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SPATIAL RESOLUTION IN BRAZILIAN SMALL ANIMAL PET SCANNERS: A BRIEF REVIEW

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ABSTRACT

Small animals PET (Positron Emission Tomography) scanners can generate molecular images for *in vivo* pharmacokinetic and pharmacodynamic studies of small animals, especially rodents. These studies make it possible to evaluate aspects such as the dynamic biodistribution of a radiopharmaceutical in a living organism, excretion times, and specificity for different indications. The concept of spatial resolution (SR) applied to PET scanners is related to the ability to reproduce the image of an object and evidences the distribution of radioactivity. The SR can be affected by some factors: i) detector size; (ii) positron range; iii) non-collinearity; (iv) the method of image reconstruction and (v) the location of the detector. The main objective of this work was to perform a brief review of the concept of spatial resolution applied to small animal PET scanners. Furthermore, an overview of qualitative and quantitative results for SR obtained with radioisotopes Gallium-68 (^{68}Ga), Fluorine-18 (^{18}F) and Sodium-22 (^{22}Na) in Brazilian PET scanners was presented. The methodology was based on a literature review in which articles published in indexed journals, national and international, containing the proposed theme were selected. The articles selected for this review presents SR studies performed in national molecular imaging centers. In Brazil, until this moment, there are six molecular imaging centers using seven small animal PET scanners from four different manufacturers. Studies concerning a qualitative analysis of PET images (HotRod simulator filled with ^{18}F) performed in four PET scanners indicated that the SR of one scanner is in the diameter limit of 1.0 mm rods and the three others is in 1.2 mm. Thus, 2.0, 1.5 and 1.2 mm diameter rods could be visually distinguished in all evaluated systems. Quantitative analysis, using a point source of ^{22}Na, was performed in only one PET scanner. In this system, the results revealed similar spatial resolution values (approximately 1.2 mm) between the NEMA NU 4/2008 method using the ^{22}Na point source (quantitative) and the HotRod simulator filled with ^{18}F (qualitative) method. Additional studies using the HotRod simulator filled with ^{68}Ga were also performed for this same PET scanner and qualitative results indicated a SR of 1.5mm. These results showed the direct influence of positron energy on his range, therefore, on spatial resolution. More details on the results obtained for spatial resolution with small animal PET scanners will be presented in the full version of this work.

1. INTRODUCTION

The concept of molecular imaging (MI) is linked to the ability to visualize, characterize, and measure the biological processes of an organism. The fact that it is a non-invasive procedure enabling differential and personalized diagnosis according to the physiological changes of an individual has facilitated the global spread of translational research based on MI [1]. In this context, nuclear medicine is a diagnostic and therapeutic method that allows the acquisition of images at the molecular level. For diagnostic imaging, SPECT (Single Photon Emission

Computed Tomography) or PET (Positron Emission Tomography) equipment can be used. Both techniques allow the detection of gamma rays emitted, directly or indirectly, by radiopharmaceuticals, thereby determining their biodistribution in vivo [1].
The increasing advancement in the use of PET technology for imaging has made it possible to perform tissue function studies and obtain images of small animals used in preclinical research trials [2]. Thus, small animal PET, or preclinical PET, was developed, as shown in Fig. 1

Fig. 1. Triumph™ LabPET Solo 4 installed at LIM-CDTN/CNEN.
Source: Author archive.

1.1. Small Animal PET Scanner

The advent of preclinical PET in 1990 revolutionized pharmacokinetic studies due to the equipment's ability to provide quantitative and three-dimensional data on the biodistribution of radiopharmaceuticals under development in a non-invasive manner and to allow physiological studies of molecular alterations before clinical manifestations [3]. Usually, rodents are the primary animals used in research on new radiopharmaceuticals. Therefore, it is necessary that the physical structure of the equipment is adapted to small animals and that its ability to differentiate organs and tissues is at a submillimeter level. This differentiation represents the concept of a parameter used to ensure the reliability of the data obtained: spatial resolution (SR) [3].

1.2. Spatial Resolution

Experimentally, spatial resolution is defined as the minimum distance between two points in an image that can be detected. In PET devices, it represents the ability of the equipment to accurately reproduce the image of an object. This parameter is directly related to the final quality of the image obtained [4]. When comparing the spatial resolution values of a human PET scanner and a preclinical PET scanner, numbers in the order of 3 to 4 mm and 1.2 mm are obtained, respectively. The possibility of using smaller detectors in small animal PET represents a resource used in the improvement of spatial resolution (SR) because it allows better efficiency in the geometric detection of the system [3]. In addition to the size of the detectors, the SR can be influenced by the range of the positrons, non-collinearity, the image reconstruction method used, and the location of the detector [4].

1.3. *HotRod* Phantom and Point Source

The HotRod phantom, exemplified in Fig. 2, is a device made of polymethylmethacrylate (PMMA) commonly used in the qualitative evaluation of the spatial resolution of small animal PET scanners. It is composed of three discs, one of which has six distinct channels, classified from G1 to G6, which allow filling with radioactive material. These channels have variable diameters, such as 2.0 mm (G1), 1.5 mm (G2), 1.2 mm (G3), 1.0 mm (G4), 0.8 mm (G5), and 0.6 mm (G6) [4].
To measure the spatial resolution using this method, the *HotRod* Phantom was initially filled with substances containing the radionuclides ^{68}Ga or ^{18}F, and then images of the phantom were acquired. In the case of the fluorine isotope, an activity of 60 MBq was used, with an acquisition time of 1 hour, a single bed position, and the simulator positioned in the center of the field of view (FOV). The images were reconstructed using the iterative MLEM method with 20 interactions [5, 6].
When filled with the gallium isotope, the images were also acquired over 1 hour, with an activity of 22.8 MBq and a single bed position. The image reconstruction followed the same protocol applied to the fluorine radioisotope [7].

Fig. 2. Left: HotRod Phantom; Center: Details of Phantom components; Right: Upper view of the disc with fillable channels arranged into six groups of different diameters [4].

Unlike the HotRod phantom, the ^{22}Na point source allows for the acquisition of quantitative data, as it presents a previously known activity [4]. The point source of sodium used in the studies carried out for this review is embedded in a PMMA acrylic cube of 10mm^2 and has an active diameter/volume of 0.25 mm (Fig. 3).
The image acquisition to measure the spatial resolution using the sodium point source followed the recommendations of the National Electrical Manufacturers Association (NEMA), according to the NU 4-2008 standard. The sodium source was positioned at the center of the field of view (FOV), with a certified activity of 1.154 MBq, and an acquisition time of 2 minutes. Image reconstruction was performed using the iterative MLEM method with 20 iterations. The image analysis was conducted through the line profile (calculation of the full width at half maximum - FWHM), using the open-source software Amide [4, 8]

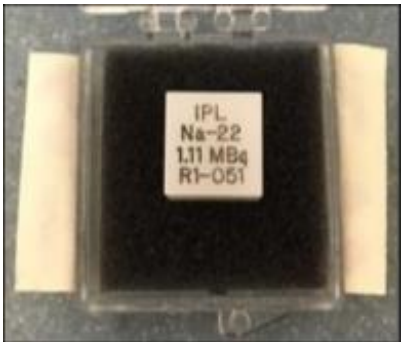


Fig. 3. ^{22}Na point source [4].
Source: Author archive.

2. METHODOLOGY

The research was structured based on a literature review on the theme of "spatial resolution in small animal PET scanners", using the keywords "small animal PET", "spatial resolution", and "image quality" for the search. The searches were limited to studies carried out in Brazilian molecular imaging centers, and research was found in three centers in the period from 2020 to 2024: Molecular Imaging Laboratory (LIM) at the Center for the Development of Nuclear Technology (CDTN), in Belo Horizonte; Laboratory of Bioimaging Preclinical Research Center (CPPC) at the Brain Institute - Pontifical Catholic University of Rio Grande do Sul (BraIns - PUCRS), in Rio Grande do Sul; and the Nuclear Medicine Laboratory (LIM-43) at the Hospital das Clínicas - Faculty of Medicine of the University of São Paulo (HCFMUSP), in São Paulo. As for the place of publication, the main source of search was the Brazilian Journal of Radiation Sciences (BJRS), except the article presented and published at the V National Week of Nuclear Engineering and Energy and Radiation Sciences (SENCIR) in 2020. Thus, five studies were found to have been published within the established requirements, as listed in Tab. 1.

Tab. 1. Articles addressing the SR in Small Animal PET Scanner published.

	Title	**Year**	**Journal / Annals**
01	Image Quality and Spatial Resolution: Comparative Analyses of Two PET Systems	2020	V SENCIR [6]
02	Spatial Resolution of a Preclinical PET Tomograph	2021	BJRS [4]
03	Performance Based on NEMA NU-4 2008 Standard of CDTN/CNEN's Small Animal PET Scanner	2022	BJRS [8]
04	Comparative Analysis of an Image quality Parameters and Qualitative Spatial Resolution of Three Small Animal PET Scanners in Brazil	2023	BJRS [5]
05	Spatial Resolution of a Small Animal PET Scanner Using ^{68}Ga Isotope	2024	BJRS [7]

3. RESULTS

During the literature review, six articles submitted in the period proposed for the search were found. After reading and analysis, two articles were excluded because they did not meet the requirements for the elaboration of this study. Subsequently, the work published in the Annals of

the National Week of Nuclear Engineering and Energy and Radiation Sciences was added to the selected literature due to the relevance of the research for the development of the proposed theme. Currently, Brazilian molecular imaging centers do not have a standard legislation that requires a quality assurance program. However, the NU 4-2008 standard was used to implement of quality control tests in Brazil [8]. NEMA NU 4-2008 specify the procedures to evaluate the performance of small animal PET scanners. These standardization measurement procedures can be used for acceptance testing before and after the installation of PET equipment [9].
According to the articles two different methods were used to evaluate the spatial resolution of small animal PET scanners:

i) *HotRod* phantom filled with radioisotopes ^{68}Ga and ^{18}F;
ii) NEMA NU 4-2008 standard using a point source of ^{22}Na.

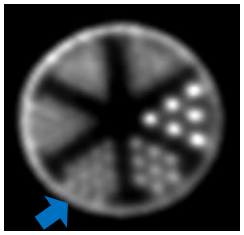
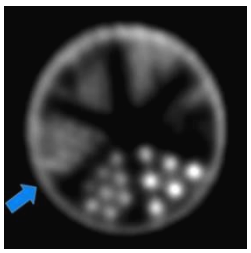
More details about the different methodologies can be found in the references cited on previous Tab 1.
The spatial resolution results obtained in the tests reported in the articles selected for this review are summarized and shown in Tab. 2.

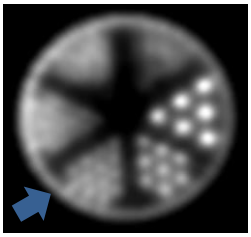
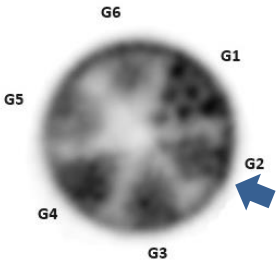
Tab. 2. Spatial Resolution.

Nuclide	Method	Center	Spatial Resolution
F-18	*HotRod* Phantom Qualitative analyse	LIM – CDTN/CNEN	1,2 mm
		LIM-43 HCFMUSP	1,2 mm
		CPPC – InsCer PUC-RS	1,2 mm
Ga-68		LIM – CDTN/CNEN	1,5 mm
Na-22	NEMA NU 4-2008 Point Source	LIM – CDTN/CNEN	1,2 mm

Tests performed with the HotRod phantom permits a qualitative analysis and the images acquired by the centers are summarized and presented on the Tab. 3.

Tab. 3. PET images of the Hot-Rod Phantom (axial view).

Nuclide	Method	Center	Image acquired
F-18	*HotRod* Phantom	LIM – CDTN/CNEN	
		LIM-43 HCFMUSP	

		CPPC – InsCer PUC-RS	
Ga-68		LIM – CDTN/CNEN	

Note: The blue arrow indicates the group of stems that can be clearly visually distinguished.
Source: Author collection.

In all images showed from the different centers it is possible to differentiate the channels present in G3, when F-18 radionuclide is used. So, in this case, qualitatively is possible to affirm that the spatial resolution is 1.2 mm. Lastly, the ^{68}Ga-filled phantom, allows us to visually distinguish the channels only of the G1 and G2 groups. From the G3 onwards, the system does not have sufficient spatial resolution to distinguish individual channels.
The worsening in the spatial resolution using Ga-68 sounds surprised but LIM/SERAF/CDTN team explained that was already expected due to the greater penetration of the ^{68}Ga positron compared to the ^{18}F positron.
In this context, positrons emitted by radionuclides used in the spatial resolution tests present different maximum range in water and theses values are showed in Tab. 4.

Tab. 4. Main physical and nuclear properties of ^{68}Ga, ^{18}F and ^{22}Na.

Nuclide	**Half-life**	**Maximum β+ range**
Ga-68	67.71 min	3,5 mm
F-18	109.77 min	0,6 mm
Na-22	2.60 y	1,8 mm

Source: IAEA, 2024 [7, 10, 11].

The annihilation of the β+ and, consequently, the emission of gamma rays at a point different from the site of concentration of the radiopharmaceutical result in the formation of an image at a different point from what was physiologically captured by the organism, resulting in a reduction in the spatial resolution and precision of the method. Therefore, consideration of the positron range is important to achieve an acceptable spatial resolution.
The longer range of the positron emitted by the gallium isotope is reflected in a worse spatial resolution when compared to the isotopes of fluorine and sodium. Thus, when performing preclinical studies with the ^{68}Ga it is necessary to first analyse the dimensions of the structure, as some organs may become difficult to visualize due to low SR [7].

Research corroborates the efficacy of the application of radioactive fluoride as a radiopharmaceutical, thus justifying its extensive use in preclinical studies and PET scans for human beings. The short range of the positron until its annihilation results in a spatial resolution that is considered acceptable by researchers [5].

4. CONCLUSION

This work allowed us to know better the concept about spatial resolution applied on small animal PET scanner using different isotopes (^{68}Ga,^{18}F and ^{22}Na). Results demonstrated clearly the direct influence of positron energy on his range, consequently, on spatial resolution. So, for a high spatial resolution it is necessary to minimize the distance travelled until annihilation.
Studies in this field are fundamental for the advancement in the development of radiopharmaceuticals, considering their applicability. The results obtained in the studies presented in this work demonstrated satisfactory values about the spatial resolution parameters for the small animal PET scanners used. Compared to international standards, such as NEMA NU 04-2008, which regulates the performance of PET systems, the equipment used can produce high-quality images and is suitable for preclinical investigations based on molecular imaging.

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