Clinical Applications of Gallium-68

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Abstract

Gallium-68 is a positron-emitting radioisotope that is produced from a $^{68}Ge/^{68}Ga$ generator. As such it is conveniently used, decoupling radiopharmacies from the need for a cyclotron on site. Gallium-68-labeled peptides have been recognized as a new class of radiopharmaceuticals showing fast target localization and blood clearance. ^{68}Ga-DOTATOC, ^{8}Ga-DOTATATE, ^{68}Ga-DOTANOC, are the most prominent radiopharmaceuticals currently in use for imaging and differentiating lesions of various somatostatin receptor subtypes, overexpressed in many neuroendocrine tumors. There has been a tremendous increase in the number of clinical studies with ^{68}Ga over the past few years around the world, including within the United States. An estimated ~10,000 scans are being performed yearly in Europe at about 100 centers utilizing ^{68}Ga-labeled somatostatin analogs within clinical trials. Two academic sites within the US have also begun to undertake human studies. This review will focus on the clinical experience of selected, well-established and recently applied ^{68}Ga-labeled imaging agents used in nuclear medicine.

Keywords

PET; radiopeptides; somatostatin receptor; neuroendocrine tumor; clinical trials

1. Introduction

Gallium-68 is one of the earliest of the positron-emitting radionuclides to have been applied to clinical medicine, dating back to the early 1960s (Anger and Gottschalk, 1963), long before [^{18}F]-fluorodeoxyglucose (FDG) (Ido T, 1978). Because of concurrent advances in positron emission tomography (PET) and radiosynthetic accessibility of ^{68}Ga-labeled agents using standard methods of the day, Gottschalk et al. began to apply ^{68}Ga clinically, initially to central nervous system processes (Anger and Gottschalk, 1963; Schaer et al., 1966). By the late 1970s, however, ^{68}Ga-based PET imaging was sidetracked in favor of new agents coming online that utilized ^{99m}Tc for single photon emission computed tomography (SPECT) and ^{18}F for PET. One reason for this temporary delay in the development of ^{68}Ga-PET could have been because early ^{68}Ga-generators provided ^{68}Ga in complex with ethylenediaminetetraacetic acid (EDTA) such that destruction of the complex was necessary for preparation of the radiopharmaceuticals. That made radiolabeling tedious, time-consuming, and accomplished with overall poor yield. At that time ^{68}Ga-generators utilized $^{68}Ga(III)$ in hydrated form until next-generation $^{68}Ge/^{68}Ga$ generators became

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commercially available, which enabled convenient elution of cationic ^{68}Ga with dilute acid (0.1 M HCl). The development of these generators was recently reviewed in detail by Maecke et al. (Fani et al., 2008). Asti et al. (Asti et al., 2008) described an effective purification of the ^{68}Ge/^{68}Ga eluate [a crucial labeling step (Zhernosekov et al., 2007)], which was applied to the production of ^{68}Ga-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid–D-Phe^1-Tyr^3-octreotide, (^{68}Ga-DOTATOC), the most widely used ^{68}Ga-based PET radiopharmaceutical (Prata, 2012). This purification technique has also been used to optimize ^{68}Ga-labeling methods for DOTA-derivatized peptides and is suitable for clinical use. Decristoforo et al. described a fully automated synthesis for ^{68}Ga-labeled peptides with high, reproducible yields (Decristoforo et al., 2007). Currently several ^{68}Ge/^{68}Ga generator systems are commercially available from distributors in Russia, Europe, United States and other countries. With the availability and reliability of commercial generator systems and effective and convenient purification steps, ^{68}Ga has the potential to become as useful for PET as ^{99m}Tc has proved for SPECT imaging. There are many examples of the use of ^{68}Ga-labeled radiotracers, including many that currently rely on ^{99m}Tc clinically, such as for myocardial perfusion and function, blood flow, renal function and liver function (Baum and Rosch, 2011; Fani et al., 2008; Roesch and Riss, 2010; Rosch and Baum, 2011; Wadas et al., 2010). ^{68}Ga-based radiopeptides have been tested pre-clinically for the targeting of somatostatin (Froidevaux et al., 1999), bombesin (Schuhmacher et al., 2005b) and melanocortin 1 receptors (Froidevaux et al., 2004). Because their pharmacokinetics are well-matched to the short physical half-life of the isotope, ^{68}Ga-based peptides are increasingly recognized as a new class of radiopharmaceuticals, showing very fast blood clearance and fast target localization. The short physical half-life of ^{68}Ga ($t_{1/2}$ = 68 min) enables improved dosimetry and repeat imaging, making these agents ideal for clinical use. However, although of demonstrated utility in pre-clinical and limited clinical studies, no ^{68}Ga-labeled pharmaceutical has been approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) and no FDA- or EMA-approved ^{68}Ge/^{68}Ga generator is available as of this writing (Ambrosini et al., 2011a). There are two sites in the US that are currently implementing ^{68}Ga-DOTATOC, one at Vanderbilt University, under an Investigational New Drug application, where a Phase I trial has recently been completed, and the other at the University of Iowa, under approval by the local Radioactive Drug Research Committee (Graham and Menda, 2011).

2. ^{68}Ga-Labeled PET Radiopharmaceuticals

There are many practical and economic advantages to ^{68}Ga. Gallium-68 is a generator-eluted, short-lived radionuclide decaying 89% through positron emission (maximum energy of 1.92 MeV, mean 0.89 MeV). The long physical $t_{1/2}$ of the parent radionuclide (270.8 d) allows the use of the generator for up to one year, obviating the need for a cyclotron on site, providing cost-effectiveness as well as convenience. However, energy of the emitted positron from ^{68}Ga is higher than that of ^{18}F (maximum energy = 0.63 MeV, mean = 0.25 MeV), the most widely used PET isotope, which can potentially lead to lower resolution (Sanchez-Crespo et al., 2004). Despite the availability of ^{68}Ga for more than 30 years, recognition of its uses for clinical PET are only now emerging and only now is it being applied to pre-clinical models of human disease (Banerjee et al., 2010). Radiometals for the clinic can be used as the chelated metal itself ["metal essential radiopharmaceutical," following the definition of Jurrison et al. for ^{99m}Tc-based radiopharmaceuticals (Jurisson and Lydon, 1999)], the pharmacokinetics of which rely entirely on the physical and chemical properties of the agent, e.g. ^{68}Ga-EDTA and ^{68}Ga-diethylene triamine pentaacetic acid (^{68}Ga-DTPA). Similarly, "target-specific gallium radiopharmaceuticals" can be defined as a class of radiopharmaceuticals for which the targeting moiety (e.g., antibody, peptide, hormone) has been radiolabeled with ^{68}Ga and can be targeted to a specific, biologically accessible protein such as a receptor. In the case of ^{68}Ga the most prevalent

such compounds to date target the somatostatin receptor (SSTR). Target-specific ^{68}Ga-based agents are mostly generated using a bifunctional chelating approach (BFCA). This approach requires the chelator to bind the metal in complex on one end with high affinity, enabling stability *in vivo*, with a targeting or affinity agent on the other end that assures concentration in the tissue of interest. Several suitable bifunctional chelators have been developed for complexation of ^{68}Ga and have been coupled to biologically active targeting agents. These include agents that contain 1,4,7-triazacyclononane-N,N′,N″-triacetic acid (NOTA), DOTA, DTPA and desferrioxamine B (DFO). Although not used in clinical trials to date, mono- and multimeric phosphinic acid derivatives of NOTA, a new class of NOTA-based chelating agents developed by Notni et al., are receiving considerable attention (Notni et al., 2010; Notni et al., 2012a; Notni et al., 2012b; Simecek et al., 2012a; Simecek et al., 2012b). The novel bifunctional triazacyclononane triphosphinic acid chelator (TRAP) ligands have many desirable properties required for a chelating agent for ^{68}Ga, including fast and selective complex formation, high complex stability, ability to be conjugated and convenient synthesis (Notni et al., 2010; Notni et al., 2012a; Notni et al., 2012b; Simecek et al., 2012a; Simecek et al., 2012b). The TRAP-peptide could be radiolabeled with ^{68}Ga excellent reproducibility and > 95% radiochemical yield in specific activities of 10 to 20 times higher than NOTA and DOTA peptides, respectively (Notni et al., 2012b).

Targeting agents are coupled *via* the BFCA leveraging standard intermediates that enable covalent attachment including active esters, isothiocyanates, maleimides, hydrazides, or haloamides (Liu and Edwards, 1999). DOTATOC (Hofmann et al., 2001; Kowalski et al., 2003), DOTA–D-Phe^1-Tyr^3-Thr^8-octreotate (^{68}Ga-DOTATATE) (Antunes et al., 2007; Reubi et al., 2000a), ^{68}Ga-DOTA-Phe^1-Nal^3-octreotide (DOTANOC) (Wild et al., 2005; Wild et al., 2003), ^{68}Ga-DOTA-bombesin (Schuhmacher et al., 2005b), ^{68}Ga-NOTA-RGD (Jeong, 2008), ^{68}Ga-DOTA-albumin (Hoffend et al., 2005; Mier et al., 2005), ^{68}Ga-DOTA-human epidermal growth factor (hEGF) (Baum et al., 2010), ^{68}Ga-phosphonate triazacyclononane [NOPO])–RGDfK and [^{68}Ga]-NOPO–NOC(Simecek et al., 2012b), are examples of such agents. Recently, a smart strategy employing copper-free click chemistry has been reported for site-specific coupling of bioactive molecules with chelating agents for radiolabeling with ^{68}Ga (Baumhover et al., 2011; Schultz et al., 2010). Fast and efficient coupling has been possible using an azide-modified bioactive function and a reactive cyclooctyne group attached to a chelating agent such as DOTA and NOTA.

With that background in mind, this review will focus strictly on clinical application of ^{68}Ga-based radiopharmaceuticals. Excellent recent and general reviews on the development of ^{68}Ga-based radiopharmaceuticals and their uses can be found elsewhere (Al-Nahhas et al., 2007; Ambrosini et al., 2011b; Bartholoma et al., 2010; Baum and Kulkarni, 2012; Breeman et al., 2011b; Graham and Menda, 2011; Maecke et al., 2005; Prata, 2012; Rice et al., 2011).

2.1. ^{68}Ga-essential Compounds in Clinical Studies

Gallium-67-citrate was first used in tumor imaging nearly 40 years ago (Edwards and Hayes, 1969). Today, ^{67}Ga-citrate/transferrin remains a widely used radiopharmaceutical for the clinical diagnosis of certain types of neoplasms, such as Hodgkin's disease, lung cancer, non-Hodgkin's lymphoma, malignant melanoma, and leukemia. Because of the convenient half-life of ^{68}Ga and the fact that it is generator-produced and therefore more widely available, considerable interest lies in the development of ^{68}Ga-labeled imaging agents. The use of PET allows quantification not possible with ^{67}Ga and gamma scintigraphy. Gallium-68-citrate has been used to quantify pulmonary vascular permeability using PET (Mintun et al., 1987). Gallium-68-citrate is not stable in the blood, and the actual radiopharmaceutical rapidly transitions to ^{68}Ga-transferrin (Gunasekera et al., 1972) *in vivo*. This agent becomes localized to the lungs immediately after intravenous injection. Other

applications of ^{68}Ga include evaluating vascular permeability in lung disease and in lung transplants (Kaplan et al., 1992a; Kaplan et al., 1992b).

Several ligand systems, such as DFO (Koizumi et al., 1987; Koizumi et al., 1988; Pochon et al., 1989; Yokoyama et al., 1982), DTPA [(Wagner and Welch, 1979), (Hnatowich and Schlegel, 1981)] and N,N′-di(2-hydroxybenzyl) ethylene diamine,N,N′-diacetic acid derivative (HBED) (Schuhmacher et al., 1986) have been studied, but proved prohibitively unstable to warrant further investigation. Interestingly, Ga(III) is known to localize to sites of infection and inflammation and has been used for ^{67}Ga-based scintigraphy (El-Maghraby et al., 2006). Many of those pre-clinical and clinical studies performed during the 1980s were carefully documented in two excellent reviews (Green and Welch, 1989; Hnatowich, 1977). Figure 1 shows selected ^{68}Ga-labeled chelating agents that have been used in clinical trials as gallium essential imaging agents.

The use of ^{68}Ga-citrate presents many clinical advantages over ^{67}Ga ($t_{1/2}$, 3.26 d). As suggested above, a common use of ^{67}Ga is in the diagnosis and therapeutic monitoring of bone infections (Hoffer, 1980). Gallium-68 has a much shorter $t_{1/2}$ than 67Ga, allowing patients to be receive higher doses for better counting statistics and enables them to be discharged almost free of radioactivity. Recently a pilot study showed the use of ^{68}Ga-citrate-based PET/CT with 31 patients with suspected bone infection, with the goal of evaluating the sensitivity and specificity of this relatively newly applied PET agent (Nanni et al., 2010). All patients underwent ^{68}Ga-citrate PET/CT (whole-body or segmental) at one hour after administration of radiopharmaceutical. The data were validated by comparing the PET/CT results with biopsy, serum inflammatory markers (for the assessment of response to therapy), white blood cell scintigraphy, clinical follow-up, and conventional diagnostic imaging [magnetic resonance imaging (MRI) or computed tomography (CT) in patients without a prosthesis or bone implant, or standard radiography in those who did]. Clinical follow-up consisted of evaluation of the patients approximately every six months for at least one year. The authors reported a sensitivity of 100%, a specificity of 76%, a positive predictive value of 85%, a negative predictive value of 100%, and an overall accuracy of 90%. These findings support a role for ^{68}Ga-citrate in the diagnosis of bone infections (Figure 2).

2.2. Target-specific ^{68}Ga-based Radiopharmaceuticals in Clinical Studies

There are now many target-specific ^{68}Ga-based radiopharmaceuticals undergoing clinical trials (Al-Nahhas et al., 2007; Breeman et al., 2011a). Peptide receptors with over-expression on a variety of human tumors are promising biological targets in nuclear oncology. Targeting SSTR has been particularly vigorously pursued for proof-of-principle for the use of ^{68}Ga-PET agents in the clinic. Somatostatin is a regulatory peptide, widely distributed in the human body, the action of which is mediated by membrane-bound SSTR present in normal human tissues, such as the thyroid, brain, gastrointestinal tract, pancreas, spleen and kidney (Patel, 1999; Reubi et al., 1997; van der Lely et al., 2003). SSTR are also abundant in a variety of human tumors, particularly neuroendocrine tumors (NET) as well as on renal cell carcinoma, small cell lung, breast and prostate cancer, and malignant lymphoma (Reubi et al., 2001). Selected, well-studied ^{68}Ga-labeled peptide-based PET imaging agents as well as recently translated ^{68}Ga-labeled receptor targeting ligands for a variety of clinical applications are discussed below.

2.2.1. SSTR-based ^{68}Ga-PET Imaging Agents—All SSTR are linked to guanine nucleotide binding proteins (G proteins) and lead to inhibition of adenylyl cyclase (AC) following hormone binding (Schonbrunn, 1999). There are five human SSTR subtypes (Hoyer et al., 1995; Reubi, 2003). All are expressed on tumors to some extent, with SSTR2

is by far the most abundant, whereas SSTR4 is rarely expressed (Krenning et al., 1993). A high density of somatostatin receptors is found in neuroendocrine tumors, such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer, and small cell lung carcinoma (Reubi, 1997). Tumors of the nervous system including meningioma, neuroblastoma, and medulloblastoma also often express a high density of SSTR. Tumors not known to originate from endocrine or neural cells may also express SSTR, such as lymphoma, breast cancer, renal cell cancer, hepatocellular carcinoma, prostate cancer, sarcoma, and gastric cancer. Certain benign lesions may also express SSTR. For instance, active granulomas in sarcoidosis express SSTR on epithelioid cells, and inflamed joints in active rheumatoid arthritis express express them as well, preferentially within proliferating synovial vessels (Howland K., 2008; Reubi, 2004). The expression of SSTR is therefore not specific for malignancy. Somatostatin inhibits secretion of hormones and so can be used in the treatment of diseases caused by their over-production. Somatostatin itself has a short biological half-life, being rapidly degraded by enzymes. Non-biodegradable analogs have been developed to mimic the effects of somatostatin.

The most important SSTR-peptide conjugated imaging agents used clinically are based on the octapeptide octreotide and its derivatives (Figure 3). The radioiodinated somatostatin analog that was first used for imaging in patients, ^{123}I-Tyr^3-octreotide (Krenning et al., 1989) had several drawbacks, necessitating development of an ^{111}In-labeled somatostatin analog, ^{111}In-DTPA-octreotide. ^{111}In- DTPA-octreotide (OctreoScan; Mallinckrodt Inc.), is the first registered commercially available radiometal-based peptide, and is the most commonly used agent for the diagnosis and staging of SSTR–positive tumors (Krenning et al., 1993; Kwekkeboom et al., 2010). Recently, ^{111}In-DTPA-octreotide imaging was shown to be an independent prognostic factor for survival in well-differentiated malignant endocrine tumors (Asnacios et al., 2008). Normal scintigraphic features of ^{111}In- DTPA-octreotide include visualization of the thyroid, spleen, liver, and kidneys. Some patients also demonstrate radiopharmaceutical uptake in the pituitary. There is generally visualization of the urinary bladder and uptake of radioactivity within the gastrointestinal tract to a certain degree. The visualization of the pituitary, thyroid, and spleen is due to SSTR-mediated uptake. Uptake in the kidneys is primarily from reabsorption of the radiolabeled peptide in the renal tubular cells after glomerular filtration. Although ^{111}In-SSTR scintigraphy is effective for whole-body imaging, there are some limitations in organs with higher physiologic uptake, such as liver. Another limitation is related to the difficulty in detection of smaller lesions due to the inherent limitations in the spatial resolution of SPECT. Many ^{99m}Tc-labeled SSTR analogs have also been investigated, for example ^{99m}Tc-depreotide (6-hydrazinonicotinic), ^{99m}Tc-vapreotide, ^{99m}Tc-P829, and ^{99m}Tc-EDDA-HYNIC-TOC. Among these only ^{99m}Tc-EDDA-HYNIC-TOC (or -TATE) has proved superior to ^{111}In-pentetreotide for the detection of SSTR-positive tumors and metastases (Decristoforo et al., 2000; Lebtahi et al., 2002; Maina et al., 2002; Storch et al., 2005). FDG PET scanning is another widely accepted molecular imaging approach in clinical oncology. Although FDG PET shows high spatial resolution for many malignancies, it is not indicated for NET because of its poor sensitivity to detect tumors with low metabolic activity and slow growth (Adams et al., 1998b). Due to the anticipated increased spatial resolution and easier quantification, an agent for PET imaging of SSTR has been aggressively sought. For these reasons DOTATOC was radiolabeled with ^{68}Ga. ^{68}Ga-DOTA-labeled somatostatin analogs ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC, are currently available in ^{68}Ga-based clinical trials for NET imaging and have become the new standard for SSTR using PET (Kwekkeboom et al., 2010). This is mainly due to their high affinity to SSTR 2, 3 and 5, respectively (Figure 3) (Reubi et al., 2000a) and because ^{68}Ga is produced in a generator rather than by a cyclotron. Because it is generator-produced, relatively straightforward labeling can be performed daily. Another advantage of ^{68}Ga-DOTATOC

or ^{68}Ga-DOTATATE would be in imaging tumors destined for treatment as their ^{90}Y- or ^{177}Lu-labeled counterparts may serve in peptide receptor radionuclide therapy (PRRT). The reported affinity of ^{68}Ga-DOTATATE for binding SSTR2 (0.2 ± 0.04 nM) is approximately 10-fold higher than that of ^{68}Ga-DOTATOC (2.5 ± 0.5 nM) (Reubi et al., 2000a). ^{68}Ga-DOTATOC binds to SSTR5 with intermediate affinity (73 ± 21 nM) and ^{68}Ga-DOTANOC has high affinity to SSTR2 (1.9 ± 0.4 nM), SSTR3 (40 ± 5.8 nM), and SSTR5 (7.2 ± 1.6 nM) (Prasad et al., 2010; Wild et al., 2008; Wild et al., 2005; Wild et al., 2010). Binding affinities of ^{111}In-DTPA-octreotide are significantly lower for SSTR2 (22 ± 3.6 nM), SSTR3 (183 ± 13 nM) and SSTR5 (237 ± 52 nM), respectively (Reubi et al., 2000b). Newer ^{68}Ga-peptide analogs exhibit significantly improved pharmacokinetics and the images obtained with them demonstrate inherently higher resolution compared to ^{111}In-DTPA-octreotide scintigraphy, and are accordingly seeing increased clinical use. A recent report by Gabriel et al. (Gabriel et al., 2007) (*vide infra*), in which 84 patients were studied, demonstrated a sensitivity of 97%, specificity of 92% and accuracy of 96% for ^{68}Ga-DOTATOC in the detection of NET metastatic to lung, bone, liver and brain, which was vastly superior compared to the corresponding SPECT agents (^{99m}Tc-labeled hydrazinonicotinyl-Tyr^3-octreotide (^{99m}Tc-HYNIC-TOC) and ^{111}In-DOTA-TOC). Selected clinical results of ^{68}Ga-SSTR targeting peptides are described below.

The first published clinical investigation on SSTR targeting using ^{68}Ga-DOTATOC PET appreared in 2001 by Henze et al. (Henze et al., 2001), who studied patients with meningiomas. It was thought that since meningiomas expressed a high degree of SSTR2, PET imaging with ^{68}Ga-DOTATOC might help to differentiate them from neurofibromas and metastases (Henze et al., 2001), which have significantly different clinical management and outcomes. They imaged three patients with ^{68}Ga-DOTATOC PET, who had a total of eight meningiomas between them. Dynamic PET images of the brain demonstrated rapid radiopharmaceutical uptake within these tumors. Quantitative analysis showed that the standard uptake value (SUV) increased immediately after injection, and reached a plateau at 60–120 min after injection (mean SUV = 10.6). There was no radiopharmaceutical uptake in adjacent healthy brain parenchyma, and even the smallest lesions (7 – 8 mm) showed high uptake with very high tumor-to-background ratios. This study provided useful information about the extent of tumor spread relative to adjacent osseous structures, especially at the base of the skull. Recently, Henze et al. (Henze et al., 2005) followed up to characterize meningiomas further with dynamic ^{68}Ga-DOTATOC PET to evaluate the utility of obtaining radiotracer kinetic parameters prior to radiotherapy. They performed dynamic PET studies in 21 patients with a total of 28 lesions. They demonstrated significant differences ($P < 0.05$; t test) between meningiomas and reference tissue (nasal mucosa) in the mean SUV (10.5 vs. 1.3), and in the kinetic parameters such as vascular fraction (vB), rate constants k_2, k_3, k_4 (1/min) and receptor binding ($k_1 – k_1/k_2$). These factors resulted in very high tumor-to-background ratios, allowing clear visualization of lesions at the skull base, demonstrating a clinically important application of ^{68}Ga PET imaging.

There have been many patient studies using ^{68}Ga-DOTATOC PET (Hofmann et al., 2001; Kowalski et al., 2003) for detection of SSTR-positive malignancies, including metastatic lesions. Hofmann et al. compared ^{111}In-octreotide scintigraphy with ^{68}Ga-DOTATOC PET in eight patients with histologically proved carcinoid tumors (Hofmann et al., 2001). They studied a total of 40 lesions that were identified either by CT and/or MRI. In total ^{68}Ga-DOTATOC PET identified 100% of these lesions, whereas ^{111}In-octreotide planar and SPECT imaging identified only 85%. Quantitative analysis of the lesions showed that ^{68}Ga-DOTATOC PET imaging resulted in higher tumor-to-non-tumor contrast with lower renal accumulation compared to ^{111}In-octreotide. Kowalski et al. (Kowalski et al., 2003) similarly presented a comparison between ^{68}Ga-DOTATOC PET and ^{111}In-DTPA-octreotide imaging – in four patients who suffered from NET and/or the attendant metastases. ^{68}Ga-DOTATOC

PET appeared superior especially in detecting small tumors or tumors bearing only a low density of SSTRs. Both ^{111}In-DTPA-octreotide SPECT and ^{68}Ga-DOTATOC PET were less sensitive in the detection of liver metastases of NET compared to CT because they demonstrated lower overall uptake than the surrounding liver.

NETs are rare lesions that occur most commonly in the gastrointestinal tract and express amine and peptide receptors, e.g. SSTR and receptors for vasointestinal peptide, bombesin, cholecystokinin, gastrin, and/or substance P. Various radiolabeled somatostatin analogs have recently been used to image NET that express SSTR (Ambrosini et al., 2011a; Reubi, 1997). A recent study addressing the use of ^{68}Ga-DOTATOC PET in NET was reported by Gabriel et al. (Gabriel et al., 2007). They compared ^{68}Ga-DOTATOC PET with ^{99m}Tc-HYNIC-octreotide and ^{111}In-DOTA-TOC scintigraphy and CT in 88 patients with known or suspected NET. Patients were placed into one of three categories: those with an unknown primary tumor, but with clinical or biochemical suspicion of neuroendocrine malignancy (13 patients); those for staging of known tumor (36 patients); and those being followed-up after therapy (35 patients). ^{68}Ga-DOTATOC PET demonstrated significantly better diagnostic efficacy with a sensitivity of 97%, a specificity of 92% and an overall accuracy of 96%. Furthermore, the combined use of PET and CT gave the highest overall accuracy.

Buchmann et al (Buchmann et al., 2007) compared the relative utility of ^{68}Ga-DOTATOC PET and ^{111}In-DTPA-octreotide SPECT in the detection of NET and its manifestations. In that study (25 patients), SUVs of positive lesions on ^{68}Ga-DOTATOC PET ranged from 0.7 to 29.3 (mean SUV) and from 0.9 to 34.4 (maximum SUV) while tumor/normal tissue ratios of ^{111}In-DTPA-octreotide SPECT ranged from 1.8 to 7.3. In imaging lung and skeletal lesions, ^{68}Ga-DOTATOC PET was superior to ^{111}In-DTPA-octreotide SPECT. In regional comparison of liver and brain, ^{68}Ga-DOTATOC PET and [111]In- DTPA-octreotide SPECT were identical. The authors concluded that ^{68}Ga-DOTATOC PET is superior to ^{111}In-DTPA-octreotide SPECT in the detection of NET in the lung and skeleton and similar for the detection of NET in the liver and brain.

Application of ^{68}Ga-DOTANOC is beginning to appear for a variety of SSTR-related diseases. Compared to ^{68}Ga-DOTATOC, which is more specific for SSTR2, ^{68}Ga-DOTANOC possesses a certain degree of selectivity for SSTR2, SSTR3 and SSSTR5 (Antunes et al., 2007) and demonstrates more favorable dosimetry (Pettinato et al., 2008). Radiotracer ^{68}Ga-DOTANOC was developed as a high-affinity somatostatin analog through exchange of an amino acid at position-3 of octreotide, with 3-Nal [3-(1-naphthalenyl)-L-alanine, in DOTANOC] instead of 3-Tyr (in DOTATOC), as shown in Figure 3. The high sensitivity of ^{68}Ga-DOTANOC is illustrated in the detection of small lesions, particularly in liver, within lymph nodes and within bone metastases (Ambrosini et al., 2008; Fanti et al., 2008; Prasad and Baum, 2010).

Involvement of SSTR in the regulation of thyroid cell proliferation has been demonstrated in different carcinoma cell lines (Ain and Taylor, 1994). Whereas the thyrotropin receptor (TSHR) activates AC with a subsequent increase of cyclic adenosine monophosphate (cAMP), SSTR activation inhibits the AC/cAMP pathway (de Jong et al., 1997). It has been shown that there is a close association between SSTR and TSHR expression (Lattuada et al., 2007; Medina et al., 1999). All patients with thyroid autonomy and most patients with active Hashimoto's disease demonstrate increased ^{68}Ga-DOTATOC uptake in the thyroid gland (Lincke et al., 2011; Lincke et al., 2009). A recent study employing a larger number of patients (n = 165) (Lincke et al., 2011) confirmed this group's previously reported finding of increased ^{68}Ga-DOTATOC uptake in normal thyroid (Lincke et al., 2009), with high target-to-background ratios. However, this study did not confirm the previously detected increased ^{68}Ga-DOTATOC uptake of goitrous and/or nodular thyroid as compared to

normal thyroid (Lincke et al., 2011). Furthermore, normal thyroid showed significant gender-specific differences for ^{68}Ga-DOTATOC uptake (higher for men), whereas the patient's age, glandular volume, history of L-thyroxine treatment, or accompanying disease proved not to influence ^{68}Ga-DOTATOC uptake on PET.

Dimitrakopoulou-Strauss et al. investigated ^{68}Ga-DOTATOC uptake in non-small lung cancer (NSCLC) and compared ^{68}Ga-DOTATOC kinetics with those of FDG (Dimitrakopoulou-Strauss et al., 2006). The study population was comprised of nine patients who were examined with both radiopharmaceuticals on two different days within one week. The results demonstrated moderate ^{68}Ga-DOTATOC uptake in primary NSCLC due to SSTR2 expression. Compared to FDG with a mean SUV 5.7, for ^{68}Ga-DOTATOC, the mean SUV was only 2.0. Interestingly, none of the eight metastases that were positive on FDG PET demonstrated any significant ^{68}Ga-DOTATOC uptake. One reason suggested for this discordant finding could be a reduction expression of SSTR in metastases as compared with the primary tumors, which would not affect FDG uptake.

Poeppel et al. recently compared the diagnostic value of PET/CT with the radiolabeled SSTR analogs ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC in the same patients with metastasized NET (Poeppel et al., 2011) (Figure 4). Forty patients with metastatic NET underwent PET/CT as part of a work-up before prospective peptide receptor radionuclide therapy (PPRT). The performance of both imaging methods was analyzed and compared for the detection of individual lesions per patient and for eight defined body regions. The radiopeptide uptake in terms of the maximal standardized uptake value (SUV_{max}) was compared between concordant lesions and to the renal parenchyma, which is always of concern from a dosimetric standpoint. The authors reported that significantly fewer lesions were detected with ^{68}Ga-DOTATATE than with ^{68}Ga-DOTATOC (254 vs. 262, $P < 0.05$). Mean ^{68}Ga-DOTATATE SUV_{max} across all lesions was significantly lower than that for ^{68}Ga-DOTATOC (16.0 ± 10.8 vs. 20.4 ± 14.7, $P < 0.01$). Mean SUV_{max} for renal parenchyma was not significantly different between ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC (12.7 ± 3.0 vs. 13.2 ± 3.3). The authors concluded that the approximately 10-fold higher affinity for SSTR2 of ^{68}Ga-DOTATATE did not prove to be clinically relevant. Radiotracers ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE possess comparable diagnostic accuracy for the detection of NET lesions, with ^{68}Ga-DOTATOC having higher tumor uptake between the two, as indicated by SUV_{max}.

An intra-individual comparison of ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE in a patient with metastases of a neuroendocrine pancreatic carcinoma demonstrated that the broader somatostatin receptor subtype profile of ^{68}Ga-DOTANOC, which binds SSTR2, 3 and 5, and internalization of the radiotracer may be clinically advantageous as a significantly higher uptake of this radiopeptide was found ($SUV_{max} = 152$) compared with the high-affinity, but SSTR2- selective radiopeptide ^{68}Ga-DOTATATE ($SUV_{max} = 103$) (Antunes et al., 2007). In addition, smaller lesions were detected when using ^{68}Ga-DOTANOC as compared to ^{68}Ga-DOTATATE, suggesting it to be the preferred agent for this indication.

Early detection of bone metastases is clinically important because of the high prevalence of such lesions in patients with advanced NET. Putzer et al. have compared the diagnostic value of CT with that of ^{68}Ga-DOTATOC PET in the detection of bone metastases (Putzer et al., 2009). Bone scans using ^{18}F-NaF or ^{99m}Tc-dicarboxypropane diphosphonate or clinical follow-up served as the reference standards for the study. Twelve of 51 patients had no evidence of bone metastases on any of the available imaging modalities, while 37 patients had ^{68}Ga-DOTATOC PET results that were ultimately determined to represent true-positives for metastatic foci. The results for ^{68}Ga-DOTATOC PET included true-negatives for 12 patients, a false-positive for one, and a false-negative for one, resulting in a sensitivity

of 97% and a specificity of 92%. Bone metastases could be detected at a significantly higher rate for ^{68}Ga-DOTATOC than could CT ($P < 0.001$). Furthermore, conventional bone scans confirmed the results of SSTR PET but did not reveal additional tumors in any patients.

Taken together these studies indicate that SSTR targeting has become a mainstay in the clinical work-up of NET, having established this technique as the method of choice for imaging and treating such lesions world-wide (Baum and Rosch, 2011). Until such SSTR targeting agents were available there were few options for the clinical oncologist for managing this devastating disease.

2.2.2. Other ^{68}Ga-Labeled Imaging Agents in Clinical Trials—Baum et al. has recently reported administration of a ^{68}Ga-labeled human epidermal growth factor receptor 2 (HER2)–targeting affibody for detection and characterization of HER2-positive lesions in patients with recurrent, metastatic breast cancer (Baum et al., 2010). In this pilot study, in which patients were administered ^{111}In- or ^{68}Ga-labeled DOTA^0-Z$_{HER2:342-pep2}$ (ABY-002), with subsequent imaging with a γ-camera, SPECT, or PET/CT, comparison was made to earlier FDG PET/CT results obtained in the same patients. Radiolabeled ABY-002 detected nine of 11 FDG–positive metastases as early as 2 – 3 h after administration. One potential limitation of this technique, however, is the high level of radiopharmaceutical uptake observed in liver and kidney with both agents.

The ^{68}Ga-bombesin analog, DOTAPEG$_2$-BN(6–14) amide [68Ga-BZH$_3$ (Schuhmacher et al., 2005a), Figure 5], has been studied in patients with gastrointestinal stromal tumors (GIST) to investigate the impact of complementary receptor scintigraphy on diagnosis and to assess for the possibility of radionuclide therapy (Dimitrakopoulou-Strauss et al., 2007). Dynamic FDG studies were performed on the same patients. Fourteen of 17 patients (25/30 lesions) were positive for uptake on FDG imaging, whereas ^{68}Ga-BZH$_3$ demonstrated an enhanced accumulation in 7 of 17 patients (8/30 lesions). One recurrent tumor in the stomach could not be delineated on FDG but showed enhanced ^{68}Ga-BZH$_3$ uptake. The median SUV for ^{68}Ga-BZH3 was 3.3, in comparison with 7.9 for FDG. The authors concluded that ^{68}Ga-BZH$_3$ may be helpful for diagnosis in a sub-group of patients with GIST, i.e., in cases where FDG is negative, in the face of tissue deemed suspicious for tumor on other (anatomic) imaging modalities (Baum and Rosch, 2011).

Baum et al. (Vitha et al., 2008), have reported the first human study using a ^{68}Ga-DOTA-labeled bisphosphonate, [(4-{[bis-(phosphonomethyl))carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)acetic acid, ^{68}Ga-DOTABPAMD,] (van der Lely et al., 2003) (Figure 6) to investigate the relationship between the presence of disseminated bone metastases and their response to therapy using the corresponding ^{177}Lu-labeled molecular radiotherapeutic (Fellner et al., 2010). As in the case of coupling DOTA-conjugated octreotide analogs for imaging and therapy of NET, bone tumors can also be both diagnosed and treated using the same low molecular weight compound, altering only the radionuclide (i.e., by replacing ^{68}Ga with the -particle emitters ^{177}Lu or ^{90}Y). Accordingly, ^{68}Ga-DOTABPAMD was administered to a patient with known extensive bone metastases due to prostate cancer and revealed intense accumulation in multiple osteoblastic lesions in the central skeleton, ribs and proximal extremities demonstrating its utility in this initial study.

Recently Jeong et al. investigated ^{68}Ga-NOTA-RGD (Figure 7) in conjunction with FDG in patients with hepatic metastases of colorectal cancer before combination therapy including FOLFOX and bevacizumab (Jeong et al., 2008) (Haubner et al., 2010). Static PET images with ^{68}Ga-NOTA-RGD were acquired 30 min after injection. In all six patients hypermetabolic liver lesions were visualized on FDG PET. Three patients also demonstrated

mild ^{68}Ga-NOTA-RGD accumulation in liver lesions, and the other half showed no radiopharmaceutical uptake. Importantly the patients with ^{68}Ga-NOTA-RGD uptake in the hepatic metastases showed a partial response to combination therapy that contained an antiangiogenic agent, whereas the other patients had stable or progressive disease. These findings indicate that PET imaging with $\alpha_v\beta_3$ integrin-targeting radiotracers might help in selection for antiangiogenic therapy, however, validation in larger studies is needed.

2.3. ^{68}Ga-Labeled Imaging Agents for Therapeutic Monitoring

The main focus of ^{68}Ga-based imaging has been to compare ^{68}Ga-DOTA-peptide PET with the other imaging techniques usually used in NET patients, such as Octreoscan™, FDG, CT, and MRI. These studies have suggested that ^{68}Ga-DOTA-peptide PET is useful in diagnosing NETs (i.e., visualization, initial staging, and detection of relapse) and in evaluating the possibility of planning molecular radiotherapy (Baum and Kulkarni, 2012). Several imaging agents that also emit -particles have been developed for imaging (and treating) NET, mainly as a consequence the marginal role of FDG for the assessment of these tumors (Adams et al., 1998a). In fact well differentiated NET are characterized by a low metabolic rate and therefore low glucose consumption, rendering FDG unsuitable for the evaluation of well differentiated lesions, while its role may still be relevant in highly proliferative, undifferentiated tumors or in cases of lesions not over-expressing SSTR. Different patterns of radiopharmaceutical uptake between ^{68}Ga-DOTA-peptides and FDG have been described within areas of the same tumor or in different lesions within the same patient (von Falck et al., 2007). Therefore much interest is currently devoted to the use of both a receptor-based radiotracer and one that relies on metabolism in order to ascertain whether the tumor has an undifferentiated component (with high FDG uptake) that may benefit from standard chemotherapy instead of SSTR-targeted therapy alone. Baum et al. have employed PET/CT using ^{68}Ga-labeled somatostatin analogs to select patients who are likely to benefit from PRRT, which consists of administration of radiotherapeutic (^{90}Y or ^{177}Lu) versions of the same peptides used for imaging of inoperable NET (Baum et al., 2012) (Figure 8).

Koukouraki et al. evaluated 22 NET patients with 74 metastases by dynamic ^{68}Ga-DOTATOC-PET. They suggested that pharmacokinetic analysis could help separate blood background radioactivity from receptor binding, which might help optimize planning of ^{90}Y-DOTATOC therapy (Koukouraki et al., 2006b). The same group also compared the pharmacokinetics of ^{68}Ga-DOTATOC PET and FDG in patients with metastatic gastroenteropancreatic (GEP)-NET who underwent image-based planning for subsequent ^{90}Y-DOTATOC therapy (Koukouraki et al., 2006a). The authors concluded that the uptake of ^{68}Ga-DOTATOC improved the selection of patients for ^{90}Y-DOTATOC therapy.

A more recent clinical study (46 patients) by Gabriel et al. (Gabriel et al., 2009) indicated that ^{68}Ga-DOTATOC-PET demonstrated no advantage over conventional anatomic imaging for assessing response to therapy when all CT information obtained during follow-up was compared. Only the development of new metastases during therapy was detected earlier in some cases when whole-body PET was used. SUV analysis of individual lesions proved of no additional value in predicting individual therapeutic response.

Overall, SSTR-targeted PET/CT enables detection of primary and metastatic disease (staging), assessment of molecular response to therapy, and long-term follow-up after initial diagnosis. Additionally, imaging allows for dosimetry before or after therapy to ensure the optimum balance between risk and benefit by enabling prediction and avoidance of potential radiotoxicity. Recently, researchers have directed their attention to the evaluation of the SUV_{max} from imaging with ^{68}Ga-DOTA-peptides to quantify therapeutic response.

Recently, Campana et al. (Campana et al., 2010b) evaluated the SUV_{max} measured on ^{68}Ga-DOTANOC PET scans in 47 patients with NET to correlate this quantitative value with the clinical findings, immunohistochemistry, and time to progression. They found that SUV_{max} was significantly higher in patients with pancreatic NET than in those with gastrointestinal or lung NETs. Regarding histologic findings, they reported a significantly higher SUV_{max} in patients with well-differentiated endocrine carcinomas than in those with poorly differentiated endocrine tumors. The SUV_{max} cut-off to differentiate between patients with stable disease/partial response at follow-up from those with progressive disease was reported to range from 17.6 to 19.3. SUV_{max} values higher than 19.3 permitted the selection of patients with slower disease progression. Significantly, they reported that patients who underwent both somatostatin analog treatment and PRRT had a better prognosis than those who were treated with somatostatin analogs alone, confirming the positive role of PRRT in the treatment of chronic NETs (Kwekkeboom et al., 2008).

A study by Boy et al. (Boy et al., 2011) found a correlation between SUV_{max} of ^{68}Ga-DOTATOC to the expression of SSTR2 at the level of mRNA (120 patients). The authors concluded that having such a novel normative database may improve diagnosis, monitoring, and therapy of SSTR-expressing tumors or inflammation on a molecular basis. Another recent study by Kaemmerer et al (Kaemmerer et al., 2011) provided for the first time the proof of concept of the utility of SSTR PET/CT for quantification of the SSTR density on tumor cells. A close correlation was found between SUV_{max} and immunohistochemical scores used for the quantitative assessment of the density of subtypes of SSTR in NEN tissue. These studies point toward uses of SSTR imaging beyond mere tumor detection and into molecular characterization of the lesions to be identified.

2.4. Cost Advantage of ^{68}Ga-Based Agents

To investigate the cost effectiveness of ^{68}Ga-based PET imaging *vs.* ^{111}In-based scintigraphy, Schreiter et al (Schreiter et al., 2012) reported a cost comparison study for patients undergoing PET/CT imaging with ^{68}Ga-DOTATOC *vs.* patients undergoing ^{111}In-DOTATOC scintigraphy. The results indicate that the main cost components of a ^{68}Ga-DOTATOC scan are the costs for the radiotracer and those for an ^{111}In-DTPA-octreotide scintigraphy study are for the Octreoscan™ kit. Although the investment costs for the scanner and the radiochemistry equipment are higher for ^{68}Ga-DOTATOC PET/CT compared with ^{111}In-DTPA-octreotide scintigraphy and SPECT, the former is less expensive in terms of personnel and material costs as well as operating and follow-up costs, at least in Germany where the study was undertaken. The cost advantage found for ^{68}Ga-DOTATOC PET/CT is expected to be similar when PET/CT is performed using other ^{68}Ga-labeled somatostatin analogs such as ^{68}Ga-DOTANOC or DOTATATE. The expenses for the peptide are similar, and all other costs are nearly the same. Using a similar argument, one can estimate that centrally produced and delivered FDG would be much less expensive ($100/per 10 mCi) than the on-site generator produced ^{68}Ga-based radiopharmaceuticals. Considering the usage of a ^{68}Ga generator, the cost of a 10 mCi dose for ^{68}Ga may vary. Considering five syntheses per week for one year, the price for a 10 mCi dose from a 10 mCi generator (~ $24,000) would be at least $92 (24,000 /5*52), assuming operation every week during the year. In addition, for every dose, we need to include expenses for the automated radiosynthesizer module and peptide synthesis, quality control and dose formulation. Since the generator can be eluted in every 2 h, depending upon the number patient studies per week, the price of the dose would vary significantly if, for example, one could generate10 doses per week instead of five. Accordingly, the average cost for ^{68}Ga-based agents seems to be higher than that for FDG for the initial few years of operation of the former. However the ease of preparation of the ^{68}Ga-based agents and their wide variety of applications in molecular imaging cannot be compared directly with FDG, which has a

different, and arguably more limited, set of indications. For specific molecular targeting one could still argue that ^{68}Ga-based PET would be less expensive overall than that based on ^{18}F. Additional considerations include more widespread dissemination of ^{68}Ga-based agents as they are generator produced, without the need for a cyclotron either on-site or the occasionally complex logistics of synthesizing and shipping compounds labeled with ^{18}F.

2.5. Caveats to Imaging with ^{68}Ga-Based SSTR-targeted Agents

A potential pitfall in interpreting images generated from SSTR-targeted PET is that foci of inflammation may cause false-positive results due to the expression of SSTR on activated lymphocytes, macrophages and fibroblasts (Jensen et al., 1997; Kwekkeboom et al., 2000; Yu et al., 1999) – a similar caveat to interpretation of images obtained by FDG PET. Other reasons for false-positive PET studies include the presence of an accessory spleen or physiologic activity within endocrine tissue such as the adrenals (Kwekkeboom et al., 2000). These minor problems are vastly outweighed by the obvious benefits of the technique elaborated throughout this review.

3. Summary and Conclusion

By linking the pharmacokinetics of certain low molecular weight biologicals such as peptides to the brief physical $t_{1/2}$ of ^{68}Ga, an array of powerful, new clinical imaging studies is emerging. That has so far proved especially true in the case of imaging of SSTR-expressing tumors, with other examples appearing. Currently ^{68}Ga-PET imaging is somewhat limited due to the relatively high cost of existing generators and the lack of FDA approval for their use, however that cost pales in comparison to the expense of operating a cyclotron on site – and is even less significant in light of the superior clinical data obtained with these newer PET agents relative to the existing, corresponding agents that employ - scintigraphy or SPECT.

Acknowledgments

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Highlights

- A summary of the emerging clinical uses of ^{68}Ga-based radiopharmaceuticals is provided.

- ^{68}Ga-PET may prove as or more clinically robust than the corresponding ^{18}F-labeled agents.

- ^{68}Ga-radiopeptides were studied for targeting of somatostatin receptors subtypes.

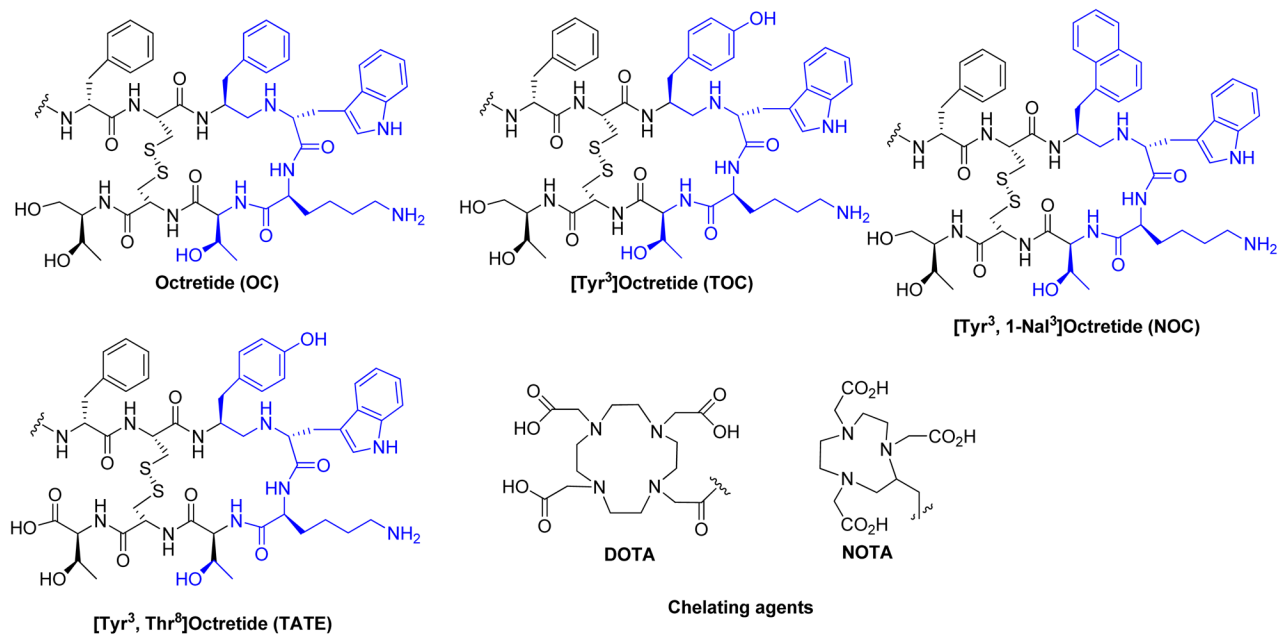- ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC, are currently in clinical trials.
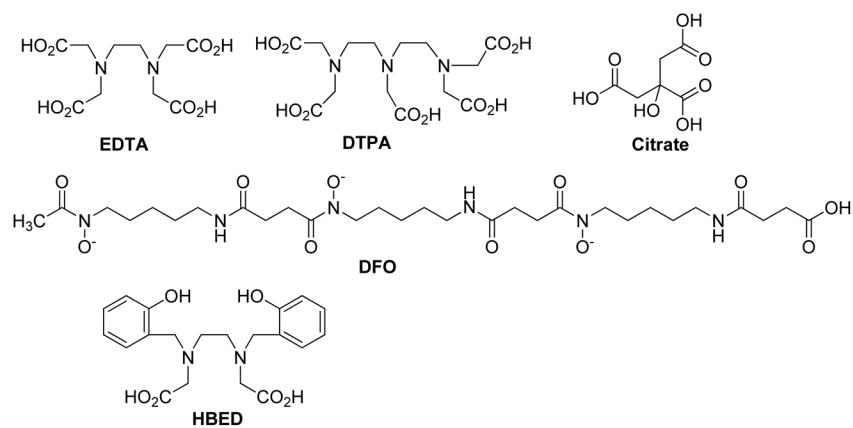
Figure 1.
Selected acyclic chelating agents that are used in clinical trials as "gallium-essential" imaging agents.
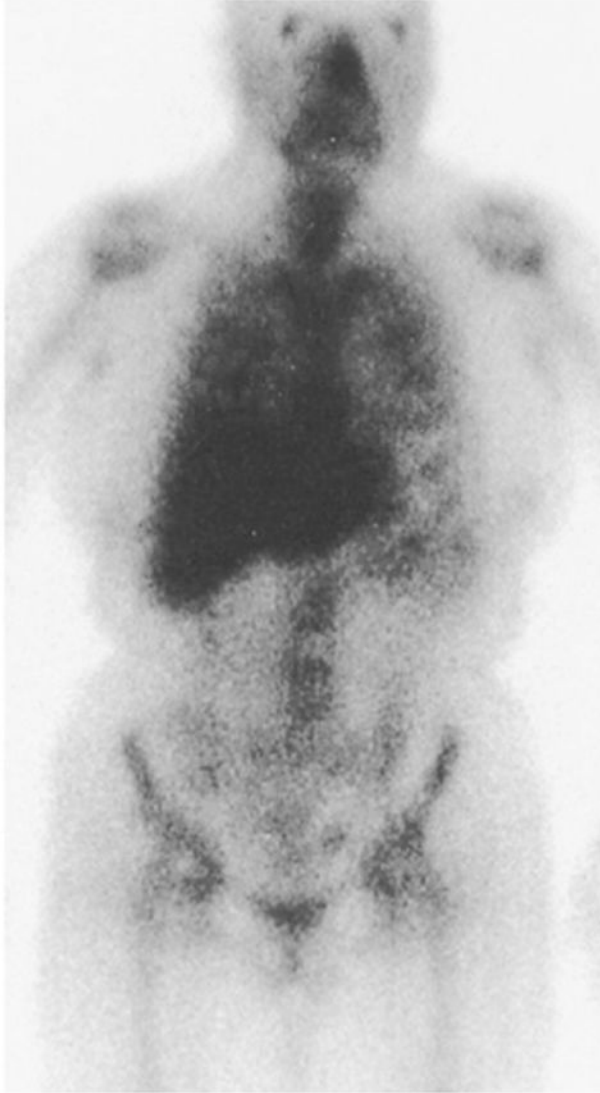
Figure 2.
A comparison of normal physiologic biodistribution of ^{67}Ga-citrate whole-body scintigraphy and ^{68}Ga-citrate PET/CT. Reprinted with permission from: Nanni et al. J Nucl Med 51, 1932–1936.

Octretide (OC)

[Tyr³]Octretide (TOC)

[Tyr³, 1-Nal³]Octretide (NOC)

[Tyr³, Thr⁸]Octretide (TATE)

DOTA

NOTA

Chelating agents

Fig. 3.
Structures of somatostatin octapeptides (octreotride, OC) and related peptide analogs, TOC,
TATE and NOC. Amino acid residues shown in blue constitute the recognition site of the
somatostatin receptor (SSTR).
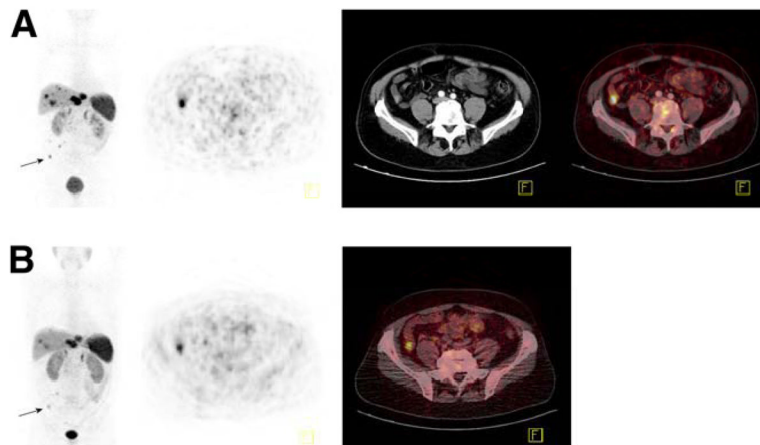
Figure 4.
Lesions demonstrating higher uptake of ^{68}Ga-DOTATOC than ^{68}Ga-DOTATATE in the same patient. (**A**) From left to right: ^{68}Ga-DOTATOC PET maximum-intensity projection (MIP), ^{68}Ga- DOTATOC PET, CT, and PET/CT fusion; (**B**) from left to right: ^{68}Ga-DOTATATE PET MIP, ^{68}Ga-DOTATATE PET, and PET/CT fusion. Arrow in the MIP images in (**A**) and (**B**) depicts ileal carcinoid. Note higher radiopharmaceutical uptake in metastatic foci within liver on the ^{68}Ga-DOTATOC (**A**) images. Axial images are obtained at the level of the carcinoid tumor. Reprinted with permission from: Poeppel et al., *J Nucl Med* 2011; 52:1864 –1870.
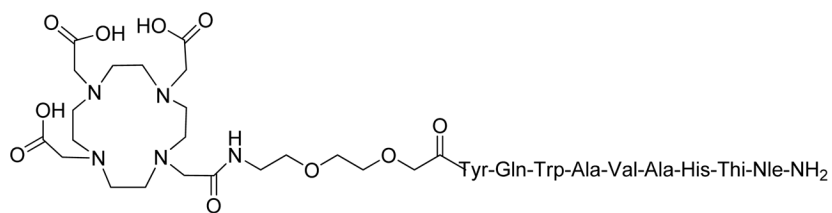
DOTA-PEG$_2$-[D-Tyr^6, βAla^{11}, Thi^{13},Nle^{14}] (BN(6-14) amide (BZH$_3$).
Thi = 3-(2-thenyl)-L-alanine

Figure 5.
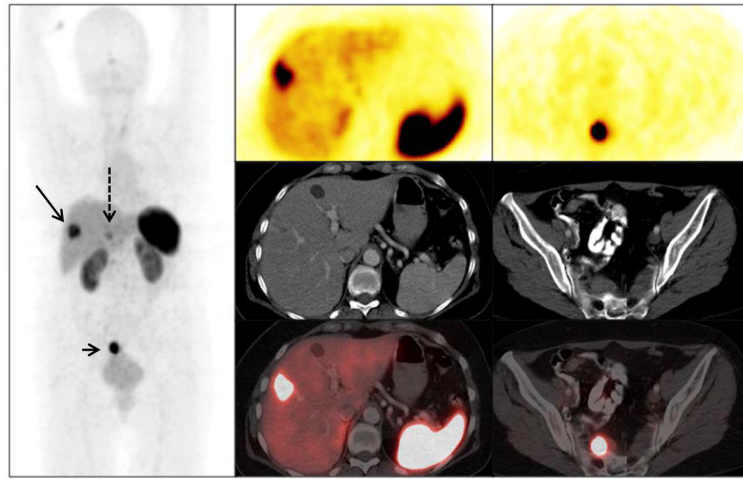Structure of the ^{68}Ga-bombesin analog, DOTAPEG$_2$-BN(6–14) amide ([68Ga]-BZH$_3$).
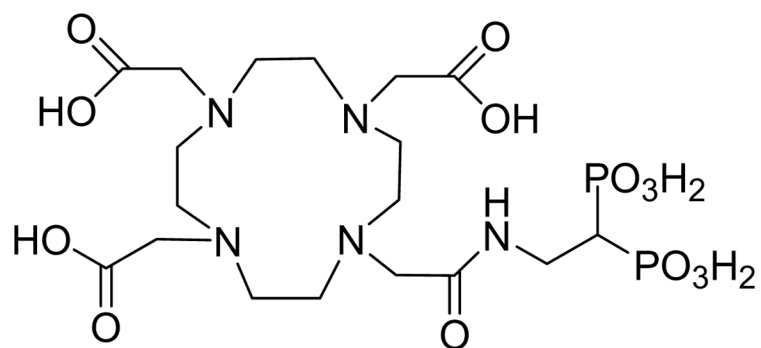
Figure 6.
Structure of the DOTA-conjugated bisphosphonate, BPAMD.

Figure 7.
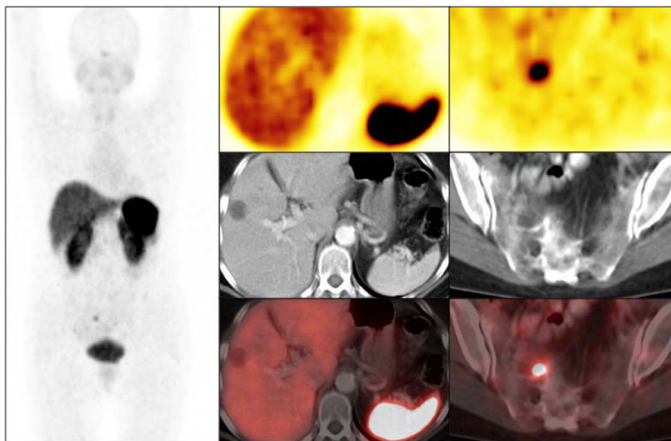Structure of ^{68}Ga-NOTA-RGD.

Figure 8A

07. 2005

Figure 8B

01. 2009

Figure 8.
A 64-year-old woman with NET diagnosed in 2001 (liver lesions identified at routine abdominal ultrasound were interpreted as benign). The patient underwent hysterectomy and ovariectomy and metastases were found in both ovaries as well as in lymph nodes resected in the lumbar region. OctreoScan™ showed positive liver lesions, but no primary tumor. Octreotide therapy (Sandostatin LAR™ 20mg) was started, but progressive disease occurred in 2007. (**A**) Gallium-68-DOTATOC imaging at that time showed an intense SSTR-positive liver lesion in S8 ($SUV_{max} = 33$) and another, small lesion in S2 ($SUV_{max} = 6.2$), long solid and dashed arrows, respectively, on the maximum intensity projection image. The primary tumor was detected in the presacral region ($SUV_{max} = 70.1$) (short arrow). Left axial images (center column) are obtained at the level of the large liver lesion; right axial images (right

column) are obtained at the level of the presacral tumor. (**B**) Peptide receptor radionuclide therapy (PRRT) was started in July 2007 (two cycles using a total of 8 GBq ^{90}Y-DOTATATE) and follow-up PET/CT in January, 2009 showed complete remission of the liver metastases and partial response of the presacral lesion. To date, the patient is alive and doing well (nearly five years after PRRT) (Courtesy: Dr Richard P. Baum).