorectal anastomosis is completed through the anus.

Result

General data comparison

A total of 109 patients successfully completed the operation with no conversion to laparotomy, no perioperative death, and postoperative pathological specimens were R0 resection. There was no significant difference in the age, gender, BMI, tumor diameter, tumor stage and other general information of the NOSES 1-type E group and Dixon group patients ($P > 0.05$), these index also have no significant difference between group A and group B ($P > 0.05$). The distance between the tumor and the anal verge was significantly different between NOSES 1-type E group group compared to Dixon group ($P < 0.05$), while there was no significant difference between group A and B ($P > 0.05$) (Table 1).

Comparison of perioperative indicators

There was no significant difference in perioperative indicators, intraoperative bleeding and operation time between NOSES I-type E group and Dixon group ($P > 0.05$), these index also have no significant difference between group Aand group B ($P > 0.05$). The exhaust time, eating time, drainage tube removal time, hospitalization costs, hospitalization time, the number of analgesic treatment days between NOSES I-type E group were significantly different from Dixon group ($P < 0.05$), while group A had no significant difference to group B ($P > 0.05$). There was no significant difference in catheterization time between NOSES I-type E group and Dixon group, while group A significantly less than group A ($P < 0.05$) (Table 2).

Comparison of complication indicators

We compared the postoperative complications among the groups, the anastomotic leakage in NOSES I-type E group were significantly lower than Dixon group ($P < 0.05$), while there was no significant difference between groups A and B ($P > 0.05$). There were no significant difference in difficulty urinating between NOSES I-type E group and Dixon group ($P > 0.05$),while it in group A significant lower than group B ($P < 0.05$). Anal stenosis, rectal Prolapse and colonic retraction in NOSES I-type E group were significantly higher than those in Dixon group ($P < 0.05$), while there was no significant difference between group A and group B ($P > 0.05$). The occurrences of anastomotic bleedings in Dixon group higher than that of in NOSES I-type E group ($P < 0.05$), while there was no significant difference between group A and B ($P > 0.05$). There were no significant differences in the incision infection rate, numbers of pelvic infection, ureteral injury, incisional hernia, and the total complication rate among the groups ($P > 0.05$) (Table 3).

Postoperative pain scores

The four patient groups were scored by VAS in the first three days after operation. The results showed that NOSES I-type E group significantly lower score than Dixon group ($P <$

TABLE 1 Comparison of the general data of the four groups.

	NOSES 1-type E group (52 cases)		Dixon group (57 cases)
	Group A (25)	Group B (27)	
Gender			
Male/Female	14/11	17/10	30/27
Age	59.61 ± 10.65	58.63 ± 8.47	60.98 ± 8.95
BMI	23.32 ± 3.12	22.28 ± 3.45	24.23 ± 2.97
Distance from anal verge	4.12 ± 0.82[ab]	3.98 ± 0.85[a]	5.84 ± 1.07
Tumor stage			
I	6	8	14
II	10	8	27
III	9	11	16

[a]$P < 0.05$ Compared with Dixon group.
[b]$P > 0.05$ Compared with group B.

TABLE 2 Comparison of perioperative indicators.

	NOSES I-type E group (52 cases)		Dixon group (57 cases)
	Group A (25)	Group B (27)	
Intraoperative situation			
Operation time/min	188.28 ± 55.20	203.61 ± 65.18	190.87 ± 57.17
Blood loss/ml	55.11 ± 52.34	75.93 ± 63.98	67.09 ± 51.03
Postoperative situation			
Hospitalization expenses/10,000 yuan	6.45 ± 2.22[ab]	6.38 ± 2.21[a]	7.81 ± 2.41
Exhaust time/day	2.3 ± 0.45[ab]	2.70 ± 0.75[a]	2.98 ± 0.93
Meal time/day	4.0 (4.0,6.0)[ab]	4.0 (4.0,6.0)[a]	6.0 (4.0,8.3)
Catheterization time/day	4.0 (3.0,5.0)[cd]	5.0 (3.0,5.0)[c]	5.0 (3.0,9.0)
Hospital stay/day	13.30 ± 8.12[ab]	13.33 ± 8.17[a]	15.16 ± 10.06
Analgesia days/day	4.44 ± 1.44[ab]	4.52 ± 1.69[a]	4.98 ± 1.49
Drainage tube removal time/day	6.40 ± 3.81[ab]	6.7 ± 4.12[a]	11.41 ± 1.81

[a]$P < 0.05$, Compared with Dixon group.
[b]$P > 0.05$, Group A compared with group B.
[c]$P > 0.05$, Compared with Dixon group.
[d]$P < 0.05$, Group A compared with group B.

0.05), There was no significant difference between group A and B ($P > 0.05$) (Table 4).

Postoperative pathological results comparison

The postoperative pathological results of the groups showed that there were no significant differences in the gross tumor type, histological type, degree of differentiation, postoperative T stage, N stage, specimen length, total number of lymph nodes, number of cases with positive resection margin, distance from the lower tumor margin, tumor length, tumor width, and thickness between NOSES I-type E group and Dixon group ($P > 0.05$),these also have no significant differences between group A and group B ($P > 0.05$) (Table 5).

TABLE 3 Comparison of postoperative complication indicators

	NOSES I-type E group (52 cases)		Dixon group (57 cases)
	Group A (25)	Group B (27)	
Anastomotic leakage	0[ab]	0[a]	4/57
Anal stenosis	1 (1/25)[ab]	2 (2/27)[a]	0
Rectal Prolapse	0[ab]	1 (1/27)[a]	0
Colon retraction	1 (1/25)[ab]	1 (1/25)[a]	0
Difficulty urinating	0[cd]	1(1/27)[c]	1/57
Anastomotic bleeding	0[ab]	0[a]	1/30
Incision infection	0[cb]	0[c]	0
Pelvic infection	1(1/25)[cb]	1 (1/27)[c]	2/57
Ureteral injury	0[cb]	0[c]	0
Incisional Hernia	0[cb]	0[c]	0
Total	3 (3/25)[cb]	6 (6/27)[c]	8/57

[a]$P < 0.05$, Comparison of NOSES I-type E group with Dixon group.
[b]$P > 0.05$, Comparison of group A with group B.
[c]$P > 0.05$, Comparison of NOSES I-type E group with Dixon group.
[d]$P < 0.05$, Comparison of group A with group B.

TABLE 4 Comparison of pain scores in the four groups three days after operation.

	NOSES I-type E group (52 cases)		Dixon group (57 cases)
	Group A (25)	Group B (27)	
1 day	5.22 ± 0.7[ab]	5.14 ± 0.64[a]	6.37 ± 0.56
2 day	4.80 ± 0.68[ab]	4.77 ± 0.88[a]	6.05 ± 0.55
3 day	3.55 ± 0.61[ab]	3.58 ± 071[a]	5.41 ± 0.61

[a]$P < 0.05$, Compared with Dixon group.
[b]$P > 0.05$, Group A compared with and group B.

Comparison of the anal function at 1 year after follow-up

At 1-year follow-up, the WIS score evaluated the anal function of the patients and the proportion of scores <10 points. The results showed that there was no difference in

TABLE 5 Comparison of postoperative pathological indexes among the four groups.

	NOSES I-type E group (52 cases)		Dixon group (57 cases)
	Group A (25)	Group B (27)	
Gross typing			
Ulcerative	12	14	33
Invasive	7	8	14
Raised	6	5	10
Histological typing			
Adenocarcinoma	18	20	34
Adenocarcinoma/partial mucinous adenocarcinoma	3	5	12
Mucinous adenocarcinoma	4	2	11
Differentiation			
Mid-differentiation	13	16	31
Low differentiation	5	6	16
Mid-low differentiation	7	5	10
pT stage			
T1	5	4	14
T2	6	6	16
T3	14	17	17
N stage			
N0	16	12	24
N1	5	8	15
N2	4	7	18
Specimen length (cm)	10.20 ± 1.81	9.80 ± 2.21	10.52 ± 3.41
Total lymph nodes	13.0 ± 5.01	12.70 ± 4.56	13.11 ± 4.46
Number of positive margins	0	0	0
Distance from tumor to inferior margin	1.21 ± 0.77	1.23 ± 0.67	1.7 ± 0.80
Tumor long diameter	3.00 (1.5, 4.00)	3.00 (3.50, 4.00)	4.00 (2.75, 5.00)
Tumor width and diameter	3.00 (1.8,4.00)	3.00 (2.00,4.00)	3.00 (2.50,3.75)
Tumor thickness and diameter	1.5 (1.12,2.00)	1.5 (1.00,2.00)	1.5 (0.8,2.00)

There were no significant differences in all indexes among the groups, $P > 0.05$.

anal function among the the groups at 1 year after surgery ($P > 0.05$) (Table 6).

Comparison of recurrence and distant metastasis at 3-year follow-up

The recurrence and distant metastasis of the groups were followed up for 3 years. The results showed that in the NOSES I-type E group, there was 2 local recurrence and 2 distant metastasis whereas in Dixon group there was 3 case of distant metastasis and 1 case of local recurrence. Statistical analysis showed that there was no significant difference in recurrence and distant metastasis numbers among the groups ($P > 0.05$) (Table 7).

TABLE 6 Anal function score and the number and percentage of cases with scores less than 10 in the four groups at 1 year after operation.

	NOSES I-type E group (52 cases)		Dixon group (57 cases)
	Group A (25)	Group B (27)	
Wexner score (X ± s)	8.55 ± 1.98^{ab}	8.21 ± 1.92^{a}	7.64 ± 2.21
Wexner score <10 number and percentages	20 (20/25)[ab]	21 (21/27)[a]	53/57

[a]$P > 0.05$ Compared with Dixon group.
[b]$P > 0.05$, Comparison between group A and B.

TABLE 7 local recurrence and metastasis in the four groups at 3 years follow-up.

	NOSES I-type E group (52 cases)		Dixon group (57 cases)
	Group A (25)	Group B (27)	
Local recurrence	1	1	1
Distant metastases	0	2	3

There was no significant difference among the groups, $P > 0.05$.

TABLE 8 The survival rate of the four groups at the 3-year follow-up.

	NOSES I-type E group (52 cases)		Dixon method (57 cases)
	Group A (25)	Group B (27)	
3 years alive Number	25	24	55
OS	25/25	24/27	55/57

There was no significant difference between the groups, $P > 0.05$.

Comparison of the survival rates at 3-year follow-up

The results showed that in the NOSES I-type E method group, 25 patients in group A and 24 patients in group B survived whereas in Dixon group, 55 patients survived. There was no significant difference in the survival rate among the groups ($P > 0.05$) (Table 8).

Discussion

The NOSES I-type E method is a combination of a laparoscopy and modified Bacon technique which has been described in detail earlier (12). As one of the sphincter-preserving surgical methods for low rectal cancer, it has greatly improved the sphincter-preserving rate, in addition to obtained cosmetic needs and reducing the occurrence of abdominal wall complications (13). However, the safety of the operation, the patient's anal function and prognosis are the fundamental reasons why it is difficult to reach a consensus and unification in clinical practice (14). The results of this study showed that there was a significant difference in the distance between the tumor and the anal verge in the general data of the NOSES I-type E group and the Dixon group. It shows that the distance between the tumor and the anal verge is related to the surgical method (15) and the NOSES I-type E method may be more suitable for anus preservation in ultra-low rectal cancer. This result is also in line with the current domestic expert consensus.

The perioperative indicators showed that compared to the Dixon method, the NOSES I-type E method patients had a better feeding time, exhaust time, drainage tube removal time, hospitalization time, hospitalization costs, and less postoperative analgesia days. Moreover, NOSES I-type E method patients displayed significantly lower postoperative complications. The pain score of patients in the first three days after operation was significantly lower in the NOSES I-type E method patients compared to the Dixon method patients. These results showed that the NOSES I-type E method had no anastomotic stoma, so there is no need to worry about anastomotic leakage and the patient can be instructed to eat and get out of bed early, and the recovery of gastrointestinal function was promoted. Another major advantage of the NOSES I-type E method is the fact that there was no assisted incision in the abdominal wall, therefore, the pain level of the patients was significantly lower than that of the Dixon method. This is why the patients were more motivated to get out of bed actively, so as to promote the rapid recovery which eventually resulted in a significant reduction in the length of hospital stay and postoperative analgesia days. The idea is consistent with NOSES (16). In addition, NOSES I-type E surgery does not need a stapler and closure device. The hospitalization time is shortened and the hospitalization costs are significantly lower than that of the Dixon method.

Our results also indicate that the difficulty urinating in NOSES I-type E group has no significant difference compared to Dixon group, but it has significant difference between group A and group B. which reveled that due to the advantages of 3D laparoscopy, there was a better pelvic nerve protection. Thus, the NOSES I-type E method can achieve the same neurological protection as Dixon surgery (17). The surgical complications showed that the NOSES I-type E method group were higher than those in the traditional Dixon group, which indicated that the NOSES I-type E method also had its shortcomings, however, there was no statistical difference in the total complication rate among groups. This is consistent with already published data (18).

There was no significant difference in postoperative pathological results between the groups. The two surgery techniques can achieve the same radical efficiency under the guidance of TME and D3 surgery principles. However, poor anal function and difficulty in achieving satisfactory stool control after NOSES I-type E method have always been concerns of surgeons. The results of this study showed that there was no significant difference in anal function scores between the two method one year after operation. This is consistent with the research results of Liu, Li (19), and Luo Xue (20), and others which reported that the patient's anal function after NOSES I-type E surgery achieved the same results as the Dixon operation technique 3 and 6 months after operation (21). This indicated that after 1 year of muscle and nerve function recovery, the two groups of patients can achieve the same therapeutic effect. We should not focus on short-term anal function but should observe a certain time limit. The results of this study also showed that the recurrence and overall survival rate 3 years after surgery were not statistically different between the two groups, which was consistent with the results of previous studies (22, 23). These data show that the two surgical methods can achieve the same therapeutic effect with comparable safety and surgical efficiency.

As on of the largest colorectal cancer diagnosis and treatment center in China, it is currently the center that has carried out more NOSES I-type E method in China. The experience of this center is as follows: (1) Select suitable patients according to tumor characteristics such as stage c/ycT1–3, distance of the tumor 3–5 cm away from the anal verge, involving no more than half of the intestinal wall with a tumor diameter less than 3 cm, early cancer or carcinoma *in situ* where local anal resection cannot be performed; male patients with preoperative perianal muscles are selected for NOSES I-type E method (2) During abdominal surgery, the sigmoid colon needs to obtain sufficient mobility, must be released upward to the splenic flexure of the colon and the rectum must be freed downward to the levator ani muscle or between the internal and external sphincter; (3) The anus should be fully expanded, the rectal anal canal should be disinfected and the purse-string suture at the distal end of the tumor should be free of tumors; (4) The skin of the anal canal should be incised 1 cm below the dentate line and all the mucosa and abdominal cavity should be removed upwards; (5) After specimen removal, the proximal colon should be pulled out through the anus for about 5 cm and the intestinal seromuscular layer and the skin of the anal canal should be sutured intermittently, which requires major intestinal tension and blood supply to prevent postoperative ischemia, necrosis, and retraction; (6) Anus reconstruction should be performed 10 days after the first operation. The seromuscular layer should be incised close to the anal margin and the mucosa should be 0.5 cm longer than the anal margin; (7) Postoperative levator training should be performed to restore muscle function around the anus.

In conclusion, the NOSES I-type E method can achieve the same radical and prognostic effect as the Dixon operation without increasing surgical complications while at the same time has the advantages of no anastomotic leakage, avoidance of permanent abdominal stoma, less trauma, and complete preservation of anal function. Its combination with 3D laparoscopy can better preserve the patient's neurological function than 2D laparoscopy. Of course, the NOSES I-type E method also has certain shortcomings, such as postoperative anal stenosis, colon retraction, and short-term poor anal function. But no surgery is perfect, only the right one is the best. Therefore, surgeons should accurately and individually assess the patient's condition and, based on their own experience, choose the NOSES I-type E method only for suitable patients. This study also has certain limitations, such as the small number of cases, the short follow-up time, and the specific survival curves of the groups. These deficiencies will be further investigated in future studies.

Conclusions

The NOSES I-type E method is a safe and effective sphincter-preserving operation for low rectal cancer and its combination with 3D laparoscopy may have better neurological protection which is worth of clinical application.

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 author/s.

Ethics statement

The ethical approval was not applicable to this study and was waived our institution.

Author contributions

JB and BW designed and directed the study, GX collected and analyzed the data, and LM wrote the article. 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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Case report: Resection of a massive primary sacrococcygeal mature teratoma in an adult using 3-dimensional reconstruction and mixed reality technology

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Introduction: Teratomas are rare neoplasms that arise from pluripotent germ cells. Sacrococcygeal teratomas are often diagnosed in infants but are rare in adults; a mature teratoma can contain hair, teeth, bony tissue, and other mature tissue types. Herein, we report for the first time a patient with a teratoma containing intact bones that formed a pseudoarthrosis.
Case report: A 49-year-old woman was admitted to hospital after a massive life-long sciatic tumor had begun to grow larger over the past year. A 16 cm × 25 cm solid mass with a clear boundary was palpable in the sacrococcygeal region. Radiography, computed tomography, and magnetic resonance imaging indicated a sacrococcygeal teratoma, although blood alpha-fetoprotein levels were normal. The teratoma was completely excised using 3-dimensional reconstruction mixed reality (MR) technology with no notable complications. Postoperative pathological examination of the excised lesion confirmed a mature teratoma. Interestingly, two intact irregular bones that formed a pseudoarthrosis were isolated; one was 11 cm and the other 6 cm. The patient is currently healthy and has experienced no recurrences.
Conclusion: Sacrococcygeal teratomas are rare, especially in adults, and often comprised lots of components, such as fat, bony tissue. However, it's first reported that formation of pseudoarthrosis in this case so far. It is difficult for surgeons to achieve complete excision without complications owing to the complex anatomic structure of the sacrum. The 3-dimensional reconstruction and mixed reality (MR) technology based on computed tomography can provide spatial visualization, which allows surgeons to examine the teratoma at different angles preoperatively. Combining 3-dimensional reconstruction and mixed reality (MR) technology in this case facilitated complete resection and prevented recurrence.

KEYWORDS
mixed reality, pseudoarthrosis, teratoma, sacrococcygeal, three-dimensional reconstruction (3D reconstruction), case report

Introduction

Teratomas are rare congenital tumors derived from germ cells; they account for 2.5% of all germ cell tumors (1) and are commonly diagnosed in infants and children but rarely in adults (2). Outside the gonads, teratomas are most commonly diagnosed in the midline regions of the body (3). These tumors can be benign or malignant depending on their differentiation levels (4); a high differentiation level and abundant mature tissue component are often found in benign teratomas, whereas malignant tumors tend to exhibit low differentiation and immature tissues (5). Three-dimensional (3D) reconstruction and mixed reality (MR) are advanced surgical technologies that play important roles in precision medicine. The former can transform two-dimensional images into 3D models, allowing surgeons to observe the complex anatomical structures of the tissues surrounding the tumor as well as the tumor-environment relationship. The latter provides an interactive experience based on the 3D virtual image, allowing surgeons to simulate the surgery and verify the procedural plan preoperatively.

In this report, we describe a rare sacrococcygeal teratoma diagnosed in an adult that contained 2 intact bones forming a pseudoarthrosis. We also describe how 3D reconstruction and mixed reality (MR) technology were used to ensure precise surgical resection. This report was prepared according to the SCARE checklist (6).

Case presentation

A 49-year-old woman presented at Shengjing Hospital (affiliated with China Medical University) after noticing that a massive sacrococcygeal tumor she had since birth had been growing over the past year. One month before her visit, the patient felt pain in her hip owing to a rapidly enlarging mass. The patient didn't receive any medical intervention and the symptoms were not released over past year. The patient was previously healthy with no history of chronic cardiovascular diseases, infectious diseases, allergy, or surgery. She did not smoke or consume alcohol, and had no familial diseases.

Physical examination revealed a palpable 16 cm long × 25 cm wide solid mass in the sacrococcygeal region, with a clear boundary and good mobility. There was an obvious osteal protuberance in the center of the mass that had poor mobility. Preoperative laboratory workups including complete blood count, urinalysis, liver function test, and renal panel were within normal range. Pelvic radiography revealed a long rod-like bone in the pelvic cavity, while pelvic enhanced computed tomography (CT) revealed a massive space-occupying lesion in the pelvic-sacrococcygeal region that was 14.5 cm × 10.5 cm × 21.5 cm. Pelvic enhanced magnetic resonance imaging revealed a massive sacrococcygeal multiloculated teratoma comprised mainly of a fatty, sebaceous material as well as a long bone lacking any obvious abnormalities on enhanced scanning (Figure 1).

A multidisciplinary consultation was arranged to decide on the optimal therapeutic approach based on 3D reconstruction and mixed reality (MR) technology, which were used to ensure precise surgical resection. The 3D reconstruction was performed using the "visual volume" software (Shenyang, China) with CT-derived data. The 3D model was then uploaded into the mixed reality (MR) image system, whereupon the surgeon could visualize the 3D model through the mixed reality (MR) helmet (Microsoft Corp, Redmond, WA, United States) (Figure 2). This enabled to discern the relationship between the teratoma and surrounding tissues (such as vessels and nerves) directly. Furthermore, the mixed reality (MR) visual software allowed the operator to move, rotate, hide, and delete elements of the 3D model, thereby allowing him to simulate the surgery and eliminate potential errors. The multidisciplinary team had concluded that the lesion was likely a sacrococcygeal teratoma, and that its final diagnosis ought to be verified *via* postoperative pathological analysis.

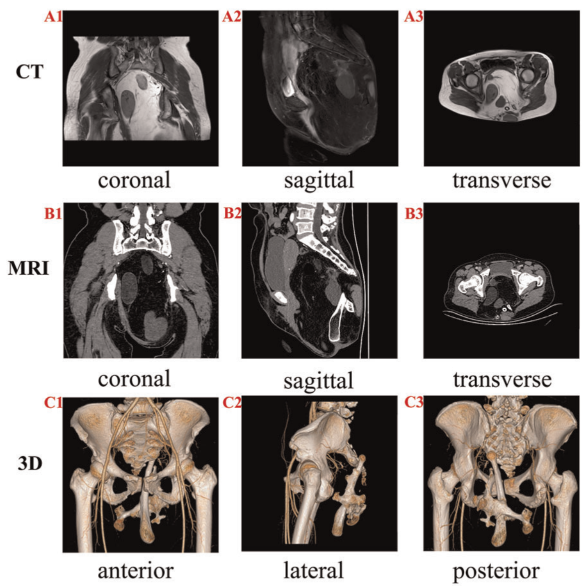

FIGURE 1
Magnetic resonance imaging (MRI) and 3D computed tomography (CT) of the patient. (A1–A3) CT showing different views of the teratoma. A huge space-occupying lesion exhibiting different densities can be observed in the pelvic cavity. A clear boundary is observed between the teratoma and pelvis. (B1–B3) MRI showing various views of the teratoma. The massive sacrococcygeal multiloculated lesion comprises a large amount of fat, sebaceous material, and long bone. (C1–C3) Various 3D views of the bone reconstruction based on CT; the 3D reconstruction allowed the visualization of the spatial positions of the bones within the teratoma as well as the lesion's relationship with the pelvis.

The surgery was performed on March 26, 2021. After administering general anesthesia and disinfecting the area, a 40 cm arced incision was created in the sacrococcygeal region from the posterior superior iliac spine to the contralateral posterior superior iliac spine along with the lower boundary of the tumor (i.e., resembling a smiley face). An intact encapsulated mass was found under the deep fascia; its upper boundary reached the sacral 5 vertebra, its lower boundary reached the anococcygeal ligament, and its bilateral boundaries were adjacent to the gluteus and surrounding soft tissue. The tumor protruded into the pelvic cavity and compressed the ampulla recti. Given that it had an intact capsule, the tumor did not invade the surrounding organs and we decided to remove the teratoma integrally to decrease the recurrence rate. The teratoma was rigid and lacked elasticity because of the two bones inside, which may break the capsule leading to incomplete resection if the surgical area was small. Therefore, we removed the coccyx to expose an enough space for surgical operation. Next, we separated the tumor from the pelvic cavity with the guidance of 3D reconstruction and mixed reality (MR) technology. Especially, when separating the deep bottom of the teratoma, meticulous operation was necessary to avoid bladder and rectum injury. Finally, we reconstructed the sacral structure to help recover sciatic function by anchoring a mesh through the suture to the surrounding tissue in order to provide mechanical support. Muscle reconstruction was achieved by suturing the anococcygeal ligament to the coccygeal stump (Supplementary Figures). Surgery was completed with no complications.

The excised specimen was transferred to the Pathology Department for cytological diagnosis. Macroscopically, it was 24 cm × 23 cm × 15 cm, and weighed 5 kg. The surface of the mass was capsulated and bosselated. The cut surface exhibited multiple cysts that contained yellow fat, gray viscous sebaceous matter, hair, muscle, and bone tissue. Of particular interest, two intact irregular bones that formed a pseudoarthrosis were isolated from the mass; one was 11 cm long and the other 6 cm (Figure 3A). Microscopically, fibrous squamous epithelium with cutaneous appendages, hair follicles, sebaceous glands, bony trabeculae, and fat tissue was observed in the section (Figures 3B–G). There were no immature neural or

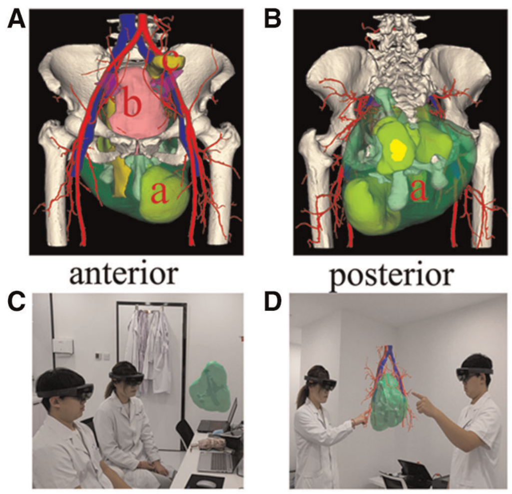

FIGURE 2
The application of 3D reconstruction and mixed reality (MR) technology in our patient. (A,B) The 3D reconstruction images accurately displaying the relationship between the teratoma and surrounding tissues through various angles. (a) teratoma; (b) bladder; (c) rectum. (C,D) mixed reality (MR) technology showing the spatial location of the teratoma and its orientation with respect to the pelvic cavity. This technology was used to devise a surgical strategy and simulate the surgical process.

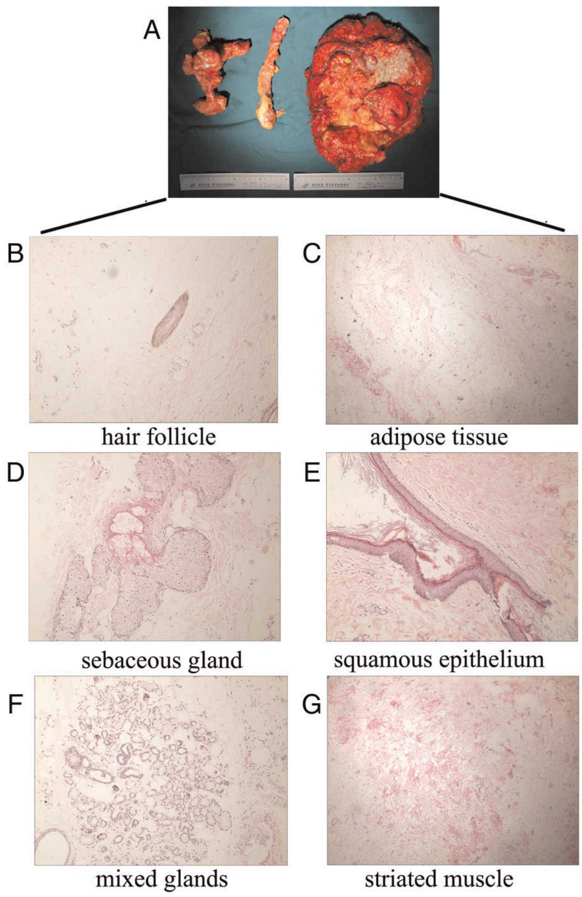

FIGURE 3
The gross appearance and pathological examination of the teratoma. (A) The teratoma measured 24 × 23 × 15 cm and weighed 5 kg. Two intact bones were isolated from the mass: one was 11 cm long with a diameter of 3 cm, and the other was irregular (6 × 6 × 5 cm). The two bones formed a pseudoarthrosis. (B–G) Pathological slides stained with hematoxylin and eosin: (B) hair follicle, (C) adipose tissue, (D) sebaceous gland, (E) squamous epithelium, (F) mixed glands, and (G) striated muscle.

embryonic tissues (which are markers of malignant transformation) in the section. The final diagnosis was a mature sacrococcygeal teratoma.

The postoperative routine blood tests were drawn every 3 days. The labs showed a slight elevation of white blood cell count, C-reactive protein level, and erythrocyte sedimentation rate, which were appropriate for a normal physiological response postoperatively. She was discharged on postoperative day 7 with no complications. Her treatment course was summarized in **Figure 4**.

Follow-up and outcomes

The patient was followed up in our clinic every 6 months after discharge to monitor for local recurrence. Physical exams, AFP, ultrasound, and pelvic MRI were performed during each clinic visit. At 1-year follow-up, her AFP remained normal, and surveillance imaging (ultrasound and MRI) didn't show any signs of recurrence. In the perspective of the patient, the symptoms including pain, disability of defecation and urination was released entirely. The life quality of the patient was significantly improved.

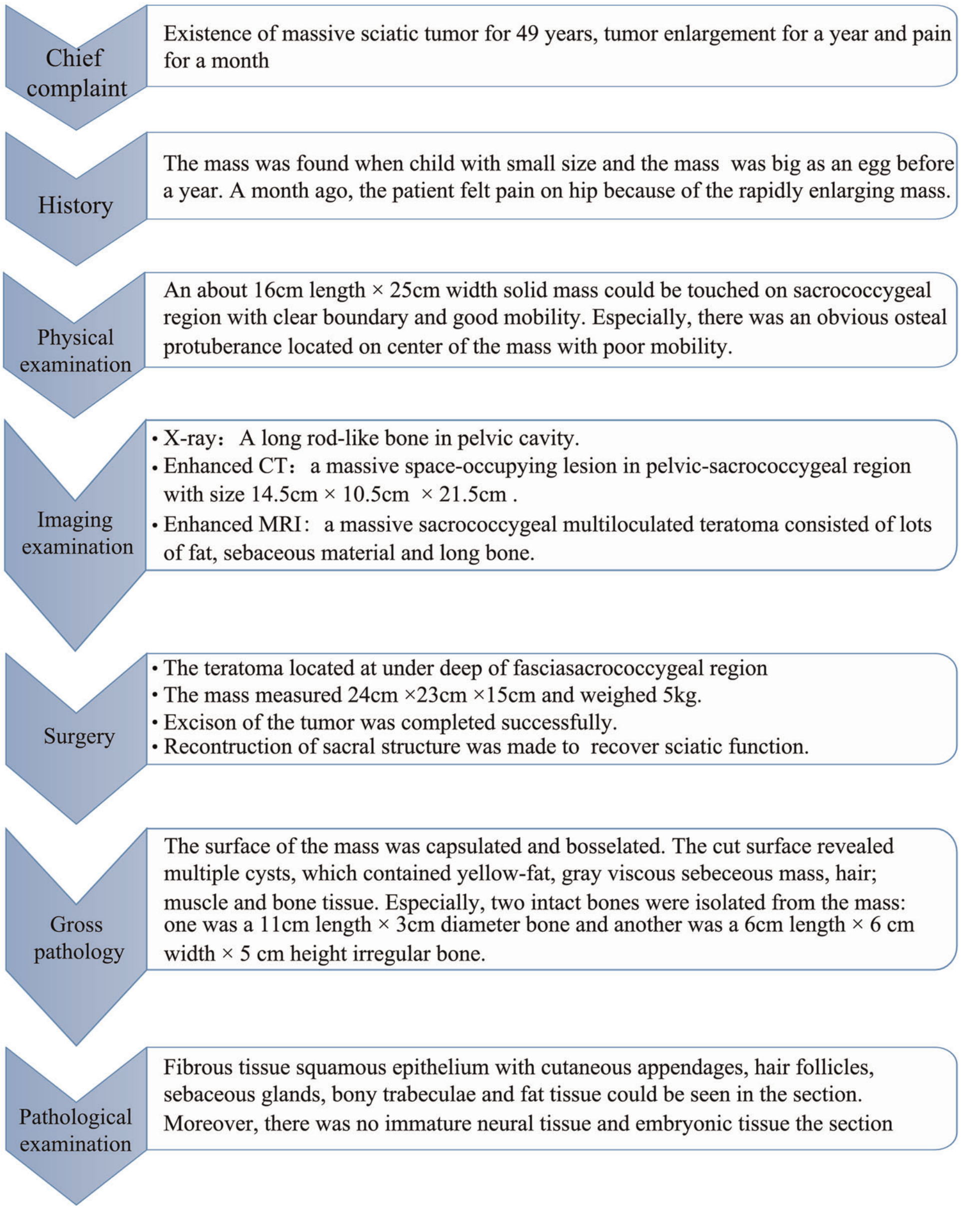

FIGURE 4
The therapeutic course of the patient. The current case report is presented based on this sequence of events.

Meanwhile, the patient satisfied with the successful surgery and uneventful recovery. She held the view that she was in good condition and enjoyed a happy life like normal person.

Discussion

Teratoma is a rare type of neoplasm that originates from primordial germ cells; its site of occurrence varies with age (7). In infants, teratomas are often discovered in the sacrococcygeal region, whereas adolescents and adults tend to have such tumors diagnosed more commonly in the gonads (5). These tumors can be divided into two types, mature and immature. Mature teratomas are often detected in adults and comprise well-differentiated components, although they tend to undergo malignant transformation (5); meanwhile, immature teratomas are more frequently found in infants and children, and exhibit partial differentiation (8). Sacrococcygeal teratomas more commonly occur in infants than in adults (9, 10). Hence, our patient's teratoma is rare not only because of its discovery in the sacrococcygeal region but also because it was diagnosed in an adult 49-year-old woman.

Sacrococcygeal teratomas can be classified into four types according to their depth of infiltration; these range from type I tumors that are located outside the sacrococcygeal region to type IV lesions that exist exclusively in the presacral region and pelvic cavity (11). Our patient's teratoma was categorized as type III, which typically entails a complicated surgery.

Surgery is the optimal treatment for sacrococcygeal teratoma (12), the planning of which requires taking two important aspects into account. One is achieving complete resection to avoid recurrence, and the other is to prevent complications as much as possible. A study showed almost 11 percent of patients recurred in 3 years postoperatively due to incomplete resection (13). Traditionally, more complete resections are associated with greater rates of surgical complications including urinary tract and bowel dysfunction, hemorrhage, and nerve injury (14); therefore, attaining the optimal balance between maximum therapeutic effect and minimal surgical complications requires surgeons to devise a definitive surgical strategy *via* thorough analysis of the imaging data. In our patient, 3D reconstruction and mixed reality (MR) technology were used to strategize for and navigate the procedure (15). With 3D reconstruction, the spatial structure and relationship between the teratoma and surrounding tissues could be displayed (16). Mixed reality (MR) technology was used to transform the 3D model into a spatial virtual image; its greatest advantage was its interactive function, given that we were able to discern the relevant anatomic structures better. In fact, we were able to simulate the surgical procedure to ensure its effectiveness *via* this interactive system. Furthermore, the two bones formed a pseudoarthrosis that meant a rigid structure within the teratoma. The rigid structure may be an obstacle to surgery, and we should ensure enough surgical incision to remove the teratoma from pelvic cavity. 3D reconstruction and mixed reality (MR) technology allowed to predict related intra-operative challenges, assisted the surgeons in devising a meticulous surgical plan to prevent unnecessary damage, and ensured complete tumor removal. Moreover, visualization aided us in explaining the planned procedure to the patient, who was thus able to understand both the surgical process and associated risks (17). We successfully removed our patient's teratoma and coccyx without damaging the gluteal artery, sciatic nerve, or rectal ampulla owing to our use of 3D reconstruction and mixed reality (MR) technology.

However, there are some limitations in terms of using 3D reconstruction and mixed reality (MR) technology in clinical practice. The spatial anatomic structure that mixed reality (MR) provides is based only on CT-derived values; in actuality, the anatomic structure may be more complicated in a narrow surgical view, and may be affected by hemorrhage and other factors (18). Mixed reality (MR) technology is also limited by the resolution of the CT; some small tissues may not be detected, which in turn may lead to hemorrhage, organ injury, nerve injury and other surgical complications.

Postoperative monitoring is also necessary (19), as the possibilities of recurrence and malignant transformation exist. The probability of malignant transformation reportedly increases with age (20); as such, regular CT and physical examinations should be performed to detect any progression in residual teratoma tissue over the course of the patient's life (20). To that end, alpha-fetoprotein is a sensitive serum marker that can be used to screen for teratoma recurrence, as well as the severity thereof (21).

Conclusion

Sacrococcygeal teratomas rarely occur in adult women. Interestingly, formation of pseudoarthrosis in the teratoma is first reported in this case. Given the risks of surgical complications and incomplete excision with these tumor types, 3D reconstruction and mixed reality (MR) technology are advanced auxiliary tools that surgeons can use to achieve satisfactory outcomes.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Ethics Committee of Shenjing hospital affiliated to China Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conceptualization, HZ; image edition, LJ; software, SL; surgical assistant, TC; investigation, JXL; resources, JTL; data curation and writing—original draft preparation, HZ; writing—review and editing, GS. 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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Supplementary material

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Safety, efficacy, and selection strategy of laparoscopic local gastrectomy for gastrointestinal stromal tumors in the esophagogastric junction

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Objective: To investigate the safety, efficacy, and selection strategy of laparoscopic local gastrectomy for stromal tumors in the esophagogastric junction.

Methods: Thirty-eight patients with mesenchymal tumors in the esophagogastric junction were retrospectively enrolled from April 2018 to July 2021 in which the upper edge of the tumor is less than 2 cm from the Z-line or has invaded the Z-line <1/2 circumference. Surgical outcomes, complications, recover, and postoperative gastroesophageal reflux of both groups were compared.

Results: 27 patients underwent wedge resection, and 11 underwent resection by opening all of the layers of the stomach wall. Operative time (90.0 vs. 181.8 min, respectively, $P = 0.001$) was shorter for the WR group vs. RASW. Blood loss (20 vs. 50 ml, respectively, $P = 0.012$) was less for the WR group vs. RASW. Recovery of the RASW group was slower in terms of time to pass gas (2 vs. 3 days, $P = 0.034$), time to oral intake (2 vs. 4 days, $P = 0.007$), time to semi-liquid food intake (4 vs. 8 days, $P = 0.003$), and postoperative hospitalization (5 vs. 8 days, $P = 0.001$) vs. WR. In terms of short-term complications (≤30 days), no significant between-group differences were observed. Cardia stenosis did not occur in either group. In the WR group, one patient experienced mild reflux at 6 months and recovered 1 year after surgery. In the RASW group, one patient experienced severe gastroesophageal reflux at 6 months and 1 year after surgery, which was not entirely relieved by taking antacids. No other patients have gastroesophageal reflux.

Conclusion: Laparoscopic local gastrectomy is safe and feasible for mesenchymal tumors in the esophagogastric junction in which the upper edge of the tumor is less than 2 cm from the Z-line or has invaded the Z-line <1/2 circumference, and has achieved an excellent short-term effect. The choice of surgery is based on the relationship between the tumor and the position of the cardia.

KEYWORDS

esophagogastric junction, gastrointestinal stromal tumors, surgical method, local gastrectomy, gastroesophageal reflux

Abbreviations
GISTs, gastrointestinal stromal tumors; LLG, laparoscopic local gastrectomy; EGJ, esophagogastric junction; WR, wedge resection; RASW, resection by opening all of the layers of the stomach wall; GerdQ, gastroesophageal reflux disease questionnaire; LECS, lower oesophageal circular muscle sphincter; UGS, upper gastric sphincter; GEFV, gastroesophageal flap valve; GEJHPZ, gastro-oesophageal junction high-pressure zone.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tissue-derived malignancies in the digestive tract, accounting for 1%–3% of all gastrointestinal malignancies, and are more likely to occur in the stomach (50%–70%) (1, 2). For GISTs with tumor diameter less than 2 cm, endoscopic treatment is preferred, while for tumor diameter larger than 2 cm, surgery is the main method of treatment (3). The goals of surgical therapy mainly include ensuring the integrity of the tumor capsule and achieving negative tumor margins. GISTs are primarily implanted in the abdominal cavity and metastasize *via* the blood, and lymph node metastasis is rare. Therefore, there is no need for lymph node dissection during the operation (4). With the widespread adoption of laparoscopic technology in the surgical field, laparoscopic local gastrectomy (LLG) has been safely and effectively applied for the surgical treatment of GISTs (5). Lukaszcryk first reported laparoscopic gastrectomy for GISTs in 1992 (6). With the increasing maturity of minimally invasive techniques, studies have found that laparoscopic technology is safe and feasible for GISTs (7, 8) and has now become the preferred method. It can significantly reduce tissue bleeding and damage, fully expose the surgical field of vision, improve the safety of the operation, shorten the hospital stay, and reduce postoperative discomfort. Currently, the most commonly used laparoscopic surgery methods for the treatment of GISTs include four types: wedge resection (WR), resection by opening all of the layers of the stomach wall (RASW), mucosa-preserving resection, and proximal gastrectomy. The main factors that affect the choice of gastric stromal tumor surgery are the size and location of the tumor (9), which have a significant impact on the perioperative outcome. However, such studies have primarily focused on the body of the stomach and the antrum, and there are few studies on the esophagogastric junction (EGJ) (10).

The incidence of GISTs in the EGJ is low, accounting for 5.8%–13.5% (11–13), so there are few reports on this topic. The anatomy of GISTs in the EGJ is complex, and the operation and functional retention are difficult. Therefore, proximal gastrectomy was often used for GISTs in EGJ in the past. However, the high incidence of postoperative gastroesophageal reflux seriously affects the quality of life of patients (14). Complications such as cardiac stenosis may occur after local gastrectomy. Therefore, there is currently no way to reconstruct the digestive tract that has been widely recognized. Xiong et al. (15) found that GISTs in the EGJ in which the upper edge of the tumor is more than 2 cm from the Z-line are often treated with WR when they are close to the greater curvature, which can ensure the integrity of the Z-line and will not affect the patency of the cardia. When approaching the lesser curvature, RASW is often used because WR will narrow the cardia and may also lead to excessive gastric wall resection, shorten the length of the lesser curvature, and cause structural malformations or abnormal movements in the stomach. For GISTs in the EGJ in which the upper edge of the tumor is less than 2 cm from the Z-line, mucosa-preserving resection is used to preserve the normal function of the cardia. Zheng et al. (16) reported a new method of conformal resection to treat GISTs in the EGJ in which the upper edge of the tumor is less than 2 cm from the Z-line or has invaded the Z-line, but it needs to be completed by laparotomy. The 2017 edition of “Consensus on Diagnosis and Treatment of Gastrointestinal Stromal Tumors in China” recommends that when GISTs in the EGJ are surgically treated, as long as the upper edge of the tumor is 1–2 cm away from the Z-line and more than 50% of the circumference of the EGJ is retained after the tumor is removed, WR can be used. It can be used to cut the transverse suture under direct vision to avoid narrowing the suture. Proximal gastrectomy was performed for GISTs in the EGJ that invaded the Z-line.

At present, LLG for GISTs in the EGJ in which the upper edge of the tumor is less than 2 cm from the Z-line or has invaded the Z-line <1/2 circumference has not been reported, which presents great challenges in terms of technology and functional preservation. This study analyzed the safety, efficacy and the selection strategy of LLG for GISTs in the EGJ in which the upper edge of the tumor is less than 2 cm from the Z-line or has invaded the Z-line <1/2 circumference.

Methods

Patients

This study was a single-center retrospective study. This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University. Patients were enrolled: (I) preoperative endoscopic ultrasonography showed mesenchymal tissue-derived tumors, and if the upper margin of the tumor was less than 2 cm from the Z-line or the upper edge had invaded the Z-line and the invasion range was less than 1/2 of the circumference; (II) aged 18–75 years, both male and female; (III) LLG was performed, including WR and RASW, with or without conversion to laparotomy; (IV) no history of gastrointestinal surgery and no history of gastrointestinal malignant tumors; (V) normal organ function; (VI) no found to have distant metastases; and (VII) complete case data and follow-up data. The exclusion criteria were: (I) resection of other organs (liver, pancreas, spleen, or colon); (II) a history of central nervous system disease or mental illness; (III) other diseases that seriously affect survival time; (IV) organ transplantation requiring immunosuppressive therapy; and (V) pregnancy or lactation.

Surgical techniques

The same group of physicians in the Gastrointestinal Surgery Department performed LLG. The trocar used a 5-hole method (**Figure 1**). A 12-mm trocar was inserted into the upper edge of the belly button as an observation opening (A). A 12-mm trocar was inserted 2-cm below the costal margin of the left anterior axillary line as the main operation opening for the surgeon (B). A 5-mm trocar was inserted 2-cm below the costal margin of the right anterior axillary line as an auxiliary operation opening for the assistant (C). A 5-mm trocar was inserted 1-cm above the flat umbilicus of the left mid-clavicular line as an auxiliary operation opening for the surgeon (D). A 12-mm trocar was inserted 1 cm below the midpoint of the line between the A hole and the C hole as an auxiliary operation hole for the assistant (E). According to the location of the lesion and the size of the tumor, the surgical method was determined.

(1) WR: for a tumor close to the fundus of the stomach or convex out of the cavity at any position where the upper edge of the tumor is less than 2 cm from the Z-line, insert a 36F thick gastric tube, expand the structure of the cardia, and use a linear stapler to simulate the line to evaluate whether the cardia is stenotic after resection. After assessing that there was no stenosis close to the edge of the tumor, a linear stapler was used to remove the tumor completely (**Figure 2**).

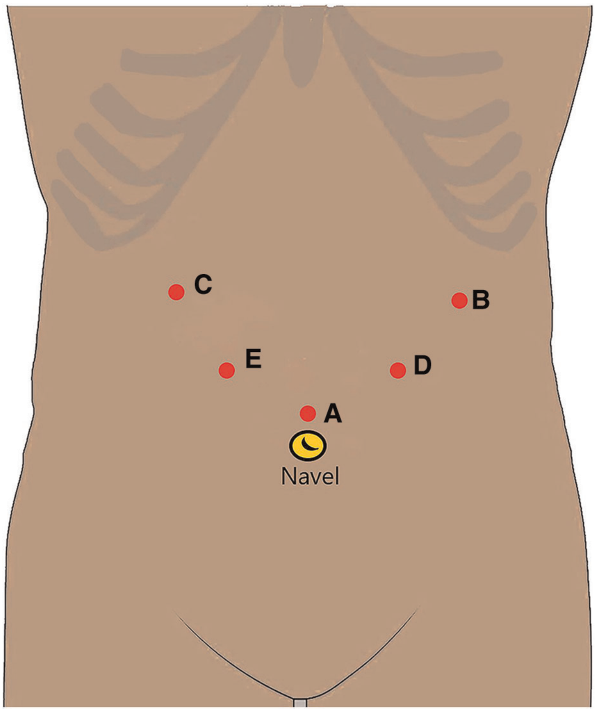

FIGURE 1
Puncture port placement.

(2) RASW: if the tumor is located directly below the cardia, close to the lesser curvature, or invades the Z-line circumference and is less than 1/2 or convex into the cavity at any position where the upper edge of the tumor is less than 2 cm from the Z-line, close to the tumor, cut the stomach wall longitudinally at the edge of the tumor throughout the entire process, and entirely remove the tumor along the periphery of the tumor with an ultrasonic knife through the gastric cavity. With the absorbable barb line perpendicular to the long axis of the oesophagus and the esophageal and gastric junction defect, the cardiac structure was reconstructed. Then the plasmic muscle layer was reinforced, embedded, and sutured. Finally, an intraoperative gastroscopy was performed to confirm that there was no stricture of the cardia. A gas-filled water injection test under the gastroscope was performed to verify that there was no air bubble overflow at the anastomosis of the esophagogastric junction (**Figure 3**).

Study outcomes

The primary outcome is the incidence of gastroesophageal reflux 1 year after surgery. Full-time staff followed up with patients at the clinic or by telephone, and evaluated the gastroesophageal reflux status with the gastroesophageal reflux disease questionnaire (GerdQ). A GerdQ score ≥8 points indicated gastroesophageal reflux disease. The following data were collected: (I) demographic, including sex, age, and body mass index; (II) auxiliary examination results, including endoscopic ultrasound, and abdominal enhanced CT (III) surgical data, including operation time, blood loss, surgical method, and complications; (IV) postoperative recovery data including time to pass gas, time to oral intake, time to semi-liquid food intake, and postoperative hospital stay; (V) postoperative pathology, including pathological type, tumor diameter and pathological margin; and (VI) the GerdQ of patients before surgery, 6 months after surgery, and 1 year after surgery. Complications were classified according to the Clavien-Dindo classification method (17).

Statistical analysis

SPSS 21.0 statistical software was used for analysis. The measurement data with a normal distribution are represented by mean ± standard deviation, and values were compared using the independent sample *t*-test. The measurement data with a skewed distribution are represented by median

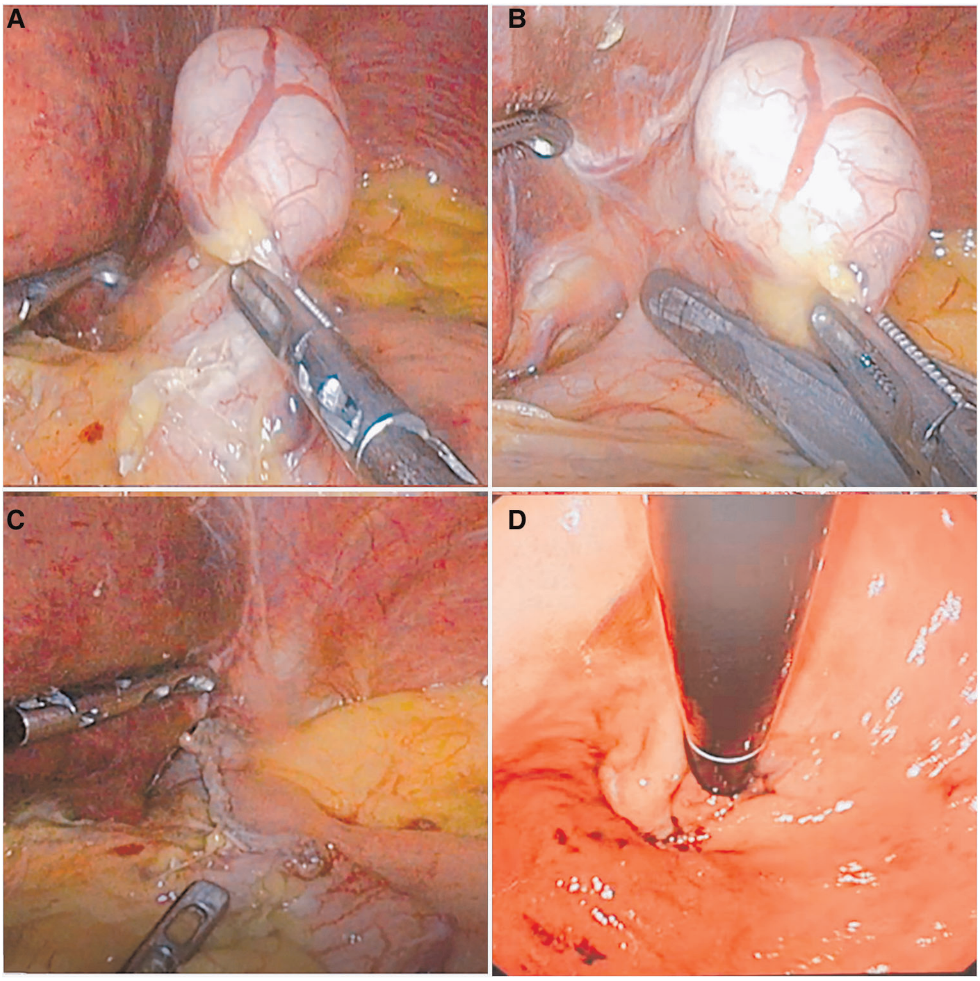

FIGURE 2
The flow chart of wedge resection. (A) The fat and blood vessels on the surface of the stomach in the cardia were opened, exposing the tumor site. (B) The tumor was pulled, and a linear stapler was made along the edge of the tumor to remove the tumor. (C) The tumor was completely resected. (D) Intraoperative gastroscopy was performed to check the patency of the cardia.

(interquartile range), and values were compared using the non-parametric test. The X^2 test was used to compare countable data. A non-parametric test was used to compare the grade data. Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics and pathology

Thirty-eight patients were enrolled from April 2018 to July 2021. Among them, 27 underwent WR, and 11 underwent RASW. The baseline characteristics and pathology of the 38 patients are shown in Table 1. For sex ($P = 0.579$), age ($P = 0.145$), BMI ($P = 0.512$) were comparable between the two groups. There was a significant difference in pathological type ($P < 0.001$) between the two groups. However, in terms of tumor diameter ($P = 0.406$) and pathological margins ($P = 0.999$), no significant between-group differences were observed. All patients achieved adequate R0 margins.

Perioperative outcomes and follow up

Operative time (90.0 vs. 181.8 min, respectively, $P = 0.001$) was shorter for the WR group vs. RASW. Blood loss (20 vs. 50 ml, respectively, $P = 0.012$) was less for the WR group vs. RASW. Recovery of the RASW group was slower in terms of time to pass gas (2 vs. 3 days, $P = 0.034$), time to oral intake (2 vs. 4 days, $P = 0.007$), time to semi-liquid food intake (4 vs. 8 days, $P = 0.003$), and postoperative hospitalization (5 vs. 8

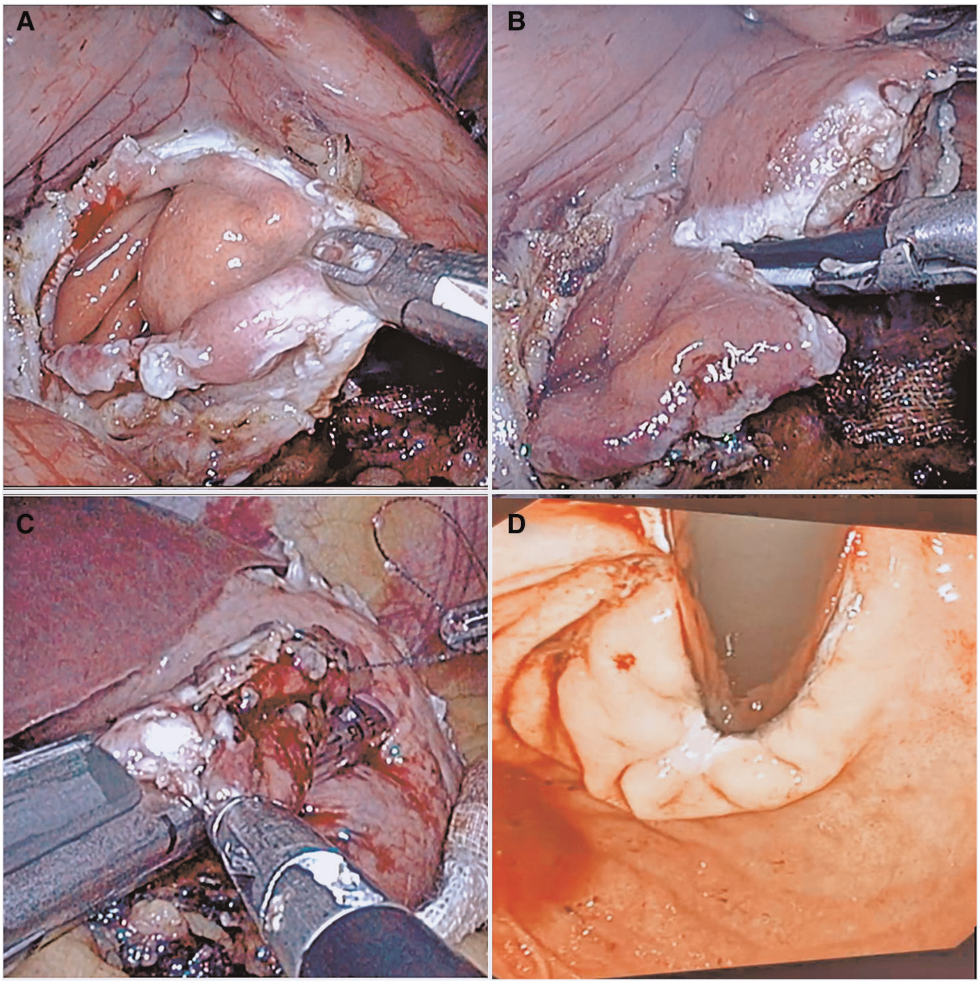

FIGURE 3
The flow chart of resection by opening all of the layers of the stomach wall. (A) The full thickness of the stomach wall was opened to expose the tumor site. (B) The tumor was pulled, and an ultrasonic knife was used to remove the tumor. (C) After the tumor was completely resected, the cardia was reconstructed using a linear cutting closer. (D) Intraoperative gastroscopy was performed to check the patency of the cardia.

days, $P = 0.001$) vs. WR. In terms of short-term complications (≤30 days), no significant between-group differences were observed. Cardia stenosis did not occur in either group. No mortality within 30 days of surgery was observed.

Thirty-eight patients were followed up after surgery, and 0 were lost to follow-up. In the WR group, 1 patient experienced mild reflux and scored 11 points at 6 months, which was entirely relieved by taking antacids intermittently. And she was entirely relieved by improving her lifestyle at 1year after surgery, and the GerdQ scored 7 points. In the RASW group, one patient experienced severe gastroesophageal reflux and scored 16 points at 6 months and 1 year after surgery, which was not entirely relieved by taking antacids. No other patients have gastroesophageal reflux. During the follow-up period, there was no death, tumor recurrence, or metastasis (Table 2).

Discussion

In this study, we used WR and RASW to treat GISTs in the EGJ. For GIST with tumor diameter less than 2 cm, we prioritized endoscopic treatment. However, some patients had difficulty in endoscopic resection under the evaluation of a gastroenterologist, and the risk was high. These patients underwent surgery. The results showed that in the context of ensuring complete resection and negative tumor margins, good results were achieved in terms of cardiac stenosis and gastroesophageal reflux, indicating the physiological anti-reflux function in the EGJ was not completely disrupted. At present, the understanding of the physiological anti-reflux structure in the EGJ is mainly divided into four parts, the lower oesophageal circular muscle sphincter (LECS), upper gastric sphincter (UGS), crural diaphragm with its

TABLE 1 The baseline characteristics and pathology of the patients.

	WR (n = 27)	RASW (n = 11)	*P* value
Sex (male/female)	8/19	5/6	0.579
Age (years)	60.5 ± 2.2	54.4 ± 3.6	0.145
BMI (kg/m^2)	23.8 ± 3.3	24.6 ± 3.3	0.512
Pathological type			<0.001*
Stromal tumor	23	2	
Low/intermediate/high (risk)	14/6/3	1/0/1	
Leiomyoma	4	9	
R0/R1 margin	27/0	11/0	0.999
Tumor diameter (cm)	3.7 ± 1.9	4.2 ± 1.7	0.406

Values are presented as mean ± standard deviation or median (interquartile range). WR, wedge resection; RASW, resection by opening all of the layers of the stomach wall; BMI, body mass index.
*Statistically significant values.

TABLE 2 The perioperative outcomes and follow up of the patients.

	WR (n = 27)	RASW (n = 11)	*P* value
Approach			0.999
Laparoscopy	27	11	
Laparotomy	0	0	
Operative time (min)	90.0 ± 33.1	181.8 ± 67.7	0.001*
Blood loss (ml)	20 (10–20)	50 (20–50)	0.012*
Time to pass gas (days)	2 (1–3)	3 (2–5)	0.034*
Time to oral intake (days)	2 (1–3)	4 (2–6)	0.007*
Time to semi-liquid food intake (days)	4 (3–6)	8 (5–8)	0.003*
Postoperative hospitalization (days)	5 (3–5)	8 (6–9)	0.001*
Complications (≤30 days)			0.999
Cardia stenosis	0	0	
Anastomotic leakage	0	0	
Anastomotic bleeding	0	0	
Atelectasis	0	1	
Mortality	0	0	
CD grade I/II/III/IV	0/0/0/0	0/1/0/0	
GerdQ (≥8 points)			
Before surgery	6 (22.2%)	4 (36.3%)	0.623
6 months after surgery	1 (3.7%)	1 (9.1%)	0.999
1 year after surgery	0	1 (9.1%)	0.289

Values are presented as mean ± standard deviation or median (interquartile range). WR, wedge resection; RASW, resection by opening all of the layers of the stomach wall; CD, Clavien–Dindo; GerdQ, gastroesophageal reflux disease questionnaire.
*Statistically significant values.

phrenoesophageal ligament, and gastroesophageal flap valve (GEFV), collectively referred to as the gastro-oesophageal junction high-pressure zone (GEJHPZ) (18, 19). The GEJHPZ functions as a multi-purpose valve. It can regulate the emptying of the esophagus to prevent retrograde reflux of stomach contents while allowing reverse exhaust and retrograde reflux (vomiting). The LECS is a smooth muscle ring in EGJ. It is formed by the noose-like fibers of the upper gastric sphincter, crossing and surrounding the esophagus. The lower boundary is approximately at the level of the His angle, and the upper boundary is approximately 3 cm above the Z-line, where the muscular layer is significantly thicker than in other parts of the surrounding esophagus (18, 20–22). The UGS is composed of gastric sling fibers and clasp fibers. Its acts to reduce the His angle through the contraction of the two fibers, thereby closing the lower end of the esophagus, which has an anti-reflux effect. The lasso fiber starts from the lower part of the lesser curvature and continues diagonally to the upper left corner of His. The lasso fiber is approximately 3-cm wide. Retaining the continuity of the lasso fiber can reduce the occurrence of gastroesophageal reflux. Hook-shaped fibers run horizontally from the muscle bundles located on the side of the minor curve, open to the front left, and are approximately 2.5-cm wide (18, 23, 24). The GEFV is a protrusion formed in the lumen at the His angle of the gastroesophageal junction. It acts like a one-way valve and helps prevent the backflow of stomach contents (18). Therefore, based on the abovementioned anatomical theory, we used the results of preoperative examination and laparoscopy to evaluate the tumor's location to determine the choice of surgery. For tumor close to the fundus of the stomach or convex out of the cavity at any position where the upper edge of the tumor is less than 2 cm from the Z-line, WR is often used. This causes minor damage to the physiological anti-reflux structure and can retain most of the Z-line and surrounding structures. Therefore, WR resulted in shorter operative time, less bleeding, and faster postoperative recovery. However, we need to pay attention to the patency of the cardia during the operation. If the tumor is located directly below the cardia, close to the lesser curvature, or invades the Z-line circumference and is less than 1/2 or convex into the cavity at any position where the upper edge of the tumor is less than 2 cm from the Z-line, WR may lead to stricture of the cardia and destroy more physiological anti-reflux structures. So, we performed RASW. More than 1/3 of the circumference in the EGJ can be retained after the tumor is removed. A longitudinal incision and transverse suture are used to reshape the structure of the cardia and restore the function of the physiological anti-reflux structure as much as possible. At present, based on the research results, our idea is feasible. Therefore, we believe that for GISTs in the EGJ in which the upper edge of the tumor is less than 2 cm from the Z-line or has invaded the Z-line <1/2 circumference, LLG can preserve the physiological anti-reflux function, effectively reducing the incidence of postoperative gastroesophageal reflux and improving the quality of life of patients after surgery.

The anatomy of the EGJ is complex, it is difficult to expose and free the anatomical structure during laparoscopic surgery, and there is a risk of tumor rupture. Therefore, surgeons with extensive laparoscopic experience and skills are recommended to operate, and adequate preoperative evaluations should be performed to reduce the risks and enhance the safety of the operation. Sakamoto et al. (25) found that WR combined with endoscopy for GISTs in the EGJ can improve the safety of the operation. Intraoperative endoscopy plays an increasingly important role in the laparoscopic resection of GISTs, especially GISTs in the EGJ. Endoscopy can not only help to confirm that sufficient surgical margins have been achieved and that the tumor resection is complete but can also check the sutures for stenosis and fistula formation during the operation. Therefore, many scholars consider laparoscopic combined endoscopic surgery essential (26, 27). In our study, WR often used a 36F thick gastric tube to support the cardiac structure, which effectively simulated and evaluated the cardia caliber after resection with a linear closer approach to avoid stenosis of the cardiac opening. For RASW, we used intraoperative endoscopy to evaluate the anastomosis. These two methods provide a safe and effective strategy, contributing to the safety of the operation.

Conclusion

Overall, it is safe, effective, and feasible to perform LLG for mesenchymal tumors in the EGJ in which the upper edge of the tumor is less than 2 cm from the Z-line or has invaded the Z-line <1/2 circumference. The choice of surgery is based on the relationship between the tumor and the position of the cardia. In the future, it may become the preferred surgical method for mesenchymal tumors in the EGJ. However, the number of cases in this study is small at present. The postoperative follow-up time is still short. In the future, prospective control studies with large samples are needed to evaluate the effectiveness of this procedure further.

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 Friendship Hospital, Capital Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: JY and JZ. Data curation: HZ and XL. Formal analysis: HZ and XL. Funding acquisition: JY and JZ. Software: HZ. Methodology: JY and ZZ. Validation: JZ and ZZ. Supervision: JY and JZ. Writing—original draft: HZ and XL. Writing—review and editing: JY and JZ. 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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A comparative study of robotics and laparoscopic in minimally invasive pancreatoduodenectomy: A single-center experience

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Objective: To retrospectively compare the short-term benefits of robotic surgery and laparoscopic in the perioperative period of minimally invasive pancreatoduodenectomy (MIPD).

Methods: This retrospective analysis evaluated patients who underwent laparoscopic pancreatoduodenectomy (LPD) or robotic pancreatoduodenectomy (RPD) from March 2018 to January 2022 in the First Affiliated Hospital of Zhengzhou University (Zhengzhou, China). Perioperative data, including operating time, complications, morbidity and mortality, estimated blood loss (EBL), and postoperative length of stay, were analysed.

Result: A total of 190 cases of MIPD were included, of which 114 were LPD and 76 were RPD. There was no significant difference between the two groups in gender, age, previous history of upper abdominal operation, jaundice (>150 μmol/L), or diabetes ($P > 0.05$). The conversion rate to laparotomy was similar in the LPD and RPD groups (5.3% vs. 6.6%, $P = 0.969$). A total of 179 cases of minimally invasive pancreatoduodenectomy were successfully performed, including 108 cases of LPD and 71 cases of RPD. There were significant differences between the laparoscopic and robotic groups in operation time [mean, 5.97 h vs. 5.42 h, $P < 0.05$] and postoperative length of stay [mean, 15.3 vs. 14.6 day, $P < 0.05$]. No significant difference was observed between the two groups in terms of EBL, intraoperative transfusion, complication rate, mortality rate, or reoperation rate ($P > 0.05$). There were no significant differences in pathological type, number of lymph nodes harvested, or positive lymph node rate ($P > 0.05$).

Conclusion: RPD had an advantage compared to LPD in reduced operation time and postoperative length of stay, technical feasibility, and safety.

KEYWORDS

minimally invasive surgery, pancreatoduodenectomy, robotic surgery, laparoscopic surgery, surgical complication

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Introduction

In the near century since Whipple first reported pancreatoduodenectomy in 1938 (1), pancreatoduodenectomy has become a standard procedure for periampullary tumours. With the development of laparoscopic technology and internal closure devices and the wide application of energy instruments, minimally invasive pancreatectomy has gradually spread around the world. However, due to the particularity of pancreatic anatomy, the development of minimally invasive pancreatic surgery has not been as smooth as that of urologic, obstetric, gynaecologic, and gastrointestinal surgeries. Gagner first reported laparoscopic pancreatoduodenectomy (LPD) in 1994 (2), and many surgeons and centers have performed LPD. At present, due to the technical requirements and limitations of LPD, minimally invasive distal pancreatectomy (MIDP) has been more widely performed by pancreatic surgeons. Thus, MIDP provides valuable experience in minimally invasive pancreatectomy for the development of MIPD. Laparoscopic total pancreatectomy (LDP) and robotic total pancreatectomy (RDP) can reduce the length of the postoperative hospital stay, and the complication rate and mortality are also acceptable (3–5).

However, in some high-flow hospitals, the complication rate and mortality of LPD can reach the same level as those of open pancreatoduodenectomy (OPD), and LPD can even have some advantages in reducing estimated blood loss and length of postoperative hospital stay (6–9). However, due to the limitations of the equipment, laparoscopic instruments have limited mobility in the cavity, which affects the operation, especially in the digestive tract reconstruction stage. Thanks to the invention of robotic surgery systems, Italian surgeon Giulianotti took the lead in applying robotic surgery to robotic pancreatoduodenectomy (RPD) in 2003 (10). The robotic system has a more flexible arm, a clearer surgical field of view, and three-dimensional visualization and aids in the elimination of tremors. Therefore, the surgeon can control the instrument more finely and flexibly (11). Compared with laparotomy, RPD has achieved similar results to LPD, such as more precise operation during surgery, no difference in perioperative complications, and shorter hospital stays (12–15). Although minimally invasive pancreatoduodenectomy has developed rapidly, there are few comparative studies on laparoscopic and robotic pancreatoduodenectomy and fewer experiences in a single center, mainly because hospitals that have conducted both methods are rare. As a hospital performing both LPD and RPD, we aimed to analyse the advantages and disadvantages of laparoscopic and robotic pancreatoduodenectomy in the perioperative period through a retrospective study.

Materials and methods

General data

The following inclusion criteria were used: (1) MIPD for periampullary benign or malignant tumours; (2) no distant metastasis; (3) no invasion of the common hepatic or superior mesenteric arteries, other organs in the abdominal cavity, or the abdominal aorta, inferior vena cava, and other large vessels; and (4) adequate general medical conditions for general anaesthesia with pneumoperitoneum. The following exclusion criteria were used: (1) inability to tolerate long-term pneumoperitoneum and anaesthesia; (2) distant metastasis; (3) invasion of the artery and other abdominal organs; (4) operations performed by other doctors; (5) neoadjuvant therapy; and (6) tumour size too large to conduct MIPD according to the surgeons' experience. After doctors informed the patients of the advantages and disadvantages of LPD and RPD, the surgical procedure was selected according to the wishes of the patients. All patients signed informed consent forms before the operation. The chief surgeon performing robotic surgery was Professor Wenlong Zhai, and the assistant was either Ke Zong, Jianwen Ye, or Wentao Liu. Laparoscopic surgery was performed by Professor Wenlong Zhai or Professor Kunlun Chen, and the assistant was one of the above doctors chosen at random. The two surgical methods were started during almost the same period. We reviewed preoperative data, such as gender, age, previous history of upper abdominal operation, jaundice (last laboratory results before operation, total bilirubin >150 μmol/l), and diabetes. We reviewed all eligible case data from March 2018, when the hospital started performing minimally invasive pancreatoduodenectomies, to January 2022. A total of 190 MIPD cases were included. There were 113 men and 77 women, with a mean age of 58.1 ± 1.5 (21-82) years. There were 114 cases in the laparoscopic group and 76 cases in the robotic group. This study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and approved by the Institutional Review Board.

Method of operation

Robotic pancreatoduodenectomy

The patient was placed in a supine 30° reverse Trendelenburg position with their legs apart and a slight right-side tilt (approximately 10°). The surgeons performed all robot-assisted surgeries with the Da Vinci Si Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). Following standard procedure, we used a pneumoperitoneum needle to establish pneumoperitoneum at 12–15 mmHg under the left costal arch, which is a safer site to avoid secondary damage. Then, a 12-mm trocar (view port) was successfully placed in the subumbilical (2–3 mm) site for pneumoperitoneum imaging and laparoscopy. The needle was removed, and the pneumoperitoneum tube was attached to the view port. After laparoscopic exploration, RA3 (robot arm 3), RA2 (robot arm 2), and RA1 (robot arm 1) trocars were placed in the right axillary midline, clavicular midline, and left clavicular midline, respectively. A 12-mm assistant trocar was placed between the view port and the RA1 trocar. A camera was placed in the view port. The assistant 12-mm trocar was used by the assistant surgeon to pass the needles and manage the suction irrigator and endostapler (Figure 1).

The gastrocolic ligament was opened for preliminary exploration of the pancreas, usually with electric scissors. The superior mesenteric vein (SMV) was found along the inferior margin of the pancreas, and the Henle's trunk was ligated and cut off. The surgeon performed an extended Kocher manoeuvre to mobilize the transverse duodenum from the ligament of Treitz beneath the SMV. The common hepatic artery lymph nodes were dissected, and the right gastric artery and gastroduodenal artery were ligated at an appropriate length. Then, the small intestine, stomach, pancreas, and bile duct were cut off (Figure 2A, B). Complete resection of the uncinate process of the pancreas with electric scissors was performed (Figure 2C). The distant small intestine was moved to the right region through the original duodenal aperture to reconstruct the digestive tract by pancreatojejunostomy anastomosis (Figure 2D), hepaticojejunostomy anastomosis, and gastrojejunostomy anastomosis in order. A 5-cm curved periumbilical incision was made to remove the specimen, and the robotic system was removed.

Laparoscopic pancreatoduodenectomy

The patient position was the same as that for RPD. A 12-mm trocar was placed in the subumbilical (1 cm) site for pneumoperitoneum imaging and laparoscopy. The scope was inserted to explore the abdominal cavity to exclude distant metastasis, and a V-shaped trocar arrangement was placed (Figure 3). LPD was performed with an ultrasonic scalpel, and the remaining operations were the same as those for RPD (Figure 4).

Perioperative observation and complication standard

The number of conversions was counted in both groups. The intraoperative and postoperative data of the patients who were not converted to laparotomy were recorded, and the pathological data of all cases were reviewed. Postoperative pancreatic fistula (PF) (16), delayed gastroparesis (DGE) (17), and haemorrhage (PPH) (18) were defined according to the International Research Group on Pancreatic Surgery (ISGPS) criteria.

Statistical methods

The statistical software SPSS 19.0 was used for statistical analysis. Normality tests and homogeneity tests of variance were carried out for the data indicators of the study, and mean ± SD

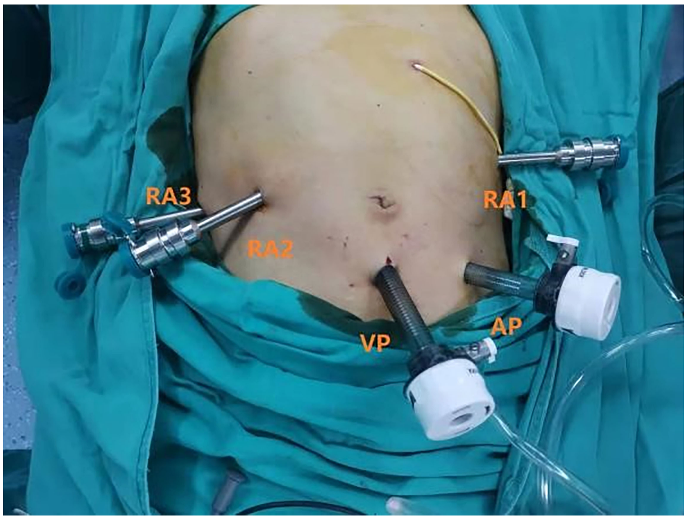

FIGURE 1
Robotic ports placement.

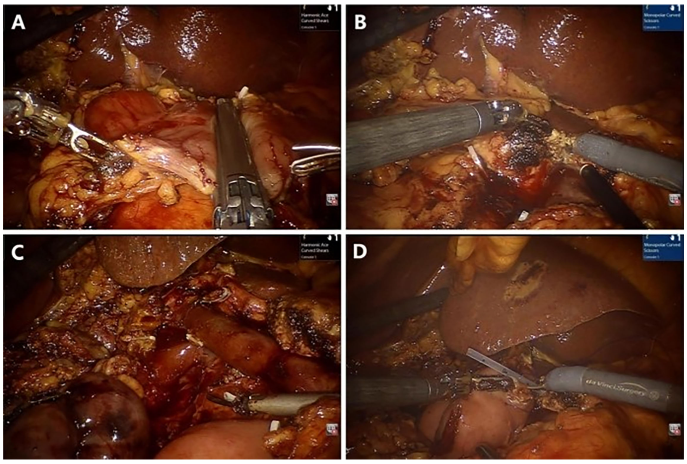

FIGURE 2
Representative photographs of the RPD: **(A)** Transection of the stomach. **(B)** Transection of the pancreas. **(C)** Complete resection. **(D)** Pancreaticojejunostomy anastomosis.

was used to describe the normally distributed continuous variables. The differences between the two groups of normally distributed data were compared by independent sample *t* tests. Qualitative data were used to calculate the composition ratio and rate, and the χ^2 test or Fisher's exact probability test was used to compare the differences between groups. Differences at $P<0.05$ were considered statistically significant.

Results

Preoperative general data and number of conversions

A total of 190 patients underwent minimally invasive pancreatoduodenectomy, including 116 in the laparoscopy

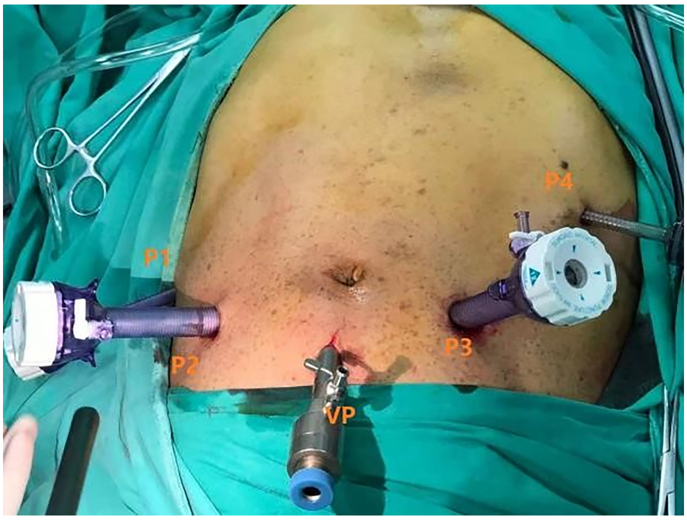

FIGURE 3
Laparoscopic port placement.

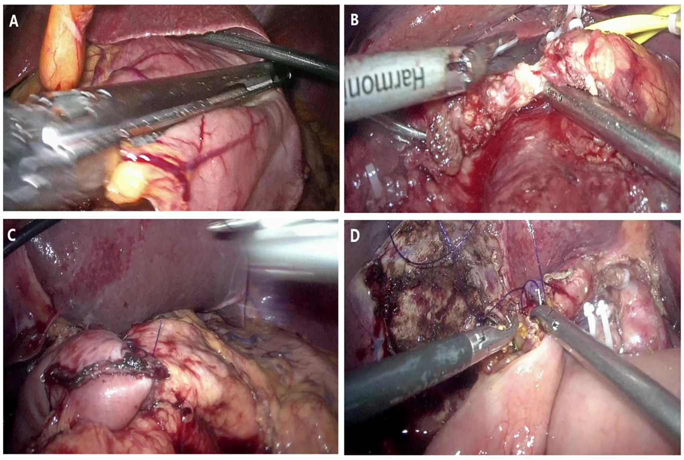

FIGURE 4
Representative photographs of the LPD: **(A)** Transection of stomach. **(B)** Transection of pancreas. **(C)** Pancreaticojejunostomy anastomosis. **(D)** Hepaticojejunostomy anastomosis.

group and 76 in the robot group. There was no significant difference between the two groups in gender, age, number of patients with upper abdominal surgical history, number of patients with preoperative bilirubin greater than 150 μmol/l, or number of patients with diabetes (Table 1).

There were six cases (5.3%) in the laparoscopic group and five cases (6.6%) in the robot group that were converted to laparotomy. There was no significant difference between them (P = 0.969) (Table 1). Therefore, a total of 179 cases successfully completed minimally invasive surgery.

Perioperative results without conversion

Among the 179 patients who successfully completed minimally invasive surgery, 108 underwent LPD and 71 underwent RPD. There was no significant difference in EBL or blood transfusion during the operation between the two groups. The operation time of RPD was significantly shorter than that of LPD (5.42 ± 0.12 vs. 5.97 ± 0.14 h, P = 0.023) (Table 2). In terms of postoperative complications, there was no significant difference in the incidence of pancreatic fistula, bile leakage, delayed gastric emptying, gastrointestinal bleeding, or abdominal bleeding. There was one case of reoperation in the laparoscopic group and one case in the robotic group, with no significant difference; there were no deaths within 30 days in either group. The postoperative hospital stay in the LPD group (15.3 ± 0.8 days) was longer than that in the RPD group (14.6 ± 1.1 days), and the difference was statistically significant (P = 0.034) (Table 2).

Pathological results without conversion

In the robotic group, the proportion of pancreatic lesions was lower and bile duct lesions was higher, but the difference was not significant compared with LPD (P = 0.098). Moreover, subgroup analysis showed that in the three groups, there was no significant difference in the

TABLE 1 General data and conversion of preoperation.

	LPD (n = 114)	RPD (n = 76)	*P*-value
Gender, M/F	77/37	36/40	0.513
Age, mean ± SD (range), years	58.1 ± 1.4 (21~82)	58.2 ± 1.7 (31~74)	0.916
Previous history of upper abdominal operation	5 (4.4%)	6 (8.5%)	0.591
Jaundice	17 (14.9%)	7 (9.2%)	0.205
Diabetes	20 (17.5%)	8 (13.8%)	0.865
Conversion	6 (5.3%)	5 (6.6%)	0.969

Jaundice: last laboratory results before operation total bilirubin >150 μmol/l. Results are presented as number (%), unless otherwise indicated.

TABLE 2 Perioperative results without conversion.

	LPD (n = 108)	RPD (n = 71)	*P*-value
Operation time, mean ± SD (range), h	5.97 ± 0.14 (4.0~8.5)	5.42 ± 0.12 (3.3~7.0)	0.023
Estimate blood loss, mean ± SD (range), mL	378.5 ± 37.1 (100~1,600)	309.0 ± 32.7 (50~1,000)	0.265
Intraoperative blood transfusion	21 (18.5%)	9 (12.7%)	0.345
Pancreatic fistula			
Biochemical leak	23 (21.3%)	16 (22.5%)	0.680
B	15 (13.9%)	5 (7.0%)	0.220
C	2 (1.9%)	3 (4.2%)	1
Bile leakage	14 (13.0%)	4 (5.6%)	0.313
Delayed gastric empty	12 (11.1%)	8 (11.3%)	1
Gastrointestinal bleeding	7 (6.5%)	2 (2.8%)	0.255
Abdominal bleeding	2 (1.9%)	1 (1.4%)	1
Reoperation	1 (0.9%)	1 (1.4%)	0.398
Mortality within 30 days	1 (0.9%)	0 (0%)	1
Postoperative hospital stay, mean ± SD (range), days	15.3 ± 0.8 (8~48)	14.6 ± 1.1 (7~40)	0.034

Results are presented as number (%), unless otherwise indicated.

pathological diagnosis of the lesions. The results of lymph node harvest and lymph node positive rate of the two surgical methods were similar. Although the robotic group harvested more lymph nodes, the difference was not statistically significant (Table 3).

Discussion

With the improvement of laparoscopic technology, the accumulation of experience, and the progress of laparoscopic equipment, laparoscopic surgery has developed rapidly and

TABLE 3 Pathological results without conversion.

		LPD (n = 108)	RPD (n = 71)	*P*-value
Pancreatic lesions		35 (32.4%)	19 (26.8%)	0.098
Duodenal and papillary lesions,		35 (32.4%)	23 (32.4%)	
Bile duct lesions		38 (35.2%)	29 (40.8%)	
Number of lymph nodes harvest, mean ± SD (range)		9.07 ± 0.6 (1~25)	9.97 ± 0.90 (3~24)	0.722
With positive lymph nodes		18 (16.7%)	11 (15.5%)	0.985
		Subgroup pathology		
		LPD	RPD	*P*-value
Pancreatic lesions		n = 35	n = 19	
	Malignant	22 (62.9%)	13 (68.4%)	1
	Benign	10 (28.6%)	5 (26.3%)	
	Pancreatitis	3 (8.6%)	1 (5.3%)	
Duodenal and papillary lesions,		n = 35	n = 23	
	Malignant	31 (88.6%)	21 (91.3%)	1
	Benign	3 (8.6%)	2 (8.7%)	
	Duodenal papillitis	1 (2.9%)	0	
Bile duct lesions		n = 38	n = 29	
	Malignant	34 (89.5%)	27 (93.1%)	1
	Benign	3 (7.9%)	2 (6.9%)	
	Cholangitis	1 (2.6%)	0	

Results are presented as number (%), unless otherwise indicated. Pancreatic lesions including benign and malignant tumours of the pancreas and chronic pancreatitis; bile duct lesions including benign and malignant tumours of the bile duct and cholangitis; duodenal and papillary lesions including benign duodenal malignancies, duodenal inflammation, malignant and benign duodenal papillary tumours, and papillitis.

become a routine surgical procedure in medical centers. However, compared with laparoscopic gastrointestinal and liver operations, LPD has not been widely performed. There may be several reasons for this: (1) the procedure of pancreatoduodenectomy is cumbersome; not only are many organs removed but also several digestive tract reconstructions are needed, the operation is complex, and the postoperative management is difficult; (2) the learning curve is long, and it is difficult for many surgeons to cross the technical gap of LPD; and (3) it is difficult to complete lymph node dissection, accurate dissociation, anastomotic reconstruction, and other operations under "chopstick-like operation" conditions and the two-dimensional laparoscopy field of view. To break through the limitations of LPD, Giulianotti et al. (10) reported robotic pancreatoduodenectomy for the first time in 2003. The improvement of the Da Vinci robotic surgery system is mainly reflected in the following three aspects: (1) the visual is a three-dimensional imaging and enlarged 10–15 times; (2) the robot arm is more flexible, and the tremor of the surgeon can be filtered; and (3) the hand–eye coordination of the operator accelerates the learning process. However, it also has some defects, such as a higher cost and a lack of direct force feedback.

At present, MIPD has been widely performed in many medical centers. Compared with traditional open surgery, LPD and RPD have certain advantages (6, 12–15, 19, 20). Croome et al. (6) included 108 cases of laparoscopy and 214 cases of laparotomy and showed that the laparoscopic group had complication rates similar to those of the laparotomy group, but the LPD group had a shorter postoperative hospital stay. In several studies comparing robotic surgery with open surgery, it was found that the blood transfusion rate during surgery and length of postoperative hospital stay were lower in the RPD group (12–14). The above articles also show that minimally invasive pancreatoduodenectomy and laparotomy can achieve similar results in terms of lymph node harvest and blood loss (6, 20). However, the comparison of perioperative results between RPD and LPD still needs further study. This study aims to evaluate the short-term benefits of the two surgical methods.

In this study, we conducted a retrospective comparison between LPD and RPD. The results showed that although robotic surgery had advantages in reducing intraoperative bleeding, the difference was not statistically significant compared with LPD (378.5 ± 37.1 vs. 309.0 ± 32.7 ml, $P > 0.05$), which was similar to the results of other studies (21–23). Compared with the LPD group, the operation time and length of hospitalization were significantly shorter in the RPD group (5.97 ± 0.14 vs. 5.42 ± 0.12 h, $P < 0.05$). Kim et al. (21) found that after propensity score matching analysis, the operation time and length of postoperative hospital stay of RPD were shorter than those of laparoscopy, with significant differences (411.6 vs. 452.6 min, P = 0.001; 14.6 vs. 11.9 days, P = 0.027). Similar results were obtained by Zhao et al. (24). The results of Park et al. (23) showed that the operation time of the RPD group was significantly shorter than that of the LPD group (400.40 vs. 352.15 *min*, P = 0.003), but the length of hospital stay was basically the same. Compared with laparoscopic surgery, the robotic system needs to be assembled before the operation, but the operation time of RPD is still significantly shorter than that of LPD, which indicates that the more flexible mechanical arms make knotting and suturing easier and thus shorten the operation time. The research of Gall et al. (25) also shows that the accuracy and efficacy of the robotic suture and knot are higher and better than LPD. The three-dimensional refined field of view and tremor elimination are more conducive to accurate dissection, reduced secondary damage, and accelerated digestive tract reconstruction, which make robotic operations more advantageous in complex surgery (24). The above conclusions were also verified in the results analysis of two randomized controlled trials (RCTs) of pancreaticoenterostomy and biliary anastomoses based on biological tissue models; that is, compared with 2D and 3D laparoscopy, robotic surgery is more efficient in anastomosis (26).

Regarding complications, there was no significant difference in all-grade pancreatic fistula, bile leakage, delayed gastric emptying, gastrointestinal bleeding, or abdominal bleeding between the two groups ($P > 0.05$). Among the more serious complications, no significant difference was found in secondary operation or 30-day mortality ($P > 0.05$). This is the same as the results of many studies (21, 24, 27, 28). The literature written by Korean surgeons (22) showed that the incidence of complications was similar after comparative analysis between LPD and RPD. Subgroup analysis showed that in patients with a soft pancreas and normal pancreatic duct, the postoperative pancreatic fistula rate was also basically the same, which may be related to their completion of 207 LPD operations, and the procedure was well developed. Another study aimed to analyse the difference between OPD and MIPD in patients with pancreatic duct dilatation and showed that patients with pancreatic duct diameters ≥3 mm can obtain more benefits from MIPD, which is associated with a lower incidence of postoperative complications and shorter hospital stays (29).

Several multicenter studies have reported that robotic surgery has more advantages in reducing conversion to laparotomy, which indicates that the robot's clear field of view and handheld operation are helpful to avoid conversion (15, 21, 30, 31). However, in our study, it was found that the difference between the two groups in conversion rate was very small and not statistically significant (six cases in LPD, 5.3% vs. five cases in RPD, 6.6%, $P > 0.05$), which was consistent with other reports (24). Thus, RPD could not significantly reduce the incidence of conversion to open surgery, which may be related to the small number of RPD cases included in our study. The main reasons that 11 cases were converted to open surgery were as follows: the portal vein invasion was too wide for resection and reconstruction under laparoscopy in pancreatic head cancer patients; the second was complicated with severe pancreatitis, and the pancreas was too hard to dissect. These are similar to other studies showing the reasons for conversion to open surgery (22, 28). A retrospective study of European multicenter showed that the risk factors for conversion from MIPD to laparotomy included laparoscopic surgery, large tumour diameter, old age, and pancreas/bile duct tumour. It was also observed that a center with medium flow (10–19 cases/year) has a higher risk of conversion than a center with high flow (more than 20 cases/year) (31). Certainly, there are many factors affecting the conversion; it is not only the patient but also the surgeon's technique. This question needs further study.

With the assembly of robotic surgical systems, the popularity of laparoscopic equipment, and the widespread use of surgical videos, an increasing number of surgeons and center are carrying out MIPD. Some studies have shown that the learning curve of RPD has advantages over LPD (25, 32, 33). Another meta-analysis indicated that there was no significant difference between robotic and laparoscopic pancreatoduodenectomy in the cases needed to pass the early stage of the learning curve; however, the results of subgroup analysis showed that the RPD learning curve of a single surgeon in a single center was shorter and the early period was easier to conquer (34). A recent network meta-analysis shows that center with high volume can enable patients to obtain better short-term results, that is, fewer complications and shorter postoperative hospital stays (35). This result indicate that those center that are about to perform MIPD or have already performed MIPD but with low flow need to seriously consider whether to continue this operation. From the authors' experiences, RPD is an easier operation and exhibits less physical consumption. It can significantly shorten the operation time and improve the operation efficiency in the early stage to speed up the recovery of patients. However, after LPD has passed the early stage, the operation time is similar to that of RPD; its unique large range of movement has its own advantages, especially when looking for a suitable section of small intestine during the reconstruction of the digestive tract. In general, laparoscopic and robotic surgery are two similar surgical methods. They have their own advantages in minimally invasive pancreatoduodenectomy. We can choose the appropriate surgical method according to the existing conditions, or the two surgical methods can help each other. We also consider that LPD can help surgeons familiarize themselves with RPD technology faster in our practice, but the specific evidence needs further study. Kim also has a similar view in his article (21). In addition, it needs to be specifically pointed out that the robotic surgery system allows the surgeon to be less tired after the surgery, which has been confirmed by relevant studies (25).

Although minimally invasive pancreatoduodenectomy has been basically developed in high-flow centers, the surgeon's pursuit of reducing the incision continues. Therefore, some hospitals are also conducting research on single-port minimally invasive pancreatoduodenectomy (SP-MIPD), but the literature is very limited (36–38), and more practice is needed to confirm the necessity and safety of this operation.

This study is a rare single-centers laparoscopic and robotic retrospective study. However, the study also has many shortcomings, such as a small sample size and a single centers. It is inevitable that some random factors will interfere, and there are still many problems to be solved. This study mainly observed the differences between LPD and RPD and may aid in the development of MIPD. We are looking forward to report the long-term results of MIPD in our future studies.

Data availability statement

The datasets presented in this article are not readily available because the datasets used and analysed during the current study are available from the corresponding author on reasonable request. Requests to access the datasets should be directed to WZ, fcczhaiwl@zzu.edu.cn.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of The First Affiliated Hospital of Zhengzhou University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KZ and KL conceived and designed the article. WZ and KC performed the operation. JY contributed to the data analysis. WL together with KZ contributed to the conception of the study and writing of the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved. 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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Laparoscopic intersphincteric resection vs. transanal total mesorectal excision in overweight patients with low rectal cancer

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Objective: Anus-preserving surgery in overweight patients with low rectal cancer has been a challenge due to the narrow operating space. Intersphincteric resection (ISR) was once a standard therapeutic option for low rectal cancer. The effectiveness of transanal total mesorectal excision (taTME) in treating this group of patients remains uncertain as a new surgical strategy. The aim of this study was to evaluate the short-term effects of taTME with ISR in overweight patients with low rectal cancer.
Methods: A total of 53 patients with low rectal cancer were treated with taTME in 31 cases and ISR in 22 cases. The surgery-related data, pathological manifestations of surgical specimens, postoperative recovery, and postoperative complications were compared.
Results: Patients in both groups completed the surgery successfully. There were no significant differences in operative time, blood loss, anastomotic distance from the anal verge and ileostomy between the two groups ($P > 0.05$). TaTME group performed or virtually finished resection of the rectal mesentery, and no positive cases of Circumferential Resection Margin (CRM) or Distal Resection Margin (DRM) were detected in either group. The number of lymph nodes found in surgical specimens did not change significantly between the two groups ($P = 0.391$). In the subgroup analysis, however, more lymph nodes were detected in female patients undergoing taTME than in male patients ($P = 0.028$). The ISR group took less time to remove the drainage tubes ($P = 0.013$) and the same results were obtained in both groups of male patients in the subgroup analysis ($P = 0.011$). There were no statistically significant differences in time to start liquid diet, time to remove catheters, time to start flatus, time to begin ambulation, postoperative hospital stay, and readmission within 30 days after surgery between the two groups ($P > 0.05$). However, female patients in the taTME group were initiated ambulation earlier than males in the subgroup analysis ($P = 0.034$). The difference was insignificant in the occurrence of postoperative complications between the two groups ($P > 0.05$).
Conclusion: taTME is safe and feasible for the treatment of overweight patients with low rectal cancer.

KEYWORDS

low rectal cancer, TME, laparoscope, intersphincteric resection, transanal total mesorectal excision

Introduction

Colorectal cancer is the third most prevalent kind of malignancies (1). Low rectal malignancies account for 75% of all rectal cancers, which are often classified as the lower rectum within 5 cm of the anal verge (2). Although the treatment of low rectal cancer has evolved extensively in recent decades, surgery remains the key to its care. Total mesorectal excision (TME), proposed by Professor Heald in 1982, is the gold standard for the surgical treatment of rectal cancer (3). Anus-preserving surgery has emerged as the ideal surgical approach pursued assuring tumor removal while maximizing patient life.

Due to low location and restricted operating space, anal preservation for low rectal cancer has been problematic for surgeons. This is especially true for male, obese patients, and narrow pelvis patients (4, 5). Since Sylla (6) et al. reported transanal TME (taTME) in 2010, there has set off a boom in anal preservation surgery for low rectal cancer. TaTME was developed as an alternative technique for mid and low rectal cancer because it could better dissect the presacral plane and the rectoprostatic plane or the rectovaginal plane and better visualize the distal rectum (7). TaTME, due to its bottom-up surgical approach, distinguishes from the traditional surgical route and has a distinct role. Therefore, it has been suggested that taTME surgery may alleviate the surgical challenge encountered by obese, males, and large tumor sizes with low rectal cancer (8). However, there are no worldwide studies to back up this claim.

Laparoscopic-assisted inter sphincteric resection (ISR) is currently one of the most commonly used surgical procedures for the treatment of low rectal cancer in clinical practice. A prospective trial of P. Rouanet showed that the 10-year overall survival (OS) following ISR was 72.2%, and disease-free survival was 60.1% (9), confirming its safety and clinical efficacy.

The purpose of this study was to examine the short-term outcomes of taTME and ISR in the treatment of overweight combined with low rectal cancer, and other complex cases such as male patients, to provide guidance for the clinical treatment of such patients.

Materials and methods

This study was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (KLLY-2021-115). All patients signed the informed consent for the surgery. This study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki.

Patient selection

Retrospectively analyzed patients with low rectal cancer combined with BMI $\geq$ 25 kg/m^2 who underwent taTME or ISR at our hospital from January 2016 to March 2022. Inclusion criteria of patients: (a) rectal adenocarcinoma; (b) distance of the lower margin of the tumor from the anal verge $\leq$5 cm; (c) cT1-3N0-1MO tumors or downstaging to T1-3N0-1MO after neoadjuvant therapy; (d) resectable tumor on preoperative CT or MRI evaluation. Exclusion criteria: (a) combined with bleeding, bowel obstruction, and perforation requiring emergency surgery; (b) tumor with distant metastasis or a history of colorectal tumor; (c) tumor invading the external anal sphincter, anal levator muscle or involving adjacent organs; (d) American Society of Anesthesiologist Physical Status (ASA-PS) $\geq$ IV (**Figure 1**).

Surgical techniques

In taTME group, transanal and transabdominal were performed simultaneously by two groups of surgeons, while the patient in the transabdominal group was operated under the conventional five-hole approach in a lithotomy position. The inferior mesenteric artery root or superior rectal artery root was ligated or resected laparoscopically, and mesenteric lymph nodes were removed. The rectal mesentery was released laparoscopically until it converged with the transanal group according to the TME principle. We will stretch the colonic ligation 15 cm distal to the sacral promontory without tension after the mesangial trimming is complete, If this cannot be achieved, the colon and splenic flexure must be mobilized. For the transanal group, after flushing the intestinal cavity with iodophor water, the intestinal cavity was closed with a purse string at least 1 cm below the tumor. If the tumor is very low and purse-string cannot be performed directly, we can first incise the rectum and free it upward for 1–2 cm before performing a purse-string suture. For patients with rectal cancer whose lower edge of the tumor is above the anorectal ring, the operator directly places a transanal manipulation platform and then completes the taTME operation. If the lower edge of the tumor is located near the anorectal ring, the internal sphincter can be incised first, and the pelvic cavity can be entered by direct visual freeing along the sphincter gap, and then the transanal manipulation platform can be placed when space enough. The rectum was separated from the bottom up until it connected to the transabdominal group before the proximal rectum and sigmoid colon were pulled out of the anus. The sigmoid mesentery and intestinal canal were dissected 12 cm from the proximal end of the tumor, following the specimen removed and a colon-anal canal manual or mechanic anastomosis performed. Depending on the intraoperative situation, the surgeon decided whether to perform further terminal ileostomy. The transanal operation is shown in **Figure 2**.

In the ISR group, the laparoscopic procedure was the same as taTME group. Depending on the distance between the lower

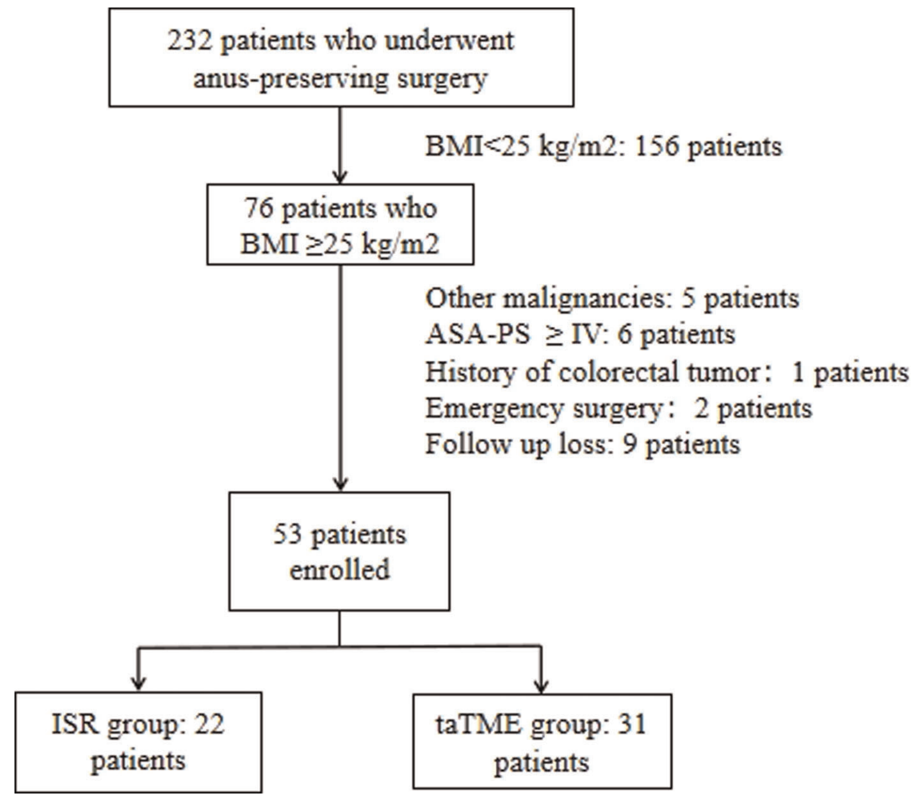

FIGURE 1
Algorithm for patient selection. Abbreviations: BMI, body mass index; ASA-PS, American Society of Anesthesiologist Physical Status.

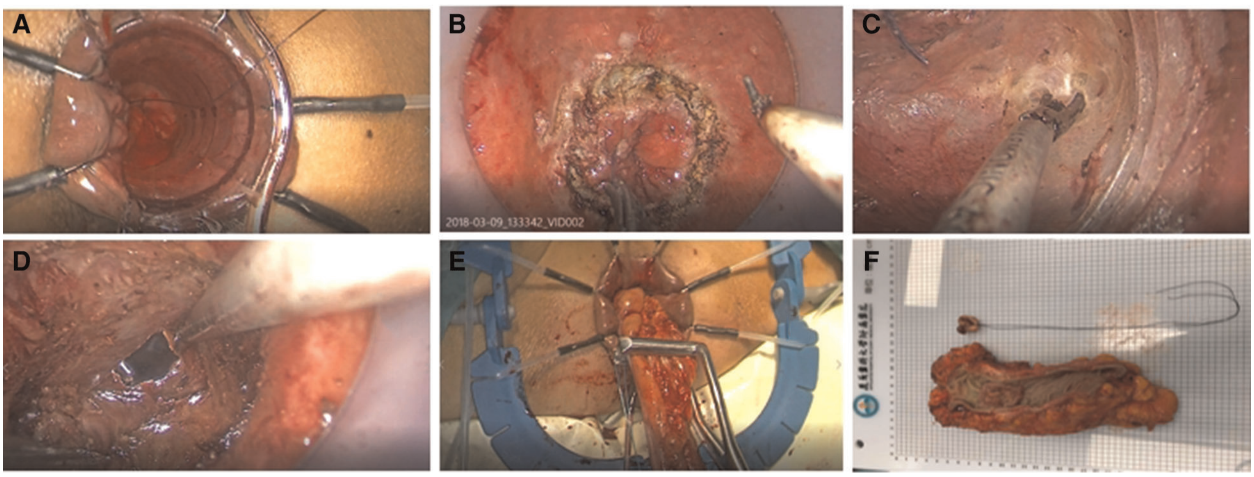

FIGURE 2
(A) Closure of intestinal cavity with purse-string suture (B) Layer-by-layer dissection of the entire rectum at a predetermined location (C) Bottom-up separation of the rectal mesentery (D) Convergence of the transanal and transabdominal groups (E) Extraction of the proximal intestine and disconnection of the proximal sigmoid colon (F) Pathological specimen.

edge of the tumor and the dentate line and the intersphincteric sulcus, the perineal operation was performed as partial ISR, subtotal ISR, or complete ISR, respectively. If the tumor was greater than 2 cm from the dentate line, laparoscopic closure of the rectum could be accomplished by laparoscopic excision of the specimen and removal of the mass through a small left lower abdominal incision. If the tumor was less than 2 cm from the dentate line, the rectum could be dissected through the anus in the intersphincteric sulcus under direct vision. The proximal rectum and sigmoid colon were dragged out *via* the anus, the mesentery was exposed, the sigmoid colon was severed, the specimen was removed, and the colon-anal tube was manually or mechanic anastomosis. According to the intraoperative situation, we decided whether to perform a terminal ileostomy. **Figure 3** shows the intraoperative view.

Observation indicators

The surgery-related data, pathological manifestations of surgical specimens, postoperative recovery, and postoperative complications were compared. Theoretically, women have a wider pelvis, which makes surgical manipulation easier. This has the potential to bias our results. Therefore, we compared the perioperative conditions of men and women in patients undergoing taTME.

Statistical methods

Statistical analysis was performed using SPSS 25.0. For quantitative data, they were presented as mean ± standard deviation (SD) if they conformed to a normal distribution and analyzed through two independent sample *t*-test methods; otherwise, as median (interquartile range) and analyzed through the Mann–Whitney *U* test. The categorical data were expressed as the number of patients (percentage) and analyzed using the chi-squared test ($\chi 2$) or Fisher's exact test. $P < 0.05$ was considered a statistically significant difference.

Results

Demographic characteristics

A total of 31 patients were included in the taTME group and 22 patients were included in the ISR group. The demographic characteristics of the patients are shown in **Table 1**. There were no significant variations in body mass index (BMI), gender, age, tumor size, ASA-PS of the patients, distance between tumor and anal verge and preoperative tumor T, N stages between the taTME group and the ISR group ($P > 0.05$).

Surgery-related and histopathological results

Patients in both groups successfully completed the operation with no intermediate openings or intraoperative complications. DRM and CRM were negative in the two groups. TaTME group had complete or near-complete resection of the rectal mesentery. The differences in operative time, intraoperative hemorrhage, anastomotic distance from the anus verg, ileostomy ratio, DRM distance and number of lymph nodes detected in the specimen were not statistically significant between the two groups (**Table 2**).

Short-term outcomes after surgery

Postoperative outcomes are shown in **Table 3**. The differences between the two groups regarding the time of starting the liquid diet, time of catheter removal, time of

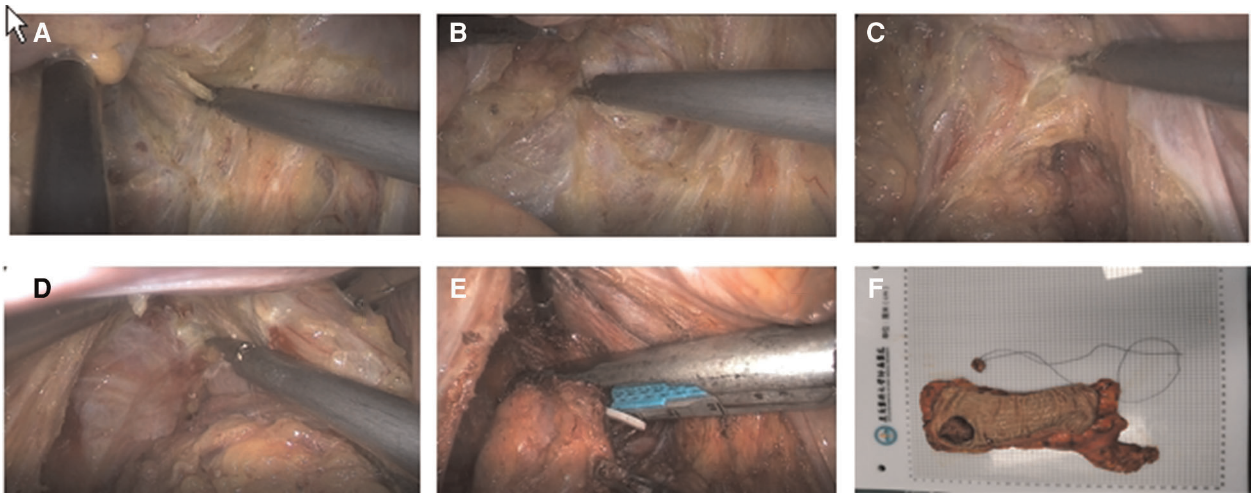

FIGURE 3
(A) Inferior ventral plexus (B) Separation of the rectal gap (C) Denonvilliers fascia (D) Puborectalis muscle and fissure of the anal levator muscle (E) Marking the lower edge of the tumor and dissecting the rectum (F) Pathological specimen.

TABLE 1 Patient characteristics.

Variables	ISR ($n = 22$)	taTME ($n = 31$)	p
Age (mean ± SD, years)	60 ± 10.79	55.1 ± 12.28	0.139
Sex (n,%)			0.219
Female	5 (22.7%)	12 (38.7%)	
Male	17 (77.3%)	19 (61.3%)	
BMI (mean ± SD, kg/m^2)	27.671 ± 1.443	27.310 ± 1.550	0.393
Tumor size (mean ± SD, cm)	3.818 ± 0.867	3.548 ± 0.810	0.251
Distance between tumor and anal verg [median (interquartile range), cm]	5 (1)	4 (1.6)	0.054
Neoadjuvant chemoradiation (n,%)	1 (4.5%)	2 (6.5%)	1
T stage (n,%)			0.465
T_{1-2}	12 (54.5%)	20 (64.5%)	
T_3	10 (45.5%)	11 (35.5%)	
N stage (n,%)			0.328
N_0	15 (68.2%)	17 (54.8%)	
N_1	7 (31.8%)	14 (45.2%)	
ASA-PS (n,%)			0.374
I-II	18 (81.8%)	29 (93.5%)	
III	4 (18.2%)	2 (6.5%)	

TABLE 2 Intraoperative and histopathological datas.

Variables	ISR ($n = 22$)	taTME ($n = 31$)	p
Operative time (mean ± SD, min)	206.091 ± 52.854	205.645 ± 58.217	0.977
intraoperative hemorrhage [median (interquartile range), ml]	20 (10)	20 (10)	0.953
Anastomotic distance from the anus verg (mean ± SD, cm)	2.273 ± 0.572	2.032 ± 0.741	0.208
Ileostomy (n,%)	10 (45.5%)	11 (35.5%0	0.465
DRM distance (mean ± SD, cm)	1.977 ± 0.587	1.739 ± 0.713	0.203
DRM involvement (n,%)	0 (%)	0 (%)	–
CRM involvement (n,%)	0 (%)	0 (%)	–
Lymph nodes detected (mean ± SD, n)	15.000 ± 1.543	14.613 ± 1.647	0.391

flatus, time of ambulation, time of postoperative hospital stay, and readmission or complications within 30 days after surgery were insignificant ($P > 0.05$), except for the patients in the ISR group who had earlier catheter drainage tubes ($P = 0.013$).

Perioperative comparison of male and female patients in taTME group

Female patients had more lymph nodes discovered in their specimens than male patients ($P = 0.028$), and female patients began to ambulate quicker than male patients ($P = 0.034$). There was no statistically significant difference in the remaining perioperative indicators between male and female patients in taTME group ($P > 0.05$) (Table 4).

TABLE 3 Postoperative short-term outcomes.

Variables	ISR ($n = 22$)	taTME ($n = 31$)	p
Starting liquid diet (mean ± SD, days)	4.591 ± 1.968	3.677 ± 1.661	0.074
Remove catheter (mean ± SD, days)	4.182 ± 1.680	5.161 ± 2.697	0.138
Remove drainage tubes (mean ± SD, days)	8.091 ± 2.136	10.387 ± 3.792	0.013
Flatus (mean ± SD, days)	3.046 ± 1.430	2.968 ± 1.169	0.829
Ambulation (mean ± SD, days)	6.136 ± 1.983	5.742 ± 1.570	0.423
Postoperative hospital stay (mean ± SD, days)	9.546 ± 2.385	8.742 ± 2.190	0.210
Readmission (n,%)	1 (4.5%)	2 (6.5%)	1
Postoperative complication (CD ≥ II) (n,%)	3 (13.6%)	7 (22.6%)	0.643
Anastomotic bleeding	0	0	
Urinary disturbance	1	1	
Pneumonia	1	1	
Intestinal necrosis	0	1	
Ileus	1	1	
Pelvic abscess	0	1	
Anastomotic leakage	0	1	
Acute cholecystitis	0	1	

CD, Clavien-Dindo classification.

Perioperative comparison between male patients in the ISR and taTME group

The drainage tubes were removed earlier in the ISR group's males ($P = 0.011$). There was no statistically significant difference in the remaining intraoperative and perioperative between the two groups of male patients ($P > 0.05$) (Table 5).

Discussion

It has been suggested that taTME surgery has potential benefits when applied to male, obese patients with low rectal cancer of large tumor size (8). The surgical safety of taTME in rectal cancer has been confirmed by many studies (10–13), but there are limited studies on its use in overweight patients, therefore it is not clear if there is a significant advantage of performing taTME in this group of patients.

There were no statistically significant differences between the two groups in terms of surgery-related and histopathological results, especially in terms of operative time,

TABLE 4 Comparison of male and female patients in taTME group.

Variables	Female of taTME (n = 12)	Male of taTME (n = 19)	p
Age (mean ± SD, years)	57.500 ± 11.033	53.579 ± 13.065	0.396
BMI (mean ± SD, kg/m^2)	27.369 ± 1.693	27.272 ± 1.500	0.868
Tumor size (mean ± SD, cm)	3.250 ± 0.989	3.737 ± 0.632	0.104
Distance between tumor and anal verg (mean ± SD, cm)	3.742 ± 1.014	4.237 ± 0.752	0.130
Operative time (mean ± SD, min)	196.250 ± 49.995	211.579 ± 63.445	0.485
intraoperative hemorrhage (mean ± SD, ml)	16.667 ± 4.924	23.684 ± 14.985	0.129
Anastomotic distance from the anus verg (mean ± SD, cm)	1.917 ± 0.793	2.105 ± 0.714	0.499
Ileostomy (n,%)	6 (50%)	5 (26.3%)	0.179
DRM distance (mean ± SD, cm)	1.5 (0.88)	2 (0.80)	0.256
lymph nodes detected (mean ± SD, n)	15.417 ± 0.452	14.105 ± 0.350	0.028
Starting liquid diet (mean ± SD, days)	3.000 ± 0.853	3.895 ± 1.792	0.118
Remove catheter (mean ± SD, days)	5.917 ± 2.678	4.684 ± 2.668	0.221
Remove drainage tubes (mean ± SD, days)	10.000 ± 3.790	10.632 ± 3.876	0.659
Flatus (mean ± SD, days)	3.000 ± 1.279	2.947 ± 1.129	0.905
Ambulation (mean ± SD, days)	5.000 ± 1.044	6.211 ± 1.686	0.034
Postoperative hospital stay (mean ± SD, days)	7.917 ± 2.065	9.263 ± 2.156	0.096
Postoperative complication (CD ≥ II) (n,%)	1 (8.3%)	6 (31.6%)	0.201

CD, Clavien-Dindo classification.

TABLE 5 Comparison between male patients in the ISR and taTME group.

Variables	ISR (n = 17)	taTME (n = 19)	p
Age (mean ± SD, years)	60.294 ± 9.726	53.579 ± 13.065	0.092
BMI (mean ± SD, kg/m^2)	27.484 ± 1.185	27.272 ± 1.500	0.644
Tumor size (mean ± SD, cm)	3.941 ± 0.933	3.737 ± 0.632	0.443
Distance between tumor and anal verg (mean ± SD, cm)	4.529 ± 0.624	4.237 ± 0.752	0.216
Operative time (mean ± SD, min)	221.118 ± 46.720	211.579 ± 63.445	0.614
intraoperative hemorrhage (mean ± SD, ml)	21.765 ± 14.256	23.684 ± 14.985	0.697
Anastomotic distance from the anus verg (mean ± SD, cm)	2.353 ± 0.493	2.105 ± 0.714	0.242
Ileostomy (n,%)	9 (52.9%)	5 (26.3%)	0.102
DRM distance (mean ± SD, cm)	1.941 ± 0.609	1.847 ± 0.164	0.676
lymph nodes detected (mean ± SD, n)	14.824 ± 1.629	14.105 ± 1.524	0.181
Starting liquid diet (mean ± SD, days)	4.118 ± 1.833	3.895 ± 1.792	0.715
Remove catheter (mean ± SD, days)	4.294 ± 2.668	4.684 ± 2.668	0.600
Remove drainage tubes (mean ± SD, days)	7.824 ± 1.944	10.632 ± 3.876	0.011
Flatus (mean ± SD, days)	3.059 ± 1.478	2.947 ± 1.129	0.800
Ambulation (mean ± SD, days)	6.059 ± 1.749	6.211 ± 1.686	0.793
Postoperative hospital stay (mean ± SD, days)	9.118 ± 2.342	9.263 ± 2.156	0.847
Postoperative complication (CD ≥ II) (n,%)	3 (17.6%)	6 (31.6%)	0.451

CD, Clavien-Dindo classification.

intraoperative bleeding and number of lymph nodes detected. Shorter operative time and less intraoperative bleeding may facilitate the patient's postoperative recovery. Some studies have concluded that taTME surgery is faster than transabdominal laparoscopic TME (LapTME) in terms of operative time (14, 15). Theoretically, taTME is performed simultaneously transabdominally and transanally, through a reverse path, from the outside to the inside, and thus should be more rapid in resolving the stenotic space compared to ISR. However, the present study did not confirm this idea. The reasons considered are as follows: (a) Patients with low rectal cancer combined with BMI > 25 kg/m^2 were selected, in which both surgical approaches face challenges, therefore the differences were not reflected; (b) Both groups included female patients with wider pelvises than men, which reduce the difficulty of surgery and therefore may have an impact on the operative time; (c) Some patients undergoing taTME may be within the learning curve; (d) A lack of sufficient data. When the 2nd reason was considered, subgroup analysis was performed for both groups. However, there were no differences in operative time between male and female patients in the taTME group and in male patients between the ISR and taTME groups. Our study confirmed that taTME did not increase the time to surgery.

DRM and CRM are essential to ensure the quality of TME (16). The quality of surgical resection is strongly associated with the long-term prognosis of the tumor (17) and is recommended for new surgical interventions (18). Obtaining the best quality resection specimen is the most difficult task in the transabdominal approach, especially in obese men with narrow pelvis and large tumors (19, 20). A study based on postoperative magnetic resonance imaging of the pelvis found that residual rectal mesenteric tissue was detected in 3.1% of taTME patients and 46.9% of LapTME patients, suggesting that the integrity of rectal mesenteric resection in taTME patients is significantly better than standard laparoscopic techniques (21). Some studies have suggested that taTME surgery reduces the rate of positive CRM (14, 19, 22, 23), but a recent meta-analysis comparing taTME, ISR, and robotic TME procedures showed that taTME surgery had the worst CRM obtained among these three procedures (24). CRM is considered a more important oncologic indicator than DRM (25–27), and its positivity is considered a strong predictor of local recurrence after rectal cancer surgery (26). However, no positive DRM or CRM was found in this study. In terms of lymph node dissection, the two groups of patients were comparable. However, in subgroup analysis, the number of lymph nodes detected was significantly higher in female than in male in the taTME group. Females usually have wider pelvises than male, suggesting that the narrow space would make the surgical operation more difficult and could affect the quality of surgical resection specimens.

The ISR group had earlier removal of the drainage tubes than the taTME group, and the same results were observed in the subgroup analysis. The placement of postoperative abdominal drains after colorectal surgery can prevent complicated abdominal blood accumulation, reduce the incidence of anastomotic leakage, and facilitate earlier detection of abdominal bleeding, anastomotic leakage or other complications (28). However, it has been suggested that the placement of postoperative abdominal drains may prolong the hospital stay and increase the risk of surgical site infection (29). It took longer for patients in the TaTME group to remove the drainage tubes, which may be explained by the fact that this group was within the learning curve of 50 cases. The operators were less confident and considered it more reliable to leave the drainage tubes for a longer period of time.

Although the rate of postoperative complications was higher in the taTME group, the difference between the two groups were not significant. The complication rate after taTME in previous studies was in the range of 32%–35.7% (14, 15, 22, 30), and this study had lower complications. Urinary disturbance, pneumonia, and Ileus were each found in one case in both groups. Ileus was relieved by conservative treatment. Intestinal necrosis, anastomotic leak, pelvic abscess, and acute cholecystitis were each found in one case in the taTME group. The patient with intestinal necrosis recovered after reoperation and the necrosis was found intraoperatively to be the result of proximal intestinal torsion. Anastomotic leak is one of the most common postoperative complications of rectal cancer (31, 32). The patient with anastomotic leak was relieved by ileostomy. The patient with pelvic abscess was considered to be caused by infection or an undetected occult anastomotic leak, and the patient with acute cholecystitis was considered to be caused by eating a large number of fatty meals after surgery, all of which improved after conservative treatment.

This study still has some limitations: (a) This is a retrospective study and included a small number of cases, which will lead to a large study bias. (b) This study failed to investigate patients' postoperative anal function, long-term quality of life, tumor recurrence rate and patients' long-term survival rate, so the comparison of the advantages and disadvantages of the two surgical approaches was not adequate. Further results need randomized controlled trials (RCT) with more cases and longer follow-up are needed to evaluate the results present in this study.

Conclusion

Based on the above findings, taTME is safe and feasible in overweight patients with low rectal cancer. More studies with large samples and high quality are needed to confirm this result.

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 Biomedical Research Ethics Committee of the Affiliated Hospital of Zunyi Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conception and Methodology: ZL, QW, MX; Data collection and curation: ZL, QW, XW, FX; Writing - review and editing: ZL, MX, QF. All authors contributed to the article and approved the submitted version.

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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Predictive value of DCE-MRI and IVIM-DWI in osteosarcoma patients with neoadjuvant chemotherapy

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Objective: To investigate the predictive value of dynamic contrast enhanced MRI (DCE-MRI) and intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) for clinical outcomes of osteosarcoma patients with neoadjuvant chemotherapy.

Methods: The present prospective single-arm cohort study enrolled 163 patients of osteosarcoma during July 2017 to July 2022. All patients received the same treatment strategy of neoadjuvant chemotherapy. Both DCE-MRI and IVIM-DWI were conducted for the patients before the chemotherapy, as well as after one or two chemotherapy treatment cycles. The imaging parameters of contrast agent transfer rate between blood and tissue (K^{trans}), contrast agent back-flux rate constant (K_{ep}), extravascular extracellular fractional volume (V_e), as well as pure diffusion coefficient (*D* value), pseudo-diffusion coefficient (*D** value), apparent diffusion coefficient (*ADC*) and the perfusion fraction (*f* value) were recorded. RECIST standard [complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)] was used as the main clinical outcome.

Results: After two treatment cycles, 112 (68.71%) cases were with CR and PR, 31 (19.02%) cases were with SD and 20 cases (12.27%) were with PD. After 1~2 treatment cycles, patients with CR/PR showed significantly markedly lower K^{trans}, K_{ep}, V_e values, while higher *D*, *ADC* and *f* values compared with SD or PD patients. Alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) were positively correlated with values of K^{trans}, K_{ep}, and V_e, while negative correlation was observed between ALP and values of *D*, *ADC* and *f*, as well as between LDH and *D* and *ADC* after the whole treatment. *D* and K_{ep} values after two treatment cycles showed the best predictive value for diagnosis of PD. The values of K^{tran}, K_{ep}, *ADC* as well as ALP and LDH were all risk factors for PD after neoadjuvant chemotherapy.

Conclusion: DCE-MRI and IVIM-DWI have the potential to predict clinical outcomes of osteosarcoma patients with neoadjuvant chemotherapy.

KEYWORDS

osteosarcoma, DCE-MRI, IVIM-DWI, clinical outcomes, predictor

Introduction

According to a recent report, osteosarcoma accounts for about 2.4% tumors in children, with an incidence around 2~5 per million in all population worldwide (1–3). Generally, surgery combined with chemotherapy is the main treatment method for osteosarcoma patients (4, 5). For patients without metastasis, neoadjuvant chemotherapy, also known as preoperative chemotherapy, is usually used to decline the tumor size and adjust the patients' condition for further surgery (6, 7). It has been reported that neoadjuvant chemotherapy could also enhance the prognosis of osteosarcoma patients (8). Deng et al. found neoadjuvant chemotherapy could regulate the tumor immunologic microenvironment in osteosarcoma (9). Another study demonstrated that preoperative neoadjuvant chemotherapy improved overall survival rate and prolonged disease-free survival of osteosarcoma (10). During the treatment of neoadjuvant chemotherapy, the early prediction of clinical efficacy is of great significance (11, 12). Previous studies demonstrated the potential use of T1 or T2-weighted imaging (T1WI or T2WI) in magnetic resonance imaging (MRI) for predicting the response of neoadjuvant chemotherapy. It was found that T2-weighted fat-saturated and contrast-enhanced T1-weighted images could be used for differential diagnosis of osteosarcoma and Ewing sarcoma (13). Another study showed that chemotherapy response could be predicted by T2WI with AUC=0.70 by using MRI-based statistical texture analysis in osteosarcoma (14). In other cancer types, such as breast cancer, it was also found that T1WI might be associated with the chemotherapy response, in which baseline contrast and entropy values on the 1-, 2-, and 3-minute postgadolinium T1WI might be different in patients with different chemotherapy response (15, 16). However, to accurately predict the efficacy of neoadjuvant chemotherapy is still a clinical challenge.

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is a newly developed method for MRI, which shows well diagnostic value for many cancers, such as rectal cancer, gastric cancer and lung cancer (17–19). Except for DCE-MRI, intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI), which has the ability to separate pure diffusion movement and perfusion, shows better efficacy than the traditional MRI or apparent diffusion coefficient (ADC) map from DWI (20, 21). However, up to now, few studies focused on the predictive value of DCE-MRI and IVIM-DWI for clinical outcomes of osteosarcoma patients with neoadjuvant chemotherapy.

In the present study, we aimed to conduct a prospective single-arm cohort study to investigate the predictive value of DCE-MRI and IVIM-DWI for clinical outcomes of osteosarcoma patients with neoadjuvant chemotherapy. This study might provide more clinical evidence for application of DCE-MRI and IVIM-DWI in osteosarcoma patients.

Methods and materials

Patients and treatment

The present prospective single-arm cohort study enrolled 163 patients of osteosarcoma who came to our hospital during July 2017 to July 2022. The inclusion criteria were: 1) the diagnosis of osteosarcoma was all confirmed by histological analysis and patients were diagnosed as osteosarcoma for the first time; 2) all patients received neoadjuvant chemotherapy during the study period. The following patients were excluded: 1) patients who received chemotherapy, radiotherapy or targeting therapy before the study; 2) pregnant patients; 3) patients with distant metastasis. All patients meeting the inclusion criteria were consecutively recruit. The written informed consent was obtained from all patients. The present study was approved by the Ethical Committee of Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University.

All patients received the same treatment strategy of neoadjuvant chemotherapy with adriamycin (ADR) + cisplatin (DDP) + methotrexate (MTX) + ifosfamide (IFO) before the surgery. Each treatment cycle included ADR 60 mg/m^2 in two days, DDP 100 mg/m^2, MTX 8~12 g/m^2, and IFO 2 g/m^2 for 5 days. One treatment cycle lasted for 3 weeks. The chemotherapy stopped for 2 weeks after one cycle of treatment. The whole chemotherapy included two-treatment cycles in 10 weeks before the surgery.

Imaging measurement of DCE-MRI and IVIM-DWI

All patients received both DCE-MRI and IVIM-DWI before the chemotherapy, as well after one cycle and two cycles of the neoadjuvant chemotherapy. The conventional MRI was conducted using a 1.5-Tesla MRI scanner (Optima MR360, GE Healthcare) as described elsewhere (22).

For DCE-MRI, patients received 1) LAVA-T1WI (Flip Angle 2° and 15°, TR 3 ms, TE 1.3 ms, FOV 240 cm, layer thickness 3 mm and layer spacing 0.5 mm), 2) LAVA-T1WI dynamic enhanced scanning with 56 phases, 6 s/phase, 26 images in 5 min and 29 seconds (Flip Angle 15°, TR 3 ms, TE 1.3 ms, FOV 240 cm, layer thickness 3 mm and layer spacing 0.5 mm). After 18 s of LAVA-T1WI dynamic enhanced scanning, patients were injected with gadolinium diamine through elbow vein (0.1 mmol/kg, 2 ml/s), following with injection of 15 ml normal saline (2 ml/s). The data was analyzed using Cinetool package (GE Healthcare). The parameters of contrast agent transfer rate between blood and tissue (K^{trans}), contrast agent back-flux rate constant (K_{ep}), extravascular extracellular fractional volume (V_e) were recorded.

For IVIM-DWI, patients received single-shot echo-planar imaging (SE-DW-EPI) sequence for cross-sectional imaging with 13 *b* values (0, 10, 20, 30, 50, 80, 100, 150, 200, 400, 600, 800 and 1000 s/mm^2). The parameters were TR 4225 ms, TE 97 ms, FOV 240 cm, layer thickness 3 mm and layer spacing 0.5 mm. Analysis of IVIM-DWI was performed by using double exponential model DWI analysis software. The following parameters were recorded: pure diffusion coefficient (*D* value), pseudo-diffusion coefficient (D^* value), apparent diffusion coefficient (*ADC*) and the perfusion fraction (*f* value).

Main clinical outcomes and data collection

In the present study, we used RECIST standard to evaluate the treatment response as described elsewhere (23). Briefly, the treatment response was defined as: 1) complete response (CR), patients with complete resolution of the target lesions; 2) partial response (PR), patients with >30% decline of target tumor's diameter; 3) progressive disease (PD), patients with ≥20% elevation of target tumor's diameter; 4) stable disease (SD), the target tumor's diameter between PR and PD. Besides, histological response was defined as good (tumor necrosis rate ≥90%) or poor (tumor necrosis rate <90%).

Patients' clinical characteristics including age, sex, TNM stage, and clinical outcomes were recorded. Serum carcinoembryonic antigen (CEA) was evaluated by enzyme linked immunosorbent assay (ELISA) using commercial kit (Abcam) before and after the whole treatment. The serum levels of alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) were tested using corresponding kits purchased from Nanjing Jiancheng Bioengineering Institute, China.

Statistical analysis

The data distribution was analyzed by Kolmogorov-Smirnov method. The measurement data was expressed as mean ± SD for normally distributed data and median (range) was used for non-normally distributed data. Comparison for continuous data were analyzed by t test (paired or unpaired) or Mann-Whitney U test. Kruskal-Wallis test or One-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test was used for comparison among three or more groups. Chi square test was used for comparing rates. Spearman's analysis was used for correlation analysis. The ROC curve was used for evaluating the diagnostic value. Logistic regression was performed to analyze the risk factor of PD using a step back method. $p<0.05$ was defined as statistically different. All calculations were made by SPSS 18.0 and GraphPad 6.0.

Results

Basic clinical characteristics of all osteosarcoma patients

This study recruit 163 osteosarcoma patients. The basic clinical characteristics of all patients when admission was shown in Table 1. Among all patients, 69 (42.33%) cases were with TNM stage I, 53 (32.52%) cases were with TNM stage II, while 41 (25.15%) cases were with TNM stage III. After two cycles of the treatment, 112 (68.71%) cases were with CR and PR, 31 (19.02%) cases were with SD and 20 cases (12.27%) were with PD. Meanwhile, 52 (31.90%) cases showed good necrotic rate (≥90%). No statistical difference was found among patients with different clinical outcomes.

Dynamic alteration of imaging parameters for osteosarcoma patients with different clinical outcomes during treatment period

Then, the imaging parameters of *D*, D^*, *ADC* and *f* value of IVIM-DWI, as well as K^{trans}, K_{ep}, and V_e of DCE-MRI before, during and after treatment were analyzed in patients with different clinical outcomes (Figure 1). As shown in Figure 2, no statistical difference was found for all parameters before the study. For parameters of DCE-MRI, after 1~2 cycles of treatment, patients with CR/PR showed markedly lower K^{trans}, K_{ep}, V_e values compared with the SD and PD patients ($p<0.05$). Meanwhile, K^{trans} and K_{ep} values were significantly elevated in PD patients compared with the SD patients ($p<0.05$). For parameters of IVIM-DWI, after 1~2 cycles of treatment, patients with CR/PR showed significantly higher values of *D*, *ADC* and *f* values compared with SD or PD patients ($p<0.05$). However, the value of D^* was only remarkably lower in CR/PR patients than PD patients ($p<0.05$). All these results indicated that the alteration of imaging parameters was associated with the clinical outcomes of the osteosarcoma patients.

TABLE 1 Basic clinical characteristics of all patients.

Variables	All patients (n=163)	CR/PR (n=112)	SD (n=31)	PD (n=20)	p^a
Age (y)	27 (7~40)	25 (7~40)	28 (9~39)	31.5 (9~40)	0.099
Sex, male (%)	98 (60.12)	66 (58.93)	19 (61.29)	13 (65.00)	0.673
TNM stage, n (%)					0.917
I	69 (42.33)	48 (42.86)	13 (41.94)	8 (40.00)	
II	53 (32.52)	37 (33.04)	10 (32.26)	6 (30.00)	
III	41 (25.15)	27 (24.11)	8 (25.81)	6 (30.00)	
Site of tumor, n (%)					0.643
Femur	84 (51.53)	56 (50.00)	17 (54.84)	11 (55.00)	
Tibia/fibula	36 (22.09)	25 (22.32)	7 (22.58)	4 (20.00)	
Humerus	21 (12.88)	16 (14.29)	3 (9.68)	2 (10.00)	
Pelvis	12 (7.36)	9 (8.04)	2 (6.45)	1 (5.00)	
Head/neck	9 (5.52)	5 (3.07)	2 (6.45)	2 (10.00)	
Other	1 (0.61)	1 (0.89)	0 (0)	0 (0)	
Necrosis, n (%)					
Good (≥90%)	52 (31.90)	–	–	–	
Poor (<90%)	111 (68.10)	–	–	–	

[a]Comparison for continuous data were analyzed by Kruskal-Wallis test post hoc for comparison among three or more groups for non-normally distributed data (age). Rates were compared by Chi square test.

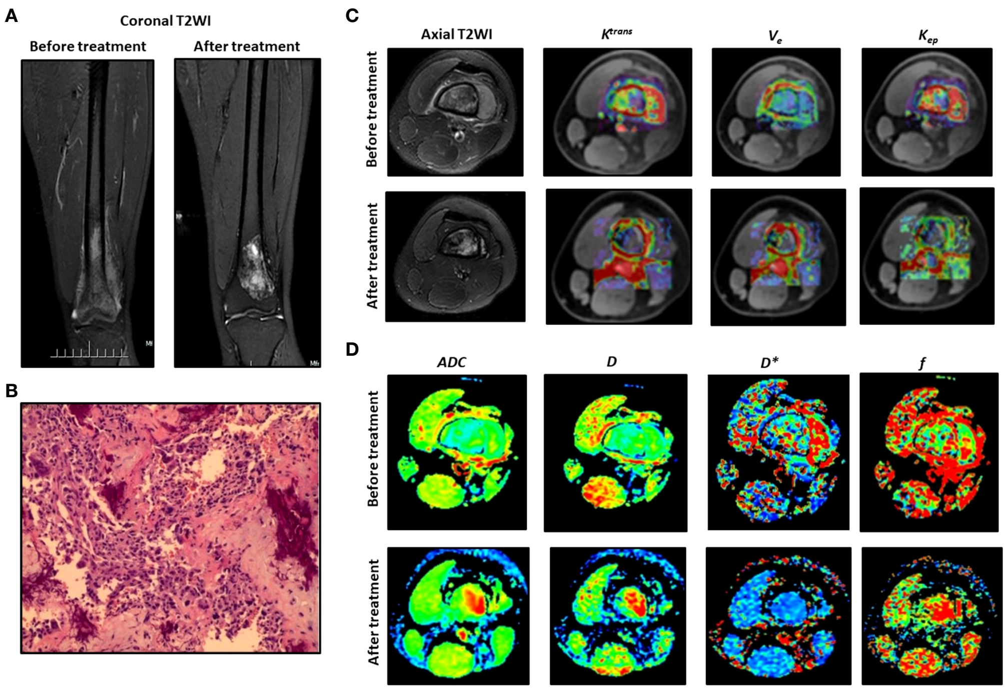

FIGURE 1
Typical DCE-MRI and IVIM-DWI images and the parameters for an 18-year-old male patient. **(A)** Coronal T2WI before and after treatment. **(B)** Histological analysis. **(C)** Axial T2WI and K^{trans}, K_{ep}, V_e. **(D)** Images for *D*, *D**, *ADC* and *f*.

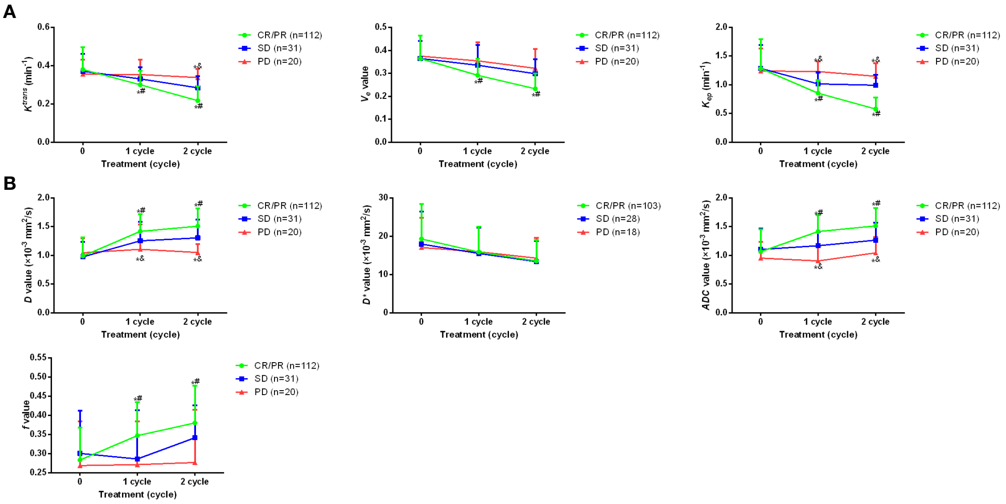

FIGURE 2
Dynamic alteration of imaging parameters for osteosarcoma patients with different clinical outcomes during treatment period. **(A)** K^{trans}, K_{ep}, and $V_e$of DCE-MRI before treatment as well as after 1~2 cycles of the treatment. **(B)** changes of *D*, *D**, *ADC* and *f* value of IVIM-DWI before treatment as well as after 1~2 cycles of the treatment. $^{*}p$ <0.05 vs PD, $^{\#}p$ <0.05 vs SD, $^{\&}p$ <0.05 vs CR/PR. Comparison for continuous data were analyzed by t test (paired or unpaired) or Mann-Whitney U test.

Association between imaging parameters and serum tumor biomarkers

To further investigate the clinical values of the changes of parameters, the correlation between parameters and serum tumor biomarkers CEA, ALP and LDH was investigated. It was found after 2 cycles of the treatment, both ALP and LDH showed remarkably lower levels in CR/PR and SD patients compared with the baseline (Figure 3). However, in PD patients, the changes of ALP and LDH showed no significant difference. Besides, CEA levels didn't alter significantly after treatment. Further Spearman's analysis showed that ALP and LDH were positively correlated with values of K^{trans}, K_{ep}, and V_e, while negative correlation was observed between ALP and values of *D*, *ADC* and *f*, as well as between LDH and *D* and *ADC* (all values after the whole treatment) (Table 2). Positive correlation was only found between CEA and *D* value for CEA.

Diagnostic value of imaging parameters for osteosarcoma patients with PD after neoadjuvant chemotherapy

Then, ROC curves were used for the diagnostic value of *D*, *D**, *ADC* and *f*, as well as K^{trans}, K_{ep}, and V_e after two cycles of the treatment for predicting PD. As shown in Figure 4, it was found that in DCE-MRI parameters, K_{ep} value after two treatment cycles showed the best sensitivity 70.00% and specificity 92.31% with AUC 0.911, and cutoff value of 1.035. In IVIM-DWI parameters, *D* value after two treatment cycles showed the best sensitivity 85.00% and specificity 81.12% with AUC 0.880, and cutoff value of 1.195.

Imaging parameters as a predictive and risk factor for PD of osteosarcoma

Binary logistic regression was then conducted for analysis of risk factor for PD of osteosarcoma after neoadjuvant chemotherapy. It was found that values of K^{trans}, K_{ep}, *ADC*, as well as ALP and LDH were all risk factors for PD after neoadjuvant chemotherapy (Table 3).

Discussion

Nowadays, neoadjuvant chemotherapy is widely applied before the surgery of cancer treatment, including osteosarcoma. However, it is still not easy to accurately predict the response to neoadjuvant chemotherapy. In our study, we demonstrated that both DCE-MRI and IVIM-DWI could predict the clinical outcomes of osteosarcoma patients after neoadjuvant chemotherapy.

Compared to the information that conventional T1WI or T2WI can provide, DCE-MRI can reflect microvascular distribution and blood perfusion in tumor tissues. In an early study, the authors compared the predictive value between non-enhanced MRI (T1WI and T2WI data) and DEC-MRI after neoadjuvant chemotherapy and found that DCE-MRI successfully predicted the chemotherapy response of 80% patients, while tumor volume measurements only

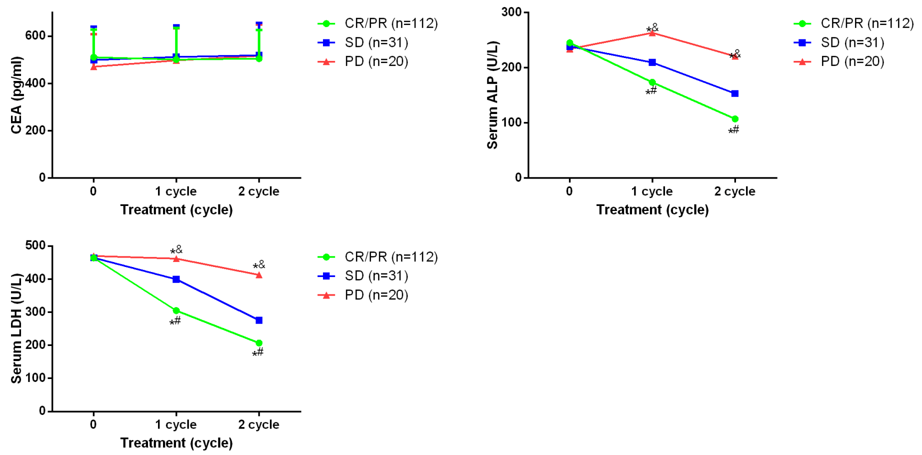

FIGURE 3
Serum levels of CEA, ALP and LDH in osteosarcoma patients before and after 2 cycles of the treatment. *p <0.05 vs PD, #p <0.05 vs SD, &p <0.05 vs CR/PR. Comparison for continuous data were analyzed by t test (paired or unpaired) or Mann-Whitney U test.

accurately predicted response of 60% patients (24). In another work, it was found that DEC-MRI could achieve significantly better diagnostic value (AUC 0.90, sensitivity 86% and specificity 93%) than conventional T2WI (AUC 0.76, sensitivity 86% and specificity 73%) for assessing response to neoadjuvant therapy in locally advanced rectal cancer (25). Currently, DCE-MRI has been used in diagnosis or prediction of many cancers. In a meta-analysis, it was found that DCE-MRI might have high sensitivity and specificity (pooled sensitivity of 0.80 and specificity 0.84) in prediction of pathological complete response after chemotherapy in breast cancer patients (26). In a recent study, Heethuis et al. found that DCE-MRI showed good predictive efficacy for complete response (with the best sensitivity of 90% and specificity of 62.9%) in esophageal cancer patients after neoadjuvant chemoradiotherapy (27). In another research, it was found that standardized index of shape (SIS) tool could be used for analyze the DEC-MRI results in advanced rectal cancer patients, which could predict non-responders after neoadjuvant chemoradiotherapy with a sensitivity of 95.9%, specificity of 84.7% and an accuracy of 91.8% (28). In 2021, Zeng et al. demonstrated that the parameters of slope, maximum signal intensity, time to peak, signal enhanced extent, washout rate, and enhancement rate in DEC-MRI had the potential to predict the response to neoadjuvant chemotherapy in osteosarcoma patients, with the best sensitivity of 83.3% and 92.3% (29). However, except for the above research, very few studies focused on application of DCE-MRI in osteosarcoma, especially for its predictive value after neoadjuvant chemoradiotherapy. In our research, we demonstrated that osteosarcoma patients with CR/PR showed markedly lower K^{trans}, K_{ep} and V_e values compared with the SD and PD patients, which were positively correlated with ALP and LDH. Besides, we also observed that K_{ep} value after two treatment cycles showed good predictive efficacy for PD in osteosarcoma patients.

TABLE 2 Spearman's analysis for imaging parameters and serum tumor biomarkers after the whole treatment.

Variables	CEA		ALP		LDH	
	Spearman's correlation	*p*	Spearman's correlation	*p*	Spearman's correlation	*p*
K^{trans}	0.145	0.065	0.280	<0.001	0.338	<0.001
K_{ep}	-0.014	0.862	0.365	<0.001	0.444	<0.001
V_e	0.107	0.175	0.228	<0.001	0.321	<0.001
D	0.156	0.047	-0.239	0.002	-0.268	0.001
*D**	0.074	0.351	-0.139	0.078	0.108	0.169
ADC	0.005	0.947	-0.203	0.009	-0.230	0.003
f	-0.137	0.080	-0.233	0.003	-0.124	0.115

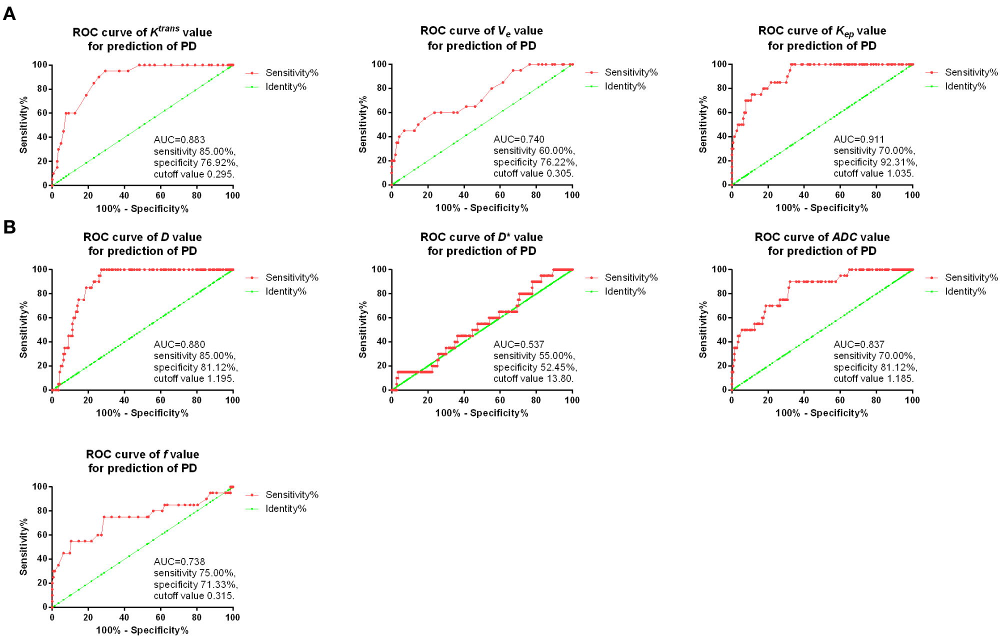

FIGURE 4
ROC curves of K^{trans}, K_{ep}, and V_e **(A)**, as well as *D*, *D**, *ADC* and *f* **(B)** in predicting PD.

Compared with other MRI methods such as diffusion-weighted MRI and DEC-MRI, DWI method gives information of water protons as endogenous contrast to assess diffusivity and tissue microstructure in tumor, while IVIM can obtain multiple quantitative parameters, which can noninvasively separate pure molecular diffusion and capillary microcirculation perfusion. Petrillo et al. demonstrated that DWI showed higher AUC (0.81) than conventional T2WI (0.76) for assessing response to neoadjuvant therapy in locally advanced rectal cancer (25). IVIM-DWI is also reported to be applied to diagnosis of several tumors. Zhang et al. reported in a retrospective study that *D* value of IVIM-DWI could be used for prediction of result of concurrent chemoradiotherapy, with AUCs of 0.987 and 0.984 for training and test groups, respectively (30). In an animal study, it was found that *ADC* values were remarkably higher in pancreatic cancer mice treated with gemcitabine (31).

TABLE 3 Binary logistic regression for analysis of risk factor for PD of osteosarcoma after neoadjuvant chemotherapy.

Variables	Wald	Odds ratio	95% CI	*p*
Age	0.016	0.994	0.908~1.089	0.901
Sex	0.304	1.630	0.287~9.237	0.581
TNM stage	0.151	0.785	0.231~2.665	0.698
Site of tumor	0.067	0.915	0.469~1.787	0.796
K^{trans} after treatment	8.356	1.341	1.099~1.636	0.004
K_{ep} after treatment	7.961	1.098	1.029~1.171	0.005
V_e after treatment	0.005	1.005	0.877~1.151	0.944
D after treatment	1.457	0.091	0.002~4.476	0.227
*D** after treatment	2.268	0.845	0.678~1.052	0.132
ADC after treatment	4.343	0.009	0.000~0.753	0.037
f after treatment	3.083	0.000	0.000~2.852	0.079
CEA after treatment	0.046	0.999	0.992~1.006	0.831
ALP after treatment	14.132	1.030	1.014~1.045	<0.001
LDH after treatment	16.434	1.023	1.012~1.034	<0.001

Besides, it was found DCE-MRI combined with IVIM-DWI could enhance the diagnostic efficacy of ductal carcinoma in situ, in which the AUCs of K_{trans}, K_{ep}, D and their combination were 0.936, 0.902, 0.860, and 0.976, respectively (32). However, up to now, no study reported IVIM-DWI in osteosarcoma after neoadjuvant chemotherapy. In our study, we observed that D, ADC and f values of IVIM-DWI were markedly higher in CR/PR patients compared with SD or PD patients, which were negatively correlated with ALP and LDH. Besides, we also found D value after two treatment cycles showed good predictive value for PD. In an early study, T2WI was found to be able to predict the chemotherapy response, with AUC=0.70 in osteosarcoma (14). In our research, we found that using K_{ep} value in DCE-MRI, the prediction of PD could achieve sensitivity 70.00% and specificity 92.31% with AUC 0.911, while D value of IVIM-DWI could also achieve the sensitivity 85.00% and specificity 81.12% with AUC 0.880 for prediction of PD, indicating that DCE-MRI and IVIM-DWI might be better than the conventional T2WI for chemotherapy response prediction.

However, we didn't observe apparent difference for DCE-MRI and IVIM-DWI for prediction of treatment efficacy after neoadjuvant chemotherapy in osteosarcoma patients. Additionally, we found that values of D, K^{trans} and K_{ep} were all risk factors for PD after neoadjuvant chemotherapy. All these results indicated that both DCE-MRI and IVIM-DWI could effectively predict the treatment efficacy of osteosarcoma patients after neoadjuvant chemotherapy.

Limitation

The study also has some limitations. First, the sample size is small and this is a single-center study. Secondly, the long-term clinical prognosis of the osteosarcoma patients is not clear and whether DCE-MRI and IVIM-DWI could also predict the patients' prognosis is not investigated.

Conclusion

In summary, we demonstrated that DCE-MRI and IVIM-DWI could be used to predict the clinical outcomes of osteosarcoma patients with neoadjuvant chemotherapy. The change of imaging parameters was associated with the clinical outcomes and both D and K_{ep} values after two treatment cycles showed potential predictive value for diagnosis of PD. This study could bring deeper insights for DCE-MRI and IVIM-DWI in prediction of clinical outcomes in osteosarcoma 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

The studies involving human participants were reviewed and approved by ethical committee of Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XX and LW conceived the idea of the study. FZ and JJL analyzed the data. QL interpreted the results. XX, LW, and QL wrote the paper. JL and XY discussed the results and revised 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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Transanal total mesorectal excision port-assisted perineal hernia repair: A case report

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Perineal hernia after abdominoperineal resection (APR) is a troublesome problem, and severe cases require surgical treatment. However, perineal hernia repair is challenging, especially when combined with intestinal adhesions. The difficulty of the operation lies in performing adhesiolysis and mesh placement under poor visibility. While there are traditional, laparoscopic and even robotic methods of performing this procedure, no easy and minimally-invasive approach has been reported. Here, we report the case of a patient with perineal hernia, who underwent transanal total mesorectal excision (TaTME) port-assisted laparoscopic perineal hernia repair. The operation was successful, the postoperative recovery was uneventful, the patient's symptoms improved significantly, and no recurrence was found during the 4-month follow-up. The availability and safety of TaTME port-assisted perineal hernia repair provide a promising approach for hernia repair. Compared with traditional perineal or laparoscopic abdominal approaches, this procedure is less invasive and results in a better field of vision.

KEYWORDS

perineal hernia, repair, TaTME, laparoscopy, APR

Background

Perineal hernia is a rare hernia, which typically occurs after abdominoperineal resection (APR) and pelvic exenteration (1). The reported incidence of perineal hernia varies widely from 0.2% to 27% (2, 3). Most patients with perineal hernia receive conservative treatment, but a few patients with obvious symptoms need surgical treatment. Pelvic floor hernia repair is challenging, especially when combined with intestinal adhesion. Typical approaches include the transperineal approach, transabdominal approach or abdominoperineal approach (4, 5). The advantage of the transabdominal approach is that the anatomical perspective conforms to the usual surgical habits and any tumor recurrence can be detected. However, when there is a stoma, the risk of mesh infection is high (6). The transperineal approach is less invasive and placement of the mesh is relatively safe because the surgical field is far away from the stoma. The disadvantage is that the visual field is poor, and if the adhesions are heavy, the operation is extremely difficult. Therefore, some patients need to undergo an abdominoperineal operation, but this method is traumatic and complicated. The recurrence and complication rate are reported to be high in both approaches, and unrelated to the choice of the repair approach (7).

One of the authors is a participant in the colorIII clinical trial and has some experience in the use of TaTME for rectal cancer (8). Combined with our own experience, our team explored a new method of perineal hernia repair, which involved using a TaTME port to release pelvic floor adhesions through a perineal approach, and then fixing mesh. In the present case, we successfully treated a perineal hernia after laparoscopic APR by employing a TaTME port-assisted perineal approach.

Case presentation

A 68-year-old woman with a history of hysterectomy underwent an APR operation for rectal cancer in 2021, and the pathological stage was T2N1M0. Four months later, she returned to our hospital with a complaint of bearing-down pain and bulging in the perineal region. In the knee–chest position, the size of the entire bulge was about 10 × 12 cm, which increased when holding breath and increasing abdominal pressure, whereupon the entire bulge became larger and a more obvious bulge of about 4 × 5 cm appeared in the upper part. The bulge could be partly reduced manually but not fully recovered, which suggested perineal hernia accompanied by intestinal adhesions (Figure 1). A contrast-enhanced CT scan confirmed the presence of a perineal hernia and ruled out cancer recurrence (Figure 2). Because the patient presented with obvious pain and a large bulge, surgery was necessary. However, the patient was diagnosed with thrombocytopenia, with a minimum platelet count of 30 × 10^9/L, so she was discharged and treated with oral drugs to raise the platelet count. Seven months later, the patient's platelet count had increased to 80 × 10^9/L. She was readmitted to hospital and underwent TaTME platform-assisted perineal hernia repair.

After successful general anesthesia, the patient was placed in the Trendelenburg position. The laparoscopy display screen was placed next to the patient's left shoulder. The chief surgeon was seated between the patient's legs and the assistant holding the laparoscope stood on the right side of the chief surgeon. A longitudinal incision of approximately 6 cm was made along the previous surgical scar, and the descending pelvic floor peritoneum could be seen after the skin and subcutaneous tissue were cut. After careful incision of the peritoneum and release of the adhesions below the incision under direct vision, a large gauze was placed into the pelvic cavity to block the small intestine.

Next, the TaTME port, which was equipped with four operating apertures and one observation aperture, was fixed *via* the wound (Figure 3). The carbon dioxide pneumoperitoneum pressure was set at 12 mmHg. A 30 oblique-viewing rigid endoscope was inserted into a 10 mm trocar. The remaining 12 mm trocar and two 5 mm trocars were used as operating apertures. When the pelvic cavity was observed under the laparoscope, multiple adhesions were found between the small

FIGURE 1
Image of the hernia preoperatively.

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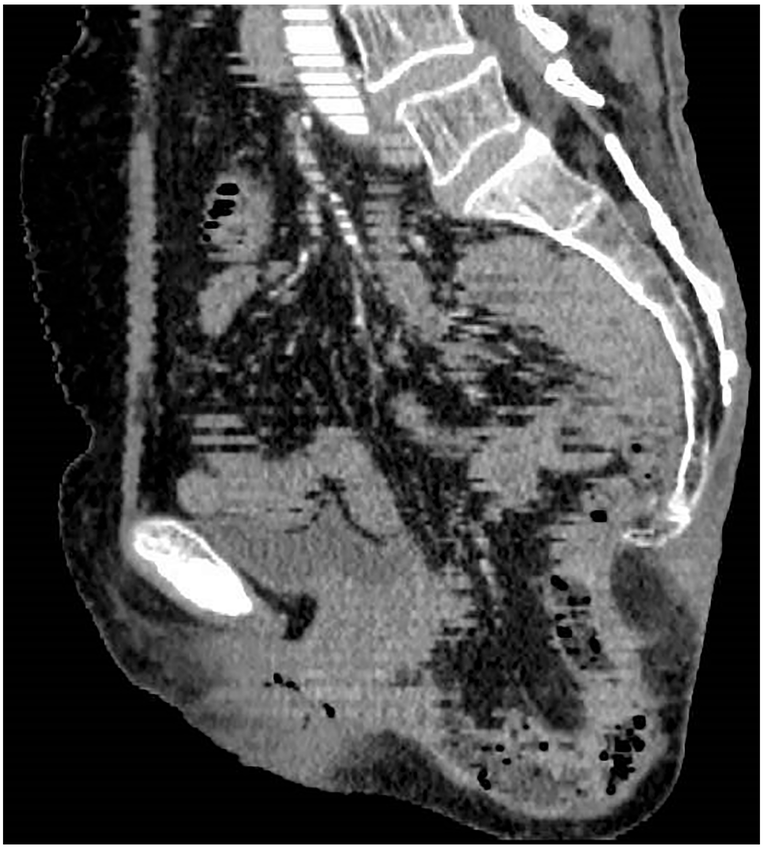

FIGURE 2
CT view of the hernia.

intestine, the mesentery and the pelvic peritoneum. Under laparoscopic view, the small intestine was pushed to the cephalic side as much as possible and the adhesions were released using a harmonic® scalpel (Ethicon Inc., Cincinnati, OH, USA) and an electrocoagulation hook (Figure 4).

Next, the TaTME port was removed, part of the pelvic floor peritoneum was trimmed, and the hernia sac was sutured intermittently with 2-0 absorbable sutures with a little tension. A thin polypropylene mesh (TiLENE Mesh 6000677, pfm medical AG, Cologne, Germany) was placed on the surface of the pelvic floor peritoneum and was fixed with a continuous suture using Prolene suture under direct vision. The back of the mesh was sutured to the anococcygeal ligament, the front was sutured to the posterior wall of the vagina, and both sides were sutured to the levator (Figure 5). The subcutaneous fat and skin were then sutured in turn. No complications occurred during or after the operation, and the patient was discharged on the seventh day after surgery. At the first follow-up examination 4 months postoperatively, the patient reported no obvious bulging and had experienced no symptoms (Figure 6). Meanwhile, CT revealed that although there were still bowels falling into the pelvis, the extent was significantly less than before (Figure 7). The timeline of this case is showed in Figure 8.

Discussion

APR is an important surgical procedure for radical resection of rectal cancer, which is suitable for patients with a tumor close to the anus with a late local stage. APR involves resection of the internal and external sphincter, mesorectum and surrounding tissue, and severing of the levator ani muscle. Due to the lack of pelvic floor tissue and inaccurate perineal suturing under limited vision, perineal hernias occur in some patients. Other than surgery, risk factors for perineal hernia include neoadjuvant radiotherapy, age, and female sex (9–11). Typical clinical manifestations of a perineal hernia may include a sensation of fullness in the perineum area, and perineal bulging and pain that may only become noticeable with the Valsalva maneuver. As with other abdominal wall hernias, complications may include intestinal obstruction and bowel strangulation and perforation. However, given that patients are typically minimally- or

FIGURE 3
The TaTME port, which was equipped with four operating trocars and one observation trocar.

asymptomatic, and the significant risks associated with perineal hernia repair such as mesh erosion, fistulization and chronic infection, as well as a high recurrence rate, the majority of cases are managed conservatively.

The approaches for perineal hernia repair include transperineal, abdominal and combined approaches, and surgical techniques include traditional open surgery and laparoscopic surgery (4, 12). Regardless of the approach and technique used, the procedures are

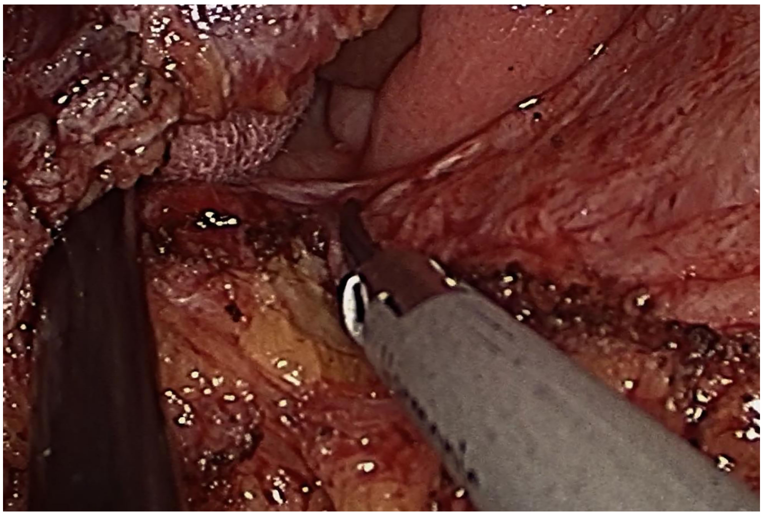

FIGURE 4
Adhesions were released using an ultrasonic knife and an electrocoagulation hook.

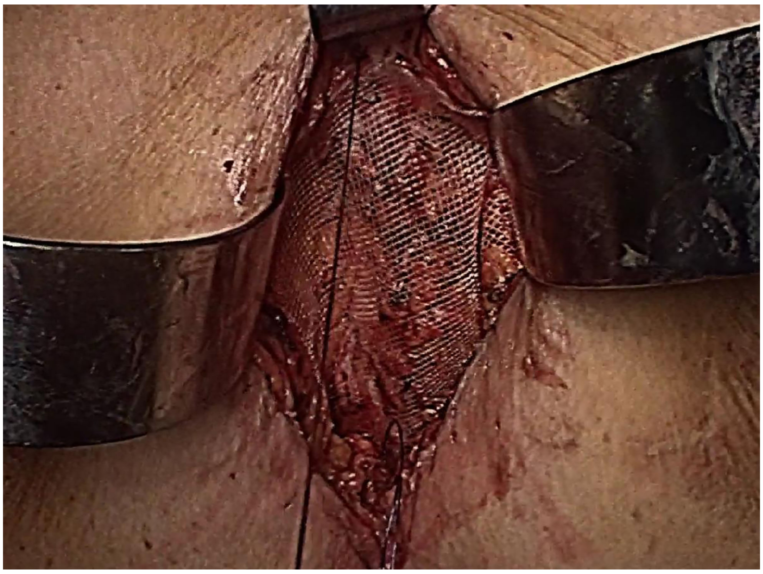

FIGURE 5
Placement of the mesh.

primary sutures, mesh placement, and muscle flap reconstruction (13). Compared with open surgery, laparoscopy can provide an adequate field of vision. More and more publications have reported the application of laparoscopy in perineal hernia repair. Thus the evidence supports a laparoscopic approach for perineal hernia repair, but it is difficult to release adhesions and suture mesh under laparoscopic view. Li et al. reported that robot-assisted laparoscopic surgery provides a good surgical visual field and precise operation, and improves the ease of suturing, mesh positioning, and access to hard-to-reach areas (14). However, considering the economic level of developing countries, robot-assisted laparoscopic surgery is unlikely to be widely adopted.

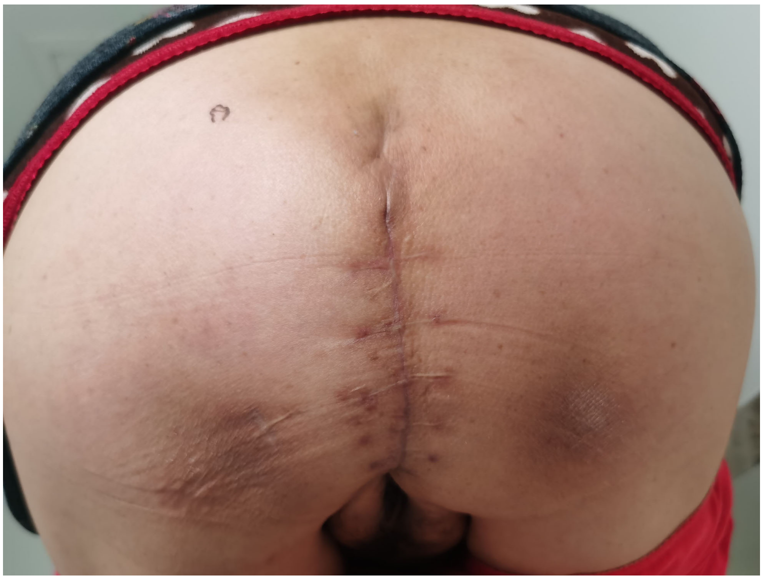

FIGURE 6
Image of the hernia postoperatively.

FIGURE 7
CT view of the hernia postoperatively.

In this case report we describe our use of TaTME platform-assisted laparoscopy for repair of a perineal hernia. This approach provided significantly improved visualization of the hernia and pelvic space, which facilitated transperineal adhesiolysis, as well as placement of mesh with wide overlap and suture fixation under direct visualization. In addition, we speculate that when the operation is difficult due to complicated adhesions, a combination of transperineal and transabdominal laparoscopy may also be used. Of course, this surgical approach also has some limitations. For example, similar to single-port laparoscopy, it is difficult for the surgeon to operate due to the lack of traction and exposure provided by an assistant. Although this patient had a smooth recovery, the short follow-up time meant that any longer-term issues have not yet come to light. In future, a randomized controlled trial will be necessary to prove whether the recurrence rate and complication rate differ between this approach and conventional repair methods.

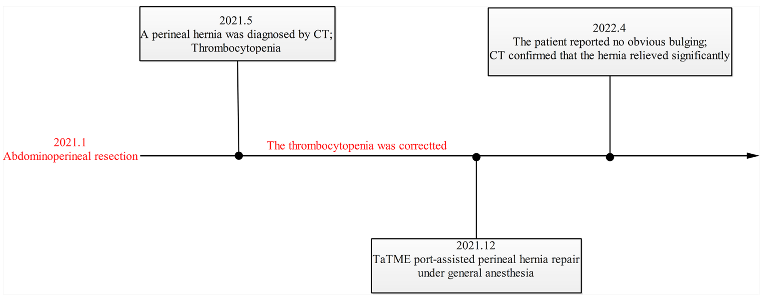

FIGURE 8
The timeline of this case.

Conclusion

To repair this case of perineal hernia, we released pelvic floor adhesions by TaTME port-assisted laparoscopy, and then sutured the mesh under direct vision. The operation was novel and smooth without any complications. The follow-up confirmed that the short-term effect was acceptable, and the long-term effect remains to be further observed. TaTME port-assisted perineal hernia repair can benefit from the respective advantages of laparoscopic technology and the transperineal approach and the learning curve is relatively short.

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 The ethics committee of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XP, YG, JZ and HZ have made substantial, direct, and intellectual contributions to the work and agree to its publication. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1036145/full#supplementary-material

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A modified tracheal transection approach for cervical esophageal lesion treatment: A report of 13 cases

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Background: Surgical interventions for tumors in the cervical esophageal region are complicated and laryngeal function is frequently sacrificed. Therefore, we attempted the tracheal transection approach to resect the tumor while preserving laryngeal function.
Methods: Three patients with papillary thyroid cancer (PTC), six with cervical esophageal cancer (CEC), and four with CEC mixed with thoracic esophageal cancer (TEC) were enrolled. The esophagus was exposed after the trachea was transected between the second and third tracheal rings. *CEC/TEC:* Resection of the esophagus or/and a portion of the hypopharynx with acceptable safety margins and repair with free jejunum or tubular stomach. *PTC*: Suture the small esophageal incision immediately after removing the tumor. The tracheal dissection was repaired with interrupted sutures throughout the entire layer after the esophageal lesion was resected. The status of the recurrent laryngeal nerve (RLN) determined whether a tracheotomy was necessary.
Results: All 13 patients had effective esophageal lesion excision, with six of them requiring intraoperative tracheotomy. Postoperative complications included a tracheoesophageal fistula (one case, 7.7%), postoperative RLN paralysis (two cases, 15.4%), and aspiration (three cases, 23.1%). Except for two patients with distant metastases, there was no recurrence in the remaining patients after 5–92 months of follow-up.
Conclusion: The tracheal transection approach, as a new surgical technique, can retain laryngeal function while ensuring appropriate exposure and satisfactory surgical resection. Before surgery, the feasibility of this approach must be carefully assessed. The RLN should be protected during the procedure. The operation is both safe and effective, with a wide range of applications.

KEYWORDS

tracheal transection approach, cervical esophageal cancer, papillary thyroid cancer, preservation of laryngeal function, surgical technique

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Introduction

Although the cervical esophagus starts superiorly at the esophageal entrance and extends down to the sternal notch, extending approximately 6–8 cm, it falls under the scope of head and neck surgery. Despite the fact that it only covers approximately 5 cm and is a small section of the esophagus, lesions such as primary cervical esophageal cancer (CEC) or invaded lesions by other cancers are not uncommon in this area. The presence of the trachea, which makes the operating space exceedingly tight, renders the care of carcinomas at this site particularly difficult. As a result, total pharyngeal, laryngeal, and esophageal resection is the gold standard for CEC treatment in the early stages (1). However, this extensive surgical resection frequently results in significant functional loss and has a negative impact on the patient's quality of life (2). For other carcinomas such as thyroid carcinoma that invade the esophagus beyond the midline, the presence of the trachea can also lead to blind areas of the visual field, and the tumor is prone to be incompletely removed. For this group of patients, we present herein an innovative operative technique to deal with cervical esophageal lesions *via* a modified tracheal transection approach to achieve better surgical results.

Materials and methods

Thirteen patients treated in the Chinese Academy of Medical Sciences, the Peking Union Medical College Cancer Hospital, and Shandong ENT Hospital between October 2016 and September 2021 were enrolled. Before surgery, all patients were given complete information about the procedure and written informed consent was obtained. The patients' preoperative clinical characteristics are shown in **Table 1** and CT findings of two patients are demonstrated in **Figure 1**.

In all 13 cases, there was only one female patient. Three patients were diagnosed with papillary thyroid cancer (PTC), six with CEC, and four with CEC and coexisting thoracic esophageal carcinoma (TEC). Patients were aged 18–69 years with an average age of 56.2 years. Only one patient with CEC accepted preoperative radiation therapy and one patient with CEC accepted preoperative chemotherapy. Because esophageal carcinoma reconstruction methods should be defined by the cancer's site, data for this section were also collected and are presented in **Table 1**. The AJCC Cancer Staging Manual, Eighth Edition, was used to establish all tumor staging (3).

Surgical techniques

For thyroid cancer treatment

Preoperative examination of the potential amount of esophageal invasion and the selection of surgical approaches depending on the situation is required for all patients. Thyroid cancer patients with less significant esophageal invasion do not need a tracheal transection. However, for locally advanced thyroid cancer, preoperative imaging such as CT scan or MRI with contrast reveals that the tumor has invaded the esophagus beyond the dorsal midline of the esophagus. In this case, the conventional surgical approach may not be able to completely remove the tumor, and a tracheal transection approach may be applied according to the intraoperative evaluation. Because esophageal invasion is frequently associated with invasion of the recurrent laryngeal nerve (RLN), preoperative laryngoscopy is also required. All procedures were done under general anesthesia. A traditional collar neck incision was used to

TABLE 1 Clinical characteristics of the 13 patients.

Number	Age	Sex	Diagnosis	Preoperative therapy	cTNM Stage	Cancer Location (cm)
Case.1	69	Female	CEC	No	T2N1M0	16–20
Case.2	62	Male	CEC&TEC	No	T2N0M0	16–18/27–30
Case.3	56	Male	PTC	No	T4aN1bM1	/
Case.4	54	Male	PTC	No	T4aN1bM1	/
Case.5	18	Male	PTC	No	T4aN1bM0	/
Case.6	60	Male	CEC	Yes (R)	T2N0M0	17–20
Case.7	52	Male	CEC&TEC	No	T1N0M0	18–23/31–37
Case.8	62	Male	CEC	No	T1N1M0	20 cm
Case.9	56	Male	CEC	No	T4N0M0	18–22/27–32
Case.10	64	Male	CEC&TEC	No	T3N0M0	20 cm
Case.11	58	Male	CEC	No	T3N0M0	15–18
Case.12	66	Male	CEC&TEC	No	T2N0M0	15–17/25–28
Case.13	53	Male	CEC	YES (C)	T1N0M0	18–20

CEC, Cervical esophageal carcinoma; TC, Papillary Thyroid carcinoma; TEC, Thoracic esophageal carcinoma; R, radiotherapy; C, Chemotherapy.

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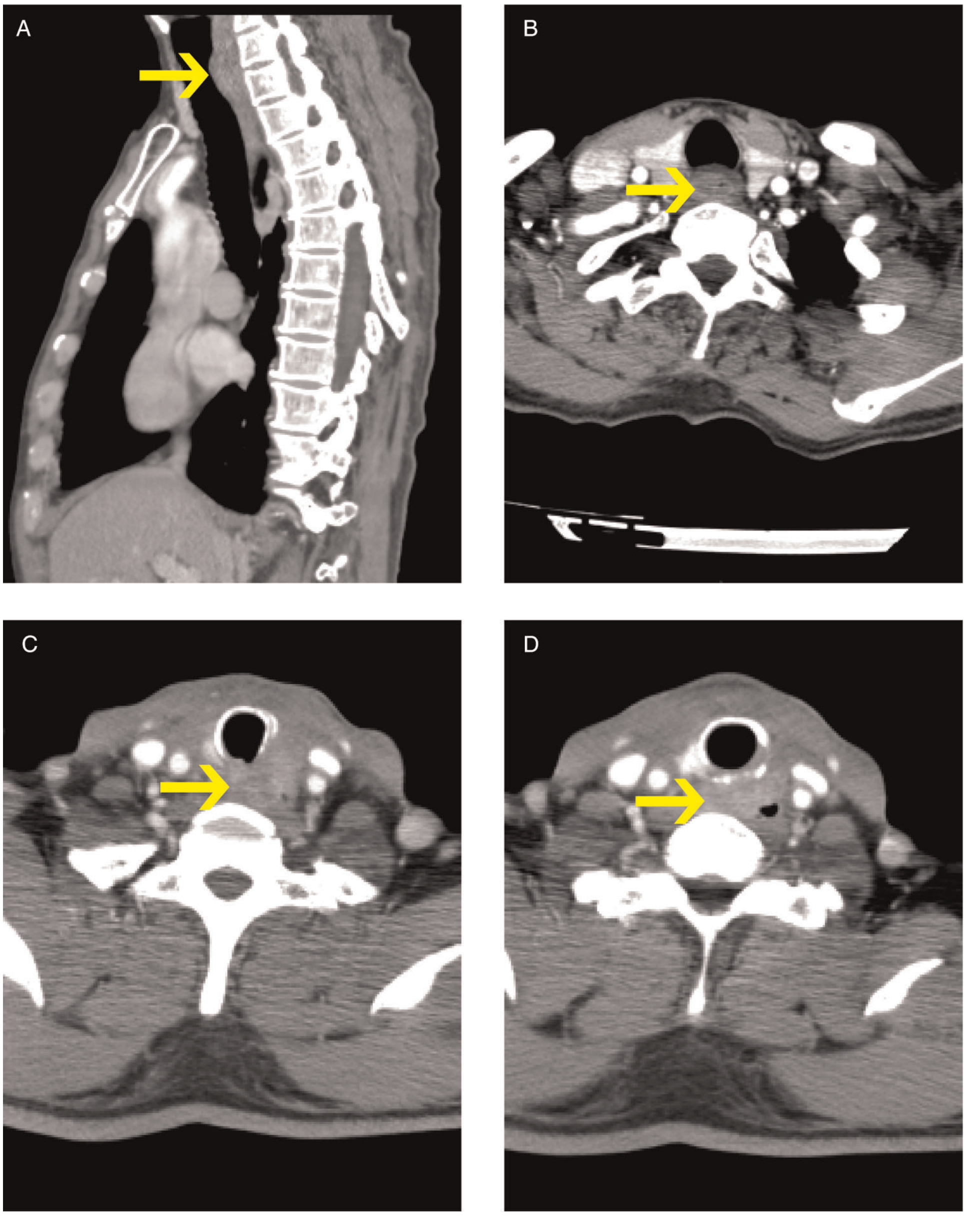

FIGURE 1
Ct findings of two patients (pictures in alphabetical order from top to bottom, left to right: ABCD. Pictures (**A,B**) show patient #1 CEC; Pictures (**C,D**) show patient #3 PTC. The arrows indicate the tumors.).

perform total thyroidectomy and neck dissection. The thyroid isthmus was initially transected, followed by lobectomy in the lobes with no nodules or smaller nodules, and if possible, with at least one RLN effectively intact. In our cohort, all three thyroid tumors were determined to have invaded at least one side of the RLN intraoperatively, which had to be sacrificed during surgery. After separating both sides of the thyroid gland from the trachea, the latter was fully exposed. Then the trachea was transected between the second and third tracheal rings.

While incising the trachea, the anesthesiologist drew the tracheal tube into the mouth in preparation for tracheal anastomosis and subsequent intubation. The prepared sterile tube was inserted into the broken end of the trachea and given to the anesthesiologist to manage ventilation. The two segments of the trachea were stretched separately up and down so that the cervical esophagus and tumor were fully exposed. Care was taken to avoid excessive stretching of the RLN. Because all three patients exhibited partial esophageal invasion, the esophageal defect could be directly sutured after *en bloc* excision of the partially invaded esophagus, the remnant thyroid lobe, and the invaded RLN. RLN signals were detected *via* intraoperative nerve monitoring (IONM).

Two patients underwent tracheotomy because their RLN signals were diminished, while the third patient had an end-to-end anastomosis of the trachea.

For esophageal cancer treatment

Some of the initial esophagectomy and neck dissection techniques were similar to the thyroid cancer surgical procedure detailed earlier. The tracheal transection approach can be performed only on patients in whom the feasibility of laryngeal preservation has been confirmed preoperatively. The trachea was transected between the second and third tracheal rings, and the posterior wall of the trachea was carefully checked to see if it had been invaded. The pharyngeal cavity was opened by cutting the pharyngeal constrictor muscle from the side, and the upper boundary of the esophageal cancer lesion was examined, and we checked for any hypopharyngeal invasion. After that, we dissected and protected both RLNs before performing cervical esophagectomy.

Total esophagectomy should be performed on patients with CEC and coexisting TEC. Depending on the tumor's location and invasive range, a free jejunal flap or gastric tube was used. Finally, we sutured the broken end of the trachea and, depending on the situation, conducted a tracheotomy (if necessary), fistulated through the anterior wall of the trachea, and placed an indwelling tracheal cannula. If the status of the RLN cannot be verified, a subcutaneous tracheostomy can also be performed without placing a tracheal tube first. The fistula can be vented by tilting the head back slightly or manually pulling the fistula opening to the sides if hypoxia is present (Figure 2).

Follow-up plan

All patients were discharged from the hospital and given a follow-up plan. Patients were examined every 3 months for the first 2 years and then every 6 months thereafter. Neck ultrasound, enhanced CT of the neck and chest, electronic laryngoscopy, and gastroscopy are routine post-operative examinations. When clinical signs or imaging tests point to the possibility of distant metastases, bone scintigraphy, magnetic resonance imaging (MRI), or positron emission computed tomography (PET) will be conducted, depending on the situation.

Results

Esophageal defects in all three thyroid cancer cases were sutured directly. Free jejunal flaps were chosen in half of the CEC or CEC combined TEC cases, and gastric pull-up was performed in the other half. Tracheotomy was required in six (46.2%) patients. Postoperative complications included tracheoesophageal fistula (one case, 7.7%), postoperative RLN paralysis (two cases, 15.4%), and aspiration (three cases, 23.1%). There was no postoperative bleeding or tracheostenosis (Table 2). All patients resumed oral intake on postoperative day 7–10, with the exception of case 2, who suffered from postoperative tracheoesophageal fistula leading to a short-term nasogastric tube feeding, which is reversed by a tracheal stent implantation. The patient resumed oral intake afterwards.

Two patients with thyroid cancer had postoperative radioactive iodine^{131} treatment, and five patients with CEC, one with thyroid cancer, and one with CEC combined with TEC received postoperative radiotherapy. The remaining four patients had no postoperative treatment and were only followed-up. This group of patients was followed-up for a total of 5–92 months. Except for two patients with definite bilateral RLN palsy who required postoperative arytenoid cartilage resection or posterior vocal cord dissection before the tracheal cannula was removed, the latter was withdrawn between 3 days and 1 month in all patients. One patient with CEC and TEC died of myocardial infarction 26 months after surgery, another patient with PTC died of brain metastasis combined with renal failure 23 months after surgery, and another patient with CEC died of bone metastasis 27 months after surgery. The remaining patients had no tumor recurrence (Table 3).

Discussion

Because of its anatomical location, the involvement of the trachea often limits visual field exposure and complicates the surgical technique, regardless of whether it is a primary cancer of the cervical esophagus or other cancers invading the esophagus. Previous surgical treatment of cervical esophageal cancer has frequently jeopardized laryngeal function. However, the larynx and trachea are frequently uninvolved in these patients, and the larynx is removed simply to fully expose the hypopharynx and esophageal entrance behind the larynx. The patient's ability to talk is lost after a total laryngectomy, which increases the burden of care and has a substantial influence on the patient's quality of life. Similarly, tracheal blockage often leads to incomplete surgical resection and is associated with a risk of recurrence in patients with thyroid cancer that significantly invades the esophagus, especially those with recurrent thyroid cancer after many surgical interventions. As a result, a surgical approach that preserves the larynx while eliminating the lesion is urgently needed. We found that the modified tracheal transection approach is a superior surgical technique, which is simple for surgeons who have mastered the tracheal sleeve resection method, a commonly used method in patients with tracheal malignancy and thyroid cancer invading the trachea (4–6). In addition, direct suturing after tracheal transection is safer than

FIGURE 2
Surgery pictures (the photos of two patients undergoing surgery were chosen to demonstrate the various surgical repairs and tracheal management techniques. Pictures A-M, R-T show patient #11; Pictures N-Q show patient #2). Pictures in alphabetical order from top to bottom, left to right: ABCDEFGHIGKLMNOPQRST. (A) Neck incision (a collar incision or a T-shaped incision). (B) Abdominal incision (free jejunum). (C) Dissect the isthmus of the thyroid and draw both lobes outward to show the trachea and bilateral RLN on the inside. (D) The trachea was transected between the second and third tracheal rings. (E) Replace the tracheal intubation. (F) Cutting the posterior wall of the trachea. (G) To figure out where the upper limit of cervical esophageal cancer is and whether the larynx can be preserved. (H) Separate the tracheoesophageal space, taking care not to overstretch the recurrent laryngeal nerves on either side. (I) The esophagus is incised from the tumor's bottom border (ensuring adequate safety borders), and the prevertebral fascia is checked for invasion. (J) The esophagus is incised from the tumor's upper border (ensuring adequate safety borders). (K) Cervical esophageal specimens that have been excised. (L) Free jejunal flap (repair of the cervical esophageal defect). (M) The free jejunum is sutured to the defective upper and lower esophageal anastomoses in preparation for micro-anastomosis of arterial and venous vessels. (N) In patients with CEC and TEC, the procedure necessitates the resection of the entire esophagus, which usually necessitates the assistance of a thoracic surgeon to free the lower esophagus so that the entire esophagus can be pulled to the neck. (O) The gastric tube is retracted to the neck for anastomosis. It is important to avoid over-distention of the RLN throughout this procedure. (P) The tracheal wall can be sutured all around in individuals with no invasion of the recurrent laryngeal nerve and no excessive intraoperative strain. (Q) Following the placement of the drainage tube, the incision was immediately closed (no tracheostomy was performed). (R) If surgery reveals an invasion of the recurrent laryngeal nerve, or if the recurrent laryngeal nerve is too stretched to determine whether the signal is intact, a subcutaneous fistula (suturing the anterior wall of the trachea to the subcutaneous tissue) is feasible. (S) Third postoperative day. No tracheal tube was inserted. The fistula will progressively close over time if there is no significant asphyxia. (T) If hypoxia is present, the fistula can be vented by slightly tilting the head back or manually pulling the fistula opening to the sides. (continued)

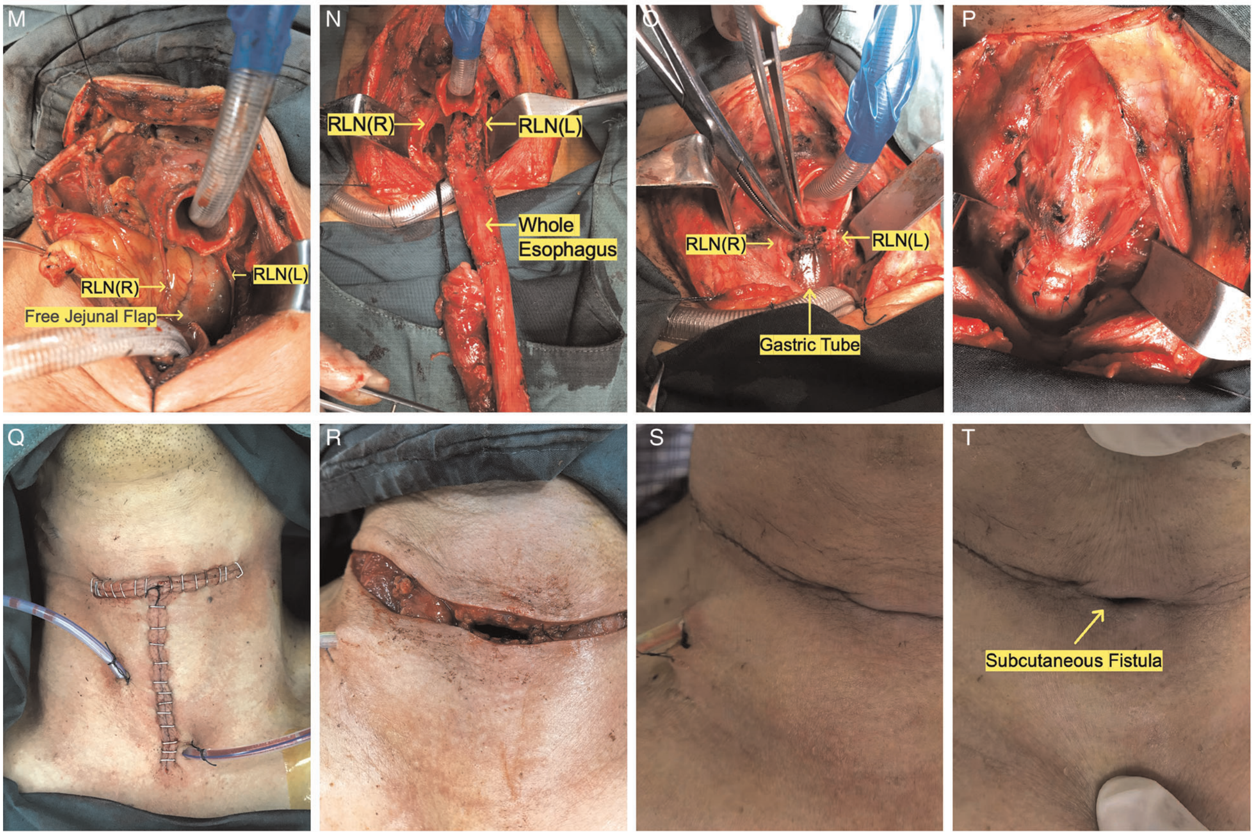

FIGURE 2
Continued.

TABLE 2 Information related to surgery and postoperative complications in 13 patients.

Number	Date of surgery	Repairing Method	Tracheotomy	SND	Pathology	pTNM Stage	Anastomotic Fistula	RLNP	Bleeding	TS	Aspiration
Case.1	2/20/2017	free jejunal flap	No	Yes	SCC	T3N1M0	No	No	No	No	Yes
Case.2	9/1/2017	gastric tube	No	Yes	SCC	T3N0M0	Yes[a]	No	No	No	No
Case.3	4/28/2017	sutured directly	Yes	Yes	PTC	T4aN0M1	No	Yes (pre-op)	No	No	No
Case.4	1/3/2017	sutured directly	No	Yes	PTC	T4aN1aM1	No	Yes (pre-op)	No	No	No
Case.5	6/20/2014	sutured directly	Yes	Yes	PTC	T4aN1bM0	No	Yes (pre-op)	No	No	Yes
Case.6	10/10/2016	free jejunal flap	No	Yes	SCC	T2N0M0	No	No	No	No	No
Case.7	9/12/2017	gastric pull up	No	Yes	SCC	TisN0M0	No	Yes (post-op)	No	No	No
Case.8	11/2/2017	free jejunal flap	Yes	Yes	SCC	T1bN1M0	No	No	No	No	Yes
Case.9	1/14/2018	gastric pull up	No	Yes	SCC	T4bN1M0	No	No	No	No	No
Case.10	1/24/2018	gastric pull up	Yes	Yes	SCC	T4bN0M0	No	Yes (post-op)	No	No	No
Case.11	6/20/2018	free jejunal flap	Yes	Yes	SCC	T3N0M0	No	No	No	No	No
Case.12	9/16/2021	gastric pull up	Yes	Yes	SCC	T1bN0M0	No	No	No	No	No
Case.13	8/26/2021	free jejunal flap	No	Yes	SCC	T0N0M0	No	No	No	No	No

SND, selective neck dissection; RLNP, recurrent laryngeal nerve paralysis; Pre-op, preoperative; Post-op, postoperative; TS, tracheostenosis; SCC, squamous cell carcinoma; PTC, papillary thyroid carcinoma.
[a]Tracheoesophageal fistula.

TABLE 3 Follow-up information of the 13 patients.

Number	Postoperative Treatment	Follow-up (month)	Results
Case.1	Radiotherapy	27	osseous metastasis, dead
Case.2	No	49	recurrence-free survival
Case.3	I^{131}	23	brain metastases and renal failure, dead
Case.4	I^{131}	61	recurrence-free survival
Case.5	Radiotherapy	92	recurrence-free survival
Case.6	Radiotherapy	58	recurrence-free survival
Case.7	No	52	recurrence-free survival
Case.8	Radiotherapy	50	recurrence-free survival
Case.9	Radiotherapy	48	recurrence-free survival
Case.10	Radiotherapy	26	myocardial infarction, dead
Case.11	Radiotherapy	43	recurrence-free survival
Case.12	No	5	recurrence-free survival
Case.13	No	6	recurrence-free survival

I^{131}, radioiodine^{131}.

tracheal sleeve resection, which is more prone to complications due to increased tension in the suture.

As one of the most prevalent endocrine malignancies (7), well-differentiated thyroid cancer is associated with an approximate 13% rate of local invasion (8), while esophageal invasion accounts for approximately 21% of invasive thyroid cancer cases (9, 10). Although the overall prognosis for thyroid cancer is favorable, locally-advanced thyroid cancer frequently causes serious complications such as airway obstruction, bleeding, or dysphagia, and survival for patients with and without the involvement of the aerodigestive tract differs significantly (10, 11), making surgery a crucial part of the treatment. Different scholars have different opinions on surgical resection for this group of patients. Some researchers feel that only shave excision can be conducted for patients with tumors that are difficult to remove cleanly by visual inspection, and that other postoperative treatments can be adjuvant (12). However, based on our experience and certain published findings (13, 14), we believe that for locally invasive thyroid cancer, we should also opt for radical excision to achieve a better prognosis. Therefore, a tracheal transection technique can better achieve tumor radicalization in papillary thyroid cancer that has invaded the esophagus beyond the midline. Furthermore, because anastomosis after tracheal transection does not increase anastomotic tension, this procedure does not significantly increase the risk of anastomotic fistula and is safe and dependable in comparison to the anastomotic dehiscence complication rate of 4%–25% reported in the literature (4, 15, 16). Due to the insufficient sample size, we could not detect any anastomotic fistula issues in our patients. We will extend the sample for further statistical analysis.

Locally advanced thyroid cancer or central metastatic lymph nodes can typically infiltrate the esophagus, particularly on the left side, and are frequently accompanied by invasion of the RLN or trachea. In addition to regular preoperative examinations, ultrasound, CT, MRI, laryngoscopy, and gastroscopy, ultrasound endoscopy if necessary, and additional tracheoscopy if there is tracheal invasion, because this group of patients requires a thorough preoperative assessment. Because the mucosa of the esophagus is a tough barrier to penetrate, differentiated thyroid cancer seldom penetrates the mucosal layer of the esophagus and is predominantly located outside the lumen; therefore, the tumor can be considered to be excised *en bloc* from the submucosal layer of the esophagus, and the myocutaneous layer can be sutured *in situ*, with no further reconstruction required because the closure is rarely under tension. Empirically, a feeding tube can aid in the identification of the esophagus during surgery. Likewise, in our group, there were no major abnormalities in all three papillary thyroid cancer instances, and all (3, 100%) of the defects were primarily closed.

It is sometimes difficult to heal *in situ* after the removal of tumors that penetrate the entire layer, which might result in esophageal stenosis. To widen the esophageal lumen and ensure the quality of swallowing after surgery, tissue transfer may be necessary (17, 18). Fascial or fasciocutaneous flaps, myocutaneous pedicled flaps, or jejunal, gastric transfers may be good options, depending on the deficits and the surgeon's inclination. During the follow-up period, only one patient in our study died due to renal failure. The remaining two patients had no recurrence at the time of the final follow-up. No patient experienced evident complications such as dysphagia and bleeding. This evidence shows that the process is both safe and effective.

Cervical esophageal cancer is uncommon, accounting for approximately 2%–10% of all esophageal malignancies (19, 20). The treatment of cervical esophageal cancer is more complicated, and a comprehensive treatment plan that combines surgery, radiotherapy, chemotherapy, and immunotherapy is becoming increasingly identified (21–24). However, the vast number of surrounding vital organs and the intricacy of the surgical stages, which have a greater impact on the patient's quality of life following surgery, make surgery for CEC a significant clinical challenge.

Squamous cell carcinoma, which accounts for more than 90% of all pathological types of cervical esophageal cancer (25, 26), requires a safer resection margin than papillary thyroid carcinoma surgery. Surgical treatment of cervical esophageal cancer in the past, particularly those affecting the esophagus's entrance and the hypopharynx, frequently sacrificed laryngeal function. Total laryngeal resection, total esophageal resection, and a permanent tracheostomy were commonly used in traditional operations (1), which resulted in language loss and pneumonia due to inadequate airway management. The larynx and trachea are frequently uninvolved in these patients, and the larynx is removed simply to fully expose the hypopharynx and esophageal entrance behind its body. As a result, an increasing number of surgeons are choosing laryngeal preservation surgery for patients who do not have considerable laryngeal and tracheal invasion. It was recently discovered that the mortality rate of complete or partial larynx-preserving operations was not significantly lower than that of larynx-non-preserving operations, and more inspiringly that larynx-preserving operations were not associated with a higher incidence of complications such as anastomotic leakage, pneumonia, graft necrosis, or infection (27–29). As a result of the improved quality of life, patients are more likely to accept this operation. Thus, a thorough preoperative evaluation is carried out to determine whether the larynx can be preserved, and there is a higher requirement for a surgical treatment that preserves the larynx while removing the lesion.

The tracheal transection method could solve all of the above concerns. The key methods to achieve a favorable surgical result are to expose the surgical field and improve the height of the gastropharyngeal anastomosis as much as possible during surgery. It was discovered that the tracheal transection method has a distinct advantage in that it can maximize operation field views, allowing for a clear exposure of the cervical esophagus. The involvement of the larynx and trachea can be reliably assessed with an adequate surgical field. The cervical esophagus can be resected and sutured under direct eyesight. Although the anastomosis height may be increased as much as possible, the suture might be more carefully placed to avoid the occurrence of a fistula. The remaining nine patients with CEC and patients with CEC combined with TEC did not develop anastomotic fistulas, with the exception of one patient with CEC combined with TEC (1, 10%) who developed a postoperative tracheoesophageal fistula. However, this is definitely lower than the 16.36% rate of anastomotic fistulas after surgery described in the literature (30).

Different from thyroid cancer surgery, the demand of deficiency repairing is essential for esophageal cancer surgery. For patient with CEC, jejunal repair is an option, whereas gastric substitution esophageal repair is essential for patients with CEC combined with TEC. There are also subtle differences in the strategy to tracheal transection for these two patient categories. As thoracic esophageal cancer is not within the area of treatment provided by our department, we will not discuss it here. In our experience, the stomach cannot be directly anastomosed to the hypopharynx in patients undergoing gastric substitution repair in order to prevent acid reflux-induced chemical pneumonia as a complication, the incidence of which have been documented in the medical literature to be approximately 11.1%–28.9% (2, 31, 32). The anastomosis is typically around 1 cm below the esophageal inlet, so the position of the tracheal transection is chosen to avoid the anastomosis as much as possible. According to the patient's condition, the tracheal transection can be conducted between the first and second tracheal rings. In comparation, for patients with CEC, particularly those with esophageal cancer invading the hypopharynx, jejunal repair is required. Since the gastric reflux is less likely as a complication of jejunal repair, the tracheal transection position can be selected mainly based on the surgical condition, and typically we select space between the second and the third tracheal rings for transection.

It should be noted that because cervical esophageal cancer is so proximal to the RLN, preoperative electronic laryngoscopy, or at the very least, indirect laryngoscopy, should be frequently evaluated in the case of vocal cord paralysis. According to the literature, the rate of laryngeal recurrent nerve injury in individuals undergoing only surgery for cervical esophageal cancer might be up to 12.96%–28.3% (29, 30). The trachea and larynx are frequently moved upward along the tracheal stump to expose the posterior cervical esophagus after tracheal transection to provide a broader operation field. Our experience is to meticulously expose and dissect the RLN on both sides before pulling. Dissection of both sides of the RLN is usually started after disconnecting the isthmus of the thyroid gland. There is some relaxation after dissection, since the RLN is usually not tight. When drawing the tracheal stump and larynx forward, it is important to be gentle, pay attention to the nerve's tension, and avoid damaging the RLN by excessive pulling. If possible, IONM can also be used.

To minimize bilateral RLN palsy affecting respiration, additional attention should be devoted to safeguarding the contralateral RLN in patients who have had one RLN palsy prior to surgery. The procedure must be carried out with caution. In our study, 20% patients experienced transient RLN palsy on one side after surgery, as well as hoarseness, which could be related to the dissection and retraction of the RLN during surgery; this incidence is slightly lower than the 28.3% reported in the literature (29). If at least one unilateral RLN signal is normal and the trachea is not considerably invaded, tracheotomy may not be necessary even after tracheal transection. Fortunately, because the RLN's integrity was intact, most of the traction-induced RLN palsy was temporary, and the two patients' bilateral vocal cord motions were normal 6 months after the operation. If the IONM is not used in the operation and the surgeon determines that the traction on the nerve during the procedure is severe, the posterior wall of the trachea can be sutured and a tracheotomy or tracheostomy performed on the anterior wall for safety.

For patients undergoing prophylactic tracheotomy, according to our experience, a subcutaneous fistula can be chosen, in which the free end of the tracheostomy stoma is sutured and fixed to the subcutaneous tissue of anterior neck while leaving the skin layer unsutured, and the tracheal tube is not placed after the operation. The patient is then observed for any obvious asphyxia, if any, the skin covering the tracheocutaneous stoma can be pulled up to expose the fistula and a tracheal intubation *via* the stoma can be conducted immediately, if none, the fistula opening will close spontaneously. The tracheal cannula can be removed for the closure of fistula as soon as possible if there are no clear signs of asphyxia after the obturator is inserted. Because the literature indicates the tracheal cannula should be removed as soon as possible in order to prevent the adverse effect of positive pressure ventilation on sutures (33, 34). Similarly, if the trachea is found to be invaded during the procedure, it can be sutured directly after the sleeve resection. A tracheostomy can be performed in the first stage and repaired in the second stage if the tracheal defect is large. Only one tracheotomy was performed in patients who had a definite loss of RLN signals during surgery. Because IONM was not employed in all of the patients, four (40%) patients had to undergo tracheotomy during surgery. Except for three patients who had postoperative aspiration (30%), one patient developed a postoperative anastomotic fistula (10%). In this group, significant problems like hemorrhage and tracheal stenosis did not occur. Even though some patients had complications such as aspiration, anastomotic fistulas, or RLN paralysis, early detection and treatment may result in a better outcome and are associated with the overall prognosis (21, 25, 30). In our study, 10 patients were enrolled, with one patient dying 26 months after surgery from myocardial infarction and another dying 27 months later after surgery from osseous metastases. Overall, for patients with CEC or CEC combined with TEC, this surgical intervention is often safe and successful.

Conclusion

The tracheal transection approach described herein is a novel surgical technique that can preserve laryngeal function while ensuring adequate exposure and satisfactory surgical resection for cervical esophageal tumors that do not involve the post-cricoid region and differentiated thyroid carcinoma that invades the esophagus beyond the midline. The extent of tumor invasion determines the appropriate approach; typically, the lower cervical border of the tumor does not surpass the thoracic entrance, the upper border does not exceed 2 cm above the esophageal entrance, and the hypopharyngeal lesion does not involve the posterior cricoid region. The laryngeal nerve should be protected during the procedure. Aspiration, recurrent laryngeal nerve paralysis, and tracheoesophageal fistula are the most common postoperative complications. The rate of complications with this approach is not higher than that associated with the conventional technique, and this surgical approach is safe, dependable, and can be applied in clinical practice.

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 Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZZ and YL designed the original study. NH and YL conducted clinical data collection and collation. WX, CA, JL, YZ, SL, ZZ were responsible for the admission, evaluation and surgery of patients. YL and ZZ wrote and revised the manuscript draft. 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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Prognostic value of final pathological stage in colon adenocarcinoma after neoadjuvant chemotherapy: A propensity score-matched study

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Background: Neoadjuvant chemotherapy (NAC) could improve local tumor control of locally advanced colon cancer (LACC), but the prognostic value of yp stage in colon cancer remains unknown. Here, we aimed to ascertain yp stage as an indicator for LACC prognosis after NAC.
Methods: The data of patients diagnosed with colon adenocarcinoma between 2004 and 2015 were extracted from the Surveillance, Epidemiology, and End Results database. After 1:2 propensity score matching, cancer-specific survival (CSS) and overall survival (OS) were compared between the NAC and Non-NAC groups of different stage classifications. The correlation between clinical and pathological factors and CSS was identified.
Results: A total of 49, 149, and 81 matched pairs of stage 0–I, II, and III patients, respectively, were generated for analysis. For stage 0–I ($p = 0.011$) and III ($p = 0.015$), only CSS in the NAC groups were inferior. Receiving NAC was an independent prognostic risk factor for patients with stage 0–I (hazard ratio, 7.70; 95% confidence interval, 1.820–32.5; $p = 0.006$) and stage III (hazard ratio, 1.73; 95% confidence interval, 1.11–2.68; $p = 0.015$).
Conclusions: The CSS was poorer among LACC patients who underwent NAC than among those who did not. The yp stage of colon cancer after NAC has distinctive significance, which may contribute to predicting the prognosis and guiding the treatment of LACC patients after NAC.

KEYWORDS

prognostic value, neoadjuvant chemotherapy, colon cancer, yp stage, survival

Abbreviations
AJCC, American Joint Committee on Cancer; CSS, cancer-specific survival; LACC, locally advanced colon cancer; LNs, number of lymph nodes; NAC, neoadjuvant chemotherapy; NAT, neoadjuvant therapy; NCCN, National Comprehensive Cancer Network; OS, overall survival; PCR, pathological complete remission; PCT, postoperative chemotherapy; PSM, propensity score matching; P stage, pathological stage; SEER, Surveillance, Epidemiology, and End Results database; Ts, tumor size; Yp stage, the final pathological stage after neoadjuvant therapy.

Introduction

Colon cancer, among the most common malignant tumors worldwide, accounted for approximately two-thirds of new colorectal cancer cases and deaths in 2020 (1, 2). Locally advanced colon cancer (LACC) patients are still routinely treated with up-front surgery followed by adjuvant chemotherapy. Although neoadjuvant therapy (NAT) is not yet standard, it is proven to improve the tumor downstaging and margin-negative resection rates in colon cancer, resulting in local tumor control and even pathological complete remission (PCR) without excess complications (3–8). In 2016, the NCCN guidelines added neoadjuvant chemotherapy (NAC) as an optional treatment for the clinical T4b colon cancer cohort (9). In regards to pathological stage (*p* stage), an important factor that affects prognosis, several studies have reported that the final pathological stage after NAT (yp stage) is a significant predictive factor of survival outcomes among patients with rectal cancer who underwent chemoradiotherapy (10, 11). However, the prognostic value of yp stage in colon cancer remains unknown. Thus, we retrospectively analyzed cancer-specific survival (CSS) and overall survival (OS) of colon cancer patients treated with or without NAC in the Surveillance, Epidemiology, and End Results (SEER) database through propensity score matching (PSM) analysis, aiming for evaluating the effectiveness of yp stage as a prognostic indicator and adjuvant treatment guideline for colon cancer.

Material and methods

Patient selection

The data of patients pathologically diagnosed with primary colon adenocarcinoma between January 1, 2004 and December 31, 2015 were extracted from the SEER database (SEER*Stat Version 8.3.9). The study inclusion criteria were as follows: (1) histological type limited to colon adenocarcinoma (International Classification of Diseases for Oncology, 3rd edition codes for adenocarcinoma: 8140/3, 8143/3, 8144/3, 8210/3, 8261/3, 8263/3, 8220/3, and 8221/3; special type adenocarcinoma: 8141/3,8211/3, 8213/3, 8255/3, 8260/3, 8262/3, 8310/3, 8323/3, 8440/3, 8460/3, 8470/3, 8480/3, 8481/3; and signet ring cell carcinoma: 8490/3); (2) non-metastatic colon cancer; (3) radical intestinal resection; and (4) receipt or non-receipt of NAC (regardless of whether he/she uses preoperative radiotherapy or not). Surgery and systemic therapy sequences were limited to systemic therapy before surgery, systemic therapy both before and after surgery, surgery both before and after systemic therapy, systemic therapy after surgery, and no systemic therapy and/or surgical procedures. Surgery and radiation sequences were limited to radiation before surgery and no radiation and/or cancer-directed surgery; and (5) accurate prognostic information. The study exclusion criteria were as follows: (1) non-primary or multiple primary cancers; (2) rectosigmoid-Junction cancer; (3) unknown American Joint Committee on Cancer (AJCC) 7th pathological stage; (4) surgery including local tumor resection, none, or unknown; and (5) patients without NAC did not receive the standard treatment which the NCCN guidelines recommended to each pathological stage. (6) survival time of 0.

Variables collected

(1) Patient information: sex, age at diagnosis, year at diagnosis, race, and insurance; (2) Tumor information: primary site, tumor size (Ts), pathological grade, histological type, tumor-node-metastasis stage, number of lymph nodes (LNs) detected; (3) Treatment data: sequence of chemotherapy, whether preoperative radiotherapy was administered; (4) Follow-up data: CSS and OS. CSS was defined as the time interval between the diagnosis of colon cancer and death caused by colon cancer. OS was defined as the time interval between the diagnosis of colon cancer and death from any cause. All the included cases were re-staged by the AJCC 7th edition according to the data provided by the SEER database.

Patient classification

In this study, patients whose systemic therapy sequence was recorded as systemic therapy before surgery, systemic therapy both before and after surgery, and surgery both before and after systemic therapy were classified into the NAC group, whereas those whose systemic therapy sequence was recorded as systemic therapy after surgery or no systemic therapy and/or surgical procedures were classified into the Non-NAC group.

Statistical analysis

All data were sorted out and analyzed by R software (version 4.1.2). Continuous variables were compared using the unpaired t-test, while categorical variables were compared using the $\chi 2$ test. CSS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Factors associated with CSS were estimated by uni- and multivariate analyses using the Cox proportional hazards model. Factors with $p < 0.05$ in univariate analysis were included in multivariate analysis.

A 1:2 PSM analysis without replacement was conducted *via* the nearest neighbor method with a caliper of 0.1 times the standard deviation of the propensity score (12). Matched variables included: age, sex, race, insurance, primary site, tumor size, pathological grade, histological type, AJCC stage, and number of LNs detected. Two-sided values of $p < 0.05$ were considered statistically significant.

Results

Baseline characteristics

A total of 97,881 patients were included in this study (**Figure 1**). Of these, 458 patients underwent NAC, whereas 97,423 did not. Baseline demographic and clinicopathological characteristics were presented in **Table 1**. We found that the proportion of patients who received NAC for colon adenocarcinoma increased gradually from 3.635% in 2006 to 8.607% in 2015 (**Figure 2**). The median survival time was 66.0 [95% confidence interval (CI), 69.8–70.3] months in the Non-NAC group and 54.0 (95% CI, 58.8–65.6) months in the NAC group ($p = 0.003$; **Table 1**).

Propensity score matching

To minimize confounding factors, we respectively matched the Non-NAC and NAC groups in stage 0–I, II, and III cohorts to achieve a balanced distribution of these baseline covariates between the paired groups. As a result, yp stage 0–I ($n = 49$) and p stage 0–I ($n = 98$), 149 yp

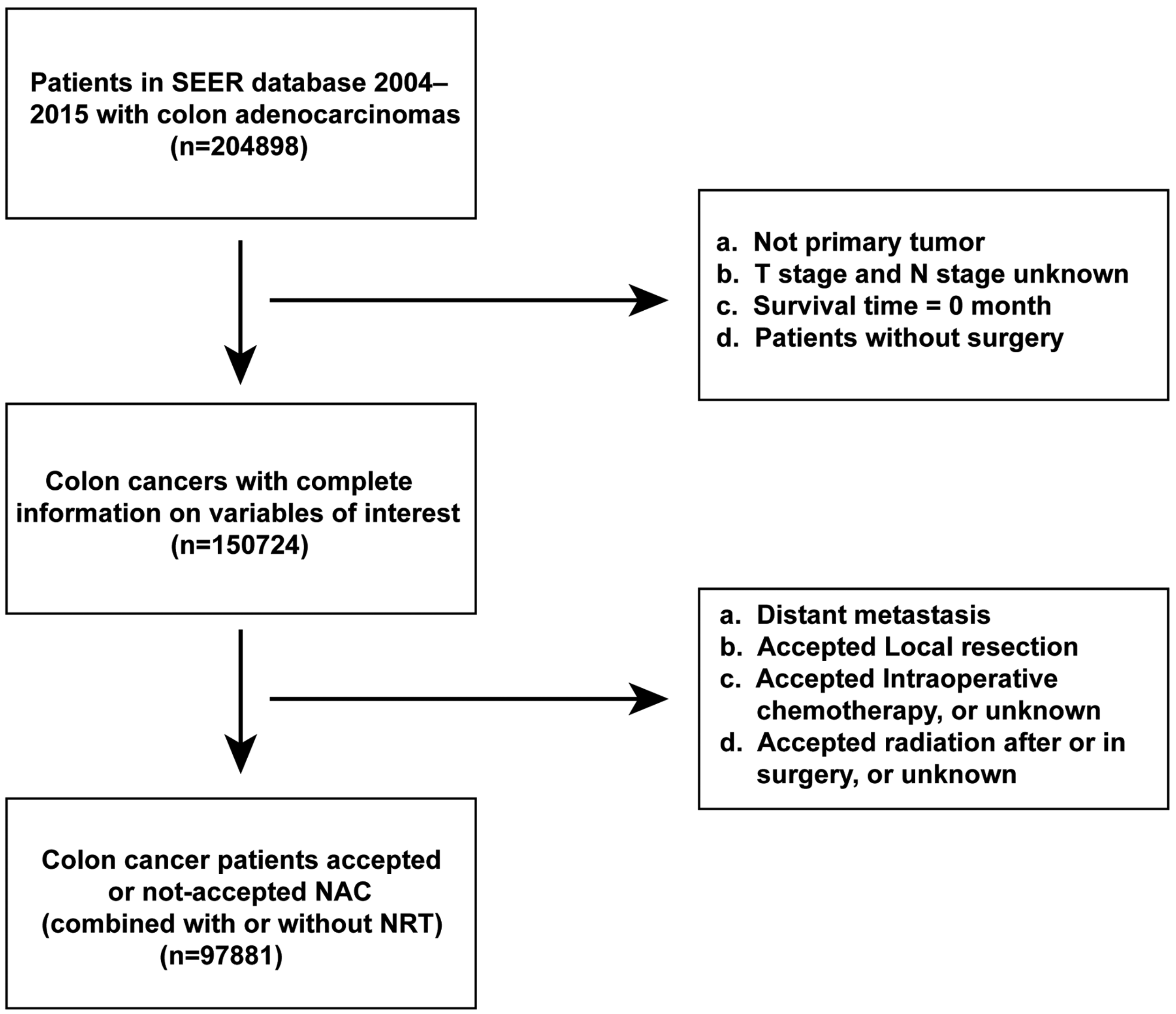

FIGURE 1
Flowchart of the patient selection process.

TABLE 1 Patient characteristics (*N* = 97,881).

Characteristics	Non-NAC group (*N* = 97,423)	NAC group (*N* = 458)	*p*-value
Age			<0.001
< 50 years	9,110 (9.4%)	88 (19.2%)	
≥ 50 years	88,313 (90.6%)	370 (80.8%)	
Sex			<0.001
Male	50,166 (51.5%)	183 (40.0%)	
Female	47,257 (48.5%)	275 (60.0%)	
Insurance			0.247
Yes	82,313 (84.5%)	397 (86.7%)	
No	15,102 (15.5%)	61 (13.3%)	
Unkown	8 (0%)	0 (0%)	
Race			0.629
White	75,272 (77.3%)	346 (75.5%)	
Black	13,987 (14.4%)	72 (15.7%)	
Others	8,164 (8.4%)	40 (8.7%)	
Location			<0.001
Left colon	61,456 (63.1%)	194 (42.4%)	
Right colon	35,967 (36.9%)	264 (57.6%)	
Differentiation Grade			<0.001
Grade 1–2	76,442 (78.5%)	324 (70.7%)	
Grade 3–4	16,983 (17.4%)	75 (16.4%)	
Unkown	3,998 (4.1%)	59 (12.9%)	
Histology type			0.124
Adenocarcinoma	87,322 (89.6%)	398 (86.9%)	
Special type adenocarcinoma	9,173 (9.4%)	56 (12.2%)	
Signet ring cell carcinoma	928 (1.0%)	4 (0.9%)	
Pathological stage			<0.001
Stage 0–I	28,349 (29.1%)	49 (10.7%)	
Stage II	34,949 (35.9%)	160 (34.9%)	
Stage III	34,125 (35.0%)	249 (54.4%)	
T-stage			<0.001
T0–2	32,768 (33.6%)	79 (17.2%)	
T3–4	64,655 (66.4%)	379 (82.8%)	
N-stage			
N0	63,298 (65.0%)	209 (45.6%)	<0.001
N1	22,515 (23.1%)	181 (39.5%)	
N2	11,610 (11.9%)	68 (14.8%)	
LNs-examined			<0.001
<12	18,286 (18.8%)	124 (27.1%)	
≥12	78,781 (80.9%)	327 (71.4%)	
Unkown	356 (0.4%)	7 (1.5%)	
Tumor size			<0.001
<4	38,306 (39.3%)	135 (29.5%)	
≥4	59,117 (60.7%)	323 (70.5%)	
PCT			0.500
Non-PCT	69,735 (71.6%)	321 (70.1%)	
PCT	27,688 (28.4%)	137 (29.9%)	
Survival time (OS)			
Median survival time (95%CI)	66.0 (69.8, 70.3)	54.0 (58.8, 65.6)	0.003

CI, confidence interval; LNs-examined, number of lymph nodes examined; PCT, postoperative chemotherapy.

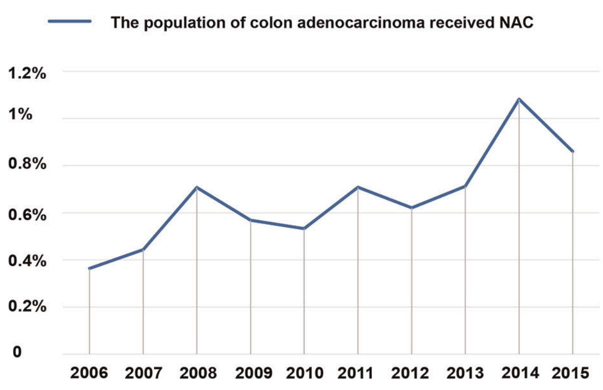

FIGURE 2
Rates of all patients with colon adenocarcinoma who received NAC were recorded in the SEER database from 2006 to 2015. The proportion received NAC in colon adenocarcinoma increased gradually from 3.635% in 2006 to 8.607% in 2015. NAC, neoadjuvant chemotherapy.

stage II ($n = 149$) and *p* stage II ($n = 295$), and 81 yp stage III ($n = 81$) and *p* stage III ($n = 160$) were matched (**Supplementary Table S1**).

For analysis of subgroups, we also matched the *p* stage 0–I group with the postoperative chemotherapy (PCT) subgroup ($n = 10$) and the non-PCT subgroup ($n = 39$) in the yp 0–I group separately. Moreover, the PCT subgroup ($n = 4$) and non-PCT subgroup ($n = 6$) of the yp stage 0–I group were also subjected to PSM matching. In stage II, non-PCT cohort in NAC group ($n = 116$) PSM matched with non-PCT cohort in Non-NAC group ($n = 229$), while PCT cohort in NAC group ($n = 33$) matched with PCT cohort in Non-NAC group ($n = 66$). The patient and tumor characteristics were well-balanced between the matched cohorts ($p > 0.05$).

CSS and OS stratified by preoperative therapy

Among stage 0–I patients, CSS was significantly poorer in the NAC group than in the Non-NAC group ($p = 0.011$) (**Figure 3A**). Interesting, the CSS of the matched NAC -PCT group ($n = 10$) and Non-NAC group ($n = 20$) was similar ($p = 0.140$) (**Supplementary Figure S1A**). However, the NAC -non-PCT group ($n = 39$) had significantly worse CSS than the Non-NAC group ($n = 78$) ($p = 0.012$) (**Supplementary Figure S1B**). Moreover, the 5-year CSS was 50% in the matched Non-NAC -PCT group ($n = 4$) vs. 33.3% in the matched Non-NAC -non-PCT group ($n = 6$), the difference of which was not statistically significant on the univariate log-rank test ($p = 0.410$) (**Supplementary Figure S1C**). Among stage II patients, there was no significant difference in CSS

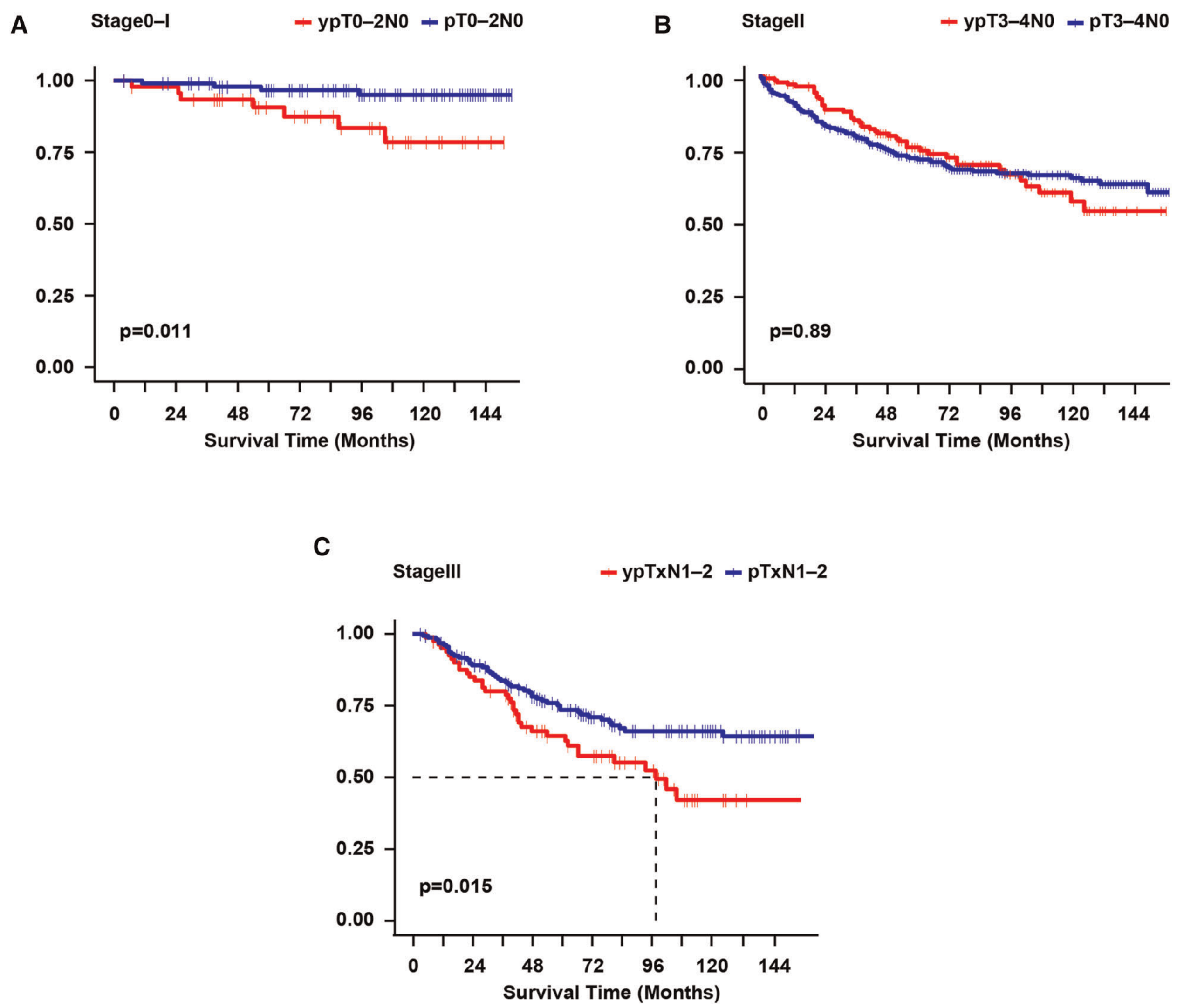

FIGURE 3
Survival curves were constructed per the Kaplan-Meier method for cause-specific survival for each pathological stage. Log-rank test for *p*-value. (A): yp stage 0-I vs. *p* stage 0-I; (B): yp stage II vs. *p* stage II; (C): yp stage III vs. *p* stage III. yp, the final pathological stage after neoadjuvant chemotherapy; *p*, pathological stage.

($p = 0.890$) between patients who received NAC and those who did not (**Figure 3B**). Additionally, the stratified analysis showed that the CSS of the NAC -non-PCT group ($n = 116$) was similar to that of the Non-NAC -non-PCT group ($n = 229$) ($p = 0.650$) (**Supplementary Figure S1D**). Consistently, the CSS of patients who received PCT (including T4b) in the yp stage II group ($n = 33$) was similar to that of patients in the p stage II group ($n = 66$) ($p = 0.660$) (**Supplementary Figures S1E,F**). Moreover, among the stage III patients, the CSS was significantly worse for the NAC vs. Non-NAC group ($p = 0.015$) (**Figure 3C**). Nevertheless, there was no significant difference in OS among the stage 0–I ($p = 0.870$), stage II ($p = 0.074$), and stage III groups ($p = 0.130$) groups (**Supplementary Figure 2**).

Prognostic factors for CSS of different stage classifications

As shown in **Supplementary Table S2**, uni- and multivariate Cox analyses demonstrated that, in the NAC group, not receiving PCT (hazard ratio [HR], 7.70; 95% confidence interval [CI], 1.820–32.500; $p = 0.006$) was an independent prognostic risk factor of CSS for patients. In the matched stage 0-I groups. In the matched stage II groups, age ≥ 50 years (HR, 2.436; 95% CI, 1.350–5.225; $p = 0.011$), T4a stage (HR, 3.065; 95% CI, 1.779–5.282; $p < 0.001$), T4b stage (HR,3.065; 95% CI, 2.308–5.110; $p < 0.001$) and poor histological differentiation (HR, 1.971; 95% CI, 1.244–3.123; $p = 0.004$) were independent risk factors, while ≥12 detected LNs (HR, 0.38; 95% CI, 0.326–0.652; $p < 0.001$) was an independent protective factor for CSS. In the matched stage III groups, only receiving NAC (HR, 1.657; 95% CI, 1.069–2.631; $p = 0.024$) was independently and significantly associated correlated with CSS.

Discussion

Due to the advantages of NAC of improving tumor downstaging, improving the R0 resection rate, and even prolonging disease-free survival time, its application in LACC is gradually increasing (3, 4, 6, 7, 13–15). Nonetheless, it remains unknown whether the final pathological stage (yp stage) of LACC patients who received NAC has a similar prognostic value to that of the usual postoperative pathological stage (*p* stage). To our knowledge, this is the first study to focus on the prognostic significance of yp stage in LACC patients after NAC. As the large difference in sample size between the NAC and Non-NAC groups, we balanced the clinical characteristics of the two groups using PSM for more reliable results. With the PSM and analysis of the survival time among stages 0–I, II, and III, respectively, we found that the CSS of LACC patients who underwent NAC was poorer than that of patients at the same pathological stage who did not, which indicated that yp stage of colon adenocarcinoma after NAC has significantly prognostic value and may provide evidence for PCT following curative surgery.

The present study found that young patients, those with right colon cancer, and those with poorly differentiated cancer were more likely to receive NAC. The shorter survival time in the NAC group may be due to worse histological grade, fewer detected LNs, later TN stage, and greater tumor bulk burden in the NAC group. As reported, *p* stage I colon cancer has good prognosis after radical resection alone. Compared with pT1-2N0 patients who did not receive chemoradiotherapy, ypT1-2N0 patients who received NAT preparation were more likely to relapse, and the recurrence rates of ypT0N0 and ypT1-2N0 were 2.7% and 12.3%, respectively (16). Moreover, several studies reported that, compared with *p* stage I patients, those with yp stage I disease had many risk factors leading to poor outcomes, such as poorer tissue differentiation, later T stage, and higher carcinoembryonic antigen levels (17, 18).

As for the stage 0–I patients in our study, the NAC group showed an inferior CSS to the Non-NAC group, which was also consistent with previous reports in NAT among rectal malignant tumors. Furthermore, the stratified analysis showed that the CSS was significantly worse in the yp stage 0–I non-PCT vs. *p* stage 0–I group, while the CSS of the yp stage 0–I with PCT group was similar to that of the *p* stage0–I group. Consistently, the 5-year CSS of the yp stage 0–I with PCT group was better than that of the yp stage 0–I non-PCT group, but the difference was not statistically significant. These results suggested that patients with yp stage 0–I colon cancer may benefit from PCT, which supports the findings of Collette et al. regarding rectal cancer in that LARC patients downgraded to ypT0-2 after preoperative radiotherapy can benefit from PCT (19).Other recent studies also demonstrated that patients with rectal cancer who reached PCR after NAT also benefited from PCT (20, 21). Patients who achieved descending stage after NAT also responded to adjuvant treatment (19). PCT for patients who respond to NAT may be beneficial by potentially eradicating residual micrometastatic disease (19, 22). Therefore, receiving adjuvant chemotherapy may contribute to the prognosis of these patients. A further randomized trial with a larger sample size is warranted to compensate for the limited sample size, especially in the PCT and non-PCT groups, of yp stage 0–I patients in our study.

As for stage II, CSS and OS were similar in the NAC and Non-NAC groups. This finding suggests that the risk of yp stage II patients may be classifiable according to the same criteria as and receive the same treatment regimen for *p* stage II. However, there was wide heterogeneity among stage II colon cancer patients, and the 5-year OS ranged from 58.4% (IIc) to 87.5% (IIa). Therefore, stage II patients require stratification to distinguish between high- and low-risk groups and guide the choice of treatment. However, the relevant information was not available in the SEER database.

Our study also found that the CSS of yp stage III patients was significantly poorer than that of *p* stage III patients, aligned with previous researches that patients with N+ after chemotherapy had a poor prognosis (23, 24). However, it is difficult to determine whether patients with a poor NAT response will benefit from PCT (25–27). Collette et al. reported that patients with a poor NAC response (ypN2) could not benefit from PCT and that the poor response may indicate resistance to treatment (19). Thus, we inferred that patients with yp stage III colon cancer may require adjustment to the adjuvant chemotherapy regimen. As another study reported that patients with *p* stage III disease had a better survival rate than those with yp stage III rectal cancer, the recurrence-free survival rate of yp stage III patients was intended to increase after treatment with second-line chemotherapy (28). Notably, the loss of DNA mismatch repair protein expression may occur in fluorouracil-based chemotherapy-insensitive colon cancer patients (29). Therefore, combination treatment with immunotherapy may be a promising research direction to improve the prognosis of patients with yp stage III colon cancer.

We also identified some independent risk factors for CSS. Poor tumor differentiation was an independent risk factor for prognosis in stage II patients. Poorly differentiated and undifferentiated tumors are more likely to metastasize distantly, the main cause of tumor death. Another independent risk factor found for CSS in this research was T4 for stage IIpatients. Regardless of LN status, colon cancer with advanced local invasion (T4) is more prone to local recurrence and distant metastasis, resulting in a low survival rate. Besides, according to the American Society of Clinical Oncology and the European Society of Medical Oncology, the number of LNs dissected (<12) is a risk factor for recurrence in patients with stage II colorectal cancer, consistent with our study findings (30, 31).

Another finding was that CSS was poorer for patients who underwent NAC than for those who did not undergo NAC, while the OS was similar between the two groups. Acknowledgedly, CSS is only related to tumor death, while OS is related to death caused by any reason. Although we adjusted variables that may lead to OS differences, including age, gender, diagnosis year, etc., we did not balance many other potential confounders between the NAC group and Non-NAC group, such as basic disease and economic status. Therefore, we speculated that there was no difference in OS because more patients in the Non-NAC group died of other causes, thus offsetting the difference in CSS between the two groups. This retrospective study had possible selective bias despite the PSM analysis and the fact that we selected patients treated with standard therapy whenever possible. Also, the SEER database lacks several important characteristics, such as chemotherapy or radiotherapy dosage, mismatch repair/microsatellite instability status, perineural invasion, and lymphatic vascular invasion. Therefore, we cannot adjust for these potential confounding factors, especially in stage II patients, which made it impossible to distinguish the low- and high-risk groups for a further stratified analysis. Thus, large-scale prospective randomized studies are needed that explore the prognostic value of the yp stage in LACC.

Conclusions

The CSS was poorer for patients who underwent NAC than for those who did not undergo NAC in the same pathological stage, while the OS was similar between the two groups. Our results suggest that the final pathological stage of colon cancer after NAC has different clinical significance from the usual postoperative pathological stage and may be used to predict prognosis and guide treatment for LACC patients after NAC.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

Ethics statement

Our institution does not require the ethical approval for reporting case which from the public database, such as SEER database.

Author contributions

XY and XF designed and supervised the study. MX and ZL extracted and analyzed the data. MX and YG 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1022025/full#supplementary-material.

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Retinal hemangioblastoma in a patient with Von Hippel-Lindau disease: A case report and literature review

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Background: Retinal hemangioblastoma (RH) is a rare benign tumor and a considerable number of which are caused by Von Hippel-Lindau disease (VHL). Herein, we described a case of VHL-associated RH with retinal detachment who underwent both laser photocoagulation and vitreoretinal surgery and received satisfactory visual recovery. In addition, we reviewed the current diagnosis, genotype-phenotype association, and treatment of VHL-associated RH.

Case description: A 34-year-old woman presented with vision loss in the right eye at our hospital. Fundus photography and angiography showed retinal detachment and multiple large hemangiomas in the right eye. The visual acuity improved significantly after laser photocoagulation and vitreoretinal surgery. Genetic analyses showed a p.Asn78Ser (c.233A>G) heterozygous missense mutation in the VHL gene.

Conclusion: We described a rare case of VHL-associated RH and may provide a new perspective towards diagnosis and treatment of this disease. RH is one of the most common manifestations of VHL and poses a serious threat to vision. Ophthalmic examination methods include fundus examination and fundus photography, etc. The management of the disease emphasizes timely follow-up, early detection of the lesion, and the decision of treatment options according to the size, location and complications of the lesion, including ablation therapy and vitreoretinal surgery. Clinicians should strengthen the understanding of this rare disease for early detection and treatment.

KEYWORDS

Von Hippel-Lindau disease (VHL), retinal hemangioblastoma (RH), case report, clinical management, vitreoretinal surgery

Introduction

Retinal hemangioblastoma (RH, also appearing in the literature as retinal capillary hemangioma, retinal capillary hemangioblastoma, or retinal angioma) is a rare benign tumor typically manifested by retinal vascular neoplasms with pink or orange color, nodular appearance, dilated and tortuous feeding and draining blood vessels, as well as exudation involving both perilesional retina and the macula (1–4). It has been reported that a considerable number of RH cases were caused by von Hippel-Lindau disease (VHL), while the rest seemed to be sporadic (1). VHL is a rare autosomal-dominant inherited tumor syndrome that has significant phenotypic heterogeneity and age-related genetic penetrance. With an incidence of approximately 1:36,000, VHL is believed to be one of the most common hereditary tumor syndromes that has various clinical manifestations mainly including RH, central nervous system hemangioblastoma(CNSH), renal cell carcinoma(RCC), pheochromocytoma (PCC) and pancreatic cysts etc (3, 5, 6). It is important to note that RH is the most common and probably the only presentation in VHL patients and is the initial manifestation in up to 77% of them (1, 4–6). The penetrance of RH would reach up to 90% in VHL patients over 60 years (7, 8), and about half of the cases present with multiple and bilateral RHs, which poses a serious threat to the patient's vision (6). As an ophthalmologist, identifying RH and determining whether it is associated with VHL is extremely important for the early diagnosis and treatment of this rare hereditary syndrome that may occur in these patients and their families.

Herein, we described a rare case of VHL-associated RH with severe visual impairment due to retinal detachment. Laser photocoagulation and vitreoretinal surgery were performed, and her vision recovered satisfactorily. In addition, we provided a literature review of VHL-associated RH to summarize the current diagnosis, genotype-phenotype association, and treatment of this disease. Our study may provide a new perspective towards ophthalmic diagnosis and treatment of VHL-associated RH.

Case report

A 34-year-old woman was admitted to the hospital with vision loss in the right eye over the last 3 days. Upon initial ophthalmological examination, the patient's visual acuity was HM/BE 20cm OD with no improvement in corrected vision and 1.0(Snellen chart)OS with corrected vision improving to 1.0 (+1.0DS/-2.0DC*10), and intraocular pressure was 17 mmHg OD and 20 mmHg OS. Nothing noteworthy was observed in the anterior segment of either eye and observations of the ocular fundus showed no abnormalities in the left eye. However, from 3 o ‘clock to 11 o ‘clock in the fundus of the right eye, the retina showed a state of grey-white bulge and flutter without retinal holes, and the macula was involved. Fundus photography further showed retinal detachment with multiple large hemangiomas in the right eye and a suspected hemangioma in the left eye (Figure 1). There were 4 orange-red hemangiomas in the superior temporal periphery and inferior temporal detachment area of the retina in the right eye with dilated and tortuous feeding and draining blood vessels as well as evident peripheral neovascular membranes. Fluorescence angiography(FA) showed early hyper-fluorescence with late leakage. Optical coherence tomography(OCT) showed retinal detachment. Prior to this visit, the patient had undergone head CT examination and found an intracranial hemangioma (Supplementary Figure 1), which was subsequently treated surgically at another hospital. Abdominal ultrasonography was also performed and showed multiple cysts present in the pancreas and right kidney while spinal CT showed no abnormalities. She was diagnosed with type 2 diabetes at the age of 32 and the HbA1c level on admission was 14.2%. Her mother suffered from diabetes and died of unknown causes at the age of 31. Her sister also underwent surgery for intracranial hemangioma. Although the patient's mother and sister were not conclusively diagnosed with VHL by clinical or genetic testing, we highly suspect them to have the disease based on the available clinical results. Moreover, we did ophthalmologic examinations for the patient's family who were willing to be examined and the results were shown in the supplementary materials (Supplementary Figure 2).

Based on family history, clinical manifestations and imaging, we suspected that the patient had VHL. To further confirm this, the patient and her family underwent genetic sequencing and the results showed a c.233A>G heterozygous missense mutation (amino acid p.Asn78Ser) in exon 1 of the VHL gene of the patient, her daughter and her son (Figure 2), and the genogram of the family was shown in the supplementary materials (Supplementary Figure 3). The patient was definitely diagnosed with VHL based on these findings.

The patient then underwent pars plana vitrectomy(PPV), lesion resection, endolaser photocoagulation and silicone oil tamponade for the right eye. During the operation, after a 23-gauge(23-G) PPV the four peripheral hemangiomas and the neovascular membranes were extracted using forceps, and an endolaser photocoagulation (argon ion laser, 532nm) was applied around the lesions to repair retinal detachment (Figure 3). As for the left eye, laser photocoagulation treatment(argon ion laser) was performed directly to the hemangioma and the surrounding area in order to induce degeneration of the tumor and its feeding and draining vessels. The retinal detachment of the right eye recovered and the hemangiomas of the left eye scarred following the treatment (Figure 4). At a follow-up examination before silicone oil

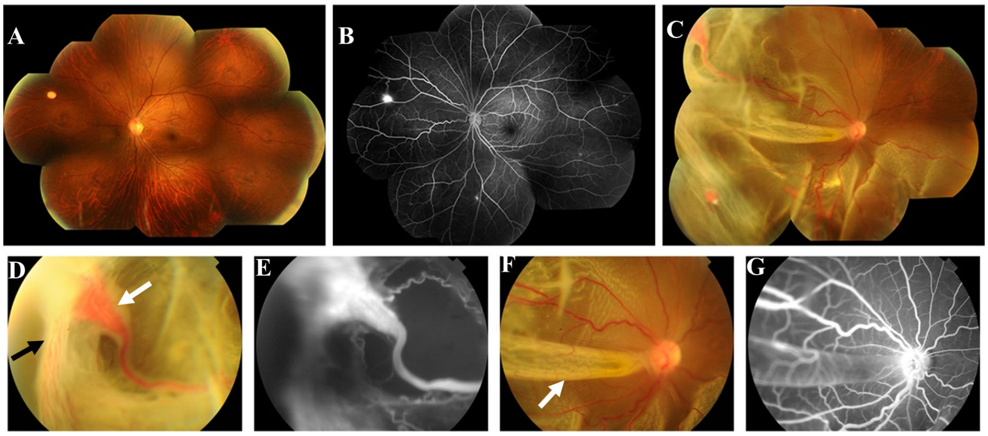

FIGURE 1
First fundus photograph and fluorescence angiography (FA) of the patient. Fundus photography of the left eye **(A)** revealed a suspected hemangioma at 10 o 'clock of the peripheral retina. FA of the left eye **(B)** indicated that there were multiple RH lesions in the peripheral retina with local hyper-fluorescence, which were not shown by fundus photography. Fundus photograph of the right eye **(C, D, F)** revealed 4 orange-red hemangiomas in the superior and inferior temporal periphery retina with dilated and tortuous feeding and draining blood vessels, and the largest of which was about 3.75 x 2.25mm(white arrow in **(D)** with neovascular membranes in its temporal side (black arrow in **(D)**. Retinal detachment could be seen from 3 o 'clock to 11 o 'clock with retinal fold formation(white arrow in **(F)**, involving the posterior pole of the eyeball. FA of the right eye **(E, G)** showed hyper-fluorescence and fluorescence leakage at the lesion, accompanied by a surrounding non perfusion area.

extraction, 3 months after the surgery, the patient's visual acuity had improved to 0.05 OD with corrected vision improving to 0.6 (+4.50DS/+1.25DC*10) and 0.6 OS with corrected vision improving to 1.0(+0.25DS/-2.50DC*15). A timeline figure of the diagnosis and treatment of this case was provided in the supplementary material (Supplementary Figure 4).

For the patient's children, both of her daughter and son present the same heterozygous pathogenic mutation in the VHL

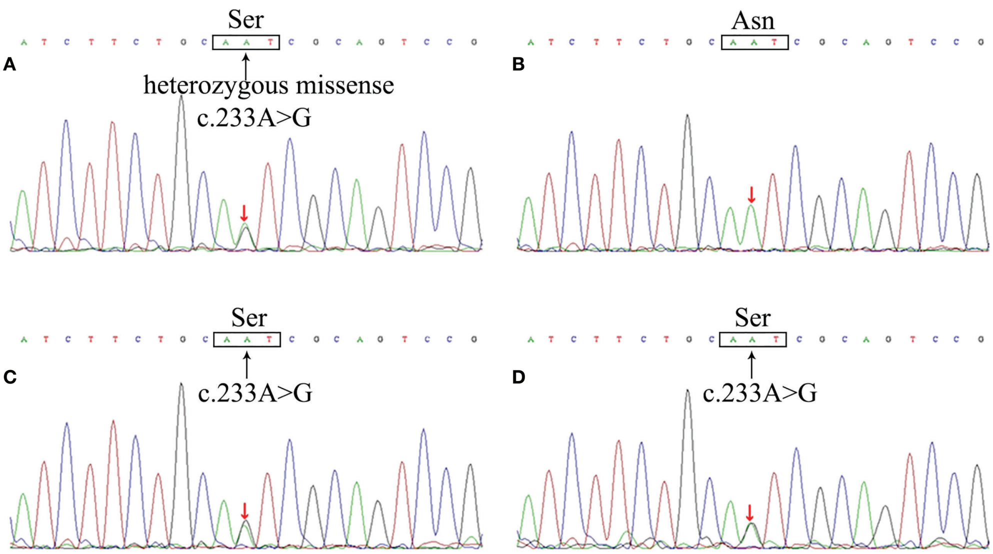

FIGURE 2
The VHL gene mutation of the patient and her family members. Sequencing analysis revealed a c.233A>G heterozygous missense mutation in VHL gene of the patient **(A)**, resulting in the substitution of Ser from Asn in the 78th amino acid site of VHL protein. The patient's daughter **(C)** and son **(D)** showed the same mutation, whereas her husband **(B)** did not.

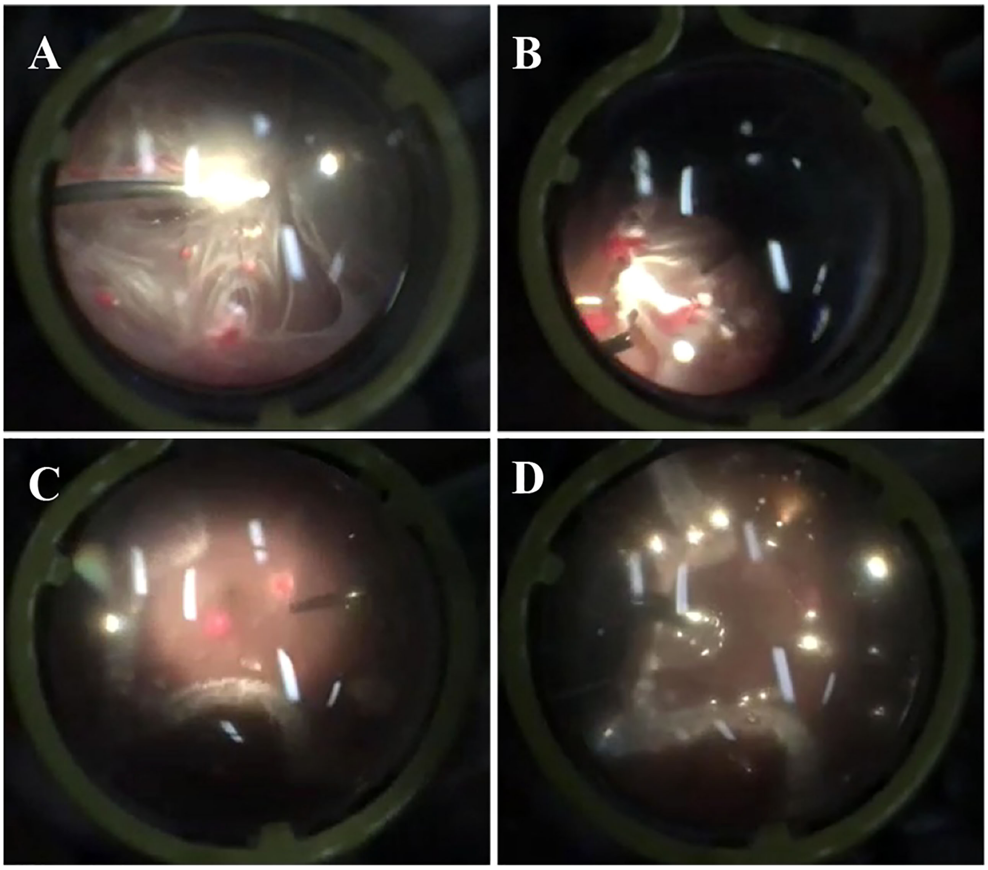

FIGURE 3
Screenshots of the surgery for the patient's right eye. The above screenshots mainly showed the process of pars plana vitrectomy **(A)**, lesion resection **(B)**, endolaser photocoagulation **(C)** and silicone oil tamponade **(D)**.

gene, and her son (12 years old) had already had multiple retinal hemangiomas. We performed laser photocoagulation treatment for the patient's son and suggested further cranial and abdominal examinations, but the patient refused. Follow-up examinations showed ideal recovery in his both eyes. However, it was with regret that we were informed of his death due to a cerebral hemorrhage 2 years after the treatment.

Discussion

Pathogenesis, diagnosis and clinical manifestations

VHL is a rare hereditary tumor syndrome with RH as one of its most common and first clinical manifestations (5, 7, 9). Biallelic inactivation of VHL gene, a known tumor suppressor gene, is considered to be the pathogenesis of VHL in accordance with Knudson's two-hit hypothesis of tumorigenesis (3, 5, 6, 9, 10). In most cases, VHL patients receive one germline mutant allele from their parents and then acquire another allele for somatic mutation through deletion, insertion, missense, truncation mutation or promoter hypermethylation. As a result, the VHL protein(pVHL) may be lost or inactivated resulting in changes of various cellular functions in both hypoxia-inducible factor(HIF) dependent and independent way (5, 10). In fact, the most critical function of pVHL is its adaptive response to hypoxia conditions, which is achieved through its interaction with HIF. Widely expressed in cells throughout the body, pVHL interacts with elongin B, C and Cullin-2 through one of its two protein-binding domains, α-domain to form a complex that acts as an E3 ubiquitin ligase (11–13). Under normoxic conditions, the complex recognizes and mediates ubiquitination degradation of the HIF-α subunit through the β domain of pVHL, whereas in anoxic conditions, the HIF-α subunit remains stable and binds to HIF-β subunit to activate a large number of target genes that mediate the regulation of different processes such as angiogenesis(VEGF, PDGF, CTGF), proliferation (TGFα), apoptosis(CyclinD1), and metabolism(GLUT-1, 6-PFK,

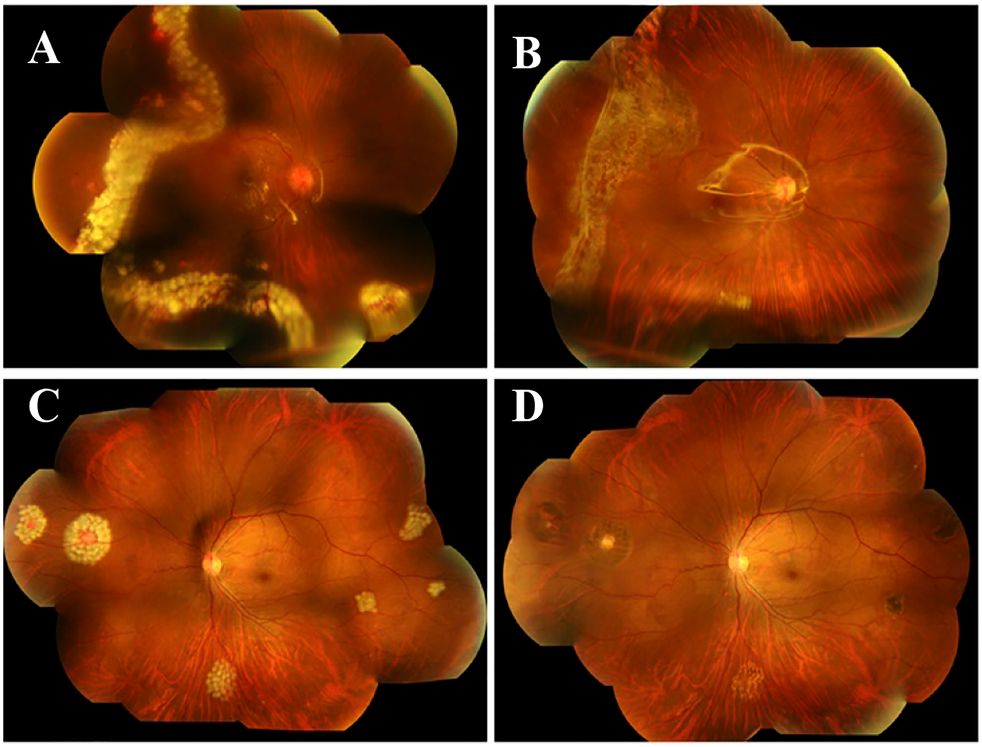

FIGURE 4
Fundus photography one day and 3 months after the surgery. Fundus photography one day after the surgery showed that the retinal detachment of the right eye recovered **(A)** and the hemangiomas of the left eye scarred **(C)** following the treatment. Fundus photography 3 months after the surgery **(B, D)** showed good fundus recovery in the both eyes.

PDK) (3–6, 9, 10, 14). Therefore, the loss or inactivation of pVHL produces a similar effect to that in anoxic environment and eventually leads to multiple tumorigenesis.

The current clinical diagnostic criteria for VHL are as follows: ① one typical VHL tumor(including RH, CNSH, RCC, PCC or pancreatic neoplasm etc.)with a clear family history of VHL;②two hemangioblastomas(RH or CNSH) or one hemangioblastoma and a visceral tumor(PCC, RCC or pancreatic neoplasm etc.) (3, 6, 10, 15). Although VHL patients with typical lesions can be diagnosed based on clinical diagnostic criteria, there are still many suspected cases with atypical lesions that require genetic testing for further confirmation or exclusion (3, 5, 15). However, genetic testing is not a panacea as it was reported that the detection rate of VHL gene mutations were much lower in patients who lacked typical clinical manifestations(24%) than in classic cases with typical features(95%) (16). Therefore, recognizing that no single diagnostic method is enough to completely avoid negative results, it is very important to combine the patient's clinical manifestations and the results of various tests, including genetic tests.

As RH is the main feature of VHL in the eye, identification of VHL-associated RH is crucial for ophthalmologists to establish early diagnosis and provide further screening and treatment. Under the ophthalmoscope, RH usually presents as pink or orange nearly round lesions with obvious dilated and tortuous feeding and draining blood vessels around the tumor in most cases. Secondary exudation, proliferation, hemorrhage, and even exudative or tractive retinal detachment may occur resulting in visual impairment in some cases (2–6, 9, 10, 17). According to the distribution of the lesions in the retina, RH can be divided into peripheral RH and juxtapapillary RH. The former is considered to be the most common ocular lesion of VHL, which is usually located in the superior or inferior temporal region of the peripheral retina. The latter occurs on the optic nerve head or within the juxtapapillary region. Although less common than peripheral RH, it causes more serious damage to vision and limits treatment due to its special location and higher possibility of retinal detachment and macular exudation (9, 18, 19). High resolution fundus photography and FA can improve the detection rate of RH that are difficult to find under the ophthalmoscope. FA often shows marked early hyper-fluorescence with late leakage. For advanced lesions, ocular ultrasound and OCT can be helpful in assessing the extent of macular exudation and retinal detachment (3, 5, 9, 20). Although diagnosis of RH is generally not difficult based on its characteristics, in some cases it should be distinguished from other retinal vascular tumors such as retinal cavernous hemangioma, Wyburn-Mason syndrome, and retinal vasoproliferative tumor (9).

In our case, the patient mainly presented with significant visual impairment of the right eye caused by retinal detachment, and fundus photography revealed four retinal hemangiomas in the temporal peripheral retina with obvious dilated feeding blood vessels and significant hyperplasia. On this basis, we believed that the patient's retinal detachment was mainly tractional and caused by secondary hyperplasia of hemangioma, although exudation could not be ruled out. FA further confirmed the location and size of the hemangioma in the right eye, as well as several small lesions that had not been detected by fundus photography in the left eye. Considering bilateral, multifocal onset and severe secondary retinal detachment, the patient's medical history and family history were carefully examined. Finally, combining the patient's history of CNSH, multiple cysts in the pancreas and right kidney, and clear family history, we determined the clinical diagnosis of VHL. To further verify the diagnosis, genetic test was performed on the patient and her family, and the results were as described above.

We noticed that both the patient and her mother had diabetes at their early 30s, and considering the patient's history of pancreatic cysts, we wondered whether the onset of diabetes might be related to pancreatic cysts caused by VHL. B. Mukhopadhyay et al. reported that extensive serous microcystic adenomas of the pancreas in patients with VHL is closely related to diabetes mellitus (21). Yun Hyi Ku et al, reported a case of VHL with multiple renal and pancreatic cysts associated with gestational diabetes mellitus (22). However, more studies have shown that while the majority of VHL patients may have pancreatic tumors, they are mostly asymptomatic and diabetes is rare in these cases (21–23). In fact, animal studies have shown that loss of the VHL gene in islet β cells leads to impaired glucose tolerance in mice, but whether this is associated with pancreatic tumors remains unclear (24, 25). In addition, in our case, the patient's level of blood glucose was very high(HbA1c 14.2%), but no diabetic retinopathy was observed, which might be related to the short course of the onset of diabetes.

Genotype-phenotype association

It has been reported that there is significant heterogeneity in the clinical manifestations of VHL within and between families, which may be largely related to the diversity of VHL gene mutations (7, 14).With regard to ocular VHL disease, the germline mutations of VHL gene with the highest correlation with RH are missense mutation, truncation mutation and complete deletion (7, 12, 26, 27). Wai T. Wong et al. reported that patients with complete VHL deletion had a lower incidence of RH and better vision than missense mutation and truncation mutation. Moreover, the frequency of juxtapapillary RH in patients with truncation mutation was the lowest among the three mutants (26). Dollfus et al. found that patients with complete deletion were associated with a higher incidence of RH, while Michael Reich et al. suggested that patients with truncation mutations had a higher RH incidence (4, 7). Furthermore, this genotype-phenotype association appears to differ in different ethnic groups (27, 28). These results make the genotype-phenotype of ocular VHL disease quite controversial, possibly because the studies were conducted in groups of different race, age and sample size, which also suggests that environmental factors may be involved in the regulation of RH phenotype. Pradeep Mettu et al. further studied the relationship between missense mutations and VHL-associated RH. Their results showed that almost all missense mutations (98.5%) were located in the α or β domain of VHL protein, among which patients with α domain mutation had a higher RH incidence. Moreover, patients with α domain mutation were more likely to have juxtapapillary RH, while β domain mutation was associated with high occurrence of periphery RH (12).

In our case, the patient was detected with a heterozygous missense mutation(c.233A>G) in the VHL gene, leading to an amino acid type change in the VHL protein sequence (p.Asn78Ser) which is located in the β domain. We found that the patient presented mainly with peripheral RH, which was consistent with Pradeep Mettu's results. In fact, our case is not the first to report that a missense mutation at this locus of VHL gene leads to the pathogenesis of VHL. The first case was reported by F. Chen et al. in 1995, and several other cases were reported in German, Polish, Japanese and Chinese families respectively, indicating that this mutation is relatively common in different races. All of the patients presented with type 1 VHL (without PCC) except one case presenting with type 2 VHL(with PCC), and most of them were associated with RH or CNSH (29–33). Therefore, we believe that VHL patients with c.233A>G missense mutation mainly present type 1 VHL characterized by hemangioma.

Treatment and follow-up

Clinical management of VHL should be multidisciplinary and comprehensive because of its feature of multi-organ involvement. Here we focus on the treatment of VHL-associated RH. Currently, the selection of therapeutic options for VHL-associated RH is mainly based on the location and size of the lesion and whether there is serious vision-threatening complication such as vitreous hemorrhage, epiretinal membrane or retinal detachment (3, 34). For peripheral RH without the above complications and with a small lesion diameter (usually less than 4.5mm), ablation therapy is mainly used in clinical practice, including laser photocoagulation, cryotherapy, radiotherapy, photodynamic therapy and trans-pupil warm therapy, etc. Among them, laser photocoagulation is relatively common-used, especially for lesions with a diameter of less than 1.5mm, which can often play a very good ablative effect (34–36). In our case, multiple small peripheral RH lesions in the patient's left eye were treated with direct argon ion laser photocoagulation (532 nm wavelength) of the tumor and its surroundings. Postoperative fundus photography showed good degeneration of the tumor and feeding vessels without retinal hemorrhage or other adverse reactions, indicating the advantages of laser therapy. Cryotherapy has been used to treat lesions 1.5-4.5mm in diameter, but its use is decreasing due to the potential for uncontrollable acute retinal exudation and vitreous contracture (3). Radiotherapy, photodynamic therapy and trans-pupil warm therapy are rarely used because of their unstable efficacy (37–41). Considering that RH, as a vasogenic tumor, is associated with hypoxia response, anti-VEGF and anti-HIF therapy provide a new idea for the treatment of VHL-associated RH (10, 15, 42). Unfortunately, it has not achieved satisfactory results, but it is undoubtedly a promising treatment and deserves further study in the future.

Studies have shown that vitreoretinal surgery is an effective salvage treatment for peripheral RH patients with vitreous hemorrhage, epiretinal membrane, exudative or tractive retinal detachment, or oversized lesions, and can also be used as one of the early treatment methods for small RH lesions with exudative or tractive tendency (3, 17). Surgical options include PPV with ablation therapy,PPV with feeding vessel ligation or PPV with lesion resection, which are still controversial in application at present. In order to avoid vitreous hemorrhage and proliferative vitreoretinopathy, attention should be paid to effectively close the feeding and draining vessels and complete resection of the posterior hyaloid and epiretinal membranes. In addition to hemorrhage and proliferative vitreoretinopathy, postoperative complications include cataract, neovascular glaucoma, retinal detachment, and iatrogenic retinal rupture. In our case, due to the large RH lesion in the patient's right eye with severe hyperplasia and tractive retinal detachment, we performed PPV, lesion resection, endolaser photocoagulation and silicone oil tamponade. The peripheral location of the tumors makes them easier to remove surgically with minimal visual sequelae. And the 23G PPV procedure ensured minimal iatrogenic injury. Postoperative follow-up showed that the patient had flat retina with no residual lesions, good visual recovery, and no reoccurrence of RH or retinal detachment, suggesting good surgical efficacy. In fact, there have been studies comparing the outcomes and postoperative complications of PPV combined with ablation/ligation or lesion resection. In the study of Gaudric et al., a preliminary comparison found that the visual recovery of patients after ablation was better than that after resection while there seemed to be no difference in reoccurrence of RH and retinal detachment between the two procedures (43). Krzystolik et al. reported that resection was more likely to cause RH recurrence than ablation/ligation (44). Others chose between the two procedures primarily based on their clinical experience, with good recovery but high incidence of postoperative complications seen in both procedures (45–47). In conclusion, vitreoretinal surgery is an effective method for the treatment of severe VHL-associated RH with retinal detachment, but postoperative complications are prone to occur.

For juxtapapillary RH, although active laser treatment can effectively control the progression of RH lesions, it may lead to poor prognosis of vision and impaired visual field due to damage to the retinal nerve fiber layer (3, 48). In contrast, photodynamic therapy, radiotherapy and anti-VEGF therapy have better safety but less satisfactory efficacy. Therefore, in the current situation that there is no ideal treatment for juxtapapillary RH, observation and follow-up can be regarded as a better strategy, especially for those with no obvious exudation. If the lesion progresses rapidly with significant exudation and impaired vision, laser photocoagulation may be considered as appropriate. And vitreoretinal surgery remains the primary consideration in juxtapapillary RH patients with retinal detachment.

For the management of VHL-associated RH, one of the core principles to be followed is early detection of lesions and timely treatment, which requires regular follow-up of patients. All VHL patients and their at-risk relatives should undergo annual ophthalmic examinations starting in childhood, including visual acuity examination, fundus examination, fundus photography, FA, etc. by experienced ophthalmologist (5, 6). For patients with VHL-associated RH who have received previous treatment, especially vitreoretinal surgery, our experience is to conduct ophthalmic follow-up at 2 weeks, 1 month, 2 months, 3 months, 6 months, and 1 year after surgery to evaluate treatment outcomes and disease changes. Follow-up should include visual field examination, intraocular pressure measurement, and anterior segment examination in addition to the above annual screening items to assess postoperative complications. Although VHL-associated RH can have a great impact on patients' vision, CNSH and RCC, as the primary lethal factors of VHL, are the biggest threats to patients' health (6). Therefore, ophthalmologists should not only pay attention to the diagnosis and treatment of ocular complications of VHL, but also to patients' general condition and other organ involvement. The death of the patient's son in our case taught us a painful lesson about the critical importance of screening for VHL complications outside the eye. For screening and follow-up of other organ lesions, please refer to other literature (5, 6).

Conclusion

VHL is a rare tumor syndrome with multiple organ involvement and complex genotype-phenotype association. The pathogenesis involves inactivation of VHL tumor suppressor genes in accordance with two-hit hypothesis. The clinical manifestations include RH, CNSH, RCC, PCC and pancreatic neoplasms, among which RH is the most prominent. Ophthalmologic examination such as fundus examination and fundus angiography together with genetic testing are of great importance in the diagnosis of VHL-associated RH. Ophthalmic treatment includes ablation therapy(laser photocoagulation, cryotherapy, etc.) and vitreoretinal surgery. The choice of treatment should be based on the size, location and complications of the lesions. Regular follow-up is important for early detection and control of VHL-associated RH. Here we report a case of binocular RH caused by VHL, in which one of the more severe eyes with retinal detachment was treated surgically and the other eye was treated with laser photocoagulation, and the binocular vision recovered well after surgery. It is hoped to provide a new perspective for the clinical management of VHL-associated RH.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Hainan Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XH perform the surgery. YH, WH and XH collected the data, prepared the material. YH and WH prepared the manuscript. All authors commented on previous versions 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.963469/full#supplementary-material

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Construction and validation of a prediction model of extrahepatic metastasis for hepatocellular carcinoma based on common clinically available data

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Objective: This study aimed to investigate the clinical characteristics and risk factors of patients with hepatocellular carcinoma (HCC) with extrahepatic metastases (EHM) and to establish an effective predictive nomogram.

Methods: Clinical and pathological data from 607 patients with hepatocellular carcinoma admitted to the Affiliated Hospital of Qinghai University between 1 January 2015 and 31 May 2018 were documented, as well as demographics, clinical pathological characteristics, and tumor-related parameters to clarify clinical risk factors for HCC EHM. These risks were selected to build an R-based clinical prediction model. The predictive accuracy and discriminating ability of the model were determined by the concordance index (C-index) and the calibration curve. The results were validated with a bootstrap resample and 151 patients from 1 June 2018 to 31 December 2019 at the same facility.

Results: In multivariate analysis, independent factors for EHM were neutrophils, prothrombin time, tumor number, and size, all of which were selected in the model. The C-index in the EHM prediction model was 0.672 and in the validation cohort was 0.694. In the training cohort and the validation cohort, the calibration curve for the probability of EHM showed good agreement between the nomogram prediction and the actual observation.

Conclusion: The extrahepatic metastasis prediction model of hepatocellular carcinoma constructed in this study has some evaluation capability.

KEYWORDS

primary hepatic carcinoma, extrahepatic metastases, risk factors, clinical features, the prediction model

Introduction

Hepatocellular carcinoma (HCC) is the leading malignant tumor from the liver, which is the seventh most common, and has the second highest death rate (in all 36 tumors) (1). It has already been reported in the article that the risk factor for poor prognosis is the lack of diagnosis of extrahepatic metastasis (EHM) (2). Therefore, an accurate evaluation of HCC metastases is critical for improved prognosis.

HCC is a kind of cancer that develops as a result of a secondary liver illness [such as viral hepatitis (HBV or HCV), alcoholic or fatty liver disease]. Liver function indices are intimately linked to the occurrence and development of HCC (3, 4). Besides, studies have reported that primary tumor progression characteristics (such as vascular invasion, tumor size and number, etc.) are independent risk factors for EHM (5, 6). The above parameters can be risk factors for metastatic HCC and will be included in this study as observational information. Since patients with HCC usually receive antitumor treatment during the clinical course, it may give a confounding effect on the analysis of metastatic factors. As a result, we evaluated the clinical features and risk factors of patients with HCC and EHM who did not receive anti-tumor therapy, and we created an effective EHM diagnostic nomogram.

Patients and methods

Patients and study design

A retrospective study was conducted on patients who were diagnosed with HCC from 1 January 2015 to 31 December 2019 at the Affiliated Hospital of Qinghai University (Xining, China). Inclusion criteria were as follows: 1) according to the Guidelines for diagnosis and treatment of primary liver cancer, the patient was diagnosed with HCC (2021 Edition) (7) and 2) with a complete medical record. Exclusion criteria were as follows: 1) no prior history of anticancer treatment; 2) no priors for other cancers; and 3) without other confirmed or suspected cancers. The training cohort consisted of patients between 1 January 2015, and 31 May 2018, and the validation cohort consisted of patients between 1 June 2018 and 31 December 2019. Depending on whether EHM was present at the time of the first diagnosis, the training cohort was further split into extrahepatic metastatic (observation group) and non-extrahepatic metastatic (control group) groups. Age and sex-related demographic data as well as clinicopathological characteristics such as body mass index, smoking and drinking history, blood tests, assessments of HBV and HCV infections, results of liver function tests, and tumor-related parameters were prospectively gathered.

Diagnosis and definitions

The appearance of a newly detected tumor confirmed on two radiologic images, with or without an elevation of serum tumor markers, was defined as metastasis. A patient with a smoking history was defined as having smoked continuously or cumulatively for 6 months or more in the past. Drinking more than three standard glasses of alcohol per day or more than seven standard glasses of alcohol per week for 1 month or more, either continuously or cumulatively, is considered a drinking history.

Follow-up

During the 2 years following diagnosis, all patients were seen once every 3 months. An abdominal ultrasound, blood test, and liver function test were performed at each of the follow-up visits. When a tumor recurrence or metastasis was suspected, a contrast-enhanced CT or MRI was performed, and the results were reviewed individually by two experienced doctors.

Statistical analyses

Statistical analyses to identify risk factors were performed using IBM SPSS Statistics 23.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using the Mann–Whitney *U* test for variables with an abnormal distribution. Categorical variables were compared using the chi-squared or Fisher exact test. In the univariate analyses, $p < 0.05$ was considered statistically significant. Multivariate logistic regression analysis was used to evaluate the independent risk factors of extrahepatic metastases. In the multivariate analyses, $p < 0.05$ was considered statistically significant.

A nomogram was formulated based on the results of multivariate logistic regression analysis and by using the 'rms' package in R version 4.12 (http://www.r-project.org/). A final model selection was performed by a forward conditional selection process. The predictive performance of the nomogram was measured by concordance index (C-index) and the calibration curve. Bootstraps with 1000 resample were used for these activities (Figure 1).

Results

Presentation of patients

In this study, during the defined study period (January 1st,2015 to December 31st,2019), 1673 cases were identified as HCC in the Affiliated Hospital of Qinghai University. 1066 cases

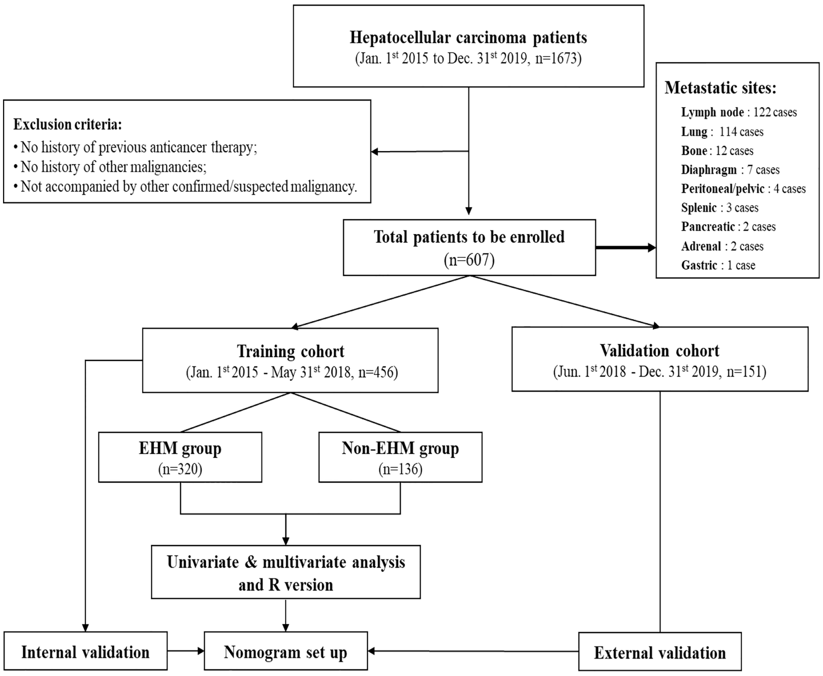

FIGURE 1
After the screening of medical records for the study, 607 cases were identified for final enrolment based on exclusion criteria. The training cohort was used to identify factors that were able to predict EHM, thereby establishing a nomogram for this study. This nomogram was then validated regarding its accuracy in the evaluation of EHM risk by using both the training cohort and validation cohort.

were excluded according to the exclusion criteria, and 607 cases were finally enrolled, including 456 patients in the training cohort from 1 January 2015 to 31 May 2018, and 151 patients in the validation cohort from 1 June 2018 to 31 December 2019 (Figure 1). Among all the 170 EMH patients enrolled at the time of diagnosis, 122 patients (71.8%) had lymph node metastasis, 114 patients (67.1%) had lung metastasis, 12 patients (7.1%) had bone metastasis, 7 patients (4.1%) had diaphragm metastasis, 4 patients (2.9%) had peritoneal or pelvic metastasis, 3 patients (2.2%) had splenic metastasis, and pancreatic metastases in 2 cases (1.5%), adrenal metastases in 2 cases (1.5%) and gastric metastases in 1 case (0.8%).

Baseline of characteristics and multivariate analysis

The training cohort was concentrated on 136 cases in the EHM group, of which 112 (81.4%) were male and 24 (17.6%) were female, aged 53.42 (48.15, 62.69) years; 320 cases in the control group, of which 255 (79.7%) were male and 65 (20.3%) were female, aged 53.83 (46.82, 63.32) years. Table 1 shows further characteristics of training and validation patients. According to univariate analysis and multivariate analyses, neutrophils, prothrombin time, tumor count, and size have been shown to be independent risk factors for EHM in initial patients (Table 2 and Figure 2).

Construction and validation of the initial patients EHM nomogram

Based on the results of the multivariate logistic regression analysis in the training cohort, neutrophil, prothrombin time, tumor number, and tumor size were used as variables to construct the nomogram (Figure 3). When the ROC curve was plotted using the training cohort, the area under the ROC curve was calculated as 0.672 (Figure 4A). In the validation cohort, the nomogram displayed a C index of 0.694 (Figure 5A). This result indicates that there is some discrimination in the mode and can be relied on to accurately predict the extrahepatic metastases of hepatocellular carcinoma. Model consistency was assessed by drawing calibration curves using data from the Training and Validation cohorts (Figures 4B, 5B). The diagonal line represents the precise match between the expected and real circumstances, the dashed line represents the model's theoretical forecast, and the solid line represents the actual prediction obtained by repeated sampling. The two curves are less discontinuous from the diagonal line, suggesting that the model-anticipated results are more consistent with what actually occurred and the model-predicted results are more credible.

TABLE 1 Baseline clinical characteristics of inital patients.

Variable	Training cohort (n = 456)	Validation cohort (n = 151)
Age, years	53.69 (47.03, 63.14)	54.21 (48.04, 62.62)
Sex		
Male	367 (80.5%)	126 (83.4%)
Female	89 (19.5%)	25 (16.6%)
History of diabetes	66 (14.5%)	39 (25.8%)
History of Cirrhosis	313 (68.6%)	118 (78.1%)
History of Smoke	135 (29.6%)	57 (37.7%)
History of Drink	100 (21.9%)	44 (29.1%)
BMI	22.66 (20.57, 24.91)	23.51 (21.24, 25.80)
Child-Pugh		
A	245 (53.7%)	91 (60.2%)
B	186 (40.8%)	54 (35.8%)
C	25 (5.5%)	6 (4.0%)
WBC, $\times 10^9$/L	5.10 (3.80, 6.91)	4.89 (3.82, 6.42)
NE, %	65.04 (57.20, 74.50)	67.25 (59.63, 73.25)
HB, g/L	143.00 (124.00, 159.00)	146.00 (128.00, 165.25)
PLT, $\times 10^9$	125.00 (79.00, 182.00)	133.00 (78.50, 183.00)
ALT, U/L	67.50 (38.00, 153.50)	64.50 (44.00, 175.00)
AST, U/L	81.00 (48.00, 185.00)	102.50 (50.75, 204.50)
TP, g/L	63.40 (58.00, 68.00)	65.95 (60.58, 73.00)
ALB, g/L	33.25 (29.63, 37.00)	35.20 (31.48, 39.75)
GLO, g/L	29.50 (25.90, 33.50)	29.80 (26.88, 34.45)
TBIL, μmol/L	27.75 (17.10, 46.15)	25.10 (16.00, 43.35)
DBIL, μmol/L	11.87 (7, 20.48)	11.45 (7.28, 19.88)
ALP, U/L	144.00 (98.00, 246.85)	145.00 (96.75, 265.50)
Cr, μmol/L	58.00 (50.00, 66.13)	59.00 (49.75, 67.25)
CHE, U/L	3382.50 (2323.25, 4970.50)	4308.00 (3023.50, 5981.75)
INR	1.14 (1.03, 1.29)	1.10 (0.99, 1.21)
TT, s	19.50 (17.80, 21.00)	19.20 (17.88, 20.80)
DD, mg/L	3.60 (1.70, 7.00)	3.60 (1.50, 8.55)
APTT, s	36.10 (32.10, 44.10)	35.00 (30.05, 39.63)
FIB, g/L	3.26 (2.33, 4.26)	2.67 (2.05, 4.16)
PT, s	13.70 (12.30, 15.48)	13.15 (11.90, 14.53)
AFP, ng/ml	337.46 (13.24, 2000.00)	200.09 (20.68, 2000.00)
CEA ≥5 ng/ml	47 (10.30%)	23 (15.2%)
CA19-9 ≥35 U/ml	55 (12.10%)	12 (7.9%)
HBsAg, positive	326 (71.5%)	116 (76.8%)
Anti-HCV, positive	15 (3.3%)	1 (0.7%)
Tumor number	4 (4, >4)	4 (4, 4)
Tumor sizes, cm	7.60 (4.46, 11.14)	6.58 (4.30, 11.78)
Vascular invasion	185 (40.6%)	45 (29.8%)
Tumor Location		
Left lobe	42 (9.2%)	12 (8.0%)
Right lobe	202 (44.3%)	69 (45.7%)
Bilateral lobe	212 (46.5%)	70 (46.3%)

BMI, Body Mass Index; WBC, White Blood Cell Count; NE, Neutrophil; HB, Hemoglobin; PLT, Platelet Count; ALT, Alanine Amiotransferase; AST, Aspartate Aminotransferase; TP, Total Protein; ALB, Albumin; GLO, Globulin; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALP, Alkaline Phosphatase; Cr, Creatinine; CHE, Cholinesterase; INR, International Normalized Ratio; TT, Thrombin Time; DD, D-Dimer; APTT, Activated Partial Thromboplastin Time; FIB, Fibrinogen; PT, Prothrombin Time; AFP, α-Fetoprotein; CEA, Carcinoembryonic Antigen; CA19-9, Carbohydrate Antigen 19-9; HBsAg, Hepatitis B Surface Antigen; Anti-HCV, Anti-Hepatitis C Virus Antibody.

TABLE 2 Univariate analysis for predicting EHM in the training cohort.

Variable	EHM group (n = 320)	Non-EHM group (n = 136)	p-Value
Age, years	53.83 (46.82, 63.32)	53.42 (48.15, 62.69)	0.959
Sex			0.511
Male	255 (79.7%)	112 (82.4%)	
Female	65 (20.3%)	24 (17.6%)	
History of diabetes	51 (15.9%)	15 (11.0%)	0.173
History of cirrhosis	219 (68.4%)	94 (69.1%)	0.886
History of smoke	94 (29.4%)	41 (30.1%)	0.869
History of drink	70 (21.9%)	30 (22.1%)	0.965
BMI	22.66 (20.57, 24.91)	22.59 (20.67, 24.83)	0.742
Child-Pugh			0.158
A	179 (55.9%)	66 (48.5%)	
B	127 (39.7%)	59 (43.4%)	
C	14 (4.4%)	11 (8.1%)	
WBC, $\times 10^9$/L	5.03 (3.74, 6.58)	5.37 (4.12, 7.64)	0.053
NE, %	63.70 (55.96, 73.45)	69.50 (59.03, 76.50)	0.001
HB, g/L	144.50 (126.00, 160.00)	139 (120.25, 157.00)	0.044
PLT, $\times 10^9$	125.00 (79.00, 177.75)	124.5 (79.50, 188.50)	0.711
ALT, U/L	63.00 (35.00, 144.50)	77.00 (43.00, 163.00)	0.031
AST, U/L	76.50 (45.00, 170.00)	104.50 (64.00, 242.00)	0.002
TP, g/L	63.30 (58.00, 68.00)	64.00 (57.70, 70.00)	0.427
ALB, g/L	33.45 (30.43, 37.00)	32.00 (28.10, 36.78)	0.039
GLO, g/L	29.00 (25.60, 32.50)	31.20 (26.33, 34.88)	0.005
TBIL, μmol/L	25.35 (16.05, 44.00)	31.60 (20.05, 52.70)	0.007
DBIL, μmol/L	11.38 (6.60, 19.08)	13.20 (8.33, 23.17)	0.038
ALP, U/L	133.00 (89.00, 217.75)	170.00 (110.25, 297.00)	0.000
Cr, μmol/L	58.00 (51.00, 66.13)	57.00 (50.00, 66.75)	0.603
CHE, U/L	3563.00 (2571.50, 5067.00)	2966.00 (2001.00, 4229.00)	0.001
INR	1.13 (1.02, 1.26)	1.18 (1.06, 1.34)	0.002
TT, s	19.6 (17.70, 21.00)	19.40 (18.00, 21.00)	0.658
DD, mg/L	3.30 (1.53, 6.78)	3.80 (2.63, 7.70)	0.019
APTT, s	35.95 (31.60, 43.20)	37.45 (32.65, 48.38)	0.066
FIB, g/L	3.21 (2.30, 4.21)	3.33 (2.41, 4.36)	0.351
PT, s	13.60 (12.20, 15.30)	14.1 (12.72, 15.98)	0.004
AFP, ng/ml	246.34 (12.16, 2000.00)	370.29 (17.92, 2000.00)	0.507
CEA ≥5 ng/ml	30 (9.38%)	17 (12.5%)	0.637
CA19-9 ≥35 U/ml	38 (11.88%)	17 (12.5%)	0.770
HBsAg, positive	231 (76.7%)	95 (72.5%)	0.348
Anti-HCV, positive	9 (3.5%)	6 (5.3%)	0.417
Tumor number	4 (2, >4)	4 (4, >4)	0.001
Tumor sizes, cm	7.00 (4.00, 10.60)	9.2 (5.91, 11.82)	0.000
Vascular invasion	115 (35.9%)	70 (51.5%)	0.002
Tumor location			0.027
Left lobe	36 (11.3%)	6 (4.4%)	
Right lobe	145 (45.3%)	57 (41.9%)	
Bilateral lobe	139 (43.4%)	73 (53.7%)	

BMI, Body Mass Index; WBC, White Blood Cell Count; NE, Neutrophil; HB, Hemoglobin; PLT, Platelet Count; ALT, Alanine Amiotransferase; AST, Aspartate Aminotransferase; TP, Total Protein; ALB, Albumin; GLO, Globulin; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALP, Alkaline Phosphatase; Cr, Creatinine; CHE, Cholinesterase; INR, International Normalized Ratio; TT, Thrombin Time; DD, D-Dimer; APTT, Activated Partial Thromboplastin Time; FIB, Fibrinogen; PT, Prothrombin Time; AFP, α-Fetoprotein; CEA, Carcinoembryonic Antigen; CA19-9, Carbohydrate Antigen 19-9; HBsAg, Hepatitis B Surface Antigen; Anti-HCV, Anti-Hepatitis C Virus Antibody.

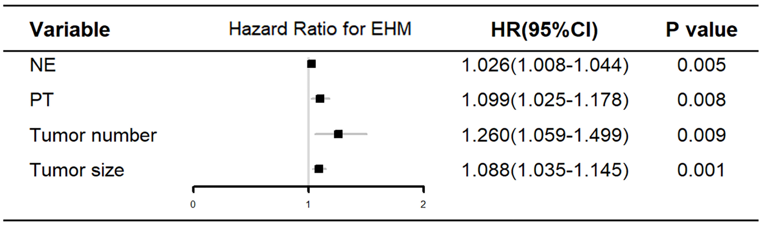

FIGURE 2
Multivariate analysis of the clinical characteristics for predicting EHM in the training cohort. NE, neutrophil; PT, prothrombin time.

Follow-up

The 415 patients were fully monitored for 23.694 person-months (median, 15.118 months; range, 3.7 to 62.6 months), in which 308 (74.2%) died. In all 415 patients enrolled, the overall survival (OS) of patients with EHM was significantly worse than non-EHM patients (Figure 6, 6.7 months *vs.* 23.1 months, p = 0.00).

A total of 372 patients were enrolled in this study without metastasis at the time of initial diagnosis and all were followed up. A total of 372 patients were enrolled in this study without metastasis at the time of initial diagnosis, all of whom underwent follow-up. Based on the EHM occurring during the follow-up period, the patients were divided into observational metastases and non-methane groups. The characteristics of the patients are listed in Table 3. According to univariate analysis and multivariate analyses, neutrophils, Total Protein, Carcinoembryonic Antigen and tumor sizes have been shown to be independent risk factors for EHM in followed up patients (Table 4) .

Discussion

The incidence of HCC has increased in many countries in recent years. The primary risk factors for HCC worldwide include chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) and the consumption of aflatoxin-contaminated food. The prevalence of HCC caused by metabolic syndrome, obesity, diabetes, excessive alcohol consumption, and non-alcoholic fatty liver disease (NAFLD) is gradually increasing (8). Thus, as the etiology of the disease has changed, the risk factors for EHM of HCC may also be changed, and further research is required.

For patients with HCC with EHM, most previous studies examined only the relationship between clinicopathological characteristics and the prognosis of patients with HCC (5, 9–11). However, the common shortcoming was that the patients enrolled previously received anti-tumor treatment, and the lab results were incidentally altered (to exhibit low white blood cell counts, low platelet counts, poor liver or kidney function, and so on) (9), which may bring inevitable interference to the analysis of metastases. Therefore, this study investigated the clinical

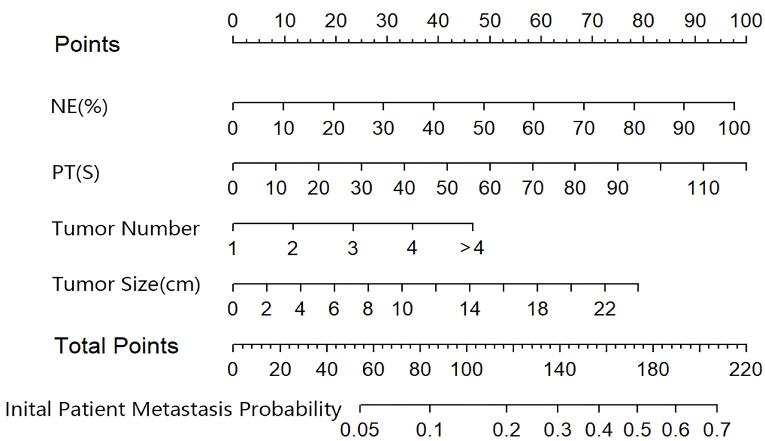

FIGURE 3
The nomogram predicting initial patient EHM probability. NE, neutrophil; PT, prothrombin time.

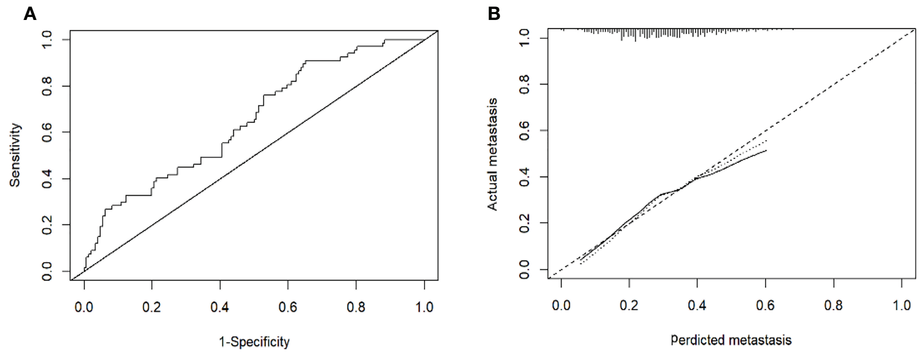

FIGURE 4
(A): Receiver operating characteristic curves for EHM of the patients in the training cohort. The receiver operating characteristic curves at the initial diagnosis are shown, and its area ROC curves are provided. **(B)**: Calibration plots of EHM in the training cohorts. The calibration curves derived from the training cohorts are almost a diagonal line that would represent perfectly reliable prediction.

characteristics and risk factors of patients with HCC with EHM who did not receive anti-tumor treatment, and established an effective diagnostic nomogram for EHM. In our study, 28% (170) of all 607 HCC patients included had extrahepatic metastases, consistent with previous study results (9, 12). In the initially diagnosed patients, the metastatic sites included the lymph node (122, 71.8%), lung (104, 61.2%), bone (12, 7.1%), diaphragm (7, 4.1%), peritoneum (4, 2.3%), spleen (3, 1.8%), pancreas (2, 1.2%), adrenal gland (2, 1.2%), and stomach (1, 0.6%). The lung may be the most common site of EHM from HCC speciously, but in our study, the proportion of lymph node metastases was the highest (122, 71.8%). Additionally, a similar finding was obtained by another Chinese study (13). In that research study, among the 132 patients with extrahepatic metastases from hepatocellular carcinoma diagnosed by whole-body PET/CT, 72 (54.5%) had metastases in the lymph node, 32 (24.2%) had metastases in the bones, and 28 (21.2%) had metastases in the lungs. This may due to the main symptom of patients with simple lymph node metastases rarely present with clinical symptoms, and only a small proportion of patients are noted when the enlarged lymph nodes caused a compression effect, for example, the jaundice caused by bile duct compression. As a result, the rate of missed lymph node metastases was high and easily ignored in a relatively earlier stage of metastasis.

According to the univariate and multivariate analysis of EHM in our research (Table 2 and Figure 2), there may be a potential relation between HCC patients with EHM and the tumor number. This relationship was also mentioned in another report which showed that the number of tumors >2 can be easier found in patients with EHM (14). They therefore concluded that the number of tumors could be associated with aggressive biological features. Coincidentally, in our research, the tumor counts are independent predictors for EHM (Figure 2). Similar findings for HCC metastasis were noted previously, which

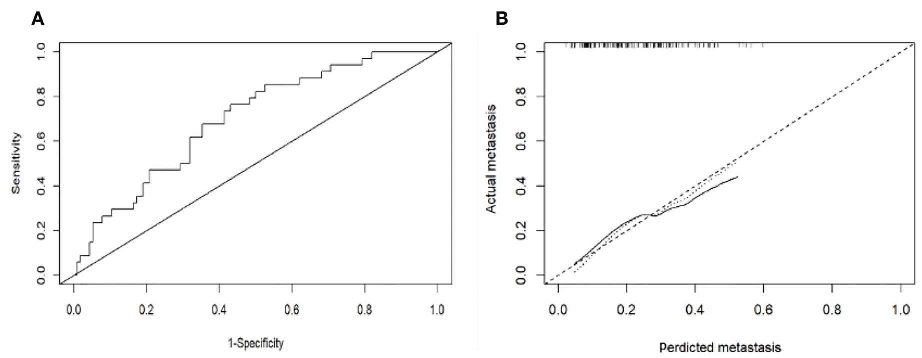

FIGURE 5
(A): Receiver operating characteristic curves for EHM of the patients in the validation cohort. The receiver operating characteristic curves at the initial diagnosis are shown, and its area ROC curves are provided. **(B)**: Calibration plots of EHM in the validation cohort. The calibration curves derived from the validation cohort are almost a diagonal line that would represent perfectly reliable prediction.

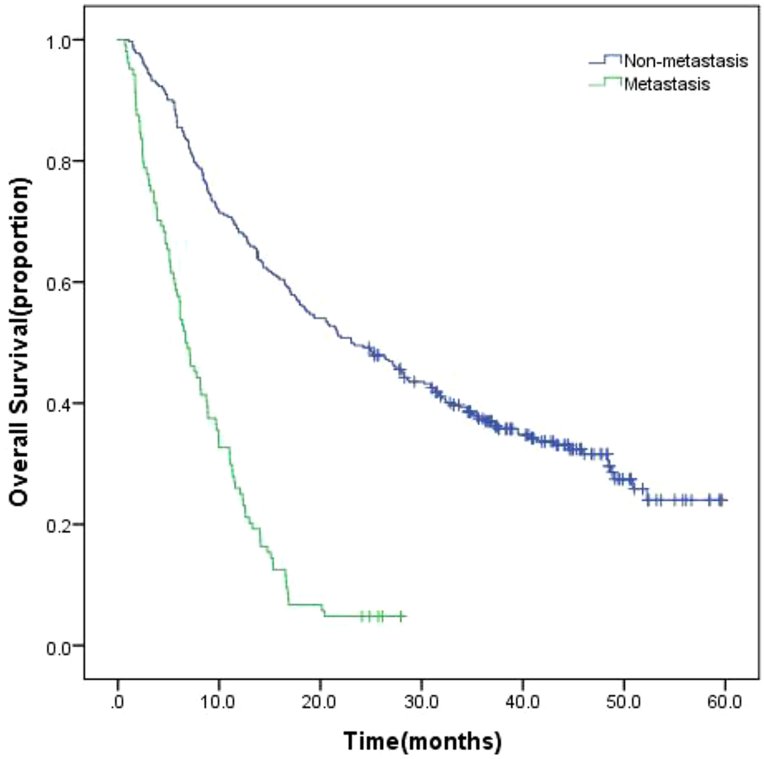

FIGURE 6
Kaplan-Meier survival curves of all enrolled patients.

revealed that a multiple tumor number was a risk factor for EHM in HCC (15, 16).

A close relationship between HCC size and EHM seems to exist according to our results (Figure 2). One possible explanation is that the lager lesion contains more tumor stem cells, which are frequently identified as the source of malignant phenotypes such as aggressive growth, portal vein thrombosis, or metastasis. Another explanation is that the tumor biology changes beyond a certain mass, just as tumors in general cannot grow beyond a critical small size (9, 17, 18).

In this study, we also demonstrated that an elevated neutrophil was a significant independent predictor for EHM of HCC. Neutrophil is one of the most simple and effective markers of inflammation and is associated with poor prognosis in various cancers (11, 19, 20). Therefore, the immanent reason may be that the high neutrophil count is a symbol of an adequate environment for tumor progression, which has been shown to promote tumor growth and metastasis by secreting chemokines, vascular endothelial growth factor, and matrix metalloproteinase-9, which are involved in the development of local inflammation and angiogenesis (21–23).

Currently, angiopoietin-2 (Ang-2), microRNAs (miRNAs), and lncRNA BACE1-AS are available as a test for the evaluation of EHM in HCC (24–27). However, the above parameters are mainly laboratory-based and are not available in most hospitals. Therefore, our results identified the risk factors for EHM of HCC which are based on noninvasively clinically readily available data and developed a nomogram with some predictive ability. We constructed a predictive model of EHM of HCC by taking the above independent risk factors as variables. It is used to predict the initial probability of patient EHM, and validated internally and externally, confirming its certain predictive capacity for EHM. The calibration curves were drawn and showed that the nomogram predictions overlapped well with the actual clinical situation, with good agreement and credible prediction results.

In previous studies (9, 12, 14, 28), most researchers focused on the observation of the patient's prognosis. Therefore, only a preliminary analysis of the reference indicators associated with EHM was performed. This study further explored the independent risk factors for EHM and developed a nomogram with some predictive ability, building on the previous work. It has a role to play in reducing missed EHM and designing optimal therapies for those patients. This study is a single-center study only and the model could be further improved with a larger sample size and multi-center data.

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TABLE 3 Baseline clinical characteristics of followed up patients.

Variable	EHM group (n = 282)	Non-EHM group (n = 90)
Age, years	54.62 (47.26,63.37)	53.12 (47.93,62.67)
Sex		
Male	228 (80.85%)	66 (73.33%)
Female	54 (19.15%)	24 (26.67%)
History of diabetes	46 (16.31%)	23 (25.56%)
History of cirrhosis	202 (71.63%)	62 (68.89%)
History of smoke	87 (30.85%)	32 (35.56%)
History of drink	65 (23.05%)	24 (26.67%)
BMI	23.04 (20.83, 25.34)	22.49 (20.24, 25.44)
Child-Pugh		
A	158 (56.03%)	65 (72.22%)
B	113 (40.07%)	24 (26.67%)
C	11 (3.90%)	1 (1.11%)
WBC, $\times 10^9$/L	4.80 (3.62, 6.37)	5.14 (3.84, 6.86)
NE, %	62.87 (55.73, 72.10)	63.55 (56.235, 72.55)
HB, g/L	144.00 (125.75, 161.00)	144.50 (126.25, 164.00)
PLT, $\times 10^9$	124.50 (71.00, 178.75)	132.00 (83.75, 193.50)
ALT, U/L	66.00 (37.00, 143.00)	60.00 (37.75, 174.00)
AST, U/L	78.50 (45.00, 180.25)	63.50 (44.75, 151.75)
TP, g/L	64.80 (59.48, 68.73)	63.45 (58.68, 68.55)
ALB, g/L	33.75 (30.30, 38.20)	34.40 (31.28, 38.53)
GLO, g/L	29.25 (26.18, 33.30)	28.70 (24.98, 32.68)
TBIL, μmol/L	26.50 (16.55, 45.33)	19.50 (13.43, 31.10)
DBIL, μmol/L	11.50 (7.13, 20.18)	9.25 (5.48, 14.68)
ALP, U/L	128.85 (88.85, 224.13)	135.45 (90.50, 229.40)
Cr, μmol/L	59.00 (51.00, 67.50)	54.00 (48.00, 64.00)
CHE, U/L	3816.00 (2625.00, 5451.50)	3946.00 (3172.00, 5356.00)
INR	1.11 (1.01, 1.25)	1.07 (0.98, 1.21)
TT, s	19.50 (17.90, 21.00)	19.00 (17.40, 20.80)
DD, mg/L	3.10 (1.50, 6.80)	3.60 (1.50, 6.05)
APTT, s	35.65 (30.90, 43.40)	34.80 (30.90, 40.50)
FIB, g/L	2.94 (2.21, 4.02)	3.62 (2.36, 4.80)
PT, s	13.40 (12.10, 15.03)	12.80 (11.80, 14.55)
AFP, ng/ml	112.21 (11.59, 2000.00)	440.33 (25.91, 2000.00)
CA19-9 ≥35 U/ml	29 (10.28%)	13 (14.44%)
CEA ≥5 ng/ml	33 (11.70%)	9 (10.00%)
HBsAg, positive	211 (74.82%)	62 (68.89%)
Anti-HCV, positive	8 (2.84%)	1 (1.11%)
Tumor number	4 (2, 4)	4 (4, >4)
Tumor sizes, cm	5.96 (3.68, 9.91)	7.59 (4.55, 11.18)
Vascular invasion	100 (35.46%)	24 (26.67%)
Tumor location		
Left lobe	35 (12.41%)	6 (6.67%)
Right lobe	133 (47.16%)	36 (40.00%)
Bilateral lobe	114 (40.43%)	48 (53.33%)

BMI, Body Mass Index; WBC, White Blood Cell Count; NE, Neutrophil; HB, Hemoglobin; PLT, Platelet Count; ALT, Alanine Amiotransferase; AST, Aspartate Aminotransferase; TP, Total Protein; ALB, Albumin; GLO, Globulin; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALP, Alkaline Phosphatase; Cr, Creatinine; CHE, Cholinesterase; INR, International Normalized Ratio; TT, Thrombin Time; DD, D-Dimer; APTT, Activated Partial Thromboplastin Time; FIB, Fibrinogen; PT, Prothrombin Time; AFP, α-Fetoprotein; CEA, Carcinoembryonic Antigen; CA19-9, Carbohydrate Antigen 19-9;HBsAg, Hepatitis B Surface Antigen; Anti-HCV, Anti-Hepatitis C Virus Antibody.

TABLE 4 Univariate and multivariate analysis for predicting EHM in followed up patients.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Age, years	0.999	0.978-1.021	0.951			
Sex						
Male						
Female	1.452	0.901–2.341	0.126			
History of diabetes	0.893	0.549–1.452	0.647			
History of cirrhosis	0.676	0.428–1.066	0.092			
History of smoke	0.831	0.537–1.285	0.405			
History of drink	0.756	0.473–1.211	0.245			
BMI	0.978	0.915–1.046	0.517			
Child–Pugh						
A	0.256	0.034–1.913	0.184			
B	0.300	0.039–2.289	0.245			
C						
WBC, $\times 10^9$/L	1.063	0.970–1.164	0.192			
NE, %	1.028	1.009–1.048	0.004	1.021	1.000–1.044	0.044
HB, g/L	1.000	0.994–1.006	0.930			
PLT, $\times 10^9$	1.002	0.999–1.005	0.187			
ALT, U/L	1.000	1.000–1.001	0.245			
AST, U/L	1.001	1.000–1.001	0.093			
TP, g/L	0.975	0.950–1.001	0.057	0.970	0.942–0.998	0.039
ALB, g/L	0.975	0.932–1.020	0.267			
GLO, g/L	0.975	0.944–1.007	0.123			
TBIL, µmol/L	1.002	0.997–1.007	0.376			
DBIL, µmol/L	1.003	0.997–1.009	0.331			
ALP, U/L	1.001	1.000–1.003	0.117			
CHE, U/L	1.000	1.000–1.000	0.765			
INR	1.009	0.970–1.049	0.663			
TT, s	0.997	0.936–1.063	0.932			
DD, mg/L	1.012	0.993–1.031	0.224			
APTT, s	1.014	0.984–1.044	0.368			
FIB, g/L	1.102	0.952–1.277	0.194			
PT, s	1.015	0.922–1.117	0.765			
AFP, ng/ml	1.000	1.000–1.000	0.309			
CA19-9 ≥35 U/ml	1.000	0.999–1.001	0.917			
CEA ≥5 ng/ml	6.240	2.832–13.747	0.000	1.281	1.100–1.491	0.001
HBsAg, positive	1.290	0.796–2.091	0.302			
Anti-HCV, positive	0.273	0.037–2.016	0.203			
Tumor number	1.049	0.892–1.235	0.562			
Tumor sizes, cm	1.083	1.032–1.136	0.001	1.072	1.014–1.134	0.014
Vascular invasion	1.705	1.051–2.764	0.031			
Tumor location						
Left lobe	1.294	0.547–3.059	0.558			
Right lobe	0.939	0.606–1.454	0.778			
Bilateral lobe						

BMI, Body Mass Index; WBC, White Blood Cell Count; NE, Neutrophil; HB, Hemoglobin; PLT, Platelet Count; ALT, Alanine Amiotransferase; AST, Aspartate Aminotransferase; TP, Total Protein; ALB, Albumin; GLO, Globulin; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALP, Alkaline Phosphatase; Cr, Creatinine; CHE, Cholinesterase; INR, International Normalized Ratio; TT, Thrombin Time; DD, D-Dimer; APTT, Activated Partial Thromboplastin Time; FIB, Fibrinogen; PT, Prothrombin Time; AFP, α-Fetoprotein; CEA, Carcinoembryonic Antigen; CA19-9, Carbohydrate Antigen 19-9;HBsAg, Hepatitis B Surface Antigen; Anti-HCV, Anti-Hepatitis C Virus Antibody.

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 study was censored on October 19,2020 and was approved by the Ethics Committee of The Affiliated Hospital of Qinghai University. All subjects signed an informed consent form. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LZ is responsible for writing, LR, MQ, WW and XS are responsible for document of patients data. FY, MD and HW are responsible for document. following up, ZW, HF are responsible for guiding research and revising papers. 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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En bloc resection of huge primary tumors with epidural involvement in the mobile spine using the "rotation–reversion" technique: Feasibility, safety, and clinical outcome of 11 cases

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Background: En bloc resection of spinal tumors provides better local control and survival outcomes than intralesional resection. Safe margins during en bloc resection of primary spinal tumors with epidural involvement are required for improved outcomes. The present study describes a "rotation–reversion" technique that has been used for en bloc resection of huge primary tumors in the mobile spine with epidural involvement and reported the clinical outcomes in these patients.

Methods: All patients with primary spinal tumors who were treated with the rotation–reversion technique at our institution between 2015 and 2021 were evaluated retrospectively. Of the patients identified, those with both huge extraosseous soft-tissue masses and epidural involvement were selected for a case review. Clinical and radiological characteristics, pathologic findings, operative procedures, complications, and oncological and functional outcomes of these patients were reviewed.

Results: Of the 86 patients identified with primary spinal tumors who underwent en bloc resection using the rotation–reversion technique between 2015 and 2021, 11 had huge extraosseous soft-tissue masses with epidural involvement in the mobile spine. The average maximum size of these 11 tumors was 8.1 × 7.5 × 9.7 cm. Median follow-up time was 28.1 months, mean operation time was 849.1 min (range 465–1,340 min), and mean blood loss was 6,972.7 ml (range 2,500–17,700 ml), with 10 (91%) of the 11 patients experiencing perioperative complications. The negative margin rate was 91%, with only one patient (9%) experiencing local recurrence. Ten patients were able to walk normally or with a crutch at the last follow-up, whereas one was completely paralyzed preoperatively.

Conclusion: The rotation–reversion technique is an effective procedure for the en bloc resection of huge primary spinal tumors, with the extension of invasion in selected patients including not only the vertebral body but also the pedicle and part of the posterior arch.

KEYWORDS

en bloc resection, spinal tumor, epidural involvement, huge mass, safe margin, rotation-reversion technique

1 Introduction

Primary tumors occurring in the mobile spine are rare, with an estimated incidence of 2.5–8.5 per million people per year, accounting for 4%–13% of all primary bone tumors (1). Primary spinal tumors can occur in any region of the spine, most commonly in the thoracic and lumbar spine.

En bloc resection of tumors with oncologically appropriate margins is the optimal treatment for primary malignant tumors of the mobile spine (2–5). Obstacles to en bloc resection of spinal tumors include regional anatomical limitations and large tumor volumes (6–8). Due to the lack of surrounding anatomical barriers over the surface of the vertebral body, bone tumors that break through the cortical bone and longitudinal ligament can easily grow into huge masses outside the spinal column (9). Factors associated with large tumor sizes include the long duration of symptoms before seeking medical care (sometimes from months to years) and recurrence after non-standard operations (e.g., curettage or intralesional resection). Serious damage to surrounding neurovascular structures is a frequent cause of morbidity associated with en bloc resection of large spinal tumors (10).

Tumor epidural extension is commonly seen in spinal tumors, as is tumor extension that includes not only the vertebral body but also the pedicle and part of the posterior arch (11, 12). The inability to visualize dorsal structures of the vertebral column has limited the ability to achieve negative tumor margins during the surgical management of spinal tumors with epidural involvement. Recurrences along the dura are frequently due to inadvertent intraoperative contamination (12).

Although several studies have described the en bloc resection of multi-level spinal tumors (13–16), less is known about methods that achieve safe margins in huge spinal tumors with epidural involvement, in which extensions include not only the vertebral body but also the pedicle and part of the posterior arch.

The present study retrospectively analyzed a group of patients with huge primary tumors in the mobile spine and epidural involvement who underwent en bloc resection using the "rotation–reversion" technique. The details of this technique are described, and its safety and feasibility are determined by analyzing oncological and clinical outcomes.

2 Patients and methods

2.1 Study participants

The medical records and follow-up results of patients with primary spinal tumors who underwent en bloc tumor resection using the rotation–reversion technique at our institution between 2015 and 2021 were retrospectively reviewed. Imaging and medical records were reviewed manually, and patients who met the following inclusion and exclusion criteria were selected for this study.

Patients were included if histological examination of preoperative core needle biopsy samples confirmed a diagnosis of primary tumor of the mobile spine; if extension and location of the tumor, as classified by the Weinstein–Boriani–Biagini (WBB) staging system (17), involved both extraosseous soft tissues (layer A) and the extradural layer (layer D), with the extension of intraosseous invasion including not only the vertebral body but also the pedicle and part of the posterior arch; and if they were followed up postoperatively for >6 months. Patients were excluded if they had tumor extension with intradural involvement (layer E), if their clinical or imaging data were incomplete, or if they were lost to follow-up.

Factors recorded for each patient included their clinical and radiological characteristics, pathology results, operative procedure, complications, and oncological and functional outcomes. All patients provided written informed consent, and the study protocol was reviewed and approved by the ethics committee of the Third Affiliated Hospital of Southern Medical University.

2.2 Evaluation and decision making

Radiographs, CT, MRI of the spine, and PET-CT were performed on all patients. Histological diagnosis was achieved based on core needle biopsy preoperatively. The treatment strategy for each patient was determined by a multidisciplinary collaboration performed by the same team consisting of surgeons, radiation oncologists, medical oncologists, radiologists, and pathologists. Once the surgical plan was determined, an elaborated design of the surgical procedures and the potential complications were discussed and planned carefully by our multidisciplinary collaboration team before the operation. Selective arterial embolization (SAE) was performed 1 day prior to the surgery in all cases. Intraoperative neuromonitoring was only used for the thoracic spine with more than three levels involved or with the cervical spine involved. All surgeries were performed by the same surgeon (HL).

2.3 Surgical technique

The surgical procedure was designed to provide adequate surgical margins as described (17, 18). The surgical approach was based on the location and extent of tumor invasion and the affected spinal level. Surgical approaches included three cases with a one-stage posterior approach and eight with the combined anterior and posterior approach.

2.3.1 One-stage posterior approach

Patients who underwent en bloc resection using a one-stage posterior approach were placed in the prone position (Figure 1). Transpedicular screws were inserted into the segments adjacent to the lesion, and all structures surrounding the part of the posterior arch of the diseased vertebra(e) were separated according to the designed margin. The great vessels and structures surrounding the ventral side of the vertebra(e) were carefully dissected along the anterior margin using a spatula and the surgeon's fingers. If the great vessels and surrounding structures could not be bluntly dissected, due to large tumor size or severe adhesions, only the planned osteotomy levels at the caudad and cephalad of the vertebra(e) invaded by tumor were bluntly dissected, and two wire saws were installed. The tumor was subsequently resected en bloc using the rotation–reversion technique. Briefly, after excision of the normal healthy bony structure (lamina and pedicle), a safe window was opened at the posterior arch of the vertebra(e) invaded by the tumor, allowing entry into the spinal canal, and nerve roots on the unaffected side were sectioned. Because the nerve roots on the side of the tumor invasion and part of the dural mater were covered by the tumor, they could not be exposed directly due to the lamina and pedicle invasion, making it very difficult to obtain safe margins along the dura. Osteotomy was performed at the caudad and cephalad discs or the vertebral bodies of the vertebra(e) invaded by the tumor. The specimen was rotated around the longitudinal axis to the side of the lesion, enabling direct visualization of the dorsal structures of the spinal column. This allowed the dura to be

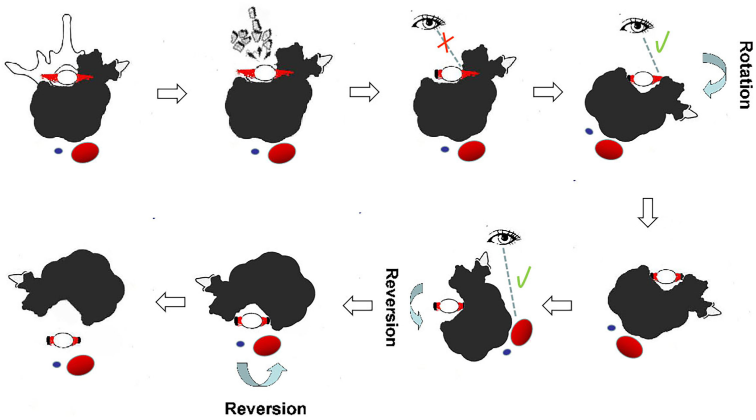

FIGURE 1
Illustration of en bloc resection using the rotation–reversion technique through a single posterior approach in the thoracic spine. A safe window was opened at the posterior arch, and nerve roots on the unaffected side were sectioned. The dura was separated from the lesion, and the nerve roots on the side covered by the tumor were sectioned under direct visualization by the rotation technique. The great vessels and surrounding structures at the ventral side of the tumor-invaded vertebrae were bluntly dissected under direct visualization using the reversion technique from the posterior approach. Reversal of the entire mass was continued until it was completely removed posteriorly.

separated from the lesion and the nerve roots to be sectioned without violating the tumor pseudocapsule at the lamina of the side covered by the tumor. With the use of the reversion technique, the great vessels and surrounding structures at the ventral side of the tumor-invaded vertebra(e) could be reversibly rotated. The vertebra(e) was thereafter somewhat on the longitudinal axis, allowing blunt dissection to be carefully performed under direct visualization from the posterior approach, thereby avoiding damage without violating the tumor pseudocapsule. Finally, the entire mass was removed posteriorly using the reversing maneuver. The anterior defect was reconstructed, followed by fixation of the pedicle screws using a posterior approach.

2.3.2 Combined approach

Some patients underwent combined procedures, as described (Figure 2). First, the tumor was released anteriorly from surrounding neurovascular structures all along the anterior margins. If sagittal en bloc resection was planned, osteotomy was performed using an ultrasonic osteotome, with an anterior approach performed from the healthy side of the spine anteroposteriorly along the sagittal plane of the vertebra(e). Second, the patient was placed in a prone position for posterior en bloc resection. Transpedicular screws were inserted into the upper and lower segments, and all the structures surrounding the diseased vertebra(e) along the posterior margin were released. A temporary rod was fixed to stabilize the spine and avoid spinal cord injuries during osteotomy. Finally, the lesion was removed en bloc using the rotation–reversion technique described above.

2.4 Follow-up

All patients were evaluated radiographically and by CT scans and MRI immediately after surgery and during follow-up. Oncologic outcomes were evaluated, including monitoring the sites for residual lesions, local recurrence, and signs of metastases. Functional results evaluated included neurologic function, hardware failure, and interbody fusion.

3 Results

3.1 Patient characteristics

Eleven patients with primary spinal tumors who underwent en bloc resection using the rotation–reversion technique criteria were included. The demographic and clinical characteristics of these patients are summarized in Tables 1, 2. Figures 3–6 illustrate the en bloc resection techniques performed in four of these patients.

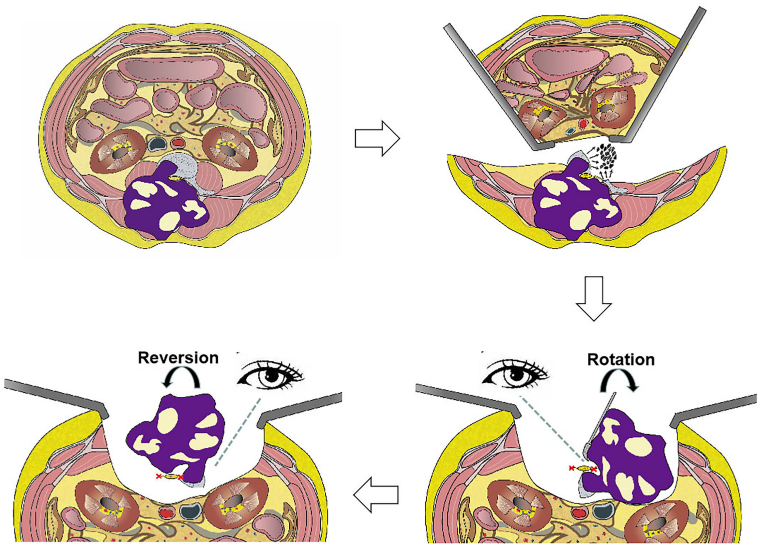

FIGURE 2
Illustration of en bloc resection using the rotation–reversion technique using a combined anterior and posterior approach in the lumbar spine. The retroperitoneal space was entered through a bilateral anterior pararectus approach, and the aorta and inferior vena cava were separated from the diseased vertebral body. The left hemivertebral body and pedicle of the diseased vertebrae were piecemeal removed as a safe window to enter the spinal canal. The mass in the bilateral paravertebral soft tissue that was not infiltrated by the tumor was separated using a posterior approach. The dura was separated from the mass, and the bilateral never roots of the diseased vertebrae were sectioned under direct visualization by the rotation technique. Finally, the entire mass was removed posteriorly using the reversion technique.

TABLE 1 Clinical characteristics of the patients included in this study.

No.	Age	Sex	Histology	Levels involved	Max-diameter, cm	Enneking stage	WBB classification	Previous surgery	Pre-OP chemo	Pre-OP radiation	Surgical approach	Staged surgery	Operation time, min	Blood loss, ml	Reconstruction method	Complications	Margin	Follow-up, months	LR	Oncological status	Interbody fusion, months
1	46	F	Malignant neurilemmoma	L3	8.1 × 6.8 × 9.1	IIB	7-2/A-D	–	+	–	Combined	–	1,060	4,500	AV/PS	Wound problem	Wide	42	–	NED	–
2	41	M	GCT	T9–T11	8.5 × 9.3 × 6.0	S3	2-8/A-D	–	–	–	Combined	–	485	4,000	EC/PS	Pneumonia, IF	Marginal	69	–	NED	32
3	61	M	Malignant neurilemmoma	L4–L5	9.1 × 7.7 × 19.5	IIB	1-6/A-D (SEBR)	–	+	–	Combined	–	980	4,000	TM/PS	IF	Marginal	27	–	DOD	–
4	36	M	Solitary fibroma	L5	5.6 × 7.9 × 16.9	S3	9-1/A-D	–	+	–	Combined	–	860	9,600	TM/PS	Wound problem	Marginal	35	–	NED	7
5	65	F	Malignant paraganglioma	T1–T3	8.2 × 6.8 × 8.4	IB	5-10/A-D	–	–	+	Combined	+	1,340	17,700	TM/PS	Wound problem, pneumonia	Marginal	29	–	NED	6
6	40	M	Osteosarcoma	T11–L2	8.8 × 9.4 × 11.9	IIB	5-1/A-D	+	+	+	Combined	–	1,180	12,200	TM/PS	Dura tear, CSFL, DVT	Intralesional	8	+	DOC	–
7	70	M	Chondrosarcoma	C7–T1	8.4 × 4.5 × 6.7	IIB	2-6/A-D, F (SEBR)	+	–	–	Combined	–	465	5,500	TM/PS	Pneumonia	Marginal	12	–	NED	5
8	34	F	Myxoid chondrosarcoma	T2–T5	14.2 × 10.8 × 11.4	IB	1-7/A-D	–	–	–	Posterior	–	880	5,500	TM/PS	Pneumonia	Marginal	28	–	DOD	–
9	22	F	GCT	T9–T11	6.0 × 6.3 × 5.0	S3	3-10/A-D	–	–	–	Posterior	–	560	5,200	AV/PS	Pneumonia	Marginal	36	–	NED	6
10	46	M	Osteosarcoma	L4–L5	6.1 × 6.3 × 5.5	IIB	7-11/A-D (SEBR)	+	+	–	Combined	–	1,050	6,000	TM/PS	Wound problem	Marginal	15	–	NED	7
11	25	M	GCT	T5–T7	6.0 × 7.2 × 6.2	S3	4-12/A-D	–	–	–	Posterior	–	480	2,500	AV/PS	Pneumonia	Marginal	8	–	NED	–

AV, artificial vertebrae; AWD, alive with disease; CSFL, cerebrospinal fluid leakage; Chemo, chemotherapy; DOC, died from other cause; DOD, died of disease; DVT, deep venous thrombosis; EC, expandable cage; F, female; GCT, giant cell tumor; IF, instrumentation failure; LR, local recurrence; M, male; NED, no evidence of disease; Pre-OP, preoperative; PS, pedicle screw; SEBR, sagittal en bloc resection; TM, titanium mesh; WBB, Weinstein–Boriani–Biagini.

3.2 Oncology results

En bloc resection was achieved in all 11 patients. One wide margin (patient 1) was achieved with the epidural extension of the tumor fully contained by the ligamentum flavum in the resected specimen (Figure 3). Marginal margins were obtained at the tumor capsule along the dura in nine patients. One patient (patient 6) had an intralesional margin due to intracanal tumor contamination following initial surgery (Figure 5).

Perioperative complications were classified as major or minor (19). Any complication that substantially alters an otherwise smooth and expected course of recovery was considered a major complication; others were defined as minor. Six patients (55%) experienced major complications, and five (45%) experienced minor complications, with 10 (91%) of the 11 patients experiencing a perioperative complication. One patient (patient 6) experienced local recurrence 3 months after surgery; this patient, who had T11-L2 osteosarcoma with intralesional margins due to contamination following previous operations, died of deep vein thrombosis 8 months after surgery. Patients 3 and 8 died of lung metastases at 27 and 28 months, respectively, after surgery without local recurrence.

3.3 Functional results

All 11 patients had different degrees of postoperative neurological deficits due to the resection of nerve roots of the diseased vertebra(e). No postoperative ischemic spinal cord injury or delayed neurologic deficit occurred. At the last follow-up after rehabilitation, two patients were able to normally walk (Frankel E), and eight were able to walk with crutches (Frankel D). One patient (patient 8) with complete paralysis (Frankel B) preoperatively did not experience significant improvement in motor function. Interbody fusion was confirmed by CT scans in six (55%) of the 11 patients. Instrumentation failures were observed in two patients (patients 2 and 3), both of whom underwent revision surgery while normal spinal alignment was maintained.

4 Discussion

4.1 Background and rationale

A system for the surgical staging of primary musculoskeletal tumors, first proposed by Enneking in 1980, elucidated the principles of tumor excision and the concept of surgical margins based on other types of oncological surgery (18). En bloc resection is performed to remove the tumor in a single piece with tumor-free margins and without any tumor contamination (20). Wide or radical margin en bloc resection was

TABLE 2 Epidemiologic, clinical, and surgical data.

Parameter	Value
Patients (n)	11 (4 F and 7 M)
Age, mean (range)	44.2 ± 15.6, (22–70) years
Diagnosis	
GCT	3
Malignant neurilemmoma	2
Osteosarcoma	2
Chondrosarcoma	2
Malignant paraganglioma	1
Solitary fibroma	1
Site	
CT	1
T	5
TL	1
L	4
Median size tumor	
Anteroposterior dimension (range)	8.1 ± 2.4 cm (5.6–14.2 cm)
Transverse dimension (range)	7.5 ± 1.8 cm (4.5–10.8 cm)
Axial dimension (range)	9.7 ± 4.8 cm (5.0–19.5 cm)
Enneking staging (no., [%])	
S3	4 (36.4%)
IB	2 (18.2%)
IIB	5 (45.5%)
WBB classification	
Sectors involved	
5 sectors	3
6 sectors	2
7 sectors	2
8 sectors	2
9 sectors	2
Layers involved	
A–D	10
A–D, F	1
Pre-OP treatment	
Chemotherapy	5
Radiation	2
Pre-OP neurologic status	
ASIA B	1
ASIA C	9
ASIA D	1
Parameter	Value
Post-OP neurologic status (last follow-up)	
ASIA B	1
ASIA D	8
ASIA E	2
Surgical approach (no., [%])	
Anterior-posterior	8 (72.3%)
Posterior	3 (27.3%)
Level of resection	
One-level	2
Two-level	3
Three-level	4
Four-level	2
Margin (no., [%])	
Marginal	9 (81.2%)
Wide	1 (9.1%)
Intralesional	1 (9.1%)
Operation time mean (Range)	849.1 ± 308.8 min (465–1,340 min)
Blood loss mean (Range)	6,972.7 ± 4,489.1 ml (2,500–17,700 ml)
Complications	
Pneumonia	6
Wound problem	4
IF	2
CSFL	1
Dura tear	1
DVT	1
Perioperative complication (no., [%])	10 (90.9%)
Major	6 (54.5%)
Minor	5 (45.5.0%)
Follow-up mean	28.1 ± 17.9 mons (8–69 months)
Local recurrence (no., [%])	1 (9.1%)
Metastases (no., [%])	3 (27.3%)
Dead (no., [%])	3 (27.3%)
Died from disease with evidence of LR at time of death	1 (9.1%)
Died from disease without evidence of LR at time of death	2 (18.2%)

(Continued)

TABLE 2 Continued

CSFL, cerebrospinal fluid leakage; DVT, deep venous thrombosis; F, female; GCT, giant cell tumor; IF, instrumentation failure; LR, local recurrence; M, male; Pre-OP, preoperative; Post-OP, postoperative; WBB, Weinstein–Boriani–Biagini.

recommended for the removal of primary malignant tumors (18). The WBB classification was later developed in order to apply these principles of tumor resection to the removal of spinal tumors (17). The WBB classification system also provided a common terminology for describing the details of the tumor and evaluating the results of treatment for spinal tumors (17).

Regional anatomical constraints and important tissue structures surrounding the spine restrict the application of the Enneking system in the resection of spinal tumors (6–8, 11). Resection with tumor-free margins can seldom be achieved in huge tumors originating from the spine, because of the complex anatomy, large tumor volumes, and invasion of important structures (21, 22). The proposed approaches consist usually of the posterior approach alone, or combined anterior and posterior approaches for separation of the anterior structures involved (23, 24). Frequently, the dura sac and nerve root cannot be easily

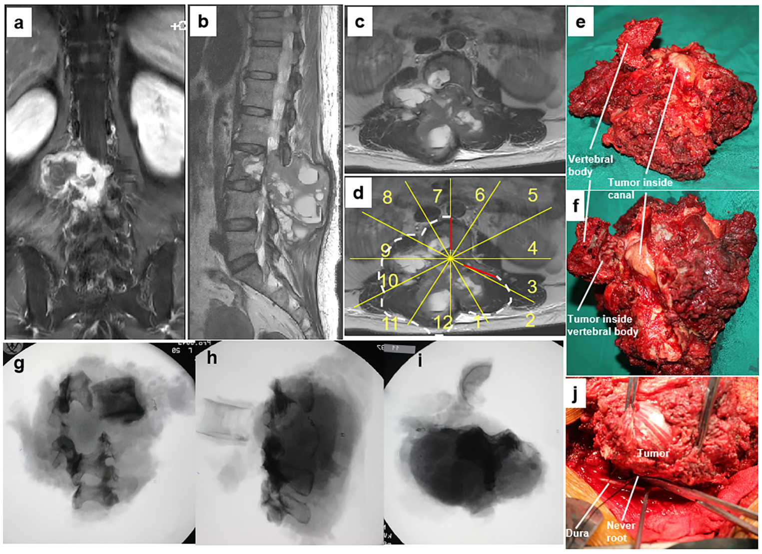

FIGURE 3
A 46-year-old woman with a malignant neurilemmoma at L3 with a huge mass in the posterior elements **(A–C)**. En bloc resection through a combined anterior and posterior approach was designed based on WBB classification along the margins, as highlighted by white dotted line (sectors 7–2, D, WBB) **(D)**. The dura was separated from the mass, and bilateral nerve roots of L3 were sectioned under direct visualization using the rotation technique **(J)**. Photographs of the gross specimen **(E, F)** showing that the epidural extension of the tumor was fully contained by the ligamentum flavum. Radiographs of the specimen **(G–I)** showing the margins of en bloc resection. WBB, Weinstein–Boriani–Biagini.

released from the lesion without direct visualization, as the lamina and pedicle invasion made lesion removal difficult because of its connection with the sac through the nerve root(s), limiting the ability to obtain safe margins along the dura. The rotation–reversion technique was developed and utilized in the en bloc resection of huge primary tumors with tumor invasion that included not only the vertebral body but also the pedicle and part of the posterior arch in the mobile spine.

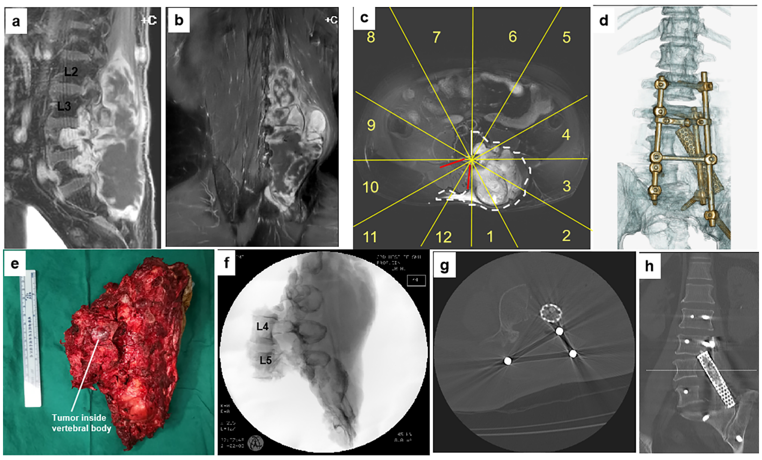

FIGURE 4
A 61-year-old man with a malignant neurilemmoma at L4–5. Preoperative MR images **(A–C)** show the tumor invading the left side of the L4 and L5 vertebrae sectors 1–6, **(D)**, WBB with a huge mass in the posterior elements (from L2 to S3). The patient underwent a two-stage surgery, consisting of anterior release followed by posterior sagittal en bloc resection with instrumentation. A photo of the gross specimen **(E)** and postoperative CT scan imaging **(F–H)** showing the margins on sagittal scans of en bloc resection. Postoperative CT scan reconstruction shows structural reconstruction with instrumentation after sagittal resection **(D)**. WBB, Weinstein–Boriani–Biagini.

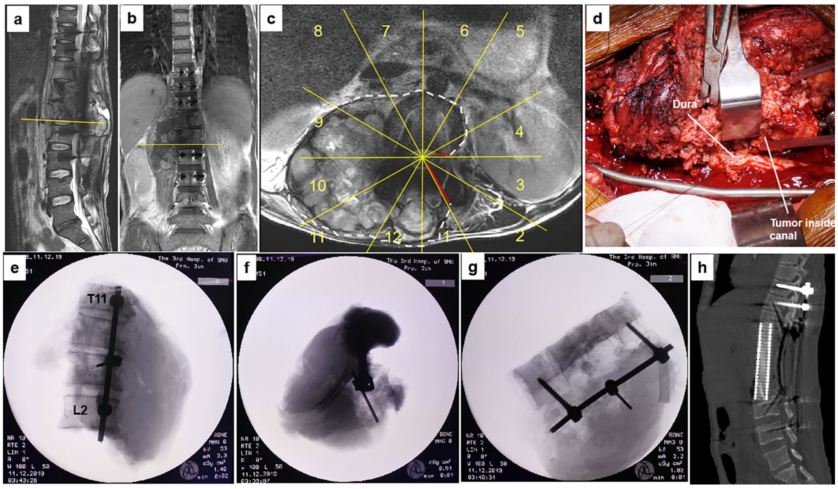

FIGURE 5
A 40-year-old man with osteosarcoma at T11-L2. This patient experienced a local tumor recurrence after two rounds of intralesional excision surgeries combined with radiotherapy in another hospital. MR images **(A–C)** show tumor recurrence along the right side of T11 to L2 paravertebral with epidural involvement (sectors 4–1, D, WBB). Based on the WBB classification, a four-level (T11-L2) en bloc spondylectomy was performed using the rotation–reversion technique after three courses of chemotherapy. However, due to intracanal tumor contamination caused by the initial operations, the margin along the dura was considered positive **(D)**. Radiographs of the specimen **(E–G)** and postoperative CT scans showing structural reconstruction with instrumentation after tumor resection **(H)**. WBB, Weinstein–Boriani–Biagini.

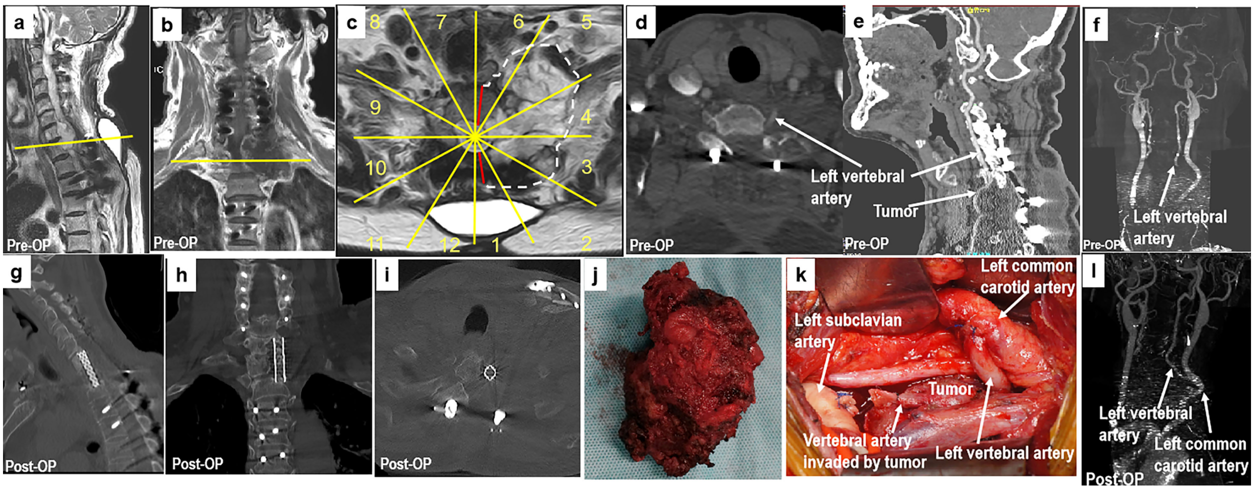

FIGURE 6
A 70-year-old man with chondrosarcoma at C7–T1. The patient had undergone a piecemeal resection of a tumor in the paravertebral region of the cervicothoracic junction at another hospital. Ten months later, the patient experienced numbness in his upper left arm. MR images **(A–C)** show tumor recurrence along the left side of C7 to T1 paravertebral CT scans **(D, E)**, and CT angiography **(F)** shows that the left vertebral artery was invaded by the tumor (sectors 1–5, **D, F**, WBB). Based on the WBB classification of the tumor, sagittal en bloc resection was performed using the rotation–reversion technique with a combined approach. The left vertebral artery was cut off outside the tumor and anastomosed with the left common carotid artery **(K)**. Postoperative CT angiography showing fluent blood flow in the left vertebral artery **(L)**. Postoperative CT scanning **(G–I)** and a photograph of the gross specimen **(J)** showing the margins of sagittal en bloc resection. WBB, Weinstein–Boriani–Biagini.

4.2 Can the rotation–reversion technique achieve oncologically appropriate margins in en bloc resection of huge primary tumors with epidural involvement in the mobile spine?

The WBB classification system has defined the margins of extraosseous and intraosseous lesions of the spine, and this stage was set on the premise that the spinal cord can not be resected. Without dural resection, marginal en bloc resection may be the best margin at the tumor capsule along the dura, obtained in most of the spinal tumors with epidural extension. If the epidural layer is only displaced anteriorly by the tumor, but without infiltration (layer D), surgical dissection may involve separating the intact tumor capsule from the dura surface. If the epidural extension of the tumor is fully contained by natural barriers, such as the ligamentum flavum or longitudinal ligament, on the resected specimen, the margins along the dura could be considered wide (24). If there is intradural involvement (layer E), the infiltrated dura should be removed entirely with the specimen to obtain safe margins (11, 12). The rotation–reversion technique provides direct visualization of the ventral and dorsal structures of the spinal column, allowing the tumor to be sectioned with safe margins and confirming that the margins along the dura are not contaminated. Of the 11 patients in this study, 10 (91%) had negative margins, including one with wide and nine with marginal margins. Similarly, a systematic review reported that the negative margin rate obtained following en bloc resection of 229 primary spinal tumors was 86.1% (25), and a study from a single center of 220 spinal tumors that underwent en bloc resection found that the negative margin rate was 85.9% (23). Careful planning and efficient design of surgical procedures can be successful in obtaining oncologically appropriate margins, even in difficult cases (9).

4.3 What are the complications of the rotation–reversion technique?

The mean operation time in this study was 849.1 min, and the mean blood loss was 6,972.7 ml. In comparison, a study of en bloc resection of 22 spinal tumors reported a shorter mean operation time (493 min; range 150–840 min) and a lower volume of blood loss (1,895 ml; range 150–6,500 ml) (26). These findings cannot be readily compared because of differences in study populations and the small numbers of patients in each study. Tumor volume was significantly greater in the present study, with all tumors having expanded into the canal with extradural extension. These factors made surgical manipulations in the present study more difficult and time-consuming, resulting in higher intraoperative blood volumes. A systematic review and meta-analysis of 44 articles that included 306 patients who underwent en bloc resection for spinal tumors found that the mean operation time was 12.1 h (range 2–42 h) and that the median blood loss was 3.7 L (range 0.1–37 L) (25). More recently, another patient-level meta-analysis including 582 patients who underwent en bloc spondylectomy reported a median operation time of 555 min and a median blood loss of 2,000 ml (27).

Morbidities of en bloc resection of spinal tumors are thought to be worse than morbidities associated with the resection of other tumors because en bloc resection of spinal tumors is more technically demanding (10). The rate of perioperative complications in the present study (91%) was higher than rates reported previously (35% to 65%) (10, 26, 28), potentially because patients in the present study required more difficult manipulations of neurovascular structures due to the huge volumes of these tumors and the involvement of the dura with nerve roots. However, none of the patients in the present study died intraoperatively or experienced other fatal complications. In comparison, the mortality rate of patients who have undergone en bloc resection of spinal tumors was reported to range from 0% to 7.7% (22, 29, 30). The most frequent major complication observed in the present study was wound healing problems, occurring in four (36%) of the 11 patients. Wound healing problems may be caused by the need to excise large amounts of soft tissue and vascular structures to obtain safe margins due to the huge volume of the tumors, which may result in insufficient coverage and reduced blood supply to the wound. Pneumonia was the most frequent minor complication, occurring in six patients. Pneumonia may be related to atelectasis, which is caused by pleural rupture during an operation. None of the patients in the present study experienced injuries to important vessels or the spinal cord during surgery. The rotation–reversion technique allowed careful separation of the surrounding neurovascular structures from the tumor under direct vision, thereby avoiding serious complications caused by intraoperative rough manipulations.

4.4 How does the rotation–reversion technique alter oncologic and functional outcomes after tumor resection?

Only one (9%) of the 11 patients died of disease with evidence of local recurrence at the time of death. None of the other 10 patients experienced recurrence throughout follow-up. Reconstruction of the integrity of the spinal column after en bloc resection is critical for optimal postoperative functional results. Spinal reconstruction is regarded as particularly challenging when tumors are huge and involve multiple vertebral levels, as more vertebral bone and surrounding structures must be resected totally to excise the entire tumor mass. The instrument failure rate after en bloc resection of spinal tumors has been found to range from 7% to 40% (10, 22, 31), in agreement with the instrument failure rate in the present study, 18.2%. Interbody fusion was confirmed in six (55%) patients in the present study. The lower fusion rate in the present study may be due to the diminished vitality and poor healing capacity of the bone, resulting from the extensive intraoperative vascular dissection required to separate the huge masses.

4.5 Limitations

One important limitation of the present study was the small sample number, as this study included only 11 patients. In addition, patients with extraosseous soft tissues and intraosseous tumors without dural involvement were not included. Furthermore, the results of the present study could not be compared with the results of other studies of en bloc resection, due to wide variations in patient and tumor parameters and the relatively short follow-up time. Additional studies with larger numbers of patients, longer follow-up times, and control groups are needed to establish a definitive role of the rotation–reversion technique in the en bloc resection of spinal tumors.

5 Conclusions

The rotation–reversion technique based on the WBB classification is a feasible, safe, and effective procedure for en bloc resection of large primary spinal tumors that extend not only into the vertebral body but also into the pedicle and part of the posterior arch. This procedure is reliable in achieving safe oncological margins with satisfactory local control in selected patients.

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 the ethics committee of The Third Affiliated Hospital of Southern Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

ML: writing—original draft, data curation, and funding acquisition. ZZ: investigation and methodology. WC: formal analysis and software. ZL: validation and project administration. SWD: resources and visualization. CH: formal analysis and investigation. HL: conceptualization, funding acquisition, project administration, supervision, and writing—review and editing. DJ: supervision. SB: writing—review and editing. 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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Bench surgery with autotransplantation for bilateral Wilms tumor—A feasible technique for renal sinus invasion

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Purpose: Bilateral Wilms tumor (BWT) with renal sinus invasion requires extremely difficult surgical care. This study presents an alternative strategy for tumor removal while at the same time preserving the renal parenchyma.
Materials and methods: In total, 9 cases of synchronous BWT were admitted to our hospital between May 2016 to Aug 2020. We retrospectively reviewed the clinical data, surgical technique, and functional and oncological outcomes of these cases.
Results: The 9 cases included 3 males and 6 females, with a median age of 12 months at surgery (range 7–40). A total of 14 kidney units had renal sinus invasion (77.8%), whereas multifocal neoplasms were observed in 7 units (38.9%). The local stage distribution revealed 1 kidney with stage I, 10 kidneys with stage II, and 7 kidneys with stage III. Nephron-sparing surgery was performed on 15 kidney units (83.3%), among which 13 (72.2%) underwent bench surgery with autotransplantation (BS-AT), whereas 2 (11.1%) were subjected to tumor enucleation *in vivo*. Urinary leakage was the most prevalent postoperative complication. We observed negative margins. During the mean follow-up of 28.4 months, 2 patients (22.2%) succumbed from sepsis and renal failure, respectively, whereas the other 7 (77.8%) survived without recurrence. Survivors experienced an estimated glomerular filtration rate of 81 ± 15.4 ml/(min × 1.73 m^2). The endpoint renal volume of 9 renal units receiving BS-AT significantly increased ($P = 0.02$).

Abbreviations
BWT, bilateral Wilms tumor; BS-AT, bench surgery with autotransplantation; NSS, nephron-sparing surgery; DDS, Denys-Drash syndrome; WAGR, Wilms tumor, Aniridia, Genitourinary abnormalities, intellectual disability; CT, computerized tomography; eGFR, estimated glomerular filtration rate; KT, kidney transplantation; RN, radical nephrectomy; HCA, hypertonic citrate adenine; AKI, acute kidney injury; ESRD, end-stage renal disease.

Conclusions: In summary, the surgical management of bilateral Wilms tumor requires meticulous operative approach and technique. Besides, BS-AT provides a viable alternative to nephron-sparing surgery for BWT patients with renal sinus invasion.

KEYWORDS

bilateral Wilms tumor, bench surgery, autotransplantation (AT), nephron-sparing surgery (NSS), renal sinus invasion

Introduction

Wilms tumor is the most prevalent pediatric kidney tumor originating from undifferentiated embryonic lesions. Bilateral Wilms tumor (BWT) accounts for 4%–13% of Wilms tumor cases, among which 65% are synchronous BWT (1, 2). Patients with synchronous BWT are at greater risk of developing renal failure. The potential risk factors include recurrent tumor, intrinsic renal disease, inadequate renal parenchyma, predisposition syndromes, and chemotherapy- and/or radiotherapy-induced nephrotoxicity (3–5).

Synchronous BWT presents a significant challenge for clinicians. Based on a surgical standpoint, there is a delicate balance between tumor removal and preservation of renal function. The most widely used surgical modality is nephron-sparing surgery (NSS), allowing patients to forego renal replacement therapy (6). Ideal candidates are patients with a unifocal mass in the upper or lower pole of the kidney, sparing at least a third of the kidney, no signs of metastases or renal sinus invasion, and favorable histology (7). Nonetheless, surgeons are impressed by the prevalence of renal sinus invasion and multifocal lesions in BWT patients (8, 9). Generally, NSS is performed *in vivo* using an open transperitoneal approach, which intraoperatively increases the promising rate of tumor rupture and incomplete resection (10).

Tumor resection *ex vivo* using bench surgery with autotransplantation (BS-AT) is the ultimate approach to NSS (11). In 1975, John first described BS-AT, as a hypothesis (12). Only a limited minority of BWT patients underwent BS-AT in the past few decades (8, 13). To our knowledge, comprehensive and specific strategy for BS-AT and management of postoperative complications remain unreported. This work described an experience of surgical management of synchronous BWT, particularly the use of BS-AT.

Materials and methods

General data

In this retrospectively study, we reviewed the clinical data of 9 patients with synchronous BWT admitted to the First Affiliated Hospital of Sun Yat-sen University between May 1, 2016, to Aug 30, 2020. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University (IRB-2021-129). Informed patient consent was waived due to its retrospective nature.

Among the 9 patients, 3 were male and 6 were female. Case 1 had multiple anomalies (hemihypertrophy, hypospadias and cryptorchidism), whereas case 2 had Denys-Drash syndrome (DDS). Pulmonary nodules were observed in case 4 but disappeared after preoperative chemotherapy. Case 7 had an indirect hernia. Case 8 had a thrombus in the right renal vein and inferior vena cava. Case 9 had WAGR (Wilms tumor, Aniridia, Genitourinary abnormalities, intellectual disability) syndrome with other ocular anomalies (cataract and glaucoma). **Table 1** presents the clinical data of the 9 patients. Only 2 patients did not receive any treatment before reaching our hospital, prehospital managements for other 7 patients varied. Except for case 2, biopsies were performed on 8 patients before preoperative chemotherapy. All patients were treated with 2-drug preoperative chemotherapy (vincristine and actinomycin D), 2 with additional doxorubicin (cases 1 and 8), and 3 with additional carboplatin and etoposide (cases 1, 2, and 5). The tumors had varying degrees of shrinkage. Postoperative chemotherapy was administered according to the SIOP 2016 chemotherapy protocol guidelines based on the local stage and pathological results. None of the patients had received radiotherapy.

Pre-operative evaluations included urological ultrasonography, computerized tomography (CT), and renal dynamic radionuclides. The Schwartz formula was used to evaluate the estimated glomerular filtration rate (eGFR). The absolute renal volume was calculated using the formula for a prolate ellipsoid (max length × max width × max depth × 0.532) (14). Renal function was monitored using serum creatinine, CT, and renal dynamic radionuclides.

BS-AT technique

This procedure involves radical nephrectomy (RN), *ex vivo* tumor removal with bench surgery, and kidney autotransplantation. A transverse upper abdominal incision was made to completely expose the tumor. Notably, damage to blood vessels and tumor rupture should be avoided in the process of RN. Tumors were marked with electric coagulation before extracting the involved kidney. The renal vessels were set aside for approximately 1.0 cm–1.5 cm, and the ureter for

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TABLE 1 Clinical characteristics of 9 patients.

Case	Gender	Age at surgery (months)	Associated anomalies or thrombus	Stage (L/R)	Renal hilum involved (L/R)	Renal pelvis invaded (L/R)	blood loss (L/R) (ml)	Type of surgery (L/R)	Histology	Margin	Complication
Group 1: Staged surgery											
1	M	12	Hemihypertrophy, hypospadias, cryptorchidism	II/II	−/+	+/+	20/30	BS-AT/BS-AT	Necrosis, epithelial	–	Urinary leakage, hypertension
2	F	9	DDS	II/II	−/−	−/−	20/20	BS-AT/tumor enucleation *in vivo*	Mixed	–	Urinary leakage, hypertension
3	F	7	–	II/II	+/+	+/+	40/35	RN/BS-AT	Necrosis, mixed	–	Urinary leakage, chylous ascites hydronephrosis
4	M	40	–	III/III	+/+	+/+	30/10	BS-AT/RN	Necrosis, mixed	–	–
5	F	15	–	III/III	+/+	−/−	50/30	BS-AT/BS-AT	Mixed, NRs	–	–
6	F	8	–	III/II	+/+	+/+	150/20	BS-AT/BS-AT	Necrosis, mixed	–	hydronephrosis
Group 2: Simultaneous surgery											
7	M	10	Indirect hernia	III/III	+/+	−/−	200/100	BS-AT/BS-AT	Epithelial, NRs	–	DIC, sepsis
8	F	34	Thrombus in the renal vein and vena cava	II/II	+/+	+/+	80/20	BS-AT/RN	Necrosis, stromal	–	AKI, urinary leakage, hypertension
9	F	13	WAGR, cataract, glaucoma	II/I	+/−	+/−	40/60	BS-AT/tumor enucleation *in vivo*	Necrosis, stromal,	–	–

RN, radical nephrectomy; ESRD, end stage renal disease; DIC: disseminated intravascular coagulation; BS-AT: bench surgery with autotransplantation; AKI: acute kidney injury; WAGR: Wilms tumor, Aniridia, Genitourinary abnormalities, intellectual disability.

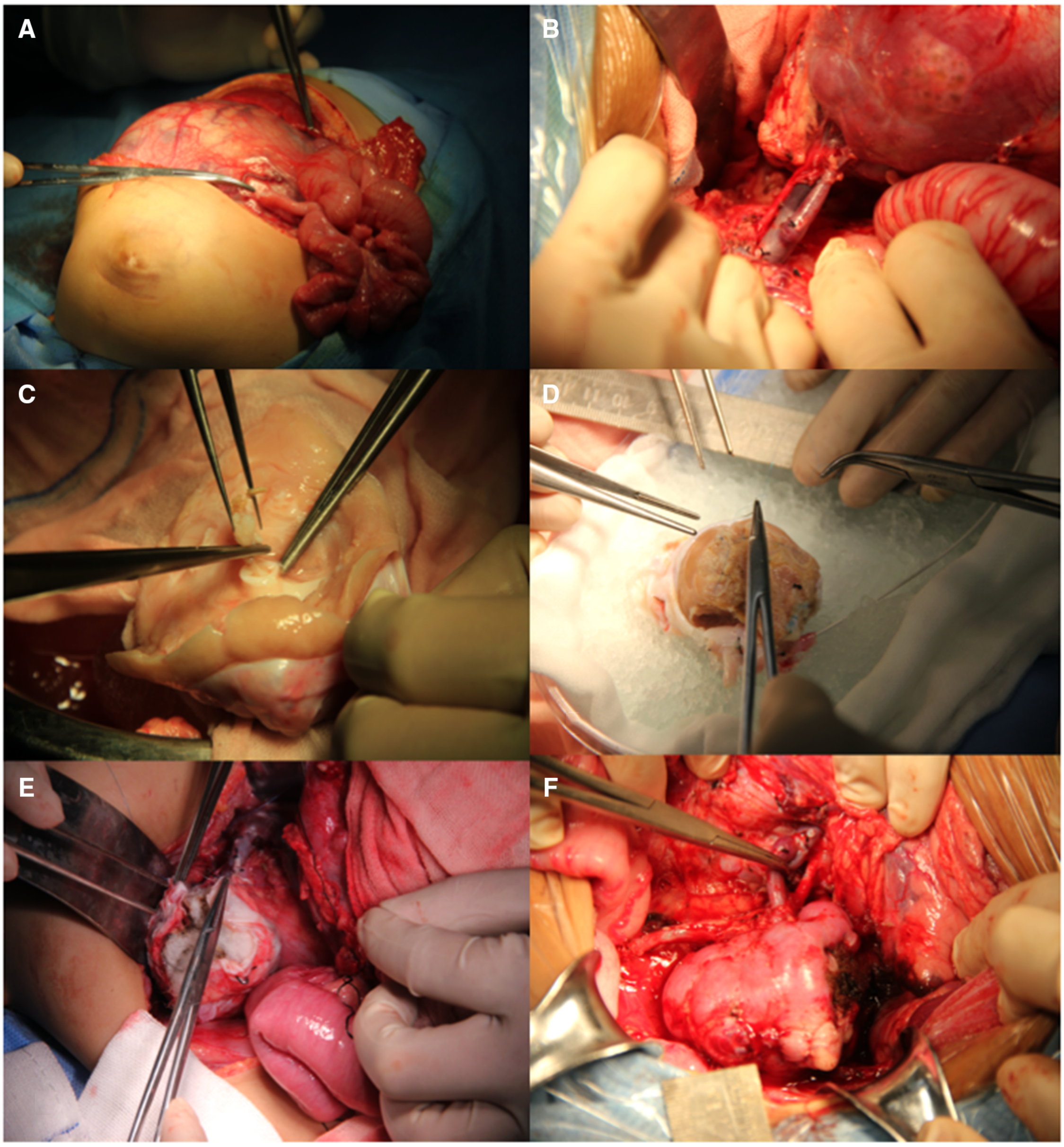

FIGURE 1
Surgical procedure of BS-AT. (A) Transverse upper abdominal incision. (B) Renal pedicle was well exposed. (C) Tumor removal in the renal pelvis. (D) Residual renal parenchyma and renal pelvis system were reconstructed with cooling perfusion. (E) Hemostatic sponge was used to cover the residual kidney. (F) Orthotopic kidney transplantation with vascular and ureteral anastomoses.

approximately 4.0 cm–5.0 cm. The kidney was immediately transferred to a workbench and perfused with hypertonic citrate adenine (HCA) solution. Neoplasms were exposed after sharply opening the capsule. Tumor excision was performed using a scalpel or ultrasonic scalpel, and the margins of the residual kidney were sent for frozen section examination. The renal pelvis was opened in cases of tumor invasion. Hemorrhage and leakage were detected and treated in the process of bench surgery. Non-absorbable sutures were used to repair the remaining kidney parenchyma, whereas absorbable sutures were used to reconstruct the renal pelvis. Subsequently, a double-J tube was inserted into the anastomosed ureter. Thereafter, the remaining kidney was orthotopically transplanted and covered with a hemostatic sponge. Urine output was monitored following vascular and ureteral anastomoses. During the entire procedure, the kidneys were placed on ice to maintain hypothermia (Figure 1). Enoxaparin sodium (1000 U, qd, 3–5 days) and subsequently followed by clopidogrel (12.5 mg, qd, 1 month) were applied postoperatively.

FIGURE 2
Abdominal CT scans of case 8. (A,C) Preoperative CT images reveal bilateral kidney lesions invading the renal sinus with bilateral hydronephrosis, a filling defect is noted within the right renal vein and inferior vena cava (white arrow). (B,D) Postoperative CT images reveal the absence of right kidney and Normal left morphology.

Statistical analysis

Descriptive statistics appropriately included mean ± SD, median with continuous variables, and percentages as appropriate. The student's *t*-test was used for comparisons between continuous variables. Statistical analysis was performed using the SPSS version 26.0 software for Macs.

Results

The median age at the time of surgery was 12 months (range, 7–40 months), whereas the mean interval between neoadjuvant chemotherapy and surgery was 3.4 ± 1.6 months. The local stage distribution revealed: 1 kidney in stage I, 10 kidneys in stage II, and 7 kidneys in stage III.

A total of 6 patients (cases 1–6) underwent staged operations, whereas 3 patients (cases 7–9) underwent a single-stage operation. Among the 18 renal units, 14 kidneys (77.8%) had renal sinus invasion, including 14 with hilar involvement and 11 with renal pelvic invasion. Multifocal neoplasms were observed in 7 kidney units (38.9%).

A total of 3 patients (cases 3, 4, and 8) received one side NSS and contralateral RN, whereas the other 6 patients received bilateral NSS. RN was performed in 3 kidney units due to the absence of adequate renal tissue, tumor thrombus, and unsuccessful reconstruction of the renal pelvis. In total, 15 kidney units received NSS, 13 underwent BS-AT, and 2 underwent tumor enucleation *in vivo*, accounting for 83.3%, 72.2%, and 11.1%, respectively (Figures 2, 3). Figure 4 shows the surgical approach. The median blood loss on each side was 32.5 ml (range 10–200 ml), and 3 patients required blood transfusion (cases 6–8).

The pathological results revealed favorable histological types in all children, and we observed negative margins. Necrosis was observed in 6 patients, whereas nephrogenic rests were noted in

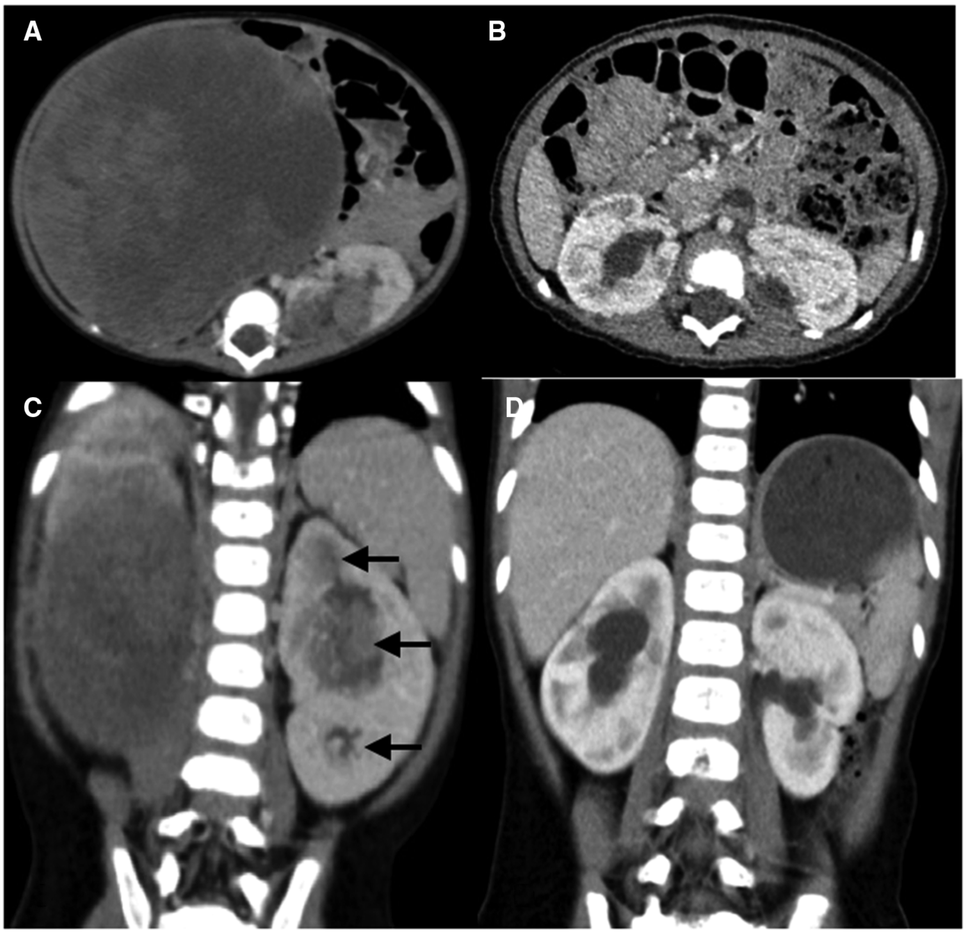

FIGURE 3
Abdominal CT scans of case 6. (A,C) Preoperative CT images reveal a huge renal mass in the right kidney and multifocal neoplasms in the left kidney (black arrow), with bilateral renal sinus invasion. (B,D) Postoperative CT images reveal multiple perfusion defects in both kidneys and bilateral mild hydronephrosis, without evidence of recurrence or metastasis.

2 patients (cases 5 and 7). The histology of the residual kidney in case 2 showed diffuse nephritis with mesangial sclerosis.

A total of 4 patients experienced urinary leakage, adequate drainage with ultrasound-guided percutaneous nephrostomy resolved this problem; transplanted renal artery stenosis was not observed in the postoperative CT scans; 3 children had postoperative hypertension (within 3 months), for effective oral antihypertensive drugs, and oral antihypertensive drugs were discontinued when blood pressure normalized; 2 patients had chylous ascites, whereas 1 developed perinephritis. The disorder was appropriately resolved using drainage and antibiotics. Case 8 developed acute kidney injury (AKI) after surgery and necessitated hemodialysis for 2 weeks until the renal function improves.

The endpoint of follow-up was May 09, 2022. All patients were followed up for an average of 28.4 ± 16.1 months; 2 children died due to end-stage renal disease (ESRD) (case 1) and postoperative sepsis (case 7), respectively (Table 2); 7 children survived and finished postoperative chemotherapy with no evidence of tumor recurrence. Case 1 had an eGFR of less than $50\ ml/(min \times 1.73\ m^2)$ preoperatively and rapidly developed renal insufficiency after surgery. Case 2 had an eGFR higher than $80\ ml/(min \times 1.73\ m^2)$ 2 months after surgery, but developed ESRD 11 months postoperatively and was eventually subjected to allograft renal transplantation 28 months after BS-AT. No statistically significant differences were noted in eGFR after 2 weeks, 1 month, and 3 months postoperatively compared to the preoperative levels ($P > 0.05$). However, the follow-up endpoint eGFR decreased significantly from preoperative levels ($P = 0.048$). Nevertheless, the mean eGFR of survivors was $81 \pm 15.4\ ml/(min \times 1.73\ m^2)$. In our cohort, 11 renal units survived, 9 of which were subjected to BS-AT. In these 9 units, the intraoperative renal volume was $37.63 \pm 14.79\ cm^3$, whereas the follow-up endpoint renal volume was $62.38 \pm 24.05\ cm^3$, with a statistical difference ($P = 0.02$) (Figure 5; Supplementary Table 1).

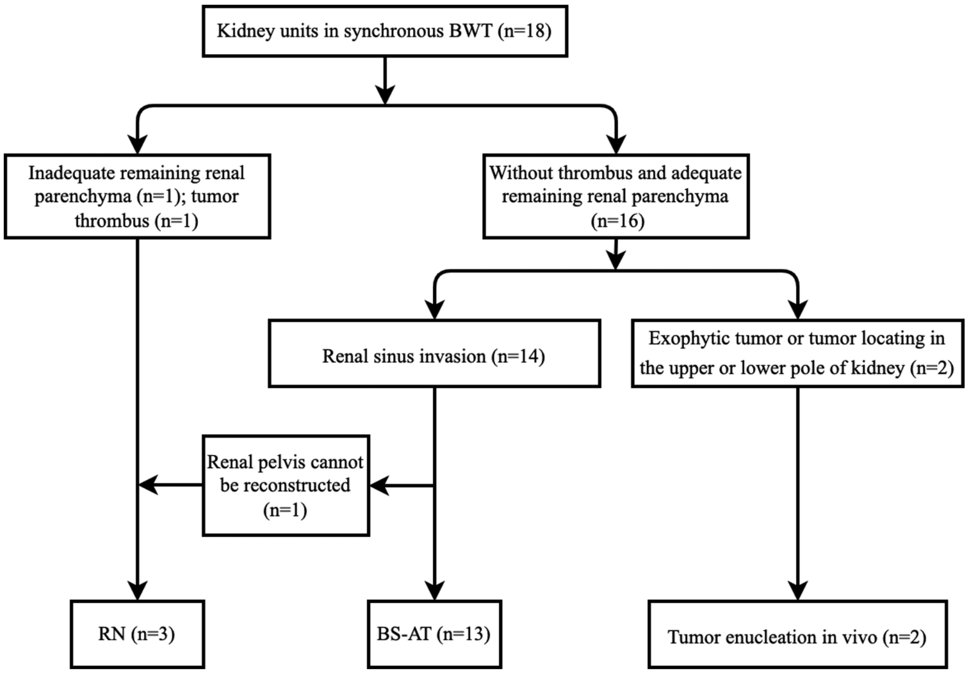

FIGURE 4
Flow chart of surgical strategy.

TABLE 2 Functional and oncological outcomes of 9 patients.

Case	eGFR (ml/min/m^2)					Follow-up (m)	Outcome
	Preop*	Postop# (2 weeks)	Postop# (1 month)	Postop# (3 months)	Postop# (endpoint)		
1	43	19	13	7	6	4	Death, ESRD
2	114	98	129	66	4	36	Alive with allograft KT
3	71	82	70	82	83	40	Alive
4	91	101	91	88	89	38	Alive
5	114	79	70	78	77	47	Alive
6	185	161	127	210	122	23	Alive
7	129	41	–	–	41	1	Death, sepsis
8	105	10	52	119	66	35	Alive
9	161	156	175	203	127	32	Alive

ESRD, end stage renal disease; eGFR, estimated glomerular filtration rate; KT, kidney transplantation.
*The preoperative eGFR was presented before the first surgery in case 1–6.
#The postoperative eGFR was presented after the second surgery in case 1–6.

Discussion

Proper surgical techniques are the mainstay of multimodal therapies that improve oncologic outcomes for BWT. The available options for synchronous BWT include unilateral RN with contralateral NSS, bilateral NSS, or bilateral RN, and the most common surgical procedure is unilateral RN with contralateral NSS (1). Drysdale reviewed BWT from 4 centers and discovered that unilateral RN with contralateral NSS was the preferred option in low-income centers, whereas bilateral NSS was more prevalent in high-income centers (15). Presumably, patients in low-income centers may have a higher stage distribution. Herein, 94.4% of renal units were distributed in stage II or stage III, 6 cases (66.7%) received bilateral NSS, and 61.1% of renal units were preserved without recurrence. Despite the small number of cases, our results were encouraging. **Figure 4** shows our surgical strategy. Tumor enucleation *in vivo* was performed if

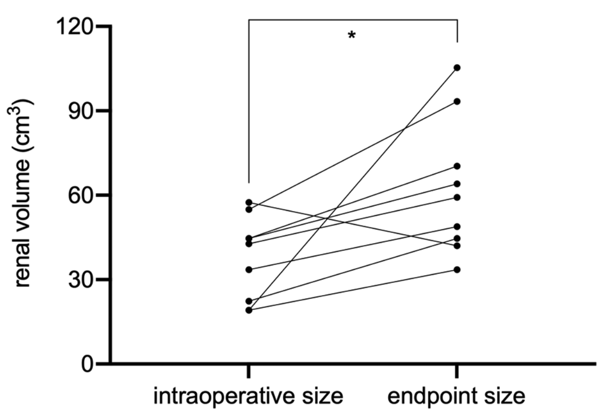

FIGURE 5
Renal volume at surgery and follow-up endpoint (*P = 0.02).

neoplasms located at the periphery or polar region; RN was performed in cases of thrombus or absence of adequate renal parenchyma. Meanwhile, RN remains inevitable if the renal pelvis cannot be reconstructed following tumor eradication. We admitted BS-AT increases the surgical difficulty, but it contributes rescuing more renal units as the ultimate approach to NSS (11). Notably, Our study indicated that BS-AT is a practical option in cases of renal sinus invasion.

In order to contribute the renal preservation, preoperative chemotherapy is used to promote tumor regression. Increased utilization of preoperative chemotherapy could further expand the number of patients eligible for partial nephrectomy (16). In the SIOP 2016 protocol, NSS is the preferred option in BWT patients. If NSS seems impossible, the tumors could be biopsied, preferably with the Tru-cut needle. In non-responsive to preoperative chemotherapy BWT patients, WT1 mutations or unfavorable histology need to be ruled out. A biopsy should be performed to confirm histology to decide further treatment (17–19). Meticulous assessment of renal function is necessary to substantially renal parenchyma in synchronous BWT. Preoperative imaging helps in delineating the extent of kidney involvement. Besides the spatial location of the tumor, the vascular supply and renal sinus must have to be thoroughly assessed. After surgery, most bilateral cases often develop varying degrees of renal insufficiency (20). A similar observation was made in our series. Although postoperative eGFR within 3 months was not statistically different from preoperative, the follow-up endpoint of eGFR was statistically decreased. Perhaps, the remaining renal parenchyma was at increased risk of glomerulosclerosis and progressive renal failure (21). The decreased renal volume also contributes to the eventual ESRD and decreased GFR (5, 14). Case 1 suffered preoperative renal impairment [eGFR less than 50 ml/(min × 1.73 m^2)], which was considered to be associated with intrinsic renal disease and nephrotoxic chemotherapy. The renal function of case 1 rapidly deteriorated after the staged surgery, this case suggested that neoadjuvant chemotherapy should not trigger nephrotoxicity before BS-AT. Since the tumor size is unlikely to shrink further and postoperative chemotherapy depends on surgical pathology, neoadjuvant chemotherapy should not last more than 12 weeks (17, 22). In our study, BS-AT was performed within 1 month after the completion of preoperative chemotherapy. Because of DDS, case 2 showed dramatic deterioration of renal function 11 months postoperatively. During this time-lapse, the patient completed postoperative chemotherapy, and tumor recurrence was not observed. Allograft kidney transplantation is advised to be performed 2 years after the completion of chemotherapy (23). Given the possibility of tumor recurrence and chemotherapy-related nephrotoxicity, allograft kidney transplantation is not recommended in conjunction with an initial bilateral nephrectomy. At the same time, allograft kidney transplantation is not necessary for patients with good renal function after BS-AT.

Herein, tumor size did not play a significant role in surgical planning. Despite the massive tumor in the right kidney of case 6 (**Figure 3**), the remaining renal parenchyma measured 44.69 cm^3, and we successfully performed NSS using BS-AT. Kubiak et al. discovered that favorable postoperative renal function can be anticipated if at least 30% of the renal parenchyma is preserved (24). The minimum renal volume after tumor removal in our study was 16.76 cm^3, and the volume of surviving renal units significantly increased at the follow-up endpoint. This change could be explained by hypertrophy of the remaining nephrons because of an increase in glomerular capillary pressure and flow, which serves to minimize renal functional loss (21). Also, we noted that among the surviving renal units, the volume remained unrestored after tumor enucleation *in vivo*. We proposed the following explanations: a severely reduced number of nephrons will probably not compensate *via* hypertrophy (14), and tumor resection *in vivo* causes more severe thermal ischemia-reperfusion injury.

Brilliant surgical skills and cooperation among transplant surgeons and pediatric surgeons are vital for the successful implementation of BS–AT. Notably, it is difficult to discriminate tumor tissue from normal kidney tissue after perfusion (25). Visible tumors should be marked before RN. Complete tumor excision and a margin of the normal renal parenchyma are still recommended (26). Repeated frozen sections in bench surgery can be performed to achieve negative margins. At our Organ Transplant center, ice-cold HCA solution is routinely used to perfuse donor kidneys to alleviate ischemia-reperfusion injury. A similar study revealed that vascular clamping during tumor excision *in vivo* took no more than 30 min (20). Nonetheless, bench surgery allows surgeons sufficient time to clarify the spatial relationship between the tumor and renal sinus, resect the tumor, and perform retroperitoneal lymph node sampling. To ensure patient safety, the renal vein was ligated when the kidney was taken out. Surgical members paid enhanced attention to secondary bleeding. A vascular clamp was used for blocking the proximal renal vein or partial occlusion of vena cava.

Individualized surgical procedures should be investigated, including: (1) simultaneous or staged operation; (2) which kidney is the priority for treatment. Warmann et al. recommended single-stage surgery, and tumor resection should be started on the more affected side; the contralateral kidney should be first treated in patients when NSS is unfeasible (27). In our series, the staged surgery appeared to alleviate surgical trauma and intraoperative blood loss, AKI was not present. Considering the subsequent contralateral RN, we first performed NSS on the less involved side.

Several early complications are linked to nephrectomy, such as intestinal obstruction, extensive hemorrhage, wound infection, and vascular damage (28). In this study, the most prevalent postoperative complication was urinary fistula, specifically in patients with renal pelvic involvement. Consequently, we recommend efficient drainage insertion and meticulous reconstruction of the renal collecting systems. Besides the Double-J tube in the ureter, drainage tubes were placed in the perirenal and pelvic cavities to guarantee adequate drainage. Refractory urinary fistulas are managed *via* a percutaneous puncture or retrograde intubation. Absorbable barbed sutures are widely used in adult NSS given the renal growth capacity. In our study, we used non-absorbable sutures as we were concerned about secondary bleeding after BS-AT. We observed that renal volume of 9 renal units receiving BS-AT significantly increased. With the accumulation of surgical experience, absorbable sutures can be attempted in future works. Absorbable sutures are recommended as a precaution against urolithiasis, and additives of papaverine as well as hemostatic cotton to prevent vascular spasms and deformation. We observed no postoperative vascular embolization or transplanted renal artery stenosis. Case 7 highlighted the importance of anti-infective treatment after the implementation of BS-AT. In order to avoid aggravation of postoperative infection, anti-infection therapy should be intensified after BS-AT. Furthermore, for patients with bilateral reconstruction of renal collection system, staged procedures seemed to be safer.

Considering that this was a retrospective study involving a small sample size, there is a need for additional comparable data from multiple centers and a longer follow-up period. As a feasible technique that preserves the renal parenchyma, BS-AT is expected to be applied in patients with one solitary kidney, metachronous BWT, or other tumors affecting the renal sinus. A highly experienced team must centralize the surgery for effective treatment of these patients.

Conclusion

In conclusion, we found that it was technically practical to apply BS-AT in the management of synchronous BWT albeit in our relatively small series. Moreover, patients with renal sinus invasion can benefit from BS-AT, which contributes to achieving a leisurely NSS without compromising tumor control. Therefore, meticulous surgical approaches and excellent skills are paramount to achieving acceptable oncological and functional outcomes.

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.

Author contributions

WCX and LJC designed the surgical protocol and reviewed the manuscript; GPF, LJ, CHD, LLS, JH and WCL participated in the management of the patients and performed the surgery. WWR and FQ participated in data analysis. XLL was involved with patient care. GPF and LJ wrote the original draft. WCX provided financial support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declared 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1047975/full#supplementary-material.

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Nomogram predicts CR-POPF in open central pancreatectomy patients with benign or low-grade malignant pancreatic neoplasms

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Introduction: Central pancreatectomy (CP) is a standard surgical procedure for benign and low-grade malignant pancreatic neoplasms in the body and neck of the pancreas. Higher incidence of clinically relevant postoperative pancreatic fistula (CR-POPF) after CP than after pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) has been reported, but no nomogram for prediction of CR-POPF after open CP has been previously established.

Methods: Patients undergoing open CP for benign or low-grade malignant pancreatic neoplasms in the department of Hepatobiliary and Pancreatic (HBP) surgery of Shanghai Changhai Hospital affiliated to Naval Medical University between January 01, 2009 and December 31,2020 were enrolled. Pre-, intra- and post-operative parameters were analyzed retrospectively.

Results: A total of 194 patients, including 60 men and 134 women, were enrolled with median age of 52 years (21~85 years). 84 patients (43.3%) were overweight (BMI>23.0 Kg/m2) and 14 (7.2%) were obese (BMI>28.0 Kg/m2). Pathological diagnoses ranged from serous cystic neoplasm (32.5%), solid pseudopapillary neoplasm (22.2%), pancreatic neuroendocrine tumor (20.1%), intraductal papillary mucinous neoplasm (18.0%) to mucinous cystic neoplasm (5.2%). All patients had soft pancreatic texture. Main pancreatic duct diameters were $\leq$0.3cm for 158 patients (81.4%) and were $\geq$0.5cm in only 12 patients (6.2%). A stapler (57.7%) or hand-sewn closure (42.3%) were used to close the pancreatic remnant. The pancreatic anastomosis techniques used were duct to mucosa pancreaticojejunostomy (PJ)-interrupted suture (47.4%), duct to mucosa PJ-continuous suture (43.3%), duct to mucosa "HO" half-purse binding PJ (5.2%) and invaginating pancreaticogastrostomy (4.1%). Post-surgical incidences of CR-POPF of 45.9%, surgical site infection of 28.9%, postpancreatectomy hemorrhage of 7.7% and delayed gastric emptying of 2.1% were found. Obesity and pancreatic anastomosis technique were independent risk factors of CR-POPF, with a concordance index of 0.675 and an Area Under the Curve of 0.678.

Discussion: This novel nomogram constructed according to obesity and pancreatic anastomosis technique showed moderate predictive performance of CR-POPF after open CP.

KEYWORDS

body mass index (BMI), obesity, pancreatic anastomosis technique, clinically relevant postoperative pancreatic fistula (CR-POPF), central pancreatectomy (CP), nomogram

Introduction

Many benign or low-grade malignant pancreatic neoplasms are asymptomatic but recent advances in imaging techniques have allowed increased detection rates (1). Prognoses tend to be good and when complete resection (R0 resection) is required, parenchyma-sparing surgeries better preserve the exocrine and endocrine pancreatic function (2). Parenchyma-sparing surgeries include central pancreatectomy (CP), duodenum-sparing head resection and enucleation. CP preserves much of the pancreatic head and distal pancreatic volume, allowing better retention of exocrine and endocrine function than pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) and has become the standard surgical procedure for benign and low-grade malignant pancreatic neoplasms in the body and neck of the pancreas (3–6).

However, CP leaves two divided pancreatic remnants, creating more opportunities for postoperative pancreatic fistula (POPF) formation. There have been many reports of higher POPF incidence following CP than after PD or DP (5–10). POPF is a severe and challenging complication of CP, contributing to post-operative morbidity, due to post-pancreatectomy hemorrhage, surgical site infection or abdominal abscess, mortality and prolonged hospitalization (5–10). It has been described as the "Achilles heel" of CP (11). Establishment of a system predictive of CR-POPF risk after CP is necessary to inform individualized treatment plans for affected patients. However, since CP is seldom performed (8), post-CP CR-POPF prediction has not been developed. Nomograms have been widely used to predict CR-POPF risk after pancreatectomy with favorable results (12–14). The current study uses data from the largest single-center open CP cohort so far reported to establish a nomogram predictive of CR-POPF for post-CP patients with benign and low-grade malignant pancreatic neoplasms.

Patients and methods

Patients and study design

A total of 194 patients undergoing CP for benign and low-grade malignant pancreatic neoplasms in the department of Hepatobiliary and Pancreatic (HBP) surgery of Shanghai Changhai Hospital affiliated to Naval Medical University between January 01, 2009 and December 31,2020 were enrolled. Inclusion criteria were as follows: 1. >18 years; 2. benign and low-grade malignant pancreatic neoplasm; 3. open central pancreatectomy (OCP). Exclusion criteria were as follows: 1. minimally invasive central pancreatectomy (MICP), including laparoscopic or robotic CP; 2. pancreatic cancer, including pancreatic ductal adenocarcinoma (PDAC) and its subtypes, adenosquamous carcinoma (ASC), acinar cell carcinoma (ACC) and neuroendocrine carcinoma (NEC); 3. chronic pancreatitis; 4. non-pancreatic primary disease, tuberculosis of lymph nodes, Castleman's disease. (Figure 1).

Comprehensive demographic, pre-, intra- and post-operative data of all patients who underwent CP in the 12 years of interest were collated from electronic medical records. Perioperative parameters were analyzed retrospectively. All patients gave written informed consent for participation, and the Ethics Committee of Shanghai Changhai Hospital granted the ethical approval.

Open central pancreatectomy surgical techniques

Midline upper abdominal laparotomy was performed and the pancreas was exposed by division of the gastrocolic ligament. The inferior border of the pancreas was mobilized

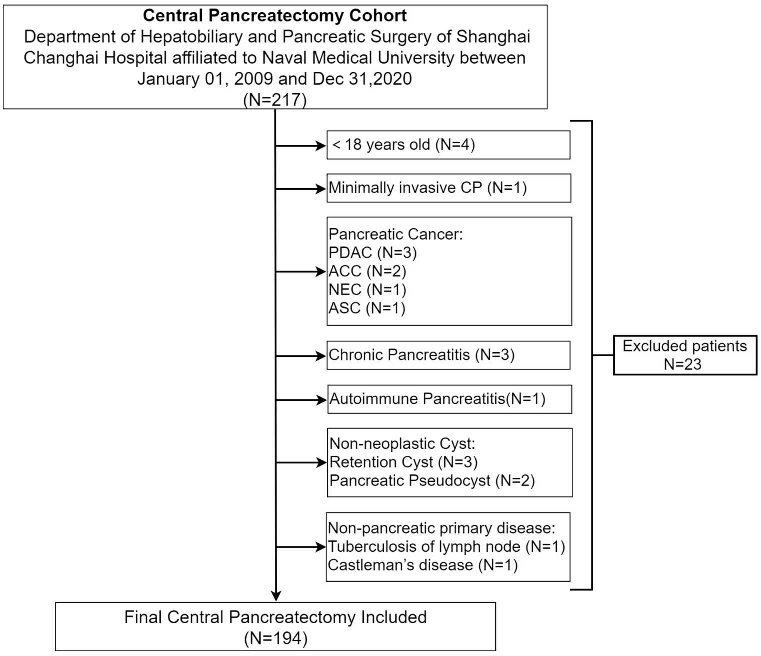

FIGURE 1
Flow chart of open central pancreatectomy selection.

in front of superior mesenteric vein (SMV) and a tunnel created between the posterior surface of the pancreatic neck and portal vein (PV)/SMV. If necessary, resection was extended to the right of the PV/SMV with division of the gastroduodenal artery (GDA) and pancreatic head transection along the left of bile duct.

The proximal pancreatic remnant was closed by hand-sewn closure or stapler. Use of suture involved location of the main pancreatic duct (MPD), which was not usually dilated in the transection, and oversewing of the MPD with a silk thread before closure of the proximal pancreatic stump by vertical mattress suture with silk thread. Use of stapler involved transection of the pancreatic neck by mechanical stapler (Figure 2). After the pancreatic neck was transected, by taking care to ligate and cut small branches to or from the pancreas, the PV/SMV, splenic veins (SV) and splenic artery (SA) were freed from the posterior of the pancreatic body, SV and SA were carefully protected during this process. A lesion in the body or neck of the pancreas was excised with a margin of 1 to 2 mm from both pancreatic stumps. Approximately 1 cm distal to the pancreatic stumps was mobilized. An appropriately sized stent was placed within the MPD. Different pancreatic anastomosis techniques (Figure 3) were performed in the distal pancreatic remnant: end-to-side duct to mucosa pancreaticojejunostomy (PJ) (interrupted suture and continuous suture), end-to-side duct to mucosa "HO" half-purse binding PJ or invaginating pancreaticogastrostomy (PG). PJ involved two-layer and duct-to-mucosa anastomosis, with continuous suture (15), interrupted suture, or "HO" half-purse binding PJ (16). The pancreatic stump was closed directly by the jejunal wall with linear MPD drainage. Invaginating PG involved two-layer invaginating anastomosis with interrupted suture. Two silicone or latex suction drains were placed under the pancreatic remnant and the PJ/PG anastomosis after CP and pulled out through the left and/or right of the midline upper abdominal incision.

Post-operative management

Patients received 24h antibiotic prophylaxis following open CP. Octreotide was only given as a POPF prophylactic in cases where there was evidence of CR-POPF or acute pancreatitis. Laboratory testing of drain fluid amylase activity was conducted routinely every 2 days from postoperative day (POD) 1 until drainage removal. Abdominal drainage volume was measured every day. When the drain amylase level less than 5000 U/L and drain output less than 300 mL per day, and there were no signs of intraabdominal infection, we removed the abdominal drain. An emergency CT was performed if signs of intraabdominal infection were detected and if fluid accumulation could be seen, a percutaneous drainage tube was placed using ultrasound or CT guidance.

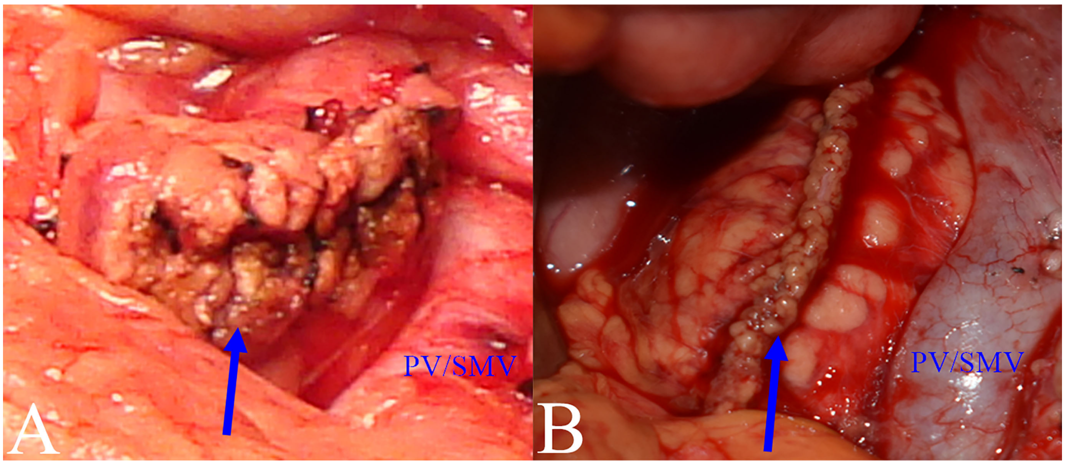

FIGURE 2
Closure methods for pancreatic remnants. **(A)** Hand-sewn closure: pancreatic remnant after closure (blue arrow). **(B)** Stapler closure: pancreatic remnant after closure (blue arrow).

Definition of post-operative complications

Grade B and grade C, but not grade A, POPFs were considered to have clinical significance and to be defined as CR-POPF, based on the definition given by the International Study Group for Pancreatic Fistula (ISGPF) in 2016 (17). Post-pancreatectomy hemorrhage (PPH) was diagnosed and graded based on the definition given by the International Study Group of Pancreatic Surgery (ISGPS): PPH-ISGPS (2007) (18), Delayed Gastric Emptying (DGE) was diagnosed and graded based on the ISGPS definition: DGE-ISGPS (2007) (19). Post-operative

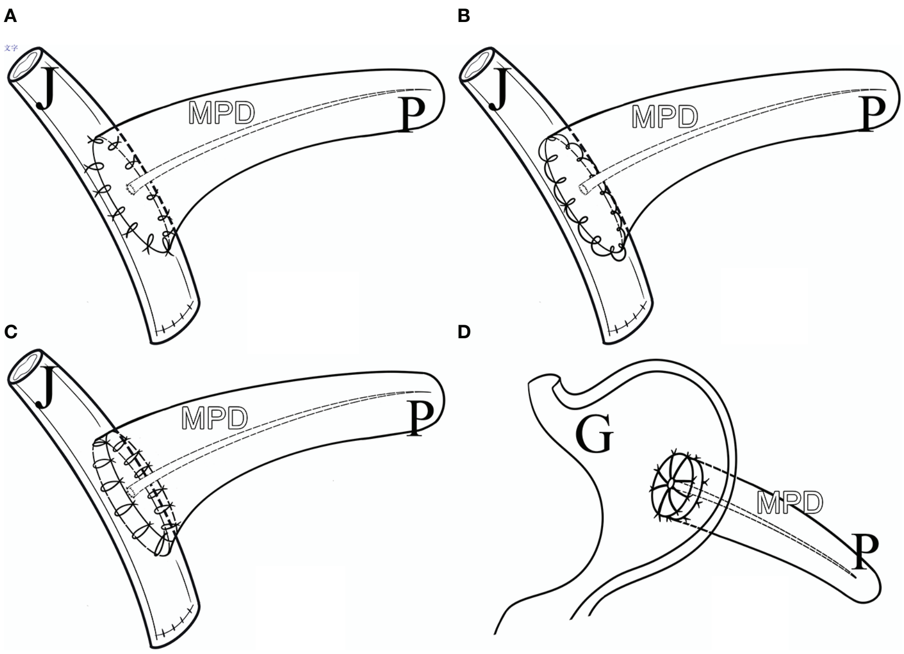

FIGURE 3
Pancreatic Anastomosis Techniques. **(A)** Duct to Mucosa PJ (Interrupted Suture). **(B)** Duct to Mucosa PJ (Continuous Suture). **(C)** Duct to Mucosa "HO" half-purse binding PJ. **(D)** Invaginating PG. P, pancreas; J, jejunum; G, gastro; MPD, main pancreatic duct.

complications were assessed based on the Clavien-Dindo classification (2004) (20).

Statistical analysis

Continuous variables are described as medians (quadrants) and are compared using the Mann-Whitney U test. Categorical variables are reported as integers and percentages and are compared by the $\chi 2$ test or Fisher's exact test. Cut-off values for certain parameters were determined by receiver operating characteristic (ROC) curve. Univariate and multivariate risk factor analysis was conducted by using logistic regression analysis, and a nomogram predicts CR-POPF was established based on the result of multivariate risk factor analysis. Three statistical approaches were used to verify the nomogram: concordance index analysis, ROC curve and calibration plot. Statistical analyses were conducted using GraphPad Prism 9, SPSS 24.0 software and R software version 4.1.2. All statistical significance levels were two-sided and a value of $p < 0.05$ was considered to indicate significance.

Results

Baseline features

The 194 patients consisted of 60 men and 134 women, with a median age of 52 years (range: 21~85 years), among them 148 patients>50 years and 46 patients ≤ 50 years. 113 patients (58.2%) were asymptomatic, 70 (36.1%) complained of abdominal discomfort, 9 (4.6%) had a history of hypoglycemia prior to surgery and 2 (1.0%) had experienced weight loss. 16 patients (8.2%) had history of diabetes and 14 (7.2%) had history of pancreatitis. 84 patients (43.3%) were overweight (BMI>23.0 Kg/m^2) and 14 (7.2%) were obese (BMI>28.0 Kg/m^2). Most patients had normal CA19-9 and CEA levels.

The most common pathological diagnosis was serous cystic neoplasm (63/194, 32.5%), followed by solid pseudopapillary neoplasm (43/194, 22.2%), pancreatic neuroendocrine tumor (39/194, 20.1%), intraductal papillary mucinous neoplasm (35/194, 18.0%), mucinous cystic neoplasm (10/194, 5.2%) and other tumors (4/194, 2.1%). The mean duration of surgery was 128min (range: 60~275 min) and the median estimated intraoperative blood loss was 179 ml (range: 20~800 ml) with 3 patients receiving intraoperative blood transfusion. A soft pancreatic texture was present in all cases. The MPD diameter was ≤0.3cm in 158 patients with only 12 patients having an MPD > 0.5cm in diameter.

The pancreatic remnant was closed by either stapler (112/194, 57.7%) or hand-sewn closure (82/194, 42.3%). Four pancreatic anastomosis techniques were used (Table 1): duct to mucosa PJ (interrupted suture) (92/194, 47.4%), duct to mucosa PJ (continuous suture) (84/194, 43.3%), duct to mucosa "HO" half-purse binding PJ (10/194, 5.2%) and invaginating PG (8/194, 4.1%).

Post-operative complications

Among the 194 patients enrolled in this study, we have not found the amylase activity of fluid output *via* the operatively placed drain in 22 of them, so we can't judge whether they have POPF or not, in the remaining 172 patients, the incidences of Grades B and C POPF were 45.3% (78/172) and 0.58% (1/172), respectively. 12 patients (6.2%) received postoperative erythrocyte transfusion. 56 patients (28.9%) had surgical site infection (SSI). 15 patients (7.7%) had post-pancreatectomy hemorrhage (PPH): 3 (20.0%) experienced early and 12 (80.0%) experienced late hemorrhage; 11 (73.3%) had extraluminal and 4 (26.7%) had intraluminal hemorrhage; 2 cases had grade A, 10 grade B and 3 grade C PPH. 4 patients (2.1%) had postoperative delayed gastric emptying (DGE): 2 cases were grade A and 2 were grade C. 1 patient (0.52%) died on POD 3 and the cause of death is diabetic ketoacidosis with septic shock. The average length of the hospital stay is 9.8 days (range: 3~47 d).

The rate of postoperative diabetes mellitus was 5.2% (10/194) and of postoperative pancreatitis, 5.7% (11/194). 1 patient with a pathological diagnosis of pancreatic neuroendocrine tumor experienced symptomatic PJ stricture 6 years after CP which was treated by resection of the PJ, followed by new two-layer end-to-side PJ with internal drainage of the Wirsung duct. 1 patient with a pathological diagnosis of intraductal papillary mucinous neoplasm relapsed 18 months after CP with pancreatic ductal adenocarcinoma and was treated by pylorus preserving pancreaticoduodenectomy (PPPD).

Univariate and multivariate analysis of CR-POPF-associated factors

The following perioperative parameters were conducted to univariate and multivariate analyses: gender, age, symptoms, hypertension, diabetes, pancreatitis, abdominal surgery, smoking, alcoholism, BMI, ASA score, closure methods of pancreatic remnant, pancreatic anastomosis technique, pathology, largest tumor diameter, diameter of pancreatic duct, operation time, estimated blood loss and laboratory tests of blood or serum. The results showed that BMI ≥28kg/m2 (hazard ratio [HR] 7.663; 95% confidence interval [CI] 1.557–37.721) and pancreatic anastomosis technique (invaginating PG was set as the reference: hazard ratio for duct to mucosa PJ-Continuous suture: 4.364 [0.701, 27.183]; duct to mucosa "HO" half-purse binding PJ: 7.328 [0.778, 69.001]; duct to mucosa PJ-Interrupted suture: 1.489 [0.237, 9.348]) were independent risk factors for CR-POPF (Table 2).

TABLE 1 Clinicopathological Characteristics and Postoperative Complications.

Variable	CP (N=194)	CR-POPF		P-value	Severe Complication		P-value
		Absent (N=93) (50.1%)	Present (N=79) (45.9%)		Absent (N=124) (64.2%)	Present (N=69) (35.8%)	
Gender				0.059			0.072
Male	60 (30.9%)	25 (43.9%)	32 (56.1%)		33 (55.0%)	27 (45.0%)	
Female	134 (69.1%)	68 (59.1%)	47 (40.9%)		91 (68.4%)	42 (31.6%)	
Age (year)				0.135			0.165
>50	148 (76.3%)	76 (57.1%)	57 (42.9%)		99 (66.9%)	49 (33.1%)	
≤50	46 (23.7%)	17 (43.6%)	22 (56.4%)		25 (55.6%)	20 (44.4%)	
Symptoms				0.102			0.088
Present	81 (41.8%)	42 (61.8%)	26 (38.2%)		57 (71.3%)	23 (28.7%)	
Absent	113 (58.2%)	51 (49.0%)	53 (51.0%)		67 (59.3%)	46 (40.7%)	
History of Diabetes				0.085			0.138
Present	16 (8.2%)	10 (76.9%)	3 (23.1%)		13 (81.3)	3 (18.7%)	
Absent	178 (91.8%)	83 (52.2%)	76 (47.8%)		111 (62.7%)	66 (37.3%)	
History of Hypertension				0.341			0.220
Present	41 (21.1%)	19 (47.5%)	21 (52.5%)		23 (56.1%)	18 (43.9%)	
Absent	153 (78.9%)	74 (56.1%)	58 (43.9%)		101 (66.4%)	51 (33.6%)	
History of Pancreatitis				0.056			0.246
Present	14 (7.2%)	9 (81.8%)	2 (18.2%)		11 (78.6%)	3 (21.4%)	
Absent	180 (92.3%)	84 (52.2%)	77 (47.8%)		113 (63.1%)	66 (36.9%)	
History of Abdominal Surgery				0.436			0.392
Present	50 (25.8%)	20 (48.8%)	21 (51.2%)		29 (59.2%)	20 (40.8%)	
Absent	144 (74.2%)	73 (55.7%)	58 (44.3%)		95 (66.0%)	49 (34.0%)	
History of Smoking				0.526			0.467
Present	21 (10.8%)	11 (61.1%)	7 (38.9%)		15 (71.4%)	6 (28.6%)	
Absent	173 (89.2%)	82 (53.2%)	72 (46.8%)		109 (63.4%)	63 (36.6%)	
History of Alcoholism				0.436			0.697
Present	10 (5.2%)	6 (66.7%)	3 (33.3%)		7 (70.0%)	3 (30.3%)	
Absent	184 (94.8%)	87 (53.4%)	76 (46.6%)		117 (63.9%)	66 (36.1%)	
Overweight				0.060			0.026
BMI>23.0 Kg/m2	84 (43.3%)	35 (46.1%)	41 (53.9%)		46 (55.4%)	37 (44.6%)	
BMI ≤ 23.0 Kg/m2	110 (56.7%)	58 (60.4%)	38 (39.6%)		78 (70.9%)	32 (29.1%)	
Obesity				0.004			0.045
BMI>28.0 Kg/m2	14 (7.2%)	2 (15.4%)	11 (84.6%)		5 (38.5%)	8 (61.5%)	
BMI ≤ 28.0 Kg/m2	180 (92.8%)	91 (57.2%)	68 (42.8%)		119 (66.1%)	61 (33.9%)	
ASA score				0.264			0.820
1	104 (53.6%)	47 (52.2%)	43 (47.8%)		69 (67.0%)	34 (33.0%)	
2	60 (30.9%)	31 (56.4%)	24 (43.6%)		36 (60.0%)	24 (40.0%)	
3	30 (15.5%)	15 (55.6%)	12 (44.4%)		19 (63.3%)	11 (36.7%)	
Pre-operative parameter							
CA199	24.76 ± 82.94	14.36 ± 14.92	19.84 ± 48.01	0.024	24.92 ± 94.03	24.47 ± 58.16	0.840
CEA	2.19 ± 2.02	2.35 ± 2.56	1.95 ± 1.31	0.122	2.31 ± 2.32	1.97 ± 1.32	0.180
Total bilirubin	12.26 ± 5.01	12.14 ± 4.7	12.87 ± 5.63	0.503	11.96 ± 4.55	12.81 ± 5.77	0.137
Albumin	42.10 ± 3.77	42.19 ± 3.57	42.6 ± 3.85	0.416	41.99 ± 3.67	42.31 ± 4	0.446
Blood glucose	5.35 ± 1.75	5.36 ± 1.28	5.26 ± 1.77	0.686	5.45 ± 1.76	5.18 ± 1.74	0.570

(Continued)

TABLE 1 Continued

Variable	CP (N=194)	CR-POPF		P-value	Severe Complication		P-value
		Absent (N=93) (50.1%)	Present (N=79) (45.9%)		Absent (N=124) (64.2%)	Present (N=69) (35.8%)	
Serum amylase	71.33 ± 44.03	69.03 ± 40.42	72.47 ± 53.22	0.590	75.08 ± 50.04	62.33 ± 26.06	0.186
PT, s	12.95 ± 0.76	12.96 ± 0.84	12.95 ± 0.69	0.259	12.97 ± 0.82	12.9 ± 0.65	0.131
WBC, 10^9/L	5.72 ± 1.66	5.51 ± 1.71	5.91 ± 1.59	0.582	5.61 ± 1.72	5.9 ± 1.56	0.340
HGB, g/L	131.93 ± 14.64	131.41 ± 14.16	134.64 ± 14.87	0.489	130.89 ± 14.23	133.82 ± 15.4	0.211
PLT	210.15 ± 53.93	210.2 ± 52.67	212.64 ± 56.33	0.619	209.8 ± 54.68	210.78 ± 53.4	0.755
CRP	3.74 ± 10.00	5.02 ± 14.88	2.66 ± 1.93	0.095	4.66 ± 13.21	2.44 ± 1.21	0.118
PCT	0.03 ± 0.03	0.02 ± 0.01	0.04 ± 0.04	0.206	0.03 ± 0.01	0.04 ± 0.04	0.115
Intra- and post-operative parameter							
Closure methods of pancreatic remnant				0.207			0.055
Stapler	112 (57.7%)	50 (50.0%)	50 (50.0%)		65 (58.6%)	46 (41.4%)	
Hand-sewn closure	82 (42.3%)	43 (59.7%)	29 (40.3%)		59 (72.0%)	23 (28.0%)	
Pancreatic anastomosis technique				0.004			<0.001
Duct to Mucosa PJ (Interrupted Suture)	92 (47.4%)	51 (68.0%)	24 (32.0%)		72 (78.3%)	20 (21.7%)	
Duct to Mucosa PJ (Continuous Suture)	84 (43.3%)	33 (41.8%)	46 (58.2%)		43 (51.8%)	40 (48.2%)	
Duct to Mucosa “HO” half-purse binding PJ	10 (5.2%)	3 (30.0%)	7 (70.0%)		3 (30.0%)	7 (70.0%)	
Invaginating PG	8 (4.1%)	6 (75.0%)	2 (25.0%)		6 (75.0%)	2 (25.0%)	
Pathology				0.820			0.954
SCN	63 (32.5%)	29 (49.2%)	30 (50.8%)		40 (63.5%)	23 (36.5%)	
SPN	43 (22.2%)	21 (55.3%)	17 (44.7%)		28 (65.1%)	15 (34.9%)	
NET	39 (20.1%)	19 (54.3%)	16 (45.7%)		27 (69.2%)	12 (30.8%)	
IPMN	35 (18.0%)	18 (56.3%)	14 (43.7%)		21 (60.0%)	14 (40.0%)	
MCN	10 (5.2%)	4 (80.0%)	1 (20.0%)		6 (66.7%)	3 (33.3%)	
Others (Paraganglioma, PEComa)	4 (2.1%)	2 (66.7%)	1 (33.3%)		2 (50.0%)	2 (50.0%)	
Largest tumor diameter, cm				0.094			0.095
≥2.0	154 (79.4%)	77 (57.5%)	57 (42.5%)		101 (67.3%)	49 (32.7%)	
<2.0	40 (20.6%)	16 (42.1%)	22 (57.9%)		23 (53.5%)	20 (46.5%)	
Diameter of main Pancreatic Duct, cm				0.777			0.737
≤0.1	22 (11.3%)	9 (53.0%)	8 (47.0%)		16 (72.7%)	6 (27.3%)	
0.2	59 (30.4%)	28 (53.8%)	24 (46.2%)		40 (69.0%)	18 (31.0%)	
0.3	77 (39.7%)	40 (54.1%)	34 (45.9%)		43 (55.8%)	34 (44.2%)	
0.4	24 (12.4%)	10 (47.6%)	11 (52.4%)		15 (62.5%)	9 (37.5%)	
≥0.5	12 (6.2%)	6 (75.0%)	2 (25.0%)		10 (83.3%)	2 (16.7%)	
Operation Time, min	128.09 ± 30.95	128.17 ± 34.46	128.86 ± 27.66	0.187	128.91 ± 33.05	126.67 ± 27.45	0.194
Estimated Blood Loss, ml	179.23 ± 113.66	167.96 ± 107.44	197.47 ± 128.33	0.732	173.15 ± 103.02	191.3 ± 131.72	0.250
Post-operative PH	7.37 ± 0.06	7.38 ± 0.05	7.37 ± 0.06	0.498	7.38 ± 0.05	7.37 ± 0.06	0.397
Post-operative BE	-2.11 ± 2.06	-2.06 ± 1.97	-2.1 ± 2.15	0.538	-2.2 ± 2	-1.97 ± 2.21	0.609

TABLE 2 Univariate and mutivariate factor analysis for POPF.

Variable	Univariate				Mulitivariate			
	P	HR	Lower limit	Upper limit	P	HR	Lower limit	Upper limit
Gender, male:female	0.060	1.852	0.975	3.519				
Symptoms, present:absent	0.103	0.596	0.320	1.110				
History of Diabetes, present:absent	0.099	0.328	0.087	1.235				
History of Pancreatitis, present:absent	0.076	0.242	0.051	1.157				
BMI, ≥28: <28kg/m^2	0.011	7.360	1.579	34.300	0.012	7.663	1.557	37.721
ASA score	0.669	0.915	0.609	1.375				
CA19-9, ≥37: <37u/ml	0.548	1.515	0.391	5.871				
Closure methods of pancreatic remnant, staple:hand suture	0.208	1.483	0.803	2.736				
Largest tumor diameter, ≥2: <2cm	0.127	0.564	0.270	1.176				
Diameter of Pancreatic Duct, ≥2: <2mm	0.923	0.970	0.526	1.789				
Albumin(preoperative minus POD1), ≥0: <0	0.127	0.480	0.187	1.231				
Pathology, SCN : SPN:NET : IPMN : MCN:Others	0.926	NA	NA	NA				
Pancreatic anastomosis technique	0.010				0.012			
Duct to Mucosa PJ (Continuous Suture)	0.104	5.833	0.696	48.873	0.114	4.364	0.701	27.183
Duct to Mucosa “HO” half-purse binding PJ	0.852	1.176	0.213	6.505	0.082	7.328	0.778	69.001
Duct to Mucosa PJ (Interrupted Suture)	0.150	3.485	0.637	19.070	0.671	1.489	0.237	9.348
Invaginating PG	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

*P < 0.05 by Logistic regression model.
Cut-off value of tumour diameter was calculated by ROC curve.
NA, not applicable.

Construction and validation of nomogram

Obesity (BMI≥28kg/m2) and pancreatic anastomosis technique (Table 2) were selected for construction of the nomogram for prediction of CR-POPF (Figure 4) and validation was performed by concordance test and ROC curve (Figure 5). The concordance test produces results that range from 0.5, indicating a totally random predictive performance, to 1.0, indicating a perfect predictive performance. A moderate predictive performance of the current nomogram was demonstrated by a concordance index of 0.675 and an Area Under the ROC Curve of 0.678 (Figure 5). The close alignment of the three lines representing apparent incidence, ideal incidence and optimum-corrected should be noted as an indication of satisfactory calibration (Figure 6).

Discussion

The recent advances in imaging techniques have led to the diagnosis of more asymptomatic benign or low-grade malignant pancreatic neoplasms (1). The prognosis of benign or low-grade malignant pancreatic neoplasms is good and parenchyma-preserving surgeries are often used for resection in order to preserve the functions of the pancreas (2). In 1957, the first 2 cases of CP with pancreaticojejunostomy (PJ) were described in 2 patients with chronic pancreatitis (8) and CP was first proposed for treatment of neoplasms in 1984 (8). CP has since become a standard surgical technique for the treatment of benign and low-grade malignant lesions located in the pancreatic body and neck (3–6). The advantages of CP include (21): (1) the endocrine and exocrine function of the pancreas were better preserved; (2) preservation of spleen. The rate of post-operative diabetes mellitus was 5.2% (10/194) in the current study.

However, the two separated edges of the pancreas generated by CP generate increased opportunity for the formation of postoperative pancreatic fistula (POPF). Besides, patients for whom CP is advised usually have benign or low-grade pancreatic malignancies with soft texture and a small MPD in the vast majority of cases, all of these have been demonstrated to be significant risk factors for POPF (12–14). These risk factors are independent of the surgeon’s intervention and the incidence of POPF after CP has been reported to exceed that after standard PD or DP (5–10). POPF remains a severe and challenging complication of CP and is a key contributor to most of the postoperative complications, such as post-pancreatectomy hemorrhage and abdominal abscess, promoting operation-related morbidity, mortality and prolonged hospitalization (5–10). Indeed, POPF is the “Achilles heel” of CP (11). Patients with pancreatic cancer and chronic pancreatitis were excluded in the current study, and 81.4% (158/194) of the cohort had a main pancreatic duct diameter ≤ 0.3cm, the rate of CR-POPF was 45.9%, the incidence of PPH was 7.7%, of SSI 28.9%, of DGE 2.1% and of death 0.52%.

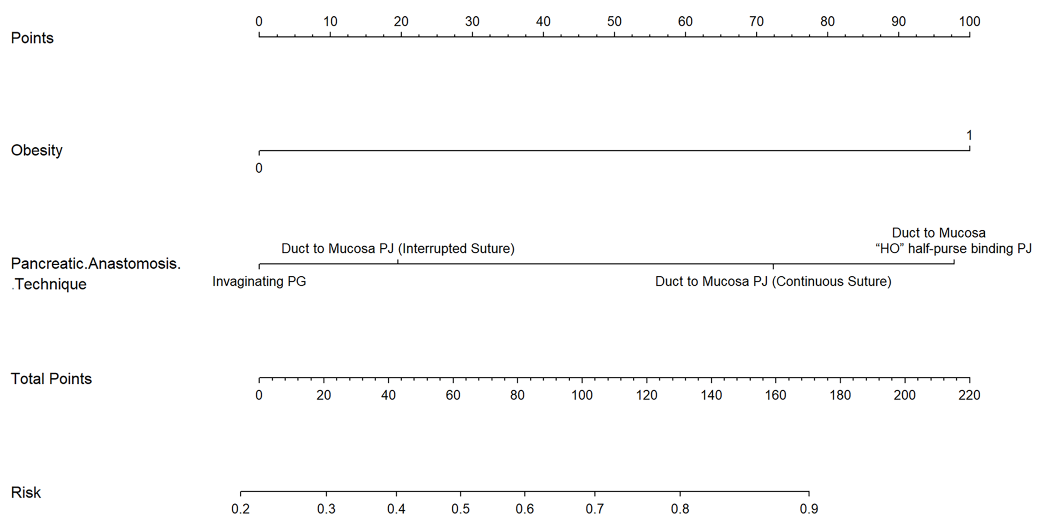

FIGURE 4
A Novel Nomogram for Predicting CR-POPF in OCP Patients. This nomogram is used by adding the points identified by each variable on the points scale. The sum of these points is projected on the bottom scale and indicates the rate of CR-POPF in individual patients. PJ: pancreaticojejunostomy; PG: pancreaticogastrostomy.

The establishment of a system to predict incidence of CR-POPF after CP is expected to contribute to better patient management. However, the rarity with which CP is performed (8) has meant that such predictions have not been standardized. The largest single-center series of CPs to be published to date are reported during the current study and univariate and multivariate analyses demonstrated that obesity and pancreatic anastomosis technique were independent risk factors of CR-POPF.

Many studies have reported that obesity is an independent risk factor for CR-POPF (22–25). Both the modified Fistula Risk Score (mFRS) (13) and the alternative Fistula Risk Score (aFRS) (14), used to determine clinical risk of pancreatic fistula, incorporate BMI. The prevalence of obesity has tripled since 1975 and continues to show a pandemic-related trend of global increase, according to the World Health Organization (WHO). Surgeons will operate with increasing frequency on overweight and obese people as a consequence. The pancreas, which buried

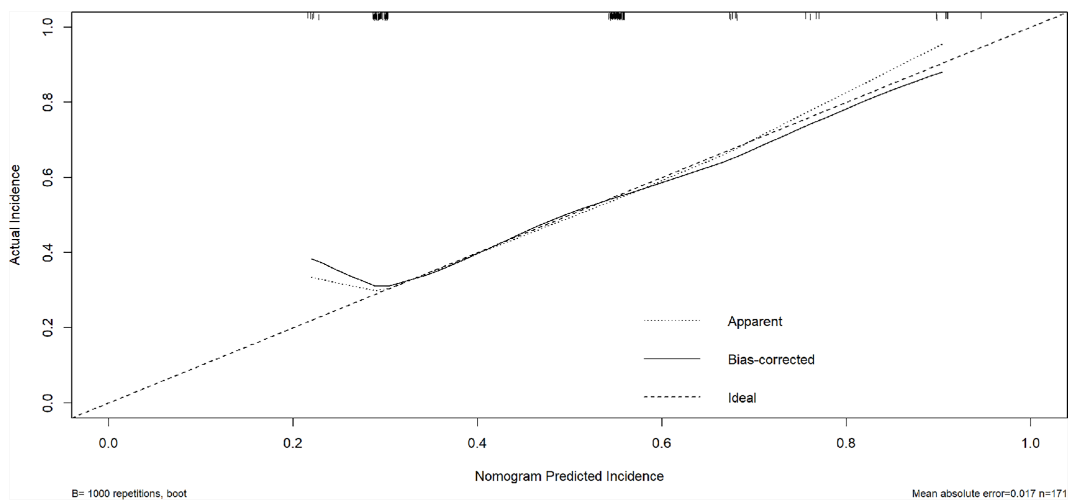

FIGURE 5
ROC of the Novel Nomogram of CR-POPF in OCP Patients. A ROC curve was constructed to evaluate the model. The area under the ROC curve was 0.678. ROC, receiver operating characteristic.

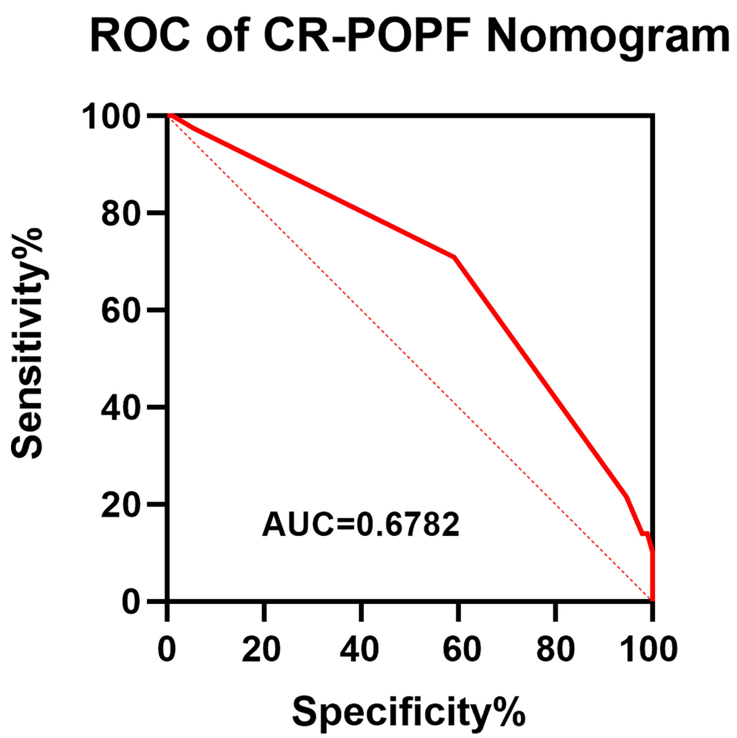

FIGURE 6
Calibration plot of nomogram predicts CR-POPF. The X–axis represents the nomogram–predicted survival, while the actual survival was plotted on the Y–axis. And the apparent incidence of CR-POPF, the ideal incidence, the bias-corrected incidence were shown as different lines.

behind the stomach, is a retroperitoneal organ. The enlarged anterior and posterior diameter of the abdominal cavity in obese patients, combined with excessive abdominal and visceral adipose tissue (26, 27), reduces the operative space and may also result in a thickening of the omentum or mesentery. Increased fat deposition in visceral organs and a heavy omentum restrict surgical exposure and blur the operative field, precipitating technical difficulties, especially pancreatic anastomosis (28). Hence, the higher the BMI, the higher the incidence of post-pancreatectomy complications, including POPF, SSI and DGE.

Soft texture of the pancreas is a highly relevant risk factor for CR-POPF (12–14). Patients with a high BMI and increased fatty infiltration have been shown to have a higher rate of soft pancreas (23). In addition, adipose tissue has a poor blood supply and heals slowly, contributing to higher POPF incidence in obese patients.

The common complication of post-operative peripancreatic fluid accumulation in overweight/obese patients may be attributed to a wider resection area, more tissue damage, larger dead space, more frequent drainage dysfunction and delayed mobilization than in patients with normal BMI (29). Obese patients also have a stronger inflammatory response to surgical invasion (30) and high levels of inflammatory factors in patients with high BMI have also been found (31). Accumulation of postoperative peripancreatic fluid and infection may activate pancreatic enzymes, promoting CR-POPF formation (17).

In addition, obesity is associated with comorbidities, such as diabetes mellitus, insulin resistance, chronic inflammation, hypertension, cardiovascular diseases, pulmonary diseases and hormones associated with metabolic syndrome (32), which may also contribute to worse perioperative outcomes, especially CR-POPF.

No statistical differences have been demonstrated between the two closure methods of pancreatic remnant: hand-sewn closure and stapler (33). The incidence of POPF following use of stapler was 50% and following hand sewn suture was 40.3% during the current study, with no statistically significant difference (p=0.207).

Four pancreatic anastomosis techniques were performed during the present study and incidences of CR-POPF from low to high were: invaginating PG (25%), duct to mucosa PJ-interrupted suture (32%), duct to mucosa PJ-continuous suture (58.2%) and duct to mucosa "HO" half-purse binding PJ (70%), with statistically significant differences (p=0.004). 81.4% patients had a main pancreatic duct diameter ≤ 0.3cm, making invaginating PG superior to duct to mucosa PJ (34).

We acknowledge some limitations to this study. First, it is a single center retrospective study, the retrospective nature is subject to selection bias, despite great efforts being made to seek information from medical records. Second, although the sample size was the largest published so far, it was not large enough to divide into separate cohorts for internal validation. Third, skinfold thickness, waist circumference and bioelectrical impedance are alternative measurements of obesity (26) but are expensive, difficult to standardize or not widely available. As a result, BMI was used as a reasonable indicator of body fat in the current article. Fourth, external validation was not performed and multicenter prospective randomized controlled trials are required to verify the findings in the future.

In conclusion, rates of CR-POPF in post-central pancreatectomy patients with benign or low-grade malignant pancreatic neoplasms were high (45.9%). Obesity and pancreatic anastomosis technique are two independent risk factors of CR-POPF. A nomogram to predict the incidence of CR-POPF following OCP was constructed. The nomogram showed moderate predictive performance and may help identifying patients at high risk of CR-POPF and facilitating early individualized perioperative intervention.

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.

Author contributions

(I) Conception and design: LO, GJ and X-GH; (II) Administrative support: GJ, X-GH and GL; (III) Provision of study patients: GJ, X-GH, Y-JZ, GL, T-LH; (IV) Collection and assembly of data: LO, Y-WR, GN, R-DL; (V) Data analysis and interpretation: LO, R-DL, Y-WR, GN, Z-PH; (VI) Manuscript writing: LO; (VII) All authors contributed to the article and approved the submitted version.

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Conflict of interest

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A new approach: Laparoscopic right hemicolectomy with priority access to small bowel mesentery

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Background: For laparoscopic right hemicolectomy, the intermediate approach is commonly employed. However, this approach possesses several disadvantages. In this study, we compare priority access to the small bowel mesentery and the intermediate approach.

Methods: The clinical data of 196 patients admitted to the First Hospital of Chongqing Medical University for laparoscopic right hemicolectomy from January 2019 to January 2022 were retrospectively collected and divided into the small bowel mesenteric priority access and traditional intermediate access groups. The operative time, intraoperative bleeding, number of lymph node dissection, postoperative anal venting time, toleration of solid and liquid intake, and postoperative hospital stay and complications were compared between the two different approaches.

Results: In total, 81 cases of small bowel mesenteric priority access and 115 cases of intermediate approach for right hemi-colonic radical resection were compared. The operative time was 191.98 ± 46.05 and 209.48 ± 46.08 min in the small bowel mesenteric priority access and intermediate access groups, respectively; the difference was statistically significant. There were no significant differences in the intraoperative bleeding and lymph node clearance. However, the scatter plot analysis showed that severe intraoperative bleeding was relatively less frequent in the small mesenteric priority access group, compared with that in the intermediate approach group. Additionally, there were no statistically significant differences in the first exhaust and defecation times, hospital stay after operation, toleration of solid and liquid intake, and postoperative complication between the two groups.

Conclusion: In laparoscopic right hemicolectomy, the small bowel mesenteric priority approach can significantly shorten the operation time compared with the intermediate approach. It can reduce intraoperative bleeding and the operation is simple and safe to perform, making it suitable for less experienced surgeons. Therefore, the small bowel mesenteric priority approach has the potential to be a suitable alternative and deserves further clinical promotion and application.

KEYWORDS

laparoscopy, colon tumor, right hemicolectomy, surgery, priority access to the small bowel mesentery

Introduction

Colorectal cancer is a major disease threatening human health (1–3), with its diagnosis and treatment arousing immense concern worldwide (4–6). Laparoscopic radical colorectal resection has become an established technique for treating colorectal cancer. It includes complete mesocolic excision (CME) and total mesocolic excision (TME) (7–9), which are two surgical methods that have become gradually standardized in the recent years. However, the choice of access for laparoscopic radical colorectal resection remains controversial.

Compared with laparoscopic radical rectal cancer resection, laparoscopic radical right hemicolectomy is more complicated, and the surgical approach and criteria for its selection has undergone many changes, owing to factors such as vascular variation, difficulties in locating vital, adjacent tissues and organs and performing colon lymph node dissection (10, 11). Among the possible surgical approaches, the "intermediate approach" proposes ligation of the dissociated mesenteric vessels first, and better aligns with the principle of the no touch isolation technique in surgical oncology (12–14). Due to the aforementioned difficulties, surgeons experienced with laparoscopic techniques often prefer the intermediate approach when performing laparoscopic radical right hemicolectomy. However, the disadvantage of the intermediate approach is that the complexity of colon anatomy may lead to difficulties in performing operation steps (15, 16), such as those involving separating and revealing mesenteric-related vessels in obese patients, accessing the correct anatomical plane, and disconnecting the vessels in areas where lesions are located. Before it become clear whether a tumor can be radically resected, the operator may be very passive.

Additionally, the risk of injury to both Henle's stem and superior mesenteric vessels is increased due to large anatomical variations after right hemicolectomy (**Figure 1**). The transition from the duodenum to the pancreas head surface is also prone to damage by inadvertent entry into the pancreatic tissue, resulting in bleeding (17).

Finally, the approach is challenging for novice surgeons to perform; thus, surgeons are constantly exploring new surgical approaches and improved points of access (18, 19). In this study, we compared the clinical data from patients who underwent the small bowel mesenteric priority approach and the traditional intermediate approach for radical right hemicolectomy.

Methods

Search strategy

A total of 196 patients were admitted to the First Hospital of Chongqing Medical University for laparoscopic radical right hemicolectomy to treat right colon cancer which from January 2019 to January 2022. Each procedure was performed by an experienced chief surgeon. Their clinical data were retrospectively collected and included in this study. Patients were divided into two groups: those who underwent the small bowel mesenteric priority approach and those who underwent the traditional intermediate approach.

Surgical approach

Patients from the intermediate approach group were placed in the supine position, and a 5-hole Trocar puncture was used to turn the greater omentum towards the liver and stomach. The small intestine was moved to the left upper abdomen, with the ileocecal region as a guide to fully reveal the "yellow-white junction line" between the root of the ileocecal mesentery and the retroperitoneum, and the right Toldt space was entered and extended to the right and cephalic side. The left edge of the superior mesenteric artery was treated with the ileocolic, right and midcolic vessels for D3 lymph node dissection, after which the gastrocolic and hepato colic ligaments were severed and the right colon was freed. Finally, the specimen was removed through a median epigastric incision and intestinal resection anastomosis was performed (20).

Patients from the small bowel mesenteric access group had a 10-mm Trocar inserted in the lower left umbilicus, a 12-mm Trocar inserted in the lower left umbilicus, a 5-mm Trocar inserted at the Mai's point, and a 5 mm Trocar placed under the rib arch in the left abdomen and left midclavicular line. Intraoperative separation was first performed laparoscopically. The transverse colonic mesentery was lifted by a surgical assistant to reveal the direction of mesenteric vascular alignment. Then, the small intestine was dissected along the inferior edge of the ileocolic vessels at the anticipated separation of the small intestine 10–15 cm from the ileocecal region, and the corresponding segment of the small intestine was naked. After clearing the lymphatic adipose tissue at the root of the vessel, the colonic branch of the gastrocolic trunk vessel was cut off with a hemolock clamp, and the ascending colon and ileocecal part were separated from the inner side. The transverse colon was lifted upward to reveal the transverse colonic mesentery. After recognizing the mesocolic vessels, the roots of the mesocolic vessels and the lymphatic adipose tissue along them were cleared and the right branch of the mesocolic vessels was cut off with hemolock clamps. Subsequently, the gastrocolic ligament was lifted and separated to the right to the hepatic flexure of the colon with an ultrasonic knife followed by the release of the hepatic flexure adhesions. The right half of the transverse colon was freed, and the lateral peritoneum was excised from the lateral part of the ileocecal and ascending colon. The greater omentum was cut in the middle, and the gastrocolic ligament

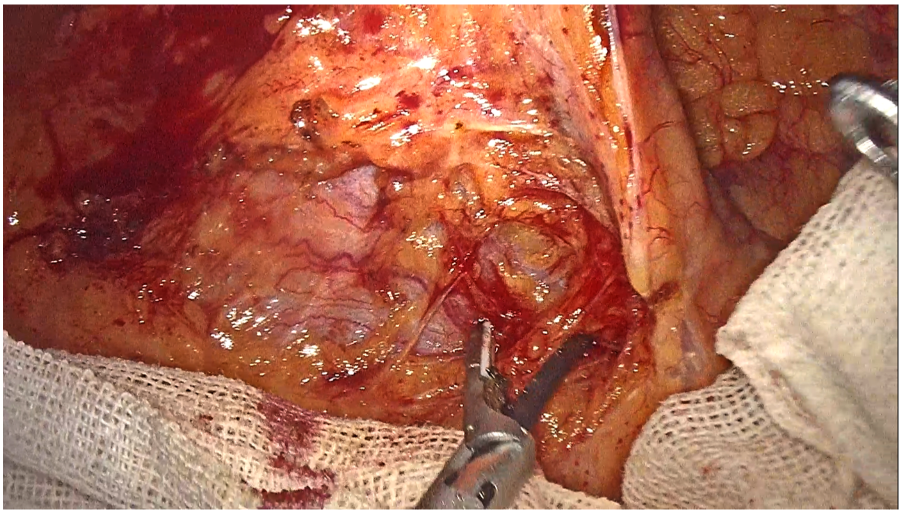

FIGURE 1
Toldt gap cannot be found in the intermediate approach (narrow field of view, no obvious reference or gap in the field, indistinguishable tissue structures below the open level, bleeding makes the gap more difficult to find).

was separated from the pre-excision site. Then, the transverse colon was separated from the pre-excision site by nudging.

A 5-cm median parasternal incision was made in the abdomen, and the ileum was cut at the preexcised site of the naked small intestine. Finally, the specimen was removed and ileo-transverse colonic anastomosis was performed (Figure 2).

Study selection

The inclusion criteria were as follows: the tumor was in the right colon; colon cancer was clearly identified by preoperative colonoscopy and pathological examination; the tumor was confined to the intestinal wall and did not invade the posterior peritoneum and surrounding organs; and patients underwent extracorporeal anastomosis.

Data extraction

The exclusion criteria were as follows: extensive tumor infiltration; distant metastasis such as that in the liver and lung; intestinal obstruction; a history of abdominal surgery, extensive adhesions in the abdominal cavity, and the inability to perform laparoscopic surgery for exploration; patients did not undergo extracorporeal anastomosis.

Statistical analysis

The count data were expressed as percentages (%) and chi-squared (x^2) tests, while the measurement data were expressed as means ± standard deviations ($x \pm s$). For comparison of the two groups and multiple groups, the t-test and one-way ANOVA were conducted, respectively. Data analysis was conducted using SPSS 22.0 (IBM, Armonk, NY, USA). A statistical value of $P < 0.05$ indicated statistical significance.

Results

Baseline data

In this study, there were 81 cases of small bowel mesenteric priority access and 115 cases of traditional laparoscopic right hemi-colonic radical resection. There were no statistically significant differences in the demographics data of patients, including sex, age, tumor site and tumor stage etc. between the two groups (Table 1).

Comparison of intraoperative conditions

Intraoperative conditions were compared between the small bowel mesenteric priority approach and the traditional intermediate approach for radical right hemicolectomy for colon cancer (Figure 3). The results showed that the operative time was shorter in the small mesenteric priority access group (191.98 ± 46.05) than that in the conventional intermediate access group (209.48 ± 46.08) (Figure 3A). Furthermore, although the difference in intraoperative bleeding was not statistically significant (Figure 3B), scatter plot analysis showed relatively fewer cases of high intraoperative bleeding

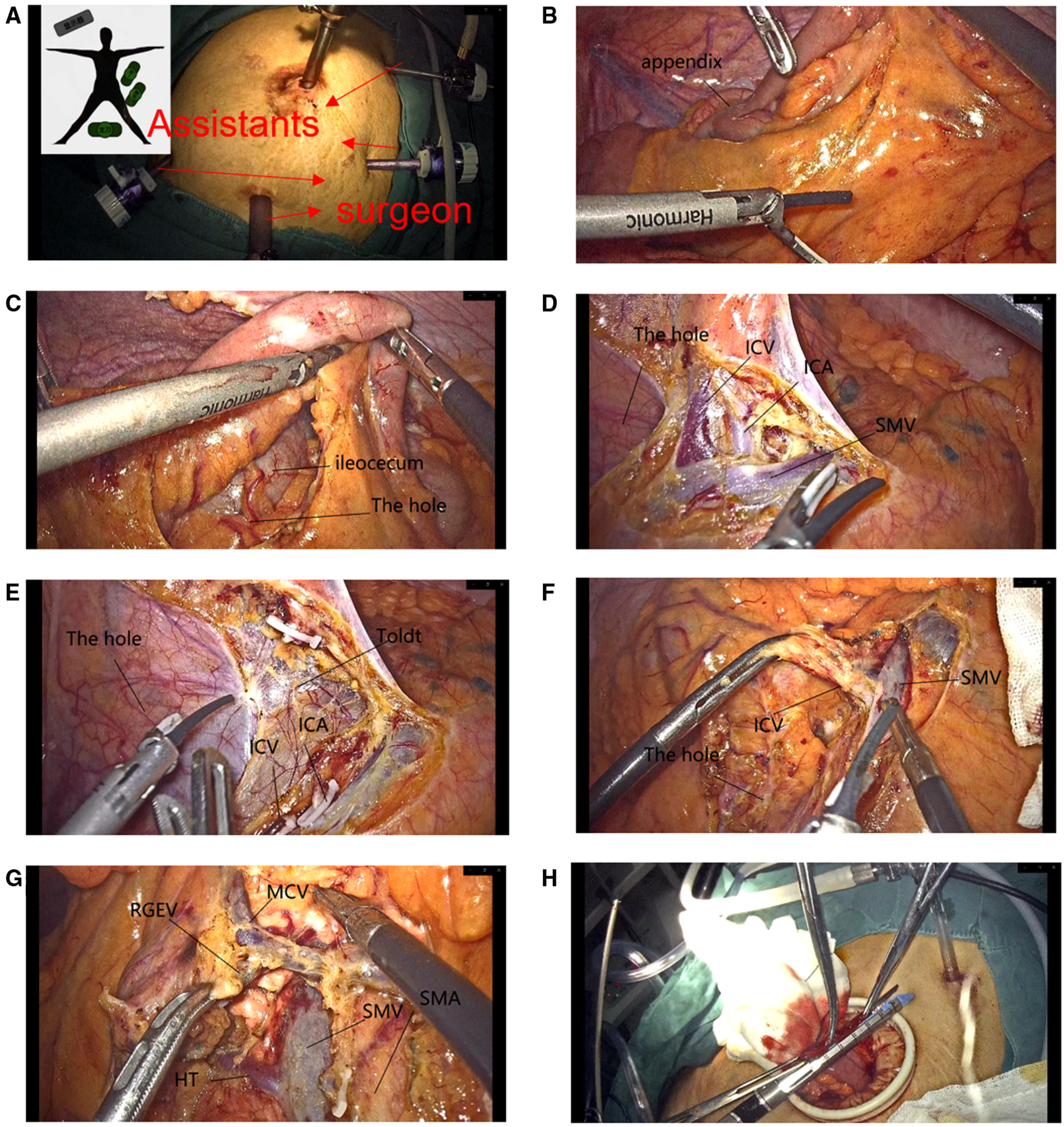

FIGURE 2
(A) Trocar. (B) Opened directly through the mesentery of the small intestine to create a "hole". (C) Enlargement of the "hole" allows clear visualization of the inferior mesenteric structures of the small intestine and ileocecum. (D) The superior mesenteric vein along the ileocolic vein is easy to find. (E) The gap was extended to the ascending colon and the ileocecal region by cutting the blood vessels while extending the gap. (F) Dissection of the ileocolic vessels. (G) Overall vascular. (H) Anastomosis of the small intestine and transverse colon.

in the small bowel mesenteric priority access group, compared with that in the intermediate approach group. The highest intraoperative bleeding volume was 300 ml. In addition, the number of lymph nodes cleared was similar for both approaches (18.38 ± 6.11 vs. 20.10 ± 7.98) (Figure 3C) and was not statistically significant (The former data is the small bowel mesenteric priority approach, and the latter is the traditional intermediate approach.). However, these results strongly suggest the feasibility of the small bowel mesenteric priority approach.

Table 1 Comparison of preoperative baseline data between the two groups of patients ($n = 196$).

Characteristics	1[a] ($N = 81$)	2[b] ($N = 115$)	Total ($N = 196$)	*P* value
Year	61.09 ± 13.95	63.23 ± 13.26	62.34 ± 13.55	0.28
BMI	22.78 ± 2.61	22.16 ± 3.48	22.41 ± 3.16	0.18
Total protein	67.68 ± 7.60	65.93 ± 7.48	66.80 ± 7.54	0.11
Albumin	39.02 ± 5.64	38.90 ± 5.14	38.96 ± 5.33	0.88
Hemoglobin	107.08 ± 29.56	107.24 ± 26.43	107.16 ± 27.63	0.97
Charlson comorbidity index	5.26 ± 1.97	5.53 ± 1.74	5.40 ± 1.87	0.30
Gender				0.67
Female	41 (20.92%)	63 (32.14%)	104 (53.06%)	
Male	40 (20.41%)	52 (26.53%)	92 (46.94%)	
Stage				0.44
1	11 (5.61%)	12 (6.12%)	23 (11.73%)	
2	37 (18.88%)	63 (32.14%)	100 (51.02%)	
3	33 (16.84%)	40 (20.41%)	73 (37.24%)	
Anatomical_location				0.86
Ascending colon	33 (16.84%)	45 (22.96%)	78 (39.80%)	
Hepatic flexure	29 (14.80%)	39 (19.90%)	68 (34.69%)	
Ileocecal	19 (9.69%)	31 (15.82%)	50 (25.51%)	
Hypertension				0.42
0	54 (27.55%)	84 (42.86%)	138 (70.41%)	
1	27 (13.78%)	31 (15.82%)	58 (29.59%)	
Diabetes				0.11
0	66 (33.67%)	104 (53.06%)	170 (86.73%)	
1	15 (7.65%)	11 (5.61%)	26 (13.27%)	

[a]The small bowel mesenteric priority approach.
[b]The traditional intermediate approach.

Comparison of postoperative recovery

The time to first anal discharge and bowel movement was 2.96 ± 0.80 vs. 3.09 ± 0.97 days and 3.95 ± 1.16 vs. 3.89 ± 1.26 days, in the small bowel mesenteric priority approach and traditional intermediate approach groups, respectively. Similarly, the time to tolerate fluid and semi-fluid was 2.65 ± 1.70 vs. 2.78 ± 1.39 and 6.44 ± 3.63 vs. 6.21 ± 1.98 days (The former data is the small bowel mesenteric priority approach, and the latter is the traditional intermediate approach.), in the small bowel mesenteric priority approach and traditional intermediate approach groups, respectively (**Table 2**).

There were no postoperative deaths in both groups; the incidence of postoperative complications was 12.24% and 16.33% in the two groups, respectively, with no statistically significant difference. There were 19 cases of abdominal infection, 4 cases of chylous ascites, 11 cases of pulmonary infection, 6 cases of intestinal obstruction, 1 case of incisional infection, 0 cases of anastomotic stenosis and 1 case of anastomotic leakage in the intermediate access group, in addition to 17 cases of abdominal infection, 7 cases of chylous ascites, 3 cases of pulmonary infection, 2 cases of intestinal obstruction, 0 cases of incisional infection, 1 case of anastomotic stenosis and 0 cases of anastomotic leakage in the small bowel mesenteric priority access group.

Discussion

Right colon cancer includes malignant tumors occurring in the cecum, ascending colon, and hepatic flexure. With the popularization and development of laparoscopic surgery, laparoscopic D3 lymph node dissection and CME for radical right hemicolectomy has become the standard for right colon cancer treatment (21) due to many procedural advantages, such as less trauma, accurate access at an anatomical level, standardized ligation of the mesenteric root vessels and lymph node dissection, and fewer complications and shorter recovery time for patients (22, 23). However, radical resection of right hemicolectomy includes its drawbacks, particularly vascular variation and difficulty in removing colonic lymph nodes. Furthermore, it involves several important organs and tissues such as the ureter, pancreas, and duodenum (24, 25), hence that the selection of an appropriate approach is vital to surgery success.

The traditional intermediate approach is currently the most widely used approach. However, this approach has many disadvantages. First, when searching for the Toldt gap, the mesentery must to be incised from below the ileocolic vessels. Due to the large vascular variation, bleeding during the separation of the vessels leads to an unclear field, and it is easy to enter the wrong level which results, in bleeding and injury to the ureteral genital vessels and retroperitoneal organs such as the anterior renal fascia. Furthermore, the integrity of the colonic mesentery is damaged. The anatomy of the middle approach from the duodenum to the anterior space of the pancreatic head may cause accidental injury the stem of Henle and entry into the pancreatic tissue, resulting in hemorrhage and unclear vision. Another disadvantage is that in obese patients, as it is challenging to enter the correct level through the middle approach in these patients. As the anatomical layers of obese patients are not well demarcated, they can lead to bleeding and complications during the operation (26). Finally, the complexity of the operation of the intermediate approach creates a steep learning curve for novice surgeons, thus requiring both experienced surgeons and surgical assistants.

This study retrospectively analyzed the clinical data of patients undergoing laparoscopic radical right hemicolectomy for right colon cancer in our gastrointestinal surgery department from 2019 to 2022. The clinical results were compared between patients who underwent the small bowel mesenteric priority approach and those who underwent the traditional intermediate approach for radical right

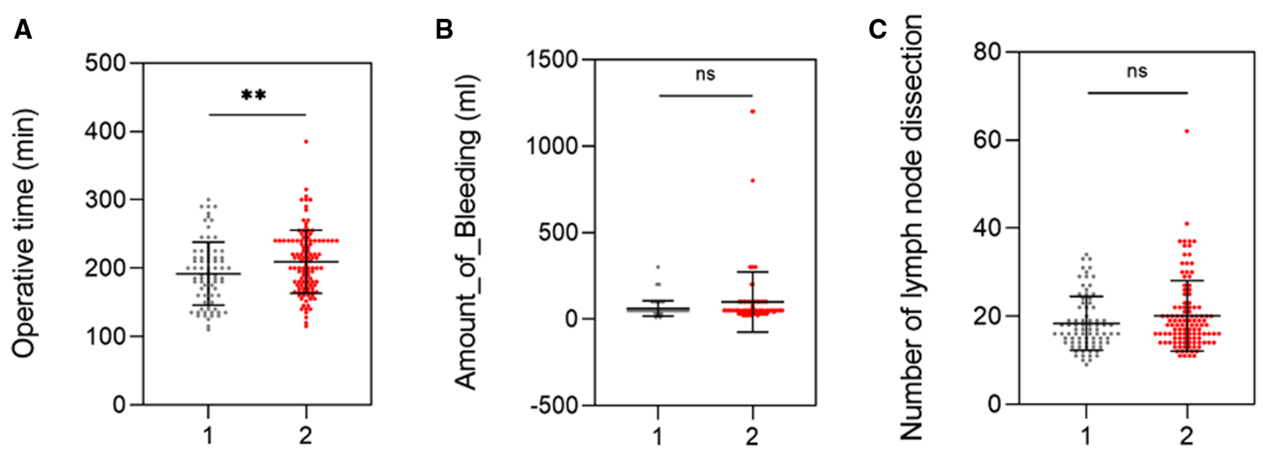

FIGURE 3
Comparison of intraoperative variables between the two groups of patients. (A) Operative time. (B) Amount of bleeding. (C) Number of lymph node dissection.

TABLE 2 Comparison of postoperative indexes between two groups of patients ($n = 196$, $x \pm s$).

Characteristics	1[a] ($N = 81$)	2[b] ($N = 115$)	Total ($N = 196$)	P value
First_exhaust_time				0.34
Mean ± SD	2.96 ± 0.80	3.09 ± 0.97	3.04 ± 0.90	
First_defecation_time				0.72
Mean ± SD	3.95 ± 1.16	3.89 ± 1.26	3.91 ± 1.22	
Time_of_first_tolerance_to_liquid				0.56
Mean ± SD	2.65 ± 1.70	2.78 ± 1.39	2.73 ± 1.52	
Time_of_first_solid_tolerance				0.56
Mean ± SD	6.44 ± 3.63	6.21 ± 1.98	6.31 ± 2.78	
Hospital_days_after_operation				0.97
Mean ± SD	8.36 ± 4.10	8.37 ± 2.30	8.37 ± 3.16	
Ileus	2	6	8	
Anastomotic leak	0	1	1	
Incision infection	0	1	1	
Lung infection	2	11	13	
Abdominal infection	17	19	36	
Chylous ascites	7	4	11	
Anastomotic stenosis	1	0	1	
Postoperative_complication				0.91
0	57 (29.08%)	83 (42.35%)	140 (71.43%)	
1	24 (12.24%)	32 (16.33%)	56 (28.57%)	

[a]The small bowel mesenteric priority approach.
[b]The traditional intermediate approach.

hemicolectomy. The results showed that the operation time of the small bowel mesenteric priority approach (experimental group) was shorter than that of the traditional intermediate approach (control group). Although the difference in intraoperative bleeding was not statistically significant, the scatter plot analysis showed that the priority small bowel mesenteric approach reduced the risk of intraoperative hemorrhage, compared with that of the intermediate approach. The two approaches were consistent in terms of the number of lymph nodes cleared and postoperative recovery.

The feasibility and favorable clinical results of the priority access to the small intestine mesentery are well demonstrated. This may be because when compared with the traditional intermediate approach, the small intestine mesenteric approach has several advantages. The small intestine mesentery at the expected dissection point is cut first, which is conducive to judging the blood supply at the dissected small intestine after completion of the right hemicolectomy, thus preventing the occurrence of anastomotic leak due to the loss of blood supply at the anastomosis. Additionally, because the anatomical position of the ileocolic vein is relatively fixed, the first large vessel revealed after vertically cutting the small intestinal mesentery is the ileocolic vein. This avoids the difficulty in determining the location and course of the right hemi-colon vessels and reduces bleeding caused by accidental damage to vessels and tissues during surgery. Another advantage of the small intestine mesenteric priority approach is that it opens the small intestine mesentery first, which prepares for the subsequent step with the genetic branches of the mesenteric vessels. It also clears the operation field as the Toldt gap is expanded while dissecting the vessels. Furthermore, the small intestine mesentery is opened first, so the operator can cut the small intestine mesentery and can extend the Toldt gap to the caudal side by cutting the "hole" in the small intestine mesentery. This approach also opens the medial gap at the largest level, which is more convenient for the implementation of total colonic mesocolic resection. In this study, the surgical operations in both the control and experimental groups were performed by an experienced surgeon, and the learning curve for this surgeon who was proficient in the traditional method (25 cases) and on the learning curve for the new method (13 cases). The new method has been widely promoted and studied among young surgeons in our hospital, and for surgeons who mastered laparoscopic operations and were proficient in gastrointestinal anatomy, the learning curve was concentrated in 10–15 cases The learning curve for the traditional method in our hospital is 25–30 cases, which is also more aligned with the global learning curve markers (27, 28). Therefore, it can also be concluded that the new method is more simple for novices to learn and master. However, due to the small number of young surgeons in our hospital, CUSUM analysis has not been used for the time being, and the accurate learning curve of the new method needs to be further analyzed.

The approach avoids the need to turn the intestinal canal to find the caudal approach gap to expand the right colonic gap, reducing both operation time and patient discomfort, especially for patients who have obesity and mesenteric hypertrophy. It also reduces the risk of damaging blood vessels on the surface of Henle's stem and the pancreatic head. Even if there are accidental injuries to the vessels, it will be easier to handle due to greater exposure.

This study has some limitations. First, it is limited to the intermediate approach and the small bowel mesenteric priority approach. Future studies can explore the comparison of the therapeutic efficacy of the small bowel mesenteric priority approach with other approaches or combined approaches, and the results may improve the precision of laparoscopic techniques and clinical outcomes. Second, this is a single-center, retrospective study with a relatively small sample size and a limited study duration. It is necessary to validate the results of this study through conducting future studies with longer duration and large sample sizes.

In conclusion, compared with the traditional intermediate approach, the small bowel mesenteric priority approach in laparoscopic right hemicolectomy has the advantages of safety, minimal invasiveness, simplicity, and good operability. It is more conducive to ensuring an adequate surgical field and accurate anatomical positioning, and it can ensure similar clinical treatment results while better reducing the operating time, intraoperative bleeding, and other indicators.

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

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

Conceptualization: FP. Data collection and analyses: GT. Writing—original draft preparation: FP. Writing—review and editing: ZW. Had primary responsibility for final 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1064377/full#supplementary-material.

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Catheter malposition analysis of totally implantable venous access port in breast cancer patients

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Background: To investigate the occurrence of catheter malposition in breast cancer patients undergoing Totally Implantable Venous Access Port (TIVAP) implantation and analyze the effect of TIVAP implantation site on the incidence of catheter malposition.

Methods: Clinical data of Breast cancer patients underwent TIVAP implantation in our department from 2017 to 2021 was collected by reviewing the electronic medical records. The catheter malposition rate, location and management of malposed catheters in TIVAP implantation were analyzed. We divided the patients into the left internal jugular vein (IJV) group and the right IJV group according to the site of TIVAP implantation and compared the difference in the catheter malposition incidence between the two groups. In addition, we counted the catheter malposition rate of TIVAP implantion *via* the left and right IJV in right breast cancer patients to analyze the effect of tumor status on the side of TIVAP implantation on the catheter malposition rate.

Results: A total of 1,510 catheters were implanted in 1,504 patients, and 16 (1.06%) had catheter malposition. The catheter malposition rate was 4.96% (7/141) for TIVAP implanted *via* the left IJV and 0.66% (9/1,369) for right IJV, with a statistically significant difference ($\chi^2 = 18.699$, $P < 0.05$). 743 TIVAPs were implanted in patients with right-sided breast tumor, of which the incidence of catheter malposition was 5.15% (7/136) for TIVAP implanted *via* left IJV and 0.82% (5/607) for right IJV, with a statistically significant difference ($\chi^2 = 10.290$, $P < 0.05$). Malposed catheters were found in the subclavian vein, IJV, brachiocephalic vein, internal thoracic vein, undefined collateral veins, and outside the blood vessels. All malposed catheters were successfully adjusted to the proper position by simple manipulative repositioning or percutaneous positioning with the assistance of digital subtraction angiography (DSA), except for 1 case was removed the port because the catheter tip was located outside the vessel.

Conclusion: The catheter malposition rate of ultrasound-guided TIVAP implantation *via* IJV is low, and the malposed catheter can be successfully adjusted to the proper position by simple manipulative repositioning or DSA-assisted percutaneous positioning, however, the catheter malposition incidence of TIVAP implanted *via* left IJV is higher than that *via* the right side.

KEYWORDS

totally implantable venous access port, breast cancer, ultrasound guidance, internal jugular vein, catheter malposition

Introduction

Chemotherapy is a necessary treatment for many cancers. Central venous access is the main way of chemotherapeutic drugs infusion. The use of Totally Implantable Venous Access Port (TIVAP) was first proposed by Niederhuber et al. (1) in 1982. Compared to the Peripherally Inserted Central Venous Catheter or Central Venous Catheter, TIVAP has become the preferred method of chemotherapy for cancer patients due to its low complication rate, long duration of use, and little effect on normal life (2–5).

The application of central venous access is often accompanied by complications such as infection, thrombosis, catheter malposition, accidental arterial puncture, pneumothorax, and cardiac tamponade (6). Catheter malposition is one of the common complications. In general, the catheter of the central venous access is often placed in the superior vena cava (SVC), and catheter malposition means that the catheter tip is not in the SVC. Some clinical practice guidelines for central venous access indicate that catheter tip position can be determined by intraoperative fluoroscopy or postoperative chest *x*-ray (7). Intraoperative fluoroscopy controls the position of the catheter tip well, but this approach requires the assistance of radiologists and the cooperation of operating room equipment, and the procedure is slightly complicated (8). It is also feasible to implant a venous port using blind insertion after ultrasound-guided access to the IJV, and taking postoperative chest *x*-ray to determine the catheter position. This technique is currently used in the most majority of Asian countries and some countries outside of Asia. However, the risk of catheter malposition in this way is higher than using intraoperative fluoroscopy. Catheter malposition may interfere with chemotherapeutic drug delivery and may lead to related complications, which should be taken seriously by clinicians. At present, few studies are focusing on catheter malposition, and the factors associated with catheter malposition are unclear. Therefore, by collecting clinical data of patients who underwent TIVAP implantation at our department, we analyzed the incidence of catheter malposition, the site and the management of malposed catheters, and tried to analyze the influencing factors of catheter malposition.

Materials and methods

General information

This study is a retrospective analysis of breast cancer patients undergoing ultrasound-guided TIVAP implantation *via* the IJV in the Second Breast Surgery Department of the First Affiliated Hospital of Zhengzhou University from October 2017 to July 2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University (NO.2022-KY-0793-001).

The inclusion criteria were as follows: 1. Breast cancer patients (including patients with recurrence and metastasis); 2. Need for adjuvant chemotherapy; 3. Patients and their families consented to undergo TIVAP placement; 4. Patients were in good general condition and can tolerate TIVAP implantation. The criteria for removal from the study were as follows: 1. Auxiliary examination suggests anatomical abnormalities or thrombosis in the neck vessels; 2. Skin and soft tissue infection in the operation area; 3. Severe abnormalities in coagulation function; 4. Combination of other serious underlying diseases that cannot tolerate the procedure; 5. Patients and their families refused TIVAP implantation.

Selecting other side for venipuncture due to failed venipuncture on one side can affect the catheter malposition rate. To reduce this selection bias, we excluded cases in which the TIVAP was implanted on the other side due to a failed IJV puncture on one side. A total of 1,504 cases were included in the final analysis.

Implantation procedures

The criteria for selecting the TIVAP implantation sites varied between the different medical groups: 1. IJV on the same side of the normal breast is preferred for surgery. 2. Clinical practice has found that the catheter malposition rate seems higher when TIVAP was implanted *via* the left IJV, so the right IJV is preferred for TIVAP implantation.

The procedures were performed by experienced surgeons in the operating room under strict sterile conditions.

Patients lay supine with heads turned to the opposite side of the operation. Ultrasound exploration of the IJV was performed to identify the puncture site. The surgical area was disinfected and covered with sterile cloth. Local infiltration anesthesia was applied to the operative area, the IJV puncture was performed under ultrasound guidance, and a guide wire was placed after the successful puncture. A subcutaneous pocket was created on the chest wall in the sub-clavicular region to place the subcutaneous reservoir. A 0.5 cm incision was made at the puncture point of the neck. A tearable sheath with a skin dilator was inserted into the IJV along the guidewire. The guidewire was removed and the intravenous catheter was placed into IJV. The length of the catheter was calculated based on the following formula: height/10–4 cm. A subcutaneous tunnel was made between the subcutaneous pocket and the neck incision using a tunneling needle, and the catheter was passed through the subcutaneous tunnel and connected to the reservoir. After confirming that the port and catheter were functional, the reservoir was secured to the chest wall with sutures. Finally, the incision was sutured with absorbable sutures.

Imaging evaluation

The position of the catheter was observed by chest *x*-ray after the operation. As our procedures were performed without intraoperative fluoroscopy, catheter tip was acceptable as long as it was located in the SCV (that is, the catheter tip was in the range from near the right tracheobronchial angle to the right atrium), otherwise, the catheter was considered malposed. All medical imaging diagnostic reports were doubly confirmed by 2 senior radiologists.

Data collection

Clinical data were collected by reviewing the electronic medical record, including the age, gender, tumor site, TIVAP implantation site, postoperative imaging information (whether catheter malposition occurred, the location of the malposed catheter), and the management of the malposed catheters.

Statistical analysis

SPSS21.0 was used for statistical analysis. Age was expressed by mean ± standard deviation (Mean ± SD). Continuous correction χ^2 tests were used for statistical analysis to compare the difference in the catheter malposition rate between TIVAP implantation *via* the left and right IJV, and the effect of tumor status on the side of TIVAP implantation on the incidence of catheter malposition. The difference was statistically significant when the bilateral $P < 0.05$.

TABLE 1 Patients' characteristics ($N = 1{,}504$).

Characteristics	*N* (%)
Age (years) (mean ± SD)	49.1 ± 9.5
Gender	
Female	1,497 (99.5)
Male	7 (0.5)
Tumor site	
Right	740 (49.2)
Left	740 (49.2)
Bilateral	24 (1.6)

Result

Patients characteristics

1,504 patients were enrolled in this study, of which 6 patients underwent TIVAP implantation twice, and a total of 1,510 catheters were implanted. The specific clinical characteristics were shown in Table 1, and the detailed data of 1,510 TIVAP implantation were shown in Table 2.

Analysis of catheter malposition results

The postoperative chest *x*-ray results showed that 16 of the 1,510 cases had catheter malposition, the catheter malposition rate was 1.06%, of which the catheter malposition rate of TIVAP implantation *via* the left and right IJV was 4.96% (7/141) and 0.66% (9/1,369), respectively. According to statistical calculation, the difference was statistically significant ($\chi^2 = 18.699$; $P < 0.05$); The catheter malposition rate in 743 patients with right breast tumors was 1.62% (12/743), and the malposition rate of TIVAP implantation *via* the ipsilateral and contralateral IJV of the tumor was 0.82% (5/607) and 5.15% (7/136) respectively, the difference was statistically significant ($\chi^2 = 10.290$; $P < 0.05$). Detailed data are shown in Table 3.

TABLE 2 Details of TIVAP implantation ($N = 1510$).

Characteristic	*N* (%)	Implanted site	
		Right IJV, *N* (%)	Left IJV, *N* (%)
TIVAP implanted on patients with right breast cancer	743 (49.2)	607 (81.7)	136 (18.3)
TIVAP implanted on patients with left breast cancer	743 (49.2)	738 (99.3)	5 (0.7)
TIVAP implanted on patients with bilateral breast cancer	24 (1.6)	24 (100)	0 (0)
Number	1,510 (100)	1,369 (90.7)	141 (9.3)

TABLE 3 Catheter malposition rate.

Details	*N* (%)
Total of catheter malposition	16 (1.06)
Catheter malposition of right IJV catheterization	9 (0.66)
Catheter malposition of left IJV catheterization	7 (4.96)
malposition of right tumor catheterization	12 (1.62)
Catheter malposition of right IJV catheterization	5 (0.82)
Catheter malposition of left IJV catheterization	7 (5.15)

Location and management of malposed catheter

The malposed catheters entered into the subclavian vein (SCV) (Figure 1), IJV (Figures 2A–C), brachiocephalic vein (Figure 2D), internal thoracic vein (Figure 3), and undefined collateral vein (Figure 4). In addition, digital subtraction angiography (DSA) showed extravascular malpositioning in 1 case (Figure 5). Except for 1 case was removed the port because the catheter tip was located in extravascular, the rest of malposed catheters were adjusted by simple manipulative repositioning or percutaneous repositioning with DSA, and all adjusted catheter tips were located in the SVC. However, the success rates differed between the two methods. The success rate of catheter adjustment by DSA was 100%, but 28.6% (2/7) of the catheters adjusted by manipulative repositioning remained malposed and were finally adjusted successfully by percutaneous repositioning with DSA. As detailed in Table 4.

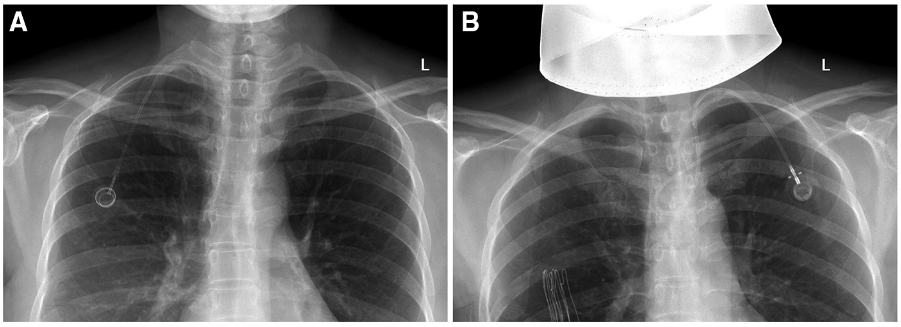

FIGURE 1
Catheter malposition to SCV. (A) The tip of the catheter is located in the right SCV; (B) The catheter turns back into the left SCV at the junction of the brachiocephalic vein and the SVC.

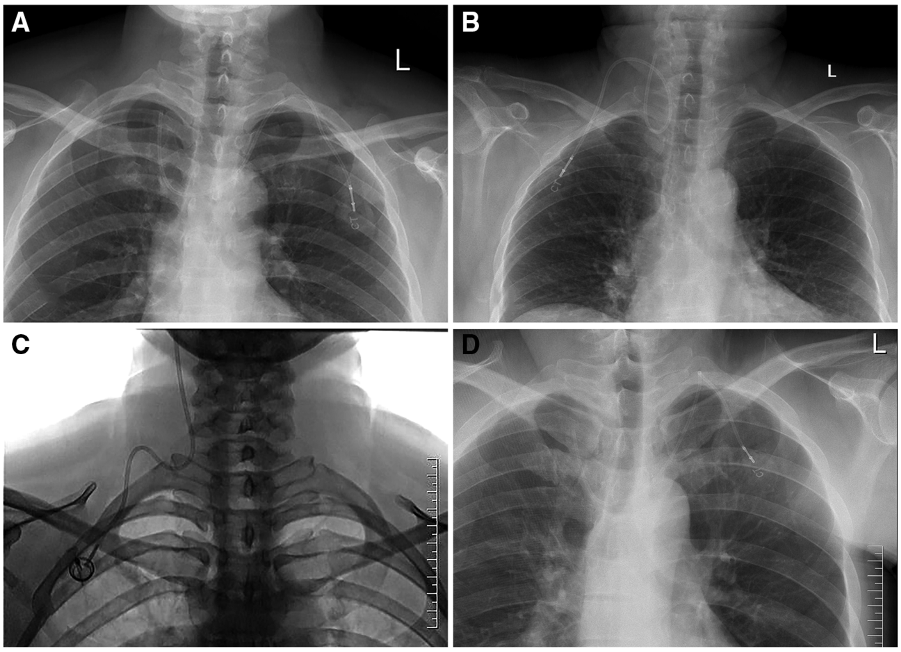

FIGURE 2
Catheter malposition to IJV and brachiocephalic vein. (A) The tip of the catheter is located in the contralateral IJV; (B) The catheter is turned back, and the tip of the catheter is located in the ipsilateral IJV; (C) The catheter is located in the IJV and runs toward the head; (D) The tip of the catheter is located in the contralateral brachiocephalic vein.

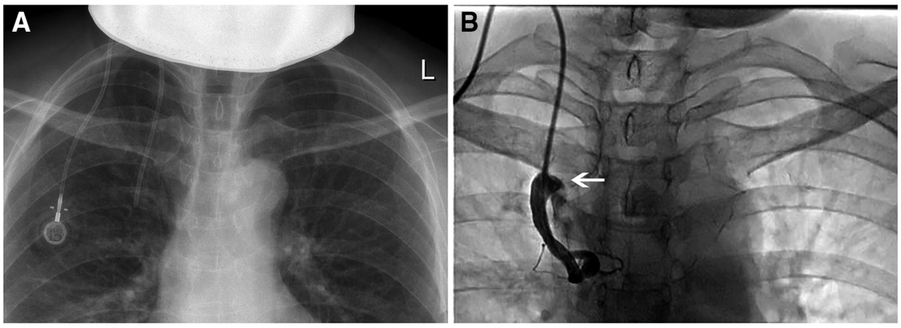

FIGURE 3
Catheter malposition to internal thoracic vein. (A) The chest *x*-ray suspected that the catheter was not in the SVC; (B) Injected the contrast medium through the port, the catheter was located in the internal thoracic vein, and part of the contrast medium flowed back into the SVC (arrow).

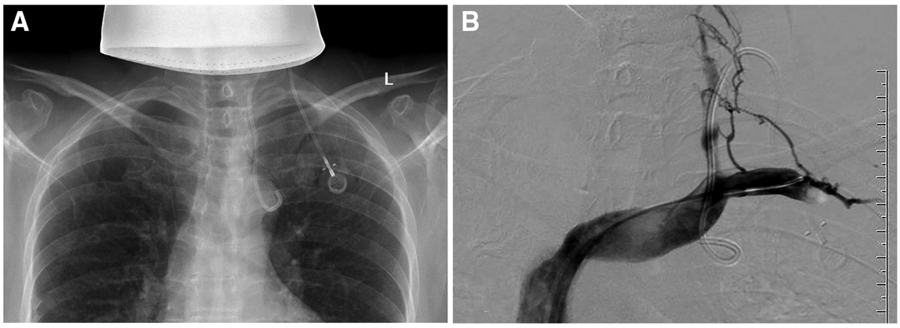

FIGURE 4
Catheter malposition to an undefined collateral vein. (A) Chest *x*-ray shows that the tip of the catheter is located at the aortic arch; (B) Fluoroscopy showed that the tip of the catheter turns back into an angle under the left clavicle, and DSA radiography shows that the vein where the catheter is located is not visible, considering that the head end enters the venule branch.

Discussion

Catheter tip position

The ideal position of the central venous catheter tip is still under debate, but it is generally considered that the lower 1/3 of the SVC or the junction of the SVC and right atrium is the desired position (7, 9, 10). Malposed catheters are often seen in the IJV, SCV, brachiocephalic vein, and right atrium; a few catheters may enter into the azygos vein, superior intercostal vein, and internal thoracic vein; the excessive length of the catheter insertion may lead the catheter into the right ventricle, coronary sinus, or even inferior vena cava (11, 12). It has been reported that malposed catheters may affect intravascular flow patterns, thereby increasing the risk of catheter-related thrombosis (2, 7); studies by Luciani et al. (13) and Schutz JC et al. (14) confirmed that higher catheter tip position is associated with a significant risk of port malfunction; complications such as arrhythmias, cardiac tamponade and cardiac perforation may occur when the catheter tip is located in the right atrium or deeper (6, 8, 11, 12, 14–16). Although guidelines issued by the National Kidney Foundation indicate that the catheter tip located in the right atrium can ensure optimal blood flow, accelerate the diffusion of chemotherapeutic drugs through the blood, and further reduce the risk of vascular injury (17), this position is often used in dialysis treatment, for the infusion of chemotherapeutic drugs, the catheter can meet the treatment demand when placed at the distal of the SVC.

Catheter malposition rate

The catheter malposition rate of TIVAP implantation is about 0.3%–10% (3, 4, 16, 18, 19). The rate of catheter malposition in our study is 1.06%, which is consistent with previous studies. The catheter malposition rate varied with the methods of TIVAP implantation. Compared with procedures performed using body markers, the incidence of catheter malposition is lower when the procedure is performed under

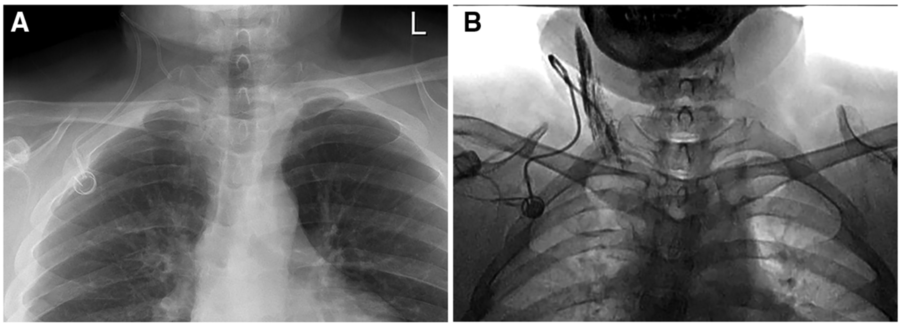

FIGURE 5
The catheter tip is located in the extravascular. (A) The catheter tip is seemingly located in the IJV; (B) No blood was drawn back from the port, and DSA shows that the contrast medium was overflowing, indicating that the catheter tip is not in the blood vessel.

TABLE 4 Details of catheter malposition and management.

Catheter malposed vessels	*N*	Treatment
Ipsilateral SCV	6	1 case was successfully adjusted by percutaneous repositioning; 4 cases were successfully adjusted by manipulation; 1 case was successfully adjusted by percutaneous repositioning after failures of the manipulation
Ipsilateral IJV	3	2 cases were successfully regulated by percutaneous repositioning and 1 case was successfully regulated by manipulation
Contralateral IJV	3	2 cases were successfully adjusted by percutaneous repositioning; 1 case was successfully adjusted by percutaneous repositioning after failing of the manipulation
Ipsilateral internal thoracic vein	1	Successfully regulated by percutaneous repositioning
Contralateral brachiocephalic vein	1	Successfully regulated by percutaneous repositioning
Undefined collateral vein	1	Successfully regulated by percutaneous repositioning
Not in the blood vessel	1	Removal of the venous access port

ultrasound guidance; if intraoperative fluoroscopy is used, catheter malposition will not occur because the catheter position can be adjusted timely; in addition, studies have shown that the catheter malposition rate of TIVAP implantation *via* SCV is usually higher than that *via* IJV, which may be related to the anatomical relationship between SCV, IJV and SVC (20).

Only a few scholars have compared the catheter malposition incidence of TIVAP implantation *via* the left and right IJV. In a prospective study of the incidence and risk of central venous catheter malposition, PikwerA et al. (19) found that the catheter malposition incidence of TIVAP implanted through the left IJV was higher than that through the right side [3.8% (4/104) VS1.4% (14/1023)], but the difference was not statistically significant; the same result was obtained in a retrospective study by Xing Lei et al. (11) on patients undergoing chemotherapy for breast cancer. This difference in malposition rates is more likely related to the anatomical characteristics of the left and right neck vessels. Compared with the left IJV, the right IJV migrates at a relatively straighter course and shorter distance toward the ipsilateral brachiocephalic vein and SVC, and the left jugular vessel has more branches (4, 8, 21, 22), therefore, TIVAP implantation *via* the left IJV may be associated with more unsuccessful placements and catheter malposition. Our study also obtained the result that the surgery performed through the right IJV had a lower malposition rate, but our result was statistically significant. This may provide some evidence for the selection of TIVAP implantation site in clinical practice.

In some studies on TIVAP implantation in breast cancer patients, the tumor site is considered in the selection of the TIVAP implantation site, and TIVAP implantation *via* the IJV contralateral to the tumor is preferred (2, 18). Some medical groups in our department also make this selection. However, few studies have analyzed the effect of the tumor status of the TIVAP implanted side on the incidence of catheter malposition in breast cancer patients. In this study, we analyzed the rate of catheter malposition in patients with right breast cancer implanted with TIVAP at different sites in our center (Left breast cancer patients were not included in this study because the right IJV is the preferred puncture vein for them, whether in consideration of tumor site or the clinical experience of the lower catheter malposition rate in right operation. This results in few left breast cancer patients undergoing surgery through the left IJV, preventing statistical analysis.). The result suggested that for patients with right breast cancer, the catheter malposition rate for TIVAP implantation *via* the left IJV was similarly higher than that for the right side[5.15% (7/136) vs. 0.82% (5/607)], and the difference was statistically significant, so we believed that the tumor status on the TIVAP implanted side had little effect on the incidence of catheter malposition. Therefore, in TIVAP implantation in breast cancer patients, the tumor site can be ignored and the right IJV is the first choice for the operation to reduce the incidence of catheter malposition.

Management of malpositioned catheters

For malposed catheters, percutaneous repositioning with the assistance of DSA is the most effective way. It allows real-time observation of the catheter orientation and catheter tip position to achieve accurate repositioning. In addition, simple manipulative repositioning is also an available way and is less costly to treat. In our clinical practice, although manipulative repositioning cannot adjust the ectopic catheter to the proper position every time, it still has a high success rate, especially for simple malposition positions such as ipsilateral SCV and IJV. Therefore, for some medical centers that cannot perform percutaneous repositioning techniques or for patients with financial difficulties, simple manipulative repositioning can be tried first. In addition, it has been shown that intracavitary electrocardiography can indirectly determine the position of the catheter tip by observing the change in P-wave height during the procedure (23), which can improve the success rate of the operation. However, this technique has not been widely used in the clinic.

This work had some limitations. First, we did not study whether other factors such as the number of IJV punctures during the procedure and other underlying diseases of the patient's comorbidities influenced the occurrence of catheter malposition. Second, the number of cases operated *via* the left and right IJV in this study varied greatly because of the different selection criteria for the TIVAP implantation site between medical groups. Third, this study only involved catheter malposition that occurred immediately after surgery, but factors such as implantation site, position change, and lifestyle habits can cause catheter movement within the vessel during the use of the port, resulting in catheter malposition and catheter dysfunction (24). Our study did not involve this aspect. Therefore, randomized controlled trials with large samples warrant further study.

In conclusion, the application of TIVAP implanted *via* IJV in breast cancer patients during chemotherapy is safe and effective. The catheter malposition rate is low, and the majority of malposed catheters can be successfully adjusted to the proper position using manipulative repositioning or DSA-assisted percutaneous repositioning. However, the catheter malposition incidence of TIVAP implanted *via* the left IJV is higher than that *via* the right side, therefore right IJV puncture may be preferred to reduce the incidence of catheter malposition.

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 full name of the ethics committee: Ethics Committee of The First Affiliated Hospital of Zhengzhou University. The affiliation of the ethics committee: First Affiliated Hospital of Zhengzhou University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

WL: participated in drafting manuscripts and data analysis. QH: collected and organized the data. LL and JC: analyzed the image data. XL and YG: designed the study and helped to revise 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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Analysis of survival factors after hepatic resection for colorectal cancer liver metastases: Does the R1 margin matter?

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Introduction: The effect of liver margin on colorectal cancer liver metastases (CRLM) after hepatectomy has been controversial. In this study, we conducted a postoperative follow-up study of 205 patients with CRLM to clarify whether a positive margin is significant and to define the risk factors affecting CRLM survival.

Methods: The data of 205 patients with CRLM who underwent surgical treatment at the Third Hospital of Peking University in the Department of General Surgery from January 2009 to December 2020 were retrospectively analyzed. The general data, surgical data and postoperative follow-up of the patients were statistically analyzed.

Results: There were 130 cases (63.4%) of R0 resection and 75 cases (36.6%) of R1 resection. There were 136 males and 69 females, age 61 ± 11 years, and body mass index (BMI 24.5 ± 3.3 kg/m^2). The overall survival rates at 1, 3, and 5 years for the entire cohort were 93.4%, 68.4%, and 45.5% in the R0 resection group vs. 93.2%, 53.7%, and 42% in the R1 resection group, respectively, which were not statistically significant ($P = 0.520$). The 1-, 3-, and 5-year disease-free survival rates of 63.2%, 33.3%, and 29.7% were significantly better in the R0 resection group than in the R1 resection group of 47.9%, 22.7%, and 17.7% ($P = 0.016$), respectively. After multivariable analysis, carbohydrate antigen 19-9 (CA19-9) > 39 U/ml (HR = 2.29, 95% CI: 1.39–3.79, $P = 0.001$), primary tumor perineural invasion (HR = 1.78, 95% CI: 1.01–3.13, $P = 0.047$), and BMI > 24 kg/m2 (HR = 1.75, 95% CI: 1.05–2.93, $P = 0.033$) were independently associated with poorer overall patient survival. The number of liver metastases >2 (HR = 1.65, 95% CI: 1.10–2.47, $P = 0.016$), the maximum diameter of metastases ≥50 mm (HR = 1.67, 95% CI: 1.06–2.64, $P = 0.026$), and vascular invasion of the primary tumor (HR = 1.65, 95% CI: 1.03–2.64, $P = 0.038$) were also independently associated with poorer disease-free survival.

Conclusion: In patients undergoing hepatectomy for CRLM, the negative effect of the R1 margin should be downplayed, and although the disease-free survival of the R1 margin is shorter than that of the R0 margin, it has no impact on overall survival. To improve overall survival, extra attention should be given to the factors of preoperative BMI, preoperative CA19-9, and the presence of perineural invasion of the primary tumor.

KEYWORDS

colorectal cancer, liver metastasis, hepatectomy, R1 margin, BMI, CA19-9

Introduction

Colorectal cancer (CRC) is the third most common malignant tumor in the world and has the second highest mortality rate (1). The liver is the most common site of CRC metastasis and liver metastases are one of the leading causes of death in CRC patients. Approximately half of CRC patients will develop liver metastases (2, 3). Liver metastases are detected at the time of diagnosis of colorectal cancer in approximately 20%–25% of patients, and in 40%–50% of patients, liver metastases are detected after radical colorectal cancer surgery (4, 5). In recent years, the survival rate of colorectal cancer liver metastasis (CRLM) has increased significantly due to the development of chemotherapeutic agents, targeted drugs and combination therapy (6). However, radical surgery remains the most critical method to achieve long-term survival in CRLM, with 5-year survival rates ranging from 40%–60% (2, 4, 7, 8). The liver margin is an important factor in determining whether radical treatment can be achieved. Over the years, knowledge of the R0 margin of the liver has gradually narrowed from 1 cm to ≥1 mm (9–12). Even though the R1 margin of the liver is now recognized as less than 1 mm, there are conflicting reports on whether the R1 margin is an independent risk factor for CRLM. The objective of this study was to clarify whether the R1 margin is significant and to define the risk factors affecting the survival of CRLM by conducting a postoperative follow-up study of 205 patients with CRLM.

Materials and methods

Patient selection

Patients with CRLM treated in the Department of General Surgery at the Third Hospital of Peking University from January 2009 to December 2020 were selected, and their clinical data were summarized. Inclusion Criteria: (1) Primary tumor is clearly colorectal cancer or clearly diagnosed as colorectal cancer by surgical pathology; (2) Complete medical record information; (3) Both colorectal and liver were treated surgically; (4) Patients were followed up regularly. Exclusion criteria: (1) Primary tumor or liver metastases are not resectable; (2) Palliative resection of the liver (R2 resection); (3) Liver undergoing radiofrequency ablation; (4) Liver metastases as recurrent lesions; (5) Perioperative death; (6) Incomplete clinical data; (7) None of the postoperative follow-ups were completed. The study was reviewed and approved by the Ethics Committee of Peking University Third Hospital and was conducted with the informed consent of the patients. A total of 308 patients with CRLM were treated at our center from January 2009 to December 2020, including 39 cases without surgery, 33 cases with colorectal surgery but without liver surgery, 6 cases with liver R2 resection, 4 cases with liver radiofrequency ablation, 2 cases with perioperative death, 19 cases with loss to follow-up, and 205 cases finally included in the study (**Figure 1**).

Study design

Analysis of the effects of age, sex, BMI, primary tumor site, timing of hepatic metastasis (synchronous or metachronous), number of liver metastases, maximum diameter of metastases, carcinoembryonic antigen (CEA), CA19-9, neoadjuvant chemotherapy, postoperative adjuvant chemotherapy, American Society of Anesthesiologists (ASA score), surgery interval (staging or simultaneous surgery), operative time, intraoperative blood loss, type of hepatic resection (anatomical or nonanatomic resection), whether to transfuse blood, surgical approach (laparoscopy or open), T-stage of primary tumor, N-stage of primary tumor, primary tumor deposit, primary tumor vascular invasion, primary tumor perineural invasion, histological grading of primary tumor and liver margin on overall survival (OS) and disease-free survival (DFS) were performed, and the independent risk factors for OS and DFS were defined. The timing of hepatic metastasis was divided into synchronous liver metastasis and metachronous liver metastasis. Synchronous liver metastasis was defined as liver metastasis detected at the diagnosis of primary colorectal cancer or within six months after radical surgery for primary colorectal cancer (13), and metachronous liver metastasis was defined as liver metastases detected six months after radical surgery for primary colorectal cancer. Primary tumor deposits were defined according to the American Joint Committee on Cancer AJCC 8th edition staging as an isolated tumor nodule within the lymphatic drainage area of the primary tumor with no identifiable lymph nodes, blood vessels, or nerve structures within it. The resection margin refers to the distance from the tumor edge to the liver section. When there are multiple lesions, the closest distance is taken as the resection margin. R0 is defined as complete microscopic resection with margins ≥1 mm. R1 is defined as less than 1 mm from the resected surface of the liver under the microscope. For multiple lesions, R1 resection is defined as long as R1 is present in one lesion. OS was defined as the time interval between hepatectomy and death or the last follow-up visit. DFS was defined as the time interval between the time of hepatectomy and the first detection of recurrence or death. Recurrence is confirmed by reoperation pathology; if not operated, two or more imaging tests are required for diagnosis (enhanced computed tomography, enhanced magnetic resonance imaging, PET-CT examination).

Follow-up protocol

All patients were reviewed every 3 months for 2 years after hepatectomy, including medical history, physical examination,

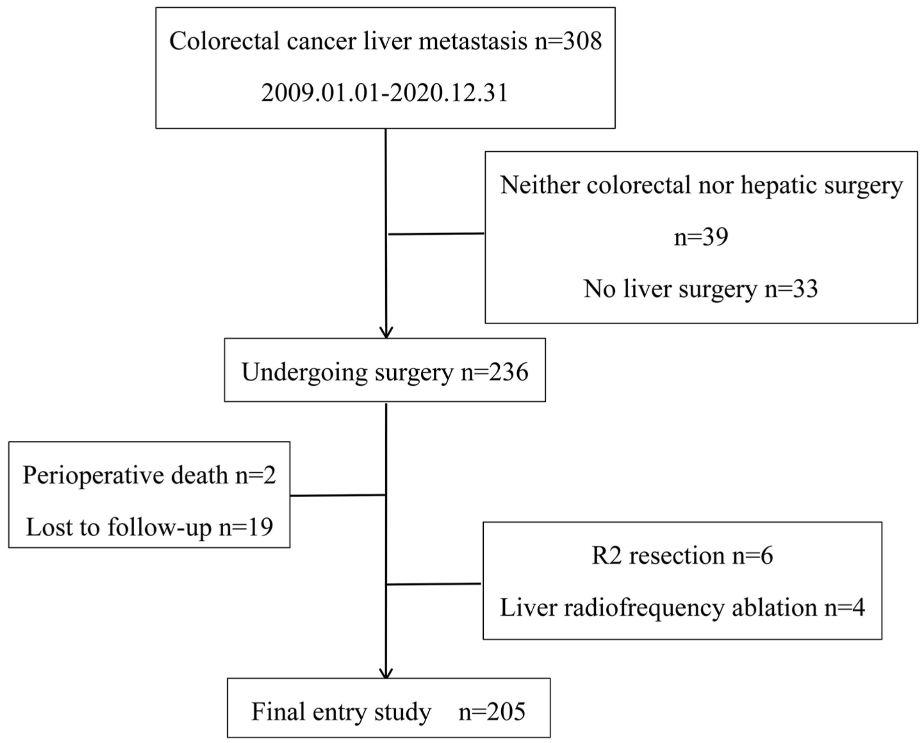

FIGURE 1
Patient inclusion and exclusion flow chart.

tumor markers and imaging tests. Postoperative review every 6 months for 2–5 years. If patients fail to visit our center for follow-up examinations, they need to be followed up by telephone every 3–6 months to record their general condition, various review results and survival status.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (version 18.0 software), X-Tile (version 3.6.1 software), and R language (version 4.1.3 software). Continuous variables were expressed as ($\grave{x} \pm S$) or M (Q1, Q3) and compared using independent samples *t* test or Mann-Whitney *U* test. Categorical variables were expressed as cases and percentages and compared using the x^2 test or Fisher's exact test. For survival data, the Kaplan-Meier method was used for description, survival curves were plotted, and the log-rank test was applied for comparison. For prognostic analysis, since it is easier to explain the results when converting continuous variables into categorical variables in clinical practice, X-Tile software was first applied to find the best cutoff values of continuous variables to be converted into categorical variables. Univariate Cox regression in R was subsequently applied to screen candidate influences, and then only variables with *p* values less than 0.05 and clinically significant variables were included in the multivariate Cox proportional risk model. The final independent risk factors affecting OS and DFS were identified by Cox regression multifactor analysis, and *p* values less than 0.05 were considered statistically significant. After multivariate analyses, a nomogram was constructed using the RMS package in R to visually predict the 1-year, 3-year, and 5-year OS rates for CRLM. The maximum value for each variable was set at 100 points. Calibration plots were used to determine whether the predicted survival rates were consistent with the actual survival rates. The nomogram was internally validated for discrimination and correction by 1,000 bootstrap resampling.

Results

Patient characteristics

The baseline characteristics of the 205 patients are shown in Table 1. There were 130 (63.4%) R0 resections and 75 (36.6%) R1 resections. There were 136 males and 69 females, age 61 ± 11 years, range 27–87 years, and BMI 24.5 ± 3.3 kg/m^2.

Regarding the primary tumor characteristics, approximately two-thirds of patients presented with colon cancer ($n = 129$; 62.9%), and a small percentage presented with rectal cancer

TABLE 1 Demographic and clinical characteristics of 205 patients with colorectal cancer liver metastases.

Variables	All patients	R0	R1	*P* value
Number, %	205	130 (63.4)	75 (36.6)	
Sex, *n*, %				
Female	69 (33.7)	46 (35.4)	23 (30.7)	
Male	136 (66.3)	84 (64.6)	52 (69.3)	0.491
Age, years, mean ± SD	61.5 ± 11.1	60.9 ± 11.3	62.4 ± 10.8	0.342
BMI, kg/m^2, mean ± SD	24.5 ± 3.3	24.4 ± 3.3	24.6 ± 3.4	0.658
Surgery Interval, *n*, %				
Staging surgery	73 (35.6)	49 (37.7)	24 (32)	
Simultaneous surgery	132 (64.4)	81 (62.3)	51 (68)	0.413
ASA score, *n*, %				
I	31 (15.1)	23 (17.7)	8 (10.7)	Ref
II	153 (74.6)	90 (69.2)	63 (84)	0.114
III	21 (10.3)	17 (13.1)	4 (5.3)	0.572
Operative time, min, mean ± SD	394.7 ± 165.2	373.4 ± 152.4	431.7 ± 180.5	**0.015**
Primary site, *n*, %				
Colon	129 (62.9)	78 (60)	51 (68)	
Rectum	76 (37.1)	52 (40)	24 (32)	0.254
Timing of hepatic metastasis, *n*, %				
Synchronous	147 (71.7)	92 (70.8)	55 (73.3)	
Metachronous	58 (28.3)	38 (29.2)	20 (26.7)	0.695
No. of liver metastases, *n*, %				
≤2	126 (61.5)	84 (64.6)	42 (56)	
>2	79 (38.5)	46 (35.4)	33 (44)	0.223
Size of largest tumour, mm, mean ± SD	33 ± 24	31 ± 22	37 ± 27	0.086
Preoperative CEA level, *n*, %				
≤5 U/ml	56 (27.3)	38 (29.2)	18 (24)	
>5 U/ml	149 (72.7)	92 (70.8)	57 (76)	0.419
Preoperative CA19-9 level, *n*, %				
≤39 U/ml	121 (59)	74 (56.9)	47 (62.7)	
>39 U/ml	84 (41)	56 (43.1)	28 (37.3)	0.421
Neoadjuvant chemotherapy, *n*, %				
No	116 (56.6)	82 (63.1)	34 (45.3)	
Yes	89 (43.4)	48 (36.9)	41 (56.7)	**0.014**
Blood loss, ml, M (Q1, Q3)	450 (200, 900)	400 (122, 800)	500 (200, 1100)	**0.023**
Type of hepatic resection, *n*, %				
Anatomical	40 (19.5)	32 (24.6)	8 (10.7)	Ref
Anatomical + Wedge	47 (22.9)	24 (18.5)	23 (30.7)	**0.006**
Wedge	118 (57.6)	74 (56.9)	44 (58.6)	**0.048**
Transfusion, *n*, %				
No	121 (59)	78 (60)	43 (57.3)	
Yes	84 (41)	52 (40)	32 (42.7)	0.708
Postoperative chemotherapy, *n*, %				
No	13 (6.3)	6 (4.6)	7 (9.3)	
Yes	192 (93.7)	124 (95.4)	68 (90.7)	0.190

(*continued*)

TABLE 1 Continued

Variables	All patients	R0	R1	*P* value
Surgical approach, *n*, %				
Open	67 (32.7)	52 (40)	15 (20)	
Laparoscopy	138 (67.3)	78 (60)	60 (80)	**0.004**
Primary tumor T stage, *n*, %				
T1/T2	20 (9.8)	13 (10)	7 (9.3)	
T3/T4	160 (78.1)	100 (76.9)	60 (80)	0.827
Missing data	25 (12.1)	17 (13.1)	8 (10.7)	
Primary tumor N stage, *n*, %				
N0	77 (37.6)	48 (36.9)	29 (38.7)	Ref
N1	66 (32.2)	42 (32.3)	24 (32)	0.873
N2	35 (17.1)	22 (16.9)	13 (17.3)	0.958
Missing data	27 (13.1)	18 (13.9)	9 (12)	
Primary tumor deposit, *n*, %				
No	112 (54.6)	74 (56.9)	38 (50.7)	
Yes	62 (30.3)	36 (27.7)	26 (34.7)	0.292
Missing data	31 (15.1)	20 (15.4)	11 (14.6)	
Primary tumor vascular invasion, *n*, %				
No	113 (55.1)	74 (56.9)	39 (52)	
Yes	61 (29.8)	36 (27.7)	25 (33.3)	0.399
Missing data	31 (15.1)	20 (15.4)	11 (14.7)	
Primary tumor perineural invasion, *n*, %				
No	122 (59.5)	78 (60)	44 (58.7)	
Yes	52 (25.4)	32 (24.6)	20 (26.7)	0.764
Missing data	31 (15.1)	20 (15.4)	11 (14.6)	
Primary tumor histologic grade, *n*, %				
G1/2	154 (75.1)	100 (76.9)	54 (72)	
G3	43 (21)	27 (20.8)	16 (21.3)	0.795
Missing data	8 (3.9)	3 (2.3)	5 (6.7)	

($n = 76$; 37.1%). Synchronous liver metastases were present in the majority ($n = 147$; 71.7%), and metachronous liver metastases were present in only 28.3%. Of the primary tumor pathological stages, the majority of patients had T-stage 3 or 4 ($n = 160$; 78.1%), and half had N-stage N1 or N2 ($n = 101$; 49.3%). Less than one-third of patients showed positive results for vascular invasion of the primary tumor ($n = 61$; 29.8%), perineural invasion ($n = 52$; 25.4%) and cancer nodules ($n = 62$; 30.3%). There was a high percentage of G1 or G2 histological grading ($n = 154$; 75.1%).

In terms of tumor load, preoperative CEA was normal in a minority of patients ($n = 56$; 27.3%), while preoperative CA19-9 was normal in a majority of patients ($n = 121$; 59%). The number of metastases ≤2 was 126 (61.5%), and the maximum diameter of metastases was 33 ± 24 mm. Nearly half of the patients received neoadjuvant chemotherapy preoperatively ($n = 89$; 43.4%), and the remaining patients preferred direct surgery ($n = 116$; 56.6%). Almost all patients received adjuvant chemotherapy postoperatively ($n = 192$; 93.7%).

The percentage of laparoscopic surgery was higher in our center ($n = 138$; 67.3%) and slightly lower in open surgery ($n = 67$; 32.7%). Colorectal and liver surgery was performed in 132 cases (64.4%) at the same time, and colorectal surgery was performed first, followed by liver surgery in 73 cases (35.6%). The liver was resected anatomically in 40 cases (19.5%) and nonanatomically in 165 cases (80.5%). The duration of surgery was approximately 394.7 ± 165.2 min. As many as 153 (74.6%) of all patients had ASA scores of grade II.

Clinical characteristics of patients based on cutting margin Status grouping

The R0 resection group and the R1 resection group were different in terms of type of hepatic resection, surgical approach, operative time, intraoperative bleeding, and neoadjuvant chemotherapy (**Table 1**). Specifically, patients who underwent anatomic resection were more likely to have R0 margins than those who underwent combined anatomic/wedge resection ($P = 0.006$) and wedge resection ($P = 0.048$). Laparoscopic surgery had a great minimally invasive advantage, but the proportion of R1 margins was higher than that of open surgery ($P = 0.004$). The R1 group had a longer operative time ($P = 0.015$) and more intraoperative bleeding ($P = 0.023$). The rate of R0 resection was higher in patients without neoadjuvant chemotherapy ($P = 0.014$).

Survival analysis

The median follow-up time for the entire cohort was 60.1 months, with a median survival time of 50.1 months. The differences in overall survival rates of 93.4%, 68.4%, and 45.5% at 1, 3, and 5 years in the R0 resection group and 93.2%, 53.7%, and 42% in the R1 resection group were not statistically significant ($P = 0.520$, **Figure 2A**). The R0 resection group had significantly better disease-free survival rates of 63.2%, 33.3%, and 29.7% at 1, 3, and 5 years, respectively, than the R1 resection group (47.9%, 22.7%, and 17.7%, respectively) ($P = 0.016$, **Figure 2B**).

Stratifying the neoadjuvant chemotherapy variables, the overall survival rates at 1, 3, and 5 years in the subgroup without neoadjuvant chemotherapy were 92.7%, 67.4%, and 43.7% in the R0 resection group and 92.3%, 54.2%, and 34.4% in the R1 resection group, respectively, which were not statistically significant ($P = 0.48$, **Figure 3A**). The disease-free survival rates at 1, 3, and 5 years in the R0 resection group were 63%, 34.6%, and 29.7%, respectively, which were better than 52.6%, 17.3%, and 11.6%, respectively, in the R1 resection group ($P = 0.046$, **Figure 3B**). The overall survival rates at 1, 3, and 5 years in the R0 resection group were 93.5%, 69.8%, and 49.9% vs. 92.5%, 53.8%, and 48.4% in the R1 resection group in the subgroup treated with neoadjuvant chemotherapy were not statistically significant ($P = 0.52$, **Figure 4A**). The difference in disease-free survival rates of 63.7%, 30.6%, and 23% at 1, 3, and 5 years in the R0 resection group vs. 43.9%, 26%, and 21.7% in the R1 resection group was not statistically significant ($P = 0.22$, **Figure 4B**).

Defining independent risk factors for Os and DFS

The best cutoff values for the continuous variables in the cohort were selected using X-Tile software. Cox proportional risk regression analysis was used to determine the factors affecting overall survival. In the univariate analysis, operative time (HR = 2.17, $P = 0.015$), number of liver metastases (HR = 1.93, $P = 0.001$), maximum diameter of metastases (HR = 1.68, $P = 0.021$), preoperative CEA level (HR = 2.00, $P = 0.005$), preoperative CA19-9 level (HR = 2.58, $P < 0.001$), intraoperative bleeding (HR = 1.58, $P = 0.036$), surgical approach (HR = 0.65, $P = 0.029$), primary tumor N stage (N1: HR = 1.79, $P = 0.02$; N2: HR = 2.19, $P = 0.005$), primary tumor deposit (HR = 1.67, $P = 0.02$), primary tumor vascular invasion (HR = 1.66, $P = 0.026$), and primary tumor perineural invasion (HR = 1.63, $P = 0.035$) were significantly associated with the overall survival of CRLM patients. BMI (HR = 1.48, $P = 0.057$) approached statistical significance but was clinically significant. BMI and the abovementioned indicators were eventually included in the multivariable analysis. After adjusting for other competing risk factors, CA19-9 > 39 U/ml (HR = 2.29, 95% CI: 1.39–3.79, $P = 0.001$), primary tumor perineural invasion (HR = 1.78, 95% CI: 1.01–3.13, $P = 0.047$), and BMI > 24 kg/m^2 (HR = 1.75, 95% CI: 1.05–2.93, $P = 0.033$) were independently associated with poor overall survival of patients (**Table 2**).

The same approach was used to define the factors affecting disease-free survival. In the univariate analysis, liver margin (HR = 1.5, $P = 0.016$), BMI (HR = 1.41, $P = 0.042$), surgery interval (HR = 1.41, $P = 0.05$), operative time (HR = 1.82, $P = 0.015$), number of liver metastases (HR = 1.95, $P < 0.001$), maximum diameter of metastases (HR = 1.81, $P = 0.002$), preoperative CEA level (HR = 1.96, $P = 0.001$), preoperative CA19-9 level (HR = 1.58, $P = 0.006$), intraoperative bleeding (HR = 1.64, $P = 0.007$), T-stage of primary tumor (HR = 2.46, $P = 0.009$), and N-stage of primary tumor (N1: HR = 1.87, $P = 0.002$. N2: HR = 1.94, $P = 0.006$), primary tumor deposit (HR = 1.50, $P = 0.03$), primary tumor vascular invasion (HR = 1.98, $P < 0.001$), and primary tumor perineural invasion (HR = 1.70, $P = 0.006$) were significantly associated with disease-free survival in patients with CRLM. After controlling for all confounding factors, R1 margin (HR = 1.5, 95% CI: 1.03–2.19, $P = 0.036$) remained an independent risk factor for disease-free survival. In addition, the number of metastases >2

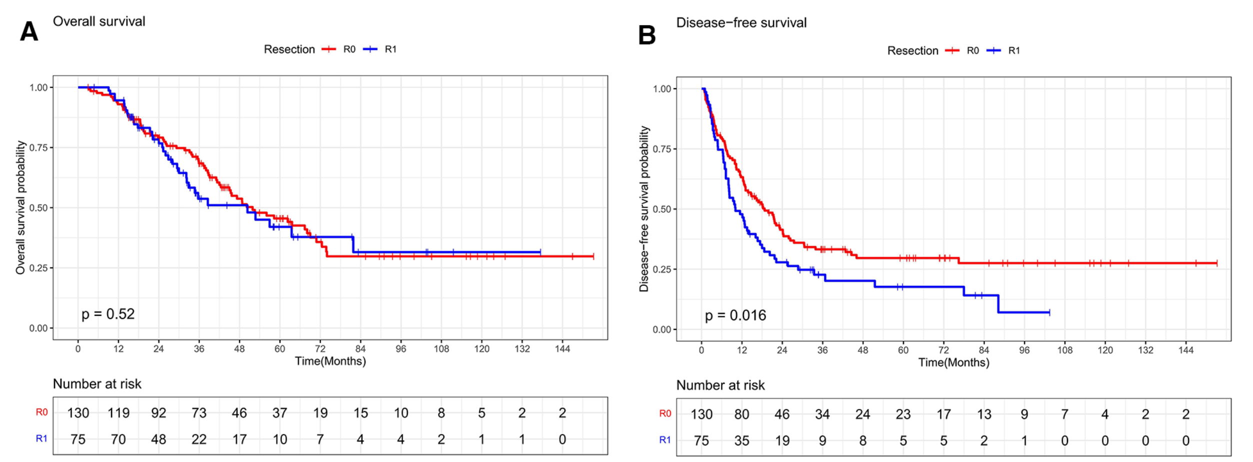

FIGURE 2
(A) Overall survival curves of R0 and R1 in CRLM patients (R0 ≥ 1 mm, R1 < 1 mm). (B) Disease-free survival curves of R0 and R1 in CRLM patients (R0 ≥ 1 mm, R1 < 1 mm).

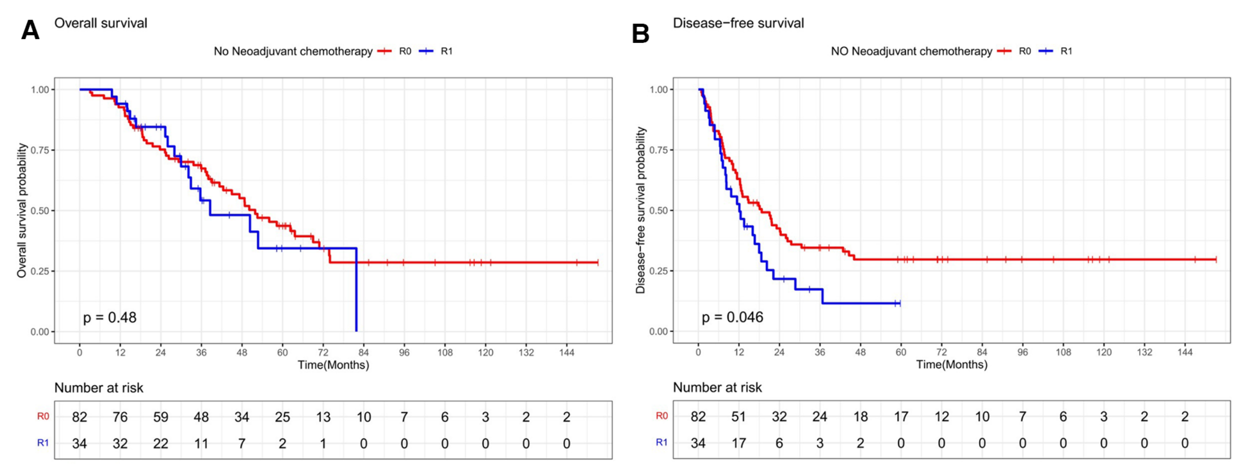

FIGURE 3
Os and DFS survival curves for R0 and R1 in patients not receiving neoadjuvant chemotherapy.

(HR = 1.65, 95% CI: 1.10–2.47, *P* = 0.016), the maximum diameter of metastases ≥50 mm (HR = 1.67, 95% CI: 1.06–2.64, *P* = 0.026), and vascular invasion of the primary tumor (HR = 1.65, 95% CI: 1.03–2.64, *P* = 0.038) were also independently associated with poorer disease-free survival (**Table 3**).

Nomogram of Os prognosis

We created a nomogram containing the three factors mentioned above, thus enabling a more visual observation of the impact of each factor on prognosis (**Figure 5**). The calibration curve showed a good match between the actual and predicted probability of survival (**Figure 6**).

Discussion

The most critical factor in achieving long-term survival in patients with CRLM is radical surgery, and the cutting margin is an essential focus. There have been conflicting opinions about the impact of cutting margins on the prognosis of patients with CRLM. First, the definition of the R1 cutting margin is different. As early as 1986, Ekberg et al. (14) reported the factors influencing the prognosis of liver

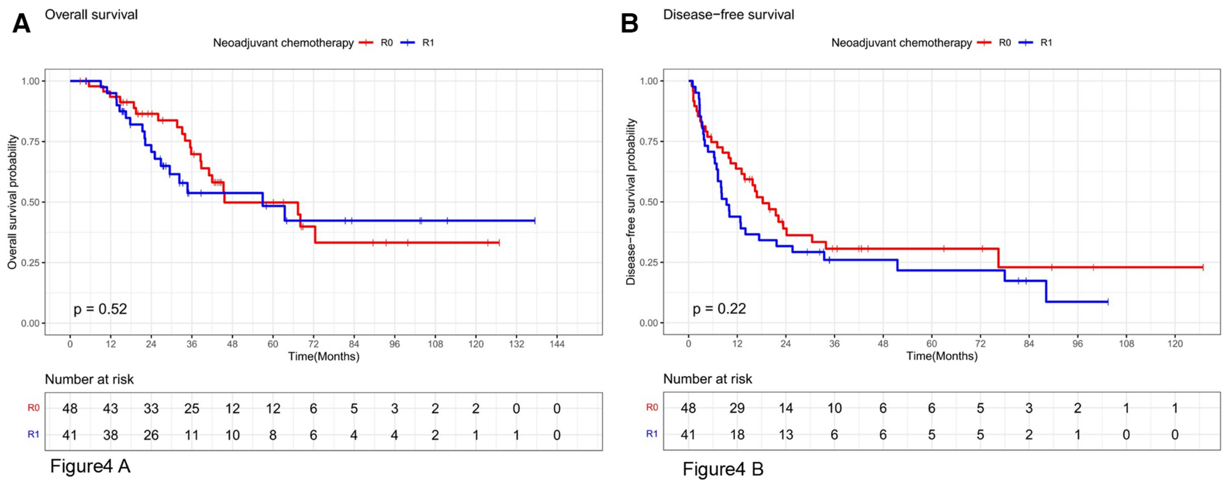

FIGURE 4
Os and DFS survival curves for R0 and R1 in patients receiving neoadjuvant chemotherapy.

metastases from colorectal cancer, where the extent of the tumor-free margin was the only treatment variable associated with survival time. Patients with tumor-free margins ≥10 mm (R0) had a significantly longer survival than those with margins <10 mm (R1). After that, everyone started to follow the "1 cm rule". Both retrospective studies (15, 16) and prospective studies (17) have shown that the R1 (<10 mm) cut margin is an independent risk factor for patients with CRLM. Later, Fong Y et al. (18) first reported that there was no significant difference in prognosis between patients with negative cut margins but less than 1 cm and those with cut margins greater than 1 cm. Kokudo et al. (19) concluded that the minimum cut margin is not a significant prognostic factor affecting patient survival and that 2 mm can be considered the minimum clinically acceptable requirement. Pawlik TM et al. (20) analyzed the data of 557 patients with metastatic liver resection for colorectal cancer using a multicenter database and found no statistically significant 5-year survival and recurrence rates in three groups with margins of 1–4 mm, 5–9 mm and ≥1 cm, suggesting that a margin of less than 1 cm should not be a contraindication to surgical resection. In a prospective analysis of 293 patients, Hamady et al. (21) found no significant effect of 1-, 2-, 5- and 10-mm tumor-free margin widths on patient survival or recurrence rates. The awareness of the R1 cut margin is gradually narrowing. In 2015, the EGOSLIM (Expert Group on OncoSurgery management of Liver Metastases) group recommended a minimum acceptable margin of 1 mm for liver metastases from colorectal cancer (22).

However, even with the definition of R1 as a less than 1 mm margin, the prognostic impact of R1 remains highly controversial. Some studies concluded that R1 resection (tumor-free margin <1 mm) exhibited worse overall survival than R0 resection (tumor-free margin ≥1 mm) (23–25). However, different results were obtained in our study. Of the 205 patients included in our center, 130 (63.4%) were resected in R0, and 75 (36.6%) were resected in R1. OS at 1, 3, and 5 years was not significantly different between the R0 and R1 groups ($P = 0.520$), but DFS differed significantly between the two groups, with the R1 group being more susceptible to recurrence, and after correction for multifactorial analysis, the cut margin remained an independent risk for disease-free survival factor ($P = 0.036$). This is in agreement with that reported by Montalti R et al. (26). Although it has been shown that 50%–70% of intrahepatic microsatellite metastases are located within 1–2 mm from the tumor margin (27), the current electrosurgical devices used in liver resection, whether open or laparoscopic, can play an active role (28, 29). First, when liver tumors are removed with an electrotome, ultrasonic knife, or Cavitron Ultrasonic Surgical Aspirator (CUSA), some of the chopped liver tissue at the edge of the resection will be aspirated by suction. Second, after removal of the tumor, the surgical incision margin will be hemostatic with the application of energy instruments, which can cause cauterization coagulation necrosis of the tissue approximately 2–3 mm deep in the incision margin, achieving the same effect as RF ablation. Thus, even though some tumors may not have enough margin for resection, electrosurgical devices may destroy the remaining tumor cells. This may have caused some R0 cut margins to be incorrectly estimated as R1 cut margins, thus diminishing the difference between R0 and R1.

Other reports suggest that the widespread use of neoadjuvant chemotherapy and postoperative adjuvant chemotherapy has reduced the prognostic impact of the R1 margin, resulting in no significant difference in overall survival between R1 and R0 (30, 31). Margonis GA et al. (32)

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TABLE 2 Univariate and multivariable analysis of various clinical factors affecting the overall survival of the entire cohort.

	Univariate analysis			Multivariable analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Liver margin						
R0	Ref					
R1	1.15	0.76–1.74	0.520			
Sex						
Female	Ref					
Male	0.8	0.53–1.19	0.269			
Age						
<60	Ref					
≥60	1.1	0.74–1.63	0.645			
BMI, kg/m2						
≤24	Ref			Ref		
>24	1.48	0.99–2.2	**0.057**	1.75	1.05–2.93	**0.033**
Surgery Interval						
Staging surgery	Ref					
Simultaneous surgery	1.18	0.78–1.77	0.441			
ASA score						
I	Ref					
II	1.054	0.64–1.75	0.839			
III	0.542	0.35–1.73	0.542			
Operative time, min						
≤214	Ref			Ref		
>214	2.17	1.16–4.07	**0.015**	1.90	0.81–4.48	0.142
Primary site						
Colon	Ref					
Rectum	0.97	0.65–1.44	0.864			
Timing of hepatic metastasis						
Synchronous	Ref					
Metachronous	0.81	0.51–1.26	0.339			
No. of liver metastases						
≤2	Ref			Ref		
>2	1.93	1.31–2.86	**0.001**	1.33	0.79–2.26	0.277
Size of largest tumour, mm						
<50	Ref			Ref		
≥50	1.68	1.08–2.62	**0.021**	1.15	0.65–2.03	0.631
Preoperative CEA level, U/ml						
≤5	Ref			Ref		
>5	2.00	1.24–3.25	**0.005**	1.08	0.58–2.03	0.808
Preoperative CA19-9 level, U/ml						
≤39	Ref			Ref		
>39	2.58	1.73–3.83	**<0.001**	2.29	1.39–3.79	**0.001**
Neoadjuvant chemotherapy						
No	Ref					
Yes	0.87	0.59–1.3	0.51			
Blood loss, ml						
≤950	Ref			Ref		
>950	1.58	1.03–2.43	**0.036**	0.97	0.57–1.66	0.914
Type of hepatic resection						
Anatomical	Ref					
Anatomical + Wedge	0.99	0.57–1.74	0.981			
Wedge	0.79	0.49–1.27	0.323			
Transfusion						
No	Ref					
Yes	1.17	0.79–1.73	0.43			
Postoperative chemotherapy						
No	Ref					
Yes	0.75	0.36–1.55	0.435			
Surgical approach						
Open	Ref			Ref		
Laparoscopy	0.65	0.44–0.96	**0.029**	0.88	0.52–1.49	0.634
Primary tumor T stage						
T1/T2	Ref					
T3/T4	2.12	0.92–4.87	0.076			
Primary tumor N stage						
N0	Ref			Ref		
N1	1.79	1.1–2.92	**0.02**	1.00	0.55–1.80	0.988
N2	2.19	1.27–3.78	**0.005**	1.26	0.68–2.32	0.459
Primary tumor deposit						
No	Ref			Ref		
Yes	1.67	1.08–2.56	**0.02**	1.35	0.81–2.24	0.257
Primary tumor vascular invasion						
No	Ref			Ref		
Yes	1.66	1.06–2.59	**0.026**	1.20	0.67–2.14	0.536
Primary tumor perineural invasion						
No	Ref			Ref		
Yes	1.63	1.04–2.57	**0.035**	1.78	1.01–3.13	**0.047**
Primary tumor histologic grade						
G12	Ref					
G3	1.42	0.9–2.23	0.132			

concluded that in the modern era of systemic chemotherapy, the impact of margin status on prognosis appears to be small compared to patient and tumor factors, and re-excision of R1 to R0 status does not improve long-term prognosis. However, some studies have given a different opinion and concluded that even with the addition of preoperative chemotherapy, it still does not change the outcome of R1 predicting poor outcome (33, 34). In this study, neoadjuvant chemotherapy

TABLE 3 Univariate and multivariable analysis of various clinical factors affecting the disease-free survival of the entire cohort.

	Univariate analysis			Multivariable analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Liver margin						
R0	Ref			Ref		
R1	1.5	1.08–2.09	**0.016**	1.5	1.03–2.19	**0.036**
Sex						
Female	Ref					
Male	0.97	0.69–1.37	0.878			
Age						
<60	Ref					
≥60	0.87	0.63–1.20	0.388			
BMI, kg/m2						
≤24	Ref			Ref		
>24	1.41	1.01–1.97	**0.042**	1.43	0.94–2.17	0.093
Surgery Interval						
Staging surgery	Ref			Ref		
Simultaneous surgery	1.41	1.0–2.0	**0.05**	0.87	0.54–1.40	0.565
ASA score						
I	Ref					
II	1.23	0.77–1.97	0.381			
III	0.94	0.48–1.83	0.855			
Operative time, min						
≤214	Ref			Ref		
>214	1.82	1.12–2.95	**0.015**	1.31	0.66–2.58	0.438
Primary site						
Colon	Ref					
Rectum	0.89	0.64–1.25	0.511			
Timing of hepatic metastasis						
Synchronous	Ref					
Metachronous	0.86	0.72–1.04	0.126			
No. of liver metastases						
≤2	Ref			Ref		
>2	1.95	1.41–2.71	**<0.001**	1.65	1.10–2.47	**0.016**
Size of largest tumour, mm						
<50	Ref			Ref		
≥50	1.81	1.24–2.65	**0.002**	1.67	1.06–2.64	**0.026**
Preoperative CEA level, U/ml						
≤5	Ref			Ref		
>5	1.96	1.32–2.92	**0.001**	1.40	0.84–2.34	0.196
Preoperative CA19-9 level, U/ml						
≤39	Ref			Ref		
>39	1.58	1.14–2.20	**0.006**	1.36	0.90–2.03	0.142
Neoadjuvant chemotherapy						
No	Ref					
Yes	1.11	0.80–1.53	0.549			
Blood loss, ml						
≤950	Ref			Ref		
>950	1.64	1.14–2.35	**0.007**	1.01	0.63–1.63	0.952
Type of hepatic resection						
Anatomical	Ref					
Anatomical + Wedge	1.52	0.94–2.47	0.089			
Wedge	0.88	0.57–1.35	0.557			
Transfusion						
No	Ref					
Yes	0.97	0.70–1.36	0.875			
Postoperative chemotherapy						
No	Ref					
Yes	1.74	0.77–3.95	0.184			
Surgical approach						
Open	Ref					
Laparoscopy	0.86	0.61–1.21	0.398			
Primary tumor T stage						
T1/T2	Ref			Ref		
T3/T4	2.46	1.25–4.84	**0.009**	1.55	0.76–3.17	0.232
Primary tumor N stage						
N0	Ref			Ref		
N1	1.87	1.25–2.78	**0.002**	0.97	0.59–1.59	0.911
N2	1.94	1.21–3.13	**0.006**	1.18	0.68–2.06	0.548
Primary tumor deposit						
No	Ref			Ref		
Yes	1.50	1.04–2.16	**0.03**	1.09	0.71–1.66	0.700
Primary tumor vascular invasion						
No	Ref			Ref		
Yes	1.98	1.38–2.85	**<0.001**	1.65	1.03–2.64	**0.038**
Primary tumor perineural invasion						
No	Ref			Ref		
Yes	1.70	1.17–2.47	**0.006**	1.11	0.71–1.73	0.642
Primary tumor histologic grade						
G12	Ref					
G3	1.06	0.71–1.60	0.764			

was stratified for analysis, and among the 116 patients without neoadjuvant chemotherapy, R0 resection was 82 (70.7%) and R1 resection was 34 (29.3%). There was no difference in 1-year, 3-year, or 5-year OS between the two groups ($P = 0.48$), and the difference in DFS was statistically significant ($P = 0.046$). Of the 89 patients who received neoadjuvant chemotherapy, 48 (53.9%) were resected for R0 and 41 (46.1%) for R1. There was no difference in 1-year, 3-year, or 5-year OS ($P = 0.52$) or

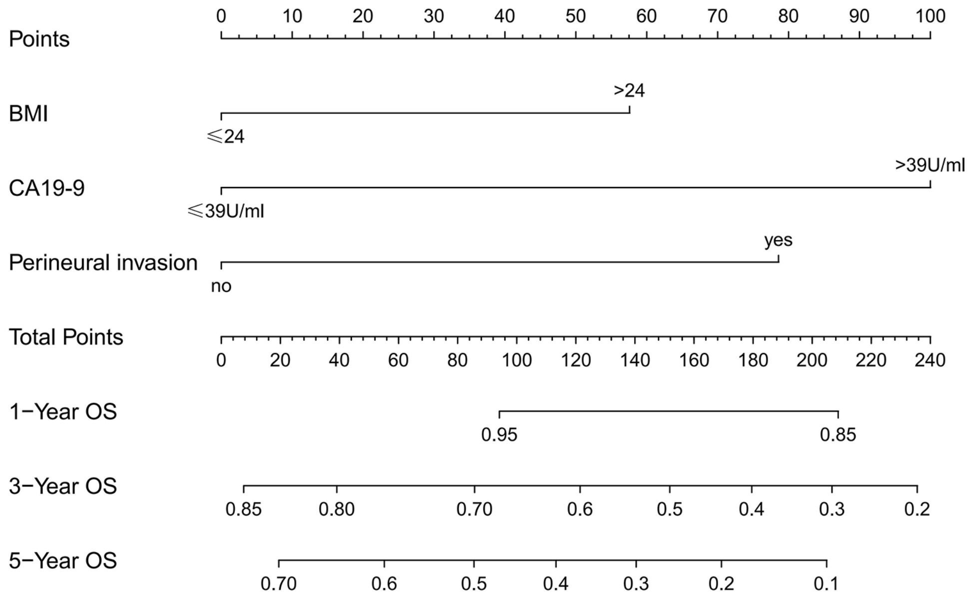

FIGURE 5
Nomogram predicting 1-, 3-, and 5-year overall survival in patients undergoing hepatectomy for CRLM.

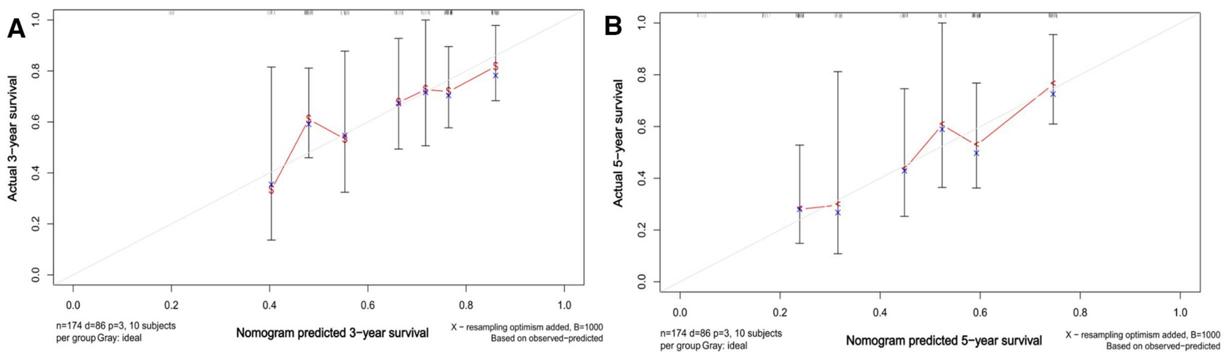

FIGURE 6
Calibration plots of the nomogram of OS predictions for CRLM hepatectomized patients. A and B show the predicted and actual 3- and 5-year survival probabilities for CRLM hepatectomized patients, respectively.

DFS ($P = 0.22$) between the two groups. The prognostic impact of R1 was not altered by neoadjuvant chemotherapy. The sample of only 13 patients without postoperative adjuvant chemotherapy in this study was too small to stratify, and therefore, it was not possible to assess whether the prognostic impact of R1 resection was influenced by postoperative adjuvant chemotherapy.

More interestingly, this study found that BMI >24 kg/m2 (HR = 1.75, 95% CI: 1.05–2.93, $P = 0.033$) was independently associated with poor overall survival in patients with CRLM. This has been scarcely reported in previous studies. Obesity is increasing worldwide, and it is a generally accepted view that it is a risk factor for the development of CRC (35). However, the relationship between overweight and the prognosis of patients with CRLM, especially after hepatectomy, is unclear. Meyerhardt JA et al. (36) reported that among women with stage II–III colon carcinoma, obesity (BMI ≥ 30 kg/m^2) was associated with a significant increase in overall mortality (HR = 1.34, 95% CI: 1.07–1.67, $P = 0.007$). However, the mechanism of this correlation has not been fully determined. However, excessive obesity, especially high visceral fat content, is associated with insulin resistance and elevated insulin levels in the circulation. Raised insulin levels can contribute to increased circulating levels of insulin-like growth factor I (IGF-I), which promotes cell proliferation and inhibits apoptosis and is positively associated with the risk of colorectal cancer (37). However, such results have only been reported in female patients. In addition, obese patients may have more comorbidities at the same time, such as diabetes, hyperlipidemia, vasculopathy and other chronic diseases, which may cause more postoperative complications and indirectly affect the survival period. Although univariate analysis in this study found the association between BMI > 24 kg/m^2 and prognosis to be close to statistically significant ($P = 0.057$), after adjusting for confounding factors, BMI > 24 kg/m^2 was still found to be an independent prognostic factor for survival in patients with CRLM. This is something that has not been found in previous reports and is a focus of attention for surgeons.

The relationship between tumor markers and the prognosis of patients with CRLM is more frequently reported as CEA and prognosis (7, 26, 30). In our experience, CEA > 5 U/ml (HR = 2, 95% CI: 1.24–3.25, $P = 0.005$) and CA19-9 > 39 U/ml (HR = 2.58, 95% CI: 1.73–3.83, $P < 0.001$) in the univariate analysis were risk factors, but after adjusting for confounders, CA19-9 > 39 U/ml (HR = 2.29, 95% CI: 1.39–3.79, $P = 0.001$) remained an independent risk factor for OS. CA19-9 levels have been previously reported as a prognostic risk factor for patients with initially unresectable CRLM (38). The results of Sawada Y et al. (39) also suggest that high CA19-9 levels may reflect unfavorable tumor biology, especially in patients with advanced CRLM. Jiang LM et al. (40) followed up 85 patients who underwent liver resection combined with microwave ablation for CRLM and found that high CA19-9 levels were a poor prognostic factor for OS. Previously, there was a general focus on CEA and neglect of CA19-9. Our study is a reminder that CA19-9 is also a risk factor for 0S and should be taken seriously. A more detailed treatment plan should be developed for patients with high preoperative CA19-9 and intensive postoperative follow-up, thus achieving improved survival rates.

In addition to this study, primary tumor perineural invasion was established as an independent predictor of OS. Furthermore, a nomogram containing the above three factors was created to effectively and visually predict OS. This study included a very comprehensive set of study variables, so the final model showed good predictive performance.

In summary, this study established three independent risk factors for OS, however, the R1 margin was not included. This also suggests that the negative effect of the R1 margin should be downplayed. More attention should be paid to BMI > 24 kg/m2, and more in-depth studies are needed to explore the mechanisms of poor prognosis due to high BMI so that survival rates in this group can be improved in a targeted manner. And whether or not the CEA is normal, elevated CA19-9 should be a cause for concern and a more detailed treatment plan should be developed.

Our study also had some limitations. Firstly this is a retrospective study and the sample size of this study is small due to the limited number of patients in a single institution. Validation on prospective, multicentre and large-scale patients is necessary. After a rigorous and careful statistical analysis, we still obtained several risk factors for poor prognosis of liver metastases from colon cancer, and our statistical power is still good. Secondly almost all of our cohort had adjuvant chemotherapy administered postoperatively and it was not possible to assess whether the prognostic impact of the R1 margin was due to the adjuvant chemotherapy given postoperatively. Although some studies have drawn some conclusions (30)(, 32), further validation in populations not treated with adjuvant chemotherapy is still needed. This will allow a more accurate assessment of the role of the R1 margin. Finally, although this study included variables that produced confounding factors for analysis in the study as much as possible, the results of genetic examinations were not included in the study due to the large time span and the fact that there were some early patients who did not have genetic examinations; therefore, the effect of confounding factors of genetic examinations could not be eliminated (23).

Conclusion

The negative effect of the R1 margin should be downplayed in patients undergoing liver resection for colorectal cancer liver metastases. Although the disease-free survival of the R1 margin is shorter than that of the R0 margin, it has no effect on the overall survival. The intraoperative preoccupation with the R0 resection margin at the expense of preserving the liver parenchyma is more than worth the cost. To improve overall survival, extra attention should be given to the factors of preoperative BMI, preoperative CA19-9, and the presence of perineural invasion of the primary tumor.

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 Peking University Third Hosptial Medical Science Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XNA and DRX: contributed to conception and design of the study. XNA, MT, and JLL: organized the database. XNA, HYW, and DRX :analyzed and interpreted the data. XNA, TS, and DRX: performed the statistical analysis. XNA: wrote the manuscript. DRX: contributed to manuscript revision. All authors contributed to the article and approved the submitted version.

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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Construction of a nomogram for preoperative prediction of the risk of lymph node metastasis in early gastric cancer

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Background: The status of lymph node metastasis (LNM) in patients with early gastric cancer (EGC) is particularly important for the formulation of clinical treatment. The purpose of this study was to construct a nomogram to predict the risk of LNM in EGC before operation.
Methods: Univariate analysis and logistic regression analysis were used to determine the independent risk factors for LNM. The independent risk factors were included in the nomogram, and the prediction accuracy, discriminant ability and clinical practicability of the nomogram were evaluated by the receiver operating characteristic curve (ROC), calibration curve and clinical decision curve (DCA), and 100 times ten-fold cross-validation was used for internal validation.
Results: 33 (11.3%) cases of AGC were pathologically confirmed as LNM. In multivariate analysis, T stage, presence of enlarged lymph nodes on CT examination, carbohydrate antigen 199 (CA199), undifferentiated histological type and systemic inflammatory response index (SIRI) were risk factors for LNM. The area under the ROC curve of the nomogram was 0.86, the average area under the ROC curve of the 100-fold ten-fold cross-validation was 0.85, and the *P* value of the Hosmer-Lemeshow test was 0.60. In addition, the clinical decision curve, net reclassification index (NRI) and Integrated Discriminant Improvement Index (IDI) showed that the nomogram had good clinical utility.
Conclusions: We found that SIRI is a novel biomarker for preoperative prediction of LNM in EGC, and constructed a nomogram for preoperative prediction of the risk of LNM in EGC, which is helpful for the formulation of the clinical treatment strategies.

KEYWORDS
early gastric cancer, lymph node metastasis, systemic inflammation response index, nomogram, risk

Introduction

Gastric cancer ranks fifth in incidence among malignant tumors, which is one of the leading causes of cancer-related deaths (1). With the popularity of gastric cancer screening programs, the promotion of health awareness and the improvement of endoscopic equipment, more and more early gastric cancers have been diagnosed

(2–4). Early gastric cancer is defined as gastric cancer that invades no deeper than the submucosa, regardless of lymph node metastasis status (5). The prognosis of early gastric cancer is significantly better than that of advanced gastric cancer, and the 5-year overall survival rate after radical resection is more than 90% (6). However, the prognosis of early gastric cancer with lymph node metastasis is worse than that without lymph node metastasis, and has a higher risk of postoperative recurrence (7). Endoscopic resection is the main treatment besides surgery and has been widely accepted, especially in Asia, where is a high incidence of early gastric cancer, because of the minimally invasive, preservation of gastric function, rapid postoperative recovery and prognosis after curative resection that is not inferior to radical surgical resection (8). Endoscopic resection includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). According to the guidelines of the Japanese Gastric Cancer Association, endoscopic resection is indicated for early gastric cancer with an extremely low possibility of lymph node metastasis (9). Since endoscopic resection does not dissect the perigastric lymph nodes, additional surgery is needed for patients with non-curative endoscopic resection or high risk of lymph node metastasis (9, 10). Therefore, accurate preoperative assessment of lymph node metastases is crucial to the choice of surgical approach.

Lymph node metastasis is an important factor in the prognosis of early gastric cancer and the selection of lymph node dissection. Previous studies have shown that the lymph node metastasis rate of early gastric cancer is about 2%–20% (9, 11). At present, some studies have constructed and validated different predictive models, which mainly include risk factors such as depth of invasion, vascular invasion, neural invasion, degree of differentiation and mixed tissue types (12–15). However, most models were based on the results of postoperative pathology, which is not known preoperatively. Some studies used biomarkers to predict the risk of lymph node metastasis in early gastric cancer. Ma et al. (16) constructed a risk stratification model composed of four mi-RNAs (miR153-3p, miR-708, miR-940 and miR-375). Chen et al. (17) predicted lymph node metastasis based on collagen signaling in the tumor microenvironment. Wang et al. (18) predicted lymph node metastasis by tumor-associated neutrophils (TANS). however, their clinical use was limited by complex detection techniques and lack of confirmation from big data. Inflammation plays an important role in the occurrence, invasion and migration, distant metastasis and chemotherapy resistance of gastric cancer (19–21). However, it remains unclear whether the levels of inflammatory markers in peripheral blood are associated with lymph node metastasis in early gastric cancer. On the other hand, gastroscopy, ultrasound endoscopy and computed tomography (CT) are routine preoperative tests, which allow the surgeon to obtain information about the lesion and the perigastric lymph nodes before surgery. Therefore, the purpose of this study was to analyze the relationship between preoperative clinicopathological data and lymph node metastasis, and to construct a nomogram for preoperatively predicting the risk of lymph node metastasis in early gastric cancer, which guides the formulation of a clinical treatment plan.

Materials and methods

Patients

We retrospectively analyzed 292 patients with early gastric cancer who underwent surgery at the Second Affiliated Hospital of Nanchang University from July 2017 to December 2021. The inclusion criteria were as follows: (1). postoperative pathologically confirmed early gastric cancer, (2). radical gastrectomy and standard D2 lymph node dissection were performed. The exclusion criteria were as follows: (1). distant metastases; (2). patients with neoadjuvant therapy; (3). two or more sites of primary gastric cancer; (4). previous history of cancer or remnant gastric cancer; (5). patients with preoperative infection or insufficient evidence of infection but temperature >38 degrees Celsius; (6). patients with hematologic disorders or liver, kidney and cardiac dysfunction; (7). incomplete preoperative clinical information.

Clinicopathologic characteristics

The clinicopathological data of the patients were obtained from the hospital's electronic health record system. The clinical data mainly included sex, age, history of hypertension, history of diabetes and body mass index (BMI). Meanwhile, we collected the test indicators of patients within one week before surgery, such as tumor markers, hemoglobin, albumin value, prealbumin values and inflammatory markers. The levels of inflammatory markers were divided into high and low groups, according to the best cutoff value of the ROC curve. In addition, AFP, CEA, CA199 and CA125 in this research center were considered abnormal when they were above 8.1 ng/ml, 5.0 ng/ml, 37.0 U/ml and 35.0 U/ml, respectively. According to the results of gastroscopy, the location, maximum diameter, macroscopic features and presence of ulcer of tumor were determined. The tumor location was divided into upper 1/3, middle 1/3 and lower 1/3 of gastric. The macroscopic features were divided into elevated type, flat type and depressed type. According to the presence or absence of ulcers, it was divided into ulcerative and non-ulcerative types. According to the pathological results, the histological types were divided into differentiated type and undifferentiated type; differentiated type included well or moderately differentiated adenocarcinoma, papillary adenocarcinoma and tubular adenocarcinoma; undifferentiated type included poorly differentiated adenocarcinoma, undifferentiated adenocarcinoma, signet ring cell carcinoma and mucinous adenocarcinoma. The preoperative CT results (such as the thickness of the lesion, the presence of perigastric lymph nodes and the maximum short-axis diameter of lymph nodes) were collected. If the maximum short-axis diameter of perigastric lymph nodes was greater than 5 mm, they were considered as enlarged lymph nodes. The CT results were confirmed by two radiologists above the deputy director.

Statistical analysis

For continuous variables, the normality test was first performed with a single-sample *K-S* test, If the variables conformed to the normal distribution, they were described by mean and standard deviation, and analyzed by *t* test. Otherwise, they were described by median and quartile spacing, and analyzed by the Mann-Whitney *U* test. Categorical variables were described with rates, Chi-square test (or Fisher's exact test in specific conditions) was used for data analysis. The random forest algorithm was used to calculate the importance ranking of meaningful variables in univariate analysis, and these variables were included in multivariate logistic analysis. The stepwise backward regression method was selected to analyze the risk factors of lymph node metastasis in early gastric cancer. A nomogram was constructed according to the results of the multivariate logistic regression model. The predictive ability of the nomogram was evaluated by the C index and ROC curve. The calibration curve and Brier score were used as the indicators of internal calibration. Meanwhile, the Hosmer-Lemeshow test was used to evaluate the goodness of fit of the nomogram. 100 times ten-fold cross-validation was used for internal validation. Finally, in order to measure the clinical practicality, the net benefit was measured by a clinical decision curve. A control model was constructed with the variables of absolute indications or expanded indications for endoscopic resection in the Japan Gastric Cancer Association guidelines, and the models were compared by applying the Net Reclassification Index (NRI) and the Integrated Discriminant Improvement Index (IDI). All of the data were analyzed using the R software (version 4.1.1). *P* values (two-sided) < 0.05 were considered statistically significant in all statistical analyses.

Ethical approval statement

All procedures performed in studies involving human participants have followed the ethical standards of our institutional research committee and were performed in accordance with the Declaration of Helsinki. As it is a retrospective study, this study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University and was granted an exemption from notification consent.

Results

Clinicopathologic features of patients

The clinicopathological characteristics of patients with early gastric cancer are shown in **Table 1**. Lymph node metastasis was found in 33 (11.3%) of 292 patients with early gastric cancer. The average number of dissected lymph nodes was 22 ± 8. The average age of the patients was 60 years old (28–86 years old), the average maximum diameter of the tumor was 2.24 ± 1.17 cm, the average hemoglobin was 131.93 ± 20.08 g/L, the average albumin was 42.45 ± 3.77 g/L, and the average prealbumin was 254.13 ± 65.56 mg/L. 58.2% of the tumors were located in the lower 1/3 of the stomach. 164 cases (56.2%) in the mucosal (T1a) and 128 cases (43.8%) had invaded to the submucosal (T1b), and the lymph node metastasis rates were 3.1% and 21.9%, respectively. More than 50% of the patients showed thickening of lesions on CT, 52 patients (17.8%) found enlarged lymph nodes on CT, and the rate of lymph node metastasis was 30.8%. The percentages of AFP, CEA, CA199 and CA125 above the normal range were 4.8%, 7.2%, 3.4% and 1.7%, respectively.

Predictors for LNM in ECG patients

Figure 1A shows the correlations between 29 variables. In univariate analysis, 10 variables were associated with lymph node metastasis in early gastric cancer, which included preoperative albumin level, enlarged lymph nodes on CT, ulcers, macroscopic features, tumor size, depth of invasion, carbohydrate antigen 199 (CA199), neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory response index (SIRI) and histological type (**Table 1**). The importance of 10 variables was ranked by random forest algorithm, and the results showed that the presence of enlarged lymph nodes on CT and the depth of invasion were important variables for lymph node metastasis (**Figure 1B**). Multivariate analysis showed that enlarged lymph nodes on CT (OR: 6.765 $P < 0.001$), depth of invasion (OR: 8.622 $P < 0.001$), CA199 (OR: 6.138 $P = 0.02$), systemic inflammatory response index (OR: 4.971 $P = 0.046$) and histological type (OR:3.908 $P = 0.003$) were independent risk factors for lymph node metastasis in early gastric cancer (**Table 2**).

TABLE 1 Univariate analysis of preoperative clinicopathological factors.

Variables	Overall	LNM (−)	LNM (+)	*P* value
N	292	259	33	
HB [mean (SD)]	131.93 (20.08)	132.60 (19.73)	126.73 (22.22)	0.114
ALB [mean (SD)]	42.45 (3.77)	42.62 (3.71)	41.10 (4.01)	0.028
pALB [mean (SD)]	254.13 (65.56)	255.62 (64.60)	242.44 (72.69)	0.277
Fib [mean (SD)]	2.85 (0.79)	2.84 (0.75)	2.92 (1.07)	0.577
Hypertension (%)				0.069
No	241 (82.5)	218 (84.2)	23 (69.7)	
Yes	51 (17.5)	41 (15.8)	10 (30.3)	
Diabetes (%)				0.910
No	254 (87.0)	226 (87.3)	28 (84.8)	
Yes	38 (13.0)	33 (12.7)	5 (15.2)	
Sex (%)				0.280
Male	180 (61.6)	163 (62.9)	17 (51.5)	
Female	112 (38.4)	96 (37.1)	16 (48.5)	
Location (%)				0.486
Upper third	23 (7.9)	22 (8.5)	1 (3.0)	
Middle third	99 (33.9)	86 (33.2)	13 (39.4)	
Lower third	170 (58.2)	151 (58.3)	19 (57.6)	
Age (%)				0.805
<40	12 (4.1)	10 (3.9)	2 (6.1)	
40–60	129 (44.2)	114 (44.0)	15 (45.5)	
>60	151 (51.7)	135 (52.1)	16 (48.5)	
CT				
Thickness of lesion (%)				0.719
Absence	128 (43.8)	115 (44.4)	13 (39.4)	
Presence	164 (56.2)	144 (55.6)	20 (60.6)	
Enlarged LN, ≥5 mm (%)				<0.001
Absence	240 (82.2)	223 (86.1)	17 (51.5)	
Presence	52 (17.8)	36 (13.9)	16 (48.5)	
Ulcer (%)				0.010
Absence	163 (55.8)	152 (58.7)	11 (33.3)	
Presence	129 (44.2)	107 (41.3)	22 (66.7)	
Morphology (%)				0.028
Elevated type	51 (17.5)	44 (17.0)	7 (21.2)	
Flat type	95 (32.5)	91 (35.1)	4 (12.1)	
Depressed type	146 (50.0)	124 (47.9)	22 (66.7)	
Size (%)				0.007
<2 cm	116 (39.7)	108 (41.7)	8 (24.2)	
2–3 cm	131 (44.9)	117 (45.2)	14 (42.4)	
>3 cm	45 (15.4)	34 (13.1)	11 (33.3)	
T1 (%)				<0.001
1a	164 (56.2)	159 (61.4)	5 (15.2)	
1b	128 (43.8)	100 (38.6)	28 (84.8)	
BMI (%)				0.087

(*continued*)

TABLE 1 Continued

Variables	Overall	LNM (−)	LNM (+)	*P* value
<23.9	206 (70.5)	178 (68.7)	28 (84.8)	
≥24.0	86 (29.5)	81 (31.3)	5 (15.2)	
AFP (%)				1.000
<8.1 ng/ml	278 (95.2)	247 (95.4)	31 (93.9)	
≥8.1 ng/ml	14 (4.8)	12 (4.6)	2 (6.1)	
CEA (%)				0.128
<5.0 ng/ml	271 (92.8)	243 (93.8)	28 (84.8)	
≥5.0 ng/ml	21 (7.2)	16 (6.2)	5 (15.2)	
CA199 (%)				0.016
<37.0 U/ml	282 (96.6)	253 (97.7)	29 (87.9)	
≥37.0 U/ml	10 (3.4)	6 (2.3)	4 (12.1)	
CA125 (%)				0.926
<35.0 U/ml	287 (98.3)	254 (98.1)	33 (100.0)	
≥35.0 U/ml	5 (1.7)	5 (1.9)	0 (0.0)	
FAR (%)				0.055
Low (<0.055)	81 (27.7)	77 (29.7)	4 (12.1)	
High (≥0.055)	211 (72.3)	182 (70.3)	29 (87.9)	
FpAR (%)				0.118
Low (<0.012)	148 (50.7)	136 (52.5)	12 (36.4)	
High (≥0.012)	144 (49.3)	123 (47.5)	21 (63.6)	
NLR (%)				0.040
Low (<2.239)	142 (48.6)	132 (51.0)	10 (30.3)	
High (≥2.239)	150 (51.4)	127 (49.0)	23 (69.7)	
PLR (%)				0.255
Low (<110.254)	82 (28.1)	76 (29.3)	6 (18.2)	
High (≥110.254)	210 (71.9)	183 (70.7)	27 (81.8)	
LMR (%)				0.675
Low (<2.599)	156 (53.4)	140 (54.1)	16 (48.5)	
High (≥2.599)	136 (46.6)	119 (45.9)	17 (51.5)	
SII (%)				0.072
Low (<381.237)	108 (37.0)	101 (39.0)	7 (21.2)	
High (≥381.237)	184 (63.0)	158 (61.0)	26 (78.8)	
SIRI (%)				0.016
Low (<0.458)	72 (24.7)	70 (27.0)	2 (6.1)	
High (≥0.458)	220 (75.3)	189 (73.0)	31 (93.9)	
PNI (%)				1.000
Low (<43.620)	174 (59.6)	154 (59.5)	20 (60.6)	
High (≥43.620)	118 (40.4)	105 (40.5)	13 (39.4)	
Histological type (%)				0.013
Differentiated	161 (55.1)	150 (57.9)	11 (33.3)	
Undifferentiated	131 (44.9)	109 (42.1)	22 (66.7)	

Development and validation of the nomogram

Based on the results of multivariate analysis, we established a nomogram for preoperatively predicting the risk of lymph node metastasis in early gastric cancer. When applying the

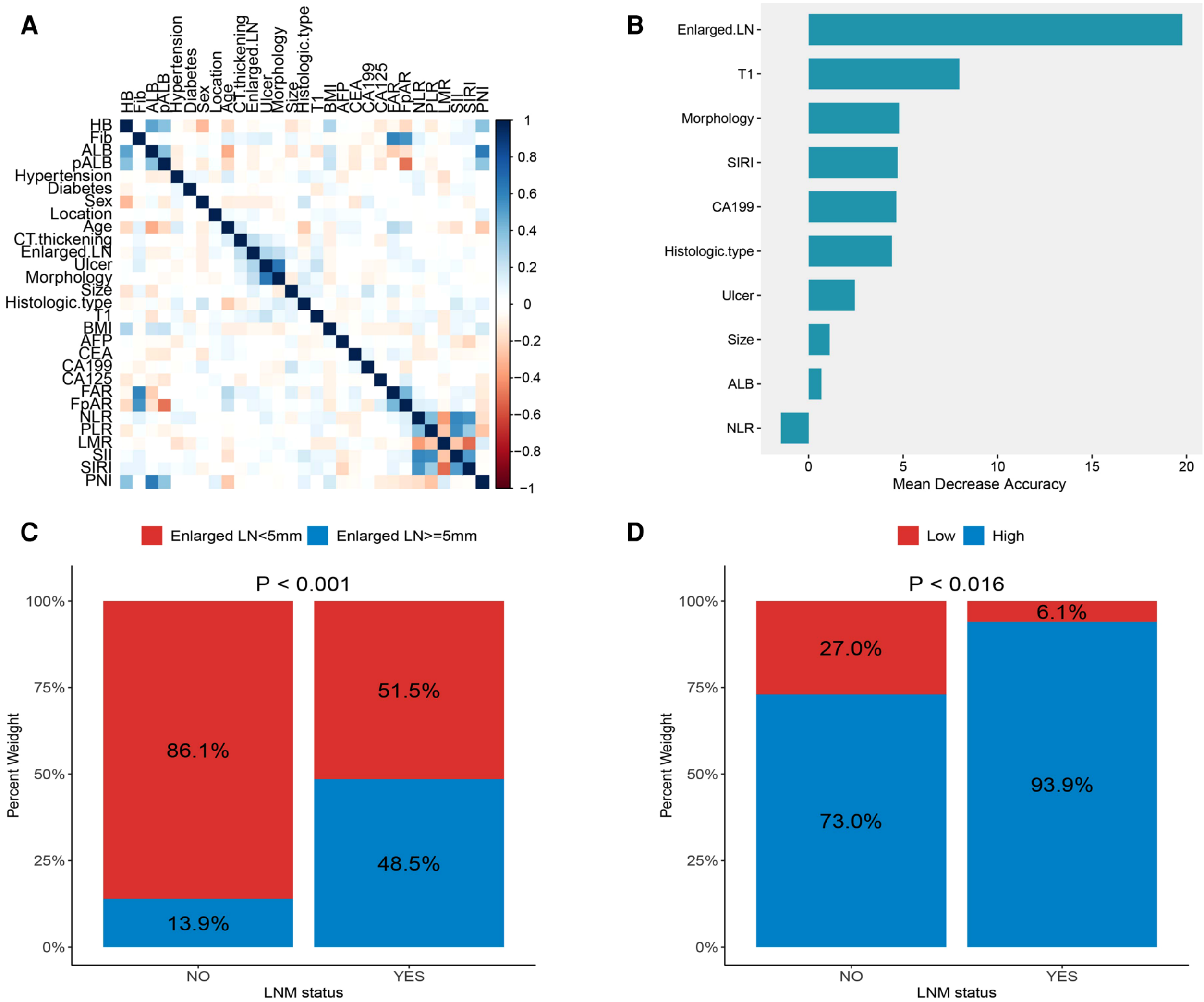

FIGURE 1
(A) correlations between variables; (B) the importance ranking of significant variables in univariate analysis; (C) the proportion of enlarged lymph nodes found on CT in different lymph node status; (D) proportion of systemic inflammatory response index (SIRI) in different lymph node status.

nomogram, we can calculate an individualized total score for each patient and estimate the risk of lymph node metastasis (Figure 2). The *P* value of the Hosmer-Lemeshow test was 0.60, indicating a good fit of the nomogram. The area under the ROC curve was 0.86, the C-index was 0.86, and the C-index after 1,000 bootstrap corrections was 0.84, which indicated that the nomogram had good discriminative ability (Figure 3A). The calibration curve showed that the nomogram predicts the risk of lymph node metastasis in good agreement with the actual situation (Figure 3B). The Brier score was 0.07, which indicated that the prediction calibration of model is good. The accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the nomogram were 69.5%, 66.8%, 90.9%, 98.3% and 25.9%, respectively. The nomogram was internally validated by 100 times 10-fold cross-validation. The average area under the ROC curve was 0.85, and the average Brier score was 0.08. These indicators did not change much after cross-validation, which proved that the performance of the nomogram is good and has good generalization ability.

The clinical decision curve (DCA) showed that the nomogram had better clinical utility than the control model (Figure 4) (Table 4). Meanwhile, both the Net Reclassification Index (NRI) and the Integrated Discriminant Improvement Index (IDI) indicated that the nomogram was superior to the control model, and the corresponding *P* value was 0.001 (Table 3).

Discussion

At present, there are various surgical methods for the treatment of early gastric cancer, including open surgery,

TABLE 2 Multivariate analysis of preoperative clinicopathological factors associated with LNM.

Factors		OR	95% CI	*P* value
Enlarged LN on CT	Absence	Reference		
	Presence	6.765	2.755–17.361	<0.001
T1	1a	Reference		
	1b	8.622	3.209–28.427	<0.001
CA199	<37.0 U/ml	Reference		
	≥37.0 U/ml	6.138	1.265–28.972	0.020
SIRI	Low (<0.458)	Reference		
	High (≥0.458)	4.971	1.256–33.973	0.046
Histological type	Differentiated	Reference		
	Undifferentiated	3.908	1.619–10.259	0.003

laparoscopic surgery, robotic surgery, and endoscopic surgery, but R0 resection is the only effective way to cure early gastric cancer. For EGC patients without lymph node metastasis, endoscopic *en bloc* resection can achieve the curative effect, while patients with non-curative endoscopic resection require additional salvage surgery (10, 22). Therefore, it is particularly important to accurately predict the risk of lymph node metastasis before surgery for the formulation of treatment plans for early gastric cancer.

In this study, a nomogram was constructed to predict the risk of lymph node metastasis in early gastric cancer based on preoperative clinicopathological factors. The lymph node metastasis rate of early gastric cancer in the study was 11.3%, which was consistent with previous studies (9, 11). The study found that tumor invasion into the submucosa, undifferentiated type, carbohydrate antigen CA199 ≥ 37.0 U/ml and enlarged lymph nodes on CT were independent risk factors for lymph node metastasis. Previous studies have confirmed the correlation between these risk factors and lymph node metastasis (23–25). In addition, the study found that the systemic inflammatory response index (SIRI) is also an independent risk factor for lymph node metastasis in early gastric cancer. As far as we know, this is the first study to investigate the relationship between systemic inflammatory response index and lymph node metastasis in early gastric cancer.

Gastric cancer is a highly heterogeneous tumor. Some studies have confirmed that tumor-related inflammation plays an important role in the occurrence, development, treatment response and prognosis of gastric cancer (26, 27). Tumor-

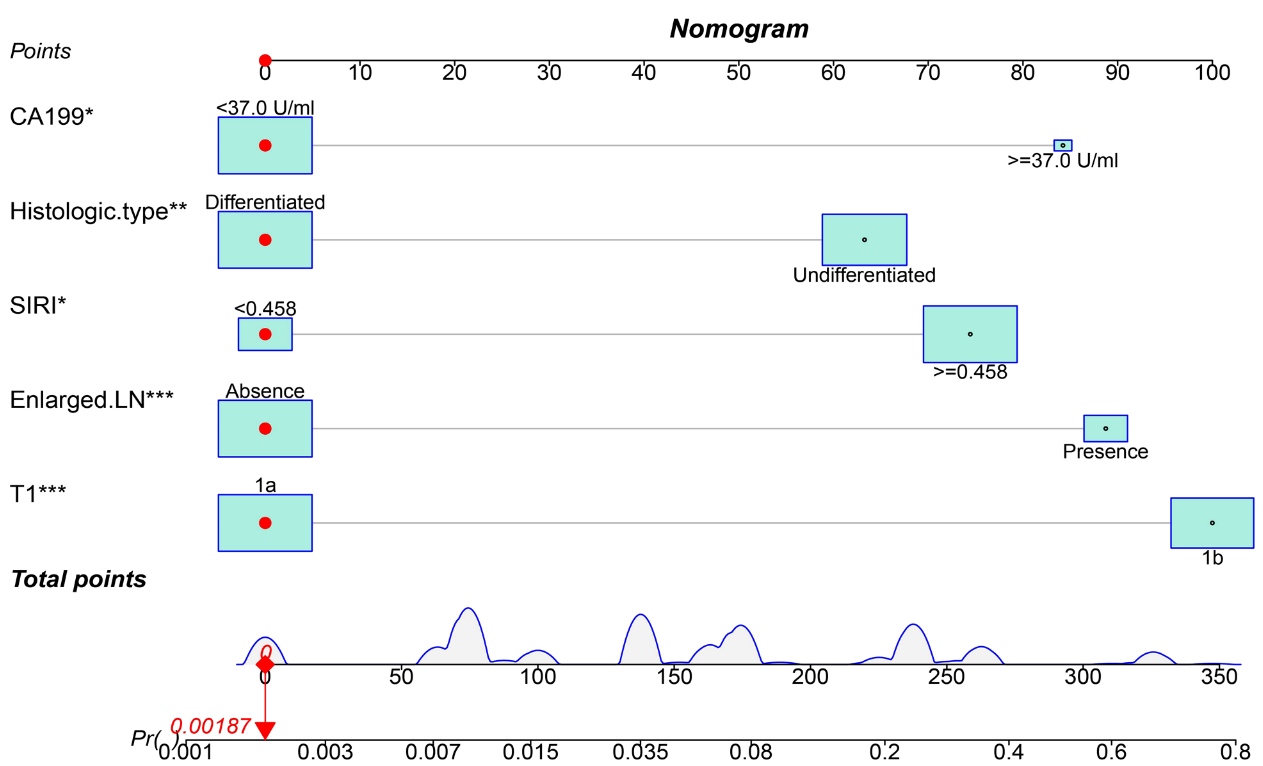

FIGURE 2
A nomogram for predicting the risk of lymph node metastasis in early gastric cancer. The scores for each variable were summed, and the total score corresponds to the probability of lymph node metastasis.

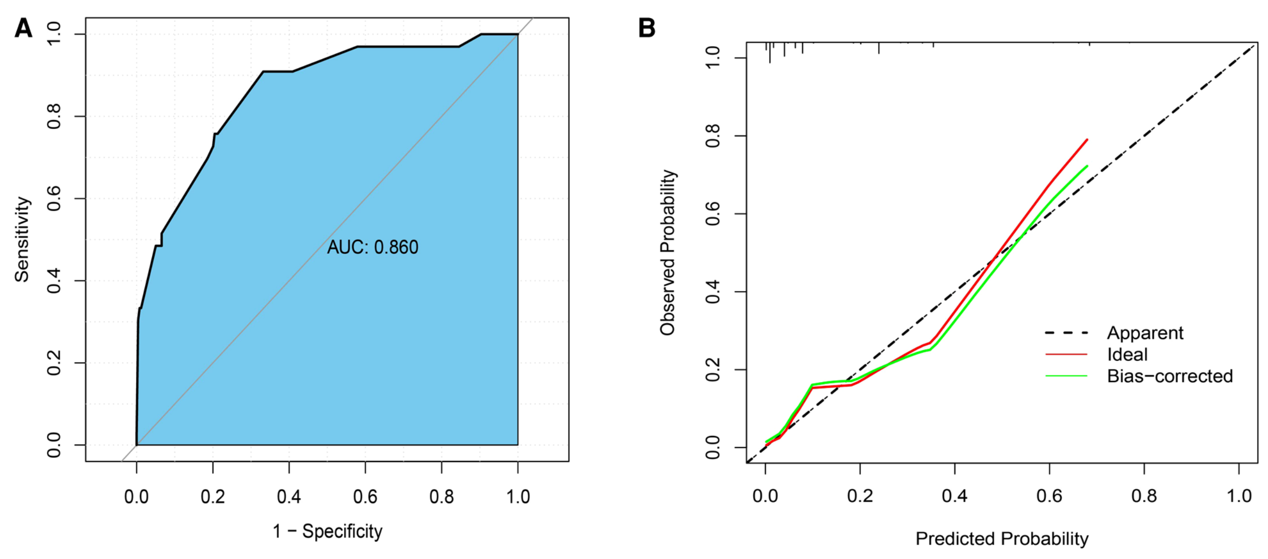

FIGURE 3
(A) the receiver operating characteristic curve (ROC) of the nomogram; (B) the calibration curve.

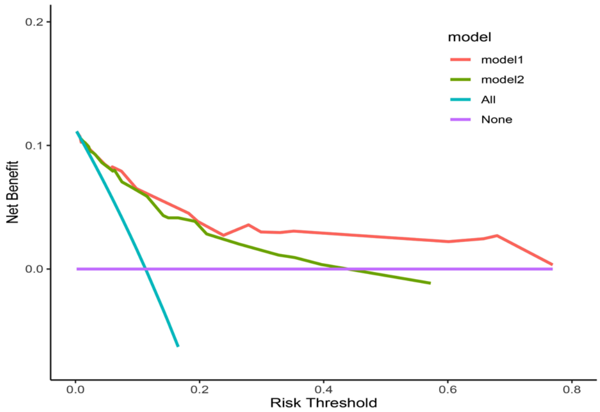

FIGURE 4
The DCA curve. Model 1 is the nomogram in the study, and Model 2 is the control model, which is composed of variables such as tumor size, histological type, ulcer and invasion depth.

TABLE 3 Model performance comparison.

	AUC	AUDC	NRI	*P* value (NRI)	IDI	*P* value (IDI)
Model 1	0.860	0.028	0.336	0.001	0.121	0.001
Model 2	0.829	0.015	Reference		Reference	

related inflammation leads to neutrophilia, thrombocytosis, lymphocytopenia and elevated fibrinogen levels, while the systemic inflammatory state of individuals can be reflected by changes in the levels of leukocytes and fibrinogen in peripheral blood (28, 29). Therefore, the relationship between inflammatory markers in peripheral blood and lymph node metastasis of early gastric cancer was analyzed completely in this study. Univariate analysis showed that neutrophil-to-lymphocyte ratio (NLR) and systemic inflammatory response index (SIRI) were associated with lymph node metastasis, while platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune inflammatory index (SII), prognostic nutritional index (PNI), fibrinogen to albumin or prealbumin ratio (FAR/FpAR) were not associated with lymph node metastasis, and multivariate analysis showed that only SIRI was a risk factor for lymph node metastasis. Lou et al. (30) confirmed that NLR was associated with lymph node metastasis in early gastric cancer, but only two inflammatory markers (NLR and PLR) were included in the study. Previous studies have confirmed that the higher the systemic inflammatory response index, the later the TNM staging of gastric cancer patients, the poorer prognosis and chemotherapy efficacy, the higher the risk of recurrence, and the predictive performance of the SIRI is better than other inflammatory markers (29, 31–34). In this study, it was found that EGC patients with high SIRI are prone to lymph node metastasis, and the ability of SIRI to predict lymph node metastasis was also superior to other inflammatory markers.

CT scan is a routine examination for preoperative assessment of lymph node status in early gastric cancer, and it is mainly judged that lymph nodes are malignant according to their diameter (35). However, inflammatory reactive lymph nodes are enlarged and smaller lymph nodes may have metastases, which can lead to inaccurate assessment of lymph nodes in some patients (36). Therefore, the appropriate size criteria as an indicator to assess lymph node status remains controversial. Saito et al. (35) reported that the accuracy of

CT in assessing lymph node status was about 70%. Wei et al. (23) and Yin et al. (24) showed that the presence of enlarged lymph nodes on CT was a risk factor for lymph node metastasis in early gastric cancer. In this study, the cut-off value of the lymph node diameter was 5 mm, and the diameter > 5 mm was identified as enlarged lymph nodes. The results showed that the accuracy rate and recall rate of CT in evaluating lymph node status were 81.8% and 60.6%, respectively, which also confirmed that enlarged lymph nodes found on CT were independent predictors of lymph node metastasis in early gastric cancer.

The depth of tumor invasion and histological type are also risk factors for predicting lymph node metastasis in early gastric cancer. Previous studies have shown that the incidence of LNM in intramucosal and submucosal of early gastric cancer is 0%–7% and 10%–25% (37), respectively. In this study, the incidence of LNM in intramucosal cancer was 3.1% (5/164), and the incidence of LNM in submucosa cancer was 21.9% (28/128). To a certain extent, the depth of tumor invasion reflects the growth time of the tumor, and the deeper the depth of invasion, the greater the risk of lymph node metastasis. While capillaries are enriched in the mucosal layer, lymphatic vessels are mainly present in the submucosa (38). This phenomenon explains the difference in the incidence of LNM with different depths of invasion. At present, endoscopic ultrasonography has high accuracy in diagnosing the depth of invasion of early gastric cancer. Kim et al. (39) showed that the accuracy of endoscopic ultrasonography for T1a with lesions < 2 cm was 84.6%, and the accuracy of early gastric cancer with lesions > 2 cm was also 83.2%. Therefore, endoscopic ultrasonography is helpful to accurately assess the depth of invasion before surgery. Due to the differences between the results of endoscopic ultrasonography and postoperative pathology, in order to accurately analyze the relationship between the depth of invasion and lymph node metastasis, the depth of invasion diagnosed by postoperative pathology was included in the model in this study. Undifferentiated type and mixed type of early gastric cancer have worse biological behavior and a higher possibility of lymph node metastasis (40, 41). Due to the limited number and shallow sampling of preoperative endoscopic biopsy specimens, there was often a discrepancy between preoperative and postoperative histological results. However, studies have shown that histological differences in early gastric cancer range from 9.4% to 16.3% (42, 43), which is acceptable. Therefore, endoscopy biopsy should be performed with as many sites as possible to improve the accuracy of diagnostic histological types.

Serum tumor markers are widely used in the diagnosis of tumors, assessment of treatment efficacy and disease monitoring. Previous studies have shown that the elevated levels of CA199 and CA724 in EGC patients are closely related to lymph node metastasis, and the elevated levels of CEA and CA125 indicate a poor prognosis of EGC (24, 25, 44). In this study, only CA199 was associated with LNM in EGC.

The nomogram constructed in this study has high specificity and positive predictive value, which provides an effective tool for accurately predicting lymph node metastasis before surgery. The ROC curve and DCA curve show that our model has good discriminative ability and clinical applicability.

This study has some limitations. First of all, our study is a single-center retrospective study with a small sample size, which may have selection bias. The prediction model has only carried out internal cross-validation and not external validation, so multi-center big data is needed for further validation. Secondly, indicators such as Helicobacter pylori infection, carbohydrate antigen 724, peripheral blood circulating tumor cells and interleukin-6 were not included in the study, and the accuracy of the model needs to be further improved.

Conclusion

We found that systemic inflammatory response index (SIRI) is a novel biomarker for preoperative prediction of lymph node metastasis in early gastric cancer. The nomogram constructed by five preoperative clinicopathological factors can accurately predict the risk of lymph node metastasis of early gastric cancer, and provide guidance for EGC patients to choose the appropriate treatment plan.

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

ZTL and CH: conceived and designed the study, YSH, YL, FLZ and HKT: collected the data, ZTL, CH and HKT: analyzed the data, searched the literature and evaluated the quality, and ZTL, CH and HKT: prepared the first draft of the manuscript and corrected it. 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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Therapeutic effect of postoperative adjuvant transcatheter arterial chemoembolization based on the neutrophil-to-lymphocyte ratio

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Aim: To evaluate the feasibility of the preoperative neutrophil-to-lymphocyte ratio (NLR) as an index to guide postoperative adjuvant transcatheter arterial chemoembolization (PA-TACE) in patients with liver cancer.

Methods: We recruited a total of 166 patients with liver cancer who underwent surgery alone or surgery plus PA-TACE between January 2013 and June 2017 and compared the 1, 2, and 3-year recurrence-free survival (RFS) and overall survival (OS) between patients with high and low NLRs, surgery and surgery plus PA-TACE groups, and relevant subgroups using the Kaplan–Meier method. We also evaluated the independent factors affecting the prognosis of liver cancer after surgery using a Cox risk ratio model and correlation between NLR levels and high-risk recurrence factors of liver cancer with logistic regression analysis.

Results: The 1, 2, and 3-year RFS rates were all significantly higher in the low-NLR group compared to the high-NLR group ($P < 0.05$). However, the 1, 2, and 3-year OS rates were similar in the low- and high-NLR groups ($P > 0.05$). After propensity score matching, the 1, 2, and 3-year RFS and OS rates were significantly better in patients treated with surgery plus PA-TACE compared with surgery alone ($P < 0.05$). The 1, 2, and 3-year RFS and OS rates were also significantly better in the surgery plus PA-TACE subgroup compared with the surgery-alone subgroup in the high-NLR group ($P < 0.05$), but there was no significant difference in RFS or OS between the surgery plus PA-TACE and surgery-alone subgroups at 1, 2, and 3 years in the low-NLR group ($P > 0.05$). Multivariate analysis in the high-NLR group showed that a poorly differentiated or undifferentiated tumor was an independent risk factor for postoperative RFS. Multiple tumors were an independent risk factor for postoperative OS ($P < 0.05$), while PA-TACE was an independent protective factor for postoperative RFS and OS ($P < 0.05$). In the low-NLR group, AFP > 400 μg/L was an independent risk factor for postoperative OS ($P < 0.05$). Multivariate logistic regression indicated that patients with a maximum tumor diameter of >5 cm were at increased risk of having high NLR levels compared to patients with a maximum tumor diameter of <5 cm ($P < 0.05$).

Conclusion: PA-TACE can improve the prognosis of patients with a high preoperative NLR (≥2.5), but has no obvious benefit in patients with low preoperative NLR (<2.5). This may provide a reference for clinical selection of PA-TACE.

KEYWORDS

hepatic carcinoma, neutrophil-to-lymphocyte ratio, postoperative adjuvant transcatheter arterial chemoembolization, prognosis, propensity score matching

Introduction

Radical hepatectomy is currently one of the most effective treatments for liver cancer; however, the 5-year overall survival (OS) rate is still not ideal, ranging from 25%–55%, largely due to the high postoperative recurrence rate (60%–100%) (1). TNM staging, positive margins, and microvascular infiltration are among the factors known to affect recurrence after radical hepatectomy (2). Previous studies showed that the median survival of patients with liver cancer recurrence was 54 months less than that of patients without recurrence (3), indicating the need for postoperative adjuvant treatment of liver cancer in patients with high-risk recurrence factors. Transcatheter arterial chemoembolization (TACE) is one of the main treatments for patients with advanced hepatocellular carcinoma (HCC), and is also widely recommended for the preoperative and postoperative treatment of patients undergoing radical hepatectomy (4). Several studies (5–7) have shown that postoperative adjuvant TACE (PA-TACE) can improve recurrence-free survival (RFS) and OS, and can significantly improve the prognosis of HCC patients. However, the indicators used to identify the postoperative liver cancer patients likely to benefit from PA-TACE are limited, and the indications for PA-TACE differ among medical centers. Further studies are therefore needed to identify potential indicators to evaluate the effect of PA-TACE, and to develop comprehensive and accurate standards to guide clinical decision-making, reduce tumor recurrence in patients after HCC surgery, and improve survival through individualized treatment.

The neutrophil-to-lymphocyte ratio (NLR), as an indicator of systemic inflammation, has been shown to be related to the prognosis of HCC patients, with a higher NLR predicting a worse prognosis (5, 8, 9). The mechanism may be related to the complex nature of the tumor itself and the interaction between the tumor and tumor microenvironment, coupled with the role of the chronic inflammatory environment in the occurrence and development of liver cancer (10). TACE-induced ischemia and hypoxia affect the activity of immune cells, leading to changes in the inflammatory environment. Although previous studies showed that a high NLR was related to a poor prognosis in PA-TACE-treated liver cancer patients (8), the causative role of PA-TACE in this poor prognosis is unclear.

In this study, we collected clinical data for patients with liver cancer treated with radical hepatectomy alone or with radical hepatectomy plus PA-TACE to investigate the correlation between their prognosis and preoperative NLR level. We further explored the possibility of using NLR as an index to screen for patients suitable for postoperative PA-TACE in order to provide a reference for choosing TACE after radical hepatectomy. We also analyzed the independent factors affecting the prognosis of liver cancer after surgery and performed a preliminary study on the correlation between NLR levels and high-risk recurrence factors of liver cancer and between PA-TACE frequency and RFS in patients with liver cancer.

Materials and methods

Study patients

We retrospectively analyzed the clinical data for patients with liver cancer who underwent surgery at the Liver Center of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China between January 2013 and June 2017. The inclusion criteria (11–13) were as follows: (1) preoperative liver function Child–Pugh score A/B, and liver reserve function indicating sufficient residual liver volume; (2) not accompanied by tumor rupture or any signs of sepsis; (3) radical liver tumor resection, and postoperative medical examination confirming no cancer cells in the resection margin; (4) HCC confirmed by postoperative medical examination and immunohistochemical analysis; (5) no portal vein or other large blood vessel invasion or distant metastasis; and (6) patients in the intervention group who received one or two TACE treatments after surgery. The exclusion criteria (11, 13, 14) were as follows: (1) tumor recurrence demonstrated within 2 months after surgery or during TACE therapy; (2) complicated with other tumors; (3) adjuvant treatments other than TACE performed during the interval between the first diagnosis of recurrence or metastasis after surgery; (4) loss to follow-up in <1 year; and (5) diseases with abnormal blood cell counts caused by blood, immune system, or other non-liver cancer causes. We collected clinical data [age, sex, history of hepatitis B, cirrhosis, preoperative blood routine, liver function, alfa-fetoprotein (AFP) levels] and tumor data [tumor size, number of lesions, degree of differentiation, microvascular invasion (MVI) grade]. The tumor data were issued by the Imaging Center of the First

Affiliated Hospital of Chongqing Medical University and the Clinicopathology Department of the Molecular Medicine Testing Center of Chongqing Medical University.

Ethics and informed consent

This retrospective study was conducted in line with the ethical guidelines of the Declaration of Helsinki revised in 1975, and was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. 2019-021).

Therapies

Patients who met the conditions for surgery underwent segmental hepatectomy, hemihepatectomy, or tumor resection according to the size, location, and distribution of the tumor. 1–1.5 months after surgery, patients at high risk of recurrence (e.g., maximum lesion diameter >5 cm, MVI > M1, and less-differentiated tumor) received TACE after multidisciplinary discussion and evaluation. Seldinger technology was used to puncture the catheter through the femoral artery under local anesthesia with 1% lidocaine. PA-TACE was conducted for the entire remnant liver of these postoperative patients under the guidance of hepatic and CT angiography. Firstly, tiny doses (0.5–1.0 ml) of lipiodol were used to observe if deposition occur in the remnant liver. For patients with lipiodol deposition, chemotherapeutic agents (oxaliplatin, irinotecan, fluorouracil, epirubicin, or pirarubicin) and lipiodol were used to chemoembolize the corresponding artery after assessing the drug dose based on body surface area and liver function. TACE without lipiodol would be performed for these without lipiodol deposition. After treatment, radiography was conducted again to evaluate the effect of embolization if necessary. A total of one or two TACE treatments were given with an interval of ≥3 weeks, and liver function was assessed before surgery to confirm the patient's ability to withstand interventional therapy. None of the patients with HCC received any other types of adjuvant therapy, such as targeted therapy, immunotherapy, or absolute alcohol injection, from the time of surgery to the first diagnosis of recurrence or metastasis.

Follow-up

All patients were followed-up regularly in the outpatient clinic (every 3 months in the first year after surgery and every 6 months thereafter). Outpatient follow-up evaluations included liver and kidney function tests, hepatitis B virus-DNA quantification, tumor markers, abdominal color Doppler ultrasound, or enhanced computed tomography of the abdomen and chest. The follow-up endpoint was June 20, 2020 and the median follow-up time was 47 months [95% confidence interval (CI): 43.2–50.7 months]. The diagnostic criteria for tumor recurrence were consistent with the initial diagnostic criteria for HCC. The follow-up endpoint of the study was the patient's time of death or loss to follow-up.

Statistical analysis

Statistical analysis was carried out using SPSS 22.0 (IBM Corp., Armonk, NY, USA). The study endpoint was OS rate, based on death from any cause from the time of first surgery. Propensity score matching (PSM) was used to reduce the differences in baseline data between the groups. The groups were matched according to the 1:1 nearest-matching method, with the caliper value set to 0.3. Results were compared between groups using χ^2 and number-rank tests, survival analyses were carried out using the Kaplan–Meier method, independent factors affecting prognosis were analyzed using a Cox proportional risk model, and the correlation between high-risk factors for recurrence and NLR levels was analyzed by logistic regression. $P < 0.05$ was considered statistically significant.

Results

Baseline patient information

A total of 166 patients were enrolled in this study, of whom 85 underwent radical hepatectomy alone and 81 underwent radical hepatectomy combined with PA-TACE. There were no significant differences between the two groups in terms of sex, hepatitis B history, preoperative liver function, preoperative AFP levels, and preoperative NLR levels. The surgery-alone group included higher proportions of patients aged >55 years, with liver cirrhosis, and with single tumors. After PSM to eliminate differences, 80 pairs of patients were successfully matched with no significant differences in any baseline items between the groups ($P > 0.05$) (**Table 1**). Based on a previous study (15) and the median NLR in the current study, we divided the enrolled cases into a high-NLR group (NLR ≥ 2.5) and low-NLR group (NLR < 2.5). There were no significant differences in any items between the groups ($P > 0.05$) (**Table 2**). The surgery-alone and surgery plus PA-TACE groups were also further divided into high-NLR and low-NLR subgroups. There were 45 patients in the high-NLR and 40 in the low-NLR subgroup in the surgery-alone group, and 39 and 42, respectively, in the surgery plus PA-TACE subgroup, with no significant differences in any items between the paired subgroups (**Tables 3, 4**). The high-NLR and low-NLR

TABLE 1 Basic characteristics of patients in terms of treatment options [cases (%)].

Characteristic	Pre-PSM			After PSM		
	Operating group ($n = 85$)	Operation + TACE group ($n = 81$)	*P*	Operating group ($n = 80$)	Operation + TACE group ($n = 80$)	*P*
Age (>55)	49 (57.6)	32 (39.5)	0.019	44 (55.0)	32 (40.0)	0.057
Gender (male)	75 (88.2)	70 (86.4)	0.725	70 (87.5)	69 (86.3)	0.815
Hepatitis B history	72 (84.7)	73 (90.1)	0.294	70 (87.5)	72 (90.0)	0.617
Liver cirrhosis	61 (71.8)	45 (55.6)	0.030	56 (70.0)	44 (55.0)	0.050044
Pre-operative liver function (A)	84 (98.8)	79 (97.5)	0.966	79 (98.8)	78 (97.5)	1.000
AFP (>400 μg/L)	21 (24.7)	21 (25.9)	0.857	21 (26.25)	21 (26.25)	1.000
Number of lesions (single)	76 (89.4)	63 (77.8)	0.042	71 (88.8)	63 (78.8)	0.086
Maximum diameter of lesions (>5 cm)	47 (55.3)	42 (51.9)	0.657	42 (52.5)	41 (51.3)	0.874
NLR (≥2.5)	45 (53.0)	39 (48.1)	0.537	40 (50.0)	38 (47.5)	0.752

AFP, alpha foetoprotein; NLR, neutrophil-to-lymphocyte ratio; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization.

TABLE 2 Basic characteristics of patients in terms of NLR level [cases (%)].

Characteristic	high NLR ($n = 84$)	low NLR ($n = 82$)	*P*
Age (>55)	38 (45.2)	43 (52.4)	0.353
Gender (male)	76 (90.5)	69 (84.1)	0.220
Hepatitis B history	74 (88.1)	71 (86.6)	0.770
Liver cirrhosis	53 (63.1)	53 (64.6)	0.837
Pre-operative liver function (A)	83 (98.8)	80 (97.6)	0.983
AFP (>400 μg/L)	22 (26.2)	20 (24.4)	0.790
Number of lesions (single)	69 (82.1)	70 (85.4)	0.574
Treatment programs (Operation + TACE)	39 (46.4)	42 (51.2)	0.537

AFP, Alpha foetoprotein; NLR, Neutrophil-to-lymphocyte ratio.

TABLE 3 Basic characteristics of surgery-alone subgroup.

Characteristic	high NLR ($n = 45$)	low NLR ($n = 40$)	*P*
Age (>55)	25	24	0.679
Gender (male)	42	33	0.226
Hepatitis B history	37	35	0.500
Liver cirrhosis	29	32	0.112
Pre-operative liver function (A)	45	39	0.471
AFP (>400 μg/L)	9	12	0.286
Number of lesions (single)	39	37	0.604

AFP, Alpha foetoprotein; NLR, Neutrophil-to-lymphocyte ratio.

groups were also divided into surgery and surgery plus PA-TACE subgroups. The high-NLR group included 45 patients in the surgery-alone subgroup and 39 in the surgery plus PA-TACE subgroup, and the low-NLR group included 40 and 42 in the surgery-alone and surgery plus PA-TACE subgroups, respectively, with no significant differences in any items between the subgroups (Tables 5, 6).

In the surgery plus PA-TACE group, subgroups were created using PA-TACE frequency. The proportion of patients with AFP > 400 μg/L in the one-time group ($n = 50$) was significantly higher than that in the two-time group ($n = 31$; $P < 0.05$). After PSM to eliminate the differences, 31 pairs of patients were successfully matched with no significant differences in any baseline items between the groups ($P > 0.05$; Table 7). Patients were then divided by the frequency of PA-TACE in the high- and low-NLR subgroups of the surgery plus PA-TACE group. In the low-NLR subgroup, the proportion of patients with MVI > M1 in the one-time group ($n = 22$) was significantly lower than that in the two-time group ($n = 20$; $P < 0.05$). After PSM, 19 pairs of patients were successfully matched with no significant differences in any baseline items between the groups ($P > 0.05$). In the high-NLR subgroup, there was no significant difference in each item between the one-time group ($n = 28$) and two-time group ($n = 11$; $P > 0.05$; Table 8).

Results of survival analysis in every group and subgroup

Effect of the NLR level on RFS and OS in patients after HCC treatment

The 1, 2, and 3-year RFS rates were significantly higher in the low-NLR compared with the high-NLR group (80.5%, 65.6%, and 59.1% vs. 65.5% 54.8%, and 42.9%, respectively; $P = 0.039$). The 1, 2, and 3-year OS rates were also higher in the low-NLR than the high-NLR group, but the differences were not significant (93.9%, 80.5%, and 72.9% vs. 89.3%, 73.8%, and 63.0%, respectively; $P = 0.145$; Figures 1A,E).

TABLE 4 Basic characteristics of surgery plus PA-TACE subgroup.

Characteristic	high NLR ($n = 39$)	low NLR ($n = 42$)	P
Age (>55)	13	19	0.273
Gender (male)	34	36	0.847
Hepatitis B history	37	36	0.314
Liver cirrhosis	24	21	0.296
Pre-operative liver function (A)	38	41	1.000
AFP (>400 μg/L)	13	8	0.143
Number of lesions (single)	30	33	0.858

AFP, Alpha foetoprotein; NLR, Neutrophil-to-lymphocyte ratio.

Effect of treatment methods on RFS and OS after liver cancer surgery

After eliminating the differences between the groups by PSM, the 1, 2, and 3-year RFS and OS rates were significantly better in the surgery plus PA-TACE compared with the surgery-alone group (RFS: 75.0%, 67.5%, and 59.7% vs. 71.3%, 52.2%, and 43.2%, respectively; $P = 0.044$; OS: 96.3%, 83.7%, and 78.6% vs. 86.3%, 70.0%, and 57.2%, respectively; $P = 0.005$; Figures 1B,F).

Comparison of RFS and OS in patients with high and low NLR under the same treatment

In the surgery plus PA-TACE group, there was no significant difference in RFS or OS at 1, 2, and 3 years between the high-NLR and low-NLR subgroups (RFS: 74.4%, 71.8%, and 59.0% vs. 73.8%, 61.7%, and 59.2%, respectively; $P = 0.856$; OS: 97.4%, 87.2%, and 76.9% vs. 95.2%, 80.9%, and 78.4%, respectively; $P = 0.902$; Figures 1C,G).

In the surgery-alone group, the 1, 2, and 3-year RFS rates were significantly higher in the low-NLR subgroup compared with the high-NLR subgroup (87.5%, 69.5%, and 59.1% vs. 57.8%, 40.0%, and 28.9%, respectively; $P = 0.003$). The 1, 2, and 3-year OS rates were also higher in the low-NLR than in the high-NLR subgroup, but the difference was not significant (92.5%, 80.0%, and 67.3 vs. 82.2%, 62.2%, and 50.8%, respectively; $P = 0.085$; Figures 1D,H).

Comparison of RFS and OS in treatment subgroups with the same level of NLR

In the high-NLR group, the 1, 2, and 3-year RFS and OS rates were significantly higher in the surgery plus PA-TACE compared

TABLE 5 Basic characteristics of high-NLR subgroup.

Characteristic	Operating group ($n = 45$)	Operation + TACE group ($n = 39$)	P
Gender (male)	42	34	0.558
Hepatitis B history	37	37	0.148
Pre-operative liver function (A)	45	38	0.464
AFP (>400 μg/L)	9	13	0.166
Number of lesions (single)	39	30	0.245

AFP, Alpha foetoprotein; TACE, Transcatheter arterial chemoembolization.

TABLE 6 Basic characteristics of low-NLR subgroup.

Characteristic	Operating group ($n = 40$)	Operation + TACE group ($n = 42$)	P
Gender (male)	33	36	0.690
Hepatitis B history	35	36	0.813
Pre-operative liver function (A)	39	41	1.000
AFP (>400 μg/L)	12	8	0.248
Number of lesions (single)	37	33	0.074

AFP, Alpha foetoprotein; TACE, Transcatheter arterial chemoembolization.

TABLE 7 Basic characteristics of patients in terms of PA-TACE frequency in surgery plus PA-TACE group.

Characteristic	Operation + TACE group			After PSM		
	One-time ($n = 50$)	Two-time ($n = 31$)	P	One-time ($n = 31$)	Two-time ($n = 31$)	P
Age (>55)	20	12	0.908	13	12	0.796
Gender (male)	45	25	0.389	28	25	0.471
Hepatitis B history	47	26	0.270	29	26	0.422
Liver cirrhosis	27	18	0.720	15	18	0.445
Pre-operative liver function (A)	49	30	1.000	30	30	1.000
AFP (>400 μg/L)	17	4	0.035	8	4	0.199
Number of lesions (single)	41	22	0.246	26	22	0.224
MVI (>M1)	34	27	0.053	23	27	0.409

AFP, Alpha foetoprotein; MVI, microvascular invasion; PSM, Propensity score matching; TACE, Transcatheter arterial chemoembolization.

TABLE 8 Basic characteristics of patients in terms of PA-TACE frequency in high- and low-NLR subgroup of surgery plus PA-TACE group.

Characteristic	Low-NLR subgroup			High-NLR subgroup			Low-NLR subgroup (after PSM)		
	One-time ($n = 22$)	Two-time ($n = 20$)	P	One-time ($n = 28$)	Two-time ($n = 11$)	P	One-time ($n = 19$)	Two-time ($n = 19$)	P
Age (>55)	8	11	0.226	12	1	0.102	6	10	0.189
Gender (male)	20	16	0.570	25	9	0.924	17	15	0.656
Hepatitis B history	20	16	0.570	27	10	0.490	17	16	1.000
Liver cirrhosis	9	12	0.217	18	6	0.844	8	11	0.330
Pre-operative liver function (A)	21	20	1.000	28	10	0.282	18	19	1.000
AFP (>400 μg/L)	7	1	0.069	10	3	0.900	6	1	0.094
Number of lesions (single)	20	13	0.095	21	9	0.974	17	12	0.127
MVI (>M1)	12	17	0.033	22	10	0.660	12	16	0.141

AFP, Alpha foetoprotein; MVI, microvascular invasion; NLR, Neutrophil-to-lymphocyte ratio; PSM, Propensity score matching.

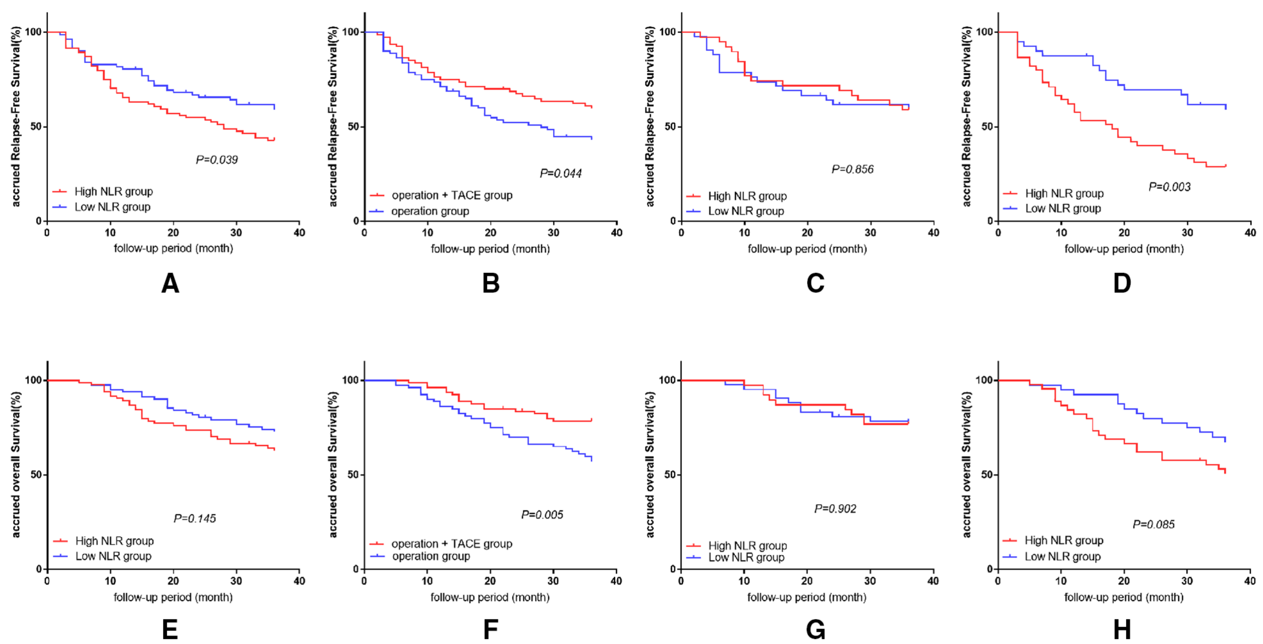

FIGURE 1
Results of survival analysis in every group and subgroup. (A) Effect of NLR level on RFS in patients after HCC treatment. (B) Effect of treatment methods on RFS after liver cancer surgery. (C) Comparison of RFS in patients with high and low NLR in surgery plus PA-TACE group. (D) Comparison of RFS in patients with high and low NLR in surgery-alone group. (E) Effect of NLR level on OS in patients after HCC treatment. (F) Effect of treatment methods on OS after liver cancer surgery. (G) Comparison of OS in patients with high and low NLR in surgery plus PA-TACE group. (H) Comparison of OS in patients with high and low NLR in surgery-alone group.

with the surgery-alone subgroup (RFS: 74.4%, 71.8%, and 59.0% vs. 57.8%, 40.0%, and 28.9%, respectively; $P = 0.004$; OS: 97.4%, 87.2%, and 76.9% vs. 82.2%, 62.2%, and 50.8%, respectively; $P = 0.012$; Figure 2). However, in the low-NLR group, there was no significant difference in RFS or OS between the surgery plus PA-TACE subgroup and surgery-alone subgroups at 1, 2, and 3 years (RFS: 73.8%, 61.7%, and 59.2% vs. 87.5%, 69.5%, and 59.1%, respectively; $P = 0.821$; OS: 95.2%, 80.9%, and 78.4% vs. 92.5%, 80.0%, and 67.3%, respectively; $P = 0.339$; Figure 3).

Multivariate analysis of recurrence and survival in patients with HCC after surgery

After PSM matching in the high-NLR group, multivariate analysis showed that a poorly differentiated or undifferentiated tumor was an independent risk factor for postoperative RFS, and multiple tumors was an independent risk factor for postoperative OS [hazard ratio (HR) = 2.10, $P =$ 0.011 and HR = 3.73, $P = 0.001$, respectively], while PA-TACE

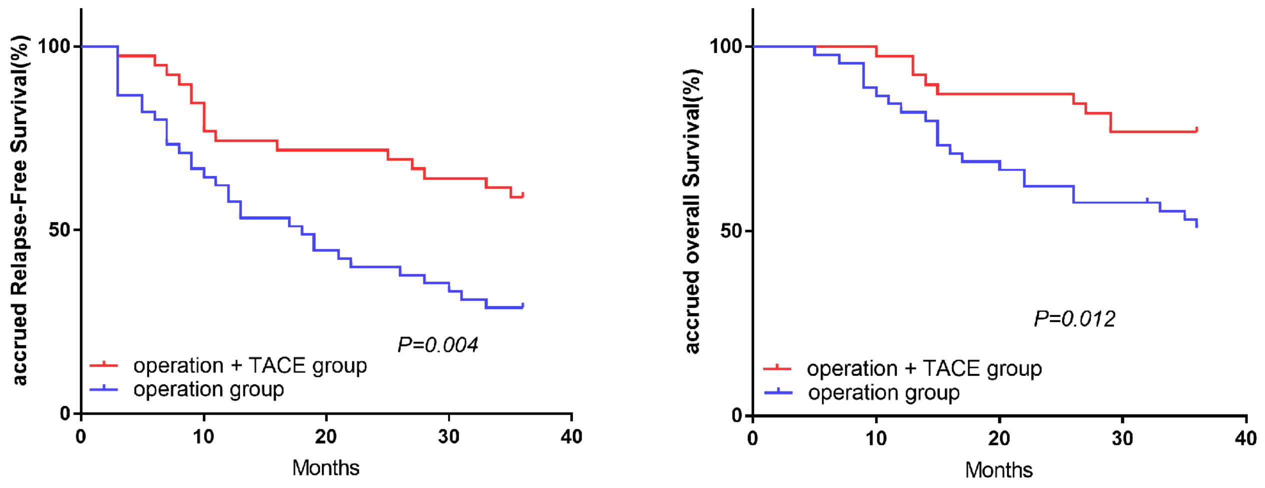

FIGURE 2
Effect of treatment methods on RFS and OS in high-NLR group.

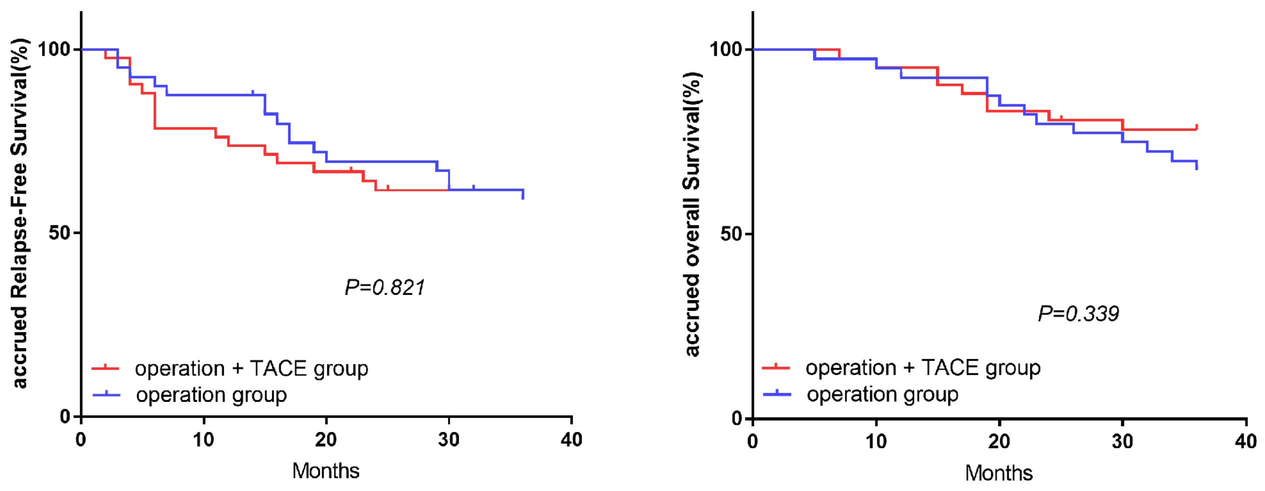

FIGURE 3
Effect of treatment methods on RFS and OS in low-NLR group.

was an independent protective factor for postoperative RFS and OS (HR = 0.46 and 0.32, $P = 0.012$ and 0.004, respectively). In the low-NLR group, AFP > 400 μg/L was an independent risk factor for postoperative RFS and OS (HR = 2.02 and 3.70, $P = 0.044$ and 0.003, respectively; **Table 9**).

Logistic regression analysis of correlation between high-risk factors for recurrence of liver cancer and NLR

Among several high-risk recurrence factors, such as AFP > 400 μg/L, multiple tumors, maximum tumor diameter >5 cm, and poorly differentiated tumors, multivariate logistic regression identified maximum tumor diameter >5 cm as being correlated with the NLR level. Patients with a maximum tumor diameter >5 cm were at increased risk of having high NLR levels compared with patients with a maximum tumor diameter <5 cm (OR = 5.12, 95% CI: 2.64–9.92, $P < 0.05$).

Effect of PA-TACE frequency on RFS in patients after HCC treatment

The OS-related survival analysis was not performed due to the small number of cases in each group and the disparity

TABLE 9 Multivariate analysis of recurrence and survival in patients with HCC after surgery.

Factors	High-NLR group				Low-NLR group			
	RFS		OS		RFS		OS	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Hepatitis B history	–	–	–	–	–	–	–	–
Liver cirrhosis	–	–	–	–	–	–	–	–
AFP (>400 μg/L)	–	–	–	–	–	–	3.23 (1.39–7.50)	0.006
Number of lesions (multiple)	–	–	3.73 (1.76–7.92)	0.001	–	–	–	–
Maximum diameter of lesions (>5 cm)	–	–	–	–	–	–	–	–
Method	0.46 (0.25–0.84)	0.012	0.32 (0.14–0.70)	0.004	–	–	–	–
Differential	2.10 (1.18–3.74)	0.011	–	–	–	–	–	–

AFP, Alpha foetoprotein; NLR, Neutrophil-to-lymphocyte ratio.

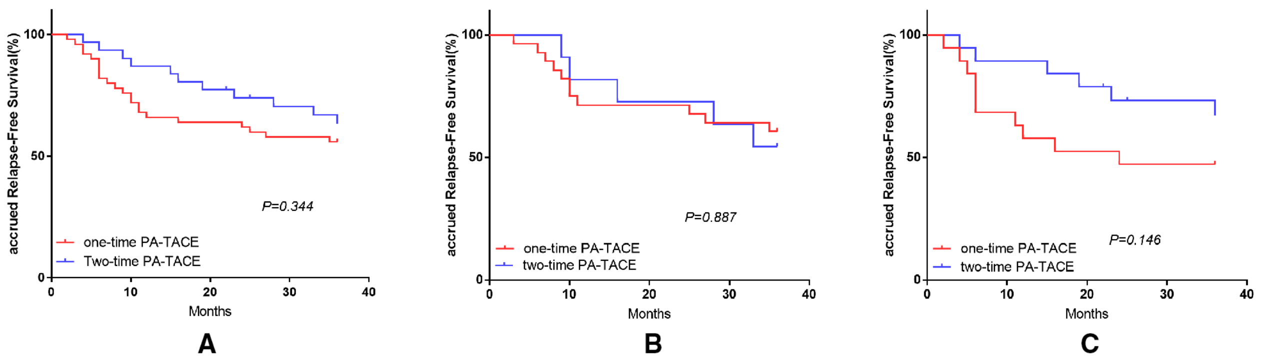

FIGURE 4
Effect of PA-TACE frequency on RFS in HCC patients in surgery plus PA-TACE group and its subgroups. (A) Comparison of RFS in patients with one-time and two-time PA-TACE in surgery plus PA-TACE group. (B) Comparison of RFS in patients with one-time and two-time PA-TACE in the high NLR subgroup. (C) Comparison of RFS in patients with one-time and two-time PA-TACE in the low NLR subgroup.

in the number of cases with OS endpoints between groups. Only survival analysis for RFS at 1, 2, and 3 years was performed. In the surgery plus PA-TACE group, there was no statistically significant difference in RFS at 1, 2, and 3 years between one- and two-time PA-TACE groups (66.0%, 62.0%, and 56% vs. 87.1%, 74.1%, and 63.5%, respectively; $P = 0.344$; **Figure 4A**). In the high- and low-NLR subgroups, there was no statistically significant difference in RFS at 1, 2, and 3 years between one- and two-time PA-TACE groups (High-NLR group: 71.4%, 67.9%, and 60.7% vs. 81.8%, 72.7%, and 54.5%, respectively; $P = 0.887$; Low-NLR group: 57.9%, 47.4%, and 47.4% vs. 89.5%, 73.3%, and 67.2%, respectively; $P = 0.146$; **Figures 4B,C**). In the low-NLR group, no statistically significant difference was found in 1, 2, and 3-year RFS among the surgery, one-time PA-TACE, and two-time PA-TACE groups (87.5%, 69.5%, and 59.1% vs. 57.9%, 47.4%, and 47.4% vs. 89.5%, 73.3%, and 67.2%, respectively; $P = 0.269$; **Figure 5**).

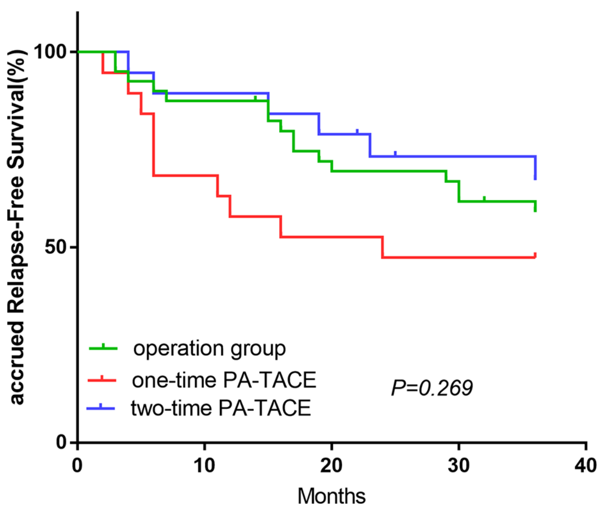

FIGURE 5
Comparison of operation and one- and two-time PA-TACE groups in low-NLR group.

Discussion

The high recurrence of tumors after radical hepatectomy means that postoperative adjuvant therapy plays a significant role in improving the patient prognosis. Yang et al. (16) showed that postoperative adjuvant treatments such as PA-TACE, radiotherapy, and sorafenib improved the prognosis of patients with microvascular invasion after surgery. Clinical research into the indications of PA-TACE after liver cancer surgery is currently focused mainly on postoperative tumor-related indicators such as MVI grade, tumor volume, tumor number, tumor differentiation, and Ki-67 (11, 17, 18). A few laboratory indicators, such as AFP, serum gamma-glutamyl transferase, and the ferritin/hemoglobin ratio, have also been related to prognosis (5, 18), but are not widely used. This has led clinicians to mainly use PA-TACE for patients with a high risk of recurrence (large tumor diameter, multiple tumors, MVI positive, and poor tumor differentiation) according to postoperative tumor-related indicators. The proportion of patients with a low risk of recurrence receiving PA-TACE is small, and the benefit of PA-TACE in these patients is unclear. Xie et al. (19) found that PA-TACE may benefit patients with a low risk of recurrence more than patients with a high risk of recurrence. However, a meta-analysis by Chen et al. (18) showed that PA-TACE did not improve the prognosis among patients with a tumor diameter ≤5 cm, single tumor, or MVI negative, and may even have promoted postoperative recurrence in some patients. We therefore aimed to address this controversy by examining the value of NLR for predicting the prognosis of patients with liver cancer treated with surgery combined with PA-TACE.

The relationship between NLR and cancer progression has been demonstrated in numerous studies (9, 20, 21), with a high NLR related to the recurrence and poor prognosis of HCC. The upregulation of inflammatory pathways in the body under a high NLR environment leads to more aggressive tumor behaviors (9, 20). One reason for the increase in NLR is an increase in neutrophils, which leads to an increased production of neutrophil-derived cytokines, such as vascular endothelial growth factor (VEGF), matrix metalloproteinases, and interleukin-18. VEGF promotes angiogenesis and matrix metalloproteinases exacerbate inflammation and exudation, while interleukin-18 damages the function of NK cells and T cells, thereby impairing the host's immune response to tumor antigens (22–24). A decrease in lymphocytes also increases the NLR and is another important factor in suppressing cell-mediated immunity (25), which mainly depends on lymphocytes. A large number of lymphocytes in the tumor site has been associated with a good prognosis, and a decrease in lymphocytes may lead to tumor cell immune escape, which is a predictor of poor prognosis (26, 27). At the same time, neutrophils can inhibit lymphocyte-mediated cell lysis, further aggravating the poor prognosis (28).

We conducted this retrospective study in 166 patients, and the 1, 2, and 3-year RFS and OS rates were all significantly better in the surgery plus PA-TACE group compared with the surgery-alone group. This was similar to the results of previous studies (29–31), and thus confirmed the effect of PA-TACE in patients with liver cancer. The 1, 2, and 3-year RFS rates were significantly better in the low-NLR compared with the high-NLR group. Although the 1, 2, and 3-year OS rates showed no significant difference between the low- and high-NLR groups, the survival curves suggested that the low-NLR group still had a better prognosis. Multivariate analysis of the subgroups showed that PA-TACE was an independent protective factor for postoperative RFS and OS among patients with a high NLR, but this effect did not apply to patients with a low NLR.

These differences between the subgroups were maintained after further stratification by the NLR level: the prognosis in the surgery plus PA-TACE group was significantly superior to that in the surgery-alone group in the high-NLR group, while the prognoses of the two subgroups were similar in the low-NLR group. After stratification by treatment, a low NLR was associated with a better prognosis than a high NLR in the surgery-alone group, and the difference in OS between the two subgroups was more obvious than the difference in OS between the high- and low-NLR groups. The prognoses of the patients with high and low NLRs treated with surgery plus PA-TACE were similar. Combined with the results of multivariate analysis, we speculated that the addition on PA-TACE had no significant effect on the prognosis of patients in the low-NLR group. Whether the prognosis deteriorated in the surgery plus PA-TACE subgroup or improved in the surgery-alone subgroup, the results indicated that PA-TACE cannot benefit patients with a relatively low NLR. This inference can also explain the lack of difference in prognosis between patients with high and low NLRs in the surgery plus PA-TACE group, if PA-TACE worsens the prognosis of patients in the low NLR subgroup. This difference may be due not only to a unilateral change in the low NLR subgroup, but also an improvement in the prognosis of the high NLR subgroup treated by surgery combined with PA-TACE.

In the study of PA-TACE frequency, we found no statistically significant difference in RFS at 1, 2, and 3 years between the two groups, which might indicate that for patients with HCC, undergoing PA-TACE one or two times has a similar impact on their prognosis. This effect was particularly pronounced in the high-NLR group, suggesting that for high-NLR patients with a high risk of recurrence, two-time PA-TACE may not lead to a better outcome. However, in the low-NLR group, although the 1, 2, and 3-year RFS of one- and two-time PA-TACE groups was also not statistically different, the two-time PA-TACE group showed a significant advantage, which was no longer present when compared to the surgery group.

We speculate that the reason for this phenomenon in the low-NLR environment is that the ratio of neutrophils to lymphocytes was lower under low NLR conditions, indicating that the anti-tumor effect (mediated by antitumor-associated lymphocytes, including CD8 + T (32, 33) and natural killer T cells (34–36)) in the tumor microenvironment is to a certain extent better than the tumor-promoting effect [mediated by the monocyte-macrophage system (37, 38)]. Multiple TACE procedures kill tumor cells and at the same time help to activate the anti-tumor immune response, so that the body maintains an imbalanced state in which the anti-cancer effect is superior to promoting cancer-promoting effect for a long time, which is beneficial to obtain a better RFS. However, due to the relative lack of quantity and quality in our patient data under this grouping, this result still needs to be further confirmed by prospective studies with large samples.

One of the main reasons for the recurrence of liver cancer within 2 years after surgery is the presence of invisible intrahepatic metastases before surgery, resulting in many radical operations failing to achieve a radical cure (17, 39). PA-TACE can combat the possible surviving tumor cells through high postoperative local perfusion of chemotherapeutic drugs and selective vascular embolization to prevent possible micrometastases and recurrence (19). However, the hypoxic environment after interventional embolization can also stimulate the expression of hypoxia-inducible factor-1α and VEGF, activate related signal pathways, induce angiogenesis, and form a microenvironment that is conducive to tumor growth, thus promoting tumor recurrence, growth, and metastasis (40). PA-TACE is thus currently used clinically for patients with a high risk of recurrence and high NLR. Under these circumstances, PA-TACE plays a largely positive role, as supported by the current research. However, in the absence of clinical consensus, the use of PA-TACE in patients with low NLR levels is controversial, and the present results suggested that PA-TACE may not benefit patients with a low NLR. This effect may occur because the cell-mediated immune response can still guarantee an anti-tumor effect under low-NLR conditions, while PA-TACE creates a suitable microenvironment for tumors, which instead leads to a poor prognosis. NLR may thus be used as an indicator to exclude patients who cannot benefit from PA-TACE.

After clarifying that patients with a lower NLR may not benefit from PA-TACE, we examined the relationships between several recognized high-risk recurrence factors of liver cancer and the NLR level by logistic regression. We found that a maximum tumor diameter >5 cm was the only factor correlated with a high NLR. However, the current study did not clarify the cause and effect relationship between these, and we therefore recommend PA-TACE treatment for patients with large liver tumors after surgery. Their highly malignant biological behavior means that it is very difficult to achieve radical resection of very large HCCs in an absolute sense, and residual tumor cells after surgery are almost inevitable. However, imaging and serological examinations showed that PA-TACE could destroy the remaining tumor cells and prevent or at least delay intrahepatic recurrence (29). The current study did not provide evidence to indicate that a lower NLR represented a low risk of recurrence, and we therefore cannot reach a conclusion on the benefit of PA-TACE in patients with a low risk of recurrence.

Our study had some limitations. First, it was a retrospective study with a limited number of cases in the subgroups. In addition, the relatively long follow-up interval was not conducive to accurate evaluation of RFS. We therefore anticipate the results of future multicenter, large-sample studies. Second, the differences in age and proportions of patients with liver cirrhosis between the subgroups when dividing patients treated with surgery and surgery plus PA-TACE in the high/low-NLR groups may have had an impact on our results. The proportions of patients over 55 years old and patients with liver cirrhosis were higher in the surgery-alone compared with the surgery plus PA-TACE subgroup. This may have been mainly because of considerations of patient safety, combined with clinical research evidence and treatment experience (41), given that PA-TACE is used cautiously in patients with severe preoperative cirrhosis, ascites before or after surgery, and poor postoperative physical condition. However, even if this tendency was similar in both pairs of subgroups, it may weaken our conclusions. Third, we did not summarize the most appropriate definitions of high NLR and low NLRs. There is currently no conclusive classification of the NLR, and the clinical definition and judgment of the NLR still relies on the experience of the doctors. We hope that future research can make further breakthroughs in this area.

Conclusion

This study analyzed the relationship between preoperative NLR levels and the efficacy of PA-TACE in HCC patients, and confirmed that patients with a lower NLR before surgery were unlikely to benefit from PA-TACE, while PA-TACE could improve the prognosis of patients with a higher NLR. We therefore do not recommend PA-TACE in patients with HCC with low preoperative NLR values.

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 Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

G-YF wrote the paper. Y-FZ, KC and JT followed up the patients and collected the clinical data. G-YF, X-FW and Z-RS analyzed the data. YC and Z-RS conceived and designed this study. YC and X-FW produced diagrams and provided suggestions for the study. YC was responsible for the whole 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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Relationship between postoperative nodal skip metastasis of mid-thoracic esophageal squamous cell carcinoma and patient prognosis and its value in guiding postoperative adjuvant treatment

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Objective: To evaluate the predictive role of nodal skip metastasis (NSM) in the prognosis of lymph node-positive mid-thoracic esophageal squamous cell carcinoma, and to evaluate the significance of postoperative adjuvant treatment in patients with different sites of metastatic nodes.

Methods: A retrospective analysis was performed on clinical data of 321 lymph node-positive mid-thoracic esophageal squamous cell carcinoma patients who underwent surgery in the Fourth Hospital of Hebei Medical University. Based on the site and condition of lymph node metastasis by postoperative pathology, the patients were divided into two groups: NSM group and non-NSM (NNSM) group. The propensity score matching (PSM) method was employed to match the two groups. The prognostic factors of patients before and after PSM as well as the effect of different adjuvant treatment modes on the prognosis of patients before and after PSM were analyzed. SPSS 29.0 statistical software was used for analysis.

Results: PSM in a 1:1 matching ratio was performed, 103 patients were assigned to NSM group and NNSM group respectively. Significant differences were found in the 3- and 5-year OS and DFS between the two groups before PSM, the 3- and 5-year OS also showed a significant difference after PSM ($P < 0.05$). Multivariate analysis illustrated that gender, postoperative adjuvant treatment mode, N stage and lymph node metastasis were independent risk factors for OS and DFS after PSM ($P < 0.05$); for NSM patients, postoperative adjuvant chemotherapy and radiotherapy significantly prolonged OS and DFS before and after PSM ($P < 0.05$). But no significant difference was found in OS and DFS for NNSM patients after PSM ($P > 0.05$).

Conclusion: Postoperative NSM is a good prognostic factor for patients with mid-thoracic esophageal squamous cell carcinoma, postoperative adjuvant chemoradiotherapy was recommended for those group, thereby gaining survival benefits.

KEYWORDS

esophageal neoplasms/esophageal cancer, mid-thoracic, squamous cell carcinoma, nodal skip metastasis, adjuvant treatment, prognosis

Introduction

Esophageal cancer is one of the most common malignant tumors of the digestive tract worldwide (1), whose mortality rate is higher than morbidity rate, regarded as one of the most refractory malignancies (2). According to its anatomical location, the incidence of mid-thoracic esophageal cancer is the highest, accounting for approximately 60% of all esophageal cancer patients (3). Due to the abundant longitudinal lymphatic networks and fewer transverse lymphatic networks in the esophagus, patients with esophageal cancer have a higher rate of nodal skip metastasis (NSM) in mid-thoracic esophagus compared with other sites (4, 5). NSM has demonstrated a favorable prognostic effect in some solid tumors (6, 7). In recent years, more research has focused on NSM in esophageal cancer, however, the results of its prognostic value in patients undergoing esophagectomy remain controversial (4, 8, 9). Therefore, it is urgent to analyze the effect of NSM on the postoperative prognosis of patients with esophageal cancer. In addition, postoperative adjuvant treatment still remains one of the most common treatment approaches for patients undergoing esophagectomy in China, which has a significance prognostic effect, especially for lymph node-positive esophageal cancer patients after surgery (10, 11). However, due to the lack of robust evidence from perspective evidence-based medicine, currently, there has been no consensus on the value of postoperative adjuvant treatment in patients undergoing esophagectomy. In order to further clarify the prognostic value of NSM in patients with thoracic esophageal cancer after esophagectomy, and to analyze the impact of different postoperative adjuvant treatments on the prognosis of patients with different sites of metastatic nodes, we analyzed clinical and pathological data of 321 consecutive patients with positive lymph nodes undergoing surgery for mid-thoracic esophageal squamous cell carcinoma (MT-ESCC).

Materials and methods

(1) Inclusion criteria: Patients undergoing radical surgery for esophageal cancer at the Fourth Hospital of Hebei Medical University; pathologically confirmed node-positive squamous cell carcinoma; patients with stage pT0-4bN1-3M0 MT-ESCC, according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for esophageal cancer (12); no neoadjuvant therapy before surgery; KPS ≥ 70. The exclusion criteria mainly included patients who died during the perioperative period; those with second primary malignancy; the number of lymph nodes dissected <12; and patients with incomplete medical records and follow-up data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the the Forth hospital of Hebei Medical University and Institute. Individual consent for this retrospective analysis was waived.

(2) Clinical medical records: In total, 321 consecutive MT-ESCC patients who experienced lymph node metastasis after surgery in our hospital from January 2013 to December 2015 and met the inclusion criteria were enrolled in this study. All patients were grouped according to the site of metastatic nodes (**Figure 1**).

(3) Surgical methods: Before 2015, the surgical treatments for esophageal cancer in Department of Thoracic Surgery of our hospital practically involved oesophagectomy and two-field lymphadenectomy *via* left thoracotomy (Sweet surgery). Afterwards, the Sweet surgery was replaced by minimally invasive McKeown procedure combined with three-field lymphadenectomy as well as Ivor-Lewis surgery combined with two-field lymphadenectomy. In this study, 183 patients underwent Sweet surgery, and 46 and 92 patients underwent minimally invasive McKeown procedure and Ivor-Lewis surgery, respectively.

(4) Definition of the site of metastatic nodes: Lymph nodes were divided into three regions: cervical, thoracic mediastinal, and abdominal regions based on the Japan Esophageal Society (JES) criterion (13). NSM was defined as lymph node metastasis in the abdominal or supraclavicular region, and no metastasis in the thoracic mediastinal region; no-nodal skip metastasis (NNSM) was defined as lymph node metastasis in the thoracic mediastinum region and/or in the abdominal and cervical region (**Figure 1**).

(5) Postoperative adjuvant treatment mode: Postoperative adjuvant treatment modes in this study was selected primarily based on surgical pathology, oncologists or the hospital where the patients were treated. There were 104, 129 and 88 patients who receive non-adjuvant treatment, postoperative chemotherapy (POCT) and postoperative radiotherapy and chemotherapy (POCRT), respectively.

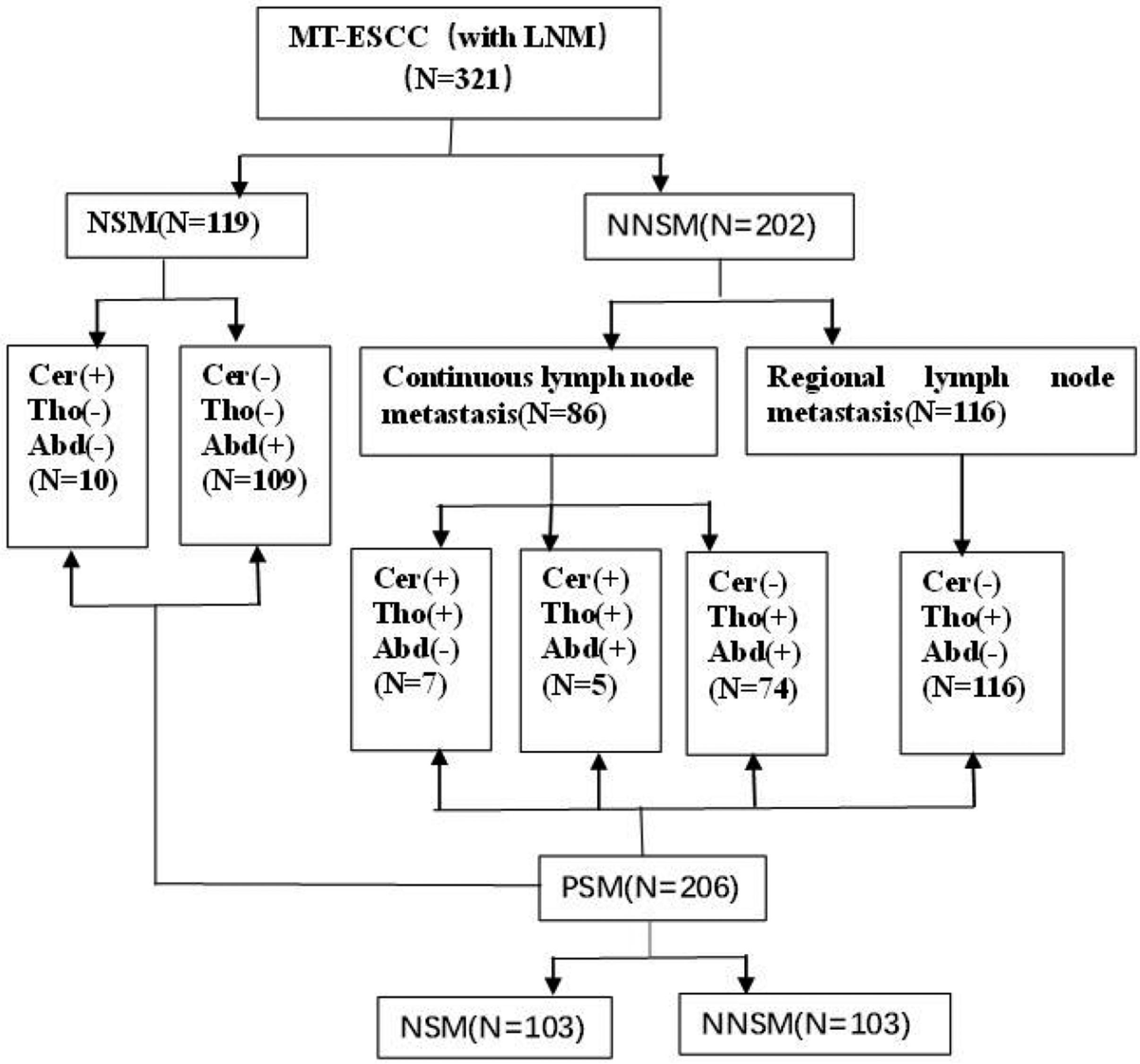

FIGURE 1
Overview of patient selection and grouping. Note: Cer: cervical; Tho: thoracic; Abd: abdominal; LNM: lymph node metastasis; MT-ESCC: mid-thoracic esophageal squamous cell cancer; NSM: nodal skip metastasis; NNSM: no-nodal skip metastasis; PSM: propensity score matching.

The interval between postoperative radiotherapy and surgery was 3–6 weeks, and the interval between the first cycle of chemotherapy and surgery was 2–4 weeks.

The target area of radiotherapy was mainly the postoperative tumor bed and the corresponding lymph node drainage area of different lesions. The prescribed dose was 45–50.4 Gy/25–28 times, 5 times per week and 1.8–2.0 Gy/time, and all were treated with intensity-modulated radiation therapy. Chemotherapy regimens were mainly platinum-based chemotherapy combined with paclitaxel or 5-fluorouracil. Chemotherapy was conducted for 4–6 cycles, with a median of 4 cycles for patients undergoing chemotherapy alone, and 3–6 cycles with a median of 4 cycles for those undergoing chemotherapy combined radiotherapy.

(6) Follow-up: They were followed up by outpatient visits every 3 months for the first 2 years after surgery, every 6–8 months for the next 3–5 years, and at least every 12 months thereafter. Patients who could not afford regular follow-up visits were followed up by telephone. The deadline for follow-up was December 31, 2020, and 3 cases were lost to follow-up, with a follow-up rate of 99.1%. Survival time was recorded from the date of surgery.
(7) Statistical analysis: SPSS 25.0 statistical software was employed for statistical analysis. Measurement data were analyzed by χ^2 or Fisher's exact test. Categorical variables

were reported as frequency and percentage. Kaplan–Meier method was used to draw survival curve, and Log-Rank test was used to assess the significance of influencing the overall survival (OS) of patients. Cox multivariate analysis and collinearity analysis were performed to explore the independent risk factors of patients' OS. Propensity score matching (PSM) method (1 : 1 matching ratio) was used for matching with the variables with different composition ratios of patients grouped according to different sites of metastatic nodes between the two groups, to eliminate the bias by balancing the observable potential confounding factors. $P < 0.05$ indicated that the difference was statistically significant.

Results

(1) The analysis results of the composition ratio of general clinical and pathological indicators in patients with different sites of metastatic nodes

There were significant differences in the composition ratios of the three indicators, T stage, N stage and TNM stage, between the NSM group and NNSM group ($P < 0.05$) (**Table 1**).

(2) PSM analysis results of patients with different sites of metastatic nodes

Three indicators, T stage, N stage and TNM stage were entered into the logistic binary regression model and collinearity analysis to explore the independent risk factors for NSM patients' OS. The results of collinearity analysis showed that VIF values were all less than 2 (**Table 2**), so collinearity between T, N and TNM stages was excluded. The results indicated that T stage and N stage were independent risk factors ($P < 0.05$) (**Table 3**).

With NSM as the treatment group and NNSM as the control group, and with T stage and N stage as covariates, PSM was conducted with a 1 : 1 matching ratio. The number of patients was found to be 103 in NSM group and NNSM group respectively. No significant difference was noted in the composition ratio of general clinical and pathological data after PSM between the two groups ($P > 0.05$) (**Table 1**).

(3) Analysis results of the effect of different sites of metastatic nodes on the prognosis of patients

The 3- and 5-year OS rates of patients before and after PSM were 34.9%, 26.5%, and 37.4%, 29.1%, respectively, with a median OS of 27.6 months (95% CI: 24.9–30.3) and 29.0 months (95% CI: 25.8–32.2) respectively. DFS rates were 26.5%, 21.2% and 29.6%, 22.8%, respectively, with a median DFS of 18.0 months (95% CI: 15.1–20.9) and 19.0 months (95% CI: 15.9–22.1) respectively. Univariate analysis showed significant differences in OS and DFS among patients in the NSM and NNSM groups before PSM. After PSM, OS still show significant different, but no significant difference was detected in DFS after PSM (**Table 4**, **Figure 2**).

The potential prognostic factors of patients were entered into the COX multivariate regression model. The results showed that gender, age, N stage, site of metastatic nodes and postoperative adjuvant treatment mode were independent risk factors affecting OS of 321 patients before PSM ($P < 0.05$). Gender, age, N stage and postoperative adjuvant treatment mode were independent risk factors that affected their DFS ($P < 0.05$). Gender, N stage, site of metastatic nodes, and postoperative adjuvant treatment mode were independent risk factors for OS of 206 patients after PSM ($P < 0.05$), while gender and postoperative adjuvant treatment mode were independent risk factors that affected their DFS ($P < 0.05$) (**Table 5**).

(4) Analysis of different postoperative adjuvant treatment modes for patients with different sites of metastatic nodes before and after PSM

The results showed that POCRT showed good efficacy in 321 patients before PSM regardless of their metastatic nodes status ($P < 0.05$) (**Table 6**). POCRT also had significant clinical benefits including prolongation of OS and DFS of patients in the NSM group after PSM ($P < 0.05$), while patients in the NNSM group tended to gain survival benefit from postoperative adjuvant treatment,though OS and DFS did not reacht significant different ($P > 0.05$) (**Table 7**, **Figure 3**).

(5) Failure mode

Of 321 patients, 146 cases (45.5%) had local regional recurrence, 104 cases (32.4%) had distant metastasis, and 49 cases (15.3%) had local recurrence and distant metastasis until the date of last follow-up. There were 57 (47.9%) and 89 (44.1%) patients with recurrence in the NSM and NNSM groups, respectively, suggesting no significant difference between the two ($X^2 = 0.445$, $P = 0.505$), in addition to (30.3%) and 68 (33.7%) with distant metastases respectively, suggesting no significant difference ($X^2 = 0.398$, $P = 0.528$).

After PSM, among the 206 patients, 95 cases (46.1%) had local regional recurrence, 65 cases (31.6%) had distant metastasis, and 31 cases (15.0%) had local regional recurrence and distant metastasis. There were 49 (47.6%) and 46 (44.7%) patients with recurrence in the NSM and NNSM groups, respectively, suggesting no significant difference ($X^2 = 0.176$, $P = 0.675$); distant metastases were found in 31 patients (30.1%) and 34 cases (33.0%) respectively, suggesting no significant difference ($X^2 = 0.202$, $P = 0.653$).

TABLE 1 Analysis results of the composition ratio of general clinical and pathological indicators of patients before and after PSM.

Variable	Before PSM (%)		X^2	P	After PSM (%)		X^2	P
	NSM	NNSM			NSM	NNSM		
Gender			0.050	0.822			0.060	0.745
Male	90 (75.6)	155 (76.7)			77 (74.8)	79 (76.7)		
Female	29 (24.4)	47 (23.3)			26 (25.2)	24 (23.3)		
Age			1.277	0.258			0.178	0.673
<60 years	63 (52.9)	120 (59.4)			57 (55.3)	60 (58.3)		
≥60 years	56 (47.1)	82 (40.6)			46 (44.7)	43 (41.7)		
KPS			0.322	0.570			0.072	0.789
70	110 (92.4)	190 (94.1)			95 (92.2)	96 (93.2)		
≥80	9 (7.6)	12 (5.9)			8 (7.8)	7 (6.8)		
Lesion length			1.751	0.186			0.020	0.888
≤5.0 cm	69 (57.1)	100 (49.5)			58 (56.3)	57 (55.3)		
>5.0 cm	51 (42.9)	102 (50.5)			45 (43.7)	46 (44.7)		
Degree of differentiation		0.563	0.453			1.040	0.308	
Non/poorly-differentiated	24 (20.2)	34 (16.8)			19 (18.4)	25 (24.3)		
Moderately/well-differentiated	95 (79.8)	168 (83.2)			84 (81.6)	78 (75.7)		
T stage			13.891	0.000			0.036	0.849
T1 + T2	33 (27.7)	23 (11.4)			17 (16.5)	16 (15.5)		
T3 + T4	86 (72.3)	179 (88.8)			86 (83.5)	87 (84.5)		
N stage			26.565	0.000			0.033	0.856
N1	101 (84.9)	115 (56.9)			85 (82.5)	84 (81.6)		
N2 + N3	18 (15.1)	87 (43.1)			18 (17.5)	19 (18.4)		
TNM			6.006	0.014			0.116	0.733
II	9 (7.6)	4 (2.0)			5 (4.9)	4 (3.9)		
III + IVa	110 (92.4)	198 (98.0)			98 (95.1)	99 (96.1)		
Vascular tumor thrombus		0.575	0.448			0.739	0.390	
No	110 (92.4)	191 (94.6)			95 (92.2)	98 (95.1)		
Yes	9 (7.6)	11 (5.4)			8 (7.8)	5 (4.9)		
No. of lymph node dissected		0.731	0.392			0.513	0.474	
≤21	42 (35.3)	81 (40.1)			37 (35.9)	42 (40.8)		
≥22	77 (64.7)	121 (59.9)			66 (64.1)	61 (59.2)		
Postoperative adjuvant treatment		1.594	0.451			5.110	0.078	
Non-adjuvant treatment	43 (36.1)	61 (30.2)			37 (35.9)	29 (28.2)		
POCRT	33 (27.7)	55 (27.2)			30 (29.1)	22 (21.4)		
POCT	43 (36.1)	86 (42.6)			36 (35.0)	52 (50.5)		

Note: PSM, propensity score matching; KPS, Karnofsky score; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy; POCRT, postoperative radiotherapy and chemotherapy; NSM, nodal skip metastasis; NNSM, no-nodal skip metastasis.

TABLE 2 Collinear analysis of T, N and TNM stage.

model	Unnormalized coefficient		Normalization Coefficient	t	P	Collinear statistics	
	B	Error of standard	Beta			Tolerance	VIF
constant	0.940	0.422		2.226	0.027		
T stage	0.137	0.060	0.163	2.294	0.022	0.560	1.784
N stage	0.275	0.055	0.267	4.969	0.000	0.977	1.024
TNM stage	0–0.022	0.174	−0.009	−0.128	0.899	0.559	1.788

TABLE 3 Results of logistic binary regression analysis of factors affecting NSM.

Indicator	Regression coefficient	Standard error	χ^2	P value	OR	95% CI	
						Lower limit	Upper limit
T stage	0.916	0.348	6.910	0.009	2.499	1.262	4.948
N stage	1.366	0.298	21.059	0.000	3.921	2.187	7.027
TNM stage	0.227	0.685	0.109	0.741	1.254	0.328	4.802

TABLE 4 Analysis results of prognosis of patients with different sites of metastatic nodes before and after PSM.

Grouping	Before PSM						After PSM					
	OS (%, month)			DFS (%, month)			OS (%, month)			DFS (%, month)		
	3-years	5-years	Median	3-years	5-years	Median	3-years	5-years	Median	3-years	5-years	Median
NSM	45.4	35.3	33.0	33.6	28.6	20.4	42.7	34.0	31.4	32.0	26.2	19.7
NNSM	28.7	21.3	25.0	22.3	16.8	16.0	32.0	24.3	27.6	27.2	19.4	18.4
X^2	10.925			6.601			3.911			1.405		
P	0.001			0.010			0.048			0.236		

Note: PSM, propensity score matching; NSM, nodal skip metastasis; NNSM, no-nodal skip metastasis; PSM, propensity score matching.

Discussion

Lymph node metastasis is one of the poor prognostic indicators for patients with esophageal cancer after esophagectomy. The number of positive lymph nodes has been included in N stage by AJCC staging system for esophageal cancer, and is widely recognized and applied by clinicians as an important prognostic factor for patients undergoing esophagectomy (14). However, another important prognostic factor, the distribution of positive lymph nodes, has not been included, but valued by the JES TNM staging for esophageal cancer (13). In clinical practice, the significance of site of positive metastatic nodes in the prognosis of esophageal cancer patients has not attracted sufficient attention. This is related to the insufficient clinical research on site of metastatic nodes in esophageal cancer patients and the inconsistent research conclusions. In this study, we analyzed the mid-thoracic esophageal cancer which had the highest incidence in esophageal cancer and the highest incidence rate of NSM. A retrospective analysis of 321 MT-ESCC patients in this study suggested that patients with different sites of metastatic nodes had different prognosis. Among them, the prognosis of patients in the NSM group was significantly better than that of the NNSM group, and the site of metastatic nodes was one of the independent risk factors for predicting the prognosis of patients. This was similar to the results of Xu et al. (8) in which the clinical data of 300 MT-ESCC patients with lymph node metastasis were retrospectively studied, including 66 cases (22.0%) in the NSM group. The study showed that the prognosis of patients before and after PSM was better in the NSM group than in the NNSM group (Before PSM, 3-year OS was 62.1% vs. 34.1%, $P < 0.001$; after PSM, 3-year OS was 66.7% vs. 40.0%, $P = 0.025$). Subsequent multivariate analysis revealed that NSM was independent factors responsible for OS benefit in MT-ESCC patients. However, several studies reported that NSM

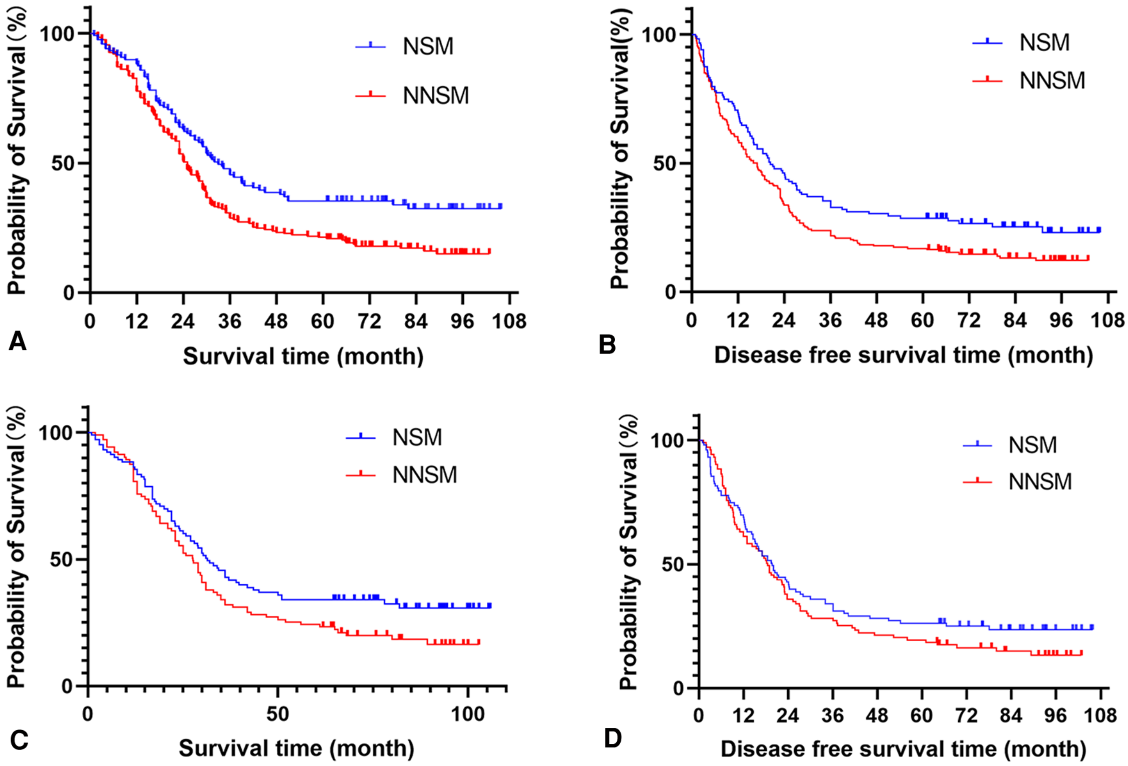

FIGURE 2
Analyse of patients survival and disease free survival time according the lymph node metastases status. (A) Survival analysis of all cohorts before propensity score matching. (B) Disease free survival analysis of all cohorts before propensity score matching. (C) Survival analysis of all cohorts after propensity score matching. (D) Disease free survival analysis of all cohorts after propensity score matching. Note: NSM: nodal skip metastasis; NNSM: no-nodal skip metastasis.

cannot be used to predict the prognosis of patients undergoing esophagectomy. For example, Zhu et al. (15) retrospectively analyzed 207 patients undergoing esophagectomy for esophageal cancer, including 58 patients (26%) who developed NSM. The median OS of those patients was 30 months, and the 3- and 5-year OS rates were 42.3% and 36.7%, respectively. NSM was not a significant prognostic factor for all patients in the whole group or those with mid-thoracic esophageal cancer ($n = 131$) ($P = 0.767$, 0.864). The results of this study showed that NSM was a significant prognostic factor for prolongation of OS and DFS in the NSM group before and after PSM, as compared with NNSM group, but DFS did not show a significant survival benefit after PSM in the NSM group. This might be related to the small proportion of patients in NSM group at the earlier T stage and N stage after PSM.

Given that the mechanism of lymph node metastasis may be related to the lymphatic drainage, micrometastasis and the biological behavior of tumor cells at the anatomical location of the tumor, the favorable prognosis of NSM patients may be related to the following factors. First, in this study, the grouping of 321 patients before PSM showed that the proportion of patients at the earlier T stage and N stage was higher in the NSM group than in the NNSM group, which was similar to many previous related studies (4, 8, 9, 16–18). Second, the number of sites of metastatic nodes also affected the prognosis of patients undergoing surgery for esophageal cancer (19). In this study, lymph node metastasis was detected in merely one region in the NSM group was one, while 42.6% (86/202) of patients in the NNSM group had lymph node metastasis in 2–3 regions. Third, tumor biological factors were involved in the occurrence and development of NSM, and the biological characteristics of tumors might play an essential role in the skip metastasis in tumor cells, leading to relatively lower malignancy of tumor cells in NSM patients, thereby contributing to better prognosis (20, 21).

Neoadjuvant chemoradiotherapy is currently the recommended treatment plan for patients with locally advanced esophageal cancer. However, due to various reasons, most centers in China have provided postoperative adjuvant treatment, especially in the adjuvant treatment mode of esophageal cancer in the past few years. Due to the lack of robust evidence from the perspective of evidence-based medicine, postoperative adjuvant therapy of esophageal cancer has currently not been recommended in relevant treatment guidelines for esophageal cancer. However, it has been widely accepted by most clinicians that postoperative adjuvant

TABLE 5 Results of multivariate analysis of influencing factors of OS and DFS of patients before and after PSM.

Variable	Multivariate analysis results of influencing factors of DFS				Multivariate analysis results of influencing factors of OS			
	Before PSM ($N = 321$)		After PSM ($N = 206$)		Before PSM ($N = 321$)		After PSM ($N = 206$)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender								
Male	Reference value		Reference value		Reference value		Reference value	
Female	1.409 (1.041–1.908)	0.027	1.607 (1.087–2.378)	0.017	1.416 (1.038–1.932)	0.028	1.522 (1.012–2.290)	0.044
Age								
<60 years	Reference value		Reference value		Reference value		Reference value	
≥60 years	0.770 (0.598–0.993)	0.044	0.922 (0.671–1.268)	0.619	0.747 (0.577–0.967)	0.027	0.845 (0.610–1.172)	0.313
KPS								
70	Reference value		Reference value		Reference value		Reference value	
≥80	0.647 (0.398–1.054	0.080	0.720 (0.395–1.313)	0.284	0.703 (0.427–1.156)	0.165	0.820 (0.443–1.519)	0.529
Lesion length								
≤5.0 cm	Reference value		Reference value		Reference value		Reference value	
>5.0 cm	1.145 (0.892–1.471)	0.288	1.341 (0.976–1.843)	0.070	1.163 (0.898–1.507)	0.252	1.183 (0.0850–1.646)	0.319
Degree of differentiation								
Non/poorly-differentiated	Reference value		Reference value		Reference value		Reference value	
Moderately/well-differentiated	0.981 (0.711–1.353)	0.905	0.888 (0.603–1.307)	0.547	0.887 (0.631–1.247)	0.490	0.0748 (0.496–1.126)	0.164
T stage								
T1 + T2	Reference value		Reference value		Reference value		Reference value	
T3 + T4	0.838 (0.566–1.242)	0.380	0.667 (0.392–1.133)	0.134	0.0808 (0.539–1.213)	0.304	.0673 (0.382–1.187)	0.171
N stage								
N1	Reference value		Reference value		Reference value		Reference value	
N2 + N3	0.512 (0.391–0.670)	0.000	0.695 (0.464–1.042)	0.078	0.0481 (0.365–0.634)	0.000	0.569 (0.378–0.858)	0.007
TNM stage								
II	Reference value		Reference value		Reference value		Reference value	
III + IVa	0.643 (0.293–1.413)	0.272	0.554 (0.200–1.535)	0.256	0.655 (0.284–1.513)	0.322	.0674 (0.238–1.910)	0.457
Vascular tumor thrombus								
No	Reference value		Reference value		Reference value		Reference value	
Yes	1.091 (0.656–1.814)	0.737	1.277 (0.652–2.503)	0.476	1.126 (0.648–1.958)	0.674	1.004 (0.493–2.046)	0.991
No. of lymph node dissected								
≤21	Reference value		Reference value		Reference value		Reference value	
≥22	1.116 (0.865–1.440)	0.399	0.996 (0.720–1.376)	0.979	1.134 (0.872–1.475)	0.349	1.251 (0.891–1.758)	0.196
Site of metastatic nodes								
NSM	Reference value		Reference value		Reference value		Reference value	
NNSM	0.818 (0.626–1.070)	0.143	0.837 (0.610–1.151)	0.274	0.749 (0.565–0.0994)	0.045	0.700 (0.505–0.971)	0.033

(*continued*)

TABLE 5 Continued

Variable	Multivariate analysis results of influencing factors of DFS				Multivariate analysis results of influencing factors of OS			
	Before PSM ($N = 321$)		After PSM ($N = 206$)		Before PSM ($N = 321$)		After PSM ($N = 206$)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Postoperative adjuvant treatment								
Non-adjuvant treatment	Reference value		Reference value		Reference value		Reference value	
POCRT	0.937 (0.703–1.248)	0.656	0.922 (0.644–1.318)	0.656	1.253 (0.935–1.678)	0.131	1.225 (0.850–1.765)	0.277
POCT	0.584 (0.424–0.805)	0.001	0.509 (0.333–0.777)	0.002	0.648 (0.465–0.901)	0.010	0.0580 (0.373–0.900)	0.015

Note: PSM, propensity score matching; NSM, nodal skip metastasis; NNSM, no-nodal skip metastasis; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy; POCRT, postoperative radiotherapy and chemotherapy.

TABLE 6 Effect of different postoperative adjuvant treatment modes on the prognosis of patients with different sites of metastatic nodes before PSM.

Treatment mode	*N*	OS (%, month)			X^2	*P*	DFS (%, month)			X^2	*P*
		3-years	5-years	median			3-years	5-years	median		
NSM					6.711	0.035				5.651	0.049
Non-adjuvant treatment	43	32.6	25.6	25.0			27.9	20.9	18.5		
POCRT	33	54.5	51.5	–			51.5	48.5	39.0		
POCT	43	51.2	32.6	37.0			25.6	20.9	20.4		
NNSM					9.893	0.007				6.413	0.040
Non-adjuvant treatment	61	18.0	14.8	19.0			16.4	14.8	14.0		
POCRT	55	40.0	29.1	30.0			30.9	25.5	23.1		
POCT	86	29.1	20.9	23.0			20.9	12.8	13.3		

NSM, nodal skip metastasis; NNSM, no-nodal skip metastasis; PSM, propensity score matching; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy; POCRT, postoperative radiotherapy and chemotherapy.

TABLE 7 Effect of different postoperative adjuvant treatment modes on the prognosis of patients with different sites of metastatic nodes after PSM.

Treatment mode	*N*	OS (%, month)			X^2	*P*	DFS (%, month)			X^2	*P*
		3-years	5-years	median			3-years	5-years	median		
NSM					6.188	0.045				6.257	0.041
Non-adjuvant treatment	38	31.6	26.3	23.9			34.2	21.1	18.5		
POCRT	30	53.3	50.3	39.0			50.0	46.7	27.3		
POCT	35	45.7	31.4	33.0			20.0	14.3	16.1		
NNSM					5.164	0.076				5.453	0.065
Non-adjuvant treatment	28	25.0	17.9	19.0			21.4	17.9	16.0		
POCRT	22	45.5	40.9	35.0			36.4	31.8	25.3		
POCT	53	30.2	20.8	25.0			26.4	15.1	14.3		

NSM, nodal skip metastasis; NNSM, no-nodal skip metastasis; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy; POCRT, postoperative radiotherapy and chemotherapy.

treatment provides survival benefit for patients with lymph node-positive esophageal cancer. However, the individuals who do gain benefit from adjuvant therapy after esophageal cancer surgery need to be further explored. In this study, we analyzed the efficacy and prognosis of different postoperative adjuvant treatment options for patients with different sites of

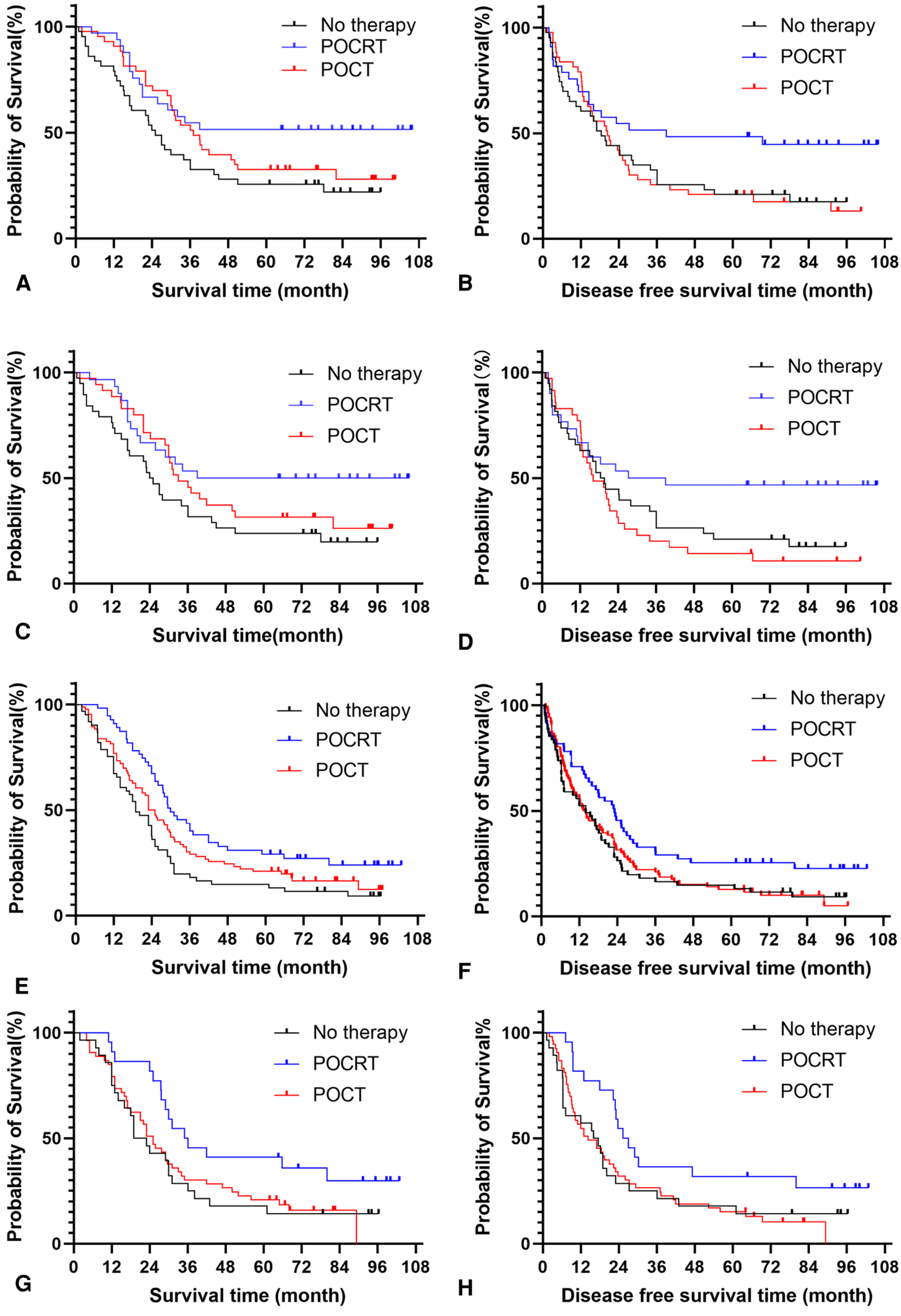

FIGURE 3
Analysis of postoperative adjuvant treatment modes for patients with different sites of metastatic nodes before and after propensity score matching. (A) Survival analysis of NSM patients before propensity score matching. (B) Disease free survival analysis of NSM patients before propensity score matching. (C) Survival analysis of NSM patients after propensity score matching. (D) Disease free survival analysis of NSM patients after propensity score matching. (E) Survival analysis of NNSM patients before propensity score matching. (F) Disease free survival analysis of NNSM patients before propensity score matching. (G) Survival analysis of NNSM patients after propensity score matching. (H) Disease free survival analysis of NNSM patients after propensity score matching. Note: NSM: nodal skip metastasis; NNSM: no-nodal skip metastasis; PORT: postoperative radiotherapy; POCT: postoperative chemotherapy; POCRT: postoperative radiotherapy and chemotherapy.

metastatic nodes. The results showed that POCRT promoted survival benefits, specifically prolongation of OS, in the NSM group. Among 2,285 patients undergoing surgery for esophageal cancer in a study, Shang et al. (4) divided 1,137 with lymph node metastasis into NSM group ($n = 156$), local lymph node metastasis (LNM) group ($n = 665$) and mediastinal lymph node metastasis (MNM) group ($n = 316$). Several patients received adjuvant POCRT. The results suggested that the prognosis of patients was significantly better in the LNM group than in the MNM group after adjuvant therapy ($P < 0.05$), but significantly worse in the LNM group than in the NSM group, showing no significant difference ($P > 0.05$). This study was different from our study, in which the patients were grouped in a Chinese fashion. Specifically, the former had subdivision of NSM, while the latter did not make subdivision of local lymph nodes and non-local lymph nodes. In this study, postoperative adjuvant treatment did not provide benefit in DFS of patients in the NNSM group after PSM. One of the reasons might be that there were >2 regions of lymph node metastasis in the NNSM group, which led to poor inherence in the prognosis in this group. The second reason is that in this retrospective study, the postoperative adjuvant treatment schemes were diverse for patients, which might affect the efficacy. This study had a small sample size, which might also affect the results of the study to a certain extent. In addition, other studies on postoperative adjuvant therapy have also confirmed that postoperative adjuvant treatment could improve the patient's OS, but could not increase DFS significantly (12).

This study has several limitations. First, this study is a retrospective study, which is not as convincing as a prospective study. Second, the conclusions of this single-center study cannot be generalized to all diagnosis and treatment centers for esophageal cancer. Third, to elucidate the predictive effect of NSM on patients undergoing esophageal cancer surgery, only patients with mid-thoracic esophageal cancer were enrolled in this study, and the remaining esophageal sites were excluded. This may have introduced inevitable selection bias. Fourth, a small sample size in this study may affect the results of the study to a certain extent. In addition, some patients in this study received Sweet surgery, which led to limited scope of neck lymph node dissection. However, PSM analysis was performed in this study to minimize the bias by balancing the potential confounding factors in the study. Moreover, in this study, we found that these patients with NSM after esophageal cancer surgery might have special prognosis. An issue that should arouse great concern is whether the current defining of N stage in the postoperative TNM staging of esophageal cancer with the number of lymph nodes is applicable in clinical practice? In addition, patients with lymph node metastasis may receive different postoperative adjuvant treatments, and the survival benefits from postoperative adjuvant treatments may vary from person to person. All these need further exploration and in-depth study in clinical practice.

In conclusion, NSM is a good prognostic factor for patients receiving surgery for MT-ESCC. It is recommended that MT-ESCC patients with NSM after esophagectomy undergo postoperative adjuvant chemoradiotherapy, thereby gaining survival benefits,. The final conclusion needs to be confirmed by multi-center, prospective, randomized controlled studies.

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 the Forth hospital of Hebei Medical University and Institute. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

(I) Conception and design: HMG; (II) Administrative support: WBS; (III) Provision of study materials or patients: YML; (IV) Collection and assembly of data: HMG, XHZ, SGL; (V) Data analysis and interpretation: WBS, HMG, XHZ, SCZ; (VI) Manuscript writing: All authors. (VII) All authors contributed to the article and approved the submitted version.

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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Simultaneous bilateral laparoscopic cortical-sparing adrenalectomy for bilateral pheochromocytomas in multiple endocrine neoplasia type 2

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Purpose: This study aimed to assess the feasibility of synchronous bilateral laparoscopic or open cortical-sparing adrenalectomy (SB-LCSA or SB-OCSA) for bilateral pheochromocytomas (bPHEOs) in multiple endocrine neoplasia type 2 (MEN2).
Methods: Altogether, 31 patients (54.8% were women) were diagnosed with MEN2-related bPHEOs, and 29 of them underwent varying specific adrenalectomies. We systematically analyzed and evaluated their clinical profiles, mutation types, tumor histopathological features, and follow-up records.
Results: All 31 patients with bPHEOs presented with *RET*-C634 (90.3%) and *RET*-M918T (9.7%) mutations, and the median age at initial presentation was 38 years (range, 23–78). bPHEOs were synchronous in 27 patients and metachronous in 4 (12.9%) patients. In total, 29 patients underwent initial cortical-sparing adrenalectomy (CSA) including 23 (79.3%) undergoing synchronous bilateral CSA (18 SB-LCSA and 5 SB-OCSA) and 6 (20.7%) undergoing metachronous CSA. SB-LCSA and synchronous surgery were associated with less bleeding volume and shorter length of hospital stay than SB-OCSA and metachronous surgery (all P's < 0.05). Corticosteroid replacement treatment was necessary for 14 patients (45.2%) after bilateral CSA. During a median follow-up period of 7 years (range, 1.8–23), three of these patients (10.3%) had a recurrent disease that required reoperation.
Conclusion: SB-LCSA is feasible for treating synchronous bPHEOs and should be recommended as a prioritized surgical approach.

KEYWORDS

multiple endocrine neoplasia type 2, pheochromocytoma, simultaneous bilateral adrenal-sparing adrenalectomy, laparoscopy, RET proto-oncogene

Introduction

Bilateral pheochromocytomas (bPHEOs) are extremely rare and may present either synchronously or metachronously. An overwhelming majority of these bPHEOs only develop as benign tumors, generally one of the clinical presentations of a syndrome, with 96% having a genetic predisposition (1–4). Approximately 89% of patients with bPHEOs develop multiple endocrine neoplasia type 2 (MEN2) caused by germline mutation of the *RET* (rearranged during transfection) proto-oncogene and von Hippel–Lindau (VHL) disease caused by the *VHL* gene (1). Other relatively less common genes associated with bPHEO include neurofibromatosis type 1 (*NF1*), succinate dehydrogenase (SDH) complex subunit D (*SDHD*), *SDHA*, *SDHB*, *SDHC*, SDH assembly factor 2, MYC-associated factor X, fumarate hydratase, transmembrane protein 127, and several recently reported genes that have not yet been rigorously evaluated, such as *KIF1B*, *SLC25A11*, and *MDH2* (1, 4–9). The *SDHB* mutation causing PHEO (paraganglioma) generally develops into a malignancy and metastasizes in ≥40% of affected patients (9, 14).

Currently, bPHEOs may be treated by a bilateral posterior retroperitoneal approach, laparotomy incision, or laparoscopic resection, while adequate preoperative treatment is administered with α-blockers. However, performing total adrenalectomy or cortical-sparing (adrenal-sparing) adrenalectomy (CSA) as the standard management of bPHEOs remains controversial. The main concerns on the risk of malignancy or future recurrences from remnants include the potential for the difficulty of reoperation and complications, the likelihood of corticosteroid independence to be balanced against the risks associated with chronically treated adrenal cortical insufficiency after CSA, and the inconsistent evidence of retrospective studies with small sample sizes. Recently, results of several international multicentre studies suggested laparoscopic/open operative CSA (LCSA/OCSA) as the successful surgical approach for patients with hereditary bPHEOs (1–3, 12). In particular, the bilateral LCSA (B-LCSA) approach should be considered a viable alternative option for patients requiring surgical intervention (1–4, 10–14).

However, regarding synchronous bilateral laparoscopic or open CSA (i.e., SB-LCSA or SB-OCSA) for bPHEOs associated with MEN2, less practical experience has been reported to date (1–4, 10–22). In the present study, 31 patients had bPHEOs originating from MEN2 in an ethnic Han Chinese cohort, of whom 29 underwent varying bilateral CSA including synchronous/metachronous LCSA/OCSA. Herein, their clinical presentation, genetic analysis, operative procedures, and surgical outcomes are described, and we further evaluated the safety and value of applying SB-LCSA for MEN2-related bPHEOs.

Participants and methods

Participants

This retrospective study analyzed prospectively collected data from November 1998 to April 2021. Of 258 patients (20.5%) belonging to 83 unrelated families, 53 presented with MEN2-related PHEOs (23–28). MEN2 was diagnosed based on genetic screening indicating germline mutations of the *RET* or clinical features and a clear family history for early cases. Subsequent *RET* testing was performed to confirm the diagnosis. In all individuals with MEN2, an initial clinical study, biological/imaging monitoring, and *RET* testing were conducted according to the following published criteria, as reported previously (23–28): each patient's clinical history/manifestations, physical examination, and biochemical tests, including plasma and 24-h urinary catecholamines (adrenaline, noradrenaline, and dopamine), vanillyl mandelic acid, and, after 2018, the addition of plasma metanephrines and normetanephrines. Imaging examinations included Doppler ultrasonography, computed tomography (CT), T2-weighted magnetic resonance imaging (MRI), and emission CT if indicated. The study protocol was approved by the Ethics Committee of the 903rd PLA Hospital, and written informed consent was obtained from all the participants or their legal guardians.

Overall, bPHEOs were diagnosed in 31 of 53 patients (58.5%) with MEN2-related PHEOs, depending on the biological/imaging examination and histopathological findings. In the 31 patients, of whom 29 (93.5%) received surgery, preoperative preparation was performed with adequate time to normalize blood pressure with alpha-blockers, and varying doses of phenoxybenzamine or terazosin were administered as the first choice to minimize perioperative cardiovascular complications. When blood pressure and heart rate control was poor, additional nifedipine or propranolol/metoprolol was provided; also, a high-sodium diet and fluids were provided preoperatively (10–14, 26, 29). On the morning of the operation day, phenoxybenzamine or terazosin was provided, while 100 mg of hydrocortisone was also infused intravenously. During the operation, the arterial blood pressure was monitored continuously, and 100–200 mg of hydrocortisone was infused intravenously. Of the remaining other two patients presenting MEN2A with synchronous bPHEOs, one (P26; male, 78 years) opted for treatment with terazosin over surgery and died of medullary thyroid carcinoma (MTC) in the lung and liver metastasis 2 years after the diagnosis of initial bPHEO and the other (P27; male, 25 years) declined further surgery for "watchful waiting" because of the absence of PHEO-related symptoms and a family factor (**Table 1**, **Figure 1**). Seven of these surgeries had OCAS *via* a laparotomy or lateral retroperitoneal open approach, which occurred before the year 2008. Subsequently,

TABLE 1 Demographic, clinical, and operative data of patients with MEN2-related bilateral pheochromocytomas.

Patient (No.)	Syn/Meta bPHEO (*n*, Syn %)	*RET* mutation	M/F	Age at operation (years)	Tumor size (cm), L/R	Surgery procedures	Multifocal (*n*, %)	Postoperative (*n*, %)		Follow-up[a] (years)
								Steroid dependency	Recurrence	
P1	Syn	C634Y	M	56	6.0/5.5	SB-OCSA	Yes	—	—	17.5
P2		C634Y	M	38	2.0/7.0	SB-OCSA	Yes	—	—	15.0
P3		C634Y	M	42	3.2/4.6	SB-OCSA	Yes	Yes	—	16.5
P4		C634R	M	34	10.0/3.5	SB-OCSA	Yes	Yes	—	23.0
P5		C634Y	F	28	5.0/3.8	SB-OCSA	—	Yes	—	15.3
P6		C634Y	M	48	2.5/1.5	SB-LCSA	Yes	—	—	9.0
P7		C634Y	M	42	4.4/2.5	SB-LCSA	Yes	—	—	2.5
P8		C634G	F	45	4.0/4.0	SB-LCSA	Yes	—	—	5.5
P9		C634Y	M	42	2.2/2.8	SB-LCSA	—	—	—	7.0
P10		C634Y	F	38	3.3/3.8	SB-LCSA	Yes	—	—	6.0
P11		C634R	F	46	2.9/4.3	SB-LCSA	Yes	—	—	4.0
P12		C634Y	M	58	8.5/5.5	SB-LCSA	Yes	Yes	—	1.8
P13		C634Y	M	35	2.8/2.8	SB-LCSA	—	Yes	—	11.0
P14		C634Y	M	36	6.0/5.2	SB-LCSA	Yes	Yes	—	10.0
P15		C634Y	F	49	3.6/1.1	SB-LCSA	Yes	Yes	—	6.0
P16		C634Y	F	32	5.0/3.8	SB-LCSA	Yes	Yes	—	11.0
P17		M918T	F	23	6.0/5.0	SB-LCSA	Yes	Yes	—	3.5
P18		M918T	F	50	8.1/5.1	SB-LCSA	Yes	Yes	—	3.0
P19		C634G	F	52	3.0/3.5	SB-LCSA	Yes	—	—	3.8
P20		C634F	F	34	2.1/2.7	SB-LCSA	—	—	—	6.0
P21		C634Y	F	30	5.2/2.2	SB-LCSA	Yes	—	—	2.3
P22		C634S	F	37	1.2/3.5	SB-LCSA	—	—	—	5.0
P23		C634W	F	34	4.5/1.5	SB-LCSA	Yes	—	—	2.5
P24		C634Y	F	45 (two-step)	2.3/2.9	R-OCSA/l-LCSA	Yes	Yes	Yes	10.0
P25		C634R	F	24 (two-step)// 29/ 40	6.0/3.7	MB-OCSA// R-OCSA/l-LCSA/	Yes	Yes	Yes	15.3

(*continued*)

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TABLE 1 Continued

Patient (No.)	Syn/Meta bPHEO (*n*, Syn %)	*RET* mutation	M/F	Age at operation (years)	Tumor size (cm), L/R	Surgery procedures	Multifocal (*n*, %)	Postoperative (*n*, %)		Follow-up[a] (years)
								Steroid dependency	Recurrence	
P26		C634Y	M	78	3.0/3.4	Died	/	/	/	2.0
P27		M918T	M	25	1.7/1.8	Refused	/	/	/	0.3
P28	*Meta*	C634R	M	37/41	2.0/4.0	L-LCSA/R-LCSA	Yes	—	—	4.0
P29		C634Y	F	30/40	4.5/5.3	L-OCSA//SB-LCSA	Yes	Yes	Yes	7.0
P30		C634Y	F	27/44	7.5/11.0	R-OCSA/l-OCSA	Yes	Yes	—	20.2
P31		C634Y	M	44/49	4.3/4.5	R-OCSA/l-OCSA	Yes	—	—	16.0
Total	27/4 (87.1)	C634/M918T	14/17 (54.8[b])	38[c]	4/3.8	29/31 (93.5)[d]	24/31 29 (82.8)	14/29 (48.3)	3/29 (10.7)	7.0 (1.8–23)[e]

Syn, synchronous; Meta, metachronous; bPHEO, bilateral pheochromocytoma; M, male; F, female; CSA, cortical-sparing adrenalectomy; LCSA, laparoscopic CSA; SB-LCSA, synchronous bilateral LCSA; MB-LCSA, metachronous bilateral LCSA; OCSA, open CSA; SB-OCSA, synchronous bilateral OCSA; MB-OCSA, metachronous bilateral OCSA. —, negative.

[a]From the time of initial bilateral CSA to present.

[b]F %.

[c]Median age at initial diagnosis of bPHEO.

[d]Number and proportion of patients who had operation.

[e]Median of follow-up and time ranges except for two patients (P26 and P27) having no surgery.

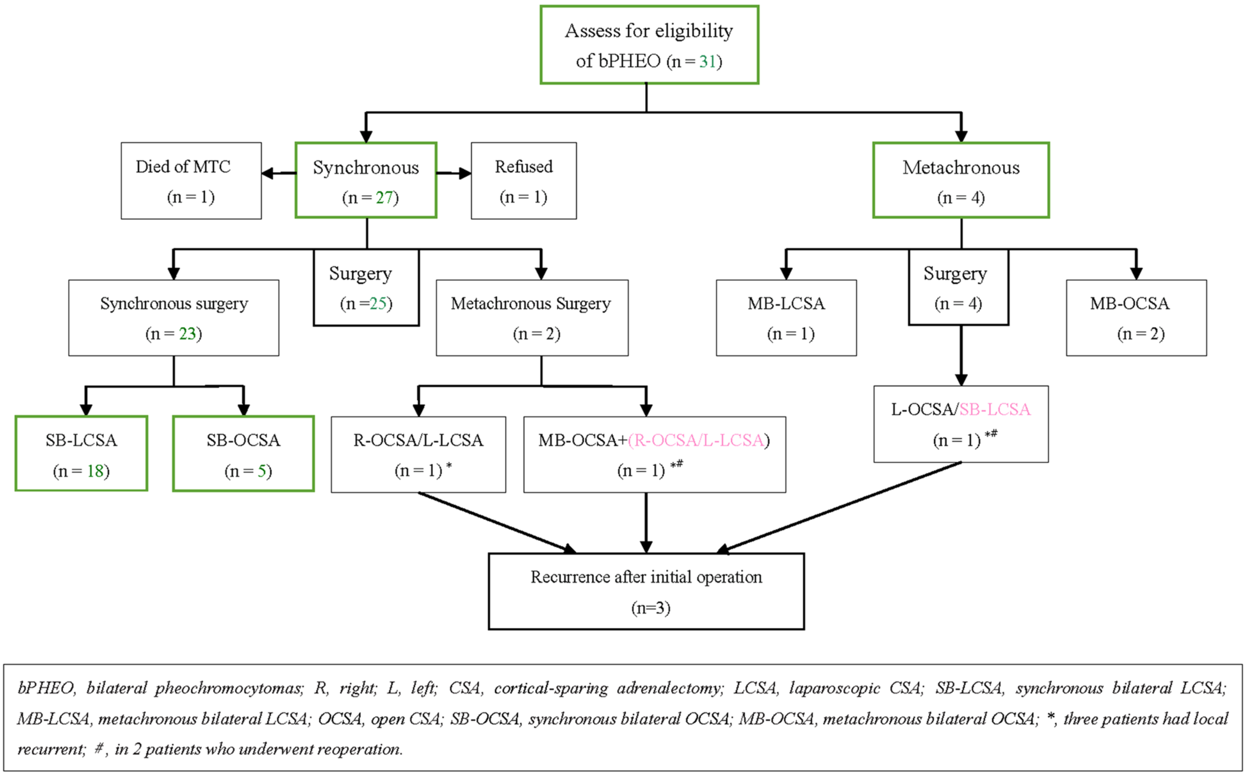

FIGURE 1
Study population and outcome by the type of operative intervention in those who had surgical intervention.

19 patients had LCSA, and all the tumors were initially removed transperitoneally. The remaining three patients underwent at least an LCSA and/or OCAS as a hybrid surgery (**Tables 1**, **2**).

Intraoperative blood loss volume was defined as the total amount of blood lost (from skin incision to the end of surgery). Length of hospital stay was defined as the length of postoperative stay in the department. Complications were classified using the modified Clavien–Dindo classification (CDC, grades I–V) (30), although operative time was not evaluated because of a relatively longer time span. Overall survival was assessed from the date of initial PHEO diagnosis to the time of the last follow-up.

Surgical approach

Intravenous inhalation combined with general endotracheal anesthesia was used. SB-LCSA/metachronous B-LCSA (i.e., MB-LCSA), synchronous/metachronous bilateral OCSA (i.e., SB-OCSA or MB-OCSA), or hybrid LCSA/OCSA was performed (**Figure 1**). LCSAs were all performed transabdominally with the patient in supine 40°–70° laterally [placed either on the left or right (easy side) lateral supine position for the first CSA and then changed to the contralateral supine for the second procedure]. Left LCSA procedures were performed using the three-trocar technique, and in the right LCSA procedures, a fourth trocar was added for retraction of the liver when necessary (12, 21, 31). OCSAs were performed transperitoneally with the patient in supine or using the posterior retroperitoneal approach. In SB-OCSA cases, during the surgical procedure, the patients should remain in supine in contrast to that in MB-OCSA.

Combined with preoperative imaging information, careful exploration was performed to avoid leaving PHEO tumors and completely preserve the uninvolved adrenal tissues during the operation. After complete hemostasis of the operative wound, a gel sponge or absorbable hemostatic gauze was placed, and two drainage tubes were placed on both sides.

RET screening using targeted sequencing

Briefly, peripheral blood genomic DNA samples obtained from at least 258 individuals from 83 individual families were prepared for targeted sequencing using an Illumina HiSeq 2000 Analyzer. The methods used for DNA target capture, enrichment, elution, and targeted sequencing were previously described (25, 27, 28). The targeted sequencing results were

TABLE 2 Characteristics of synchronous versus metachronous presentation of bilateral pheochromocytomas.

Variables	Synchronous PHEO[a]	Metachronous PHEO[a]	*P* value
Patient[b], no. (%)	27 (87.1%)	4 (12.9%)	
Gender (male/female)	12/15	2/2	0.829
Mean age at diagnosis (years)	40.8 ± 12.0	43.5 ± 4.0	0.660
Median age at surgery (years)	38	42.5	
RET mutation (no.)	27	4	
C634F/G/Y/R/S/W (no.)	24	4	
M918T (no.)	3	0	
Adrenergic symptoms[c]			
Symptomatic	22	2	0.158
Asymptomatic	5	2	
Tumor size (cm)			
Mean	3.9 ± 1.9	5.4 ± 2.7	0.055
Median	3.5	4.5	
Tumor multicentric, no. (%)	20 (64.5%)	4 (12.9%)	0.248
Surgery procedures	25	4	
LCSA (no.)	18	1	
OCSA (no.)	5	2	
Hybrid (no.)	2	1	

PHEO, pheochromocytoma; CSA, cortical-sparing adrenalectomy; LCSA, laparoscopic CSA; OCSA, open CSA; hybrid, both have OCSA and LCSA.
[a]Initial synchronous or metachronous PHEO.
[b]Available data.
[c]Including hypertension, palpitations/tachycardia, headaches, perspiration, etc.

further validated by Sanger sequencing using an ABI 3700 Genetic Analyzer (PerkinElmer, Fremont, CA, USA).

Statistical analysis

All data were analyzed using the IBM SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The frequency of occurrence, percentages, and comparisons of enumeration variables were assessed using the chi-square test (χ^2) or Fisher's exact test and Student's *t*-test for comparison between independent treatment groups. Significance was set at $P < 0.05$.

Results

Clinical and diagnostic data

Of all 31 patients with bPHEOs, 17 (54.8%) were women (**Table 1**). The median age at initial diagnosis of bPHEO was 38 years (range, 23–78). The median tumor size was 3.8 cm (range, 1.1–11.0), and the tumor was >5.0 cm in 38.7% of the cases (**Figures 2A–D**). Twenty-seven patients (87.1%) presented with initial synchronous PHEOs, and four patients (12.9%) had initial metachronous PHEOs; the incidence of a contralateral PHEO was 4, 5, 10, and 17 years after the first diagnosis/surgery of a unilateral PHEO (mean, 9 years). However, the mean age at diagnosis was not significantly different between patients with synchronous and those with metachronous PHEOs [(40.8 ± 12.0) vs. (43.5 ± 4.0) years, $P = 0.660$)], although patients with metachronous PHEOs may have an older median age by >4.5 years than those with synchronous PHEOs (**Tables 1–3**). Additionally, at the time of diagnosis of initial PHEOs, 7 patients (22.6%) were asymptomatic, and 24 (77.4%) presented with adrenergic symptoms, including hypertension ($n = 24$), headache ($n = 9$), palpitations/tachycardia, ($n = 7$), perspiration ($n = 2$), and paroxysms ($n = 12$). Among 25 patients (80.6%) who had available biochemical data, 14 (56%) presented with elevated catecholamines/MNs in plasma or urine. The diagnosis was made according to clinical features suggestive of PHEOs in 20 patients (64.5%) and according to mutations in 11 others (4 also had clinical features of the disease) (35.5%), which revealed that the mean size of a PHEO was 5.7 ± 2.0 cm in the patients discovered due to symptoms, which was larger than that of a PHEO detected through mutation-based screening (mean size: 3.2 ± 1.5 cm) ($P = 0.003$) (data not shown). The characteristics of synchronous vs. metachronous bPHEOs in the 31 patients are summarized in **Tables 1**, **2**, respectively.

Moreover, all 31 patients presenting with bPHEOs were only associated with 11 and 16 exons of *RET*, predominantly in exon 11 mutation, and 28 participants (90.3%) harboring *RET*-C634F/G/R/S/W/Y mutations, followed by a C634Y (61.3%, 19/31), C634R (12.9%, 4/31), C634W (3.2%, 1/31), C634G (6.5%, 2/31), C634F (3.2%, 1/31), and C634S (3.2%, 1/31) and affected by MEN2A, belonged to 14 unrelated families. The three other participants (9.7%) carrying *RET*-M918T in exon 16 belonged to three different MEN2B families (**Tables 1**, **2**). The mean age at bPHEO diagnosis was not significantly different between patients with C634 and those with M918T mutations [40.9 ± 11.4 vs. 32.7 ± 15.0 years; $P = 0.256$). Additionally, the mean tumor size was not significantly different (4.0 ± 2.0 vs. 4.6 ± 2.5 cm; $P = 0.502$), although those with *RET*-M918T were relatively younger by 8 years and had a tumor size that was approximately larger

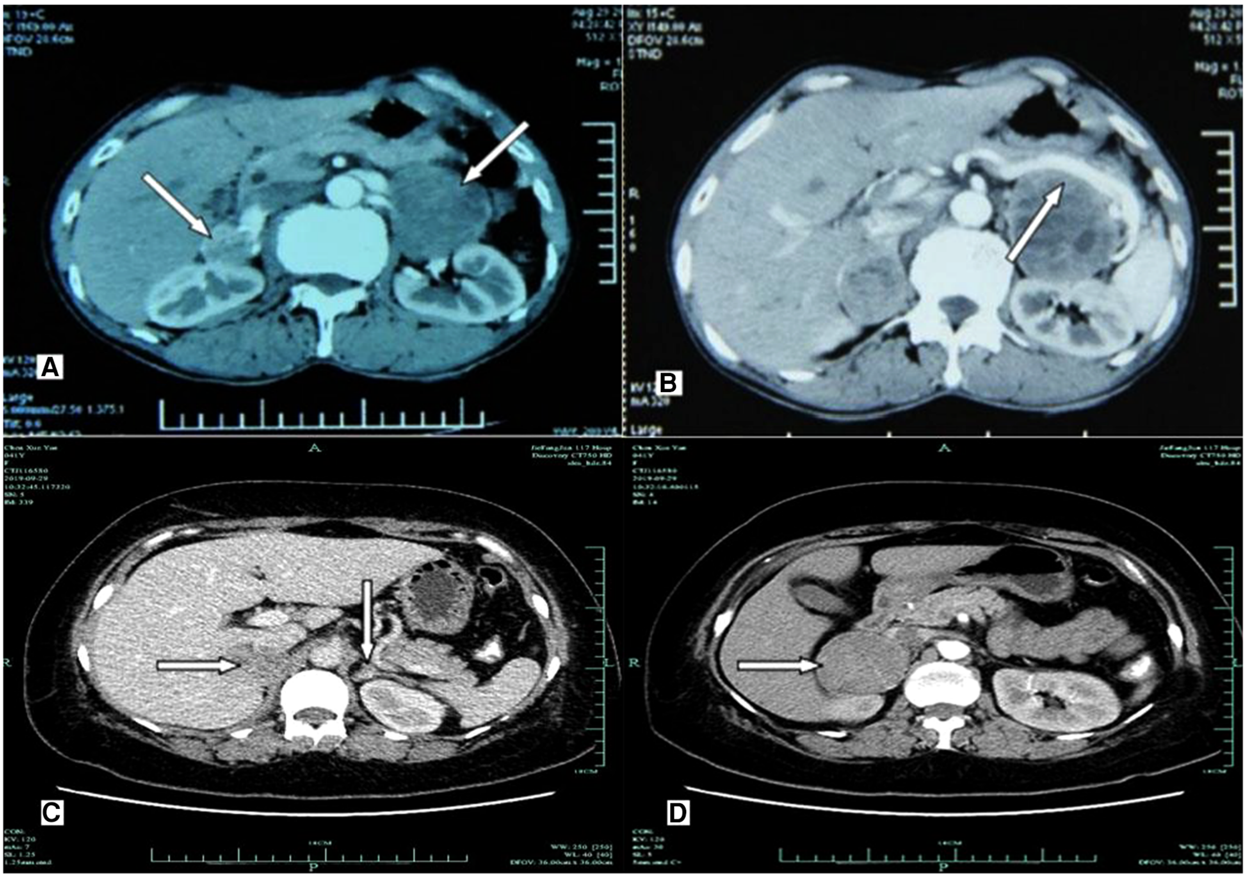

FIGURE 2
Imaging examination of computerized tomography scanning using ultravist 300 disclosed hypoechoic nodules in bilateral adrenal glands. (A,B) A 36-year-old male patient (P14; *RET*-C634Y) presenting with primary bilateral multifocal pheochromocytoma. (A) CT scan showing irregular enhancement of multiple nodules with intact capsule in both adrenal glands. (B) Contrast-enhanced CT imaging revealing inhomogeneous nodules with well-defined and heterogeneous enhancement in both adrenal glands (white arrows). The maximum diameter of tumors was 6.0 cm × 5.3 cm × 4.8 cm in the left, and the maximum diameter was 5.2 cm × 4.5 cm × 3.0 cm in the right, while having multiple low density lesions with no obvious enhancement, respectively. No areas of obvious necrosis or hemorrhage were observed. The splenic artery and vein showed compression and displacement (white arrow). (C,D) A 40-year-old female patient (P29; *RET*-C634Y) having bilateral pheochromocytoma. (C) Contrast-enhanced CT scanning showing that two primary inhomogeneous nodular and heterogeneous mild/moderate enhancement in the right adrenal (white arrows). A nodule (1.2 cm × 0.8 cm × 0.6 cm) with equal density in the left adrenal gland was enhanced to the same extent as the Normal adrenal tissue (white arrows), as possibility of recurrence of pheochromocytoma. (D) Larger one with clear boundary in the right adrenal was about 5.3 cm × 4.3 cm × 3.0 cm in diameter (white arrows).

by 0.6 cm (Table 1). However, the diagnosis of initial PHEOs was also made after the diagnosis of MTC in 18 cases (58.1%), simultaneously in 5 cases (16.1%), and prior to the diagnosis of MTC in the 8 remaining cases (25.8%). The diagnosis of bPHEOs in all 31 patients was MTC (100%), and the youngest patient, aged 23 years, was diagnosed with synchronous PHEOs and presented with *RET*-M918T.

Surgical procedures

Except for two patients (P26 and P27) who did not receive surgery, each of the other 29 patients (93.5%) underwent varying bilateral CSA. In 23 patients (79.3%), initial CSA was simultaneously performed on both sides, of whom 18 with SB-LCSA and 5 with SB-OCSA received the same anesthesia; whereas metachronous bilateral CSA was recorded in 6 cases (20.7%), including 1 with MB-LCSA, 2 with MB-OCSA, and 3 with LCSA/OCSA hybrid surgery (Table 1, Figure 1). Subsequently, dissection and ligation of the central adrenal vein were performed during the operation (Tables 1, 2). In particular, the surgical approach was initial LCSA in 19 cases (SB-LCSA in 18 participants with synchronous PHEOs and MB-LCSA in 1 patient with metachronous PHEOs). The LCSA approach was performed transabdominally and used for these 19 patients. OCSA was initially performed in 7 patients (5 SB-OCSA in 5 patients with synchronous PHEOs and 2 MB-OCSA in 2 patients with metachronous PHEOs), with

TABLE 3 Presence of perioperation and postoperation in synchronous/metachronous surgery.

Variables	Synchronous surgery	Metachronous surgery	P value
Patient (no.)	23 (79.3%)	6 (20.7%)	
Gender (male/female)	10/13	2/4	0.653
Mean age at surgery (years)	40.4 ± 9.0	37.5 ± 8.1	0.360
Median age at surgery (years)	38	40	
Tumor size (cm)			
Mean	4.1 ± 1.9	4.8 ± 2.5	0.245
Median	3.8	4.4	
LCSA/OCSA (no.)	36/10	6/9	0.005
Times of recovery (days)	19.5 ± 4.2	40.2 ± 8.9	0.000
Length of hospitalization (days)	11.4 ± 4.5	20.3 ± 8.4	0.016
Postoperative			
Complications[a]	0	0	
Steroid replacement	10	4	0.313
Recurrence, *n* (%)	0	3	0.000
Metastasis, *n* (%)	0	0	
Follow-up (years)	7.8 ± 5.6	10.0 ± 4.8	0.381

B-LCSA/B-OCSA, bilateral laparoscopic cortical-sparing adrenalectomy/bilateral open cortical-sparing adrenalectomy.
[a]Clavien–Dindo classification, ≥grade II.

TABLE 4 Factors related to perioperation and postoperation in simultaneous bilateral laparoscopic or open surgery.

Variables	SB-LCSA	SB-OCSA	P value
Patient (no.)	18 (78.3%)	5 (21.7%)	
Gender (male/female)	6/12	4/1	0.062
Mean age at surgery (years)	40.6 ± 8.9	39.6 ± 10.5	0.831
BMI (kg/m^2)	21.8 ± 2.7	22.0 ± 1.7	0.906
Tumor size (cm)			
Mean	3.8 ± 1.7	5.1 ± 2.3	0.060
Median	3.5	4.8	
ASA score (I/II/III/IV/V)	6/11/1/0/0	0/5/0/0/0	
Blood loss (ml)	75.0 ± 27.4	242.0 ± 100.8	0.003
Length of hospitalization (days)	10.0 ± 2.9	13.2 ± 1.6	0.046
Postoperative			
Complications[a]	0	0	
Steroid replacement, *n* (%)	7 (38.9%)	3 (60%)	0.397
Recurrence, *n* (%)	0	0	
Follow-up (mean, years)	5.3 ± 3.2	10.6 ± 5.4	0.000

CSA, cortical-sparing adrenalectomy; SB-LCSA, synchronous bilateral laparoscopic CSA; SB-OCSA, synchronous bilateral open CSA; hybrid, laparoscopic and open CSA.
[a]Clavien–Dindo classification, ≥grade II.

5 patients in the transperitoneal supine position and 2 patients in the posterior retroperitoneal position (**Tables 1**, **2**; **Figure 1**). For the remaining three other individuals, one (P24) presented with synchronous bPHEOs, one had OCSA (right) and LCSA (left) interval 3 months (two-step surgery) in 2012, and the other (P29) who had initial unilateral PHEOs underwent initial OCSA (left) retroperitoneally in 2009. In 2020, due to recurrences of the left and newly developed right PHEOs (**Figures 2C,D**), an SB-LCSA (second surgery) was performed. Unfortunately, the third patient (P25) had synchronous PHEOs initially, underwent MB-OCSA with a 1-month interval in 2002, and underwent a second right OCSA or left LCSA in 2007 and 2018, respectively, due to recurrences of the right or left PHEOs. In total, 61 adrenal operations (30 right and 31 left) were performed using the LCSA ($n = 42$) or OCSA ($n = 19$), including the LCSA/OCAS hybrid surgical procedures ($n = 3$) (**Tables 1–3**, **Figure 1**).

The perioperative information including preoperative, intraoperative, and postoperative variables was compared between synchronous and metachronous CSA. Synchronous CSA had a significantly less recurrence rate and shorter length of hospital stay than metachronous CSA (**Table 3**). SB-LCSA had significantly less blood loss and a shorter length of hospital stay than SB-OCSA or SB-OCSA/hybrid surgery (**Table 4**; the latter data not shown). Meanwhile, the differences in surgical parameters were not significant between synchronous and metachronous CSA or between SB-LCSA and SB-OCSA (**Tables 3**, **4**).

Postoperatively, all 29 participants had histopathology verifying bPHEOs, of whom 24 patients (82.8%) had initial multicentric tumors, which are primarily noted in MEN2A ($n = 22$) and MEN2B ($n = 2$), and on the left in 19, right in 17, and bilateral multifocal in 12 patients (**Table 1**). The highest number of PHEOs was 9, of which 4 occurred on the left and 5 on the right, in a 56-year-old patient with C634Y mutation (P1; **Table 1**). No conversion to an open procedure was necessary. No serious intraoperative and postoperative complications (CDC, ≥grade II) were recorded. Laparoscopic manipulation and surgical removal of the PHEO resulted in eight peaks of hypertension [systolic blood pressure (SBP) > 180 mmHg], associated in four cases with bouts of sinus tachycardia and in two low peaks of hypotension (SBP < 60 mmHg) despite initial ligation of the central adrenal vein.

Outcomes

Patients were all followed up for a median of 7 years (range, 1.8–23) from the time of initial CSA; 14 (48.3%) of them required lifelong steroid [glucocorticoid (prednisone or hydrocortisone) and mineralocorticoid] replacement (**Table 1**), and 2 (6.9%) of them had transient adrenal insufficiency and oversupplementation during the adjustment of drug dosage within 3 and 6 months postoperatively, although none developed the risk of Addisonian crisis.

The presence of recurrent PHEOs was diagnosed in three patients (10.7%; P29, P25, and P24), of whom one (P29) had a recurrence or developed contralateral PHEOs at 10 years postoperatively, and the other (P25) had bilateral recurrences at 4 and 16 years after the first operation; two underwent reoperation with no postoperative complications. Additionally, one patient (P24) had unilateral recurrence (tumor size, 1.5 cm) 3 years after MB-LCSA but declined surgery (**Table 1**). The former patient (P29) was diagnosed with recurrence due to adrenal symptoms, and the latter two patients (P25 and P24) had recurrence identified during re-examinations, with no lateral predisposition (two left adrenal beds and two right adrenal beds). The three patients with MEN2A had a mean time of recurrence of approximately 8 years (range, 3–16). Moreover, none of the tumors were malignant.

Discussion

To the best of our knowledge, the present study is the first to detail the clinical presentation, management, and outcomes of patients with MEN2-related bPHEOs in an ethnic Han Chinese cohort. We identified bilateral disease in approximately 59% of the patients with PHEOs, which is similar to that previously reported by Castinetti et al. (2), who identified it in 61% of their cases. In this series, the bilateral disease was only associated with *RET*-C634 mutations, such as MEN2A (90%), *RET*-M918T, and MEN2B (10%), although the absence of other *RET* mutations demonstrated a relatively single mutation genotype (2, 13, 21, 32) (**Tables 1**, **2**). Our finding also revealed that the bPHEO was exclusively benign, synchronously involved in both adrenal glands in approximately 80%, diagnosed at an asymptomatic stage in approximately 23%, and had a mean tumor size of 3.8 cm, whereas those observed in patients with PHEOs identified through mutation-based screening were less than symptomatic PHEOs ($P = 0.003$) (10, 32). In approximately 83% of multifocal cases, the affected patients mostly received the initial operation at <40 years of age (2, 3, 10, 13). However, the need for an optimal surgical procedure to manage these patients should still be highlighted regardless of whether PHEO-related deaths rarely occur. By contrast, most previous studies mainly focused on a more common cause of death and outcomes of MTC in these patients (2, 3, 10, 13). Thus, the use of prophylactic thyroidectomy in genotype-specific age or the extent of thyroidectomy based on genotype and serum calcitonin levels had become routine and the recommended formal practice guidelines (1–4, 9–13, 23–26, 33, 34).

By contrast, the second major component of MEN2-related PHEOs could be treated by laparoscopic excision based on an already established conventional procedure, which should be removed prior to surgery for either MTC or hyperparathyroidism (13, 14, 34). In the last two decades, laparoscopic bilateral adrenalectomy for bPHEOs demonstrated a sharp reduction of intraoperative hemodynamic instability, providing an equal opportunity for treating hypertension, less intraoperative blood loss, and lower overall complication rates while also causing a faster and better postoperative recovery and a better cosmetic result than the open approach (11–14, 20, 35, 36). In this study, similar results of less bleeding volume and shorter length of hospital stay were also revealed, which are possible with LCSA compared with those in OCSA or hybrid surgery (all P's < 0.05; **Tables 1–4** and **Figure 1**). The CSA approach for treating PHEOs should only be considered an alternative procedure or a relatively weak recommendation and not the established routine MEN2 practice guidelines (11–14, 34, 38, 39). The main concerns include the risk of remnant recurrences, reoperation, metastases, and the likelihood of corticosteroid independence after CSA. Nevertheless, CSA as a feasible surgical approach for unilateral/bilateral PHEOs in MEN2 patients was still performed by numerous clinicians (1–4, 10, 12, 15–23, 26, 33, 37–40). A recent multicenter study of 563 patients with MEN2-related PHEOs, which includes some patients from our cohort, has demonstrated that the incidence of malignant disease was <1%; bPHEO with CSA in one or two operated glands associated with a recurrence was 5% of 114 patients, of whom 57% were not steroid-dependent at a median of 9.5 years (range, 1–28) postoperatively (2). Another multicenter study of bPHEOs ($n = 625$) in 505 of 526 tested patients (96%) with germline mutations has detected that the majority of patients had *RET* mutations rather than *VHL* or other gene mutations (282 vs. 184 vs. 39, respectively) and that CSA was associated with a recurrence in 13% and malignant disease in 2% of patients at a follow-up of a median of 8 years (interquartile range, 4–17) (1). In this series, 29 patients underwent LCSA or OCSA to preserve most of the uninvolved adrenals using PHEO enucleation or subtotal adrenalectomy (CSA) with as much as possible rim (0.5–1.0 cm) of the normal adrenal tissue. Postoperatively, approximately 48% of these patients still required lifetime steroid replacement, and two of them (6.9%) suffered transient complications of steroid dosage. Meanwhile, approximately 10% of these patients experienced tumor recurrence, demonstrating that real recurrences are typically identified within 8 years (range, 3–16) or later after CSA, without metastatic or PHEO-related deaths (0%) (**Tables 1, 3, 4; Figure 1**). Evidently, nearly total adrenalectomy can be inevitable when a large tumor (such as P30) is in an unfavorable location, when multifocal tumors (P24) are present, or when reoperation for recurrent PHEOs (P25, P29) is necessary by the laparoscopic procedure. However, interestingly, patients (P1) with nine small multifocal tumors underwent PHEO enucleation and did not require steroid replacement postoperatively in the 17.5 years of follow-up (**Table 1**). Enucleation may be more beneficial for preserving vascularized adrenal cortical tissue/function than subtotal adrenalectomy as it preserves at least 10%–15% of one remnant of properly vascularized adrenal cortical tissue and may offer adrenal stress capacity (22, 31, 36). However, a long-term follow-up of at least 10 years is still necessary for all these patients because of persisting disease due to the risk of recurrent PHEOs of approximately 20% within 20 years after CSA (10, 11, 13). Nevertheless, the LCSA or OCSA approach did not decrease survival and may offer excellent oncologic and functional outcomes. Particularly, LCSA [including robotic surgery (37)] is a safe and effective surgical management for treating bilateral and/or multifocal PHEOs, especially for tumors <6 cm in MEN2. As for experienced surgeons, LCSA is also feasible for tumors >6 cm (36). The tran-peritoneal approach can provide more space and clearer anatomical structure, thus making it more suitable for treating large PHEOs. Thus, LCSA should be routinely recommended for bilateral and/or multifocal PHEOs (1–4, 10, 15–23, 26, 33, 35–40). Robot-assisted CSA has also been identified as an effective technique for the management of PHEOs (37). An important advantage of the robotic platform is the articulation of the instruments, which offers seven degrees of freedom, thus facilitating circumferential dissection of the tumor (41). Drawbacks of this approach mainly include a low penetration rate and increased cost (41). The robotic techniques have been demonstrated to be safe and feasible in several retrospective and prospective studies (37, 41). However, data regarding robotic CSA are derived only from small series, with no direct comparison between robotic and laparoscopic partial adrenalectomy. Nevertheless, robotic partial adrenalectomy represents an alternative option for partial adrenalectomy for experienced surgeons.

Additionally, treating patients with synchronous bPHEOs can be challenging, and no uniform standard surgical approach (for neither synchronous nor metachronous) has been established. Following laparoscopic device innovation, the accumulation of sufficient experience, and proficient surgical skills, synchronous surgery including SB-LCSA was increasingly used in clinical practice for treating these bPHEOs (10, 15–23, 41). Walz et al. (16) have reported that 15 patients with bPHEOs (average tumor size of 4.6 cm; 2 cases of recurrent PHEOs on one side) underwent synchronous bilateral laparoscopic adrenalectomy, in which 14 (93.3%) bilateral tumors were removed under the same anesthesia. In another case, the procedures were split due to cardiac arrhythmias during laparoscopic removal of a 12-cm right-sided PHEO, and the contralateral 3-cm tumor was extirpated 5 weeks later retroperitoneoscopically. Kittah et al. (10) have reported that of 75 patients (98.7%) with synchronous PHEOs (41 MEN2, 13 VHL, 7 NF1, and 14 other PHEOs; the median tumor size of 3.0 cm), 74 underwent a synchronous bilateral adrenalectomy and synchronous bilateral CSA was successfully performed in 18 (24%) of them. Nine (44.4%) of the 18 patients required steroid replacement, 3 (16.7%) had recurrence at a median of 16.2 years (range, 3.6–51.9), and 2 developed metastatic PHEOs 20 years postoperatively. Meanwhile, in the present study, 27 patients (87.1%) had initial synchronous PHEOs. Of these, 23 bPHEOs were simultaneously and successfully removed, where the median size of the tumors was 3.8 cm, and 10 (43.5%) of them required steroid replacement at a median follow-up of 10.5 years (range, 1.8–23); none of them had recurrent and metastatic postoperatively (**Tables 1, 3, 4**). Nevertheless, 38.9% of the 18 patients underwent SB-LCSA or 60% of 5 patients underwent SB-OCSA, who respectively required steroid replacement, and the mean tumor size was (3.8 ± 1.7) or (5.1 ± 2.3) cm, with no significant difference ($P = 0.397$; $P = 0.060$). SB-LCSA can be safely performed and used for synchronous bPHEO surgery, which had the advantages of less blood loss and a shorter length of hospital stay than MB-OCSA (**Table 4**). Moreover, one case (P28), who had a recurrent PHEO (1.2 cm) on one side and developed a contralateral PHEO (5.3 cm), was also subjected to SB-LCSA (**Table 1**). However, reoperation may be more difficult than primary operations mainly due to adhesions, although laparoscopy can also be performed. SB-LCSA or SB-OCSA is technically safe and feasible (10, 12, 16–19); in particular, SB-LCSA can be considered a preferential choice in the surgical management for synchronous bPHEOs in MEN2, even for recurrent PHEOs.

As for whether the adrenal central vein should be preserved during the CSA, deliberately preserving it may be unnecessary based on our data and those of previous studies (16, 18, 22). However, avoiding excessive separation of the remnant adrenal gland from the adjacent space is important as the vascular bed adjacent to the remnant adrenal gland is integral to preserving its function. Corresponding evidence of the presence of successful adrenal autotransplantation was low (10, 16, 18, 22, 42). Furthermore, dissociating or ligating the central vein beforehand is not necessary. In general, the surrounding adrenal tissue can be separated at 0.5–1.0 cm from the PHEO using a harmonic scalpel. Especially when the preoperative CT/MRI scan demonstrated that the PHEO was large and the splenic/renal vessels were evidently compressed and deformed, it should be preferentially separated from the surrounding tissue vessels along the surface of the PHEO capsule, and the central vein could be ligated after the boundary was clear (**Figures 2A,B**). Meanwhile, once the specimen is removed, careful examination and preliminary assessment of a possible adequate disease-free margin around the PHEO needs to be performed.

Conclusion

The integration of the clinical and molecular genetic diagnosis of MEN2 into routine practice can provide valuable information for establishing a precise treatment plan and procuring optimized guidance for long-term follow-up surveillance (9–11, 43–46). SB-LCSA with preserving adrenocortical function for treating synchronous bPHEOs in patients with MEN2 is safe and feasible and should be considered a prioritized surgical approach.

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 the Ethics Committee of the 903rd PLA Hospital, and written informed consent was obtained from all study subjects or their legal guardians.

Author contributions

X-PQ conceived and designed the experiments. X-PQ, X-DF, FD, FL, B-JL, H-YJ, KZ, K-EW, and YZ conducted the experiments and analyzed the data. X-PQ wrote the manuscript. K-EW and YZ reviewed 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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Primary breast angiosarcoma: A case report

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Background: Primary breast angiosarcoma (PBA) is a rare sarcoma, accounting for only 0.04% of all breast malignancies, with a difficult diagnosis and a poor prognosis. Mastectomy is the standard treatment, and the role of adjuvant treatment (chemotherapy and/or radiotherapy following surgery) remains uncertain with very few studies.

Case Presentation: We report the case of a 17-year-old female patient who presented with a right breast lump that had rapidly increased in size and was hemorrhaging. She was diagnosed with breast angiosarcoma by needle biopsy and pathological evaluation. However, the mass showed a quick tendency to bleed during biopsies. After that, we performed angiography and tumor vascular embolization. The patient underwent a mastectomy followed by adjuvant chemotherapy.

Conclusion: Tumor vascular embolization reduced the surgical risk of PBA with hemorrhage complications. Postoperative therapeutic roles still need further exploration and verification.

KEYWORDS

breast angiosarcoma, chemotherapy, radiotherapy, surgery, DSA (digital subtraction angiography), case report

Introduction

Breast angiosarcoma is an extremely rare and aggressive malignancy that originates from vascular or lymphatic endothelial cells, accounting for 0.1%–0.2% of all breast neoplasms. It can be divided into primary and secondary angiosarcoma. It has a poor prognosis, with a 5-year survival rate of 40% (1). Primary breast angiosarcoma (PBA) is extremely rare (2). Currently, the most common management approach is surgical excision without involved margins (R0 resection) (3). We report the case of breast angiosarcoma in a patient who appeared with a large lump and bleeding in the right breast.

Case presentation

In February 2021, a 17-year-old female patient presented with a lump on the right breast about 1.5 × 1.5 cm in size in the lower inner quadrant (**Figure 1**). The lesion

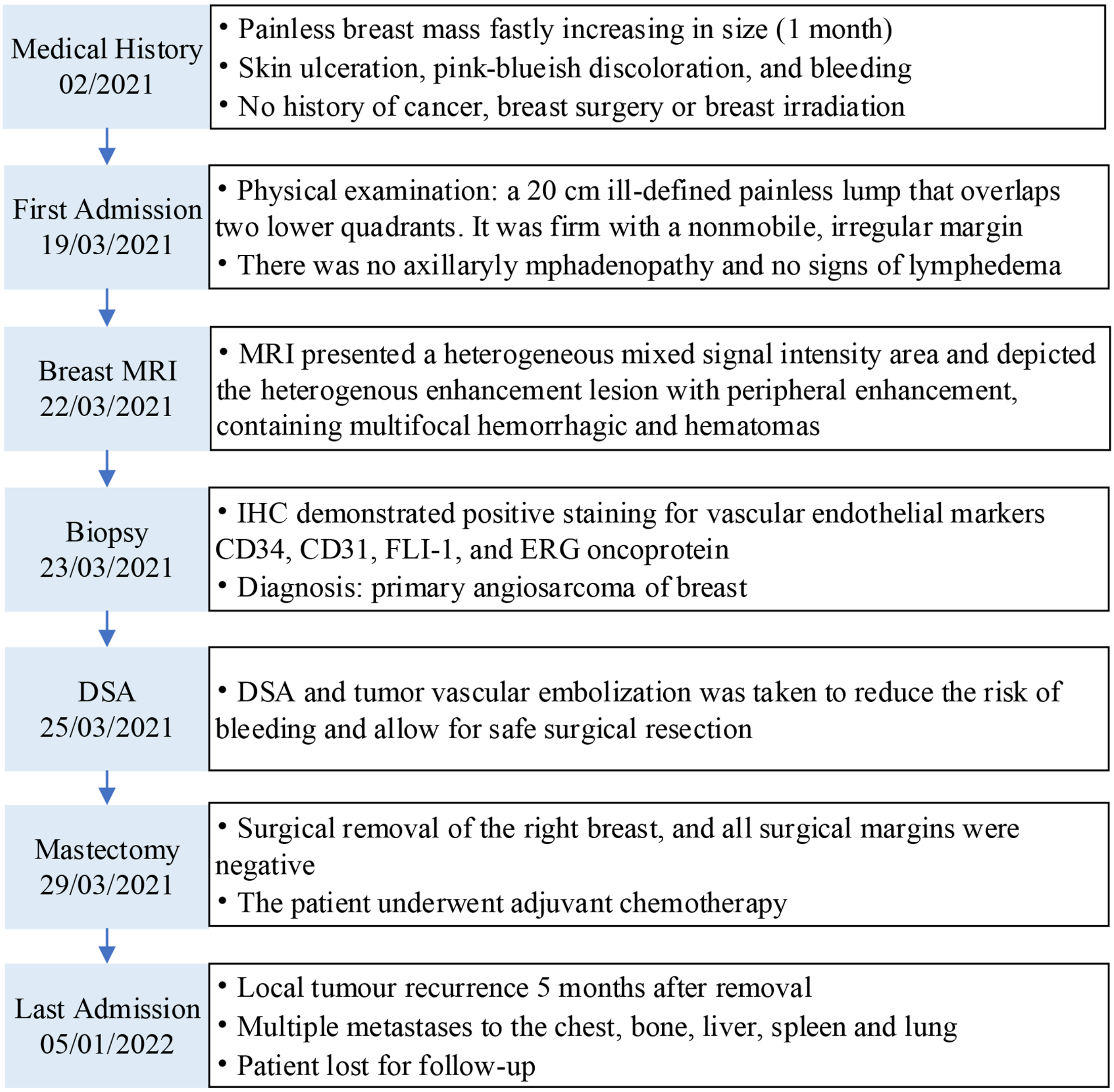

FIGURE 1
Case report timeline. MRI, magnetic resonance imaging; DSA, digital subtraction angiography; IHC, immunohistochemistry.

gradually increased in size over a period of 1 month without any pain or bleeding. She did not consult any doctor until the right breast underwent rapid enlargement after accidentally falling, reaching 20 × 20 cm. She had skin ulceration, pink-blueish discoloration, and bleeding from the breast lump for 3 days, without heat, pain, or discharge. On physical examination, the lesion appeared firm with a non-mobile, irregular margin. Axillary lymphadenopathy was negative, and there were no palpable supraclavicular nodes. The left breast was normal.

There was no other remarkable feature in the patient's medical history. She had no history of chronic illness or radiotherapy and was without a significant medical family history, including breast cancer. During hospitalization, the results of the laboratory tests were as follows: WBCs, 7,760/mm^3 (normal: 3,500–9,500/mm^3), Hb, 5.1 g/dL (11.5–15.0 g/dL), hematocrit, 18.0% (35.0%–45.0%), platelet, 80,000/mm^3 (125,000–350,000/mm^3), PT, 17.9 s (9.0–14.0 s), APTT, 39.8 s (20.0–40.0 s), INR, 1.57 (0.8–1.5), fibrinogen, 60 (200–400) mg/dl, D-dimer, 85.27 mg/L (0–0.55 mg/L). An ultrasound examination was performed, demonstrating that the right breast had heterogeneously mixed echogenicity of approximately 254 × 280 × 96 mm with an indistinct margin.

Considering the inconclusive findings on ultrasound, computed tomography (CT) scans of the head and chest were performed and revealed that the right breast had heterogeneously increased in density, with focal skin thickening, and an enhancement of the nipple. There was no obvious axillary lymphadenopathy in both axillae. In addition, the magnetic resonance imaging (MRI) showed a heterogeneous mixed signal intensity area predominantly of isointense signal intensity on T1-weighted images, and high signal intensity on T2-weighted images, containing multifocal hemorrhages and hematomas. Subsequent contrast-enhanced MRI depicted the heterogenous enhancement with peripheral enhancement (**Figure 2**). An ultrasound of the abdomen and an F-18 bone scan were negative for metastatic disease.

Thereafter, a right breast ultrasound-guided needle biopsy was performed. Vascular channels were lined by atypical, plump endothelial cells with hemorrhage and focal mitotic activity. Morphology suggested the possibility of angiosarcoma. Further immunohistochemistry demonstrated positive staining for vascular endothelial markers CD34, CD31, FLI-1, and erythroblast transformation-specific (ETS)-related gene (ERG) oncoprotein but not for cytokeratin (**Figures 3A, B, E, F**). The proliferation index (Ki-67) was estimated at 40%. So, a diagnosis of primary angiosarcoma of the breast (pT4N0M0) was made.

The patient had coagulation dysfunction for tumor-related excessive bleeding, decreased fibrinogen and platelet count, prolonged prothrombin time, and elevated D-dimer levels. She received red cell concentrates, cryoprecipitate, fibrinogen, platelets, and fresh-frozen plasma, but the anemia and coagulation did not improve significantly. A decision to undertake angiography (DSA) and tumor vascular embolization was taken to reduce the risk of bleeding and allow safe surgical resection (**Figure 4**).

After the risks associated with the surgery were explained to the patient and her family, she accepted them and wanted to be operated on as soon as possible. She underwent a right total mastectomy in March 2021, and all surgical margins were negative. Postoperative pathological examination revealed angiosarcoma with tissue necrosis, hemorrhage and 19.5 × 15.3 × 6.6 cm in size (**Figure 5**). Histopathologic examination showed the tumor was composed of atypical endothelial cells with different degrees of differentiation, forming irregular vascular cavities that coincide with each other, forming papillary and diffuse infiltration. Tumor cells exhibit fusiform or irregular shapes with little cytoplasm and hyperchromatic nuclei (**Figures 3C, D**).

After consultation with the patient and her family, she received planned radiotherapy and chemotherapy. The patient received Adriamycin-based chemotherapy every 3 weeks for eight cycles. Medical oncology planned a 50 Gy intensity-modulated radiation therapy to the chest wall (2 Gy per fraction over 5 weeks), but she was unable to complete the radiation therapy due to her poor physical condition.

The patient presented with a 3 cm × 1.5 cm bleeding right chest wall mass 5 months after removal. She was treated with surgical resection with a diagnosis of local tumor recurrence by histological examination. She presented again with a chest wall tumor that was bleeding profusely 1 month after surgery for a recurrent tumor and was admitted to the emergency department. A chest and abdominal CT scan with contrast showed multiple metastatic lesions in the chest, bone, liver, spleen, and lung. She was anemic despite the transfusion. The patient's condition has not yet improved. She left the hospital arbitrarily.

Discussion

Angiosarcoma is an extremely rare and highly malignant mesenchymal vasoformative neoplasm, characterized by rapidly proliferating and extensively infiltrating growth (4), most commonly identified in the skin of the head, neck, and scalp; the breast is an exceedingly rare primary site of occurrence (5). It occurs especially in women 30–40 years of age. The median survival time and 5-year recurrence-free survival rate are 24 months (about 2 years) and 33%, respectively (6). Currently, for the PBA, the underlying cause remains unknown. It represents about 0.05% of all malignant breast tumors (7). Primary lesions affect younger patients, and the median age is 30–50 years (8). Patients usually present with an associated palpable mass in the breast. The prognosis of patients diagnosed with PBA depends on the grade of the tumor. In patients with grade 1 tumors, the corresponding 5-year disease-free survival after the initial treatment is approximately 76%, whereas the probability drops to 15% for grade 3 tumors (9). In comparison, secondary breast angiosarcoma (SBA) is identified as chronic lymphedema resulting from axillary dissection (Stewart-Treves syndrome) or radiation-associated sarcoma (10). Radiotherapy used to treat invasive breast tumors is a well-known risk factor for the development of the so-called radiation-induced angiosarcoma (RIAS). RIAS is a late toxicity that occurs in 0.05%–0.3% of breast cancer patients who undergo breast-conserving surgery and adjuvant radiotherapy. It usually occurs 6–10 years after breast irradiation (11), but RIAS can occur as early as 1–2 years or as late as 41 years after radiation (12). SBA is relatively common in older women, as the median age is 70 years (13). About 5-year survival rates remain low, at 22.5% for secondary angiosarcoma (7). Because the clinical and radiologic findings are not specific (14), the definitive diagnosis can only be achieved by histopathological examination.

PBA originates from breast parenchyma and occasionally affects the skin (15), while SBA often involves the skin, and rarely the breast parenchyma. PBA has similar histologic and morphologic features to SBA. Tumor size ranges between 10 and 160 mm (mean: 59 mm) for post-radiation angiosarcomas

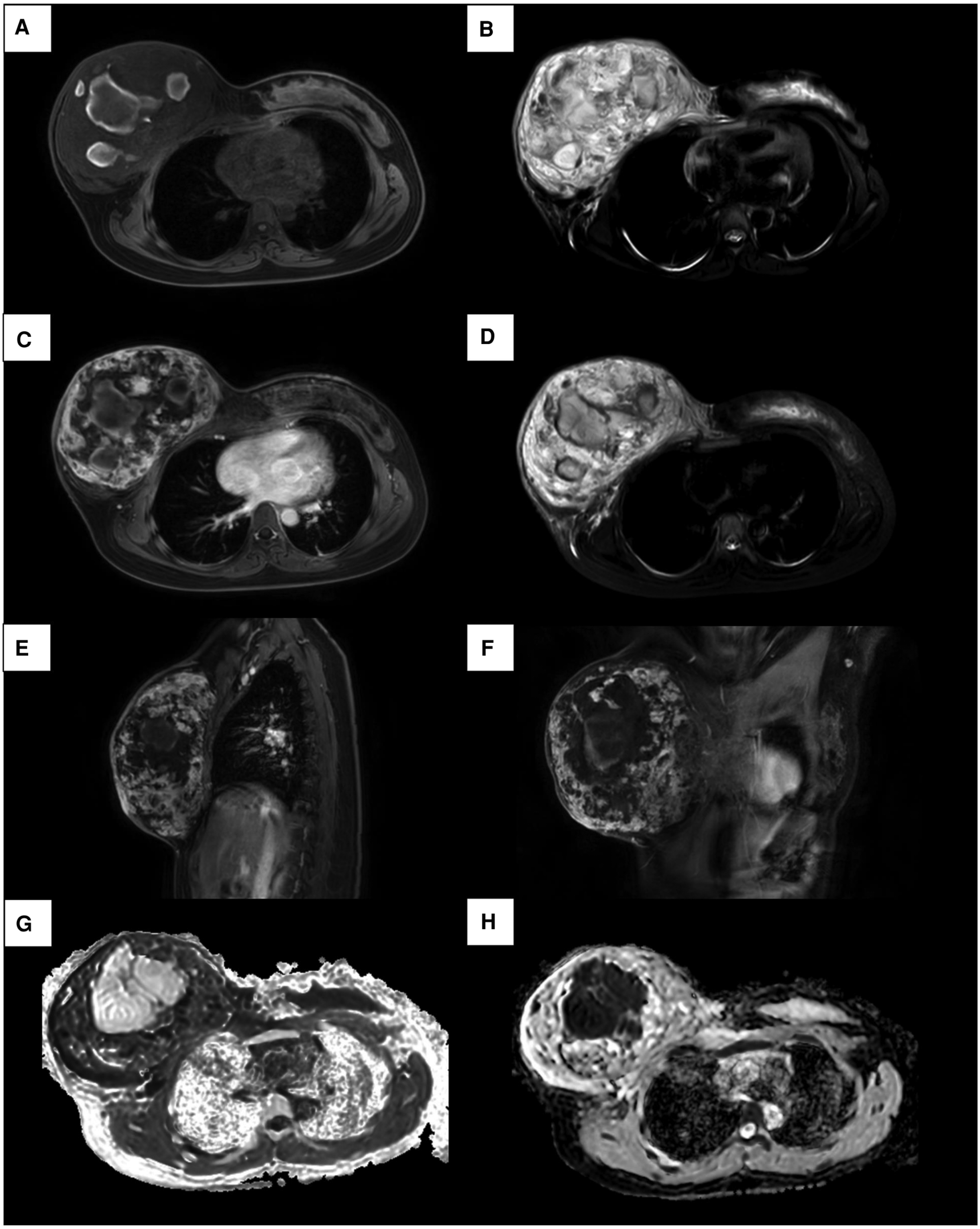

FIGURE 2
MRI images of a 17-year-old female patient with right primary breast angiosarcoma. (A) MRI images show a mixed signal intensity area predominantly composed of isointense mass on T1. (B) Mixed signal intensity area predominantly of high signal intensity on T2. (C, E, F) Enhancement sequences image showed irregular heterogeneous high signal intensity. (D) On fat-suppressed T2-weighted images, the lesion shows bright (high) signal intensity. (G) High signal intensity on DWI and (H) low signal intensity on ADC images demonstrate restricted diffusion.

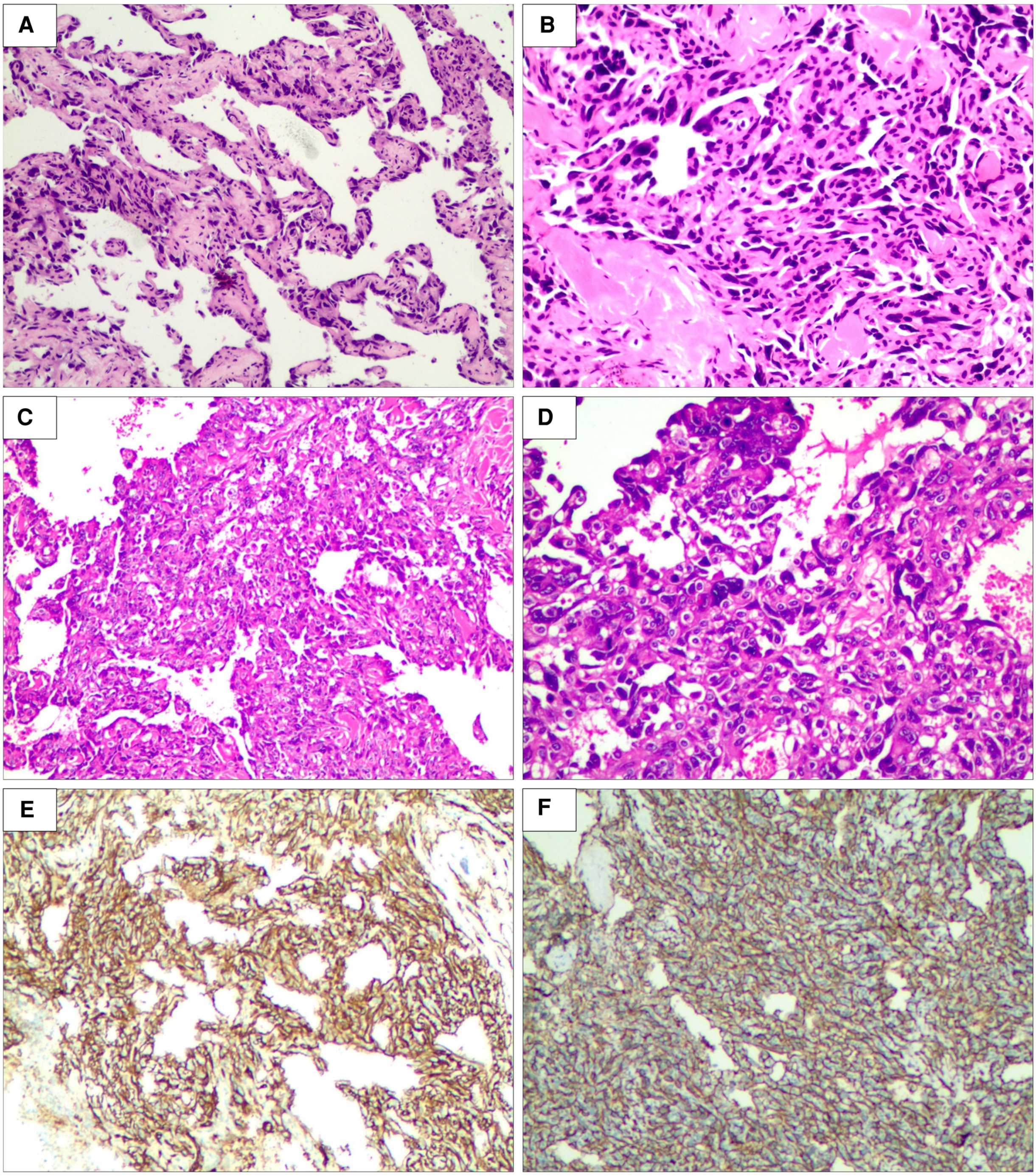

FIGURE 3
Biopsy of right breast lesion microphotography. The tumor is composed of atypical endothelial cells with different degrees of differentiation, forming irregular vascular cavities that coincide with each other, forming papillary and diffuse infiltration (×200, (A) punch biopsy and (C) excisional biopsy). Tumor cells exhibit fusiform or irregular shapes with little cytoplasm and hyperchromatic nuclei (×400, (B) punch biopsy and (D) excisional biopsy). Special stain CD31 positive (E). Special stain CD34 positive (F) (hematein–eosin staining).

and 25–150 mm (mean: 76 mm) for PBA. The pathology of angiosarcoma shows grade 1 (low grade) angiosarcoma with inter-anastomosing vascular channels, subtle endothelial atypia and relatively few mitotic figures. Grade 2 (intermediate grade) tumor cells show moderate nuclear atypia and multilayering of endothelial cells. Grade 3 (high-grade) tumors present with marked nuclear polymorphism, numerous mitoses, and necrosis (16). Most RIAS are high-

FIGURE 4
Digital subtraction angiography (DSA) image of tumor vascularization before embolization (A). DSA after embolization (B).

grade lesions with irregular anastomosing vessels lined by endothelial cells showing nuclear atypia (17). The tumor cells are usually positive for vascular markers (e.g., CD31, CD34, factor VIII-related antigen, FLI1, Ulex europaeus 1 lectin, and ERG) (18). The histological and pathological features are similar between primary and post-radiation angiosarcomas. Therefore, they could not be differentiated on pathological examination (19). Currently, the pathogenesis of angiosarcoma is not completely known.

Several physiopathological mechanisms have been proposed to explain the development of RIAS. Radiotherapy uses ionizing radiation, which either directly affects DNA structure by inducing DNA strand breaks, particularly double strand breaks, or indirectly by generating reactive oxygen species (ROS) that oxidize proteins and lipids and thereby induce additional damage to DNA, like the generation of abasic sites and strand breaks (20). Genome instability and cancer-related gene mutations may drive tumorigenesis (21).

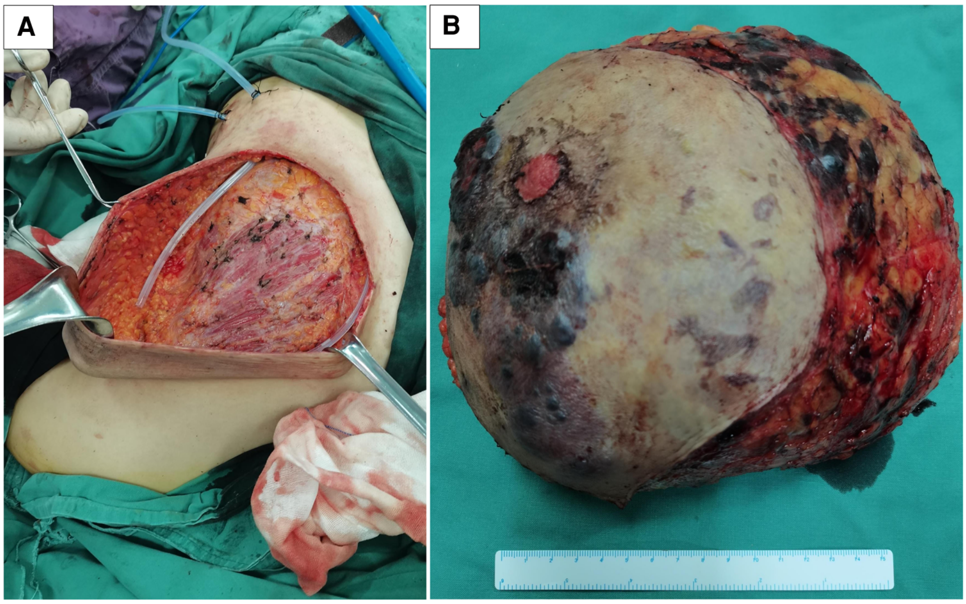

FIGURE 5
The patient was operated on successfully with less amount of blood loss (A). In the mastectomy specimen section of the right breast, the tumor was ill-defined, with a focal area of necrosis and hemorrhage (B).

Although radiation-associated angiosarcoma presents a distinct clinical pattern, the difference between radiation-induced vs. sporadic lesions remain unverified. The establishment of genetic differences between sporadic and radiation-induced angiosarcomas will facilitate discrimination between these two entities (22). As of RIAS, several gene mutations have been reported in the literature. All molecular studies carried out on radiation-induced angiosarcomas present amplification of chromosome 8q24 mapping, Myc oncogene inactivation, and the expression of the p53 gene (23).

Oncogenes of the Myc family, including c-Myc, N-Myc, and L-Myc, are master regulators of cell growth, maturation, and death, because of their transcriptional repression function. The fundamental pathogenetic differences between PBA and RIAS are impossible to differentiate morphologically. Some studies have found that Myc amplification frequently presents in secondary angiosarcoma (radiation, chronic lymphedema) and less frequently in primary angiosarcoma, suggesting that it may be utilized to distinguish RIAS of the breast and PBA (17, 19, 24–26). However, Myc overexpression could also be seen in primary angiosarcoma (27, 28).

The morphological profile of atypical vascular lesions (AVL) showing progression to angiosarcoma has not yet been clearly defined. A study identified some tumor protein p53 (TP53) variation from radiotherapy-induced ipsilateral breast carcinoma in 10 out of 12 (83.3%) cases of AVL and in 7 out of 8 (87.5%) cases of angiosarcoma. At the protein level, the elevated expression of p53 and MDM-2 proteins has been found to associate with the increased vascular endothelial growth factor (VEGF) expression that is found in nearly 80% of angiosarcoma. The genetic alterations of the TP53 gene suggest that its mutational inactivation may be implicated in the pathogenesis of vascular proliferations associated with radiotherapy (29, 30).

The VEGF family and VEGF receptors (VEGFR) that control angiogenesis are found to be frequently altered in angiosarcoma. The genetic mutation VEGFR-2 (kinase insert domain receptor = KDR) or amplification of VEGFR-3 (FMS-like tyrosine kinase 4 = FLT4) have been proposed to have a crucial role in the development of angiosarcoma (31, 32). Mutations in KDR and TP53 were mutually exclusive ($P = .02$, Fisher's exact test), with 8 out of 9 (89%) KDR missense mutations displayed in PBA samples and 9 out of 11 (82%) TP53 missense mutations observed in angiosarcoma samples that were not PBA (33). However, Guo et al. found that the gene amplification of the FLT4 gene encoding the VEGFR3 was found in 25% of secondary angiosarcoma and only associated with Myc amplification. Based on those results, they suggest that FLT4 overexpression may represent a "second hit" in the progression of secondary angiosarcoma and raise a note-worthy possibility of targeting FLT4 as a potential therapeutic option (26). Although activating VEGFR-2 mutations are relatively rare in angiosarcoma, VEGFR-2 is universally overexpressed in angiosarcoma (17, 34, 35). Itakura et al. showed a lower percentage of VEGFR-2 expression was significantly associated with poorer overall survival (31). Uncontrolled VEGF/VEGFR signaling leads to dysregulated angiogenic activity, however, the exact mechanism in angiosarcoma remains to be elucidated.

Previously published case reports have shown that radiation-induced angiosarcoma contained breast cancer-related tumor-suppressor gene BRCA1/BRCA2 mutations (11, 36–38). The defective DNA repair mechanism may also theoretically increase radiosensitivity, increasing susceptibility to carcinogenic effects in surviving cells (39, 40).

The PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene coding for the p110alpha catalytic subunit of class 1A phosphoinositide-3-kinase (PI3K) is frequently mutated in breast cancer (41). Intriguingly, a study showed that 6 out of the 10 PIK3CA alterations were found in PBA samples (32). In addition, another study showed that 9 out of the 10 PIK3CA alterations were found in PBA samples, whereas PIK3CA mutations were significantly enriched in the angiosarcoma subtype compared with other subtypes (9 out of 18 PBA samples vs. 1 out of 29 angiosarcoma samples that were not PBA; $P = .0003$, Fisher's exact test). DNA methylation may serve as a marker of breast tumor cell lineage restriction, thereby reflecting the cell type from which cancer originates and, perhaps, explaining the correlations between the histological heterogeneity and prognosis of breast cancers with their DNA methylation profiles. Each type of activating PI3K mutation is derived from a different lineage of breast malignancies, indicating the site the tumor had originated independently of tumor lineage. It may play an important permissive role in PI3K pathway activation and may provide an interaction with the breast microenvironment conducive to new tumor formation. Of clinical importance, these findings suggest that targeting PI3Kα *via* inhibitors may be useful as a novel therapeutic intervention for patients with PBA (33).

Wei et al. (42) explored the mechanisms of primary and secondary breast angiosarcoma for the discovery of new biomarkers and research into potential therapeutic targets. The study identified 18 differentially expressed genes (DEGs) enriched in the transforming growth factor-β (TGF-β), Wnt, Hippo, and PI3K-Akt signaling pathways. It is possible that genomic testing will help differentiate between the two clinical entities and lay the foundation for the discovery of effective and reliable molecular biomarkers and essential therapeutic targets in the future.

In addition, several other genetic alterations, including POT1, RAS, BRAF, PTPRB, PLCG1, ATM, MSH6, and APC, may be associated with angiosarcoma, although further research is required (43, 44). **Table 1** includes clinical, demographic, and genetic variation data for SBA and PBA.

TABLE 1 Summary of clinical features and genetic variations in various series of patients with breast angiosarcoma.

Author	AS	Age Dx (years)	Number of cases	AS location	BC Stage	ER/PR/Her2	BC Rx	Genetic variations	RT dose (Gy)	Time from RT to AS (years)	AS Rx	F/U (years)
Retter et al. (24)	SBA	67	1	Lt	T1aN0M0	−/+/−	LUM + L + H	c-MYC	50.4 + 12.5	10	BS	Alive NED (2)
Vin Chang et al. (45)	SBA	80	1	Rt + Lt	T1cN0M0	+/+/−	BS + L + C + H	KRAS, PIK3CA, RPTOR, VHL, MYC	Yes	8	BS + RT + C	Dead MT (1)
Sheu et al. (46)	SBA	79	1	Rt	TxNxM0	+/−/ND	BCS + AND + C + H	MYC, NOTCH1	Yes	14	TM	ND
Oliveira et al. (47)	SBA	73	1	Rt	T2N1M0	+/+/−	BCS + AND + C + H	c-MYC	50 + 10	6	SM	Alive NED (2)
Webb et al. (48)	SBA	34	1	Rt	ND	ND	BS	BRCA1, c-MYC	No	10	BS	ND
Shiraki et al. (49)	SBA	72	1	Rt	T1bN0M0	+/+/−	BCS + H	c-MYC	50	5	M + C	Dead MT (2.6)
Manjee et al. (50)	SBA	70	1	Lt	ND	ND	LUM	MYC	Yes	7	M	ND
Mentzel et al. (51)	SBA	36–83	20	Br				c-MYC	Yes			
Daniels et al. (52)	SBA	71 (48–94)	10					MYC	Yes	6.5 (4–14)		
Tidwell et al. (53)	SBA	68	1	Rt	TxN0M0	+/+/ND	BCS + AND	c-MYC	34	9	TM	Alive LR (0.25)
Parvez et al. (37)	SBA	62	1	Rt	Lt T1cN0M0 Rt T1bN0M0	+/ND/ND	Lt LUM + AND, Rt LUM + L + C + H	BRCA2	42.5	0.5	BS + RT	ND
Cornejo et al. (54)	SBA	73 (51–91)	17				BCS	13 (76%) MYC, 3 (18%) FLT4, 13 (76%) FLT4	Yes	7.2 (4.3–11.6)		
Silva et al. (55)	SBA	78	1	Lt	ND	ND	BCS + AND	VEGFR2	Yes	11	M + RT + C + TKI	Alive NED (3.4)
Barbosa et al. (56)	SBA	32	1	Rt	T2N0M0	+/+/+	BCS + L + C + H + Trastuzumab	TP53	Yes	3.5	TM	ND
Tajima et al. (57)	SBA	73	1	Lt	ND	ND	C	c-MYC	50	7	TM + C	Alive NED (4.5)
	SBA	71	1	Lt	ND	ND	BCS + AND	VEGF	50	9		

(*continued*)

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TABLE 1 Continued

Author	AS	Age Dx (years)	Number of cases	AS location	BC Stage	ER/PR/Her2	BC Rx	Genetic variations	RT dose (Gy)	Time from RT to AS (years)	AS Rx	F/U (years)
Azzariti et al. (58)											Lt M + ECT + C + TKI	Alive MT (3)
Fernandez et al. (59)	SBA	74 (58–87)	6					6 (100%) MYC	Yes	7.2 (4–10)	ND	ND
Mentzel et al. (60)	SBA	(46–95)	25					25 (100%) MYC, 24 (96%) MYC, 20 (80%) prox-1	Yes	1.5–13	ND	ND
Teruyama et al. (61)	PBA	52	1					FGFR4, KDR, TP53	No		Rt LUM+C	Dead MT (22)
Shiraki et al. (49)	PBA	80	1	Lt	T2N0M0	+/+/−	BCS + H	c-MYC	No		Lt M + C	Alive LR (1.5)
Al-Salam et al. (62)	PBA	29	1					HIF1α, VEGF, VEGFR, WT-1	50.4		BCS + AND + ANS + Rt + C + avastin + TKI	Alive MT (0.5)
Laé et al. (19)	PBA	36 (19–54)	15					c-MYC 1/15			M + C	5.9 (0.5–23.9)
	SBA	70 (42–89)	32					c-MYC 32/32	50 (32.5–66)	8.8 (3.3–23.2)		3.2 (0.1–9.3)
Fraga-Guedes et al. (63)	PBA	49 (30–77)	12					c-MYC 0/12			ND	9.1 (0.1–13.6)
	SBA	69 (37–88)	37					c-MYC 20/37	Yes	9.1 (1.5–27.6)	ND	9.1 (0.1–13.6)

Dx, diagnosis; BC, breast carcinoma; BC Rx, breast carcinoma treatment; ER, estrogen receptors; PR, progesterone receptors; HER2, human epidermal growth factor receptor 2; ND, non-determined; RT, radiotherapy; C, chemotherapy; H, hormone therapy; TKI, Multi-target tyrosine kinase inhibitors (sunitinib or pazopanib); ECT, electrochemotherapy; BS, bilateral surgery; L, sentinel lymph or lymphadenectomy; AS, angiosarcoma; F/U, follow up; Br, breast; SM, simple mastectomy; TM, total mastectomy; AS Rx, angiosarcoma treatment; M, mastectomy; ANS, axillary node sampling; AND, axillary node dissection; Rt, right; Lt, left; BCS, breast-conserving surgery; LUM, lumpectomy; IHC, Immunohistochemistry; D, dead; NED, no evidence of disease (AS); LR, local recurrence; MT, metastasis.

Our patient, who presented with PBA, is in agreement with a literature review involving younger premenopausal females with no previous history of cancer. The tumor was characterized by rapid growth and bleeding. It was persistent bleeding and hemostasis was difficult to achieve. Ongoing bleeding led to not only coagulation factors, and fibrinogen consumption but also coagulation disorders. Nevertheless, the source of the bleeding in this case could not be identified due to an unclear diagnosis. Furthermore, the clinical and radiologic findings were not specific.

It is frequently difficult to accurately diagnosis a breast lesion as breast angiosarcoma. Differential diagnosis should be made considering both radiological, and histopathology, and immunohistochemistry findings. Differential diagnosis includes benign hemangioma, stromal sarcoma, cystosarcoma phyllodes, metaplastic carcinoma, reactive spindle cell proliferative lesions, fibrosarcoma, myoepithelioma, fibromatosis, liposarcoma, and squamous cell carcinoma with sarcomatoid features (64). This case was initially accepted as a hemangioma. The puncture may result in tumor rupture or great vessel injury, causing hemorrhage and shock. Although a needle biopsy might further aggravate the bleeding risk and can sometimes fail to give definite results, a biopsy is considered the gold standard and an indispensable means of confirming a diagnosis. We performed a biopsy, histological, and immunohistochemical analysis, which revealed the diagnosis of PBA.

Abnormalities in coagulation function make surgery difficult due to the substantial risk of bleeding. Therefore, DSA and tumor vascular embolization were used to reduce the risk of bleeding and allow for safe surgical resection. This treatment successfully stopped tumor bleeding. The assurance of gross tumor resection with tumor-negative resection margins is the primary and preferred treatment modality for localized disease. Lymphatic metastasis is relatively rare, and therefore, axillary node dissection remains controversial in the absence of positive nodes (65). Chemotherapy may help to achieve an improved prognosis in disease control and survival and further reduce the local recurrence rate (9), but the role remains controversial at present (7). A recent study has shown that cytotoxic chemotherapies, in particular anthracycline-based regimens and taxanes can produce significant responses to therapy in a subset of patients (66). Adjuvant radiotherapy could be used to reduce the incidence of locoregional recurrence (67). However, the disease is usually resistant to currently available chemotherapy and radiotherapy, which may not alter the poor prognosis. Sher et al. reported that there was no significant survival difference between patients who had and had not received anthracyclines, taxanes, gemcitabine, and ifosfamide as adjuvant chemotherapy (68). Due to the high-level expression of VEGF in angiosarcoma, therapies targeting VEGF are hopeful to improve prognosis, however, this issue warrants being proven in a properly designed prospective study (69).

Breast angiosarcoma shows hematogenous spread like other sarcomas rather than *via* lymphogenous route. The most common site of recurrence is local-regional. Distant metastases are frequently observed at an early stage. Breast angiosarcoma has been reported to metastasize usually to the liver, bone, lung, skin, central nervous system, spleen, and subcutaneous soft tissues (65, 68). Unlike other sarcomas and breast cancer, lymph node metastasis is exceedingly rare (70). In this case, chest, bone, liver, spleen, and lung metastases were observed.

Given the rarity of PBA, especially with severe bleeding, and the poor prognosis following the identification, knowledge of this lesion prompts further assessment for diagnosis, therapy, and prognosis is crucial when evaluating a patient. The objective and unified criteria for the diagnosis, staging and treatment are still lacking.

Conclusion

We herein present a case of PBA with severe bleeding in a 17-year-old woman. The definitive diagnosis of PBA is usually difficult, and histopathological examination is the standard approach at present. Mastectomy remains the most favored therapy. Tumor vascular embolization can reduce the risk of bleeding. The role and importance of chemotherapy and radiotherapy in the treatment remains unclear. Furthermore, genetics and genomics will remain powerful approaches to understanding and treating diseases. Therapies targeting VEGFR are hopeful for improving prognosis, but the therapeutic effect still needs further exploration and verification.

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.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patient's legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

YW, LQ, LC, and YH were the team responsible for the surgical treatment of this patient. YH and PC were responsible for the research idea, study design. The first draft of the manuscript was written by YH. 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-Term outcomes of uncut roux-en-Y anastomosis in laparoscopic distal gastrectomy: A retrospective analysis

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Background: Uncut Roux-en-Y (U-RY) has been increasingly used in radical gastric cancer surgery, but it is still in the exploratory stage. There is insufficient evidence for its long-term efficacy.
Methods: From January 2012 to October 2017, a total of 280 patients diagnosed with gastric cancer were eventually included in this study. Patients undergoing U-RY were assigned to the U-RY group, while patients undergoing BillrothII with Braun (B II + Braun) were assigned to the B II + Braun group.
Results: There were no significant differences between the two groups in operative time, intraoperative blood loss, postoperative complications, first exhaust time, time to liquid diet, and length of postoperative hospital stay (all $P > 0.05$). Endoscopic evaluation was performed 1 year after surgery. Compared to B II + Braun group, the uncut Roux-en-Y group had significantly lower incidences of gastric stasis [16.3% (15/92) vs. 28.2% (42/149), $\chi^2 = 4.448$, $P = 0.035$], gastritis [13.0% (12/92) vs. 24.8% (37/149), $\chi^2 = 4.880$, $P = 0.027$] and bile reflux [2.2% (2/92) vs. 20.8% (11/149), $\chi^2 = 16.707$, $P < 0.001$], and the differences were statistically significant. The questionnaire was completed 1 year after surgery,the QLQ-STO22 scores showed that, the uncut Roux-en-Y group had a lower pain score(8.5 ± 11.1 vs. 11.9 ± 9.7, $P = 0.009$) and reflux score(7.9 ± 8.5 vs. 11.0 ± 11.5, $P = 0.012$), and the differences were statistically significant ($P < 0.05$). However, there was no significant difference in overall survival ($P = 0.688$) and disease-free survival ($P = 0.505$) between the two groups.
Conclusion: Uncut Roux-en-Y has the advantages of better safety, better quality of life and fewer complications, and is expected to be one of the best methods for digestive tract reconstruction.

KEYWORDS

gastric cancer, laparoscopic surgery, uncut Roux-en-Y anastomosis, billrothII+Braun anastomosis, quality of life

1. Introduction

Gastric cancer is one of the most common malignancies in the digestive system, and radical gastrectomy is the most effective treatment (1). There are few studies on the long-term outcomes of laparoscopic U-RY digestive tract reconstruction after resection of distal gastric cancer. Domestic and foreign experts still have great controversy about the advantages and disadvantages of U-RY digestive tract reconstruction after laparoscopic resection (2, 3).

In this study, we aimed to explore the long-term outcomes of uncut Roux-en-Y anastomosis in radical laparoscopic distal gastrectomy.

2. Methods

2.1. Selection of enrolled patients

The study was conducted in accordance with the Helsinki Declaration (as revised in 2013). This study was approved by the Ethics Committee of Weifang People's Hospital. All patients consented to data being used for research when receiving treatment. Inclusion criteria were as follows: Aged 18 to 80, gastroscopic biopsy-confirmed gastric cancer, pathological staging ($pT1{\sim}4_aN0{\sim}3M0$), obtain informed consent of patients. Exclusion criteria were as follows:received neoadjuvant radiotherapy and chemotherapy prior to surgery, Palliative surgery, history of other primary malignancies, incomplete information or loss to follow-up. A flowchart of the study is shown in Figure 1.

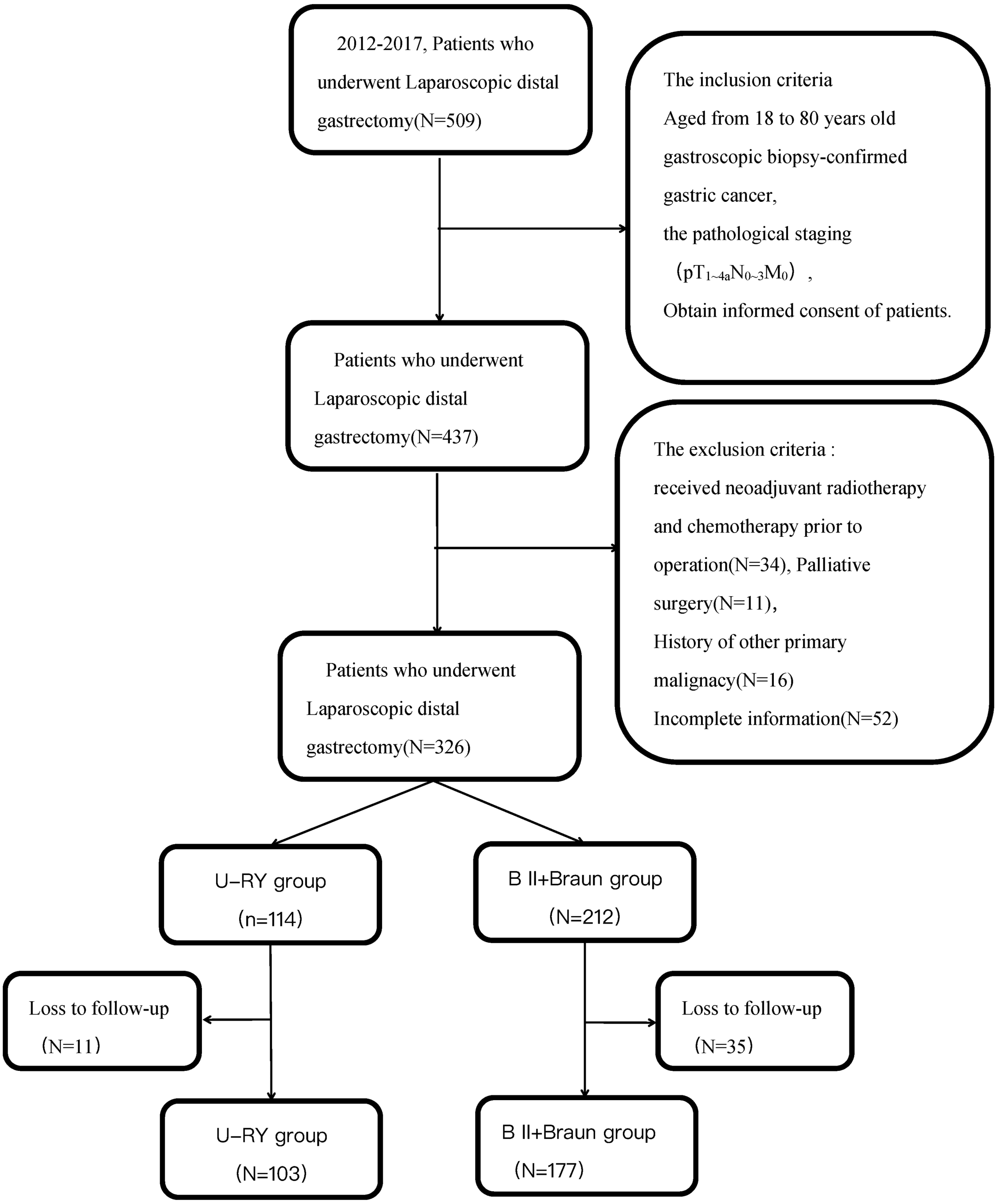

FIGURE 1
Flowchart of the study, 280 patients were included in this study.

The study protocol was approved by the research ethics committee of Weifang People's Hospital. Written informed consent was obtained from all patients prior to surgery. Each patient signed an informed consent to allow their treatment-related information to be used in future studies.

2.2. Surgical procedure

All patients underwent laparoscopic distal gastrectomy with D2 lymphadenectomy based on Japanese gastric cancer treatment guidelines. Digestive tract reconstruction was performed *in vitro*.

U-RY and B II + Braun reconstructions were established using mechanical staples. In the U-RY group, gastrojejunal anastomosis was established between the residual stomach and jejunum 25 cm distal to Treitz ligament after distal gastrectomy. Then, a side-to-side jejunojejunostomy was established between the afferent and efferent jejunal limbs approximately 30 cm away from the site of gastrojejunal anastomosis and 25 cm away from Treitz ligament. Finally, the jejunal lumen was occluded using the four-row (knifeless) stapler method at a site 3–5 cm proximal to gastrojejunal anastomosis (Figures 2, 3). Compared to U-RY group, B II + Braun group lacked the steps of the jejunal lumen that occluded, and other surgical procedures were the same.

All operations on patients with gastric cancer were performed by the same surgical team. Both methods of reconstructing the digestive tract are described in Figure 4.

2.3. Data collection and follow-up

The Operation time, digestive tract reconstruction time, intraoperative blood loss, first exhaust time, postoperative hospital stay, and perioperative complications were monitored during the perioperative period. The QoL index of the two groups 1 year after surgery was assessed using the QLQ-STO22 questionnaires. The QLQ-STO22 responses were linearly converted into scores ranging from 0 to 100 according to the EORTC scoring manual. High scores for items related to global health status and functions and low scores for items related to symptoms and single items (i.e., Appetite loss, Dyspnea, dry mouth, taste, body image, and hair loss) indicate a favorable QoL (4). Postoperative QoL scores were collected 1 year after surgery by telephone calls, letters, or outpatient visits. The follow-up period was until June 2022.

Patients were followed up every 3 months at the first 2 years after surgery and every 6 months at the following 3 years until the patient died or the study was terminated. Patients were followed up by outpatient appointment, letter or telephone consultation. The median follow-up was 46 months in the U-RY group and 46 months in the B II + Braun group. All patients were followed until death or the end of the study in June 2022.

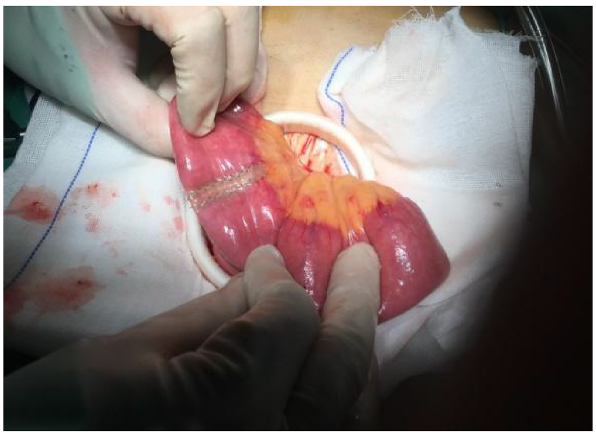

FIGURE 2
Adopt four-row staplers (knifeless) methods of jejunal occlusion.

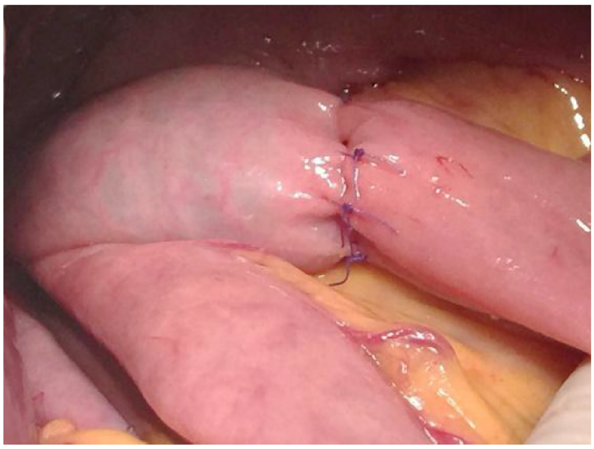

FIGURE 3
Reinforced by interrupted full-thickness sutures at the occlusion site.

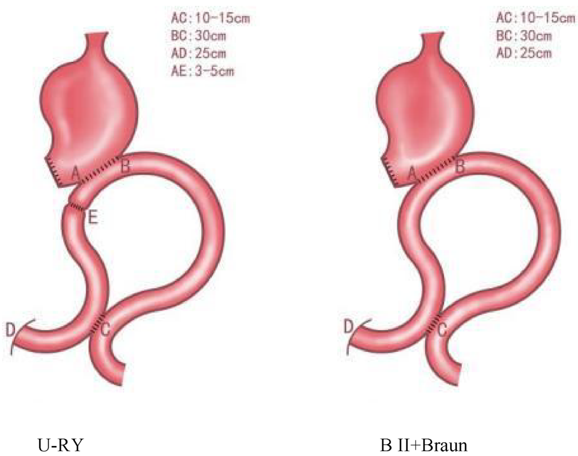

FIGURE 4
The two methods of digestive tract reconstruction are depicted.

2.4. Statistical analysis

SPSS version 26.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis. Continuous variables were compared using the Student's *t*-test and are expressed as mean ± standard deviation. The frequencies of categorical variables are expressed as rates, and rates are compared using the chi-squared test or Fisher's exact test. Here, $P < 0.05$ was considered statistically significant.

3. Results

Finally, 280 patients (male = 226, 80.7%; female = 54, 19.3%) were included in this study. These patients were divided into the U-RY group ($n = 103$) and B II + Braun group ($n = 177$) according to the technique used for digestive tract reconstruction. Baseline characteristics of the two groups were comparable (**Table 1**).

No deaths were recorded during the perioperative period. There were no significant differences between the two groups in operative time, intraoperative blood loss, postoperative complications, time to flat, time to liquid diet, and length of postoperative hospital stay (all $P > 0.05$). The incidence of specific complications in the two groups were 15.53% (16/103) and 14.12% (25/177), respectively, but the difference was not statistically significant. In the BII + Braun group, one patient developed duodenal stump anastomotic fistula after surgery and was discharged with improvement after a second operation (**Table 2**).

TABLE 1 Baseline information for two groups of patients.

	U-RY group ($n = 103$)	B II + Braun group ($n = 177$)	T/χ^2	*P*-value
Sex, *N* (%)			0.02	0.966
Male	83 (80.58)	143 (80.79)		
Female	20 (19.42)	34 (19.21)		
BMI, *N* (%)			1.330	0.722
<18.5 (thin)	2 (1.94)	4 (2.26)		
18.5–25 (normal)	71 (68.93)	114 (64.41)		
25–30 (over weight)	27 (35.92)	56 (31.64)		
≥30 (obesity)	3 (2.91)	3 (1.69)		
ASA grade, *N* (%)			0.902	0.342
I/II	86 (63.50)	155 (87.57)		
III	17 (16.50)	22 (12.43)		
Tumor size, *N* (%)			0.032	0.859
<4 cm	35 (33.98)	62 (35.03)		
≥4 cm	68 (66.02)	115 (64.97)		
Preoperative CEA, *N* (%)			0.002	0.967
Positive	84 (81.55)	144 (81.36)		
Negative	19 (18.45)	33 (18.64)		
Pathologic T stage, *N* (%)			0.891	0.827
T1	17 (16.50)	26 (14.69)		
T2	31 (30.10)	55 (31.07)		
T3	43 (41.75)	69 (38.98)		
T4a	12 (11.65)	27 (15.25)		
Pathologic *N* stage, *N* (%)			5.205	0.267
N0	3 (2.91)	11 (6.21)		
N1	43 (41.75)	73 (41.24)		
N2	31 (30.10)	61 (79.22)		
N3	26 (25.24)	30 (16.95)		
Pathologic TNM stage, *N* (%)			1.194	0.754
I	12 (11.65)	24 (13.56)		
II	49 (47.57)	73 (41.24)		
III	51 (49.51)	79 (44.63)		

3.1. Comparison of postoperative quality of life between the two groups

3.1.1. QLQ-STO22 scale

After 1 year of follow-up, 2 patients in the U-RY group had recurrence and metastasis (1 case of liver metastasis and 1 case of anastomotic recurrence). One patient in the BII + Braun group had abdominal metastasis. Three patients in the U-RY group died (one with liver metastasis, one with coronary heart disease, and one with tumor recurrence) and two patients in the BII + Braun group died (one with coronary heart disease, and one with tumor recurrence).

According to the quality of life questionnaire 1 year after surgery, there were 100 cases in the U-RY group and 175 cases in the BII + Braun group.The QLQ-ST22 scores showed that

TABLE 2 Comparison of postoperative conditions between the two groups.

	U-RY group ($n = 103$)	BII + Braun group ($n = 177$)	T/χ^2	*P*-value
Operative time (min)	237.6 ± 26.9	231.8 ± 22.9	1.928	0.055
Estimated blood loss, (ml)	85.8 ± 11.9	89.6 ± 18.1	1.904	0.058
Harvested lymph nodes (*n*)	24.1 ± 5.5	25.9 ± 9.5	1.817	0.070
Mean gas passing, (days)	68.6 ± 10.4	70.7 ± 12.7	1.466	0.144
Mean postoperative hospital stay, (days)	11.7 ± 3.7	12.0 ± 2.7	0.896	0.371
Histology, *N* (%)			1.071	0.585
Differentiated	64 (62.14)	99 (55.93)		
Undifferentiated	35 (33.98)	69 (38.98)		
Other	4 (3.88)	9 (5.08)		
Postoperative complication, *N* (%)	16 (15.53)	25 (14.12)	0.104	0.748
Anastomotic leakage	2	3		
anastomotic stenosis	1	0		
Intra-abdominal infection	3	5		
Abdominal bleeding	1	2		
Ileus	0	2		
Pneumonia	4	7		
Incision-related complications	1	3		
Duodenal stump fistula	0	1		
Delayed gastric emptying	2	2		
Clavien-Dindo complication grade, *N* (%)			0.234	0.889
I/II	13 (12.62)	19 (10.73)		
III	3 (2.91)	5 (2.82)		

TABLE 3 Comparison of QLQ-STO22 score items between the two groups in 1 year after surgery.

Group	Dysphagia	Pain	Reflux symptom	Eating restrictions	Having a dry mouth	Taste	Anxiety	Body image	Hair loss
U-RY group (n = 100)	6.6 ± 8.5	8.5 ± 11.1	7.9 ± 8.5	9.2 ± 9.7	7.0 ± 7.5	6.5 ± 6.9	8.6 ± 8.3	5.9 ± 6.4	7.3 ± 7.4
BII + Braun group (n = 175)	7.6 ± 9.6	11.9 ± 9.7	11.0 ± 11.5	10.4 ± 9.1	8.1 ± 8.3	7.7 ± 6.6	8.2 ± 9.1	6.7 ± 6.9	8.3 ± 8.6
T	0.843	2.627	2.526	1.076	1.033	1.399	0.349	0.974	1.027
P-value	0.400	0.009	0.012	0.283	0.303	0.163	0.727	0.331	0.305

compared to the BII + Braun group, the U-RY group had a lower pain score (8.5 ± 11.1 vs. 11.9 ± 9.7, $P = 0.009$) and reflux score (7.9 ± 8.5 vs. 11.0 ± 11.5, $P = 0.012$), and the difference was statistically significant at 1 year after surgery ($P < 0.05$). The U-RY group had a higher quality of life (**Table 3**).

3.1.2. Endoscopic findings

One year after surgery, a total of 241 patients underwent endoscopic evaluation, including 92 cases in the U-RY group and 149 cases in the BII + Braun group. Compared to Billroth II with Braun group, the uncut Roux-en-Y group had significantly lower incidences of gastric stasis [16.3% (15/92) vs. 28.2% (42/149), $\chi^2 = 4.448$, $P = 0.035$], gastritis [13.0% (12/92) vs. 24.8% (37/149), $\chi^2 = 4.880$, $P = 0.027$] and bile reflux [2.2% (2/92) vs. 20.8% (11/149), $\chi^2 = 16.707$, $P < 0.001$], and the differences were statistically significant. There was no reflux esophagitis in U-RY group, but 3 cases in the BII + Braun group (2.0%). There was no significant difference between the two groups ($\chi^2 = 1.876$, $P = 0.171$). No recanalization was found in the U-RY obliterated afferent jejunal limb 1 year after surgery. However, recanalization occurred in 5 cases (4.9%) during the follow-up of 1–5 years after surgery. The results of this study suggest that the risk of recanalization of the proximal jejunal closure point of the input loop increases with the prolongation of postoperative time.

3.2. Comparison of postoperative survival status of the two groups

There was no significant difference in overall survival (OS) and disease-free survival (DFS) between the U-RY group and the BII + Braun group (**Figure 5**). There was no significant difference in recurrence and metastasis between the U-RY group and the B II + Braun group (**Table 4**).

4. Discussion

Gastric cancer is a serious public health threat, and surgical treatment has become the first option (1). U-RY has been increasingly used in radical gastric cancer surgery, but it is still in the exploratory stage (5–7).

There were no significant differences between the two groups in operative time, intraoperative blood loss, postoperative complications, first exhaust time, time to liquid diet, and length of postoperative hospital stay (all $P > 0.05$); The results suggest that U-RY is safe and feasible for postoperative digestive tract reconstruction of distal gastric cancer. Postoperative complications are also an important index to evaluate the safety of operation. Postoperative complications not only prolong the length of stay, increase the cost, but also reduce trust between doctors and patients. The total incidence of postoperative complications in the U-RY group and BII + Braun group was 15.53% (16/103) and 14.12% (25/177), respectively, and there was no statistical difference ($P > 0.05$). U-RY reconstruction is a modification of BII + Braun anastomosis, which has an additional staple line across the afferent limb to block bile reflux. In terms of quality of life 1 year after surgery, the score of pain and reflux symptoms in the U-RY group was better than that in the BII + Braun group, indicating that it could significantly improve the **quality of life** of patients after surgery (8, 9). Quality of life has always been regarded as one of the important indicators for measuring the quality of life of cancer patients (10).

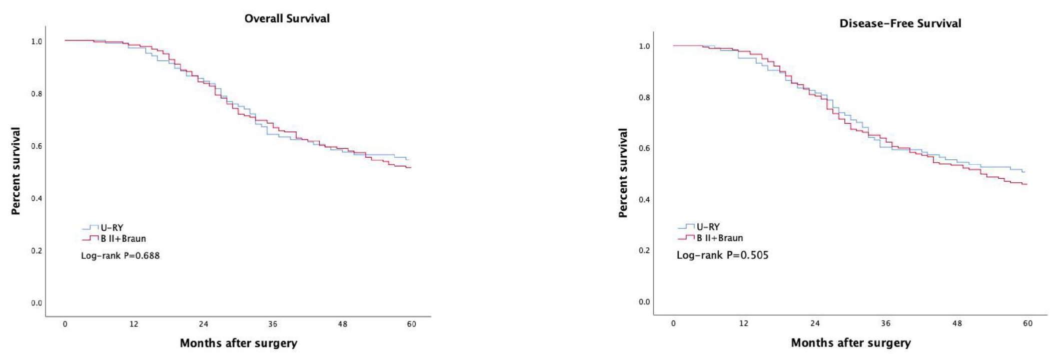

FIGURE 5
Comparison of long-term curative effect between two groups of patients. (A) Overall survival, (B) Disease-free survival.

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TABLE 4 Comparison of the long-term outcomes of the two groups.

Outcome	U-RY group (*N* = 103)	B II + Braun group (*N* = 177)	χ^2	*P*-value
Status at the last follow-up, *N* (%)			0.324	0.569
Survival	56 (54.37%)	90 (50.85%)		
Dead	47 (45.63%)	87 (49.15%)		
Local recurrence, *N* (%)	10 (9.71%)	24 (13.56%)	0.905	0.341
Distant metastasis, *N* (%)	16 (15.53%)	28 (15.82%)	0.004	0.950
Liver metastasis, *N* (%)	9 (8.74%)	17 (9.60%)		
Lung metastasis, *N* (%)	7 (6.80%)	11 (6.21%)		

In terms of postoperative gastric reflux symptoms, many studies have shown that U-RY can prevent pancreatic juice and bile reflux, reduce the incidence of Roux-en-Y stasis syndrome (RSS), and improve the quality of life of patients after surgery (11, 12). Pain is a subjective feeling, which is generally thought to be affected by postoperative abdominal adhesion, the incidence and severity of reflux symptoms, cholelithiasis, and other factors. In terms of pain score, the result of U-RY group is better than that of BII + Braun, which may benefit from the closure point of U-RY anastomosis.The symptoms of related residual gastritis caused by reflux were significantly alleviated.Reducing reflux and pain is helpful to improve the overall health status of patients in U-RY group after surgery.

The results of this study showed that there was no recanalization of the proximal jejunal closure point of the input loop within 1 year after U-RY, but recanalization occurred in 5 (4.9%) cases during follow-up 1–5 years after operation. The results suggest that with the extension of postoperative time, the risk of recanalization of the proximal jejunal closure point of the input loop will increase, resulting in alkaline reflux to the residual stomach and inflammatory lesions of the esophagus (13, 14). Since the application of U-RY anastomosis in the treatment of distal gastric cancer, the recanalization rate of the closed point has gradually decreased, not only because of the continuous development of closed materials and medical instruments, but also the distance between the closed point of the input loop and gastrointestinal anastomosis, which is also the key point to prevent recanalization and improve the quality of life. At the same time, we found that the length of the jejunal stump of the input loop was no longer surgically designed 3–5 cm in the digestive tract imaging, and the distance of the jejunal stump had changed to 4–8 cm after 5 years. Therefore, we speculate that the food deposited in the blind loop of the jejunum is pushed and hits the closing point, which leads to adaptive elongation of the intestinal stump. With the increase in the length of the intestinal stump, according to the relationship between pressure and height or length, the pressure on the closing point gradually increases, which explains why the recanalization rate will gradually increase with the extension of time.Therefore, as long as there is a distance between the closing point and gastrointestinal anastomosis, with the extension of time, it will be constantly squeezed by food, resulting in intestinal adaptation elongation, and the recanalization rate will increase. Therefore, we suggest that the shorter the length of the jejunal stump, the better. At the same time, relevant clinical studies found that the incidence of postoperative intestinal obstruction in the U-RY group was significantly higher than that in the Roux-en-Y anastomosis group ($P = 0.027$). In the U-RY group, postoperative intestinal obstruction occurred in 6 patients (17.6%), all within half a year after surgery (15). To analyze the reason, the researchers chose the closing point at the distance from the gastrojejunostomy to the 5 cm, and a "pocket" device may be formed between the gastrointestinal anastomosis and the closure point, which may lead to food confinement between the closure point and the gastrojejunal anastomosis, leading to emptying disorders or intestinal obstruction. After that, we improved the procedure and chose the closure point at 2–3 cm near the gastrojunostomy. Follow-up results showed that the quality of life of patients who underwent U-RY anastomosis at a later stage was significantly improved. However, the follow-up time and cases in the study are limited, so the problem of recanalization needs further follow up.

In our study, there was no difference in the incidence of postoperative abdominal infection and tumor recurrence between the two groups. Related clinical studies have shown that intraoperative lymph node dissection also has a significant impact on patient prognosis (16). In this study, there was no statistical significance in the number of lymph node dissection between the two groups. There was no significant difference in tumor recurrence, metastasis and long-term survival between the two groups. Adequate preoperative preparation, prophylactic use of antibiotics, use of aseptic gloves, adequate lymph node dissection, and strict adherence to aseptic and tumor-free principles ensure the safety of U-RY surgery. For gastric cancer patients undergoing surgery, the long-term effect of surgery has a direct impact on patient survival. There was no significant difference in recurrence, distant metastasis, OS, and DFS between the two groups. These results suggest that the long-term effect of U-RY on gastric cancer is the same as that of BII + Braun. However, U-RY digestive tract reconstruction is limited by mesenteric length, and there may be a problem of excessive anastomotic tension. We strictly evaluate the patient's condition and surgical indications to avoid surgical failure.

The author acknowledges that this study has some limitations. First of all, this study is a single-center retrospective study, the number of cases is relatively small, the conclusion of evidence-based medical evidence is still low, the results still need large samples, multi-center randomized controlled trials to further verify. Secondly, the QLQ-STO22 scale data are obtained by questionnaire, and the results may have a certain degree of deviation due to the influence of patients' emotions, cultural background and education level.

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 Weifang People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GZ conjectured the study and reviewed the paper; GZ and SZ analyzed the data and wrote the draft; XS and JQ selected the patients and collected the data. 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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The comparison of manual and mechanical anastomosis after total pharyngolaryngoesophagectomy

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Background: Total pharyngolaryngoesophagectomy (TPLE) is considered as a curative treatment for hypopharynx cancer and cervical esophageal carcinomas (HPCECs). Traditional pharyngo-gastric anastomosis is usually performed manually, and postoperative complications are common. The aim of this study was to introduce a new technique for mechanical anastomosis and to evaluate perioperative outcomes and prognosis.

Methods: From May 1995 to Nov 2021, a series of 75 consecutive patients who received TPLE for a pathological diagnosis of HPCECs at Sun Yat-sen Memorial Hospital were evaluated. Mechanical anastomosis was performed in 28 cases and manual anastomosis was performed in 47 cases. The data from these patients were retrospectively analyzed.

Results: The mean age was 57.6 years, and 20% of the patients were female. The rate of anastomotic fistula and wound infection in the mechanical group were significantly lower than that in the manual group. The operation time, intraoperative blood loss and postoperative hospital stays were significantly higher in the manual group than that in the mechanical group. The R0 resection rate and the tumor characteristics were not significantly different between groups. There was no significant difference in overall survival and disease-free survival between the two groups.

Conclusion: The mechanical anastomosis technology adopted by this study was shown to be a safer and more effective procedure with similar survival comparable to that of manual anastomosis for the HPCECs patients.

KEYWORDS

total pharyngolaryngoesophagectomy, anastomosis, manual, mechanical, postoperative complications

Introduction

Hypopharyngeal and cervical esophageal carcinomas (HPCECs) remain a challenging clinical problem (1). These neoplasms are relatively rare and account for approximately 5-6% of all head and neck tumors (2). Most HPCECs are usually diagnosis at locally advance stages (70-80%) for the paucity of early symptoms and exhibit a poor prognosis (3).

Given the critical location and extensive involvement of the tumor, total pharyngoesopphagectomy (TPLE) followed by digestive reconstruction have been the most popular treatment modalities in the past (4). Definitive chemoradiotherapy (dCRT) and multimodality therapy (such as neoadjuvant chemoradiotherapy followed by surgery or surgery plus adjuvant chemotherapy) have gradually become central in the therapies of HPCECs (5, 6). It is worth noting that salvage TPLE surgery is a recommended choice for residual and recurrent disease when definitive medical treatment fails (7, 8).

TPLE surgical resection is a commonly used surgical method for cervical esophageal and hypopharyngeal cancer. However, such surgery has great trauma and high perioperative risk (6), so it is urgent to improve the surgical technique and prove its safety and effectiveness. As an effective surgical tool, stapling device has been widely used in the surgical treatment of esophageal cancer, which can greatly reduce operative time and the incidence of anastomotic fistula (9). However, hand sewing is the most commonly used anastomosis method in TPLE surgery. The main reason is that after larynpharyngectomy with total esophagectomy, only the tongue root and posterior pharyngeal wall remain in the surgical field, resulting in insufficient operating space and uneven tissue thickness, which makes it impossible to imbed the head end of stapler *in situ* for effective anastomosis.

Up to now, the application of staple device in TPLE is rarely reported. Some researchers have showed that using stapler inserted orally in the anastomosis process of TPLE (10, 11). In this study, we demonstrated a new technique for directly *in situ* anastomosis (avoiding the transoral approach) by using stapling device, and retrospectively compared perioperative and survival outcomes between mechanical and manual anastomosis in a single-center.

Patients and methods

Patient selection

From May 1995 to Nov 2021, a total of 99 consecutive patients with a pathological diagnosis of HPCECs and who received TPLE at Sun Yat-sen Memorial Hospital were retrospectively screened. We selected patients for surgery based on the following criteria: aged between 18 and 75 years old; diagnosed with HPCECs; clinical staged with I- IV; and with normal hematologic, hepatic, and renal function. After 17 cases of pectoralis major myocutaneous flap graft, 2 cases of free jejunal flap graft and 5 cases of gastroesophageal anastomosis were excluded, 75 cases of pharyngogastric anastomosis (47 cases of manual anastomosis, 28 cases of mechanical anastomosis) were eventually included for study (Figure 1).

Before surgery, a diagnosis of pathologic disease was obtained in all patients by gastroscope or direct laryngoscopy. The preoperative work-up consisted of a thorough medical history and physical examination, enhanced computed tomography scan of the neck and chest, abdominal ultrasonography, and upper gastrointestinal barium meal (as well as positron emission tomography and cranial magnetic resonance, if possible). Protocol of this study was approved by the Ethics Board of Sun Yat-sen Memorial Hospital.

Surgical procedure

Pharyngo-laryngectomy and cervical lymphadenectomy were performed by head and neck surgeons. A standard collar incision was made in the cervical region. Complete resection of larynx, pharynx and cervical esophagus was performed with cervical lymph node dissection. Esophagectomy with mediastinal lymphadenectomy was performed *via* right thoracotomy. For patients with impaired pulmonary function, transhiatal blunt dissection was performed in the supine position. Median laparotomy was performed in parallel with the cervical procedure to construct the gastric tube.

The construction of tubular stomach starts from the lesser curvature of the stomach rather than the greater curvature, as described in our previous study (12). Briefly, the entire stomach was isolated, and a linear stapler was used to harvest both the cardia and the tissues at the lesser curvature in order to form a tube stomach with a diameter of approximately 3 cm (Figure 2). Then the tube stomach was inserted into the right thoracic cavity and brought up through the posterior mediastinum into the neck.

The pharyngogastric anastomosis is subsequently performed. In the manual group, the anastomosis was accomplished by discontinuous monolayer suturing of the muscle fibers and mucous membranes of the pharynx and stomach (Figure 3). For

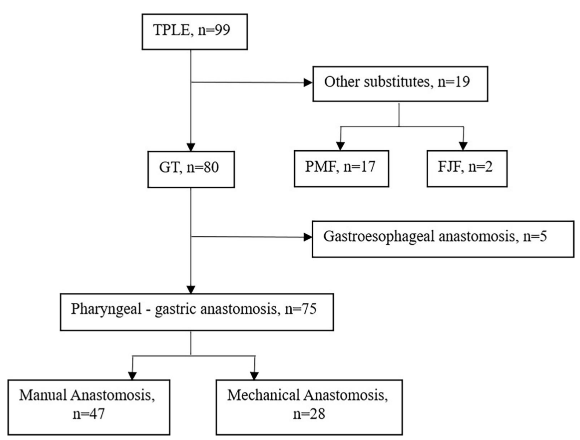

FIGURE 1
Flow chart. FJF, Free jejunal flap, GT, Gastric tube, PMF, Pectoralis major myocutaneous flap, TPLE, Total pharyngolaryngoesophagectomy.

the mechanical group, the tongue base was slightly thinned and fully isolated from the posterior pharyngeal. Then the anterior wall and the posterior wall were closed by intermittent suture from the laterals until about 2cm away from the middle junction, and purse suture was made. At this point, a disposable circular stapler was introduced into the surgical field. Put the trocar tip of the main instrument through the middle of the opening and tighten the purse string suture. Insert the anvil into the main instrument, bring the ends together. After confirming again that there was no high tension and no other tissue embedded, the stapler was activated and held for several seconds. Finally, the pharyngogastric anastomosis was reinforced with simple interrupted varus suture (Figure 4).

Data collection and follow-up

The baseline characteristics and outcomes of these patients were collected retrospectively. The pathological stage was defined according to the seventh edition of the American Joint Committee on Cancer TNM staging system (13). Postoperative complications were diagnosed and defined according to the Esophagectomy Complications Consensus Group (ECCG) recommendations (14). Disease-free survival (DFS) was defined as the time from surgery to disease recurrence or death. Overall survival (OS) was defined as the period from surgery to death from any disease cause or last follow-up.

Patients were followed up every 3 months in the first year and every 6 months beginning in the second year. Follow-up of patients was conducted as outpatient review and phone calls.

Statistical analysis

Continuous variables are presented as the mean ± SD and were compared using Student's t test or ANOVA. Categorical variables are reported as percentages and analyzed using chi-square or Fisher's exact test. OS and DFS was assessed with Kaplan-Meier curves, compared using the log-rank test, and described as the median value at specific time points with 95% confidence intervals (CI). A 2-tailed *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

This study recruited 75 patients, including 60 male and 15 female, who met inclusion criteria (Figure 1). Mean age was 57.6 ± 7.2 years and mean body mass index (BMI) was 20.6 ± 2.8. A total of 58 (77.3%) patients accepted surgery alone, 14 (18.7%) patients received salvage surgery after radical chemoradiotherapy failed, and 3 patients adopted neoadjuvant therapy. Esophageal blunt dissection (72.0%) and postoperative adjuvant therapy (56.0%) were performed in more than half of patients. Other variables are summarized in detail in Table 1. These results showed no significant differences in baseline characteristics between the two groups (28 cases in mechanical group and 47 cases in manual group, *P*>0.05).

Tumor characteristics

As shown in the Table 2, 34 cases were cervical origin, 22 cases were cervical and hypopharyngeal origin, 6 cases were cervical and thoracic origin, 6 cases were hypopharyngeal invading to esophagus, 4 cases were thoracic and hypopharyngeal origin and 3 cases were cervicothoracic and hypopharyngeal origin in all patients. 38 patients (50.7%) had lymph node involvement and 64 patients (86.4%) had moderate differentiation. For all group, R0 resection was performed in 71 patients (94.7%), and tumor residue was found in the remaining 4 patients (5.3%). Similarly, there was no significant difference in pathological feature of tumor between the mechanical group and manual group (*P*>0.05).

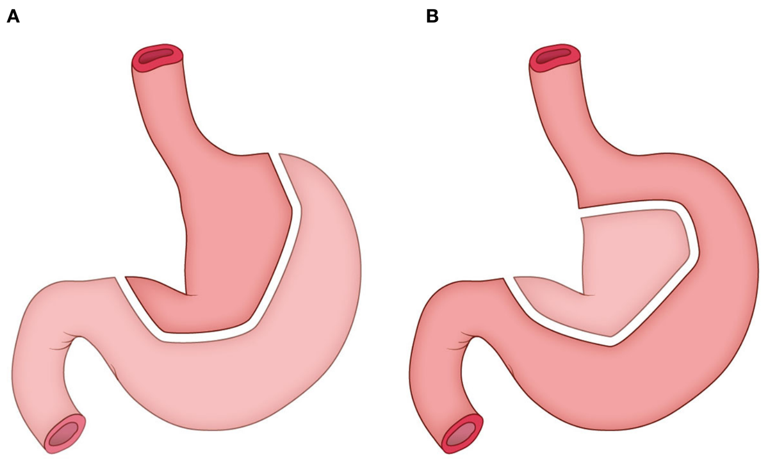

FIGURE 2
The construction of tubular stomach. **(A)** the traditional method; **(B)** the method adopted in this study.

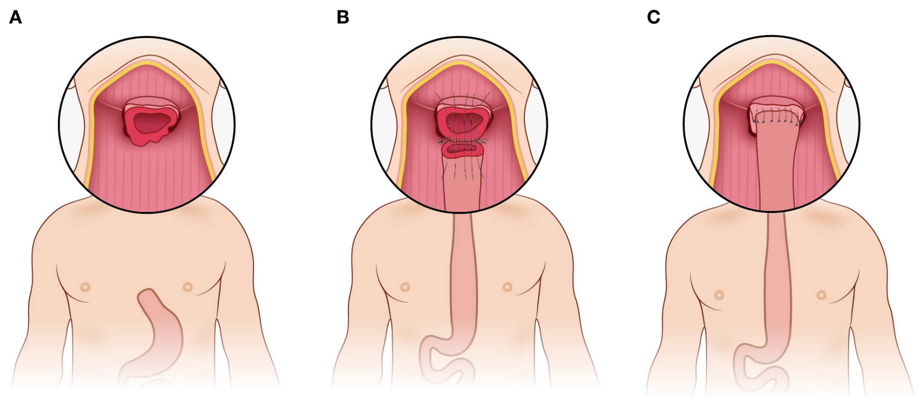

FIGURE 3
Manual anastomosis. **(A)** Exposure of the anastomotic area; **(B)** Discontinuous monolayer suturing is used for pharyngogastric anastomosis; **(C)** Completion of the manual anastomosis.

Postoperative complications and surgical outcome

The rate of total postoperative complications in the mechanical group was significantly lower than in the manual group (25.0% vs 51.1%, *P*=0.027). The incidence of anastomotic fistula was 7.1% (2/28) in the mechanical group and 27.7% (13/47) in the manual group, which was significantly different (*P*=0.032). The wound infection rate was remarkably higher in the manual group than in the mechanical group (19.1% vs 0.0%, *P*=0.036). However, there was no difference in other complications, such as pneumonia, respiratory failure, postoperative bleeding and so on (*P*>0.05, as shown in Table 3).

With regard to surgical outcome, the operation time and intraoperative blood loss were significantly lower in the mechanical group than that in the manual group (460.0 ± 81.5 min vs 504.5 ± 87.1 min, *P*=0.032; 389.3 ± 188.7 mL vs 730.9 ± 581.1 mL, *P*=0.001, respectively). Similarly, the postoperative hospital stays in the mechanical group was significantly reduced than that in the manual group (21.4 ± 8.6 days vs 27.9 ± 15.8 days, *P*=0.046). For 90-days mortality, there were 4 patients in the manual group and none in the mechanical group (8.5% vs 0.0%, *P*=0.291). The causes of death include cardiac failure, pneumonia, upper gastrointestinal bleeding and uncontrolled sepsis due to anastomotic fistula. Five patients in the manual group required reoperation, compared with only one in the mechanical group (10.6% vs 3.6%, *P*=0.515). These results are shown in Table 3.

Survival

There was no significant difference in OS between the two groups (Figure 5), with the mechanical group surviving 48.0 months (95% CI: 6.3-89.8months) and the manual group surviving 38.5 months (95% CI: 0.0-92.7 months, *P*=0.545). Similarly, the DFS was not significantly different between the two groups (Figure 6), with a median survival of 15.0 months (95% CI: 7.6-22.3 months) in the mechanical group and 11.9 months in the manual group (95%CI: 0.0-29.6 months, *P*=0.963).

Discussion

The prognosis for hypopharyngeal and cervical esophageal cancers are poor, mainly because tumors in these areas remain asymptomatic until the diseases reach an advanced stage (15). With the improvement of radiotherapy and chemotherapy technologies, locally advanced HPCECs patients can not only avoid the trauma and perioperative risk caused by surgery, but also obtain the preservation of organ function (6, 16).

However, the survival benefit of chemoradiotherapy remains unsatisfactory. The long-term survival rate of cervical esophageal cancer treated with dCRT is basically about 30% (17, 18). In addition, patients with cervical esophageal cancer who received dCRT had a high rate of local or regional treatment failure, suggesting that this treatment model has local treatment deficiency, which may be compensated by radical surgical resection to a certain extent (19). Since the result of the CROSS clinical multicenter study established the cornerstone of neoadjuvant chemoradiotherapy in esophageal cancer, the multidisciplinary treatment model has attracted increasing attention (20). Neoadjuvant therapy followed by surgery may improve the prognosis of these patients. In recent years, chemoradiotherapy has been reported as an effective treatment for advanced hypopharyngeal cancer. However, given that stage III or IV hypopharyngeal cancer often invades the cervical esophagus, and that pharygnolaryngeal and thoracic esophageal cancer frequently often occur concomitantly, surgical resection plus adjuvant therapy remains the standard of treatment (21).

TPLE is mainly indicated either for synchronous cancer of the thoracic esophagus and the head and neck or for cervical-thoracic esophageal cancer. For most patients, laryngeal preservation is not practical because their larynx and swallowing function are already impaired before treatment; In addition, most patients are diagnosed

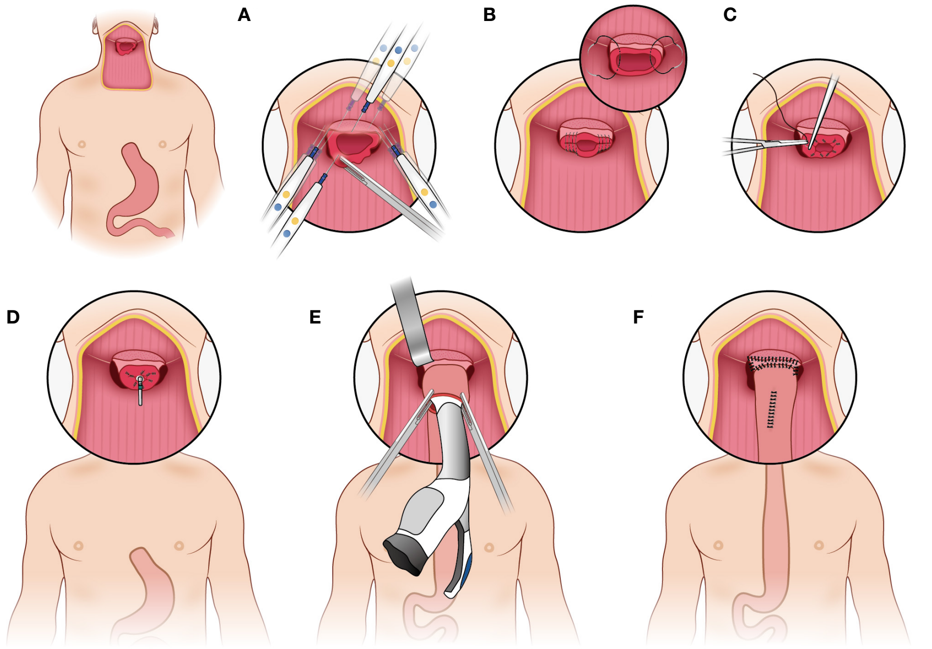

FIGURE 4
Mechanical anastomosis. **(A)** make the tongue base slightly thinned and full isolated from the posterior pharyngeal; **(B)** the anterior wall and the posterior wall were closed by intermittent suture from the laterals; **(C)** make a purse suture; **(D)** put the trocar tip of the main instrument through the middle of the opening and tighten the purse string suture; **(E)** insert the anvil into the main instrument, bring the ends together; **(F)** reinforce the anastomosis.

in locally advanced stages (e.g., tumor invasion of the tracheal membrane and recurrent laryngeal nerve palsy), and attempting to preserve a non-functioning larynx can also adversely affect the chances of cure. Total laryngectomy is almost always included in the surgical plan for better tumor control and postoperative recovery of swallowing function (1).

TPLE is considered to be the most complicated and most invasive surgery for surgeons due to the extremely wide resection field, long reconstructed conduit and poor blood flow of the distal end of the organ. Anastomotic fistula is the most troublesome postoperative complication in digestive tract reconstruction surgery because of its high morbidity and mortality (22). Anastomotic fistula following TPLE surgery is caused primarily by high tension and insufficient blood supply. Therefore, the application of surgical techniques becomes more important. In this study, we demonstrated a new anastomosis technique and compared it with traditional manual anastomosis for postoperative complications and survival.

Firstly, the tubular stomach was applied in this study to ensure sufficient length and adequate blood supply for pharyngo-gastric anastomosis. Our previous study showed that compared with pectoral major muscle skin flap reconstruction and whole stomach replacement, tubular gastric replacement can significantly reduce the occurrence of anastomotic fistula in patients with hypopharyngeal and cervical esophageal cancer (12).

After constructing a tubular stomach, the stomach is usually long enough to be pulled up to the neck, which may greatly reduce the tension at the anastomotic site. Then we appropriately thinned the tongue base and fully isolated the posterior pharyngeal wall, so as to provide enough space for the head end of the stapler, and then successfully performed the gastric-pharyngeal anastomosis in situ. At present, there are few reports on the comparison of anastomotic methods in TPLE for patients with HPCECs. Sallum et al. reported that the use of mechanical anastomosis (transoral approach) was effective in reducing operative time (60 min less) without additional morbidity compared with conventional manual suturing (10). Our results suggest that compared with manual anastomosis group, mechanical anastomosis group not only has significantly lower anastomotic fistula rate and wound infection rate, but also has obvious advantages of shorter operation time, less intraoperative blood loss and shorter postoperative hospital stay. Similarly, a prospective clinical study suggested that the use of stapler method reduced the incidence of leakage and shortened operating time compared with the hand-sewn method, which has been advocated as the preferred anastomotic method in esophagogastric anastomoses (9). The interpretation of this phenomenon is that mechanical anastomosis has easier operation, more uniform force, and less dependence on the stability of surgeon, while manual anastomosis has longer operation time, higher anastomotic tension, tighter suture leading to poorer blood flow, and largely dependence on the stability of surgeon. In addition, different from the stapler is introduced transorally down into the operative field for anastomosis in some studies (10, 11), we used stapler to perform anastomosis directly in situ, which is easier to operate and more time saving. In terms of survival benefit, there was no significant difference between the mechanical group and manual group in this study. In other words, we can say that the new technique of anastomosis does not affect survival or recurrence rate, but it provides safer and more effective perioperative outcomes for HPCECs patients.

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TABLE 1 Baseline characteristics of patients undergoing TPLE.

Variables	ALL Patients (n=75)	Mechanical Anastomosis (n=28)	Manual Anastomosis (n=47)	*P* value
Age*	57.6 ± 7.2	58.9 ± 6.6	56.7 ± 7.6	0.252
Sex				
Male	60 (80.0)	22 (78.6)	38 (80.9)	0.811
Female	15 (20.0)	6 (21.4)	9 (19.1)	
ASA				0.496
2	37 (49.3)	16 (57.1)	21 (44.7)	
3	36 (48.0)	11 (39.3)	25 (53.2)	
4	2 (2.7)	1 (3.6)	1 (2.1)	
BMI*	20.6 ± 2.8	20.7 ± 2.7	20.5 ± 3.0	0.727
Weight loss>10%				0.636
Yes	14 (18.7)	6 (21.4)	8 (17.0)	
No	61 (81.3)	22 (78.6)	39 (83.0)	
Smoking				0.197
Yes	41 (54.7)	18 (64.3)	23 (48.9)	
No	34 (45.3)	10 (35.7)	24 (51.1)	
Alcohol drinking				0.883
Yes	26 (34.7)	10 (35.7)	16 (34.0)	
No	49 (65.3)	18 (64.3)	31 (66.0)	
Diabetes				1.000
Yes	3 (4.0)	1 (3.6)	2 (4.3)	
No	72 (96.0)	27 (96.4)	45 (95.7)	
Hypertension				0.726
Yes	5 (6.7)	1 (3.6)	4 (8.5)	
No	70 (93.7)	27 (96.4)	43 (91.5)	
History of malignant tumor				1.000
Yes	5 (6.7)	2 (7.1)	3 (6.4)	
No	70 (93.7)	26 (92.9)	44 (93.6)	
History of surgery				0.277
Yes	14 (18.7)	7 (25.0)	7 (14.9)	
No	61 (81.3)	21 (75.0)	40 (85.1)	
Family history of cancer				0.268
Yes	6 (8.0)	4 (14.3)	2 (4.3)	
No	69 (92.0)	24 (85.7)	45 (95.7)	
Treatment Patterns				0.723
Surgery alone	58 (77.3)	23 (82.1)	35 (74.5)	
Salvage surgery after dCRT	14 (18.7)	4 (14.3)	10 (21.3)	
Preoperative chemotherapy	2 (2.7)	1 (3.6)	1 (2.1)	
Preoperative radiotherapy	1 (1.3)	0 (0.0)	1 (2.1)	

(Continued)

TABLE 1 Continued

Variables	ALL Patients (n=75)	Mechanical Anastomosis (n=28)	Manual Anastomosis (n=47)	*P* value
Surgical approach				0.093
Transthoracic	21 (28.0)	11 (39.3)	10 (21.3)	
Blunt dissection	54 (72.0)	17 (60.7)	37 (78.7)	
Postoperative adjuvant therapy				0.077
Yes	33 (44.0)	16 (57.1)	17 (36.2)	
No	42 (56.0)	12 (42.9)	30 (63.8)	

*, mean ± SD; ASA, American Society of Anesthesiologists; BMI, body mass index.

TABLE 2 Tumor characteristics in the two groups.

Variables	ALL Patients (n=75)	Mechanical Anastomosis (n=28)	Manual Anastomosis (n=47)	*P* value
Location of tumor				0.125
Cervical	34 (45.3)	17 (60.7)	17 (36.2)	
Cervical and thoracic	6 (8.0)	3 (10.7)	3 (6.4)	
Cervical and hypopharyngeal	22 (29.4)	5 (17.9)	17 (36.2)	
Cervicothoracic and hypopharyngeal	3 (4.0)	1 (3.6)	2 (4.2)	
Thoracic and hypopharyngeal	4 (5.3)	0 (0.0)	4 (8.5)	
Hypopharyngeal invading to esophagus	6 (8.0)	2 (7.1)	4 (8.5)	
Lymph node invasion				0.571
Yes	38 (50.7)	13 (46.4)	25 (53.2)	
No	37 (49.3)	15 (53.6)	22 (46.8)	
None dissection of thoracic lymph nodes	54 (72.0)	17 (60.7)	37 (78.7)	0.095
Degree of tumor differentiation				0.475
Highly differentiated	4 (5.3)	1 (3.6)	3 (6.4)	
Moderately differentiated	64 (85.4)	23 (82.1)	41 (87.2)	
Poorly differentiated	7 (9.3)	4 (14.3)	3 (6.4)	
Residual disease				0.291
R0	71 (94.7)	28 (100.0)	43 (91.5)	
R1/R2	4 (5.3)	0 (0.0)	4 (8.5)	
UICC stage of esophageal cancer				0.529
I	3 (4.0)	2 (7.1)	1 (2.1)	
II	34 (45.3)	13 (46.4)	21 (44.7)	
III	31 (41.4)	10 (35.8)	21 (44.7)	
IV	1 (1.3)	1 (3.6)	0 (0.0)	
None	6 (8.0)	2 (7.1)	4 (8.5)	
UICC stage of hypopharyngeal cancer				0.131
I	2 (2.7)	1 (3.6)	1 (2.1)	

(Continued)

TABLE 2 Continued

Variables	ALL Patients (n=75)	Mechanical Anastomosis (n=28)	Manual Anastomosis (n=47)	*P* value
II	2 (2.7)	0 (0.0)	2 (4.2)	
III	11 (14.6)	2 (7.1)	9 (19.2)	
IV	20 (26.7)	5 (17.9)	15 (31.9)	
None	40 (53.3)	20 (71.4)	20 (42.6)	

TABLE 3 Postoperative complication and surgical outcome in the two groups.

Variables	ALL Patients (n=75)	Mechanical Anastomosis (n=28)	Manual Anastomosis (n=47)	*P* value
Total postoperative complications				0.027
Yes	31 (41.3)	7 (25.0)	24 (51.1)	
No	44 (58.7)	21 (75.0)	23 (48.9)	
Pneumonia				0.386
Yes	10 (13.3)	2 (7.1)	8 (17.0)	
No	65 (86.7)	26 (92.9)	39 (83.0)	
Pleural effusion				1.000
Yes	2 (2.7)	1 (3.6)	1 (2.1)	
No	73 (97.3)	27 (96.4)	46 (97.9)	
Respiratory failure				0.707
Yes	8 (10.7)	2 (7.1)	6 (12.8)	
No	67 (89.3)	26 (92.9)	41 (87.2)	
Cardio-cerebrovascular complications				0.715
Yes	2 (2.7)	0 (0.0)	2 (4.3)	
No	73 (97.3)	28 (100.0)	45 (95.7)	
Anastomotic stricture				1.000
Yes	3 (4.0)	1 (3.6)	2 (4.3)	
No	72 (96.0)	27 (96.4)	45 (95.7)	
Tracheostomal stenosis				1.000
Yes	3 (4.0)	1 (3.6)	2 (4.3)	
No	72 (96.0)	27 (96.4)	45 (95.7)	
Anastomotic fistula				0.032
Yes	15 (20.0)	2 (7.1)	13 (27.7)	
No	60 (80.0)	26 (92.9)	34 (72.3)	
Tracheal fistula				1.000
Yes	3 (4.0)	1 (3.6)	2 (4.3)	
No	72 (96.0)	27 (96.4)	45 (95.7)	
Wound infection				0.036
Yes	8 (10.7)	0 (0.0)	9 (19.1)	

(Continued)

TABLE 3 Continued

Variables	ALL Patients (n=75)	Mechanical Anastomosis (n=28)	Manual Anastomosis (n=47)	*P* value
No	67 (89.3)	28 (100.0)	38 (80.9)	
Postoperative bleeding				0.515
Yes	6 (8.0)	1 (3.6)	5 (10.6)	
No	69 (92.0)	27 (96.4)	42 (89.4)	
Re-operation				0.515
Yes	6 (8.0)	1 (3.6)	5 (10.6)	
No	69 (92.0)	27 (96.4)	42 (89.4)	
90-days mortality				0.291
Yes	4 (5.3)	0 (0.0)	4 (8.5)	
No	71 (94.7)	28 (100.0)	43 (91.5)	
Use of ventilator				0.994
Yes	4 (5.3)	2 (7.1)	2 (4.3)	
No	71 (94.7)	26 (92.9)	45 (95.7)	
Intraoperative blood loss (mL)	603.3 ± 500.6	389.3 ± 188.7	730.9 ± 581.1	0.001
Operation time (min)	487.9 ± 87.2	460.0 ± 81.5	504.5 ± 87.1	0.032
Postoperative hospital stays (day)	25.5 ± 13.8	21.4 ± 8.6	27.9 ± 15.8	0.046

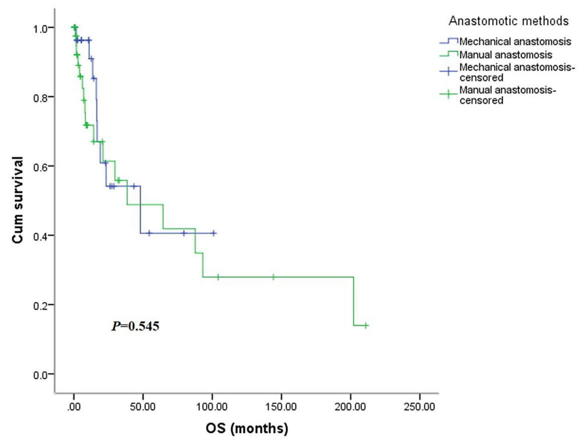

FIGURE 5
The overall survival curve of the two groups.

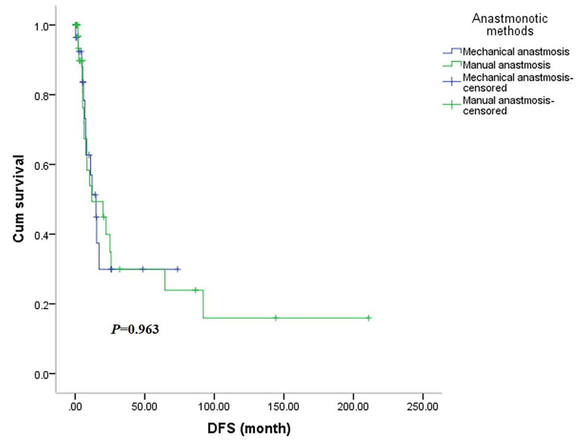

FIGURE 6
The disease-free survival curve of the two groups.

In order to control the confounding factors, all surgeries were performed by the same treatment team. However, since it is a retrospective study from only single center, large-scale case studies and prospective randomized studies are still needed to further verify these results in this study.

In conclusion, by comparing the perioperative outcomes and prognosis after different methods of gastric-pharyngeal anastomosis, we concluded that the new mechanical procedure showed its advantage over the manual procedure for patients underwent TPLE in terms of less incidences of anastomotic fistula, wound infection, intraoperative blood loss, operative time and postoperative hospital stays. This reconstructive method deserves wider application and further refinement.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

MW and QC: Idea. KexW and XiH: Design of the study. DW and KefW: Calculation. YL, WW, and XuH: Proofread. KL, BT, and RL: Error correction. 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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Comparison of the endoscopic thyroidectomy *via* areola approach and open thyroidectomy: A propensity score matched cohort study of 302 patients in the treatment of papillary thyroid non-microcarcinoma

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Background: The endoscopic thyroidectomy *via* areola approach (ETAA) is widely used in patients with benign thyroid tumors and papillary thyroid microcarcinoma (PTMC). Its safety and complication rates are reported to be similar to open thyroidectomy (OT). This study aimed to evaluate the safety and feasibility of ETAA, compared with OT, in patients with papillary thyroid non-microcarcinoma (PTNMC).

Methods: We retrospectively reviewed all patients with PTNMC who underwent ETAA or OT in our hospital from January 2017 to December 2021. A total of 302 patients were matched at a ratio of 1:1 by the propensity score matching (PSM) analysis and surgical outcomes. Safety and feasibility were analyzed between two groups.

Results: Before PSM, patients in the ETAA group were younger ($p < 0.001$) and had a larger proportion of female patients ($p < 0.001$) with a lower BMI ($p < 0.001$) compared with the OT group. The ETAA group also had a higher proportion of unilateral thyroidectomy ($p = 0.002$). PSM was used to create a highly comparable control group. After PSM, the ETAA group had a longer operative time ($p < 0.001$), larger blood loss ($p = 0.046$) and total drainage amount ($p = 0.035$), with higher C-reactive protein ($p = 0.023$) and better cosmetic outcomes ($p < 0.001$). There were no significant differences in the following clinicopathologic characteristics: number of dissected positive lymph nodes, rate of recurrent laryngeal nerve signal weakened, parathyroid autotransplantation, postoperative pain, hospital stay, complications, and oncologic completeness. There was no patient converted to OT in the ETAA group and two patients suffered from persistence/recurrence in the follow-up.

Conclusion: ETAA is a safe and feasible surgical approach for patients with PTNMC.

KEYWORDS
papillary thyroid non-microcarcinoma, endoscopic thyroidectomy *via* areola approach, safety, feasibility, cosmetic outcome

Introduction

Papillary thyroid carcinoma (PTC) has an excellent prognosis and is much more common in young women, who usually pay attention not only to surgical thoroughness and safety but also to cosmetic requirements (1). The endoscopic technique, first reported by Gagner (2), has rapidly advanced over the past two decades. It significantly improves the cosmetic outcomes and quality of life (QoL) by making incisions not from the neck but to hidden areas of the body (3). At present, the endoscopic thyroidectomy *via* areola approach (ETAA) is the most common surgical approach in China. ETAA is widely used in patients with benign thyroid tumors and papillary thyroid microcarcinoma (PTMC, defined as PTC with a diameter ≤1 cm). Its safety and complication rates are reported to be similar to open thyroidectomy (OT) (4, 5).

Although the treatment strategy for PTMC remains controversial (6), according to the 2015 American Thyroid Association (ATA) guidelines, surgery is necessary for patients with papillary thyroid non-microcarcinoma (PTNMC, defined as PTC with a diameter >1 cm) (7). However, few studies have reported the surgical outcomes and safety of ETAA in the treatment of PTNMC to date. Thus, we conduct this study to evaluate the safety and feasibility of ETAA in patients with PTNMC, compared with OT.

Materials and methods

We retrospectively reviewed 6,469 patients with PTNMC who underwent ETAA or OT from January 2017 to December 2021 in Jiefang Road District, Second Affiliated Hospital of Zhejiang University, School of Medicine. This study has been approved by the Ethical Committee of the Second Affiliated Hospital of Zhejiang University's School of Medicine.

Data from patients were collected and divided into four categories: (1) clinicopathologic characteristics including age, sex, body mass index (BMI), tumor size, Hashimoto's thyroiditis, multifocality, and extent of surgery; (2) intraoperative outcomes including operative time, blood loss, and number of dissected and positive lymph nodes; (3) postoperative outcomes such as 24-h visual analog scale (VAS), total drainage amount, white blood cell amount, C-reactive protein level, and complications; and (4) follow-up outcomes such as cosmetic satisfaction, scar self-consciousness, QoL, oncologic completeness, and recurrence.

According to national consensus and our previous study (8), the inclusion criteria were as follows: (1) PTC diagnosed by postoperative pathological results; (2) age range from 18 to 55 years; (3) BMI range from 18 to 28 kg/m^2 (9); and (4) no previous history of neck radiation therapy or surgery. The exclusion criteria were as follows: (1) age ≥55 years; (2) tumor maximum diameter evaluated by preoperative ultrasound was <1 cm or >4 cm (10); (3) extrathyroidal or capsular invasion; and (4) cervical lateral lymph node or distant metastasis. According to the inclusion and exclusion criteria, 169 patients in the ETAA group and 739 patients in the OT group were finally included. Then, the propensity score matching (PSM) analysis (11) was conducted to match 151 patient pairs to reduce the potential confounding of clinicopathologic characteristics (Figure 1).

Surgical procedures of ETAA (12) and OT (13) were described in detail in our previous article. Tumors with more than two lesions were defined as multifocal. Postoperative vocal cord paralysis, confirmed by laryngoscopy, which recovered within 6 months, was defined as transient recurrent laryngeal nerve (RLN) injury. Transient hypoparathyroidism is diagnosed when the serum parathyroid hormone is smaller than 15 pg/ml. Other complications have been defined in a previous study (8). Total complication referred to the total number of patients with postoperative complications. The follow-up duration was defined as the time between the patient's surgery day and telephone return visit in March 2022.

According to the recommended follow-up strategy in the ATA guidelines, all patients should undergo serum thyroid function testing and ultrasonography to monitor recurrence every 3 or 6 months. For patients who underwent bilateral thyroidectomy, the serum stimulated thyroglobulin (sTg) level and the percentage of sTg below 1 μg/L were evaluated 3 weeks after discharge and followed by radioactive iodine (RAI) therapy if necessary according to the guidelines. In addition, a questionnaire regarding cosmetic satisfaction, scar self-consciousness, and QoL was sent out 3 months after surgery. Cosmetic satisfaction (14) and scar selfconsciousness (15) were scaled with scores from 0 to 3, with 3 meaning very satisfied and very concerned, respectively. QoL (16) was evaluated with scores ranging from 0 (worst) to 10 (best).

Statistics

Data were analyzed *via* the statistical program SPSS version 26 (SPSS® Inc., Illinois, USA). Continuous variables were compared using independent-samples *t*-test or Mann–Whitney *U* test, presented as medians ± standard deviations. Categorical variables were analyzed by the chi-squared test or Fisher's exact test, expressed as numbers and percentages. A p-value of <0.05 indicated statistical significance.

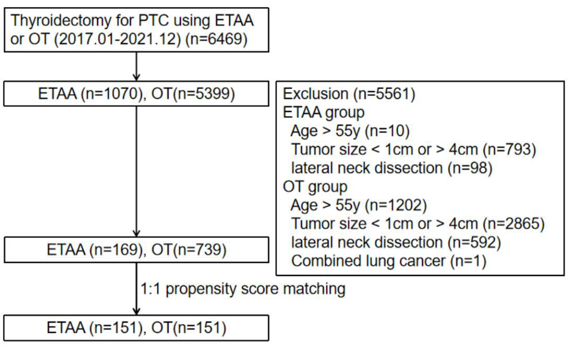

FIGURE 1
Study flowchart. ETAA, endoscopic thyroidectomy *via* areola approach; OT, open thyroidectomy; PTC, papillary thyroid carcinoma.

Results

Clinicopathologic characteristics before and after PSM

The clinicopathologic characteristics are presented in Table 1. Before PSM, 169 patients were included in the ETAA group, and 739 patients were included in the OT group. Compared with the OT group, patients in the ETAA group were younger (32.33 ± 7.72 years *vs.* 40.89 ± 9.18 years, $p < 0.001$) and had a larger proportion of female patients (88.7% *vs.* 61.4%, $p < 0.001$). Also, the ETAA group had a lower BMI (21.94 ± 2.96 kg/m^2 *vs.* 24.16 ± 3.60 kg/m^2, $p < 0.001$) and a higher proportion of unilateral thyroidectomy (73.8% *vs.* 60.9%, $p = 0.002$). However, there were no statistically significant differences in tumor size (1.43 ± 0.50 cm *vs.* 1.44 ± 0.43 cm, $p = 0.103$), rate of Hashimoto's thyroiditis (39.9% *vs.* 38.0%, $p = 0.655$), or multifocality (22.6% *vs.* 28.1%, $p = 0.146$). PSM matched a total of 151 patient pairs for subsequent analysis and there were no statically significant differences among the seven clinicopathologic characteristics mentioned above between the two groups.

Intraoperative outcomes

The intraoperative outcomes are presented in Table 2. Compared with the OT group, patients in the ETAA group had a longer operative time (165.42 ± 52.26 min *vs.* 84.47 ± 28.18 min, $p < 0.001$) and a larger blood loss (14.96 ± 5.59 ml *vs.* 14.42 ± 3.86 ml, $p = 0.046$). However, the results of the number of dissected lymph nodes (8.25 ± 6.01 *vs.* 10.87 ± 6.43, $p = 0.196$), positive lymph nodes (2.86 ± 2.33 *vs.* 3.52 ± 2.57, $p = 0.288$), the rate of metastatic lymph nodes (57.6% *vs.* 65.6, $p = 0.156$), weakened RLN signal weaken (7.9% *vs.* 9.9%, $p = 0.545$), and parathyroid autotransplantation results (43.0% *vs.* 40.4%, $p = 0.641$) were similar. No patients were converted to OT in the ETAA group.

Postoperative outcomes

The postoperative outcomes are presented in Table 3. The C-reactive protein (9.58 ± 6.99 mg/L *vs.* 6.29 ± 5.55 mg/L, $p = 0.023$) and total drainage amount (157.65 ± 74.93 ml *vs.* 121.51 ± 74.91 ml, $p = 0.035$) are higher in the ETAA group than in the OT group. There were no statistically significant differences between the two groups in the 24-h VAS (1.76 ± 0.46 *vs.* 1.72 ± 0.51, $p = 0.285$), WBC amount (9.17 ± 2.71 × 10^9/L *vs.* 9.18 ± 5.59 × 10^9/L, $p = 0.598$), drainage duration (3.16 ± 1.33 days *vs.* 3.56 ± 1.31 days, $p = 0.338$), postoperative hospital stay (3.20 ± 1.27 days *vs.* 3.60 ± 1.29 days, $p = 0.572$), and proportion of total complications (15.9% *vs.* 18.5%, $p = 0.542$). None of the patients suffered from permanent RLN palsy or hypoparathyroidism.

Follow-up outcomes

The follow-up outcomes are presented in Table 4. The patients had a higher QoL (9.58 ± 6.99 *vs.* 6.29 ± 5.55, $p < 0.001$) in the ETAA group than in the OT group, resulting from the higher cosmetic satisfaction (2.42 ± 0.62 *vs.* 1.55 ± 0.71, $p < 0.001$) and lower scar self-consciousness (0.74 ± 0.64 *vs.* 1.30 ± 0.53, $p < 0.001$). As for oncologic completeness in bilateral thyroidectomy, the stimulated Tg level before RAI (0.89 ± 2.26 μg/L *vs.* 1.17 ± 2.69 μg/L, $p = 0.597$), the rate of Tg level <1 μg/L (65.9% *vs.* 60.0%, *p*#146;= 0.404), and receiving RAI (22.0% *vs.* 25.5%, $p = 0.740$) were not statistically different. During the follow-up, two patients in the ETAA group and one patient in the OT group suffered from

TABLE 1 Clinicopathologic characteristics.

Variables	Before PSM			After PSM		
	ETAA (*n* = 169)	OT (*n* = 739)	*p*	ETAA (*n* = 151)	OT (*n* = 151)	*p*
Age (years)	32.33 ± 7.72	40.89 ± 9.18	<0.001	33.11 ± 7.52	34.29 ± 7.54	0.928
Sex (*n*, %)						
Male	19 (11.3)	285 (38.6)	<0.001	18 (11.9)	18 (11.9)	1.000
Female	149 (88.7)	454 (61.4)		133 (88.1)	133 (88.1)	
BMI (kg/m2)	21.94 ± 2.96	24.16 ± 3.60	<0.001	22.15 ± 2.96	22.03 ± 2.99	0.577
Tumor size (cm)	1.43 ± 0.50	1.44 ± 0.43	0.103	1.44 ± 0.51	1.46 ± 0.44	0.484
Hashimoto's thyroiditis (*n*, %)	67 (39.9)	281 (38.0)	0.655	61 (40.4)	66 (63.5)	0.560
Multifocality (*n*, %)	38 (22.6)	208 (28.1)	0.146	34 (38.5)	43 (28.5)	0.235
Extent of surgery (*n*, %)						
Unilateral thyroidectomy	124 (73.8)	450 (60.9)	0.002	110 (72.8)	96 (63.6)	0.084
Bilateral thyroidectomy	44 (26.2)	289 (39.1)		41 (27.2)	55 (36.4)	

BMI, body mass index; PSM, propensity score matching; ETAA, endoscopic thyroidectomy via areola approach; OT, open thyroidectomy.

TABLE 2 Intraoperative outcomes.

Variables	ETAA (*n* = 151)	OT (*n* = 151)	*p*
Operative time (min)	165.42 ± 52.26	84.47 ± 28.18	<0.001
Blood loss (ml)	14.96 ± 5.59	14.42 ± 3.86	0.046
Number of dissected lymph nodes (piece)	8.25 ± 6.01	10.87 ± 6.43	0.196
Positive (*n*, %)	87 (57.6)	99 (65.6)	0.156
Negative (*n*, %)	64 (42.4)	52 (34.4)	
Number of positive lymph nodes (piece)	2.86 ± 2.33	3.52 ± 2.57	0.288
Rate of RLN signal weaken (*n*, %)	12 (7.9)	15 (9.9)	0.545
Rate of parathyroid autotransplantation (*n*, %)	65 (43.0)	61 (40.4)	0.641
Conversion to open	0	NA	NA

RLN, recurrent laryngeal nerve; ETAA, endoscopic thyroidectomy via areola approach; OT, open thyroidectomy.

persistence/recurrence and underwent a second operation, which showed no significant difference between two groups ($p = 0.442$).

Discussion

With the development of endoscopic technology and surgical instruments, various approaches such as transaxillary, transareola, bilateral axillo-breast (BABA), and transoral surgery have been designed and new clinical procedures have been rapidly advancing (17). Each approach has its own advantages and disadvantages. ETAA has its unique strengths (18). First, the surgical procedure is well researched and widely used in China. The surgical visual angle, similar to OT, is beneficial for the bilateral thyroidectomy and dissection of the prelaryngeal and lateral neck lymph nodes. Second, all of three cambered incisions are short and hidden, which will have excellent cosmetic results after healing. Third, larger operative space means less mutual interference of surgical instruments. Additionally, it has great clinical benefits and safety in PTMC, which have been confirmed by multiple independent studies (4, 5, 18). The lack of study on PTNMC presents a challenge in the expansion of indications for ETAA. Therefore, we conducted this study to evaluate the safety and feasibility of ETAA in the treatment of PTNMC.

In our center, complete removal of tumor with a maximum diameter > 4 cm was quite a challenge despite lengthening the

TABLE 3 Postoperative outcomes.

Variables	ETAA (*n* = 151)	OT (*n* = 151)	*p*
24-h VAS (score)	1.76 ± 0.46	1.72 ± 0.51	0.285
WBC amount (109/L)	9.17 ± 2.71	9.18 ± 5.59	0.598
C-reactive protein (mg/L)	9.58 ± 6.99	6.29 ± 5.55	0.023
Drainage duration (days)	3.16 ± 1.33	3.56 ± 1.31	0.338
Total drainage amount (ml)	157.65 ± 74.93	121.51 ± 74.91	0.035
Postoperative hospital stay (days)	3.20 ± 1.27	3.60 ± 1.29	0.572
Complication (*n*)			
Total	24 (15.9)	28 (18.5)	0.542
Transient RLN palsy	4	6	0.750
Permanent RLN palsy	0	0	NA
Transient hypoparathyroidism	19	23	0.430
Permanent hypoparathyroidism	0	0	NA
Chyle fistula	2	5	0.448
Choking cough	0	1	1.000
Infection	0	0	NA
Hematoma	0	0	NA

VAS, visual analog scale; WBC, white blood cells; RLN, recurrent laryngeal nerve; ETAA, endoscopic thyroidectomy via areola approach; OT, open thyroidectomy.

TABLE 4 Follow-up outcomes.

Variables	ETAA (*n* = 151)	OT (*n* = 151)	*p*
Cosmetic satisfaction (score)	2.42 ± 0.62	1.55 ± 0.71	<0.001
Scar self-consciousness (score)	0.74 ± 0.64	1.30 ± 0.53	<0.001
Quality of life (score)	8.50 ± 0.85	7.76 ± 0.84	<0.001
Oncologic completeness			
In bilateral thyroidectomy			
Stimulated Tg level before RAI (μg/L)	0.89 ± 2.26	1.17 ± 2.69	0.597
<1 (*n*, %)	27/41 (65.9)	33/55 (60.0)	0.404
≥1 (*n*, %)	14/41 (34.1)	22/55 (40.0)	
Rate of receiving RAI (*n*, %)	9/41 (22.0)	14/55 (25.5)	0.740
Persistence/Recurrence (*n*, %)	2 (1.3)	1 (0.7)	0.442
Follow-up duration (months)	37.62 ± 14.93	30.60 ± 16.61	0.121

Tg, thyroglobulin; RAI, radioactive iodine; ETAA, endoscopic thyroidectomy via areola approach; OT, open thyroidectomy.

incision and widening the main tunnel; thus, only T1 and T2 PTNMC were included in our study (10).

Similar to our previous study (19), the ETAA group had a longer operative time and a larger blood loss, which were mainly related to the establishment of surgical space and extensive separation of the thoracic flaps. It was acceptable because the difference in blood loss did not result in changes in vital signs and hospital stay. Yang et al. (20) reported a non-visual method for establishing the operative space to reduce the operative time and separative flap area at the expense of improving surgical difficulties. In addition, experience proved to be beneficial in shortening surgical time (21).

The incidence of complications is vital to assess the safety of endoscopic thyroid surgery. The major complications include RLN injury, hypoparathyroidism, superior laryngeal nerve (SLN) injury, infection, and hematoma, which did not vary significantly between the two groups. The incidence of transient RLN injury ranged from 2.1% to 11.8% (13), and our results were similar. In the ETAA group, a magnified view and intraoperative nerve monitoring assist in the identification and protection of RLN, which can reduce the incidence of injury (22). The incidence of transient hypoparathyroidism ranged from 1.2% to 40% (23); our results were 12.9% and 15.2% in the ETAA and OT group, respectively. A magnified view and the use of carbon nanoparticles are helpful in protecting the parathyroid *in situ*. However, it is difficult to retain the inferior parathyroid with type A by ETAA when cleaning the lower VI lymph nodes or superior parathyroid with types A2 and A3 because of the easily damaged blood supply (24). We implanted ischemic and resected parathyroid tissue in the sternocleidomastoid or deltoid in order to avoid transient hypocalcemia. According to the study by Kim et al. (25), parathyroid autotransplantation is an effective therapeutic option for permanent hypoparathyroidism, but we lack relevant experience. No patients in this study suffered from permanent RLN injury or hypoparathyroidism.

Choking cough was one of the clinical symptoms due to RLN or SLN injury, which occurred in one patient from the OT group. This patient drank at the proper angle by bowing their head and the symptom was relieved within 3 weeks. Furthermore, some patients complained of subtle voice change without abnormal laryngoscope outcomes, which may be attributed to the external branch of SLN injury. In fact, SLN injury, especially external branch injury (EBSLN), was underestimated clinically because postoperative laryngoscopy and voice analysis were not routinely used in our center. When accurate laryngeal electroneuromyography was used to diagnose abnormal conductivity, Cernea et al. indicated that the incidence of EBSLN was as high as 58% (26). It was clinically rare due to its technical difficulty and cost. Therefore, we were unable to evaluate the advantages or disadvantages of ETAA in protecting SLN. No infection occurred in patients of the ETAA group, possibly due to the class I incision and unobstructed drainage. During the hospital stay, none of the patients underwent postoperative hematoma and the second surgery. To sum up, ETAA is a safe surgical method with low complication rates for patients with PTNMC.

Compared with the OT group, the CRP level was higher in the ETAA group, possibly due to the long surgical time and flap trauma. In spite of the statistical difference in total drainage amount, drainage duration and postoperative hospital day were similar. The analgesic was not used routinely and the postoperative 24-h VAS scores did not differ significantly between the two groups. Thus, the increase of surgical trauma was mild and acceptable. Jiang et al. (27) considered that the dissection plane was the major factor leading to pain. Thus, to reduce postoperative discomfort, surgeons should have a more comprehensive understanding of the anatomy.

According to the national consensus and CACA guidelines (28), all patients underwent unilateral or bilateral central lymph node dissection. The number of dissected and positive lymph nodes plays a vital role in guiding postoperative treatment. In addition, for patients who underwent bilateral thyroidectomy, the postoperative serum Tg level and the proportion of sTg of <1 μg/L are crucial for evaluating the oncological completeness (29). There were no statistically significant differences in those indexes mentioned above and in persistence/recurrence. Thus, we confirmed that the oncological completeness was comparable between the ETAA technique and OT.

According to the ATA guideline (7), when the disease-free condition was maintained for at least 1 year, the occurrence of a new lesion indicated the recurrence. Conversely, the new lesion was defined as persistent disease. However, this definition is still controversial, and our study made no distinction. Persistence/recurrence were confirmed by puncture pathology in two patients of the ETAA group 6 months after surgery and one patient of the OT group 4 years after surgery. All of them were treated with a second open surgery on account of the increase of operative difficulties and risks. Wang et al. reported the feasibility of second surgery using ETAA (30). However, most of the patients (80.4%) were diagnosed with nodular goiter, and ETAA should be cautiously performed for patients with recurrence even though they are extremely worried about the scars. In a meta-analysis involving 9,369 patients with PTC, the rate of lymph node metastasis (LNM) ranged from 13.9% to 64.7% and tumor size >1 cm was one of the aggressive factors (31). In our study of PTNMC, the proportion of metastatic lymph nodes was 57.6% and 65.6% in the ETAA and OT group, respectively, which was consistent with previous research.

Cosmetic requirements promote rapid advances in endoscopic technology. A visible neck scar may increase the concerns of patients, especially among the Asian population (32). In this research, the patients in the ETAA group demonstrated a higher cosmetic satisfaction and QoL, in line with many previous reports. Nonetheless, three patients in the ETAA group complained of numbness in the chest area resulting from injury of the cutaneous nerve, which recovered within 3 months, but possibly decreased short-term QoL.

Because this was a single-center retrospective study, selection bias in surgical approach could not be avoided. In addition, only 151 matched pairs in this study were included and their follow-up time was short, which may reduce the credibility of the long-term oncology effect. Thus, larger samples and multicenter prospective studies with long-term follow-up are needed to confirm the safety, feasibility, and long-term oncological outcomes of ETAA in the treatment of PTNMC.

Conclusion

ETAA produces similar surgical and oncological outcomes in treating PTNMC (<4 cm) compared with OT. Moreover, it provides better cosmetic outcomes despite a longer operative time and larger drainage. ETAA is a safe and feasible surgical approach for patients with PTNMC.

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

This study has been approved by The Ethical Committee of the Second Affiliated Hospital of Zhejiang University's School of Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study design: ZL, YW, and PW. Data collection: YL, ZL, and ZS. Data analysis: YL and XY. Drafting the manuscript: YL. Project supervision: YW. 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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Robotic segmentectomy for early-stage lung cancer

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Lobectomies have long been the gold standard for surgical treatment of early-stage non-small cell lung cancer (NSCLC), with segmentectomies limited to instances of benign disease or as an alternative in patients where lung preservation is indicated. However, a recently published randomized control trial has demonstrated the superiority of segmentectomy over lobectomy in terms of overall survival for early-stage lung cancer. Segmentectomy could thus be considered a standard procedure for small-sized peripheral NSCLC. While segmentectomy *via* video-assisted thoracic surgery (VATS) is the most widespread approach, development in video instrumentation and thoracic robotic surgery is rapidly gaining interest. Indeed, robotic surgery pioneers boast the advantages in three-dimensional view, improved magnification, ergonomics, dexterity, safety, and ease of surgery with this technology. This review aims to outline robotic-assisted segmentectomy indications, preoperative evaluation, and the operative conduct for the different lung segments from a single surgeon console. There are many ways to perform segmentectomies and therefore this review describes generalized approaches that can be tailored based on experience.

KEYWORDS

lung cancer, robotic-assisted surgery, non-small cell lung cancer, lobectomy, segmentectomy

Introduction

Since the Lung Cancer Study Group published the prospective randomized controlled trial in 1995 demonstrating a three-fold increase in locoregional recurrence and an increase in mortality after sublobar resection for T1N0 non-small cell lung cancer (NSCLC), lobectomies have been the gold standard for surgical treatment of early-stage NSCLC. Segmentectomy, defined as the anatomical segmental resection with sufficient margins ($\geq$2 cm or $\geq$ the size of the nodule) and lymph node assessment (N1 and N2 lymph node stations) (1), have since then been limited to benign disease or as an alternative to lobectomy in patients with limited cardiopulmonary reserve or other major comorbidities (2, 3). The goal of these sublobar resections is to preserve lung parenchyma and therefore pulmonary function, with the thought that this would reduce postoperative morbidity while achieving the primary therapeutic goal of the surgery (4). More recently, with the increase in computed tomography (CT) screening in patients at high risk for lung cancer, in addition to advances in imaging technology, early detection of smaller but none-the-less concerning peripheral lung nodules has increased in frequency. All of which raises the question of whether or not sublobar resection, or more specifically segmentectomy, could be the standard of care for peripheral early-stage NSCLC (2, 3). Up until recently, only retrospective studies have shown that in carefully selected populations, segmentectomy demonstrated oncological results comparable to lobectomy (5, 6).

Consequently, the West Japan Oncology Group and Japan Clinical Oncology Group recently published a multicentered randomized controlled trial (JCOG0802/WJOG4607L) and demonstrated the superiority of segmentectomy over lobectomy in terms of overall survival for early-stage lung cancer. This study included patients with clinical stage IA NSCLC (peripheral tumours; tumour diameter ≤2 cm; consolidation-to-tumour ratio >0.5). Reportedly, the 1,106 patients studied in Japan showed an improved 5-year overall survival in the segmentectomy group (94.3% in the segmentectomy group compared to 91.1% in the lobectomy group, $p < 0.0001$ for non-inferiority and $p = 0.0082$ for superiority), with an overall improved survival across all subgroups, especially in men, patients older than 70 years old, solid tumours as well as non-adenocarcinomas in the segmentectomy group. Additionally, the 5-year relapse-free survival was 88.0% in the segmentectomy group and 87.9% in the lobectomy group (HR: 0.998, 95% CI: 0.753–1.323). However, they noted a statistically significant increase in locoregional relapses in the segmentectomy group (11% vs. 5%, $p = 0.0018$), explained by the lesser resection in segmentectomy, and we propose limited knowledge of lymphatic drainage of the lung, but somehow a nonsignificant difference on the total relapse pattern. Of the patients with relapses, the 5-year survival was higher in the segmentectomy group (68% vs. 49%) and a higher percentage of the relapses in the segmentectomy group received treatment compared to the lobectomy group (93% vs. 80%). As expected, there was significant difference in the reduction in forced expiratory volume in 1 s (FEV1) between segmentectomies and lobectomies, which was higher in the lobectomy group; however, the proportions of median FEV1 reduction between segmentectomy and lobectomy groups at the 6 and 12 months follow-up were not clinically significant (4, 5).

The JCOG0802/WJOG4607L study is the first randomized-controlled trial to demonstrate the non-inferiority and superiority of segmentectomy over lobectomy for clinical stage IA NSCLC overall-survival and could thus be considered a standard procedure for small-sized peripheral NSCLC. While segmentectomy *via* video-assisted thoracic surgery (VATS) is the most widespread approach, development in video instrumentation and thoracic robotic surgery has gained more and more interest. Indeed, robotic surgery pioneers boast the advantages in three-dimensional view, improved magnification, ergonomics, dexterity, safety, and ease of surgery, especially with regards to the mediastinal lymph node dissection, with such technology (7–9). Furthermore, adjuncts such as the systemic injection of indocyanine green have been shown to enhance the demarcation of intersegmental plane facilitating segmentectomies (10).

This article aims to review robotic-assisted segmentectomy indications, preoperative evaluation, and the operative conduct for the different segments from a single surgeon console. There are many ways to perform segmentectomies and therefore this article outlines a generalized approach that can be tailored based on experience. The anatomy of the lung segments is outlined in **Figures 1, 2**.

Indications and preoperative considerations

The standard preoperative evaluation of early-stage lung cancer including a clinical assessment, PET-CT and pulmonary function testing apply. In order to accurately select patients who will benefit from segmentectomy, it is important to stage the mediastinum *via* endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) or video mediastinoscopy as segmentectomy is not indicated if there is lymph node involvement according to the JCOG0802/WJOG4607L study (3). Additional imaging and testing should be organized according to patient past medical history and suspicion for metastasis (11, 12).

Robotic surgery of any kind requires a dedicated team of surgeons, nurses and support staff who are trained in robotic-assisted surgery. In thoracic surgery, plans need to be in place and simulations run in preparation for the event to convert to thoracotomy.

Robotic console adjustments

The Food and Drug Administration (FDA) has approved the Da Vinci Surgical Systems (Intuitive Surgical Inc., Sunnyvale, CA, USA) for robotic anatomic lung resections with several new platform developments on the horizon. With the Si system, the robot is driven from the head of the patient, over the shoulder, forming a 15-degree angle with the patient length. The anesthesia team provides care on the backside of the patient, 90-degrees from the console, and often require the use of longer ventilation tubing as they are a further distance away than their typical location. For the Xi system, the robot can approach the patient at a 90-degree angle from the side of the bed, allowing anesthesia to be in their standard position at the head of the patient. Special attention confirming the tolerance of one-lung ventilation prior to sterile drape placement is imperative as it is difficult to reposition the endotracheal tube once the robot is docked.

Patient positioning and port placement

Patient positioning is similar to a VATS segmentectomy: the patient is placed in lateral decubitus position, with the surgical side up. The table is flexed 5–10 degrees at the level of xiphoid process to open the intercostal space maximally. Following flexion, the bed is adjusted to level the chest and the bed height is set to as low as possibleThe patient is then secured in position with the pressure points checked and padded. The patient is then prepped and draped in the usual sterile fashion, allowing sufficient exposure if there was a need for conversion to thoracotomy. Port placement is surgeon dependent based on previous experience and personal preference. **Figure 3** depicts port placement for a robotic segmentectomy using four robotic arms in the same intercostal space with an assistant port triangulated between ports 3 and 4. The initial camera port is

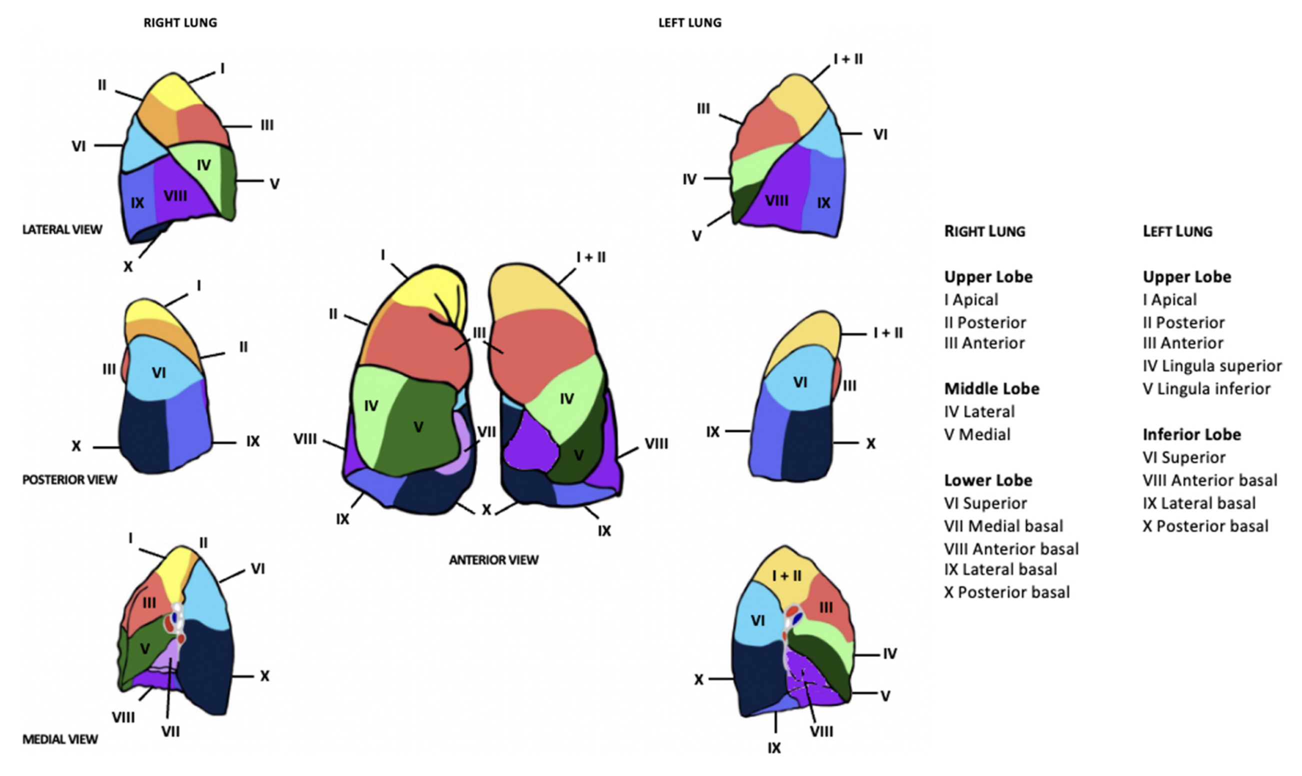

FIGURE 1
Lung segments by Elisabeth Savonitto.

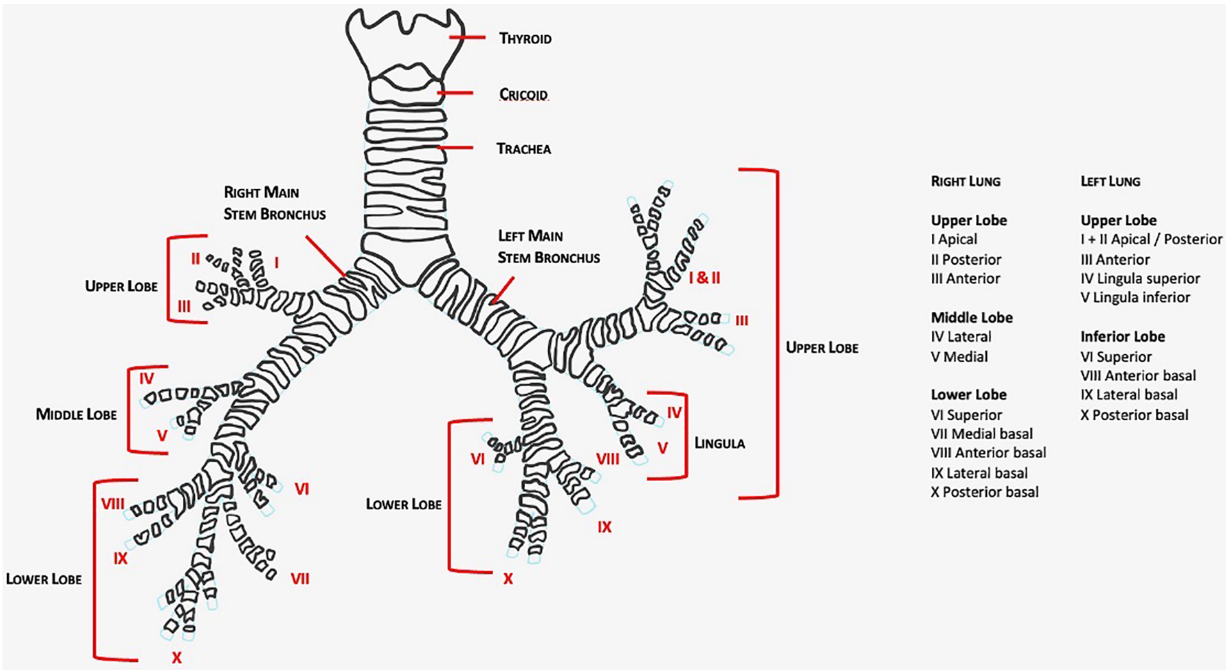

FIGURE 2
Bronchial tree by Elisabeth Savonitto.

placed in the 7th intercostal overtop the 8th rib between the mid axillary line and anterior axillary line. The hemithorax is inspected in order to optimize further port placement. Ports 1 and 2 are placed posterior to port 3 and port 4 is placed anterior to port 3 all in the same intercostal space maintaining 6 cm–10 cm between ports. The most posterior port, port 1, is placed

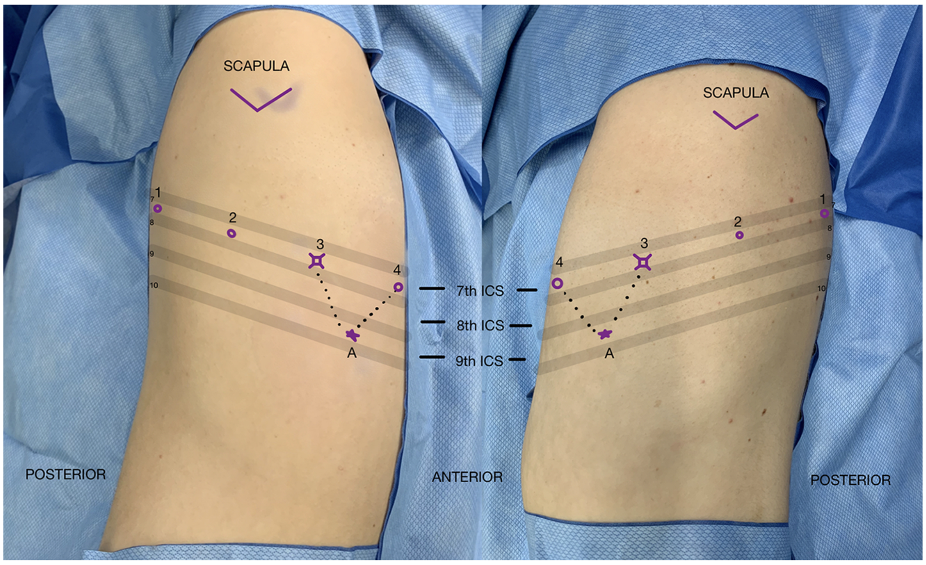

FIGURE 3
Port placement for robotic segmentectomy by elisabeth savonitto.

at minimum of 4 cm anterior to the spine. One variation is to place the most anterior port, port 4, in the 6th intercostal space, The assistant port is triangulated between ports 3 and 4 at the junction of the diaphragm and chest wall.

Similar to VATS, carbon dioxide insufflation (5–8 mmHg pressure at 4L/min flow rate) can be used to depress the diaphragm and compress the lung, but is not mandatory. A zero-degree camera is most commonly used for these operations but based on surgeon preference a 30-degree camera can be used as well.

Mediastinal lymph node dissection

As with any cancer operation, robotic segmentectomy begins with inspection of the pleura to rule out any sign of metastatic disease. According to the JCOG0802/WJOG4607L study systematic or selective lymph node dissection was mandatory, and nodal sampling was not allowed (3).

Starting with the mediastinal lymph node dissection has several advantages. First, removal of the lymph nodes helps expose the hilar structures. Second, sending off the lymph nodes for pathologic analysis at the start of the case allows the pathologist time to analyze the tissue to rule out metastatic disease. As the recent findings for the superiority of segmentectomies compared to lobectomies apply to T1N0 disease, conversion to lobectomy would be indicated if the lymph nodes were positive on frozen section analysis.

Division of the inferior pulmonary ligament allows exposure of lymph node stations 8 and 9, which are then carefully dissected and removed. With the accessory arm, the lower lobe is retracted medially and anteriorly to expose station 7, which is then dissected and removed.

Regarding lymph node stations 2R and 4R, the right upper lobe is retracted inferiorly with the accessory arm. Regarding the left-sided resections, the accessory arm is used to press caudally the left upper pole to expose lymph node stations 5 and 6. Attention is paid to avoid injury to the recurrent laryngeal nerve.

Right upper lobe apical segmentectomy

One approach is from the anterior hilum, with posterior retraction to the lung with the accessory arm. The tissue between the apical artery and vein is dissected. The upper lobe vein is then anatomized until its first branch, the apical vein, is apparent. Dissecting the vein first exposes the upper lobe arteries. It is key to expose the bifurcation between the apical and anterior lobe arteries to then dissect the apical artery. The artery is then stapled, followed by the vein. This will expose the B1 bronchus branch which can be isolated and stapled. The use of a vessel-loop can aid to pass staplers around the vessels and bronchi. The parenchymal segmental delimitation can be facilitated with either re-insufflation of the lung or with injection of indocyanine green and use of the “firefly view” to assess areas free of blood flow. The parenchyma can then be safely divided with a surgical stapler (13).

Right upper lobe posterior segmentectomy

The posterior approached dissection of the lymph nodes will help differentiate the posterior ascending artery from the superior lobar arteries. Note that this artery is absent in

10%–15% of the population. Once dissected and defined, it can be stapled. Then the fissure between the superior and inferior lobe is dissected, which will further expose the right main bronchus, which can be followed until exposure of the posterior segmental bronchus of the right upper lobe. The posterior branch of the right upper lobe can then be dissected. The posterior segment parenchyma can then be separated from the remnant upper lobe with a stapler.

Right upper lobe anterior segmentectomy

An anterior vein-first approach will facilitate the anatomy exposure. The anterior hilum is incised at the level of the right superior pulmonary vein, which is then followed until its trifurcation. The anterior segmental vein typically has a more oblique and anterior orientation. There can be multiple branches. This will then expose the superior lobar artery and its division. The anterior segmental artery has a more oblique and downward orientation towards the anterior segment parenchyma; it can then safely be stapled with a vascular load once dissected out. As the posterior vein travels between the anterior and posterior bronchus, following it will help landmark the anterior bronchus, which can then be stapled. Finally, the parenchyma can be transected in the usual fashion (14).

Superior segmentectomy of the left lower lobe

By retracting the lung anteriorly, the fissure can be dissected freely posteriorly, which will expose the bifurcation of the left pulmonary artery. Following the inferior lobar artery will expose the lingular artery and the basal trunk. The superior segmental artery can then be seen more medially and divided. The superior segmental vein will then appear to the surface and can also be divided. Finally, with either an anterior or posterior approach, the superior segmental bronchus will be seen just distal to the left main bronchus bifurcation; it can then be divided. Reinflating the lung or using the Firefly view will help demarcate the superior segment from the rest of the lower lobe and can then be transected, which is usually done through the assistant port.

Basilar segmentectomy

An anterior vein-first technique, while pulling the lung posteriorly, is the preferred approach for the basilar segmentectomy. The basilar segmental veins are isolated and stapled, by following the inferior pulmonary vein and preserving the superior segmental vein, which are usually more proximal. This will then expose the bronchus to the basilar segments, which can then be divided, with caution to preserve the superior segmental bronchus that usually has a more medial direction. The fissure can then be dissected completely, which will expose the arteries. The basilar segmental arteries can then be anatomized and divided accordingly. The parenchyma is then stapled as previously described, while preserving the superior segment of the lower lobe (11). Each of the basilar segments can be transected individually. In order to ensure division of the appropriate structures, the safest approach is to start from the peripheral parenchyma and progress medially.

Left upper apical trisegmentectomy

Anteriorly, the mediastinal pleura overlying the superior pulmonary vein is sharply incised and is bluntly dissected until exposing the inferior pulmonary vein. Posteriorly, the area between the upper and lower lobes is dissected to expose the bifurcation between the superior and inferior left pulmonary arteries. The first branches consist of the apical and posterior superior arteries, which can then be divided. The left main pulmonary artery is anatomized in a way to expose the anterior branches that pass under the aortic arch. This will expose the left superior pulmonary vein which can be dissected and followed. Its bifurcation will expose the trisegment pulmonary vein. The arteries and veins can then be stapled. Finally, their dissection will expose the bronchus. the left main bronchus is followed until its bifurcation, which will again separate to expose the superior upper bronchus and the lingular branches. The apicoposterior division can then be stapled. The segmentectomy is completed by stapling the parenchyma between the lingula and the apical trisegment, which can be demarcated as previously described (15).

Lingulectomy

Intra-operative figures of a robotic-assisted segmentectomy are shown in **Figure 4**. Using the same technique as the left upper apical trisegmenctecomy, the fissure between the upper and lower lobes is followed and divided while approaching through the posterior aspect of the lung, which then exposes the inferior lobar artery, which is followed until the first branches, the lingular artery or arteries, are exposed. They can then be divided with the assistant port or the left arm. The superior pulmonary vein will then come to the surface and will be followed until the bifurcation between the apical and lingular branches are exposed. The lingular branches are then divided through the assistant port. Finally, the left main bronchus will be followed until the lingular bronchus are anatomized, to then be divided. Finally, the parenchyma is stapled.

Postoperative management

Following segmentectomy, the average length of stay is 3–5 days (16). Pain management protocols recommended for VATS lobectomies can be employed for segmetectomies including,

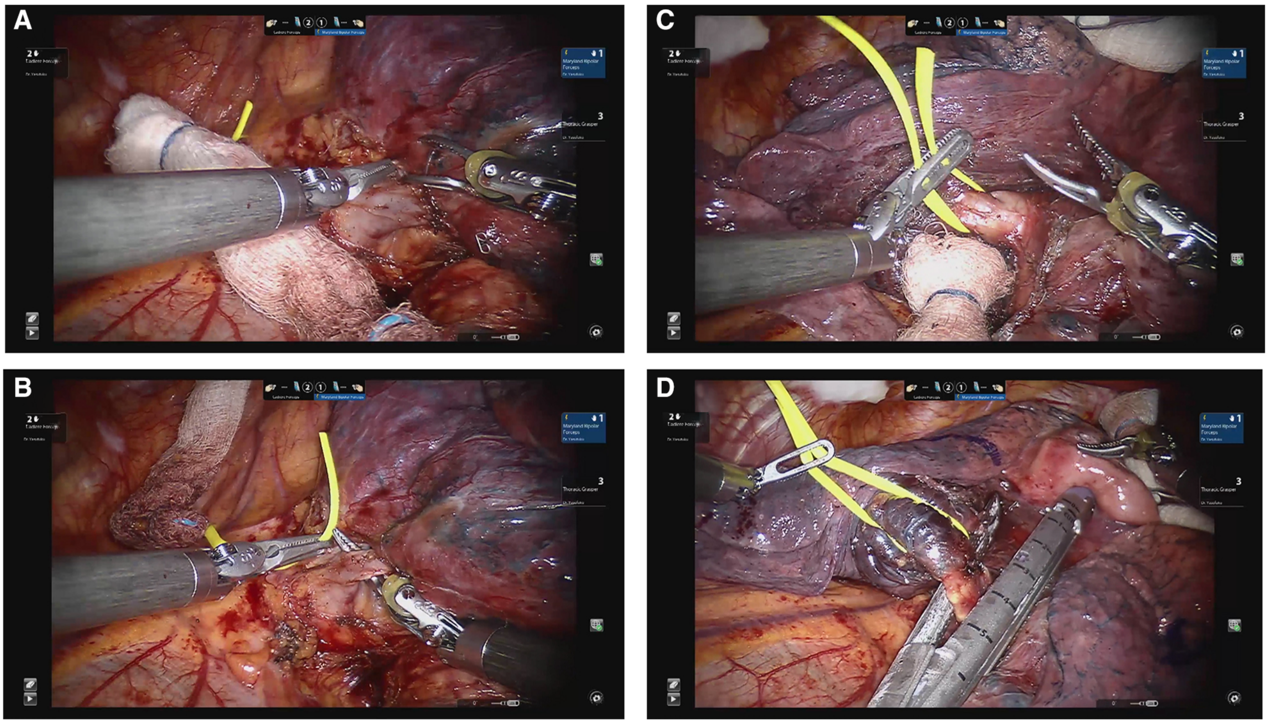

FIGURE 4
Lingulectomy. (A) Dissection of lingular vein. (B) Encircling lingular vein. (C) Dissection of lingular PA branches. (D) Division of lingular bronchus.

regional analgesic techniques such as a single shot paravertebral block or intercostal nerve blocks along with systemic analgesia including Tylenol and non-steroidal anti-inflammatory drugs or cyclo-oxygenase-2-specific inhibitors administered pre-operatively and continued postoperatively (17). Opioids are used as rescue analgesics postoperatively (17). Furthermore, adopted from VATS lobectomies, one 20-F or 24-F chest tube directed apically with minimal chest tube suction is recommended (18). The chest tube is removed when there is no air leak and the daily output is less than 450 ml (non-chylous and non-sanguinous) (18). I COUGH, a standardized perioperative pulmonary care program, can be employed to improve patient performance and reduced pulmonary complications (19).

Concluding remarks

In conclusion, the recently published randomized controlled trial JCOG0802 confirmed the superiority and non-inferiority of segmentectomies in context of peripheral T1N0 NSCLC. Many techniques have been described, and robotic-assisted thoracic surgery is on the rise. This article describes robotic-assisted segmental resections. One of the incredible things about lung cancer surgery is that although cases may start with a general approach they often unravel as unique and intricate puzzles and no matter what approach is used initially it is important to be adaptable and familiar with the tools available.

Author contributions

ES and AW conceived the concept and wrote the manuscript, and KY made substantial, direct intellectual contributions to the work. All authors contributed to the article and approved the submitted version.

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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Advances of endoscopic and surgical management in gastrointestinal stromal tumors

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As one of the most common mesenchymal malignancies in the digestive system, gastrointestinal stromal tumors (GISTs) occur throughout the alimentary tract with diversified oncological characteristics. With the advent of the tyrosine kinase inhibitor era, the treatment regimens of patients with GISTs have been revolutionized and GISTs have become the paradigm of multidisciplinary therapy. However, surgery resection remains recognized as the potentially curative management for the radical resection and provided with favorable oncological outcomes. The existing available surgery algorithms in clinical practice primarily incorporate open procedure, and endoscopic and laparoscopic surgery together with combined operation techniques. The performance of various surgery methods often refers to the consideration of risk evaluation of recurrence and metastases; the degree of disease progression; size, location, and growth pattern of tumor; general conditions of selected patients; and indications and safety profile of various techniques. In the present review, we summarize the fundamental principle of surgery of GISTs based on risk assessment as well as tumor size, location, and degree of progress with an emphasis on the indications, strengths, and limitations of current surgery techniques.

KEYWORDS
gastrointestinal stromal tumors (GISTs), surgery, risk evaluation (RE), endoscopy, LECs

Abbreviations
GISTs, gastrointestinal stromal tumors; ICCs, interstitial cells of Cajal; TKI, tyrosine kinase inhibitor; NIH, National Institutes of Health; AFIP, Armed Forces Institute of Pathology; NCCN, National Comprehensive Cancer Network of the United States; ESMO, European Society for Medical Oncology; HPFs, high power fields; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; GTV, gross tumor volume; TACE, transcatheter arterial chemoembolization; PD, pancreaticoduodenectomy; WR, wedge resection; FTR, full-thickness resection; EGJ, esophagogastric junction; EGISTs, extragastrointestinal GISTs; ESD, endoscopic submucosal dissection; EEN, endoscopic enucleation; EMD, endoscopic muscularis dissection; BLR, band ligation and resection; ESTD, endoscopic submucosal tunnel dissection; STER, submucosal tunnel endoscopic resection; POETR, per oral endoscopic tumor resection; POEM, peroral endoscopic myotomy; NR, not reported; EFTR, endoscopic full-thickness resection; OTSC, over-the-scope clip; LAES, laparoscopy-assisted endoscopic surgery; EALS, endoscope-assisted laparoscopic surgery; LECS, laparoscopy–endoscopy cooperative surgery; EAWR, endoscope-assisted wedge resection; EATR, endoscope-assisted laparoscopic trans-gastric resection; LIGS, endoscope-assisted laparoscopic intragastric surgery; sLIGS, single-incision LIGS; LAEFR, laparoscopy-assisted endoscopic full-thickness resection; NOTES, natural orifice transluminal endoscopic surgery; CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia applying nonexposure technique; NEWS, nonexposed endoscopic wall-inversion surgery.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal subepithelial tumors in the alimentary canal with an estimated incidence worldwide of 1–2 per 100,000 (1, 2). As an oncological clinical entity, they were characterized as a virtually indolent property and could progress to highly aggressive malignancies (3). The anatomical position of GISTs nearly covers the complete gastrointestinal tract, primarily the stomach (50%–60%) followed by the small intestine (20%–30%), while they are infrequent in the colorectum and esophagus and rare in extragastrointestinal sites (mesentery and omentum) (4). GISTs are supposed to arise from the spindle-shaped interstitial cells of Cajal (ICCs) situated in the muscularis propria (MP) layer, known as pacemaker cells responsible for peristalsis, or their precursors (4, 5), with potential tumorigenesis referring to gain-of-function oncogenic activating mutation of receptor tyrosine protein kinase encoded by KIT or platelet-derived growth factor receptor alpha (*PDGFRA*) gene (6). Clinical manifestation of GISTs vary from asymptomatic incidental findings to palpable presentation including bleeding, obstruction, perforation, or abdominal mass (7). Histopathological biopsy and immunohistochemical analysis are of great significance to the diagnosis of GISTs (8). Therapeutic algorithms of GISTs incorporate surgical operation, endoscopy, interventional therapy, and medication, of which surgical resection of the entire tumor is considered to be the exclusive effective way to be completely curative for resectable primaries (9, 10). After the approval of imatinib mesylate by the Food and Drug Administration (FDA) of the United States in 2002 for molecular targeted medication, the availability of tyrosine kinase inhibitor (TKI) revolutionized the therapeutic management of GISTs, and GISTs have become the paradigm of multidisciplinary and multimodal therapy with reference to gastroenterologists, oncologists, and pathology specialists (11–13). Unfortunately, recurrence and metastasis remain common despite the remarkable efficacy of TKI therapy. (14). A growing number of investigations have demonstrated the safety and prognosis-improving benefits of surgery even in the metastatic scenario and updated original operative techniques (15). The present review aims to give an overview of updated surgical management in GISTs based on risk evaluation, progress degree, tumor size, and tumor location with introduction of modalities in the process of exploration.

2. Risk evaluation

The management modality of GISTs is dependent on preoperative risk evaluation with diversified regimens varying from procedures to chemotherapy being based on the location, size, and aggressiveness of GISTs. There are noteworthy limitations of the TNM staging system for assessing progression risk of GISTs, which is not regularly indicated in clinical practice (7). Tumor size and mitotic index were well-recognized prognosis indicators for resectable primaries of which tumor size in dimension <2 cm and mitotic count <5 per 50 high power fields (HPFs) are considered very low risk and tumor size in dimension >10 cm or mitotic count >10 per 50 HPFs are considered high risk in 2001 National Institutes of Health (NIH) taxonomies based on expert consensus (16). Considering patients with GISTs located in extragastric sites present with considerably higher risk of disease recurrence in comparison with those with gastric GISTs, another risk criterion for localized GISTs was developed by the Armed Forces Institute of Pathology (AFIP) with an additional incorporation of tumor location (**Table 1**) (17). Subsequently, modified NIH criteria, including mitotic count, tumor size, and location, especially tumor rupture, came into being as demanded under the situation where preoperative tumor rupture was found to be independently correlated with dismal recurrence-free survival (RFS) of GIST patients (**Table 2**) (18). Considering that tumor size and mitotic count are nonlinear continuous indices, precluding the accurate calibration of cutoff criteria, several prognostic contour maps, and nomogram, where these variables included in nonlinear modeling, have been proposed for the optimization of risk classification, which were validated to be more applicable for risk assessment of progressive aggravation (19, 20). Considering convenience and feasibility for clinical application in the Asian population, Chinese consensus guidelines for diagnosis and management of GISTs recommend modified NIH criteria for risk evaluation (21). However, above-mentioned AFIP criteria were suggested by the National Comprehensive Cancer Network of the

TABLE 1 AFIP criteria for risk evaluation of metastasis or recurrence or tumor-related death for patients with primary GISTs (17).

Tumor size in maximal diameter (cm)	Mitotic count (per 50 HPFs)	Tumor location			
		Stomach	Jejunum and ileum	Duodenum	Rectum
≤2	≤5	0	0	0	0
>2 ≤ 5	≤5	1.9% (very low)	4.3% (low)	8.3% (low)	8.5% (low)
>5 ≤ 10	≤5	3.6% (low)	24% (moderate)	[a]	[a]
>10	≤5	12% (moderate)	52% (high)	34% (high)	57% (high)
≤2	>5	0	50% (high)	[a]	54% (high)
>2 ≤ 5	>5	16%(moderate)	73% (high)	50% (high)	52% (high)
>5 ≤ 10	>5	55% (high)	85% (high)	[a]	[a]
>10	>5	86% (high)	90% (high)	86% (high)	71% (high)

AFIP, Armed Forces Institute of Pathology; GISTs, gastrointestinal stromal tumors; HPFs, high power fields.
[a]Sample numbers are too small to ascertain corresponding risk.

TABLE 2 Modified NIH criteria for risk evaluation of metastasis or recurrence or tumor-related death for patients with primary GISTs (18).

Risk stratification	Tumor size in maximal diameter (cm)	Mitotic count (per 50 HPFs)	Tumor location
Very low	≤2	≤5	Any
Low	>2 ≤ 5	≤5	Any
Moderate	>2 ≤ 5	>5	Gastric
	<5	6 ≤ 10	Any
	>5 ≤ 10	≤5	Gastric
High	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>10	Any
	>5	>5	Any
	>2 ≤ 5	>5	Non-gastric
	>5 ≤ 10	≤5	Non-gastric

NIH, National Institutes of Health; GISTs, gastrointestinal stromal tumors; HPFs, high power fields.

United States (NCCN) and the European Society for Medical Oncology (ESMO) guidelines due to wide availability and prediction accuracy (22, 23). There are several limitations of existent risk classification criteria, which fail to perfectly predict metastasis and recurrence hazard for GISTs. Take SDH-deficient GISTs as an example, mitotic index was negatively associated with the risk of liver metastases but with a relatively extended period to develop metastases (21). Collectively, the establishment of new risk criteria-based prospective multicenter series is still warranted and the effective selection of multiple classifications for individualized patients under specific clinical circumstances is recommended for further formulation of treatment regimens.

3. Surgical management in gastrointestinal stromal tumors

3.1. Surgical management stratified by tumor stages

An overview of the management algorithm of primary and advanced/metastatic GISTs is summarized in **Figure 1**. The detailed surgical managements based on different tumor stages are as follows.

3.1.1. Localized primary GISTs

Preoperative or intraoperative biopsy for pathological identification is not a prerequisite unless presurgical molecular diagnosis is necessary for targeted medication, which is not routinely recommended in cases with removable primaries to avoid the potential possibility of tumor rupture, bleeding, and diffusion (11). Among multiple biopsy approaches, endoscopic

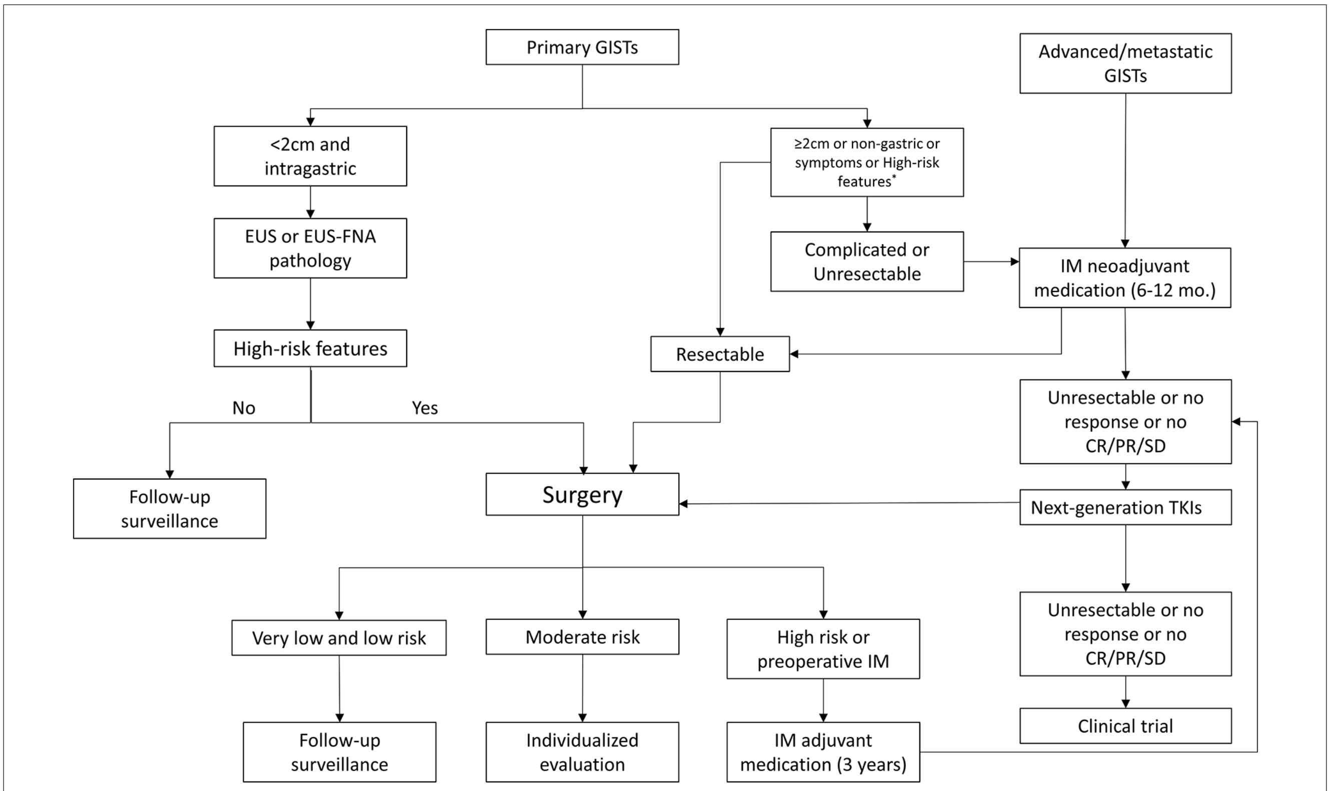

FIGURE 1
Management algorithm of primary and advanced/metastatic GISTs. GISTs, gastrointestinal stromal tumors; EUS, endoscopic ultrasonography; EUS-FNA, EUS-guided fine needle aspiration; IM, imatinib mesylate; TKIs, tyrosine kinase inhibitors; CR, Complete remission; PR, partial response; SD, stable disease; high-risk features refer to irregular and unclear border, echogenic foci, high mitotic rate, cystic degeneration, strong echo, ulcer, hemorrhage, and heterogeneity.

ultrasound-guided fine needle aspiration (EUS-FNA) is mostly used in clinical practice with distinct advantages of accuracy, safety, and relatively low possibility of dissemination. Potential limitations are inevitable considered that it is only applicable for GISTs situated in the lumen and fewer samples often lead to uncertainty of pathological diagnosis (24–26). Postoperative pathology report is of great value for the confirmation of diagnosis (27).

Surgery indications often refer to non-gastric GISTs, tumor size larger than or equal to 2 cm, or symptoms presented such as abdominalgia and gastrointestinal bleeding without regard to tumor size and location. Even though GISTs are located in the stomach with size less than 2 cm, attention should be paid on the risk under EUS or pathology for further determination of the implementation of operation. Higher risk tends to include irregular and unclear border, echogenic foci, high mitotic rate, cystic degeneration, strong echo, ulcer, hemorrhage, and heterogeneity (21, 28, 29). Without the presentation of these manifestations, regular follow-up surveillance is recommended.

It has been well-recognized that radical surgical resection is the first-line cornerstone and mainstay for the treatment of localized primary GISTs, which is the exclusive way for potentially thorough cure (30, 31). Surgery should be performed by experienced surgical specialists when open surgery or laparoscopy management was planned (7). The fundamental principle is to carefully complete *en bloc* removal of the tumor entity securing a sufficient histopathologically negative margin (R0 resection) achieving minor complications without damage of organ function and violation of tumor pseudocapsule prior to or during procedure as much as possible, which might contribute to accidental tumor perforation and rupture with tremendous risk of intraperitoneal implantation and spreading of tumor cells. To this end, “no touch, less compression” code and “extract bag” approach are available (21). Tumor excision incorporating peripheral tissues, whenever and wherever necessary and possible, in the case surrounding tissues or organs, is involved so as to realize the principle of R0 resection (7, 28). R0 resection is considered as the well-recognized favorable prognosis indicator for patients with localized primary GISTs (32). R1 resection (microscopically positive margins) is inclined to the development of tumor relapse, which occurs practically in all cases with tumor rupture (33). With respect to the situation where preoperative medication is unavailable or shows obscure benefits in patients with R0 resection that implicated major sequelae, R1 resection is recommended to be taken into consideration with no demonstration of correlation with dismal outcome especially in low-risk cases (23, 34). In addition, reoperation is a substitute for discussion as an individualized management after unexpected R1 resection and R2 excision (macroscopic incomplete excision) (7, 35). Inconsistent with surgical treatment of other malignancies, the proportion of lymphatic dissemination is comparatively diminutive and extensive lymphadenectomy is not regularly indicated with an exception of proof-positive lymphadenopathy, which implicated SDH-deficient genotyping especially in pediatric GISTs (27, 36, 37).

3.1.2. Localized advanced GISTs

Preoperative neoadjuvant molecular targeted chemotherapy with TKIs like imatinib was indicated in situations where R0 resection is laborious to perform accompanied by alarmingly significant surgery risk and morbidity and increased possibility of perioperative complication like tumor rupture and bleeding or common postoperative functional sequelae, which will seriously affect organ function (23, 38). More often than not, potential occasion refers to large tumor size (>10 cm in maximal diameter) or difficult and unfavorable tumor sites located in operatively challenging areas such as the esophagus, esophagogastric junction (EGJ), duodenum, and rectum (39–41).

The rationale is that relatively large tumor size is reported to be positively correlated with the decreased rate of radical removal and increased risk of tumor recurrence (42). Consequently, shrinkage of tumor volume by neoadjuvant administration is of great significance for subsequent surgery, which not only contributes to improving the success rate of R0 resection and function preservation of involved organ and normal tissues to the greatest extent, as the avoidance of extended total gastrectomy and preservation of the anal sphincter, but also improve the 5-year overall survival (OS) and progression-free survival (PFS) (43–45). Simultaneously, genotyping tests prior to TKI therapy are essential for the identification of types of targeted drugs, and vigilant focus should be paid on imatinib-insensitive tumors such as PDGFRA D842 V mutations (46). Prior to the operation, neoadjuvant therapy should be conducted for 6–12 months so as to realize maximal chemotherapy outcome (29, 35). With respect to the embarking moment of surgery, the ESMO–EURACAN guidelines recommend to stop neoadjuvant therapy just before surgery and resume immediately after patients’ postoperative recovery (23). Further potent evidence based on large-scale multicenter clinical trials for the consolidation of efficaciousness of preoperative neoadjuvant medication remains to be developed.

Apart from aforementioned GISTs population with preoperative neoadjuvant chemotherapy with TKI, postoperative adjuvant therapy is often indicated as an indispensable part of standard treatment. Pertinent scenarios mainly refer to those categorized as “high risk” of recurrence and metastasis according to various classification criteria and those with R1 resection (11). According to a long-term randomized multicenter clinical trial, the postsurgical administration of TKI adjuvant chemotherapy was recommended for at least 3 years (47). Individualized evaluation is often recommended for moderate-risk patients to discuss whether to carry out adjuvant chemotherapy or follow-up surveillance (35).

3.1.3. Recurrent, metastatic, or unresectable GISTs

Even though the tumor is completely removed through operation and TKI therapy presents amenable effectiveness, recurrence and metastasis are fairly commonplace, especially in high-risk patients with adverse 5-year OS and relapse-free survival (RFS) (48). Systemic therapy with TKI targeted medication based on genotyping is the first therapy and gold standard in recurrent, metastatic, or inoperable circumstances, and surgery is not generally recommended as a primary choice but considered as an available alternative and non-contraindication (28, 41, 49). As gross tumor volume (GTV) of GISTs is investigated to be positively correlated with tumor progression and negatively associated with the survival outcome of patients, debulking surgery and cytoreduction potentially decreased the likelihood of imatinib-resistant clones emerging, and the risk of secondary mutations has become a significant component of management in patients with recurrence or metastasis scenario (50, 51). Of note, debulking surgery is found to be efficacious in outcome improvement for most TKI-respondent patients and should be conducted before tumor progression (51, 52). Postoperatively, complete removal of tumor along with TKI therapy provides preferable outcomes for patients with more effectiveness and minimal complications and side effects compared with TKI alone (49, 53). As mentioned above, for those administrated with preprocedural TKI neoadjuvant regimens, adjuvant chemotherapy after surgery needs to be resumed as soon as possible (35). Specifically, patients who develop disease progression with TKI resistance will not benefit from identical TKI regimen used preoperatively, and postsurgical genetic test that is dedicated to identifying further therapeutic target is of vital value under this circumstance (41).

The indication of surgical administration in selected patients is as follows: better responding with imatinib therapy and tumor transfer from unresectable to resectable entity with minor operation-associated risk in residual lesions; localized progression with TKI resistance after targeted therapy including both sunitinib second-line therapy (54) and regorafenib third-line therapy (55) in addition to first-line treatment with imatinib (56); advanced tumor with a relatively small gross tumor volume of which lesion foci is evaluated to be completely removed through procedure; relatively limited and isolated metastatic foci or superficial lesions with operative feasibility; excision in cases with high risk of rupture necrotic metastases foci; patients in generally good condition and surgical tolerability; symptoms such as uncontrollable hemorrhage, perforation, and obstruction or acute pain with palliative emergency operation being necessary (28, 35). Surgical management for patients with general and disseminated progression following TKI medication is absolutely inadvisable, which could not present favorable survival benefits (21, 35).

Liver is one of the most common metastatic sites of GISTs; transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) play a palliative adjunctive role in tumor control with feasibility and safety in addition to surgery (57–59). However, RFA is inclined to be suitable for tumors with a maximum diameter of 3 cm and is contraindicated in patients in whom tumor is contiguous with large vessels or supersedes liver capsule (7). Efforts has been made for the establishment of successful cases of liver transplantation but prospective research are still limited, and this management regimen is not regularly considered in clinical practice with scrupulous discussion processing required by multidisciplinary specialists for comprehensive prognosis evaluation of patients and conducted in experienced transplant centers (60, 61).

Taken together, multidisciplinary cooperation should be taken into consideration for the evaluation of feasibility of debulking operation and metastasectomy for patients with recurrent or metastatic GISTs and provide them with individualized treatment algorithm-integrated systemic medication with localized palliative procedure for further outcome improvement. If surgery is planned to be conducted, with the premise of ensuring R0 or R1 excision as much as possible, scrupulous consideration of patient selection refers to feasibility and complexity of operation, the degree of disease progression, the involvement of adjacent organs, the patient's age, physical condition, possible complications, postoperative recovery time, benefits, and risks.

3.2. Surgical management in tumor location subgroups

3.2.1. Esophageal GISTs

Esophageal GISTs are comparably rare and ordinarily occur in the esophagogastric junction (62). Patients with relatively larger GISTs that are situated in the esophagogastric junction could benefit from TKI therapy followed by localized resection with avoidance of traumatic total gastrectomy, realizing organ function preservation to the greatest extent. Once the diagnosis of GISTs is established, surgery is suggested to be conducted immediately for such special anatomic location with operation difficulty (21). Choosing either complete esophagectomy or enucleation procedure is primarily based on the tumor size, location, and surgery-related risk (63). The enucleation technique could be a feasible alternative for relatively smaller and posterior wall GISTs, while radical esophagectomy is indicated for large tumors (4).

3.2.2. Gastric GISTs

The gastric subgroup constitutes a majority of occurrence sites for GISTs. As mentioned above, on the premise of the absence of risk presentation under EUS, gastric GISTs with GTV of less than 2 cm without tumor-related symptom is indicated for follow-up surveillance. Surgery is recommended for cases inconsistent with these scenarios such as those in extragastric sites.

Due to the possibility of associated risk of local recurrences, enucleation is not generally recommended (35). However, in order to preserve normal organ function, enucleation approach could be tried with regard to small GISTs situated in the posterior wall (4). GISTs with a tumor size ≤4 cm located in the stomach are reported to benefit from resection by endoscopic techniques with adjuvant therapy or additional operation, when necessary, based on risk evaluation while superiority is not shown in cases with tumor size >4 cm in which surgery is often necessary (64). Surgical resection approaches of gastric GISTs primarily incorporate wedge resection (WR) or larger resection securing a margin of 1–2 cm (65). In the case where wedge resection is not feasible, segmental resection is an appropriate option referring Biliroth I, Biliroth II, and total gastrectomy with gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction (4). Partial gastrectomy or total gastrectomy rather than proximal gastrectomy is recommended in GISTs located near the cardia or its extension (28, 35). Located in relatively favorable anatomic sites, greater curvature, or anterior wall of gastric body with tumor size of <5 cm is indicated for the application of laparoscopic procedure with safety, feasibility, less invasiveness, and comparable outcome compared to open surgery (21, 66, 67), and laparoscopic–endoscopic hybrid partial gastrectomy is a successful surgical method that secures complete resection without excessive violation of the normal anatomical structure (68). Simultaneously, this endoscopy-assisted laparoscopic operation is a recommendable alternative of open gastrectomy for gastric GISTs with feasibility and safety profile (69).

3.2.3. Duodenum GISTs

Duodenum GISTs account for a practically small proportion of all GISTs with its second part, descending part, being the most preferred site (70). Operative procedure to completely remove tumor securing an adequate margin remains to be the optimal choice for radical cure in localized primaries with resectable feasibility. However, the complex and special anatomical position of the duodenum itself, which is contiguous with the head of pancreas, common bile duct, pancreatic duct, mesenteric blood vessels, and ampulla of Vater combined with relatively insufficient procedural experience owing to its rarity, brings about enormous challenge for performing the surgery (71, 72). The available operative approaches based on diverse instruments primarily consist of open surgery, endoscopy, laparoscopy, and hybrid surgery such as endo–laparoscopic cooperative procedure. Open surgery is applicable in most cases after feasibility and safety evaluation especially in ampulla of Vater and pancreas involved complex cases in which pancreaticoduodenectomy (PD), known as Whipple resection, is ordinarily necessary but with enormous invasiveness and damage to normal organ function (73, 74). Segmental intestinal resection can be performed when the tumor size is small and lesion is remote from the essential ampulla location. Followed by presurgical neoadjuvant TKI administration, limited resection instead of PD is often accessible, which decreases compromising the proximal structures due to large invasiveness. Limited resection approaches often incorporate WR and segmental duodenum resection with intestinal anastomosis according to the lesion site and extension (75). Endoscopic resection remains challenging and is intractable to securely perform with a comparable risk of nonradical resection and tumor rupture although there are advances in endoscopy techniques identically due to anatomic characteristics of the duodenum (76). In recent years, laparoscopy and endo–laparoscopic approaches combined hybrid surgery have been explored in the operative management of GISTs, with predominant advantages of minimal invasiveness, decreased perioperative complications, and long-term survival (77–80). Consequently, meticulous consideration should be taken referring to size, location, and invasiveness to adjacent structures for the individualized evaluation of optimal procedure option.

3.2.4. Jejunum and ileum GISTs

The small intestine is the second most common site of gastrointestinal stromal tumors consisting of nearly a third of all GISTs (81). Open operation is ordinary practice while laparoscopic surgery should be taken into consideration for exploring and locating the corresponding lesion (21). In comparison with laparotomy, however, laparoscopic surgery is reported to assume less operation duration and less postsurgical complications as there was no significant between-group difference in oncological outcome according to a meta-analysis (82). Similarly, a retrospective review found that laparoscopic operation is safe and effective comparable to open operation in oncological prognosis and preferable in perioperative indicators (83). As for small intestine GISTs with size <10 cm in diameter, laparoscopic surgery can be recommended based on subgroup RFS analysis (84). Under normal circumstances, segmental resection with end-to-end intestinal anastomosis is recommended according to French clinical practice guidelines (35).

3.2.5. Colon GISTs

Consistent with their incidence in the esophagus and the duodenum, GISTs situated in the colorectum are similarly rare. Compared with the left colon, GISTs tend to occur in the right side (85). All colon GISTs are recommended to be surgically resected regardless of tumor size and malignancy degree (86). Segmental resection with end anastomosis is the frequently used operative approach parallel with GISTs in the small intestine (35). Unsophisticated laparoscopic appendectomy is often applicable for particularly rare appendiceal GISTs (4).

3.2.6. Rectum GISTs

GISTs located in rectum together with rectal vaginal space are strongly recommended for complete resection regardless of the tumor size since there are comparable risks for postsurgical recurrence and metastasis once diagnosis of GISTs is established (7) and enucleation is not regularly recommended (35). Considering that surgical difficulty and possibility of multivisceral resection will significantly increase with the enlargement of tumor size, operation should perform as early as possible (21).

There are different operative methods based on corresponding tumor location with respect to rectum GISTs. Low anterior resection and end-to-end intestinal anastomosis along with temporary colostomy are applicable for the upper section of the rectum with adequate distance to the anal sphincter. As for GISTs located in the lower rectum adjacent to the anal sphincter, abdominoperineal combined resection, known as Miles' operation, with permanent sigmoid colostomy are commonly performed (4). Research reported that transanal full-thickness resection (FTR) presents more benefits concerning lower rectum GISTs and should be discussed when referring to minor tumor size (65). Original sphincter-sparing operation approaches with less invasiveness have been explored such as transanal endoscopic operation (TEO) (87) and transanal minimally invasive surgery (TAMIS) (88). Laparoscopic resection is another applicable option for lesions located in the upper rectum of <2 cm but not regularly recommended when the tumor increases in size (21). Preoperative neoadjuvant chemotherapy is necessary for the preservation of sphincter function as much as possible by tumor shrinkage with the improvement of outcomes (89). A multicenter cohort research performed by Wang et al. (90) was investigated to the compare oncologic outcomes in patients with low rectum GISTs between a local resection cohort and a radical resection cohort; they found that local resection presented a significant superiority in sphincter preservation, minimizing operation time. and postoperative complications compared to radical resection. However, in terms of tumor size >2 cm, there was a preferable survival outcome in the radical resection cohort.

3.2.7. Extragastrointestinal GISTs

Actually, a great number of extragastrointestinal GISTs (EGISTs) reported are metastases foci of primary GISTs. Mesentery and omentum are common tumor sites of genuine primary EGISTs (91, 92). Other rare and unusual locations are pancreas (93), prostate (94), and pleura (95). With rare and aggressive malignancy, patients with EGISTs often have comparatively poor survival outcome, classified as high-risk lesions (96). Early identification and *en bloc* surgical excision as complete as possible remain the preferred treatment (97). Risk and cost-effectiveness of treatment regimens should be taken into account, and surgery combined with systemic neoadjuvant or adjuvant medication are often necessary (98) Cytoreductive debulking surgery might act as a potential palliative therapeutic strategy for symptomatic remission (99). Laparoscopy has been used for the surgical practice in EGISTs and achieved successful resection of tumor mass and oncological outcome as an available procedure option (100).

3.3. Surgical management in tumor size subgroups

GISTs with tumor size <2 cm are classified as small GISTs (101). More detailed subgroup categories include micro-GIST defined as GISTs <1 cm and mini GIST with size between 1 and 2 cm (102). Unless there are manifestations of high-risk characteristics based on EUS and biopsy, which warrant surgical management, the routine treatment for small GISTs is periodical follow-up surveillance with endoscopy and radiography (102). GISTs with size measuring equal to or larger than 2 cm (non-small GISTs) are recommended for surgical administration. With respect to those measuring over 5 cm accompanied with the presence or of symptoms or not, surgery is strongly indicated irrespective of whether the pathological diagnosis of GISTs is established or not (28).

Endoscopic resection is especially useful and safe for <2 cm GISTs. As for GISTs with 2–5 cm in size, enucleation, such as endoscopic submucosal dissection (ESD), is an available option ensuring complete excision but with risk of recurrence (28). As mentioned above, based on a long-term follow-up evaluation by Zhang et al., 4.0 cm might act as a threshold for choosing endoscopic resection in gastric GISTs stemmed from the MP layer with lower risk; however, surgery is still recommended for the population with increased risk (64). Laparoscopic resection also shows preferable outcomes and is recommended for GISTs between 2 and 5 cm, especially in easily accessible anatomic sites according to Chinese consensus guidelines (21, 103). A single-center long-term retrospective study was conducted for the comparison between surgery and endoscopy in the treatment of 2–5 cm GISTs. There were more complications and reoperation rates found in the endoscopic group compared to the surgery group with parallel outcome, and surgery, especially laparoscopic resection, is recommended more often (104). A size-matched comparison between laparoscopy and laparotomy found that gastric GISTs with size ≤8 cm might benefit more from laparoscopy based on oncologic outcomes (105). However, concerning relatively lager tumors (>5 cm) with excision needing larger incision, laparoscopic operation is not advocated due to pertinent tumor dissemination and open surgery is often encouraged (21). Patients with high risk, such as tumor size >10 cm in diameter or tumor size >5 cm plus mitotic count >5 per 50 HPFs, will benefit from neoadjuvant and adjuvant chemotherapy and achieve sound postsurgical oncological outcome.

4. Advances in laparoscopic operation

Under the premise of technical feasibility and the inexistence of operation contraindications, laparoscopy presents safe, efficient, and comparable postoperative oncological outcomes in selected patients with GISTs located in operationally facile sites like gastric and small bowel and with small size compared with open surgery (81, 106).

Recently, robotic surgical systems have been rapidly developed and received incremental interests. With kinetic stability, ergonomic design, and operation accuracy, they provide clinical surgeons with three-dimensional views and minimize the occurrence of tremors, thus reducing unnecessary tissue trauma as well as tumor manipulation and realizing the principle of minimally invasive surgery (107). Several reported research studies have confirmed the technical feasibility and safety of robot-assisted laparoscopic resection and suture reconstruction for the management of GISTs located in the upper gastrointestinal tract, especially for unfavorably positioned and relatively large series, which require more professional skills to avoid the risk of tumor rupture (108). Additionally, the Da Vinci Robot System has been introduced for optimization in laparoscopic operation, which is often preferred in complex and technically demanding cases (109–111). Researches of robot-assisted laparoscopic surgery are summarized in **Table 3**.

5. Advances in endoscopy techniques

Different from gastrointestinal epithelial tumors, it is the occurrence site of GISTs that confine the application of

TABLE 3 Research studies of robot-assisted laparoscopic surgery.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Complete resection rate	Hospitalization duration (days)	Conversion to open surgery (no.)	Complication
Yamamoto et al. (112)	2021	1	Esophagus	4.3	GIST	319	135	100%	18	0	0
Grimaldi et al. (107)	2021	17	Stomach	6.0 ± 2.8	GIST	200 (105–313)	50 (50–100)	100%	5 (3–18)	0	0
Maggioni et al. (108)	2019	6	Stomach	6.3 ± 1.8	GIST	173 ± 39	NR	100%	3 ± 1	0	0
Dreifuss et al. (109)	2022	1	Stomach	2.3	GIST	82	NR	100%	2	0	0
Vicente et al. (113)	2016	6	Stomach (3), duodenum (3)	3.9 (2.4–5.5)	GIST	245 (150–540)	NR	100%	10.5 (6–24)	0	0
Hirata et al. (114)	2022	13	Stomach (12), duodenum (1)	3.5 (2.0–8.0)	GIST (12)	160 (82–270)	25 (5–50)	100%	3 (1–4)	0	0

NR, not reported; GIST, gastrointestinal stromal tumor.

endoscopy for the evaluation of tumor features and further resection. Of note, there are comparatively high perforation and incomplete excision rates during endoscopic operation especially in GISTs with larger size or extraluminal involvement (115). However, with the increasing maturity of endoscopy, several original endoscopic approaches have been investigated for the treatment of GISTs. According to research exploring conventional ESD for esophagus and stomach GISTs with 2–5 cm in size, the perforation rate was around 20%, and no recurrence or metastasis was observed (116). The high perforation rate remains challenging and fundus was identified as the risk location of complications (117, 118). Based on the consideration of limitation of conventional ESD, several modified techniques have been developed (**Table 4**). Endoscopic enucleation (EEN) is validated to be an effective method for resection (92.3%, 60 of 64) but without the avoidance of higher perforation in the fundus (119). Derived from ESD approach, the endoscopic muscularis dissection (EMD) procedure presents a sufficient complete resection rate for gastrointestinal mesenchymal tumors originating from the MP layer (120). Inconsistent with the circumferential incision in ESD, a longitudinal incision was performed followed by electrical or blunt dissection and clips closing. Although complete resection was achieved at 96.8%, there was a higher risk of perforation than that in ESD (121). Band ligation and resection (BLR) is another operation option of EEN assuming a comparably high resection rate (41 of 41) and nearly 10% (4 of 41) perforation (122). A modified ESD with enucleation was introduced for removing GISTs, and no serious complications were reported (123).

In order to preserve the integrity of the mucosa and avoid pertinent perforation, strictures, and scars induced by endoscopic procedure, endoscopic submucosal tunnel dissection (ESTD) (124), also known as submucosal tunnel endoscopic resection (STER) (125) or per oral endoscopic tumor resection (POETR) (126), has been introduced for the treatment of GISTs originating from the MP layer based on the peroral endoscopic myotomy (POEM) (127) approach (**Table 5**). Following the creation of mucosal entrance proximal to the tumor, approximately 5 cm, a tunnel between the submucosa and MP layer was developed and the tumor was completely removed. Endoclips were employed to seal off the entrance. ESTD is evaluated to be a curative treatment option for GISTs with less invasiveness and apparent postoperative complications (128). However, due to the instinct difficulty of tunnel development in thick stomach mucosa, the majority of ESTD were performed in the esophagus or esophagogastric junction with insufficient efficacy validation in the stomach (129, 130). Moreover, limited tunneling space will preclude the *en bloc* resection of large GISTs with the routine criterion of <4 cm (126, 130).

Endoscopic full-thickness resection (EFTR) cooperated with the full-thickness suturing technique will contribute to realizing radical resection of gastric GISTs located in the deep MP layer with endoscopically manageable complications and sound oncological outcomes, which is applicable to GISTs up to 4 cm and those located in all anatomical positions of the stomach

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TABLE 4 Research studies of the conventional and modified ESD techniques.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Operation approach	Mean operation time (min)	Blood loss (ml)	Complete resection rate	Hospitalization duration (days)	Conversion to open surgery (no.)	Complication
Li et al. (118)	2013	11	Stomach	1.8 (1.2–3.0)	GIST (8)	ESD	81 (45–130)	NR	90.9%	NR	1%[a]	Perforation (27.2%)
He et al. (116)	2013	31	Esophagus (6) and stomach (25)	2.7 ± 0.7	GIST (31)	ESD	70.16 ± 16.25	NR	NR	NR	0	Perforation (19.35%) bleeding (9.68%)
Chen et al. (117)	2020	82	Stomach	3.5 ± 0.8	GIST (81)	ESD	68 (27–205)	NR	97.6%	16.1 (13.3–20.0)	0	Bleeding (9.8%) perforation (15.9%) infection (12.2%)
Jeong et al. (119)	2011	65	Stomach	1.4 (0.5–3.0)	GIST (26)	EEN	34.7 (6–90)	NR	92.3%	NR	NR	Perforation (12.3%)
Liu et al. (121)	2012	31	Esophagus (14) and stomach (17)	2.2 (0.5–4.5)	GIST (16)	EMD	76.8 (15–330)	NR	96.8%	NR	0	Perforation (12.9%)
Sawada et al. (120)	2020	6	Stomach	NR	GIMT	EMD	NR	NR	83%	NR	0	0
Ko et al. (122)	2019	41	Stomach	0.9 ± 0.5	GIST (17)	BLR	12 (4–52)	NR	100%	NR	0	Perforation (9.8%)
Chu et al. (123)	2012	16	Stomach	2.6 (2.0–4.2)	GIST (14)	modified ESD with enucleation	52 (30–120)	Minor	93.8%	NR	0	0

ESD, endoscopic submucosal dissection; EEN, endoscopic enucleation; EMD, endoscopic muscularis dissection; BLR, band ligation and resection; NR, not reported; GIST, gastrointestinal stromal tumor; GIMT, gastrointestinal mesenchymal tumor.
[a]Conversion to laparoscopic wedge resection.

TABLE 5 Research studies of tunneling techniques.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Operation approach	Mean operation time (min)	Blood loss (ml)	Complete resection rate	Hospitalization duration (days)	Conversion to open surgery (no.)	Complication
Inoue et al. (124)	2012	9	Esophagus (3) and cardia (4)	1.9 (1.2–3.0)	GIST (1)	ESTD	152.4 (40–365)	NR	100%[a]	6.3 (3–16)	2	NR
Tan et al. (131)	2017	20	Stomach	1.8 ± 0.7	GIST (20)	STER	74.9 ± 32.1	NR	95%[b]	NR	0	Pneumoperitoneum (5.0%)
Chen et al. (132)	2017	180	Esophagus (124), EGJ (43), stomach (13)	2.6 (2.0–5.0)	GIST (28)	STER	45 (15–200)	NR	90.6%%[b]	3.2	0	8.3%
Chiu et al. (126)	2019	39	Esophagus (11), stomach (39), duodenum (11)	2.1 ± 1.4	GIST (15)	POETR	90.46 ± 46.49	NR	98.0%	3.2 ± 1.0	4	4.0%

ESTD, endoscopic submucosal tunnel dissection; STER, submucosal tunnel endoscopic resection; POETR, per oral endoscopic tumor resection; NR, not reported; EGJ, esophagogastric junction; GIST, gastrointestinal stromal tumor.
[a]Of seven patients.
[b]*En bloc* resection.

(133). A dedicated full-thickness resection device for EFTR was applied in a 60-year-old patient with GIST with the advantage of protecting the peritoneal cavity from bowel contents (134). Another new technique called the clip-with-line traction-assisted preclosure assisted in EFTR was reported in a 47-year-old man with fundal GIST and was beneficial to preventing GIST falling into the abdominal cavity and the development of related complications such as peritonitis (135). Over-the-scope clip (OTSC) is an applicable device for the assistance of EFTR and verified with 100% excision success rate in treating GISTs with safety and effectiveness, which is especially recommended for a tumor size of <2 cm (136, 137). Researches of EFTR techniques are summarized in **Table 6**.

6. Advances in laparoscopy–endoscopy cooperative techniques

Since endoscopic operation alone is faced with certain limitations, such as demanding skills of experienced endoscopists and high risk of procedural complications, the application of laparoscopy performed in the process of endoscopy plays a significant role in decreasing the perforation rate and improving the complete resection rate especially in relatively large tumors in size and has been expanded into clinical practice. Based on the roles of the two kinds of procedures in the operation process, operation modalities of these cooperative techniques primarily incorporate laparoscopy-assisted endoscopic surgery (LAES), endoscope-assisted laparoscopic surgery (EALS), and integrated laparoscopy–endoscopy cooperative surgery (LECS). With respect to LAES and EALS, one technique presents the basic role with the assistance of the other. However, laparoscopy and endoscopy teams cooperate with each other for the resection of lesion in LECS with essential significance rather than assistance.

6.1. Laparoscopy-assisted endoscopic surgery

Endoscopy plays a substantial role in LAES while laparoscopy provides backup and real-time control (**Table 7**). In the research by Qiu et al. (140), LAES, reported as laparoscopy-assisted endoscopic resection (LAER), was applied for resecting GISTs ≤3 cm in diameter. EMR or ESD was performed under endoscopy. The laparoscopy team facilitates the exposure and localization of the lesion from the perspective of peritoneal cavity. Through providing traction, lesions could be easily removed by endoscopy, especially with technical difficulty such as lesion located near the EGJ (141). Simultaneously, any complications such as perforation and bleeding that occur perioperatively could be treated immediately by laparoscopy. Controllable complications and no recurrence were observed. Apart from the stomach, lesions situated in the duodenum could also benefit from LAES with feasibility (142, 143).

TABLE 6 Research studies of the EFTR technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Operation approach	Mean operation time (min)	Blood loss (ml)	Complete resection rate	Hospitalization duration (days)	Conversion to open surgery (no.)	Complication
Shichijo et al. (133)	2019	8	Stomach	2.0 (1.0–3.5)	GIST (8)	EFTR	67.5 (50–166)	NR	100%[a]	6 (4–11)	0	Perforation (63%)
Ren et al. (138)	2019	32	Duodenum	1.2 (0.5–3.0)	GIST (14)	EFTR	68 (17–186)	NR	100%[a]	6.2 (2–19)	1	Delayed perforation (3%)
Jung et al. (139)	2021	8	Stomach	1.6 (1.0–2.7)	GIST (8)	EFTR	66 (25–96)	NR	100%[a]	8.3 (5–18)	0	Bleeding (12.5%)
Wang et al. (136)	2022	40	Stomach	1.0 ± 0.3	GIST (36)	OTSC assisted EFTR	38.4 (13–157)	NR	92.5%	NR	0	0
Guo et al. (137)	2021	68	Stomach (64), duodenum (1), rectum (4)	1.3 ± 0.4	GIST (42)	OTSC assisted EFTR	53.7 ± 41.5	NR	98.5%	NR	0	Bleeding (1.5%), local peritonitis (2.9%)

EFTR, endoscopic full-thickness resection; OTSC, over-the-scope clip; NR, not reported; GIST, gastrointestinal stromal tumor.
[a]*En bloc* resection.

TABLE 7 Research studies of the LAES technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery	Complication
Qiu et al. (140)	2013	5	Stomach	≤3	GIST	81.6 ± 31.8	29.8 ± 15.4	4.6	0	40%
Acker et al. (141)	2014	1	Stomach	3	Leiomyoma	NR	NR	NR	0	0
Kato et al. (142)	2011	1	Duodenum	2	GIST	200	Negligible	NR	0	Postoperative bleeding
Irino et al. (143)	2015	3	Duodenum	1.2–2.5	Adenocarcinoma	176–262	0–20	7–12	0	1/3

LAES, laparoscopy-assisted endoscopic surgery; NR, not reported; GIST, gastrointestinal stromal tumor.

6.2. Endoscope-assisted laparoscopic surgery

The lesion is removed by laparoscopic surgery with an endoscope contributing to the orientation and exposure of the mass. According to the various lesion locations and access approaches of laparoscopy, EALS mainly consists of endoscope-assisted wedge resection (EAWR), endoscope-assisted laparoscopic trans-gastric resection (EATR), and endoscope-assisted laparoscopic intragastric surgery (LIGS).

6.2.1. Endoscope-assisted wedge resection

Table 8 summarizes corresponding researches of EAWR technique. With real-time monitoring, locating, and marking done by endoscopists, the lesion was removed by conventional laparoscopic wedge resection using a linear endoscopic gastrointestinal stapler. Subsequently, the mass resected was retrieved through the laparoscope followed by endoscopic examination of the existence of residual lesion and potential complications. EAWR is applicable for lesion not only in the anterior wall of the stomach but also in the posterior gastric wall, EGJ, and pyloric ring, which is more recommendable for an ultrasonic shear device or a vascular sealing system to avoid pertinent damage or stenosis (144, 145). More often than not, lesions situated in the posterior wall of the gastric body, limited to the central sections, were recommended for EAWR, which were easily accessible through the mentum or gastrocolic ligament by creating a small incision (146). In addition, the lesion with exophytic characteristic is another indication for EAWR.

6.2.2. Endoscope-assisted laparoscopic trans-gastric resection

EATR is more applicable for lesions located in the posterior gastric wall with a relatively large size or with intraluminal growth or near the EGJ (150, 151) (**Table 9**). As mentioned above, lesions located in the posterior gastric wall of the fundus or antrum instead of the body were preferred for this approach (146). With the assistance of endoscopic identification of the lesion location by palpation and diaphanoscopy, gastrotomy of

TABLE 8 Research studies of the EAWR technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery (no.)	Complication
Kang et al. (144)	2013	101	Stomach	4.9 ± 0.6	GIST (78)	113 ± 36	36 ± 18	4.5 ± 2.1	0	2%
Wilhelm et al. (147)	2008	55	Stomach	2.54 (0.3–6.5)	GIST	81 (35–202)	NR	7.68 (4–19)	NR	NR
Qiu et al. (140)	2013	64	Stomach	3–5	GIST	86.3 ± 28.5	31.4 ± 11.6	3.5	0	40%
Kiyozaki et al. (148)	2014	42	Stomach	2–5	GIST	140 (89–307)	0	7 (6–14)	0	2.4%
Ismael et al. (145)	2016	1	Stomach	4.7	GIST	90	NR	3	0	0
Dávila et al. (149)	2016	38	Stomach	3.4 (0.7–7.5)	GIST (32)	106 (30–300)	NR	3	1	10.5%

EAWR, endoscope-assisted wedge resection; NR, not reported; GIST, gastrointestinal stromal tumor.

TABLE 9 Research studies of the EATR technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery (no.)	Complication
Wilhelm et al. (147)	2008	34	Stomach	2.61 (0.5–5.5)	GIST	114 (40–275)	NR	7.48 (2–14)	NR	NR
Sasaki et al. (150)	2010	10	Stomach	3.7 (2.2–5.0)	GIST (NR)	145 (100–240)	10 (3–65)	8 (5–9)	0	NR
Marzano et al. (152).	2011	1	Duodenum	3	Adenoma	270	200	7	0	0

EATR, endoscope-assisted laparoscopic trans-gastric resection; NR, not reported; GIST, gastrointestinal stromal tumor.

the anterior gastric wall was performed by a laparoscopic team and the corresponding lesion was exposed. Subsequently, routine inverted laparoscopic wedge resection or full-thickness resection was conducted. Finally, the defect in the anterior gastric wall was closed using endoscopic stapler devices or laparoscopic sutures. Lesions located in the posterior of the duodenum were also indicated for applying EATR with robotic assistance. Based on the comparison analyses of Marzano et al., EAWR was recommended as the first choice for most gastric submucosal tumors (SMTs) than EATR due to gastrotomy and related complications such as increased operative time and blood loss, digestive fluid leakage, and the risk of abdominal cavity spread (152).

6.2.3. Endoscope-assisted laparoscopic intragastric surgery

Endoscopy played a significant role in identifying lesion location, and then several laparoscopic trocars penetrated both the abdominal wall and the anterior stomach wall into the gastric cavity. Stay sutures could facilitate the lift of the anterior gastric wall to the abdominal wall. With the real-time monitoring and assistance of endoscopy during the operation, the lesion was resected through wedge resection or full-thickness resection by the laparoscopic team. Finally, the lesion specimen resected was retrieved perorally, and perforation and defect were closed by endoscopists and the laparoscopic team. Gastrotomy was performed when necessary, concerning large specimen with difficulty to be retrieved though the mouth (153, 154).

LIGS was first reported by Ohashi in 1995 and often recommended in lesions situated in the posterior gastric wall with intraluminal growth and relatively small tumor size (155, 156). Compared to EATR, LIGS is safer and with decreased blood loss and postsurgical complications through gastric perforation instead of gastrotomy.

In recent years, a modified LIGS technique, known as single-incision LIGS (sLIGS), has been reported by researchers. Only a 3 cm longitudinal incision was made near the umbilicus and a wound-protecting device was placed. Following a mini-size gastrotomy, three to four ports were placed through a single port device in the single incision. The lesion resection was similar with conventional LIGS and defect of gastrotomy and abdominal wall were closed. The indications for sLIGS were parallel to those of the routine LIGS technique. Of note, single incisions often correlated with higher perioperative security and decreased complications (157–160). Researches of LIGS technique are summarized in **Table 10**.

6.3. Integrated LECS

6.3.1. Classical LECS

LECS has been reported to successfully resect gastric submucosal GISTs, which is known as classical LECS (**Table 11**). First, ESD was performed *via* intraluminal endoscopy for circumferentially dissecting three quarters of the tumor submucosa. Next, the seromuscular layer was dissected by laparoscopy along the corresponding cut line, and the tumor was

TABLE 10 Research studies of the LIGS technique.

Author		Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery (no.)	Complication
Routine LIGS	Ludwig et al. (161)	2002	8	Stomach	NR	GIST (NR)	67.1 (49–102)	NR	10.2 (6–16)	1	12.5%
	Schubert et al. (162)	2005	7	Stomach	NR	GIST (NR)	83 (56–130)	NR	NR	NR	NR
	Privette et al. (154)	2008	4	Stomach	4.6 (2.5–7.5)	GIST (2)	236 (202–265)	100 (50–200)	3.3 (3–4)	0	0
	Dong et al. (163)	2013	6	Stomach	3.50 ± 0.84	GIST (6)	83.33 ± 26.58	<20	6.6 (5–7)	0	0
	Dong et al. (153)	2014	8	Stomach	2.75 ± 1.07	GIST (8)	85 ± 25.77	20 ± 10.35	7.5 ± 1.07	0	0
Single-incision LIGS	Na et al. (160)	2011	7	Stomach	2.7 (2.3–3.8)	GIST (5)	83.6 (70–105)	NR	5.4 (4–6)	0	0
	Vogelaere et al. (159)	2013	3	Stomach	3.8 (2.7–6.8)	GIST (3)	74.6 (67–82)	<30	5 (4–6)	0	0
	Katsuyama et al. (157)	2018	4	Stomach	3.0–4.3	GIST (2)	149 (116–170)	30 (0–43)	NR	0	25%
	Zhang et al. (158)	2022	13	Stomach	3.4 ± 0.2	GIST (10)	100 ± 10	50 ± 10	7 ± 1.5	0	8%

LIGS, endoscope-assisted laparoscopic intragastric surgery; NR, not reported; GIST, gastrointestinal stromal tumor.

TABLE 11 Research studies of the classical LECS technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery	Complication rate (%)
Hiki et al. (165)	2008	7	Stomach	4.6 ± 0.3	GIST (6)	169 ± 17	7 ± 2	7.4 ± 8.1	0	0
Tsujimoto et al. (164)	2012	20	Stomach	3.8 ± 1.1	GIST (16)	157.5 ± 68.4	3.5 ± 6.4	11.6 ± 9.5	0	0
Hoteya et al. (169)	2014	25	Stomach	3.2 ± 1.4	GIST (16)	156.3 ± 50.5	NR	10.5 ± 2.4	0	0
Matsuda et al. (170)	2016	100	Stomach	3.1 ± 1.1	GIST (75)	174.3 ± 43.1	16.3 ± 37.5	8.4 ± 10.2	0	4
Obuchi et al. (171)	2014	1	EGJ	4.4	GIST	120	5	5	0	0
Ohi et al. (172)	2013	1	Duodenum	3.5	GIST	186	<10	5	0	0
Tsushimi et al. (173)	2014	1	Duodenum	0.8	NET G1	182	NR	9	0	0
Tamegai et al. (174)	2018	17	Colorectum	2.2 (0.8–4.1)	Adenoma (9)	183.3 (68–332)	7.8 (2–20)	6.4 (4–12)	0	0

LECS, laparoscopic and endoscopic cooperative surgery; NR, not reported; GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor; EGJ, esophagogastric junction.

laparoscopically resected by a stapling device. There are several advantages of this technique, according to researchers' opinion, such as it is independent of the tumor location without excessive sections of healthy tissues (164, 165). Theoretically, the application of the LECS technique is not restricted by the size of the tumor as the lesion is retrieved through the abdominal wall. However, LECS is shown to be more applicable for relatively small GISTs (166) and not recommended in large (> 5 cm) or ulcerative cases due to the increased risk of peritoneal contamination and tumor dissemination (167). Based on the research by Ri et al., subepithelial tumor located in the esophagogastric junction has a risk of conversing operation procedure from LECS to proximal gastrectomy, which is safer (168).

6.3.2. Laparoscopy-assisted endoscopic full-thickness resection

With the assistance of laparoscopy, the EFTR procedure achieved considerable improvement of avoiding excessive resection of normal tissues, and an original cooperative surgery based on the principles of LECS, called laparoscopy-assisted endoscopic full-thickness resection (LAEFR), has been developed by Abe et al. (175) (**Table 12**). Described as a hybrid natural orifice transluminal endoscopic surgery (NOTES), ESD followed by EFTR was endoscopically performed for the resection of 2/3 to 3/4 of tissue with the assistance of a laparoscopic team, which facilitates the exposure, and then the remaining tumor was completely resected and retrieved either perorally or through a laparoscope. The gastric wall defect was then hand-sewn and closed by laparoscopy. Apart from the accurate and complete removal of the tumor, the advantages of LAEFR incorporate minimal invasiveness, inexpensiveness in comparison with other laparoscopic surgery, and less perioperative adverse events managed *via* laparoscopic therapy. It is noteworthy that the closure of the artificial gastric wall perforation is easier and safer by means of laparoscopy compared to endoscopy (176). This technique is especially applicable for the resection of GISTs located in the MP layer with intraluminal growth modality (177).

6.3.3. Inverted LECS

In 2019, there was a case report in which a patient with remnant stomach GIST received inverted LECS for full-thickness resection with sound postoperative outcome (180) (**Table 13**).

TABLE 12 Research studies of the LAEFR technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery	Complication rate (%)
Abe et al. (175)	2009	4	Stomach	3.0 (2.2–4.3)	GIST (1)	201 (130–313)	27 (5–71)	7–8	0	0
Mori et al. (178)	2015	16	Stomach	28.3 (8–54)	GIST (16)	271	NR	12.3 (10–15)	0	NR
Lim et al. (179)	2017	8	Stomach	2.2 (2.1–3.3)	GIST (4)	127.5 (110–150)	30–100	4.5 (3–7)	0	0

LAEFR, laparoscopy-assisted endoscopic full-thickness resection; NR, not reported; GIST, gastrointestinal stromal tumor.

TABLE 13 Research studies of the inverted LECS technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery	Complication rate (%)
Nunobe et al. (182)	2012	1	Stomach	6	Adenocarcinoma	152	0	NR	0	0
Aoki et al. (183)	2018	3	Stomach	11.7 ± 6.2	Carcinoma	192.3 ± 51.9	11.0 ± 6.5	17.0 ± 5.1	0	0
Takechi et al. (184)	2018	1	Stomach	5.8	Adenocarcinoma	215	0	NR	0	0

LECS, laparoscopic and endoscopic cooperative surgery; NR, not reported; GIST, gastrointestinal stromal tumor.

The brief operation modality of inverted LECS is described as follows. The first step is the identification of resection line and circumferential elevation of the gastric wall like a crown using stitches. Then, the seromuscular layer is dissected after artificial perforation followed by conducting EFTR. A .laparoscopic stapler is used to dissect the residual gastric wall, and tumor tissue is perorally retrieved. The final step is the defect suture by laparoscopic devices (181). In general, inverted LECS is performed with the traction inversion of tumor toward the intragastric cavity as a crown. There is, however, still relatively lower risk of gastric content spillage during this technique owing to gastric lumen exposure. Moreover, not all sites were feasible for inverted LECS such as the posterior wall.

6.3.4. "Nonexposure" LECS techniques

For the purpose of the reduction of tumor cells seeding into the abdominal cavity, several newer innovative "nonexposure" techniques, originated from the classical LECS procedure for full-thickness resection, named as a combination of laparoscopic and endoscopic approaches to neoplasia applying nonexposure technique (CLEAN-NET), nonexposed endoscopic wall-inversion surgery (NEWS), and closed-LECS, have been developed.

6.3.4.1. Combination of laparoscopic and endoscopic approaches to neoplasia applying nonexposure technique

Inoue et al. took initiative to report the CLEAN-NET technique for the resection of a gastric neoplasm in 2012 (185). The corresponding procedures incorporate mucosal marking by endoscopy followed by the fixation of the mucosal layer into the seromuscular layer by four full-thickness stay sutures *via* laparoscopy. The next step is seromuscular layer dissection using a laparoscopic electrocautery knife and full-layer tumor dissection with pulling-out performed by a laparoscopic linear stapler, sealing the specimen into a protective mucosal "net." It is obvious that the CLEAN-NET procedure is less invasive and has the capability of completely preventing between-luminal communication and thus consequent tumor dissemination and bacterial contamination. However, potential limitations refer to the risk of incomplete resection with positive margin, mucosal laceration, and incision line determination (80, 186, 187). To ensure the normal operation of the mucosal mechanical barrier and prevent mucosa tear, a tumor <3 cm in size is recommended for the application of this technique (181). Moreover, tumors located in technically demanding and inaccessible sites with the risk of deformity of the stomach, such as EGJ, the pyloric ring, the lesser curvature, and posterior wall, restrict the operation of CLEAN-NET due to potential risk of postoperative stenosis (188). A modified CLEAN-NET technique was introduced for the improvement of resection of gastric submucosal tumor especially in technically demanding locations and large cases (>3 cm), which secure the surgical field with anchor sutures and decrease stomach deformation and pertinent complications (189–191). Researches of conventional and modified CLEAN-NET technique are summarized in **Table 14**.

TABLE 14 Research studies of the CLEAN-NET technique.

Author		Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery	Complication rate (%)
Original CLEAN-NET	Nabeshima et al. (187)	2015	2	Stomach	3.5–4.0	GIST (2)	165 (128–202)	16–29	8–9	0	NR
	Hajer et al. (192)	2018	2	Stomach	3.0–4.5	GIST (2)	150 (120–180)	<50	4–10	0	0
Modified CLEAN-NET	Hayase et al. (189)	2020	1	Stomach	3.7	GHIP	198	Minimal	9	0	0
	Fujishima et al. (190)	2017	13	Stomach	3.7 ± 0.9	GIST (13)	162 ± 59	7 ± 11	10 ± 7	0	8%
	Kanehira et al. (191)	2020	50	Stomach	3.5 (1.0–9.0)	GIST (25)	105.4 (50–220)	7.5 (1–50)	6–7	0	0

CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia applying nonexposure technique; NR, not reported; GIST, gastrointestinal stromal tumor; GHIP, gastric hamartomatous inverted polyp.

TABLE 15 Research studies of the NEWS technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery	Complication rate (%)
Mitsui et al. (194)	2014	6	Stomach	2.3 (1.7–2.6)	GIST (5)	273 (140–397)	113 (0–250)	7–8	0	0
Kim et al. (195)	2016	1	Stomach	2.0	GIST	40	<50	10	0	0
Mahawongkajit et al. (197)	2017	1	Stomach	2.2	GIST	219	<10	5	0	0
Mitsui et al. (196)	2018	28	Stomach	2.4 (1.8–5.0)	GIST (28)	184 (98–357)	NR	nr	0	10.7%
Aoyama et al. (198)	2020	43	Stomach	24.6 ± 8.6	GIST (24)	198 (173–230)	5.0	7.0 (6.3– 8.0)	0	2.3%

NEWS, nonexposed endoscopic wall-inversion surgery; NR, not reported; GIST, gastrointestinal stromal tumor.

6.3.4.2. Nonexposed endoscopic wall-inversion surgery

In 2011, the NEWS technique was first reported by Goto et al. (193) and developed as another novel nonexposure LECS, apart from CLEAN-NET, for full-thickness resection of gastric SMT without artificial perforation that avoids tumor seeding. Steps of NEWS primarily consist of marking mucosal and serosal surface around the tumor endoscopically and laparoscopically. Next, endoscopists inject sodium hyaluronate with an indigo carmine dye into the submucosal layer, which is beneficial to the following circumferential seromuscular dissection around the tumor by the laparoscopic team. Subsequently, tumor is inverted and suture closure of the seromuscular layer is performed laparoscopically. Finally, circumferential muco-submucosal incision of the intruded tumor is performed by endoscopists and tumor specimen is retrieved perorally followed by mucosal closure (80, 181, 194). Besides the benefit that precludes interluminal communication, NEWS could achieve an accurate determination of the resection line (195). However, it is obvious that the NEWS technique is restrained by tumor size as tumors with a relatively larger size (>3 cm) are laborious to be retrieved through the mouth. Simultaneously, tumor locations such as demanding EGJ and the pyloric ring also limit its application (181). NEWS is also found to be time-consuming; as reported by Mitsui et al., the median operation time in 28 patients with gastric GIST was 184 min (196). Researches of NEWS technique are summarized in **Table 15**.

6.3.4.3. Closed-LECS

Closed-LECS is also a completely non-open technique, which was reported by Kikuchi et al. for the resection of gastric SMTs (199). The detailed operation incorporates the following steps: routine ESD technique is performed after the submucosal injection. Subsequently, the incision line is marked by laparoscopy around the serosal surface followed by seromuscular suturing while inverting tumor into intragastric cavity. After the circumferential dissection of serosal muscular layer done by the endoscopic team, the lesion is removed perorally. Closed-LECS is more applicable for intraluminal and small GISTs with identical limitation of tumor size (<3 cm) for peroral approach (28). The operation process of the closed-LECS technique is roughly similar to NEWS with tumors all being retrieved perorally. Of note, endoscopic circumferential seromuscular incision is specifically performed in NEWS while not in closed-LECS (186). Researches of Closed-LECS technique are summarized in **Table 16**.

An overview and comparison of classical and modified LECS techniques are shown in **Table 17**. Collectively, a majority of newer innovated techniques are investigated in gastric neoplasm with little application reports in GISTs. The classical LECS technique will not cause mucosal defects and is independent of the size and location of the tumor, but there is a risk of abdominal spread. Modified LECS can prevent the tumor dissemination but is limited by the tumor size, location, and technical requirements. Individualized evaluation is necessary for selected patients for optimal operation approach. And further research studies in the GIST population are warranted to be investigated.

7. Conclusions

GISTs have been recognized as the paradigm of multidisciplinary and multimodal therapy integrating surgical resection with TKI neoadjuvant and adjuvant chemotherapy. Preoperative or postoperative molecularly targeted medication in a high-risk cohort could substantially contribute to the subsequent surgery resection and function preservation of the involved organ with improved survival outcome. Operation with complete resection is the mainstay for the management of patients with GISTs in clinical practice, which is often indicated in those with non-gastric GISTs, tumor size ≥2 cm, palpable symptoms, or EUS-related pathological risk. The advance of

TABLE 16 Research studies of the closed-LECS technique.

Author	Year	Cases	Tumor location	Tumor size (cm)	Tumor pathology (no.)	Mean operation time (min)	Blood loss (ml)	Hospitalization duration (days)	Conversion to open surgery	Complication rate (%)
Kikuchi et al. (199)	2017	10	Stomach	2.4 ± 0.8	GIST	253 ± 45	18 ± 55	9.2 ± 1.5	0	10%
Saito et al. (200)	2020	3	Stomach	0.9 (0.7–1.4)	Adenocarcinoma	129 (115–148)	11 (3–15)	10 (7–15)	0	0

LECS, laparoscopic and endoscopic cooperative surgery; NR, not reported; GIST, gastrointestinal stromal tumor.

TABLE 17 Overview and comparison of integrated LECS techniques.

Characteristics	Classical LECS	Modified LECS				
		LAEFR	inverted LECS	CLEAN-NET	NEWS	Closed-LECS
Tumor location indication	Any	Any	Any	Anterior wall[a]	Anterior wall[a]	Anterior wall[a]
Tumor size indication	≤5[a]	≤5[a]	≤5[a]	≤3	≤3	≤3
Non-open procedure	No	No	No	Yes	Yes	Yes
First approach	Endoscopy	Endoscopy	Endoscopy	Laparoscopy	Laparoscopy	Endoscopy
Retrieval approach	Trans abdominal	Trans abdominal or transoral	Transoral	Trans abdominal	Transoral	Transoral
Suturing approach	Hand or linear stapler	Hand	Hand or linear stapler	Linear stapler	Hand	Hand

LECS, laparoscopic and endoscopic cooperative surgery; LAEFR, laparoscopy-assisted endoscopic full-thickness resection; CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia applying nonexposure technique; NEWS, nonexposed endoscopic wall-inversion surgery.
[a]Recommended.

endoscopic and laparoscopic techniques, such as ESTD, EFTR, EAWR, and especially modified nonexposure LECS techniques have practically improved the success rate of operation, realized minimal invasiveness and more safety, and reduced perioperative complications. Robotic surgical systems are attractive treatment candidates for challenging cases. Tumor resection, to some extent, could be conducted and provide some earnings for properly selected patients with indications in recurrent and metastatic situation to improve their survival, but the benefits and risks should be considered comprehensively. Individualized evaluation from the multidisciplinary team and elaborative consideration of treatment algorithm for each patient are warranted. Further research studies in the GIST population are warranted.

Author contributions

LY and WH contributed to the conception and design. All authors contributed to the writing 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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Left hemicolectomy and low anterior resection in colorectal cancer patients: Knight–griffen vs. transanal purse-string suture anastomosis with no-coil placement

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Background: Colorectal cancer (CRC) is considered one of the most frequent neoplasms of the digestive tract with a high mortality rate. Left hemicolectomy (LC) and low anterior resection (LAR) with minimally invasive laparoscopic and robotic approaches or with the open technique are the gold standard curative treatment.

Materials and methods: Seventy-seven patients diagnosed with CRC were recruited between September 2017 and September 2021. All patients underwent a preoperative staging with a full-body CT scan. The goal of this study was to compare both types of surgeries, LC-LAR LS with Knight–Griffen colorectal anastomosis and LC-LAR open with Trans-Anal Purse-String Suture Anastomosis (the TAPSSA group), by positioning a No-Coil transanal tube (SapiMed Spa, Alessandria, Italy), in terms of postoperative complications such as prolonged postoperative ileus (PPOI), anastomotic leak (AL), postoperative ileus (POI), and hospital stay.

Results: The patients were divided into two groups: the first with 39 patients who underwent LC and LAR in LS with Knight–Griffen anastomosis (Knight–Griffen group) and the second with 38 patients who underwent LC and LAR by the open technique with the TAPSSA group. Only one patient who underwent the open technique suffered AL. POI was 3.76 ± 1.7 days in the TAPSSA group and 3.07 ± 1.3 days in the Knight–Griffen group. There were no statistically significant differences in terms of AL and POI between the two different groups.

Conclusion: The important point that preliminarily emerged from this retrospective study was that the two different techniques showed similarities in terms of AL and POI, and therefore, all the advantages reported in the previous studies pertaining to No-Coil also hold good in this study regardless of the surgical technique used. However, randomized controlled trials are needed to confirm these findings.

KEYWORDS
colorectal cancer, colorectal anastomosis, complications, no-Coil, surgical oncology

Introduction

Colorectal cancer (CRC) is considered the most common malignancy in Western countries (1). Accurate preoperative staging is crucial for planning the optimal therapeutic strategy for individual patients. In the preoperative staging of colorectal cancer, computed tomography (CT) is often necessary for devising the best plan for surgery and/or neoadjuvant therapy, particularly when local tumor extension into adjacent organs or distant metastases is detected (2). Low anterior resection (LAR), left hemicolectomy (LC), and right hemicolectomy (RC) remain the treatments of choice, ensuring the best results in terms of quality of life (QoL) and overall survival (Os) (3). It is possible to perform this type of surgery with minimally invasive laparoscopic (LS) and robotic approaches or with the open technique (4). All types of surgeries may cause different complications, and the most frequent of these are prolonged postoperative ileus (PPOI) and anastomotic leak (AL) (5–7). Several factors may contribute to PPOI occurrence, but the level of anastomosis detected is probably the most important one. The parameters used in the literature to describe the incidence rate of AL, regardless of the technicalities surrounding stapled or hand-sewn anastomoses, are at complete variance with the ones used presently, and these depend on the nature of the site in question, that is, a rate of up to 6% for ileo-colic anastomoses, up to 9% for colo-colonic anastomoses, and up to 20% for colo-rectal anastomoses (6). Different studies demonstrate that increased intraluminal rectal pressure is the major contributor to AL (8–11), and for this reason, different endorectal devices (e.g., transanal tube cuff rectum, drainage tube, and silicone transanal tube) have been proposed as promising alternatives to stoma (12, 13). No-Coil® is a transanal silicone stent that allows endorectal decompression, and it is used for the anastomosis of the lower gastrointestinal tract (**Figure 1**) (14, 15).

According to recent studies, No-Coil could be considered a useful tool in the prevention of AL-related complications, as it is characterized by ease of use and good feasibility, cost-effectiveness, and favorable patient quality-of-life outcomes after treatment (16). Nevertheless, evidence about No-Coil implementation in the surgical treatment of CRC is limited to a few studies, and definitive conclusions in terms of efficacy cannot be made. Furthermore, these studies examined No-Coil by following the LAR approach, and evidence about its efficacy by following the LC approach is scarce (17).

The aim of this study is to improve and analyze the evidence concerning the use of No-Coil and verify its results in two different types of surgeries: LC-LAR LS with Knight–Griffen colorectal anastomosis (**Figure 2**) and LC-LAR by the open technique with Trans-Anal Purse-String Suture Anastomosis (**Figure 3**). We analyzed the period of postsurgical hospitalization and the presence of flatus or other complications in all patients who underwent laparoscopic (LS) LAR/LC and open LAR/LC with a No-Coil transanal tube placed at the end of the surgical procedure.

Materials and methods

A retrospective study was conducted between September 2017 and September 2021 in which 77 patients diagnosed with a CRC of the descending colon, splenic flexure, sigma, and rectum were recruited at the Digestive Surgery Unit of "Magna Graecia" University Medical School, "Mater Domini" Hospital. LC-LAR LS with Knight–Griffen colorectal anastomosis was performed in

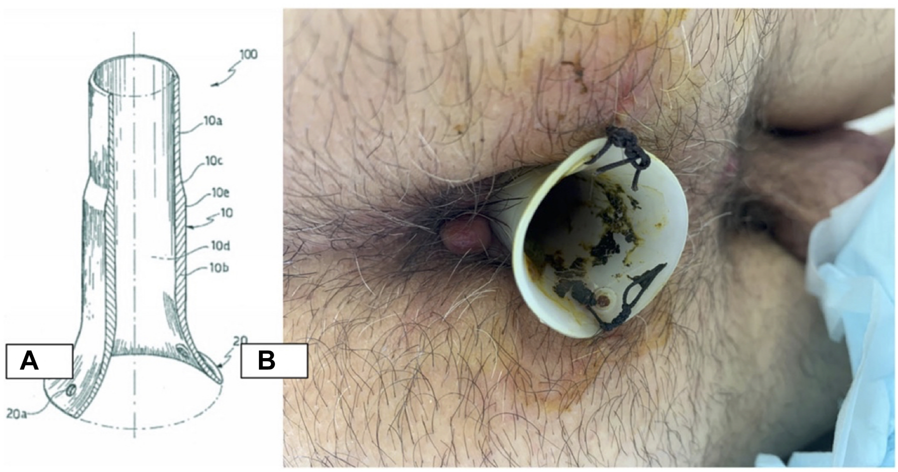

FIGURE 1
No coil structure and postoperative placement. (A) Length of 60–80 mm, thickness of 2 mm, and diameter of 20 mm. (B) Stabilized 6–8 cm far from the anus through two stitches.

39 patients. Meanwhile, 38 patients underwent LC and LAR by the open technique with Trans-Anal Purse-String Suture Anastomosis (TAPSSA) on Circular Stapler Circular by both techniques measuring 33 mm. All interventions were performed by the same surgeon (MA) in order to reduce possible interoperator errors and distortions and to achieve better accuracy. LC was performed for sigmoid and descending colon tumors, while LAR was applied for the neoplasms of the upper two-thirds of the rectum. Moreover, all patients underwent preoperative staging by total body CT with a three-phase contrast medium so that they could be accurately staged (according to the American Joint of Committee on Cancer 8th Edition) (18).

A possible limitation of this study may stem from the fact that this was a retrospective and non-randomized study, and the patients were assigned to two groups: the first group included patients who received a Knight–Griffen transanal termino-terminal anastomosis in which the section was sutured with a linear suturing machine-type ENDO-GIA and the second group included patients who received a transanal termino-terminal anastomosis in which a tobacco bag was placed on the rectal stump.

The variables analyzed were the duration of the postoperative stays in terms of days, the average time of the first postoperative flatus, and postoperative complications (AL, bleeding, perforation, occlusion, and infections).

In all patients, the surgical technique was standardized with respect to oncological radicality by ligating the artery and mesenteric vein at one centimeter from the origin to ensure a good local staging. Then, standardization was achieved by removing the nearby lymph node chain and freeing the pelvic rectum by performing a total mesorectal excision (TME), which is considered a guideline for rectal tumors.

In this study, the No-Coil tube was placed in all patients after the performance of intestinal anastomosis. It was placed through the sphincter and fixed at a 1–2 cm distance from the anus by making two dots; the tube was removed on the sixth postoperative day if there were no signs of AL. The No-Coil tube, mainly made of silicone, has a length of 60–80 mm, a thickness of 2 mm, and a diameter of 20 mm.

Non-severe surgical complications were corrected by using conservative treatment (Grades I and II according to Clavien Dindo Classification) (19).

Only one exclusion criterion was stipulated in this study: none of the patients should have been administered neoadjuvant therapy. Informed consent was obtained from all patients for performing the study and for the use of medical records. All procedures included in the protocol met the ethical standards of the Helsinki Declaration and the Guidelines for Good Clinical Practice.

Results

Statistical analyses were performed using STATA version 14. Descriptive statistics comprised frequencies and percentages and means and standard deviations. Differences between the case and the control group patients were subsequently explored by using the χ^2 test for categorical variables and the T-test for continuous variables. Furthermore, we performed a stepwise linear regression to establish the association between hospital stay (dependent variable), type of surgery, PPOI, AL events (independent variables), and No-Coil placement. All results obtained from the descriptive analysis and comparison between the two groups, called the “Knight–Griffen group” and the “TAPSSA group” (Trans-Anal Purse-String Suture Anastomosis), respectively, for a level of significance of 5% are presented in **Table 1**.

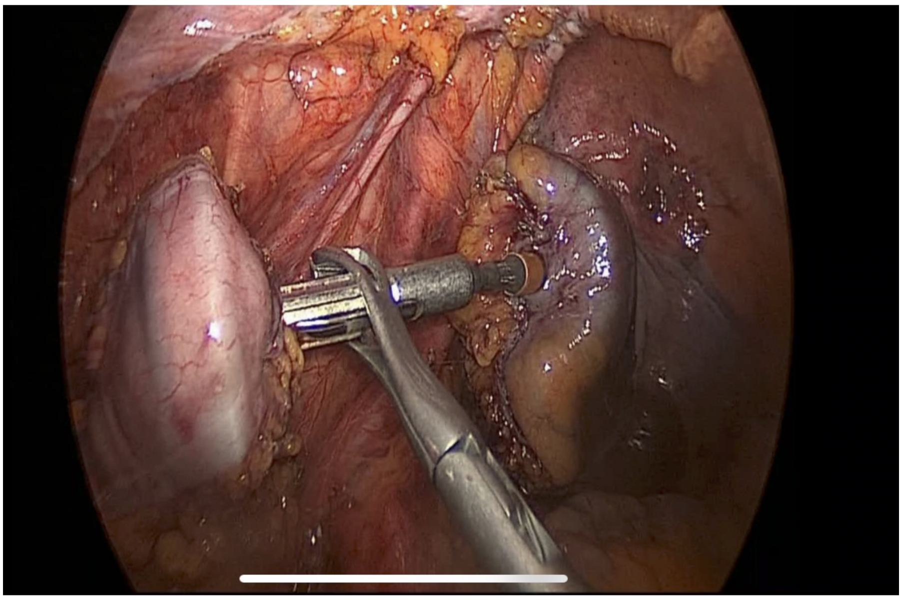

FIGURE 2
Knight–Griffen colorectal anastomosis.

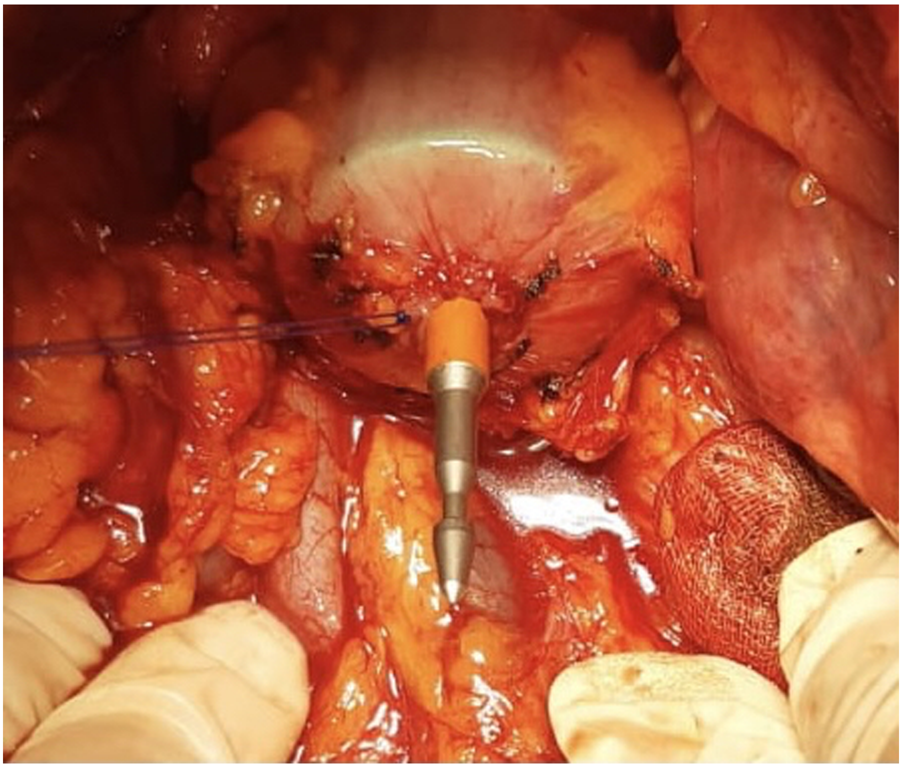

FIGURE 3
Transanal purse-string suture anastomosis.

TABLE 1 Analysis and comparison between the two groups.

	TAPSSA ($N = 38$)	Knight–Griffen ($N = 39$)	χ^2/t	p
Age	73.6 ± 5.4	71.6 ± 7.9	19.28	0.628
Gender				
Male	41		0.1225	0.122
Female	36			
Hospital stays	12.02 ± 1.8	6.89 ± 1.6		<0.001
POI	3.76 ± 1.7	3.07 ± 1.3	20.670	0.342
PPOI	9 (23.6%)	1 (2.56%)	7.597	0.006
AL	1 (2.63%)	0	1.039	0.308

No differences emerged in terms of gender ($\chi^2 = 0.1225$; $p = 0.726$) and age ($\chi^2 = 19.3$; $p = 0.628$) distribution between the two groups (**Figure 4**).

LC and LAR in LS were performed in 39 patients (50.65%) and LC and LAR by the open technique was performed in 38 patients (49.35%).

No postoperative incontinence or constipation was reported in the patients. Mean hospital stay was 7 ± 1.6 days in LS group patients and 12 ± 1.8 in open group ones (**Figure 5**). AL was present in one patient (2.63%) in the open surgery group and in none in the LS group; AL in one patient was treated with the conservative method with total parenteral nutrition and removal of the No-Coil transanal tube on the 12th day. No statistical difference was detected in AL appearance between the groups ($\chi^2 = 1.03$; $p = 0.308$). PPOI was not associated with any independent variables. AL was not associated with POI days (log-likelihood = 5.0702; LR $\chi^2 = 0.53$; Prob > $\chi^2 = 0.464$; Pseudo $R^2 = 0.050$;95% CI = 6.5269–14.271; $p = 0.528$) and also with PPOI (log-likelihood = 25.053; LR $\chi^2 = 9.36$; Prob > $\chi^2 = 0.464$; Pseudo $R^2 = 0.022$; 95% CI = 2.266–3.227; $p = 0.408$).

A comparison of the results of the two groups showed that No-Coil placement reduced the postoperative complications of AL and POI with no differences between the two surgical techniques. But in terms of PPOI and hospital stay, the LS approach with Knight–Griffen anastomoses was found to be better than the traditional open methods with TAPSSA (**Table 1**).

Discussion

The purpose of this retrospective study was to examine the differences between two types of surgery in terms of postoperative complications, AL, PPOI, POI, and hospital stay with the aid of the No-Coil® device. For the staging of the disease, particularly for the detection of liver and extrahepatic metastasis, we performed a full-body CT scan, which, according to different studies, is considered the first-choice procedure and the best imaging examination in terms of cost-effectiveness (20, 21). In this study, only one out of a total of 77 patients suffered AL. Hence, no differences were detected on the basis of the use of No-Coil after the performance of the surgery. Only a

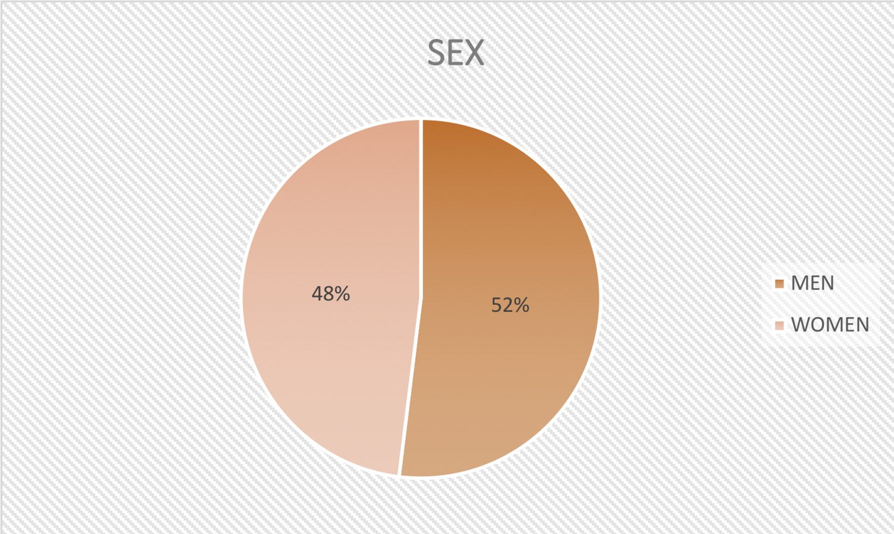

FIGURE 4
Percentage of men and women in the study.

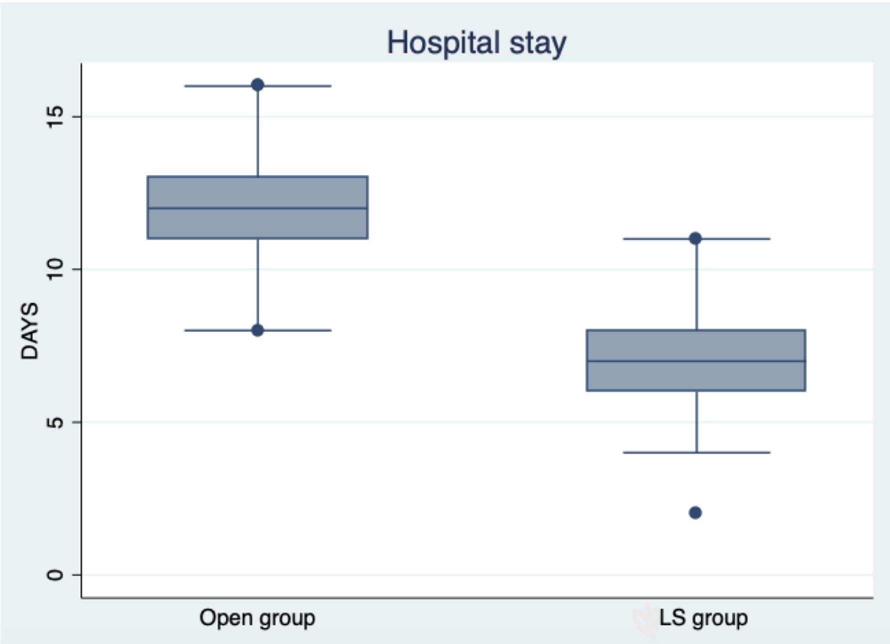

FIGURE 5
Box plot shows the difference between the open group and the LS group in terms of hospital stay.

few studies have explored the efficacy of No-Coil use in reducing this type of leak. In one of them, Montemurro et al. evaluated AL prevalence in a sample of 184 patients undergoing elective total or subtotal proctectomy with low-lying anastomosis and found an AL incidence rate of almost 4.8%, which was higher than that of this study (14). Particularly, two randomized trials considered the use of a transanal stent other than No-Coil structurally different from it. Sciuto et al., in their study, analyzed the predictive factors of anastomotic losses after laparoscopic colorectal surgery, and there were several studies between 2008 and 2018 on laparoscopic colorectal procedures with left anastomosis (7).

In these studies, the incidence rates ranged from 78% (Lee et al.) in 2017 to 50% (Van Praagh et al.) in 2016 with an average of 11.1% (22, 23).

Considering all the above factors and that in our study we had only one patient with AL, which may be attributed to the placement of No-Coil, further follow-up studies are needed so that more insights can be had about AL (15). Amin et al. analyzed the occurrence of AL following the placement of an LAR plus transanal stent, as opposed to Tau protein (defunctioning stoma), and found anastomotic leakage in 3 of 41 patients (approximately 7%) (9). In contrast, Bulow et al. found that the transanal stent was not superior to a defunctioning stoma in preventing the risk of AL after LAR (about 10.7%) (11). Chen et al., who studied 1,262 patients without, and 1,170 patients with, a transanal drainage tube after laparoscopic anterior resection for rectal cancer concluded that placement was associated with significantly lower rates of AL and reoperation, and hence, it was likely to be an effective method of preventing and reducing AL after rectal cancer surgery (24). Zhao et al., in 576 consecutive patients, indicated that the transanal drainage tube may not confer any benefit for AL prevention in patients who undergo laparoscopic low anterior resection for mid-low rectal cancer without preoperative radiotherapy (25).

Although contrary opinions are expressed in studies in the literature, almost all focus on a single technique and complication using different types of devices. These study results cannot be compared with the present results because the efficacy of different devices varies depending on the different purposes for which they are used. The device used by us is also a unique and non-fungible one, and the results obtained by us are related more to postoperative complications (AL, PPOI, POI, hospital stay) and two different patient groups that were compared, in which two different techniques were used, the Knight–Griffen group with the LS approach vs. the TAPSSA group with the traditional open method.

Our data are preliminary in nature and may have prevented us in finding the significance between the two different techniques in terms of AL and POI postoperative complications. For these reasons, other studies are necessary to confirm the evidence presented. The mean age of the patients of the groups was approximately 70 years and not lower.

This study confirmed, as shown in the literature, that laparoscopic intervention is characterized by a lower rate of PPOI than open surgery. In 13 RCTs instead, defining PPOI as a "reintegration of SNG", the incidence rate of PPOI was 14.2% (95% CI 7.2%–26%) for colon or rectum resections and 30.9% (95% CI 12.7%–57.8%) for rectal resections. After laparoscopic resections, the incidence rate of PPOI was lower, approximately 6.4% (95% CI 3.5%–11.5%), but 10% (95% CI 6.2%–15.8%) after open colorectal resection (26, 27). Logically, it is not possible to compare these data with those of our study, as the definitions of PPOI, the number and characteristics of patients, and the type of intervention are not unambiguous in nature. Nevertheless, the fact that it was never necessary to reintroduce the SNG and that on the fifth postoperative day the incidence of PPOI was low suggests that the use of No-Coil has a positive influence on PPOI.

Conclusion

According to the data collected on 77 patients, even in such a preliminary type of study, we can reasonably assume that with the positioning of the No-Coil tube, we were able to reduce the time of canalization to gases and feces and the risk of AL in both groups. Furthermore, by associating the No-Coil placement with the LS approach, we can reduce a number of postoperative complications related to PPOI and hospital stay. Another great advantage relating to the quality of life of the patients, their psychological health, and the costs for the National Health System stems from the elimination of the need to perform protective ileostomy and the subsequent stoma closure surgery. Also, we observed that the use of No-Coil allowed the patients to achieve faster mobility, given the high level of importance attached to the performance of these major surgical procedures.

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 Human Investigation Committee (IRB) of University "Magna Graecia" Medical School, "Mater Domini" Hospital, approved this retrospective study (Protocol N° 182, 18 June 2020). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MA, GC, and SM conceived the study design. FF, RoM, RiM, and RR were involved in data collection and drafting of the work. DL, FM, NA, and GN revised the work critically. MA and CB performed statistical analysis and revision and GC gave the final approval. All authors contributed to the article and approved the submitted version.

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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