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Review

Gallium-68 PET: A New Frontier in Receptor Cancer Imaging

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Abstract. *Neuroendocrine tumours (NET) are rare tumours that occur most commonly in the GI tract. Various labelled somatostatin analogues are used to image NET expressing somatostatin receptors (SSTR). In traditional nuclear medicine, most peptides used in imaging NET have been labelled with indium-111, the commonest being indium-111-octreotide (^{111}In-octreotide). Unfortunately, the unfavourable physical qualities of In-111 make it unsuitable for detecting small tumour deposits. The recent introduction of gallium-68-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (gallium-68-DOTA) compounds for positron emission tomography (PET) imaging has significantly improved the quality of imaging NET through improved resolution of PET and higher affinity of the new generation of peptides to SSTR. In the present paper, we discuss the clinical and research applications of PET radio-tracers for evaluating NET, in particular gallium-68-DOTA compounds. The recent introduction of PET imaging with gallium-68 has major bearings in current and future clinical practice. Its labelling with DOTA compounds has cleared the way for somatostatin receptor imaging with a viable PET agent, with all its inherent imaging advantages compared to single photon imaging. The pre-clinical and clinical applications of this technique has been successful in a variety of tumours, particularly NET and its labelling with other ligands and molecules will improve the management of other tumours and the assessment of infection.*

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Labelled peptides, particularly labelled somatostatin analogues, have been increasingly used in the diagnosis and therapy of tumours expressing somatostatin receptors (SSTR) on their cell surface, particularly neuroendocrine tumours (NET). Generally, NET are rare tumours and occur most commonly in the GI tract. The most common are carcinoid tumours and the gastroenteropancreatic tumours (GEP) such as gastrinomas and insulinomas. Other tumours expressing SSTR include somatostatinomas, medullary thyroid tumours, pituitary tumours, paragangliomas and phaeochromocytomas.

To date, most peptides used in imaging NET have been labelled with indium-111, the commonest being indium-111-octreotide (^{111}In-octreotide). The physical qualities of In-111, even allowing for the use of single photon emission computed tomography (SPECT), make it unsuitable for detecting small tumours. Likewise, the currently available peptides may have a reduced rate of accumulation in tumours due to their variable affinity to one or more of the five SSTR manifested on cell surfaces.

The recent introduction of gallium-68-1,4,7,10-tetraaza-cyclododecane-*N,N',N'',N'''*-tetraacetic acid (gallium-68-DOTA) compounds for PET imaging has significantly improved the quality of imaging NET through improved resolution of PET and higher affinity of the new generation of peptides to SSTR. The clinical use of this new technique and its implication on research is discussed in this review.

Peptides and Somatostatin Analogues

Peptides comprise a variable number of amino acids and have fast clearance, rapid tissue penetration, and low antigenicity, and can therefore be produced easily and inexpensively. There has been a significant increase in the development of labelled peptides for diagnostic applications in the last decade especially due to simplified methods of purification. An inherent added advantage to this diagnostic approach is its therapeutic implication since if the diagnostic

scan is positive, the peptides can be labelled with therapeutic radionuclides (yttrium-90, lutetium-177) to perform peptide receptor radionuclide therapy (PRRT). This therapy is suitable for patients with widespread disease that is not amenable to surgery, or focused radiation therapy or is refractory to chemotherapy, and is particularly useful for symptom control (1).

Most efforts at labelling peptides have been targeted at somatostatin and its receptors. Somatostatin is a regulatory peptide, widely distributed in the human body, whose action is mediated by membrane-bound receptors, SSTR, that are present in normal human tissues, such as the thyroid, brain, GIT, pancreas, spleen and kidney (2). They are also abundant in a variety of human tumours, particularly neuroendocrine tumours (3). Non-tumoral lesions, such as granulomas, can also express them. Somatostatin inhibits hormone secretion of various glands and so can be used in the treatment of diseases caused by overproduction of hormones. Somatostatin itself has a short half-life and is rapidly degraded by enzymes; hence analogues have been developed to mimic its effects which are resistant to enzyme degradation.

There are 5 somatostatin receptor subtypes but only subtypes 2 (SSTR2, which can be further divided into SSTR2A and SSTR2B), 5 (SSTR5) and to a lesser extent 3 (SSTR3) have a high affinity for commercially available synthetic analogues and even these differ in their affinity for the various analogues. Although the tissue distribution of the receptor's mRNA has been extensively examined, much less is known about the cellular distribution of the individual receptor proteins. All SSTR receptors are linked to guanine nucleotide binding proteins (G proteins) and lead to inhibition of adenylyl cyclase following hormone binding (4).

^{111}In-DTPA-octreotide and ^{90}Y-octreotide. The most commonly used somatostatin analogue is indium-111-DTPA-octreotide. It has a high affinity for SSTR2 and lower affinity for SSTR5 and SSTR3 (5). The labelled peptide undergoes receptor mediated internalisation with degradation of the peptide to ^{111}In-DTPA-D-Phe in lysosomes (6) that cannot escape and so is retained in the cell (7).

Cold (non-radioactive) octreotide is used clinically in the treatment of NET disorders and can reduce the production of hormones such as 5-hydroxytyrosine from carcinoid and gastrin from gastrinoma, and by doing so improves the quality of life of patients (8). However, at high doses, it can produce unpleasant side-effects, such as stomach cramps and diarrhoea (9). When labelled with In-111, it shows a higher sensitivity for carcinoid tumours than Iodine-123-metaiodobenzyl guanidine (^{123}I-MIBG). It also produces less hepatic uptake (10) and is now regarded as the standard method of imaging NET (11).

Normal tracer uptake is seen in the thyroid, spleen, liver, kidneys and pituitary as well as bowel and bladder, and has a predominantly renal clearance. False positives have been reported in somatostatin receptor-positive lesions that are not related to NET, such as in breast tissue, granulomas, CVA, accessory spleens and the gallbladder (12). It is very sensitive (80-100%) in the detection of carcinoid tumour where imaging can show all somatostatin receptor-positive disease. This has been successfully used in the preparation of patients for PRRT with Y-90 octreotide. It remains of value in endocrine pancreatic tumours with a sensitivity of 60-90% for gastrinomas, when only 50% are visualised on cross-sectional imaging. However, its sensitivity for detection of insulinoma is limited. Lamberts and colleagues investigated *in vivo* and *in vitro* detection of functional somatostatin receptors in human endocrine pancreatic tumours, and demonstrated a sensitivity of 61% for the detection of *in vivo* insulinomas with octreotide in 14/23 patients. The relatively low sensitivity observed was attributed to the existence of hSSTR subclass within the insulinomas, which did not demonstrate affinity to octreotide (13). In another study, Schillaci *et al.* reported a higher sensitivity of 87.5% using octreotide and SPECT in 14 patients, however, these results could be rendered biased since the patient group included in this study had biochemically proven insulinoma prior to imaging (14). ^{111}In-octreotide is also used in the detection of pituitary tumours where virtually all growth hormone producing adenomas have somatostatin receptors, but SSTR are also present on other pituitary tumour cells such as lymphoma, hence octreotide imaging here is of limited use. ^{111}In-octreotide is less sensitive in the detection of phaeochromocytomas, paragangliomas and medullary thyroid tumours. Kwekkenboom *et al.* determined a sensitivity of 65% for detecting primary and metastatic lesions in medullary thyroid carcinoma (MTC) using ^{111}In-octreotide in 11 out of 17 patients. In the same study, they concluded that octreotide was not sensitive in detecting liver metastases or intrathyroidal tumors, as it correlated with the *in vitro* presence of somatostatin receptors. In addition, the immunohistochemical presence of somatostatin in the tumor did not influence the outcome of *in vivo* somatostatin receptor imaging (15). Adams and colleagues compared receptor imaging of MTC with indium-pentetreotide to histopathological findings and demonstrated 29% sensitivity in 5/18 patients (16). Furthermore, Baudin *et al.* compared conventional imaging with octreotide imaging, and reported a similarly low sensitivity of 37% for the detection of MTC in 9/24 patients (17). In the latter case, interpretation must be taken with care as normal thyroid tissues (as well as other thyroid malignancies) can also show uptake of ^{111}In-octreotide. A number of tumours, unrelated to NET, can also demonstrate SSTR on their cell surface and hence be

detected by ^{111}In-octreotide, including small cell lung cancers, trabecular skin (Merkel cell) tumours, and 75% of primary breast cancers (1, 2, 10). Uptake has also been reported in lymphoma, melanoma, neuroblastoma, and well-differentiated astrocytomas (12).

DOTA Compounds

Labelling peptides moved a step forward with the introduction of 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (DOTA), a universal chelator capable of forming stable complexes with radiotracers of the metal group such as ^{111}In, ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{90}Y and ^{177}Lu (18). Newer analogues such as DOTA-Tyr3 octreotide (DOTATOC) have better uptake than ^{111}In-octreotide. The phenylalanine residue at position 3 is replaced by tyrosine, making the compound more hydrophilic and increasing the affinity for SSTR2, leading to higher uptake in SSTR2-positive tumours (19).

Other peptides linked to DOTA include DOTA-octreotate, which has a very high affinity for SSTR2 (5), and DOTA-lanreotide with high affinity for SSTR5. The newest addition to these compounds is DOTA-1-NaI-octreotide (DOTANOC), which has shown a high affinity for SSTR2, SSTR3 and SSTR5 (20). These products have high radiochemical purity and show rapid renal clearance but high accumulation in tumours with a striking superiority over standard peptides (20).

The Introduction of Gallium-68

The chemistry and radiopharmacy of germanium-68/gallium-68 generator (^{68}Ge/^{68}Ga) has been under investigation and thoroughly documented since the late 1970s (21, 22), most recently in the last few years by Maecke (23, 24). However, in regards to the development of clinically significant Ga-68 PET imaging, no real progress had been made since then until the 21st Century with the introduction of the PET imaging agent ^{68}Ga-DOTATOC.

The first published relevant breakthrough clinical work using ^{68}Ga-DOTATOC PET imaging came in 2001 by Henze *et al.* (25) who described ^{68}Ga-DOTATOC PET imaging in 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. They imaged three patients with ^{68}Ga-DOTATOC PET, who had a total of eight meningiomas between them. They acquired dynamic PET images of the brain demonstrating rapid tracer uptake in these tumours. Quantitative analysis showed the standard uptake value (SUV) increasing immediately after injection, reaching a plateau 60-120 min after injection (mean SUV, 10.6). There was no tracer uptake in adjacent healthy brain tissue, and even the smallest lesions (7-8 mm) showed high tracer uptake with very high tumour-to-background ratio. Furthermore, fused images with CT and MRI showed good edge correlation. Henze *et al.* (26) followed up this work and went on to further characterise meningiomas with dynamic ^{68}Ga-DOTATOC PET to evaluate 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), the rate constants $k2$, $k3$, $k4$ (l/min) and receptor binding ($k1 - k1/k2$). These factors resulted in very high tumour-to-background ratios, allowing clear visualisation of the lesions particularly at the skull base. Furthermore, they found that this type of kinetic modelling allowed them to offer a more comprehensive assessment of tumour biology, which may be used to assess the somatostatin receptor status of meningiomas after radiotherapy.

Following on from the above landmark work, the next major published work was by Hofmann *et al.* (27), who described the application of ^{68}Ga-DOTATOC PET in NET. They compared ^{111}In-octreotide scintigraphy with ^{68}Ga-DOTATOC PET in eight patients with histologically proven carcinoid tumors. They studied a total of 40 lesions that were identified either by computed tomography and/or magnetic resonance imaging. In total, ^{68}Ga-DOTATOC PET identified 100% of these lesions, whereas ^{111}In-octreotide planar and SPECT imaging identified only 85%. Furthermore, quantitative analysis of the lesions showed that ^{68}Ga-DOTATOC PET imaging resulted in higher tumour to non-tumour contrast with low kidney accumulation.

Kowalski *et al.* (28) compared ^{68}Ga-DOTATOC PET with ^{111}In-DTPA-octreotide in a smaller group of 4 patients with metastatic NET. In two patients, more lesions were detected with ^{68}Ga-DOTATOC PET compared to ^{111}In-DTPA-octreotide SPECT. They also felt that ^{68}Ga-DOTATOC PET was superior when it came to visualising smaller lesions with low tracer uptake especially with tumours bearing only a low density of somatostatin receptors.

Kowalski *et al.* (29) evaluated the pharmacokinetics of ^{68}Ga-DOTATOC to establish parameters affecting SUV in 22 patients with metastatic NET who were scheduled for ^{90}Y-DOTATOC therapy. Forty-seven metastatic lesions were examined with dynamic ^{68}Ga-DOTATOC PET and SUVs and were calculated for all frames following the injection of the tracer. Qualitative analysis showed increased uptake of ^{68}Ga-DOTATOC in 21/22 patients and in 72/74 lesions. The SUV was highly variable, with a range from 0.877 to 28.07 (mean 8.73). Quantitative evaluation based on a compartmental model revealed high receptor binding and internalisation, but low cellular externalisation and relatively low fractional blood volume. They concluded that

their findings may help optimize planning for ^{90}Y-DOTATOC therapy as DOTATOC uptake in NET is mainly dependent on receptor binding and fractional blood volume, and by using pharmacokinetic data analysis, blood background activity can be separated from the receptor binding. The same group (30) compared the pharmacokinetics of ^{68}Ga-DOTATOC PET and [^{18}F]-FDG PET in patients with metastatic NET who were scheduled for ^{90}Y-DOTATOC therapy. They evaluated 15 patients with a total of 63 lesions, with dynamic acquisition of [^{18}F]-FDG PET and ^{68}Ga-DOTATOC PET scans performed on two different days in the same week. Qualitative and quantitative data analyses were performed using a two-tissue compartment model, with multivariate analysis of the kinetic data. Qualitative analysis showed uptake of ^{68}Ga-DOTATOC in all patients, in 57/63 lesions. [^{18}F]-FDG uptake was observed in 43/63 lesions, and discordant findings were seen in 6/15 patients. The median global SUV was 7.9 for ^{68}Ga-DOTATOC and 4.6 for [^{18}F]-FDG, where global SUV was defined as the SUV measured in the last frame (55-60 min *p.i.*) of the dynamic series, for each tracer. They proceeded to select patients for ^{90}Y-DOTATOC therapy based on the uptake of ^{68}Ga-DOTATOC.

The most recent study looking into the use of ^{68}Ga-DOTATOC PET in NET was in 2007 by Gabriel *et al.* (31). They compared ^{68}Ga-DOTATOC PET imaging with ^{99m}Tc-HYNIC-octreotide scintigraphy and CT in 88 patients with known or suspected NETs. Patients were placed into one of three categories: those with an unknown primary tumour, but with clinical or biochemical suspicion of neuroendocrine malignancy (n=13 patients); those for staging of known tumour (n=36 patients); and those being followed-up after therapy (n=35 patients). ^{68}Ga-DOTATOC PET had a sensitivity of 97%, a specificity of 92% and an overall accuracy of 96%, and showed significantly higher diagnostic efficacy compared with ^{99m}Tc-HYNIC-octreotide scintigraphy and CT ($p<0.001$). Furthermore, the combined use of PET and CT gave the highest overall accuracy.

The success of SSTR PET imaging spurred our group to assess the viability of ^{68}Ga-DOTATATE PET imaging in malignant phaeochromocytomas, which have been shown to express somatostatin receptor status (32-35). We first demonstrated uptake of ^{68}Ga-DOTATATE in these lesions (36). Further work was performed in five patients who had previously undergone surgical resection of histologically proven malignant phaeochromocytomas, and re-presented with clinical and biochemical signs of recurrence (37). All patients underwent imaging with computed tomography (CT), ^{123}I-MIBG and ^{68}Ga-DOTATATE PET. Patients were administered 62-119 MBq (mean=99 MBq) of ^{68}Ga-DOTATATE intravenously and images were acquired thirty minutes post injection. Two patients (2/5) had negative ^{123}I-MIBG scintigraphy but had positive ^{68}Ga-DOTATATE PET. One patient (1/5) had weakly positive ^{123}I-MIBG scintigraphy, but a strongly positive ^{68}Ga-DOTATATE PET. One patient (1/5) had positive ^{123}I-MIBG scintigraphy and positive ^{68}Ga-DOTATATE scans, but the latter detected an extra lesion. No lesions were detected in the final patient (1/5) with any of the imaging modalities including CT, but interestingly he had a weakly positive uptake of ^{123}I-MIBG and ^{68}Ga-DOTATATE in a concurrent glomus jugulare tumour at the skull base, which was confirmed by magnetic resonance imaging (MRI). The SUV (max) for the positive lesions ranged from 4.6 to 10.4, indicating good tumour-to-background ratio. These findings present an interesting role for ^{68}Ga-DOTATATE PET in malignant phaeochromocytomas, especially those that show no or little avidity to MIBG. This opens up further treatment options with radiolabelled somatostatin analogues such as Y-90 DOTATATE (38-39) or Lu-177 octreotate (40), and is particularly relevant in cases of malignant phaeochromocytoma where recurrent or metastatic disease is usually not amenable to conventional treatment strategies.

A brief mention is also worthwhile regarding the investigation of SSTR status in patients with non-small cell lung cancer (NSCLC), which has been studied by Dimitrakopoulou-Strauss *et al.* (41). They assessed SSTR2 status with ^{68}Ga-DOTATOC PET, as well as tumour metabolism with [^{18}F] FDG PET, in nine patients with NSCLC. They discovered that tumour uptake of ^{68}Ga-DOTATOC (mean SUV=2.018) was generally lower than that of [^{18}F]-FDG (mean SUV=5.683), and that none of the eight metastatic lesions demonstrated with [^{18}F]-FDG were seen with ^{68}Ga-DOTATOC. They postulated that this may have been due to the loss of gene expression in the metastases compared to the primary lesion. These findings are interesting as they add to our understanding of tumour SSTR status and biology.

Research Applications of ^{68}Ga PET

Despite the availability of ^{68}Ga as a positron emitter for more than thirty years, its wide application in PET imaging is relatively new. However, as we discussed earlier, ^{68}Ga was introduced at an earlier stage in the clinical setting compared to its potential use in the research field in which it has only been recently introduced, alone or as part of new molecules, in animal models of human diseases.

At an earlier stage, several ligands systems such as desferrioxamine B (DFO) (42-46), diethylenetriaminepenta-acetic acid (DTPA) (47-48) and *N,N'*di(2-hydroxybenzyl) ethylene diamine,*N,N'*-diacetic acid derivative (HBED) (49) were tried but found to be quite unstable. Further pre-clinical studies employed ^{68}Ga in DOTA-coupled peptides (such as analogues of somatostatin, bombesin and melanocyte-stimulating hormones) and, as Gallium chloride, for the imaging of infections and inflammation.

Smith-Jones and co-workers showed that ^{68}Ga DFO-octreotide was a tracer that could be used *in vivo* to diagnose SSTR-positive tumours (50) with good results. They evaluated a total of three rats bearing SSTR-positive endocrine pancreatic tumours with a small animal PET scanner and showed that one hour after injection there was a selective binding of the tracer to the tumour site, with a tumour/background ratio (TBR) of 5. These results showed that the tumour was visible with PET within 30 seconds post injection and a slight increase in localized activity was noted for up to 1000 seconds. The activity in the kidney peaked at 200-300 seconds post injection and was accompanied by a shift of activity to the bladder.

Subsequently, SSTR were evaluated *in vivo* with several gallium-DOTA labelled somatostatin analogues, among which ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC are the most promising due to their high affinity to SSTR 2, 3 and 5.

Biological evaluation in living rats of ^{68}Ga DOTA-labeled oligonucleotides for labelling antisense oligonucleotides targeting activated human *K-ras* oncogene was recently published by Roivainen and colleagues (51). The biodistribution and biokinetics were evaluated *in vivo* in tumour-bearing athymic rats. They showed that oligonucleotides could be stably labelled with ^{68}Ga-DOTA chelate producing high-quality PET images and allowing quantification of the biokinetics in major organs and tumours.

A study to evaluate the superiority of third-generation somatostatin-based, gallium-labelled peptides compared to indium radiopharmaceuticals was published recently (52). Antunes and co-workers determined SSTR affinity by *in vitro* receptor autoradiography, the internalisation rate with transfected cell lines, and pharmacokinetics was studied in a rat xenograft AR4-2J tumour model. They demonstrated that gallium-DOTA-octapeptides have distinctly better pre-clinical pharmacological performances than the indium-labelled peptides, especially on SST2-expressing cells.

Another application of the ^{68}Ga labelling technique concerns the field of melanocortin peptides (53). The melanocortins are involved in many physiological functions, among which pigmentation, steroidogenesis, temperature control, cardiovascular regulation and neuromuscular regeneration are the most important. Melanocortin receptors are expressed in several types of cells such as cutaneous melanocytes, keratinocytes, fibroblasts, endothelial cells, antigen-presenting cells and leukocytes. Since melanomas overexpress melanocortin receptor, radiolabelled -MSH analogs were developed for tumour imaging and staging (54). An MSH analogue, [Nle4,Asp5,D-Phe7]-MSH (4–11) (NAPamide), was conjugated to DOTA and labelled with ^{68}Ga to characterise both *in vitro* and *in vivo* the mouse B16F1 melanoma model. PET studies using ^{68}Ga-DOTA-NAPamide revealed high contrast images even at one hour after tracer administration (53). However, receptor density in human melanomas is much lower than that in the murine tumour model and therefore the preliminary experience on 5 patients gave negative results.

Another molecule of interest that was labelled with ^{68}Ga is bombesin. Bombesin receptors are overexpressed on major human tumours, in particular prostate and breast cancer (55-56). Therefore, radioligands based on bombesin were developed and studied in a pre-clinical setting and, subsequently, in patients (57-60). One example is a pancreatic carcinoma model (AR42J) that was evaluated with ^{68}Ga-DOTAPEG2-[D-Tyr6, Ala11,Thi13,Nle14] bombesin and shown to have good uptake by the tumour with a significant tumour-to-background ratio, ranging from 5.5 to 11, proving its potential role in the clinical practice (61).

Other gallium-related studies include the successful labelling with metronidazole to assess its potential use in the evaluation of tumour hypoxia, which can modulate the response to cancer therapy (62). Another factor that can affect successful chemotherapy in cancer patients is the overexpression of multidrug resistance (MDR1) P-glycoprotein (Pgp). Sharma and colleagues (63) examined Cell tracer transport experiments and mouse biodistribution using ^{68}Ga micro-PET imaging. They concluded that this modality may enable noninvasive PET monitoring of the blood brain barrier, chemotherapeutic regimens, and MDR1 gene therapy protocols *in vivo*.

An interesting, pre-clinical application of ^{68}Ga that could eventually meet non-oncological but extremely interesting clinical interests concerns the evaluation of infection. ^{67}Ga-citrate has been used for decades for the imaging of infection as it binds to the circulating transferrin and enters inflammated cells through the transferrin receptors. ^{68}Ga has the same chemical characteristics and in theory should be at least as accurate (if not better due to enhanced resolution) compared to ^{67}Ga for the detection of infection. Màkinen and co-workers created a rat model of *Staphylococcus aureus*-induced osteomyelitis and evaluated their animals both with FDG and with ^{68}Ga small animal PET to define the accuracy of this new tracer (64). They found that ^{68}Ga-PET is feasible for the imaging of bone infections, suggesting its potential role in the clinical practice. This is still far from being applied in clinical practice, but the prospect is both exciting and promising.

Conclusion

The recent introduction of PET imaging with gallium-68 has major bearings in current and future clinical practice. Its labelling with DOTA compounds has cleared the way for somatostatin receptor imaging with a viable PET agent, with all its inherent imaging advantages compared to single photon imaging. The clinical application of this technique has been successful in a variety of tumours, particularly

NET and its labelling with other ligands and molecules will improve the management of other tumours and the assessment of infection. The pre-clinical research in the use of this tracer, in its various possible radiopharmaceutical preparations, started recently and will undoubtedly have a bigger impact on its clinical use.

References

1 Kwekkeboom DJ and Krenning EP: *In*: Peptide Receptor Imaging. Cook JR, Maisey MN, Britton KE and Chengazi V (eds.). Clinical Nuclear Medicine 4th Edition. New York, Oxford University Press, 2006.

2 Reubi JC, Schaer JC, Markwalder R, Waser B, Horisberger U and Laissue J: Distribution of somatostatin receptors in normal and neoplastic human tissues: recent advances and potential relevance. Yale J Biol Med *70*: 471-479, 1997.

3 Reubi JC: Regulatory peptide receptors as molecular targets for cancer diagnosis and therapy. Q J Nucl Med *41*: 63-70, 1997.

4 Schonbrunn A: Somatostatin receptors: present knowledge and future directions. Ann Oncol *10(Suppl 2)*: S17-S21, 1999.

5 Reubi JC, Schar JC, Waser B, Wenger S, Heppeler A, Schmitt JS and Macke HR: Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin tracers selected for scintigraphic and radiotherepeutic use. Eur J Nucl Med *27*: 273-282, 2000.

6 Duncan JR, Stephenson MT, Wu HP and Anderson JC: Indium-111-diethylenetriaminepentaacetic acid-octreotide is delivered *in vivo* to pancreatic, tumour cell, renal and hepatocyte lysosomes. Cancer Res *57*: 659-671, 1997.

7 Andersson P, Forssell-Aronsson E, Johanson V, Wangberg B, Nilsson O, Fjalling M and Ahlman H: Internalisation of indium-111 into human neuroendocrine tumor cells after incubation with indium-111-DTPA-D-Phe^1-octreotide. J Nucl Med *37*: 2002-2006, 1996.

8 Buscombe J: Radiolabelled somatostatins: towards the magic bullet? Nucl Med Commun *20*: 299-301, 1999.

9 Arnold R, Tautmann ME, Creutzfeldt W, Benning R, Benning M, Neuhaus C, Jùrgensen R, Stein K, Schàfer H, Bruns C and Dennler HJ: Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. Gut *38*: 430-438, 1996.

10 Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY, van Hagen M, Postema PT, de Jong M and Reubi JC: Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phe1]- and [^{123}I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med *20*: 716-731, 1993.

11 Kwekkeboon DJ and Krenning EP: Radiolabelled somatostatin analog scintigraphy in oncology and immune disease: an overview. Eur Radiol *7*: 1103-1109, 1997.

12 Kwekkeboon DJ, Krenning EP and de Jong M: Peptide receptor imaging and therapy. J Nucl Med *41*: 1704-1713, 2000.

13 Lamberts SW, Hofland LJ, van Koetsveld PM, Reubi JC, Bruining HA, Bakker WH and Krenning EP: Parallel *in vivo* and *in vitro* detection of functional somatostatin receptors in human endocrine pancreatic tumors: consequences with regard to diagnosis, localization, and therapy. J Clin Endocrinol Metab *71*: 566-574, 1990.

14 Schillaci O, Rita M and Scopinaro F: ^{111}In-pentetreotide scintigraphy in the detection of insulinomas: Importance of SPECT imaging. J Nucl Med *41*: 459-462, 2000.

15 Kwekkenboom DJ, Reubi JC, Lamberts SWJ, Bruining HA, Mulder AH, Oei HY and Krenning EP: *in vivo* somatostatin receptor imaging in medullary thyroid carcinoma. J Clin Endocrinol Metab *76*: 1413-1417, 1993.

16 Adams S, Baum RP, Hertel A, Schumm-Draeger PM, Usadel KH and Hor G: Comparison of metabolic and receptor imaging in recurrent medullary thyroid carcinoma with histopathological findings. Eur J Nucl Med *25*: 1277-1283, 1998.

17 Baudin E, Lumbroso J, Schlumberger M, Leclere J, Giammarile F, Gardet P, Roche A, Travagli JP and Parmentier C: Comparison of octreotide scintigraphy and conventional imaging in medullary thyroid carcinoma. J Nucl Med *37(6)*: 912-916, 1996.

18 de Jong M, Kwekkeboom DJ, Valkema R and Krenning EP: *In*: Endocrine: peptides. Cook JR, Maisey MN, Britton KE and Chengazi V (eds.). Clinical Nuclear Medicine 4th Edition. New York, Oxford University Press, 2006.

19 Kwekkeboom DJ, Kooij PP, Bakker WH, Macke HR and Krenning EP: Comparison of ^{111}In-DOTA-Tyr3-octreotide and ^{111}In-DTPA-octreotide in the same patients: biodistribution, kinetics, organ and tumour uptake: J Nucl Med *40*: 762-767, 1999.

20 Rufini V, Calcagni ML and Baum RP: Imaging of neuroendocrine tumours. Semin Nucl Med *36*: 228-247, 2006.

21 Green MS and Welch MJ: Gallium radiopharmaceutical chemistry. Int J Rad Appl Instrum B *16*: 435-448, 1989.

22 Hnatowich DJ: A review of radiopharmaceutical development with short-lived generator-produced radionuclides other than ^{99m}Tc. Int J Appl Radiat Isot *28*: 169-81, 1997.

23 Maecke HR and Andre JP: ^{68}Ga-PET radiopharmacy: a generator-based alternative to ^{18}F-radiopharmacy. Ernst Schering Res Found Workshop *62*: 215-242, 2007.

24 Maecke HR, Hofmann M and Haberkorn U: (68)Ga-labeled peptides in tumor imaging. J Nucl Med *46(Suppl 1)*: 172S-178S, 2005.

25 Henze M, Schumacher J, Hipp P, Kowalski J, Becker DW, Doll J, Macke HR, Hofmann M, Debus J and Haberkorn U: PET imaging of somatostatin receptors using [68GA]DOTA-D-Phe1-Tyr3-octreotide: first results in patients with meningiomas. J Nucl Med *42*: 1053-1056, 2001.

26 Henze M, Dimitrakopoulou-Strauss A, Milker-Zabel S, Schumacher J, Strauss LG, Doll J, Màcke HR, Eisenhut M, Debus J and Haberkorn U: Characterization of ^{68}Ga-DOTA-D-Phe1-Tyr3-octreotide kinetics in patients with meningiomas. J Nucl Med *46*: 763-769, 2005.

27 Hofmann M, Maecke H, Borner A, Weckesser E, Schoffski P, Oei L, Schumacher J, Henze M, Heppeler A, Mayer J and Knapp H: Biokinetics and imaging with the somatostatin receptor PET radioligand ^{68}Ga-DOTATOC: preliminary data. Eur J Nucl Med *28*: 1751-1757, 2001.

28 Kowalski J, Henze M, Schuhmacher J, Macke HR, Hofmann M and Haberkorn U: Evaluation of positron emission tomography imaging using [^{68}Ga]-DOTA-DPhe1-Tyr3-Octreotide in comparison to [^{111}In]-DTPAOC SPECT. First results in patients with neuroendocrine tumors. Mol Imaging Biol *5*: 42-48, 2003.

29 Koukouraki S, Strauss LG, Georgoulias V, Schuhmacher J, Haberkorn U, Karkavitas N and Dimitrakopoulou-Strauss A: Evaluation of the pharmacokinetics of ^{68}Ga-DOTATOC in patients with metastatic neuroendocrine tumours scheduled for ^{90}Y-DOTATOC therapy. Eur J Nucl Med Mol Imaging *33*: 460-466, 2006.

30 Koukouraki S, Strauss LG, Georgoulias V, Eisenhut M, Haberkorn U and Dimitrakopoulou-Strauss A: Comparison of the pharmacokinetics of (68)Ga-DOTATOC and [(18)F]FDG in patients with metastatic neuroendocrine tumours scheduled for (90)Y-DOTATOC therapy. Eur J Nucl Med Mol Imaging *33*: 1115-1122, 2006.

31 Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, von Guggenberg E, Bale R and Virgolini IJ: ^{68}Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med *48*: 508-518, 2007.

32 Jalil ND, Pattou FN, Combemale F, Chapuis Y, Henry JF, Peix JL and Proye CA: Effectiveness and limits of preoperative imaging studies for the localisation of pheochromocytomas and paragangliomas: a review of 282 cases. Eur J Surg *164*: 23-28, 1998.

33 Whalen RK, Althausen AF and Daniels GH: Extra-adrenal pheochromocytoma. J Urol *147*: 1-10, 1992.

34 van der Harst E, de Herder WW, Bruining HA, Bonjer HJ, de Krijger RR, Lamberts SWJ, van de Meiracker AH, Boosma F, Stijnen T, Krenning EP, Bosman FT and Kwekkeboom DJ: ^{123}[I]Metaiodobenzylguanidine and ^{111}[In]octreotide uptake in benign and malignant pheochromocytomas. J Clin Endocrinol Metab *86*: 685-693, 2001.

35 Maurea S, Lastoria S, Caraco C, Klain M, Varrella P, Acampa W, Muto P and Salvatore M: The role of radiolabeled somatostatin analogs in adrenal imaging. Nucl Med Biol *23*: 677-680, 1996.

36 Win Z, Rahman L, Murrell J, Todd J and Al-Nahhas A: The possible role of ^{68}Ga-DOTATATE PET in malignant abdominal paraganglioma. Eur J Nucl Med Mol Imaging *33*: 506, 2006.

37 Win Z, Al-Nahhas A, Towey D, Todd JF, Rubello D, Lewington V and Gishen P: ^{68}Ga-DOTATATE PET in neuroectodermal tumours: First Experience. Nucl Med Commun *28*: 359-363, 2007.

38 Virgolini I, Traub T, Novotny C, Leimer M, Fuger B and Li SR: Experience with indium-111 and yttrium-90-labeled somatostatin analogs. Curr Pharm Des *8*: 1781-1807, 2002.

39 Weiner RE and Thakur ML: Radiolabeled peptides in oncology: role in diagnosis and treatment. Bio Drugs *19*: 145-163, 2005.

40 Bakker WH, Breeman WA, Kwekkeboom DJ, De Jong LC and Krenning EP: Practical aspects of peptide receptor radionuclide therapy with [(177)Lu][DOTA0, Tyr3] octreotate. Q J Nucl Med Mol Imaging *50*: 265-271, 2006.

41 Dimitrakopoulou-Strauss A, Georgoulias V, Eisenhut M, Herth F, Koukouraki S and Macke HR: Quantitative assessment of SSTR2 expression in patients with non-small cell lung cancer using(68)Ga-DOTATOC PET and comparison with (18)F-FDG PET. Eur J Nucl Med Mol Imaging *33*: 823-830, 2006.

42 Yokoyama A, Ohmomo Y, Horiuchi K, Saji H, Tanaka H, Yamamoto K, Ishii Y and Torizuka K: Deferoxamine, a promising bifunctional chelating agent for labeling proteins with gallium: Ga-67 DF-HAS: concise communication. J Nucl Med *24*: 909-914, 1982.

43 Janoki AK, Harwig JF, Chanachai W and Wolf W: [^{67}Ga] desferrioxamine-HAS: synthesis of chelon protein conjugates using carboiimide as a coupling agent. Int J Appl Radiat Isot *34*: 871-787, 1983.

44 Koizumi M, Endo K, Kunimatsu M, Sakahara H, Nakashima T, Kawamura Y, Watanabe Y, Ohmomo Y, Arano Y and Yokoyama A: Preparation of ^{67}Ga-labeled antibodies using deferoxamine as a bifunctional chelate. An improved method. J lmmunol Methods *104*: 93-102, 1987.

45 Koizumi M, Endo K, Kunimatsu M, Sakahara H, Nakashima T, Kawamura Y, Watanabe Y, Saga T, Konishi J and Yamamuro T: ^{67}Ga-labeled antibodies for immunoscintigraphy and evaluation of tumor targeting of drug-antibody conjugates in mice. Cancer Res *48*: 1189-1194, 1988.

46 Pochon S, Buchegger F, Pelegrin A, Mach JP, Offord RE, Ryser JE and Rose K: A novel derivative of the chelon desferrioxamine for site-specific conjugation to antibodies. Int J Cancer *43*: 1188-1194, 1989.

47 Wagner SJ and Welch MJ: Gallium-68 labeling of albumin and albumin micro spheres. J NucI Med *20*: 428-433, 1979.

48 Hnatowich DJ and Schlegel P: Albumin microsphere labeled withGa-67 by chelation: concise communication. J Nucl Med *22*: 623-626, 1981.

49 Schuhmach J, Meratys R and Hauser H: Labeling monoclonal antibodies with a ^{67}Ga-henolicaminocarboxylic acid chelate. Eur J Nucl Med *12*: 397-404, 1986.

50 Smith-Jones PM, Stolz B, Bruns C, Albert R, Reist HW, Fridrich R and Macke HR: Gallium-67/gallium-68-[DFO]-octreotide – a potential radiopharmaceutical for PET imaging of somatostatin receptor-positive tumors: synthesis and radiolabeling *in vitro* and preliminary *in vivo* studies. J Nucl Med *35*: 317-325, 1994.

51 Roivainen A, Tolvanen T, Salomäki S, Lendvai G, Velikyan I, Numminen P, Vàlilà M, Sipilà H, Bergstròm M, Hàrkònen P, Lònnberg H and Làngstròm B: ^{68}Ga-labeled oligonucleotides for *in vivo* imaging with PET. J Nucl Med *45*: 347-355, 2004.

52 Antunes P, Ginj M, Zhang H, Waser B, Baum RP, Reubi JC and Maecke H: Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? Eur J Nucl Med Mol Imaging *34*: 982-993, 2007.

53 Froidevaux S, Calame-Christe M, Schuhmacher J, Tanner H, Saffrich R, Henze M and Eberle AN: A gallium-labeled DOTA-alpha-melanocyte-stimulating hormone analog for PET imaging of melanoma metastases. J Nucl Med *45*: 116-123, 2004.

54 Eberle AN: Proopiomelanocortin and the melanocortin peptides. *In*: The Melanocortin Receptors. Cone RD (ed.). Totowa, NJ: Humana Press Inc, pp. 3-67, 2000.

55 Gugger M and Reubi JC: Gastrin-releasing peptide receptors in non-neoplastic and neoplastic human breast. Am J Pathol *155*: 2067-2076, 1999.

56 Markwalder R and Reubi JC: Gastrin-releasing peptide receptors in the human prostate: relation to neoplastic transformation. Cancer Res *59*: 1152-1159, 1999.

57 Van de Wiele C, Dumont F, Vanden Broecke R, Oosterlinck W, Cocquyt V, Serreyn R, Peers S, Thornback J, Slegers G and Dierckx RA: Technetium-99m RP527, a GRP analogue for visualisation of GRP receptor-expressing malignancies: a feasibility study. Eur J Nucl Med *27*: 1694-1699, 2000.

58 Breeman WA, de Jong M, Erion JL, Bugaj JE, Srinivasan A, Bernard BF, Kwekkeboom DJ, Visser TJ and Krenning EP: Pre-clinical comparison of (111)In-labeled DTPA- or DOTA-bombesin analogs for receptor-targeted scintigraphy and radionuclide therapy. J Nucl Med *43*: 1650-1656, 2004.

59 Smith CJ, Sieckman GL, Owen NK, Hayes DL, Mazuru DG, Kannan R, Volkert WA and Hoffman TJ: Radiochemical investigations of gastrin-releasing peptide receptor-specific [(99m)Tc(X)(CO)3-Dpr-Ser-Ser-Ser-Gln-Trp-Ala-Val-Gly-His-Leu-Met-(NH_2)] in PC-3, tumor-bearing, rodent models: syntheses, radiolabeling, and *in vitro/in vivo* studies where Dpr=2, 3-diaminopropionic acid and X=H_2O or P(CH_2OH)$_3$. Cancer Res *63*: 4082-4088, 2003.

60 Nock B, Nikolopoulou A, Chiotellis E, Loudos G, Maintas D, Reubi JC and Maina T: [^{99m}Tc]demobesin 1, a novel potent bombesin analogue for GRP receptor-targeted tumour imaging. Eur J Nucl Med Mol Imaging *30*: 247-258, 2003.

61 Schuhmacher J, Zhang H, Doll J, Macke HR, Matys R, Hauser H, Henze M, Haberkorn U and Eisenhut M: GRP receptor-targeted PET of a rat pancreas carcinoma xenograft in nude mice with a ^{68}Ga-labeled bombesin(6-14) analog. J Nucl Med *46*: 691-699, 2005.

62 Ito M, Yang DJ, Mawlawi O, Mendez R, Oh CS and Azhdarinia A: PET and planar imaging of tumor hypoxia with labeled metronidazole. Acad Radiol *13*: 598-609, 2006.

63 Sharma V, Prior JL, Belinsky MG, Kruh GD and Piwnica-Worms D: Characterization of a ^{67}Ga/^{68}Ga radiopharmaceutical for SPECT and PET of MDR1 P-glycoprotein transport activity *in vivo*: validation in multidrug-resistant tumors and at the blood-brain barrier. J Nucl Med *46*: 354-364, 2005.

64 Mäkinen TJ, Lankinen P, Pöyhönen T, Jalava J, Aro HT and Roivainen A: Comparison of ^{18}F-FDG and ^{68}Ga PET imaging in the assessment of experimental osteomyelitis due to *Staphylococcus aureus*. Eur J Nucl Med Mol Imaging *32*: 1259-1268, 2005.

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