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REVIEW

^{68}Ga-Labeled Radiopharmaceuticals for Positron Emission Tomography

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Abstract ^{68}Ga is a promising emerging radionuclide for positron emission tomography (PET). It is produced using a ^{68}Ge/^{68}Ga-generator, and thus, would enable the cyclotron-independent distribution of PET. However, new ^{68}Ga-labeled radiopharmaceuticals that can replace ^{18}F-labeled agents like [^{18}F]fluorodeoxyglucose (FDG) are needed. Most of the ^{68}Ga-labeled derivatives currently used are peptide agents, but the developments of other agents, such as amino acid derivatives, nitroimidazole derivatives, and glycosylated human serum albumin, are being actively pursued in many laboratories. Thus, appearance of new ^{68}Ga-labeled radiopharmaceuticals with high impact are expected in the near future. Here, we present an overview of ^{68}Ga-labeled agents in terms of their clinical significances and relevances to the management of certain tumors, and pertinent pre-clinical developments.

Keywords Gallium-68 · PET · Peptide · DOTA · NOTA · BAPEN · MSA · Ga-68

Introduction

The introduction of ^{68}Ga positron emission tomography (PET) to clinical practice represents a developmental milestone in the functional and metabolic imaging fields, and was facilitated by the cyclotron-independent availability of ^{68}Ga, enabled by the use of the ^{68}Ge/^{68}Ga radionuclide generator system [1, 2]. ^{68}Ga is an excellent positron emitter. It has the characteristics of low photon emission (1,077 keV, 3.22%) and 89% positron branching [3]. Recent studies have shown that some ^{68}Ga-labeled peptides exhibited distinctly better images than their ^{111}In-labeled analogues [4–6] and than ^{18}F-based radiotracers [7]. Unlike other PET radioisotopes, like ^{18}F or ^{11}C, ionic Ga^{3+} cannot be bound covalently to targeting vectors but must be conjugated to a target vector using a bifunctional chelating agent (BCA). Nevertheless, the labeling can be done just prior to diagnostic examinations, rapidly with minimum loss of radioactivity. The only stable chemical form of Ga in solution at physiological conditions is Ga^{3+}, and this ion can form stable complexes with chelators that are either free or conjugated with macromolecules or small organic molecules [8].

There are two requirements for using gallium complexes as radiopharmaceuticals: (1) they should be resistant to hydrolysis (the formation of complexes with OH^-) and (2) they should be more stable than the Ga(III)–transferrin complex, and thus, the labeled gallium complex must be stabile in the presence of transferrin—a plasma protein. The large formation constant of Ga(III)–transferrin (log K= 20.3) [9] and the high plasma concentration of this protein (0.25 g/100 ml) favor the thermodynamic exchange of Ga (III) complexes with transferrin in vivo, and thus, the majority of radioactive gallium complexes used as radiopharmaceuticals have high thermodynamic and kinetic stabilities.

Various ^{68}Ga-labeled radiopharmaceuticals have been developed by conjugating BCAs to peptides, proteins, or

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small biological molecules *via* active esters, isothiocyanates, maleimides, hydrazides, or haloamides. ^{68}Ga-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid–Tyr3-octreotide (DOTA-TOC), ^{68}Ga-DOTA-1-Nal-octreotide (DOTA-NOC), ^{68}Ga-DOTA-bombesin, ^{68}Ga-1,4,7-triazacyclononanetriacetic acid (NOTA)-RGD, ^{68}Ga-DOTA-albumin, and ^{68}Ga-DOTA-human epidermal growth factor (hEGF) are examples of such agents (Fig. 1) [8, 10–15]. Similarly, some agents, such as ^{68}Ga–[(4,6-MeO_2sal)$_2$-BAPEN]$^+$ and ^{68}Ga-N_2S_2, are chelates of radioactive gallium and used for myocardial imaging [16–18].

Acyclic BCAs, such as ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), desferrioxamine (DFO), N,N'-di(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED), and their derivatives, have been used for labeling macromolecules with ^{111}In, $^{67/68}$Ga, or ^{90}Y for tumor imaging and therapy [19–22]. However, most of these complexes have low in vivo and in vitro stabilities due to their tendency to undergo acid- or cation-promoted dissociation [23, 24]. These limitations are overcome by using macrocyclic BCAs, such as NOTA, DOTA, or 1,4,8,11-tetraazacyclotetradecanetetraacetic acid (TETA), which can form highly stable complexes with these radiometals (Fig. 2) [23, 25].

In this review, we present overviews of ^{68}Ga-labeled agents in terms of their present clinical significances and their relevances to the management of certain tumors, and we include details of recent pre-clinical developments.

^{68}Ga-Peptides

During the last decade, the developments of easy and economical production routes for radiolabeled peptides with rapid clearance and tissue penetration and low antigenicity, and the availabilities of simplified purification methods promoted their developments for diagnostic applications. Furthermore, the use of BCAs enabled peptides to be easily labeled with therapeutic radionuclides (^{90}Y, ^{177}Lu).

Most of the early efforts made to label peptides targeted somatostatin and its derivatives. Somatostatin is a regulatory peptide and its action is mediated by membrane-bound receptors (SSTRs) that are present in normal human tissues, such as, in thyroid, brain, the gastrointestinal tract (GIT), pancreas, spleen, and kidneys [26], and they are also highly expressed in many different types of human tumors, notably neuroendocrine tumors (NET) [27], which in

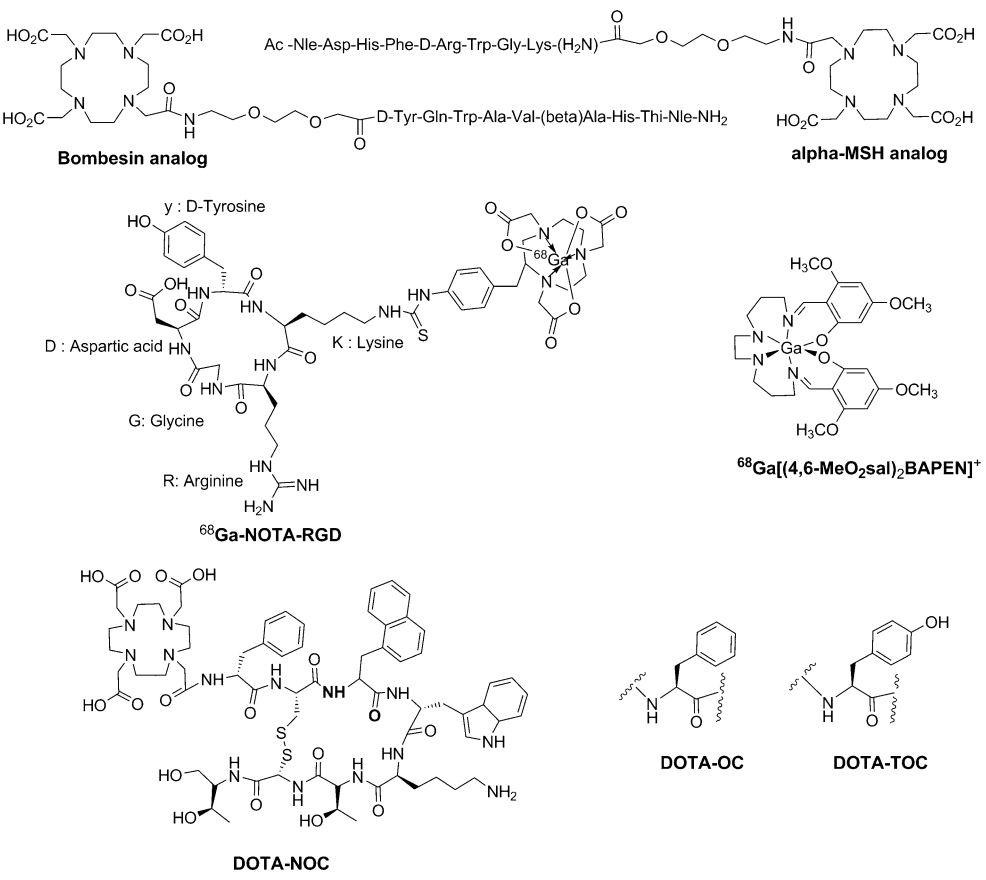

Fig. 1 Chemical structures of ^{68}Ga-labeled radiopharmaceuticals

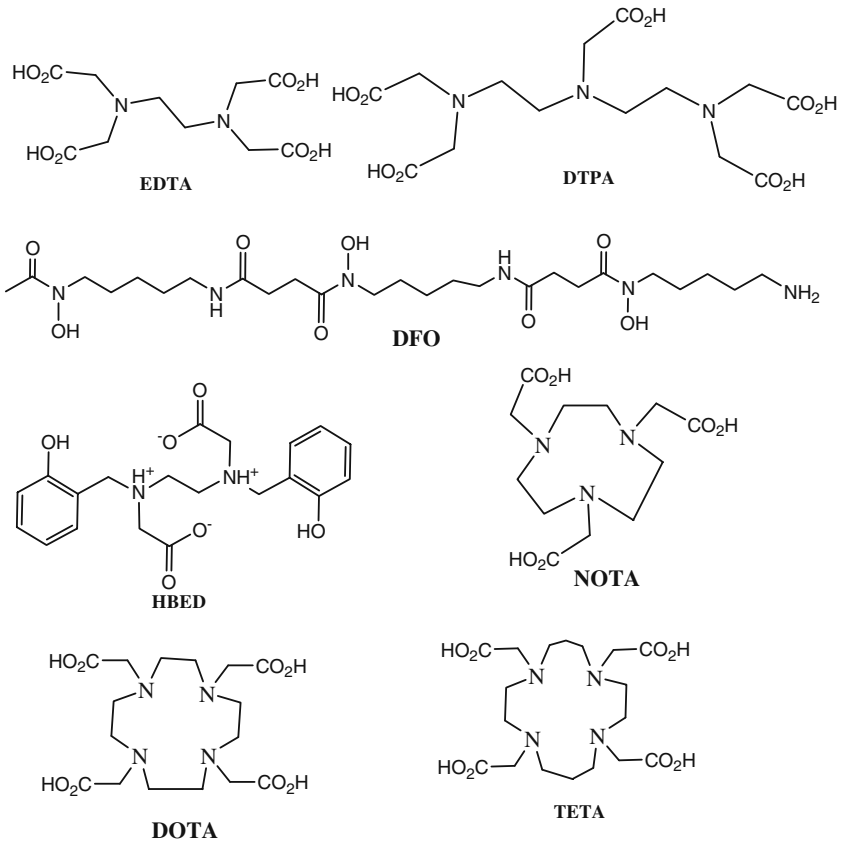

Fig. 2 Some open chain and macrocyclic BCAs used for ^{68}Ga-radiopharmaceutical synthesis

clinical practice are usually carcinoid tumors and pheochromocytomas. SSTRs are also expressed, to variable extents, in renal cell carcinoma, small cell lung cancer, breast cancer, prostate cancer, and in malignant lymphoma [4]. There are five SSTR subtypes, but subtype 2 (SSTR2), subtype 5 (SSTR5), and to a lesser extent, subtype 3 (SSTR3) have higher affinities than SSTR1 and 4, and thus, commercially available synthetic somatostatin analogues target these three high-affinity receptors [28]. These analogues are required because somatostatin is rapidly degraded by enzymes in vivo, as reflected by its short biological half-life, and thus, agents with high affinity for SSTR have been developed, which are resistant to enzyme degradation.

Somatostatin analogues, such as, DOTA-TOC show better images than ^{111}In-DTPA-octreotide, the most commonly used somatostatin analogue [29]. The phenylalanine residue at position 3 was replaced by tyrosine in DOTA-TOC, which makes the compound more hydrophilic, increases affinity for SSTR2, and increases uptake by SSTR2-positive tumors [30]. Other peptides have also been linked to DOTA, such as, DOTA-octreotate, which has high affinity for SSTR2 [28], and DOTA-lanreotide, which has high affinity for SSTR5. DOTA-NOC is the newest addition to these compounds, and has high affinity for SSTR2, SSTR3, and SSTR5. Furthermore, these DOTA-peptide products show high radiochemical purity, rapid renal clearance, and high accumulation in tumors, and overall represent remarkable advances over standard peptides [31].

In parallel with the development of the clinical applications of ^{68}Ga-labeled compounds, in vitro and animal testing of various chelators and compounds is on-going. Antunes et al. [4] demonstrated that gallium ^{67}Ga- and ^{68}Ga-DOTA-octapeptides have distinctly better pre-clinical pharmacological performances than ^{111}In-labeled peptides, especially on SSTR2-expressing cells and in animal models. In particular, ^{68}Ga-DFO-octreotide injected into rats bearing SSTR-positive pancreatic tumors demonstrated selective binding to tumor sites with a tumor to background ratio (T/B) of 5 [32]. Subsequently, several DOTA-SST analogues were evaluated in vivo, and ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-NOC were found to be the most promising [33–36].

We previously found that the PET imaging agent, ^{68}Ga-NOTA-RGD, can be used to visualize angiogenesis in ischemic tissue, and $\alpha_v\beta_3$ integrin expression was found to play an important role [13]. Because angiogenesis is known to occur at ischemic lesions during cancer development, we used two animal biodistribution models, a hind limb ischemia and a SNU-C4 (a human colon cancer cell line) xenograft model. Significantly, higher tracer uptakes were observed in ischemic compared with nonischemic muscle tissues. Small-animal PET of mice bearing SNU-C4 xenografts injected with this tracer at 1 and 2 h post-

injection with or without cold c(RGDyK) showed specific uptake of tracer by tumors (Fig. 3). Furthermore, in a subsequent biodistribution study, tumor uptake of ^{68}Ga-NOTA-RGD was 5.2±1.0% ID/g, and its tumor-to-blood ratio was 10.4±4.8.

^{68}Ga has also been successfully used to label melanocortin peptides, which have many physiologic functions; their receptors are expressed in several cell types, such as, cutaneous melanocytes, keratinocytes, fibroblasts, endothelial cells, antigen-presenting cells, and leukocytes. Melanoma is one of the tumors that can be successfully imaged with radiolabeled MSH, because melanoma overexpresses melanocortin receptor. In particular, ^{68}Ga-DOTA-rhenium-cyclized alphamelanocyte-stimulating hormone (alpha-MSH) analogue [DOTA-ReCCMSH (Arg11)] is a promising agent for the early detection of melanoma in mice [37]. Likewise, ^{68}Ga-DOTA-NAPamide, a short linear alpha-MSH analogue, has been reported to be superior to ^{111}In-DOTA-MSH for the targeting of melanocortin type 1 receptor in murine models of primary and metastatic melanoma [38]. However, receptor density in human melanoma is much lower than in murine tumor models, and thus, more work is needed to improve receptor affinity in man.

Promising pre-clinical studies using the DOTA-analogues of several other peptides, including substance P [39], neurotensin [40], and cholecystokinin (CCK) [41], have also been conducted.

DOTA-conjugated bombesin analogues labeled with ^{68}Ga have been demonstrated to be promising imaging agents and to be useful for the targeted radionuclide treatment of bombesin receptor-positive tumors. These receptors have been reported to be overexpressed in invasive primary prostate carcinoma, associated lymph nodes, breast cancer and gastrointestinal stromal tumor [42, 43].

In terms of the assessment of infection and inflammation, ^{68}Ga-DOTA-VAP-P1, a peptide inhibitor of vascular

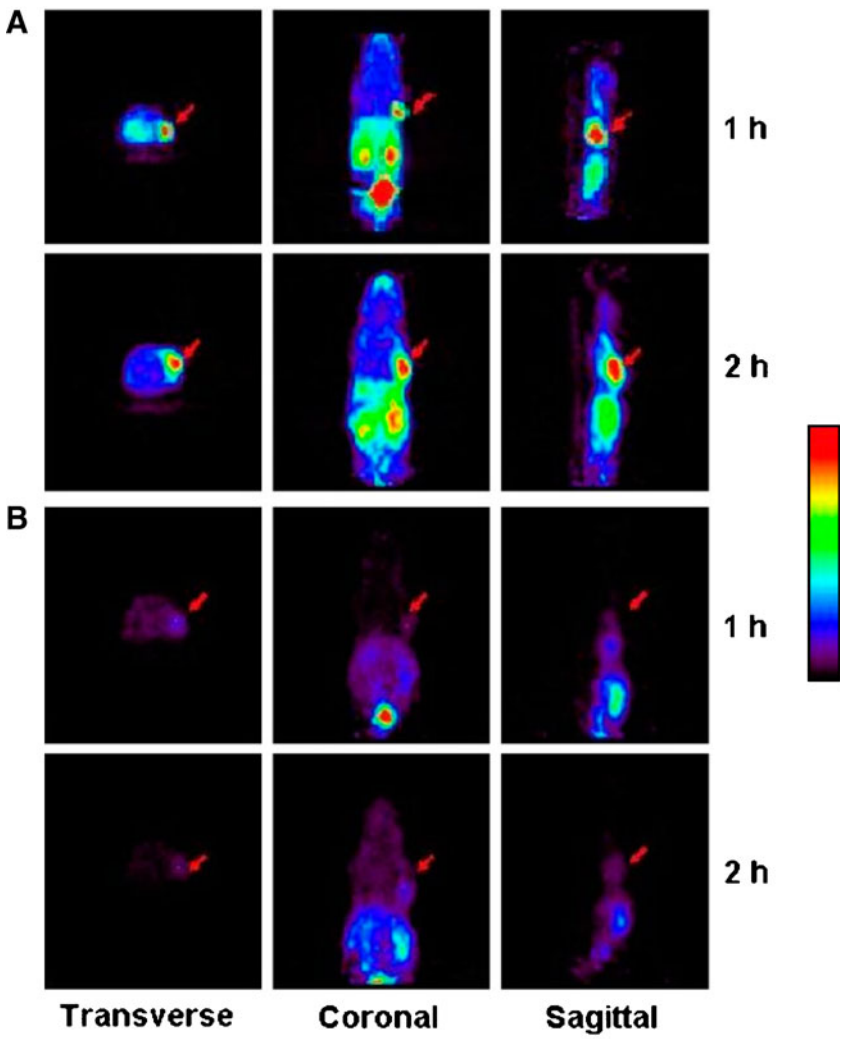

Fig. 3 Small-animal PET of ^{68}Ga-NOTA-RGD in mice bearing SNU-C4 xenografts at 1 and 2 h after injection without or with cold c(RGDyK) (**a** and **b**, respectively). *Arrows* indicate tumor positions. Reprinted by permission of the Society of Nuclear Medicine from: Jeong JM, et al. (2008) Preparation of a promising angiogenesis PET imaging agent: ^{68}Ga-labeled c(RGDyK)-isothiocyanatobenzyl-1,4,7-triazacyclononane-1,4,7-triacetic acid and feasibility studies in mice. J Nucl Med 49:830–836

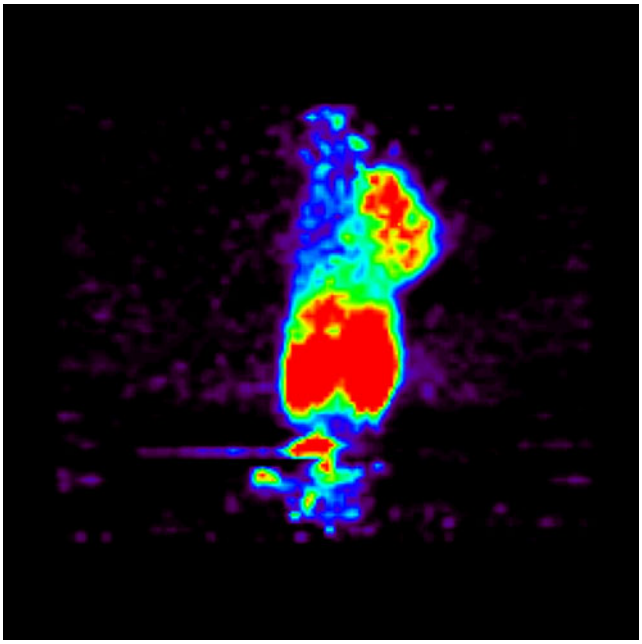

Fig. 4 Micro-PET image of ^{68}Ga-NOTA-aminoalanine in mouse colon cancer (CT-26) showing clear uptake by the cancer lesion located at the right shoulder

adhesion protein 1/semicarbazine sensitive amine oxidase (VAP-1/SSAO), is a promising agent for the assessment of inflammatory reactions in healing bones [44]. In addition, studies have suggested that ^{68}Ga PET imaging might be useful in experimental osteomyelitis caused by *Staphylococcus aureus* [45].

Non-peptide Agents Labeled with ^{68}Ga

Most non-peptide agents labeled with ^{68}Ga are complexes that are not conjugated to specific ligands. However, some non-peptide agents are conjugated with ligands via BCA. For example, three different forms of antisense oligonucleotides targeting activated human K-ras oncogene labeled with ^{68}Ga have been shown to provide a convenient means for in vivo imaging and quantification of oligonucleotide biokinetics in living animals [46].

Various ^{68}Ga-labeled agents have been developed using NOTA as the basic chelating agent, because of the high stability of the chelate formed; for example, the log *K* value of gallium-NOTA [47, 48] has been reported to be 30.98, which is much higher than that of gallium-DOTA (21.33) [49]. DOTA has eight binding sites available for complexing with metals, but NOTA has only six, and thus, no free binding site remains after complexing NOTA with gallium, which requires all six binding sites. However, it have been shown that amide oxygen or nitrogen can bind with gallium [50], and as a result, various amino acid derivatives conjugated with NOTA have been developed for imaging cancers (Fig. 4) [51]. In addition, another amino acid derivatives conjugated with DO2A and DO3A have also been reported [52].

An in vitro cellular uptake and biodistribution study in breast cancer-bearing rats, using ^{68}Ga metronidazole and ethylenedicysteine (EC) as a chelator, demonstrated the feasibility of this tracer for the assessment of tumor hypoxia [53]. Conjugates of nitroimidazole and NOTA derivatives have also been developed [54]. The molecular imaging of the functional transport activity of multidrug resistance (MDR1) P-glycoprotein (Pgp) using ^{67}Ga/^{68}Ga-(3-ethoxy-ENBDMPI) may also enable non-invasive monitoring of the blood-brain barrier, chemotherapeutic regiments, and MDR1 gene treatment protocols in vivo [55]. In addition, ^{68}Ga-mannosylated human serum albumin (MSA) has been reported to be a promising agent for sentinel node detection (Fig. 5) [56]. MSA targets the mannose receptor of macrophages present in lymph nodes after subcutaneous injection. Furthermore, this heat labile agent can be labeled straightforwardly at room temperature, because NOTA is used as the BCA.

We have formulated ^{68}Ga-BAPEN [^{68}Ga-Tris(4,6-dimethoxysalicylaldimine)-N,N′-bis(3-aminopropyl)-N,N′-ethylenediamine] as a kit for myocardial PET imaging and biodistribution studies [57]. This kit allows ^{68}Ga-labeled agents to be easily prepared.

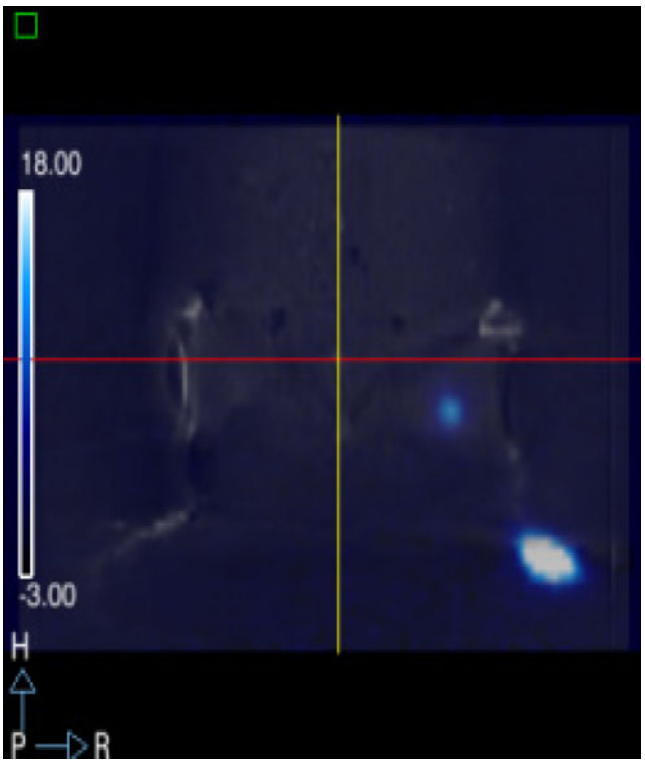

Fig. 5 A micro-PET-CT image of ^{68}Ga-MSA after injection into a mouse footpad. Radioactivity was present at the inguinal lymph node

Clinical Applications of ^{68}Ga Peptides

Hofmann et al. [58] presented the first impressive ^{68}Ga-DOTA-TOC images of neuroendocrine tumors, compared with ^{111}In-octeriotide scintigraphy, in eight patients with carcinoid tumors. ^{68}Ga-DOTA-TOC identified all lesions, whereas ^{111}In-octreotide identified only 85%. Furthermore, quantitative analysis of these lesions showed higher tumor to non-tumor contrast ratios and low kidney accumulation for ^{68}Ga-DOTA-TOC PET imaging [4]. The pharmacokinetics of ^{68}Ga-DOTA-TOC and ^{18}F-fluorodeoxyglucose (FDG) in metastatic NET patients demonstrated uptakes by 57 of 63 lesions and by 43 of 63 lesions, respectively [59]. Another comparison between these two radiopharmaceuticals in a small group of patients (n=4) with metastatic NET showed that ^{68}Ga-DOTA-TOC was better at depicting smaller lesions with low tracer uptake, especially when tumors bore somatostatin receptors at low densities [60].

A comparative study between ^{68}Ga-DOTA-TOC PET and ^{99m}Tc-HYNIC-octreotide was performed by Gabriel et al. [6] in 88 patients with as neuroendocrine tumor. ^{68}Ga-DOTA-TOC PET showed a sensitivity of 97%, a specificity of 92%, and an overall accuracy of 96%, which were significantly higher than those of single photon emission computed tomography (SPECT) using ^{99m}Tc-labeled tracer (Fig. 3).

A viability study of ^{68}Ga-DOTA-TATE for pheochromocytoma PET imaging was conducted in patients who had previously undergone surgical resection of malignant pheochromocytomas. ^{68}Ga-DOTA-TATE was positive in all five patients studied, whereas only three patients were positive by ^{123}I-metaiodobenzylguanidine (MIBG) scan [61, 62]. Due to the difficulties of diagnosing meningioma by computed tomography (CT) and magnetic resonance imaging (MRI), other methods of characterizing these intracranial lesions are being sought. Imaging meningiomas with ^{68}Ga-DOTA-TOC can provide useful clinical indications, because SSTR2 is highly expressed in most meningiomas. The first use of ^{68}Ga-DOTA-TOC in meningiomas in three patients was reported by Milker-Zabel and coworkers; the same group evaluated its kinetic parameters in meningioma [63].

Conclusion

The use of a ^{68}Ge/^{68}Ga-generator that can consistently supply ^{68}Ga, which has a half-life of 271 days, provides a convenient way of producing ^{68}Ga for more than a year. Furthermore, the cost of the generator is comparable with those of other radionuclides used for PET. In addition, diagnostic approaches based on ^{68}Ga-labeled agents have the additional advantage of facilitating treatment. For example, when a diagnostic scan is positive, these agents can be labeled with therapeutic radionuclides, such as, yttrium-90, lutetium-177, or rhenium-188. Ongoing experimental work suggests the feasibility of ^{68}Ga labeling with different biomolecules for the imaging of different tumors, myocardium, and infection. The commercial availability of ^{68}Ge/^{68}Ga-generator will undoubtedly encourage further preclinical research and clinical studies, and may open the door to new possibilities for PET.

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