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First positronium lifetime imaging with scandium-44 on a long axial field-of-view PET/CT

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Purpose: The physical properties of ⁴⁴Sc, combined with its imminent clinical application, position it as a prime candidate for *in vivo* positronium lifetime imaging. In this study, we investigate the count statistics for ortho-positronium (oPs) measurements with ⁴⁴Sc on a commercial long-axial field-of-view (LAFOV) PET/CT.

Method: A NEMA image quality phantom was filled with 41.7 MBq of ⁴⁴Sc dissolved in water and scanned on a LAFOV PET/CT. Three-photon events were identified using a prototype feature of the scanner and dedicated software. The lifetime of oPs was determined in the phantom spheres and in 4 × 4 × 4 mm³ voxels.

Results: All measured oPs lifetimes are compatible, within the uncertainties, with the literature values for water. The oPs lifetime is 2.65 ± 0.50, 1.39 ± 0.20 and 1.76 ± 0.18 ns in the three smallest spheres of the phantom and 1.79 ± 0.57 ns for a single voxel in the central region of the largest sphere. The relative standard deviation in the background regions of the time difference distributions, i.e., for time differences smaller than −2.7 ns, is above 20%—even for voxels inside the phantom spheres.

Conclusions: Despite the favorable physical properties of ⁴⁴Sc, the count statistics of three-photon events remains a challenge. The high prompt-photon energy causes a significant amount of random three-photon coincidences with the given methodology and, therefore, increases the statistical uncertainties on the measured oPs lifetime.

KEYWORDS

scandium-44, long axial field-of-view PET/CT, positronium, positronium lifetime imaging, NEMA phantom

1 Introduction

Investigating the lifetime of ortho-positronium (oPs), the spin-1 state of an electron-positron bound system, has offered valuable insights into the structural properties of matter for decades (1–8). More recently, the medical community has shown interest in measuring oPs lifetimes in human tissue (9–12). So-called *oPs lifetime imaging*, i.e., constructing a three-dimensional image of the human body with the oPs lifetime as voxel value (13), has the potential to provide diagnostic information about the tissue microenvironment, in particular oxygenation levels, that is currently unavailable in clinical routine (13–23). Recently, the first *in vivo* oPs lifetime images were determined with the dedicated multi-photon J-PET scanner prototype (24), and notably also the first *in vivo* oPs lifetime measurements with a commercial PET/CT system were demonstrated (25, 26). Different dedicated image reconstruction techniques for oPs lifetime imaging have been presented in the literature (20, 22, 27–32).

The oPs lifetime can be measured by determining the time difference between a prompt-photon, emitted during the nuclear decay along with the positron, and the two photons with 511 keV energy from the positron annihilation. The prompt-photon serves as the start time, while the detection of the annihilation photons sets the stop time. The two annihilation photons are also used to determine the place of annihilation (33). Histogramming all measured time differences gives a Positron Annihilation Lifetime (PAL) spectrum that contains several components, including the oPs lifetime. The oPs lifetime is of particular interest, as it depends on the molecular structure of the surrounding matter (9, 10). oPs lifetime measurements require a positron-emitting radionuclide with prompt-photon emission, together with the possibility of detecting and localizing three-photon events¹ (3 γ E). The detection of 3 γ E poses significant challenges, particularly in a clinical environment. Positron emission tomography (PET) systems are designed to detect photon pairs with 511 keV energy. The detection of single-photon events with different energies is not part of the core design of clinical PET/CT scanners. Nonetheless, Ref. (34) presented the first use of a clinical PET/CT scanner for oPs lifetime measurements by extending the detection and processing capabilities to 3 γ E. An accurate measurement of oPs lifetime requires the detection of a substantial number of 3 γ E. The increased sensitivity of long-axial field-of-view (LAFOV) PET/CT systems (35–38) proved to be a key factor for oPs lifetime measurement on a commercial PET/CT system.

Radionuclides with prompt-photon emission are readily available in clinics, of which ⁶⁸Ga labeled with [⁶⁸Ga]Ga-PSMA-617 and [⁶⁸Ga]Ga-DOTA-TOC is by far the most

widely adapted. ⁸²Rb and to some extent ¹²⁴I are also used in clinical routine, which is why Refs. (24, 25) relied on ⁶⁸Ga and ⁸²Rb for *in vivo* measurements. The prompt-photon branching ratio (BR $_{\gamma}$) is, of course, a key physical parameter to maximize the count statistics of 3 γ E. ⁶⁸Ga and ⁸²Rb have only a limited BR $_{\gamma}$. If the positron emission fraction is taken into account, also the seemingly high BR $_{\gamma}$ of ¹²⁴I drops significantly. ⁴⁴Sc, on the other hand, has a very high BR $_{\gamma}$ in conjunction with a high positron fraction, which makes it a prime candidate for oPs lifetime imaging (38, 39). There is legitimate hope that ⁴⁴Sc can overcome the challenge of detecting enough 3 γ E for a reliable determination of the useful lifetime of oPs (38).

Although ⁴⁴Sc is not yet available in clinical routine, production routes, purification and labeling as well as first in-human studies have been reported in the literature (40–49). ⁴⁴Sc can be paired with its therapeutic analog ⁴⁷Sc for theranostic applications, enabling seamless transitions between diagnostic imaging and targeted therapy. Adding diagnostic information from oPs lifetime imaging could boost the tailored effectiveness of therapeutic applications with ⁴⁷Sc, the β^{-} -emitting theranostic partner of ⁴⁴Sc.

In this brief report, we investigate the properties of ⁴⁴Sc for oPs lifetime imaging on a commercial LAFOV PET/CT. While Refs. (25, 34, 50) showed that ¹²⁴I outperforms ⁶⁸Ga and ⁸²Rb in terms of 3 γ E count statistics, the current study investigates the performance of ⁴⁴Sc with respect to oPs lifetime imaging and how it compares to ¹²⁴I using the methodology described in Refs. (25, 34, 50).

2 Method

⁴⁴Sc was produced at the Paul Scherrer Institute (PSI, Switzerland). The radionuclide production and post-irradiation processing at PSI have been established and are being further developed and optimized, as documented in Refs. (46, 51, 52). At Inselspital's Department of Nuclear Medicine (Switzerland) a standard NEMA image quality phantom (Data Spectrum Corp.) without lung insert was filled with a total of 41.7 MBq at scan time. The dose calibrator in the Department of Nuclear Medicine (VDC-405/VIK-202, Comcer, The Netherlands) was cross-calibrated with a ⁴⁴Sc reference activity from PSI. Ref. (53) describes the calibration of PSI's dose calibrator for ⁴⁴Sc. The activity concentration in the six phantom spheres at scan time was 40.68 kBq/mL while the background concentration was 3.90 kBq/mL. The phantom was scanned for 20 min in the so-called singles mode on a Biograph Vision Quadra (Siemens Healthineers, USA). Singles mode stores all single-crystal interactions into a list mode file. The sorting of 3 γ E is performed using the same prototype software as described in Refs. (25, 34, 50). The annihilation photon energy window is 476 to 546 keV with a double coincidence time window of 4.2 ns, while the prompt-photon energy window is 720 to 735 keV, i.e., the last two energy bins. Apart from the time and energy window selection, a minimal distance of 30 crystals

¹In this study, we do not consider three-photon decays of oPs.

(equivalent to a 100 mm radius) is applied in order to control the ^{176}Lu background (34). No reconstruction algorithm is applied, i.e., the spatial localization of the $3\gamma\text{E}$ is purely based on time-of-flight (TOF) of the 511 keV photons (34). As described in Ref. (34), Quadra resolves photon energies up to 726 keV. Beyond this energy, all detected photons are collected in a single energy bin. Since the prompt-photon of ^{44}Sc has an energy of 1157.022 ± 0.015 keV, all prompt-photon events are located in the last energy bin. The time differences between the annihilation and prompt-photons for each $3\gamma\text{E}$ were binned in order to obtain a PAL spectrum. The time bins are 133 ps wide. For the parameter fit we select only those $3\gamma\text{E}$ with time differences between -2 ns and 8.6 ns.

For the determination of the oPs lifetime, we rely on the same Bayesian fitting procedure as in Refs. (25, 34, 50). The fit model for the PAL spectrum consists of three lifetime components, i.e., direct annihilation, para-positronium and oPs, convoluted with a Gaussian function that models the detection system. Solving the convolution integral analytically, the fit model can be written in terms of error functions:

$$F(\Delta t) = b + N \cdot \sum_{c=1}^3 \frac{BR_c}{2\tau_c} e^{(\sigma^2 - 2\Delta t \tau_c + 2\Delta_0 \tau_c)/(2\tau_c^2)} \cdot \text{erfc}\left(\frac{\sigma}{\sqrt{2}\tau_c} + \frac{\Delta_0 - \Delta t}{\sqrt{2}\sigma}\right). \quad (1)$$

In Equation 1, b denotes a constant background and N is a normalization constant. The relative branching ratios of the three lifetimes $\tau_{1,2,3}$ are $BR_{1,2,3}$. The two parameters σ and Δ_0 define the Gaussian function. They represent the timing resolution and time offset. We use a Bayesian fitting procedure that minimizes a Gaussian likelihood for determining the parameter's posterior distributions. Equation 2 shows the prior distributions for the fit parameters

$$\begin{aligned} \tau_3 &\sim \mathcal{N}(1.78 \text{ ns}, 0.8 \text{ ns}), \\ BR_{1,2,3} &\sim \text{Dirichlet}(0.75, 3.1, 1.15), \\ \sigma &\sim \mathcal{N}(0.1 \text{ ns}, 0.05 \text{ ns}), \\ \Delta &\sim \mathcal{N}(0 \text{ ns}, 0.5 \text{ ns}), \\ N &\sim \mathcal{N}(A, 0.1 \cdot A), \end{aligned} \quad (2)$$

where A is the integrated of the PAL spectrum with a subtracted background b . The value of b is determined as the mean counts with time differences smaller than -2.7 ns. The values of the direct annihilation and oPs lifetime are fixed to reference values of $\tau_1 = 0.388$ ns and $\tau_2 = 0.125$ ns. Setting priors for $\tau_{1,2}$ does not impact the result significantly (25, 34). The Bayesian approach allows us to marginalize nuisance parameters. In fact, we are mostly interested in τ_3 and the branching ratios (for sanity checks and comparison with established results from the literature). We report the fit results in terms of marginalized posterior distributions. The posterior distribution for τ_3 is almost a perfect Gaussian function, hence the standard deviation is a reasonable measure for the uncertainty. However, this does

not apply to $BR_{1,2,3}$ and we therefore provide the highest density interval (HDI) of the posterior distribution in the results.

We determined the oPs lifetime for the six spheres $s_{1...6}$ of the NEMA phantom (nominal diameters: 10, 13, 17, 22, 28, 37 mm). Furthermore, we binned the spatial distribution of the detected $3\gamma\text{E}$ into voxels of $4 \times 4 \times 4$ mm³. For each voxel, the oPs lifetime is determined according to the same Bayesian fitting as for the phantom spheres.

3 Results

The left panel of Figure 1 shows the maximum intensity projection (MIP) of the $3\gamma\text{E}$ histoimage. The binning is chosen according to the CT image, i.e., $1.52 \times 1.52 \times 1.65$ mm³. Even without any reconstruction methodology, i.e., using only TOF for the localization of the $3\gamma\text{E}$, the smallest sphere s_1 of the NEMA phantom is visible. The absence attenuation correction is clearly visible through the darkening on the border of the phantom. Some ^{44}Sc activity stuck to the left wall of the phantom.

The total number of $3\gamma\text{E}$ in the full field of view collected during the 30 min scan is 539 862 149 for a triple coincidence time window from -15 ns to $+15$ ns. These are, however, mostly random $3\gamma\text{E}$. In contrast, a 20 min scan in standard coincidence mode with a larger coincidence window of 435 keV to 585 keV of the same phantom yields 2 405 451 960 net trues. This includes the standard random correction methods for coincidence PET.

On the right of Figure 1 the relative error in the background region of the PAL spectrum, i.e., for time differences that are smaller than -2.7 ns, is shown. The error inside the spheres decreases as there is a higher activity concentration. Due to the decreasing number of $3\gamma\text{E}$ towards the center of the phantom, the error increases towards the center of the phantom (there is no attenuation correction).

Figure 2 shows the measured PAL spectrum with the fit prediction for the three smallest spheres and a single voxel in the center of the largest sphere s_6 . The error bars plotted on the measurement points are the relative error in the background region of the PAL spectrum, i.e., the relative standard deviation of all time differences < -2.7 ns. The 68% HDI plotted in Figure 2 represents prediction uncertainty of the fit. The fit results corresponding to the PAL spectrum in Figure 2 are reported in Table 1 together with the fit results of the larger phantom spheres. The posterior distribution of τ_3 is Gaussian, hence we report the error on τ_3 as a standard deviation in Table 1. This does not apply to the relative branching ratios of the three lifetime components $BR_{1,2,3}$, since these are Dirichlet distributed random variables. Their error is therefore quoted as a 68% HDI.

In Figure 3 a slice of the full oPs lifetime image, together with the fit error on τ_3 with a $4 \times 4 \times 4$ mm³ binning, is presented. While the oPs lifetime image is not particularly interesting - after all, the phantom is filled with water - the marginalized uncertainty on τ_3 clearly increases in the central region of the phantom. Note that only for the four largest spheres, the error decreases visibly.

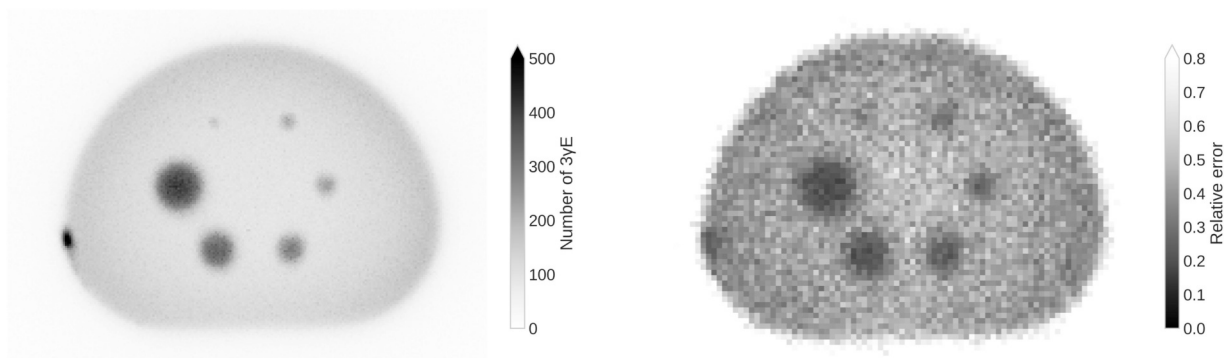


FIGURE 1

MIP of the 3γE histoimage with a voxel size that corresponds to the CT image (left) and the relative error in the background region of the PAL spectrum in a single slice with $4 \times 4 \times 4 \text{ mm}^3$ voxel size (right).

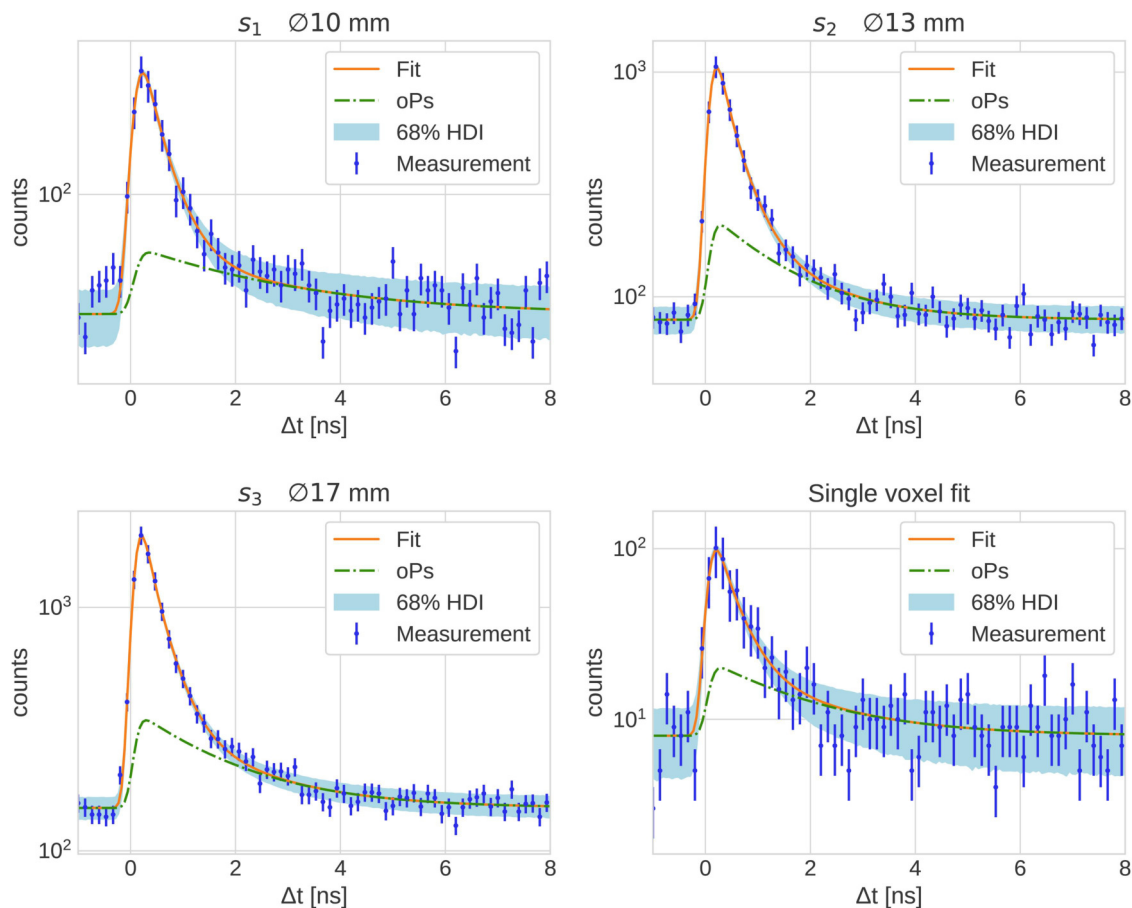


FIGURE 2

PAL spectrum of all 3γE with the fit prediction in the three smallest spheres of the NEMA phantom and of a single $4 \times 4 \times 4 \text{ mm}^3$ voxel in the center of S_6 .

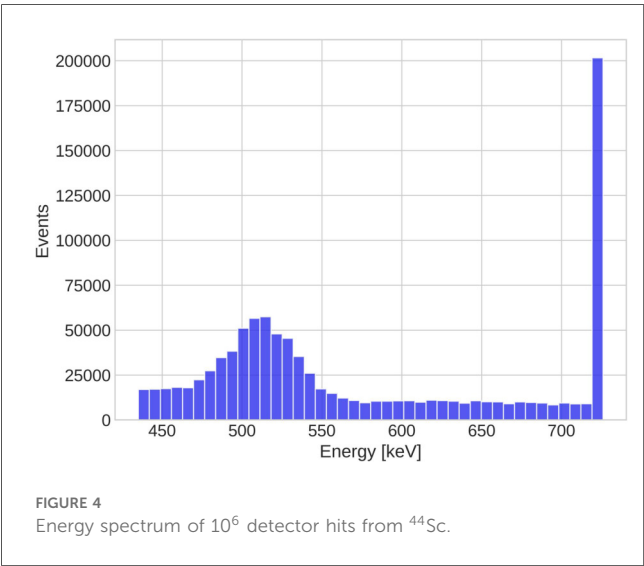
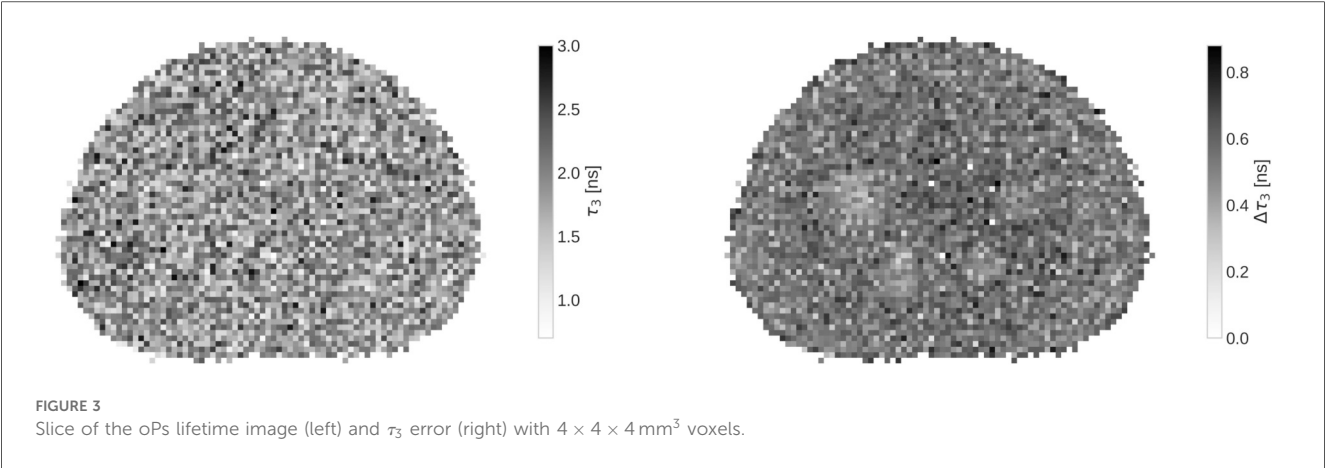
4 Discussion

From the discussion in Ref. (34), it is clear that the key question is whether the high BR_γ of ^{44}Sc can overcome the

Quadra's inability to resolve ^{44}Sc 's photopeak. Detector hits above 726 keV are collected in a single integrating bin, as clearly illustrated in Figure 4. One should, therefore, expect that more random coincidences are selected due to the high prompt-

TABLE 1 Fit results for the six phantom spheres and a single $4 \times 4 \times 4 \text{ mm}^3$ voxel in the center of s_6 .

Fit	τ_3 [ns]	BR_1	HDI_{BR_1}	BR_2	HDI_{BR_2}	BR_3	HDI_{BR_3}
$s_1 \emptyset 10 \text{ mm}$	2.65 ± 0.50	0.072	[0.0, 0.091]	0.659	[0.608, 0.736]	0.269	[0.242, 0.301]
$s_2 \emptyset 13 \text{ mm}$	1.39 ± 0.20	0.077	[0.049, 0.106]	0.623	[0.573, 0.679]	0.30	[0.267, 0.324]
$s_3 \emptyset 17 \text{ mm}$	1.76 ± 0.18	0.062	[0.041, 0.083]	0.651	[0.62, 0.687]	0.287	[0.27, 0.301]
$s_4 \emptyset 22 \text{ mm}$	1.86 ± 0.09	0.057	[0.047, 0.067]	0.655	[0.639, 0.671]	0.288	[0.281, 0.296]
$s_5 \emptyset 28 \text{ mm}$	1.73 ± 0.1	0.091	[0.08, 0.103]	0.603	[0.585, 0.622]	0.306	[0.296, 0.314]
$s_6 \emptyset 37 \text{ mm}$	1.78 ± 0.08	0.066	[0.057, 0.076]	0.642	[0.627, 0.657]	0.292	[0.285, 0.299]
Voxel	1.79 ± 0.57	0.051	[0.0, 0.063]	0.609	[0.553, 0.717]	0.34	[0.266, 0.386]



photon energy of ^{44}Sc . The right panel of Figure 3 already hints towards a high random $3\gamma\text{E}$ rate: even inside the spheres, the relative error in the background region of the PAL spectrum exceeds 20%. For a comparison, Ref. (50) only considered those voxels with less than 20% background error for oPs lifetime imaging.

The large number of random $3\gamma\text{E}$ is reflected in the statistical uncertainty of τ_3 reported in Table 1. All values for τ_3 in the phantom are consistent with the literature value of $1.839 \pm 0.015 \text{ ns}$ for water from Ref. (54) and with the results from Ref. (50) within

their statistical uncertainty [note also the reference values in Ref. (17)]. However, the marginalized uncertainties reported in Table 1 are rather large: only starting from s_3 the relative error starts dropping below 10% (and reaches even 31.9 % in a single voxel). This is likely more than the precision required to sense different oxygenation levels in lesions, as discussed in Ref. (16).

τ_3 's uncertainty is seen in Figure 3 as well. The variation on τ_3 across the whole phantom is quite large, given that the expected oPs lifetime should be the same across the whole phantom. In the right panel of Figure 3, only very few voxels have an error below 0.3 ns. The mean uncertainty on τ_3 across the slice shown in Figure 3 is 0.53 ns. Only the four largest spheres of the phantom have a visibly smaller uncertainty compared to the phantom background.

The fit of the oPs lifetime critically depends on the time differences after the peak in the PAL spectrum, i.e., on values close to the random $3\gamma\text{E}$ background. A useful quantity to characterize the $3\gamma\text{E}$ count statistics is therefore the peak signal-to-background ratio (pSBR) in a PAL spectrum. In the measurements with ^{124}I , Ref. (50) reported a pSBR of about 55.5 for a $4 \times 4 \times 4 \text{ mm}^3$ voxel in the water tube with an activity concentration of 252 kBq/ml and a scan time of 15 min. For the PAL spectrum in the $4 \times 4 \times 4 \text{ mm}^3$ voxel in Figure 2, however, the pSBR is only about 12.6. Despite the activity concentration being higher in the ^{124}I measurements of Ref. (50), the scan duration is 5 min shorter. The error on τ_3 in a single voxel (last row in Table 1) is about four times larger than the error reported in Ref. (50) for the same voxel size. A similar picture arises when looking at volumes of similar size, e.g., the sphere s_4

has a volume of 5.57 mL and is comparable with the volume of the tubes in Ref. (50). The relative error on τ_3 , however, is 4.8% while Ref. (50) reports a 1.1% error for a 5 mL tube with water. This comparison is even more striking, when considering the BR_γ per positron, which is almost 8 times higher for ^{44}Sc than for ^{124}I . With the given methodology, resolving the photopeak therefore seems key for a low random $3\gamma\text{E}$ rate. ^{44}Sc 's high BR_γ cannot overcome Quadra's limited detection capabilities for high-energy photons. Given the energy spectrum in Figure 4, it is clear that extending the prompt-photon energy window does not yield a significant reduction of random $3\gamma\text{E}$. Also, note that ^{124}I 's lower prompt-photon energy (almost half compared to ^{44}Sc) increases the probability to interact within the detector crystals. It should be emphasized that this conclusion applies to the given methodology. Different detection methods (24) or event selection procedures and/or random $3\gamma\text{E}$ estimations as e.g., in Ref. (55) may reduce the uncertainties on τ_3 in the case of high-energy prompt-photons. We leave such an investigation for future studies.

Ref. (56) did not attempt to perform a voxel-wise fit nor a fit to the three smallest spheres of the NEMA phantom. On the other hand, Ref. (57) seems to be able to fully exploit the high prompt-photon BR_γ of ^{44}Sc . Both scanners in these studies do not suffer from the limited energy range of Quadra and the event selection and reconstruction algorithms are different.

In contrast to ^{44}Sc , ^{43}Sc 's prompt photon is within Quadra's energy range and therefore, the afore mentioned discussion of the high-energy prompt-photons does not apply. However, the BR_γ per positron is in the same order of magnitude as ^{124}I and ^{82}Rb i.e., much lower than for ^{44}Sc .

5 Conclusions

Given Quadra's limited energy resolution and the current methodology for selecting $3\gamma\text{E}$, it does not seem that ^{44}Sc is able to outperform ^{124}I in terms of count statistics for oPs lifetime imaging, despite its favorable physical properties and clinical prospects.

Data availability statement

The raw data format is not publicly available. Evaluated data are available upon reasonable request. Requests to access the datasets should be directed to lorenzo.mercolli@insel.ch.

Author contributions

LM: Writing – original draft, Investigation, Data curation, Writing – review & editing, Methodology, Conceptualization, Software, Funding acquisition, Formal analysis. WMS: Writing – review & editing, Software, Methodology, Investigation. PG: Resources, Investigation, Writing – review & editing. AM: Investigation, Resources, Writing – review & editing. SB:

Resources, Writing – review & editing. MC: Software, Writing – review & editing. PM: Writing – review & editing, Funding acquisition. NR: Writing – review & editing. AR: Writing – review & editing, Funding acquisition. HS: Writing – review & editing, Methodology, Software. RS: Writing – review & editing. RS: Writing – review & editing. KS: Funding acquisition, Writing – review & editing. ES: Funding acquisition, Writing – review & editing. NM: Funding acquisition, Writing – review & editing, Resources, Conceptualization.

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Conflict of interest

WMS and MC are full-time employees of Siemens Medical Solutions USA, Inc. HS is a part-time employee of Siemens Healthineers International AG. PM is an inventor on a patent related to this work. Patent nos.: (Poland) PL 227658, (Europe) EP 3039453, and (United States) US 9,851,456, filed (Poland) 30 August 2013, (Europe) 29 August 2014, and (United States) 29 August 2014; published (Poland) 23 January 2018, (Europe) 29 April 2020, and (United States) 26 December 2017. AR has received research support and speaker honoraria from Siemens. KS received research grants from Novartis and Siemens and conference sponsorships from United Imaging, Siemens, and Subtle Medical not related to the submitted work.

The remaining 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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