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Technical note

Imaging quality of ^{44}Sc in comparison with five other PET radionuclides using Derenzo phantoms and preclinical PET

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HIGHLIGHTS

- Six PET radionuclides (^{18}F, ^{64}Cu, ^{11}C, ^{89}Zr, ^{68}Ga and ^{44}Sc) were produced at CRS ETH-PSI-USZ.
- Preclinical PET was performed with Derenzo phantoms.
- The FWHM values was determined for each radionuclide with the same preclinical PET scanner.
- In agreement with decreasing positron energies, the image resolution increased: ^{68}Ga < ^{44}Sc < ^{89}Zr < ^{11}C < ^{64}Cu < ^{18}F.
- The FWHM of the radionuclides, were in agreement with the theoretical predictions of Palmer et al. (2005).

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ABSTRACT

PET is the favored nuclear imaging technique because of the high sensitivity and resolution it provides, as well as the possibility for quantification of accumulated radioactivity. ^{44}Sc ($T_{1/2}$=3.97 h, Eβ$^+$=632 keV) was recently proposed as a potentially interesting radionuclide for PET. The aim of this study was to investigate the image quality, which can be obtained with ^{44}Sc, and compare it with five other, frequently employed PET nuclides using Derenzo phantoms and a small-animal PET scanner. The radionuclides were produced at the medical cyclotron at CRS, ETH Zurich (^{11}C, ^{18}F), at the Injector II research cyclotron at CRS, PSI (^{64}Cu, ^{89}Zr, ^{44}Sc), as well as via a generator system (^{68}Ga). Derenzo phantoms, containing solutions of each of these radionuclides, were scanned using a GE Healthcare eXplore VISTA small-animal PET scanner. The image resolution was determined for each nuclide by analysis of the intensity signal using the reconstructed PET data of a hole diameter of 1.3 mm. The image quality of ^{44}Sc was compared to five frequently-used PET radionuclides. In agreement with the positron range, an increasing relative resolution was determined in the sequence of ^{68}Ga < ^{44}Sc < ^{89}Zr < ^{11}C < ^{64}Cu < ^{18}F. The performance of ^{44}Sc was in agreement with the theoretical expectations based on the energy of the emitted positrons.

1. Introduction

Current clinical PET is the favored method of nuclear physicians because of the high sensitivity and resolution it provides, as well as the possibility for quantification of accumulated radioactivity (Mittra and Quon, 2009; Rahmim and Zaidi, 2008). The resolution of the reconstructed image is mainly dependent on (i) detector-specific effects, (ii) photon non-collinearity and the (iii) positron range of the employed PET nuclide (Rahmim and Zaidi, 2008). Detector-specific effects (e.g. size and geometry) are dependent on the type of PET scanner employed. Non-collinearity originates from the fact that the two 511 keV photons are not emitted precisely in opposite (180°-angle) directions. The corresponding resolution blurring depends on the ring diameter and is, therefore, of minor importance in the case of small-animal PET, but may be of relevance for clinical PET (Rahmim and Zaidi, 2008). The third factor is the positron range, defined as the average direct distance

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Table 1
Decay properties of PET nuclides used in this study. Data are based on the chart of nuclides of the National Nuclear Data Center (http://www.nndc.bnl.gov/chart/).

Radionuclide	Half-life	$E\beta^+_{average}$ [keV]	$I\beta^+$ [%]	$E\gamma$ [keV]	$I\gamma$ [%]	Production route
^{18}F	110 min	250	96.7	-	-	^{18}O(p,n)^{18}F
^{64}Cu	12.7 h	278	17.6	1346	0.48	^{64}Ni(p,n)^{64}Cu
^{11}C	20 min	386	99.8	-	-	^{14}N(p,α)^{11}C
^{89}Zr	78.4 h	396	22.7	909	99.0	^{89}Y(p,n)^{89}Zr
				1713	0.75	
^{44}Sc	**3.97 h**	**632**	**94.3**	**1157**	**99.9**	**^{44}Ti/^{44}Sc-generator**
				1499	**0.91**	**^{44}Ca(p,n)^{44}Sc**
^{68}Ga	68 min	830	88.9	1077	3.2	^{68}Ge/^{68}Ga-generator

which the positron travels from the decaying atom to the location of the annihilation process. Since this parameter is a function of the positron energy, it varies among different radionuclides. The higher the positron energy of a PET radionuclide, the more pronounced is the degradation of the image resolution, especially in small-animal PET (Rahmim and Zaidi, 2008).

The most widely-used PET radionuclides are the pure positron-emitters ^{18}F and ^{11}C, which can be produced at medical cyclotrons (Table 1) (Kramer-Marek and Capala, 2012). The most important PET radiotracer is 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) which has been used for almost four decades for the imaging of cancer and inflammatory diseases (Basu and Alavi, 2008). In recent times, positron-emitting radiometals have also been increasingly introduced in clinical practice (Kramer-Marek and Capala, 2012; Laforest and Liu, 2008). ^{68}Ga is obtained from a ^{68}Ge/^{68}Ga generator and, due to its short half-life, it is suitable mainly for the labeling of small molecules and peptides with fast pharmacokinetics (Table 1) (Eiber et al., 2015; Gabriel et al., 2007). Other interesting cyclotron-produced radiometals are ^{64}Cu and ^{89}Zr, which have been widely used pre-clinically, as well as in clinics (Table 1) (Anderson and Ferdani, 2009; Dijkers et al., 2010).

More recently, ^{44}Sc has attracted the attention of researchers and physicians because of its excellent characteristics for PET imaging (Table 1) (Roesch, 2012). The production of ^{44}Sc has been proposed via a ^{44}Ti/^{44}Sc-generator (Roesch, 2012) or by irradiation of natural or enriched Ca targets at a cyclotron (Krajewski et al., 2013; Müller et al., 2013; Severin et al., 2012). It has been recently demonstrated that cyclotron-produced ^{44}Sc can be made available in sufficient quantities for clinical application (van der Meulen et al., 2015). ^{44}Sc may, therefore, be an attractive alternative to the currently-used ^{68}Ga due to its almost four-fold longer half-life which allows transportation of ^{44}Sc-radiopharmaceuticals to hospitals remote from PET centers containing a cyclotron (van der Meulen et al., 2015).

While ^{11}C, ^{18}F, ^{64}Cu and ^{89}Zr have been investigated and compared in detail by Palmer et al. (2005), the question remains how ^{44}Sc fits into the sequence of these radionuclides in terms of imaging resolution. In the present study, five common PET nuclides (^{11}C, ^{18}F, ^{68}Ga, ^{64}Cu and ^{89}Zr) were investigated with regard to their relative image resolution using small-animal PET for comparison with the results obtained with ^{44}Sc. For this purpose, Derenzo phantoms were used, along with a GE Healthcare eXplore Vista small-animal PET scanner.

2. Experimental arrangement

2.1. Production of ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{89}Zr

No-carrier-added [^{18}F]fluorine was produced via the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of enriched ^{18}O-water at a Cyclone 18/9 cyclotron (18 MeV; IBA, Ottignies-Louvain-la-Neuve, Belgium) at CRS, ETH Zurich (Fischer et al., 2012). ^{11}C was produced at the same cyclotron via the ^{14}N(p,α)^{11}C nuclear reaction in the form of [^{11}C]CO_2 (Mu et al., 2013a). ^{68}Ga was obtained from a ^{68}Ge/^{68}Ga-generator IGG100-50 (Eckert & Ziegler, Berlin, Germany) (Mu et al., 2013b). ^{64}Cu was produced via the ^{64}Ni(p,n)^{64}Cu nuclear reaction and ^{89}Zr was produced via the ^{89}Y(p,n)^{89}Zr nuclear reaction at the Injector II cyclotron facility at CRS, PSI Villigen (Hohn et al., 2008). ^{44}Sc was produced at the same research cyclotron, via the ^{44}Ca(p,n)^{44}Sc nuclear reaction as previously reported by our group (Müller et al., 2013; van der Meulen et al., 2015). The quantity of the radioactivity used for phantom studies was determined in dose calibrators (ISOMED 2010, Nuclear-Medizintechnik, Dresden GmbH or VDC-505, Veenstra Instruments, The Netherlands). The factors for non-standard nuclides, such as for instance ^{44}Sc, were determined based on exact activity measurements on a N-type high-purity germanium (HPGe) coaxial detector (EURISYSMESURES, France) using *Ortec InterWinner* software version 5.0.

The radionuclidic purity of all investigated radionuclides was $>99\%$. ^{44}Sc comprised traces of ^{44m}Sc ($<1\%$) (Müller et al., 2013) and ^{88}Zr ($<1\%$) was present as a radionuclidic impurity in the ^{89}Zr solution (Hohn et al., 2008).

2.2. Preparation of the phantoms

Derenzo phantoms with a diameter of $D=19.5$ mm, a height of $H=15.0$ mm and holes with diameters ranging from 0.8 mm to 1.3 mm in 0.1 mm steps were used for this study (Supplementary material Fig. S1). The phantoms were filled (total volume of 600 µL) with the aqueous solution of the desired nuclide and ethanol (25 vol%) to enable proper filling of the capillaries.

2.3. PET imaging

All PET scans were performed with the same preclinical scanner, a small-animal eXplore VISTA PET/CT (GE Healthcare, Spain) at an energy window of 250–700 keV. The features and characteristics of this kind of preclinical PET scanner have been reported in detail by Wang et al. (2006). Based on the measured count rate (counts/s) of each radionuclide, the required scan time for ~60 Mio coincidences was determined. The 2-dimensional ordered-subset expectation maximization (2D-OSEM) algorithm was used for the reconstruction of the PET data and the images were prepared using *VivoQuant* image post-processing program software (version 2.00, Bioscan Inc., U.S.).

2.4. Quantification of the relative resolution by determination of full-width at half-maximum (FWHM)

With the “cropping” function of the *VivoQuant* software, one representative single transversal section was selected at three different depths of the phantom. A line was drawn through the