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EDITORIAL

Exploring new frontiers in molecular imaging: Emergence of ^{68}Ga PET/CT

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Abstract

Since US Food and Drug Administration approval of 18-fluorodeoxyglucose as a positron tracer, and the development of hybrid positron emission tomography/computed tomography machines, there has been a great increase in clinical application and progress in the field of nuclear molecular imaging. However, not underestimating the value of ^{18}F, there are known limitations in the use of this cyclotron-produced positron tracer. We hence turn our focus to an emerging positron tracer, ^{68}Ga, and examine the advantages, current clinical uses and potential future applications of this radioisotope.

Key words: Gallium 68; Positron emission tomography; computed tomography; Neuroendocrinology

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THE DEVELOPMENT OF POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) imaging is essentially a story of a technique in wait of a technology. Since the discovery of positron emission in 1933 by Thibaud and Joliot *et al*, and the subsequent report of the coincident nature of emissions by Klemperer and Beringer, it has in effect taken close to half a century for the full realization of PET imaging in mainstream medical practice[1].

The history of PET development is a fascinating look into the technological advances in molecular medicine, and the account of Terry Jones provides fascinating reading[1].

The first use of positron tracers was likely performed in the 1940s using ^{11}CO in animal models[2], with its first possible use in humans performed in the 1950s at the Hammersmith Hospital in London, United Kingdom using $^{15}O_2$ in studies of lung ventilation[3]. This was followed by increasing use of positron tracers in the physiological assessment of lung function, which resulted in the installation of the world's first hospital-based cyclotron in 1955. Subsequently, development shifted into myocardial perfusion[4], cerebral perfusion[5-7], and of course, glucose metabolism[8-11].

This development in positron tracers mirrored the progress in positron imaging. In the 1970s, Massachusetts General Hospital developed, what was then, the most advanced coincidence positron camera system, with a spatial resolution of approximately 1 cm[12]. This was followed by developments predominantly in single photon emission computed tomography (SPECT) with work done by Kuhl, Budinger and Gullberg, and in 1974, there were reports of the development of a dedicated single-plane positron emission transaxial tomograph, which was the precursor to the current PET systems.

These developments explain the slow implementation of PET into clinical practice, as synchronous developments in both tracer and detector technology were re-

quired to reach a certain threshold before adoption by the clinical community.

Molecular imaging has thus seen explosive growth and mainstream adoption since the US Food and Drug Administration (FDA) approval of 18-fluorodeoxyglucose (FDG) as a radiopharmaceutical in 1997, accelerated by the emergence of hybrid imaging typified by PET/computed tomography (CT) scanners. The development of such dual or hybrid modality PET/CT imaging has addressed the fundamental problems of PET imaging; namely, the limited spatial ability and the absence of anatomical landmarks, and this has resulted in widespread clinical adoption and acceptance. However, whole-body PET/CT imaging involves increased patient radiation exposure compared to single modality imaging, with the effective dose per PET/CT scan of approximately 25 mSv[13]. Hence, patient selection for PET/CT imaging has to be justified, and further dose reduction strategies are needed.

Nevertheless, the success of FDG PET/CT imaging sets the stage for the future development of positron-based functional imaging, buoyed by the realization of the advantages provided by such hybrid diagnostics.

PRINCIPLES OF MOLECULAR IMAGING

The basis of molecular imaging lies with the targeted detection of specific cell targets or receptors. Receptor-specific molecules often bind to their receptors with high affinity and low dissociation rates[14]. However, for purposes of diagnostic imaging, the concentration of receptor molecules in target tissue may be hard to differentiate from background non-specific binding[15]. Thus, molecular imaging has often been confined to nuclear-based techniques such as PET or SPECT, which are able to generate images with micromolar to picomolar concentrations of imaging probes[16].

Theoretically, there are multiple radionuclides that are of potential use in PET imaging. However in practice, most of these radionuclides are unsuitable for a variety of reasons, including availability and cost constraints, production issues, and the intrinsic decay properties of the radionuclides (Table 1). ^{18}F is the most widely used positron tracer currently, and is produced in a cyclotron, most often utilizing either a neon gas target or an oxygen-enriched water target[17]. It possesses a half-life of 109.8 min, mass of 18.0009380, with a maximum energy and range of 0.69 MeV and 2.4 mm, respectively.

However, there are distinct limitations in using ^{18}F as a positron tracer. Firstly, the short half-life of ^{18}F requires close physical proximity of a cyclotron facility to the imaging center, thus PET imaging centers are in essence "tethered" to cyclotrons.

Secondly, the infrastructure set-up and maintenance of a production cyclotron facility requires substantial financial and manpower resources, and this often limits PET imaging to countries with the necessary resources to support such molecular imaging.

Thirdly, ^{18}F is available mainly as an ion in aqueous solution that must be taken to a dry organic environment for subsequent radiolabeling, and hence requires specially designed radiopharmacy facilities in addition to the cyclotron, which implies yet again significant resource investment.

Table 1 Examples of positron emitting radionuclides

Radionuclide	Half-life	Positron decay (%)	Emax (keV)	Production
^{11}C	20.3 min	100	961	Cyclotron
^{13}N	9.97 min	100	1190	Cyclotron
^{15}O	2.1 min	100	1732	Cyclotron
^{18}F	110 min	97	634	Cyclotron
^{64}Cu	12.8 h	19	656	Cyclotron
^{68}Ga	67.6 min	89	1899	Generator
^{82}Rb	76 s	95	3150	Generator
^{124}I	4.17 d	23	2100	Cyclotron

^{68}Ga

^{68}Ga is a metallic positron emitter with a physical half-life of approximately 68 min and mass of 67.93. It decays predominantly through positron emission (89%) of 1.92 MeV and partially through electron capture (11%), into stable ^{68}Zn[18].

It is available from a long-lived parent radionuclide ^{68}Ge, with a half-life of 288 d, which can be adsorbed to solids from which ^{68}Ga can be eluted. Hence, a generator-based source can be developed, and in fact several have been described. Current ^{68}Ge/^{68}Ga radionuclide generators are most commonly based on a TIO_2 solid phase[19], from which ionic $^{68}Ga^{3+}$ can be easily eluted.

There are several advantages in using ^{68}Ga. Firstly, ^{68}Ga is generator-based, and hence there are no requirements for a cyclotron facility, with the isotope continuously available from the generator. Secondly, ^{68}Ga is a radiometal and can be more easily complexed using suitable chelating agents to targeting ligands, as compared with the more complex organic chemistry and purification requirements of ^{18}F and most other cyclotron-based positron emitters. Examples of bifunctional chelators include EDTA and diethylenetriaminepentaacetic acid (DTPA). Thirdly, the long half-life of the parent radionuclide allows the use of the generator for long periods, possibly a year and longer, and the short half-life of ^{68}Ga matches the pharmacokinetics of numerous small peptides[20].

Currently enjoying resurgence, ^{68}Ga has in fact been in clinical practice since the 1950s, and increased interest was stirred when a practical gallium parent--daughter generator system was developed in the early 1960s[21]. Researchers and clinicians then and now understood the advantages of a generator-based positron isotope[22,23].

However, as mentioned earlier, the development of nuclear-based molecular imaging has only blossomed in recent years due to the concomitant development of synergistic technologies. Despite the recognized potential of ^{68}Ga, it was not routinely used in clinical practice until recently. It is probable that advances in the development of radiolabeled peptides for diagnostic and therapeutic

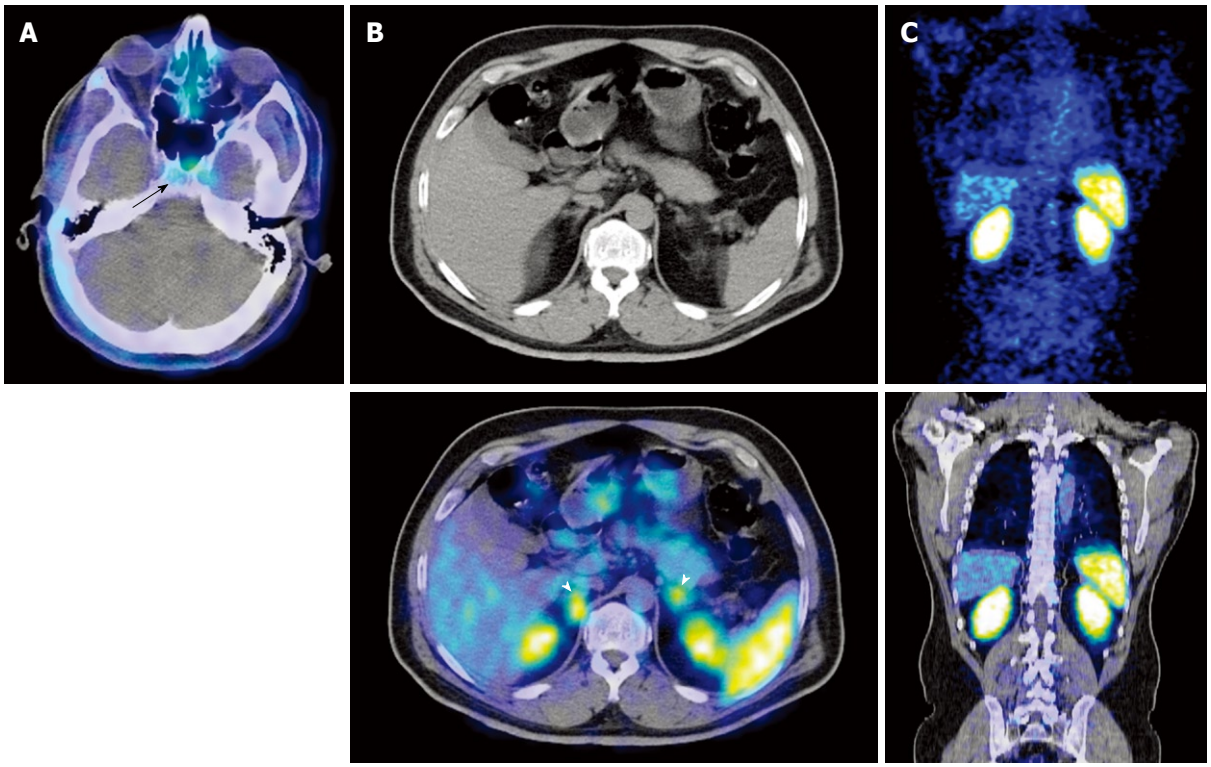

Figure 1 Examples of physiological areas of uptake in somatostatin receptor scintigraphy. A: Axial positron emission tomography (PET)/computed tomography (CT) of the base of skull demonstrates avid uptake in the pituitary fossa (black arrow) corresponding to physiological uptake in the pituitary gland; B: Axial CT and PET/CT of the abdomen demonstrates physiological uptake in the adrenals glands (white arrowheads); C: Coronal PET and PET/CT sections demonstrate avid tracer uptake in the kidneys and spleen.

purposes have contributed substantially to the current emergence of ^{68}Ga as a positron tracer, specifically in somatostatin receptor scintigraphy.

SOMATOSTATIN RECEPTOR SCINTIGRAPHY

Somatostatin is a naturally occurring peptide with various biological functions that mediates its action through several membrane-bound somatostatin receptors. Currently, five subtypes of somatostatin receptors have been identified in humans (SSRT1, SSRT2, SSRT3, SSRT4, SSRT5), with SSRT2 further classified into subtypes 2A and 2B[24].

The distribution of various SSRT subtypes in human organ systems have been studied fairly extensively (Figure 1). Somatostatin receptor expression is found in a large number of tumors. Neuroendocrine tumors are the archetypical class that has been extensively imaged and treated using somatostatin analogues, but other tumors such as neuroblastoma, meningioma, breast cancer, lymphoma, renal cell carcinoma, hepatoma and pheochromocytoma are also known to express somatostatin receptors[25,26].

The principle of somatostatin receptor imaging is based on linking a stable somatostatin type ligand to a radioisotope (e.g. ^{111}In, ^{99m}Tc, ^{68}Ga) *via* a chelating agent before administration into the patient, where uptake in the target tissue is dependent on SSRT-mediated internalization of the radioligand. *In vitro* studies have found that each of the different SSRT subtypes internalizes SSRT-ligands differently, and uptake of octreotide in SSRT-positive organs is determined predominantly by SSRT2[27].

The half-life of somatostatin itself is short (< 2 min), thus it is unsuitable for use in either diagnosis or therapy. Hence, there has been development of synthetic somatostatin analogues with a sufficiently long half-life for use in diagnostic imaging or therapeutics.

The first radiolabeled somatostatin analogue Octreoscan® [^{111}In-DTPA-octreotide, D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr(ol)] was approved in the early 1990s for use in patients with neuroendocrine disease[28]. Octreotide is an eight-amino acid analogue of somatostatin with four identical amino acids, with a longer half-life and greater affinity for SSRT2, SSRT3 and SSRT5, which makes a safe and sensitive imaging modality for the detection of gastroenteropancreatic neuroendocrine tumors[29,30].

Since then, octreotide derivatives have been developed, allowing stable labeling with radiometals, as well as increased affinity for somatostatin receptor as compared with Octreoscan®. Most of these analogues utilize 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) as the chelating agent, which forms thermodynamically and kinetically stable metal complexes. Common examples of such newer somatostatin analogues include: (1) TOC [D-Phe-Cys-Try-D-Trp-Lys-Thr-Cys-

Thr(ol)] in which replacement of Phe with Tyr at position 3 results in increased internalization and higher contrast uptake *in vivo* as compared with octreotide; (2) TATE (D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr), an analogue in the hydroxy group at the C terminus is changed to a free carboxylic group. This results in further increased binding affinity, internalization rates and selectivity for SSRT-2[31]; and (3) NOC [D-Phe-Cys-Nal-D-Trp-Lys-Thr-Cys-Thr(ol)], where replacement of Phe with Nal results in a compound with high affinity to SSRT2, SSRT3 and SSRT5[32].

^{68}Ga SOMATOSTATIN RECEPTOR SCINTIGRAPHY

The team in Zentralklinik Bad Berka, Germany has had extensive experience with receptor PET/CT imaging utilizing ^{68}Ga-labeled somatostatin analogues, where more than 2300 cases have been reported as of early 2009[33]. In general, they found that ^{68}Ga somatostatin receptor scintigraphy imaging was a flexible, fast modality, with a low radiation burden and apparently lower costs, as compared with Octreoscan®. In addition, semi-quantitative reproducible standardized uptake values were utilized in selecting patients for peptide receptor radionuclide therapy (PRRT) and evaluation of treatment response. Expression of somatostatin analogues has been found in a wide variety of tumors, and therefore, ^{68}Ga somatostatin receptor scintigraphy (SRS) has broad clinical applications. Several of these applications are discussed below.

NEUROENDOCRINE TUMORS

Neuroendocrine tumors are a heterogeneous group of tumors that phenotypically are cancers that arise from neural crest tissue, and can hence arise from any part of the body depending on the distribution of the embryological tissue. The term neuroendocrine is derived from the relationship to neural cells in the expression of certain proteins such as synaptophysin, chromogranin, protein gene product 9.5 and neuron specific enolase (NSE).

Oberndorfer first coined the term "carcinoid" in 1907 to describe epithelial cells in the gut with a homogeneous structure with generally less aggressive features as compared with carcinomas[34]. However, the use of this term is at best heterogeneous among clinicians, and this in turn results in substantial confusion. It is for this reason that the term neuroendocrine tumor is preferred.

Diagnosis and assessment of neuroendocrine tumors are based on morphological, immunohistochemical and functional characteristics. The diagnosis of neuroendocrine tumors relies heavily on the positive detection of markers by immunohistochemistry, such as NSE, protein gene product 9.5, chromogranin A and synaptophysin[35]. Neuroendocrine tumors associated with hyperfunctional symptoms are termed functional, whereas those not associated with symptoms are termed non-functional.

The World Health Organization (WHO) classification for neuroendocrine tumor for the gastroenteropancreatic system is divided into several broad categories[36], with a general categorization based on histomorphology, tumor size, angio-invasion, organ-specific invasion, proliferation index, metastasis and functional/hormonal status[37].

Neuroendocrine tumors of the gastroenteropancreatic system are by far the most common (70%), with the bronchopulmonary system also accounting for a significant proportion (25%)[38]. Our discussion will focus predominantly on the gastroenteropancreatic system, but general principles are likely applicable to neuroendocrine tumors in other parts of the body.

These were the first tumors for which SRS was utilized and proven a viable clinical tool, and SRS using Octreoscan® was considered the gold standard in the diagnosis, staging and follow-up of patients with neuroendocrine tumors. As such, these were among the first tumors for which ^{68}Ga SRS was attempted.

Hofmann *et al*[39] have compared the utility of ^{68}Ga-DOTA-TOC PET with conventional SRS in patients with histologically proven neuroendocrine tumors, and have found higher tumor to non-tumor contrast ratios, with significantly higher detection ratios for ^{68}Ga SRS. This has been followed up by Kowalski *et al*[40], who also have compared these two techniques, and have found that ^{68}Ga SRS was again able to detect more lesions and was superior in detecting smaller lesions with lower uptake.

These findings were further supported by Buchmann *et al*[41], who prospectively evaluated 27 patients with known neuroendocrine tumors with ^{68}Ga-DOTA-TOC PET and ^{111}In-DTPA-octreotide SPECT for the detection of tumor characteristics. They have concluded that ^{68}Ga-DOTA-TOC PET is superior to ^{111}In-DTPA-octreotide SPECT for the detection of neuroendocrine tumor manifestations in the lung and skeleton, and similar for their detection in the liver and brain.

Ambrosini *et al*[42] have compared the use of ^{68}Ga-DOTA-NOC PET/CT with ^{68}Ga SRS in the assessment of histologically proven, well-differentiated bronchial carcinoids, and have found that the latter is better than contrast-enhanced CT for the evaluation and determination of disease extent.

Gabriel *et al*[43] have compared the diagnostic value of ^{68}Ga-DOTA-TOC with conventional scintigraphy and dedicated CT, and have found a sensitivity of 97%, specificity of 92%, and accuracy of 96%, which represents a significantly higher detection rate compared with that of conventional SRS or diagnostic CT.

In comparing the different somatostatin analogues, Antunes *et al*[44] have compared ^{68}Ga-DOTA-NOC with ^{68}Ga-DOTA-TATE and have found that the third-generation somatostatin analogue NOC has better preclinical and pharmacological performance, especially on SSRT2-expressing cells. This has particular clinical implications because SSRT2 receptors are important for ligand internalization.

Overall, ^{68}Ga-based SRS has been reported to have higher diagnostic sensitivity, specificity and accuracy compared with conventional diagnostic imaging and first-generation SRS[45]. PET imaging has intrinsic ad-

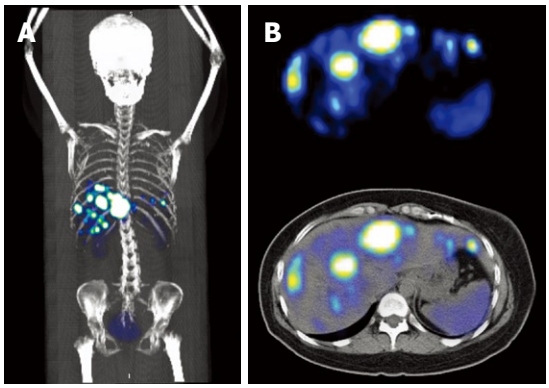

Figure 2 Metastatic pancreatic neuroendocrine carcinoma with multiple liver lesions. A: Coronal 3D reconstruction demonstrates multiple tracer avid lesions sited predominantly in the right hypochondrium; B: Axial PET and PET/CT of the liver shows multiple somatostatin receptor rich lesions in the liver.

vantages compared with conventional SRS: it has faster imaging turnover and increased spatial resolution.

Furthermore, as our understanding of tumor pathogenesis and histopathological characteristics increases, limitations of utilizing a single molecular target have emerged. Neuroendocrine tumors in particular have a wide range of cellular differentiation, and the molecular basis of SRS imaging is influenced by tumor grade (Figures 2 and 3).

Koukouraki *et al*[46] have evaluated 15 patients with 63 lesions using ^{68}Ga-DOTA-TOC and FDG-PET, and found that the global ^{68}Ga-DOTA-TOC uptake was mostly influenced by receptor affinity, whereas FDG uptake was predominantly influenced by fractional blood volume. Of further interest, Kayani *et al*[47] have compared ^{68}Ga-DOTA-TATE with FDG-PET/CT and have found a significant correlation between tumor uptake and histological grade, with ^{68}Ga SRS superior for well-differentiated neuroendocrine tumors and FDG-PET superior for poorly differentiated tumors.

These findings illustrate the heterogeneous nature of tumors and the challenge posed in molecular imaging, and raise the possibility of dual tracer imaging techniques in evaluating neuroendocrine tumors. However, further work in determining patient selection criteria needs to be done to balance the risk of increased radiation exposure against potential benefits.

NEUROGENIC AND NEUROECTODERMAL TUMORS

Although SRS has been used predominantly for neuroendocrine tumors, the expression of SSRTs is also found in a variety of other tumors, making them amenable to SRS.

Somatostatin receptor expression is found in neurogenic tumors (neuroblastoma, ganglioneuroblastoma and ganglioneuroma), which are tumors of the sympathetic nervous system that originate from neural crest tissue[48], but are histologically differentiated by the stage of neuroblast maturation[49]. The expression of SSRTs in these tumors allows for targeted imaging and therapy, and there is a direct association with the level of differentiation in such tumors, with SSRT expression being higher in benign ganglioneuroma and associated with favorable outcomes in advanced tumors[50]. The use of ^{68}Ga SRS in establishing prognosis and assessing suitability for PRRT are possibilities, and needs further study.

Neuroectodermal tumors (pheochromocytoma and paraganglioma) arise from either the chromaffin tissues of the adrenal medulla or other paraganglionic sites, and often express SSRTs. With regard to phaeochromocytoma, immunohistochemical assessments have found positive SSRT3 staining for a large majority of tumors (90%), with a significant portion (25%) demonstrating SSRT2A staining[51]. Pheochromocytoma is often staged locally using conventional diagnostic imaging modalities (CT or MRI), with metaiodobenzylguanidine (MIBG) scintigraphy utilized for N and M assessment.

Current understanding of the use of functional imaging in pheochromocytoma involves MIBG imaging in the detection of more well-differentiated tumors and FDG-PET in the detection of poorly differentiated types[52].

The role of SRS in the imaging assessment of pheochromocytoma is still indistinct, with the overall sensitivity of octreotide SRS reported to be about 30%[53].

However, several studies have demonstrated the complementary nature of SRS and MIBG functional imaging, where conventional SRS is able to detect tumor foci deemed negative by MIBG assessment, possibly because of dedifferentiation of the norepinephrine transporter system[54]. This result has been corroborated by a study in which ^{68}Ga-DOTA-TATE was used to assess malignant pheochromocytoma in comparison with CT and ^{123}I-MIBG in a small group of five patients, in whom SRS findings were positive for several lesions that had negative or low MIBG uptake (Figure 4)[55].

It is therefore possible to use SRS to determine disease prognosis, as well as suitability for PRRT. With the newer and expanded range of improved somatostatin analogues, and the increased intrinsic resolution of PET over planar imaging, ^{68}Ga SRS shows promise for clinical application.

NON-MEDULLARY THYROID TUMORS

The thyroid gland is composed of two major cell types: follicular cells that produce thyroxine and triiodothyronine, and parafollicular cells that produce calcitonin. Thyroid tumors can arise from these epithelial cells, or from the supporting stromal tissue itself, thus exhibiting a wide range of morphological and biological patterns.

Malignant thyroid tumors are classified according to several subtypes: follicular (encapsulated and widely invasive), papillary (classical or variants), anaplastic, and medullary[56]. Papillary and follicular type thyroid cancer form the majority of thyroid tumors.

The basis of SRS depends on the expression of SSRTs on the target tissue, and such receptors are widely

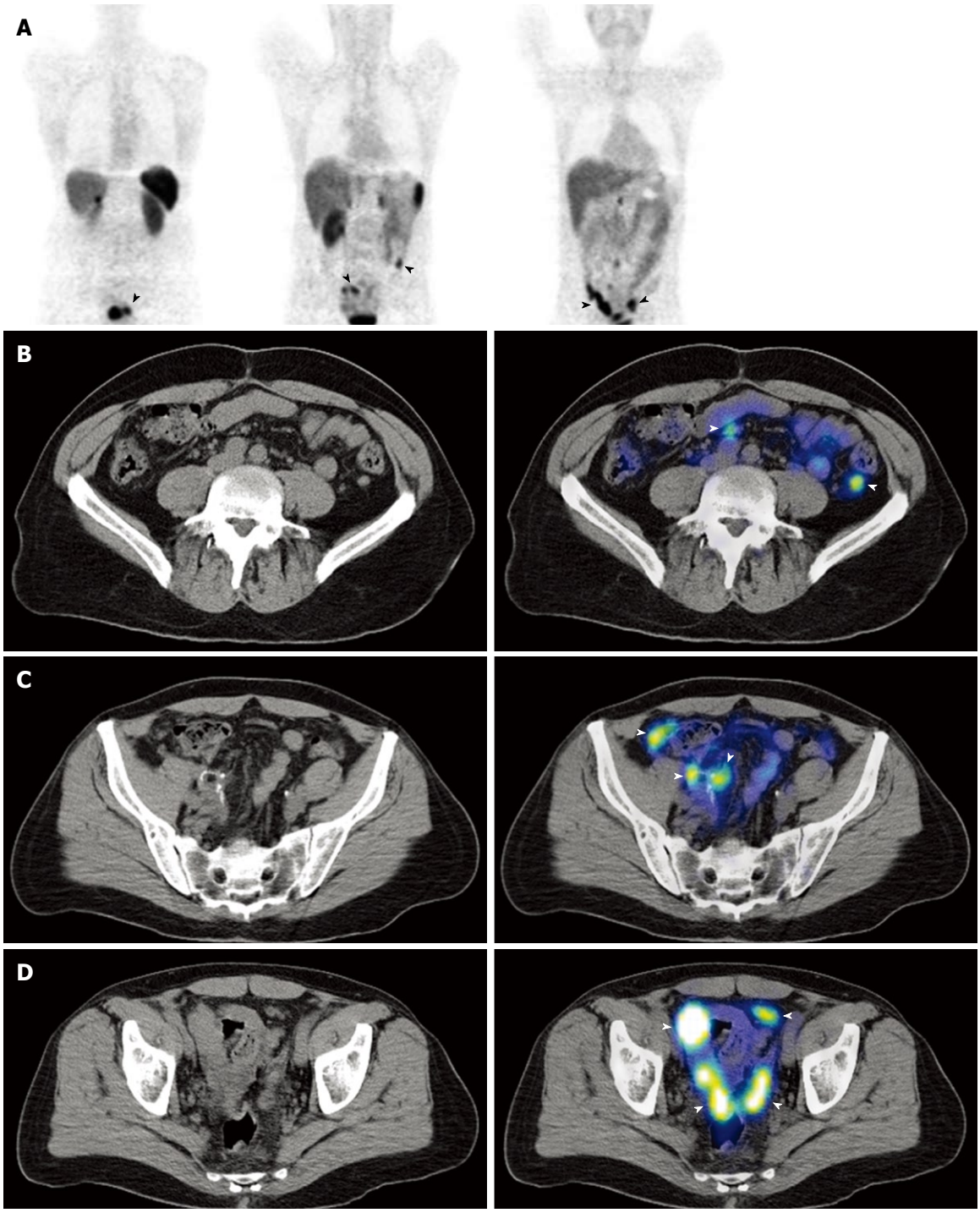

Figure 3 Metastatic appendiceal neuroendocrine carcinoma with multiple peritoneal deposits. A: Coronal PET images demonstrate multiple tracer avid foci projected over the abdomen and pelvis (black arrowheads); B-D: Axial CT and PET/CT sections of the abdomen show multiple somatostatin receptor rich peritoneal deposits (white arrowheads).

distributed in human thyroid diseases. However, there have been conflicting reports on the frequency and intensity of expression of specific receptor subtypes.

Pisarek *et al*[57] have reported that the SSTR1 protein was expressed in 88.8%, SSTR2A and 2B in 44.4%, SSTR3 in 55.5%, SSTR4 in 11.2%, and SSTR5 in 33.3% of cases, and have concluded that SSTR1 is the dominant form in thyroid gland tumors and hyperplasia.

In contrast, Druckenthaner *et al*[58] have reported that SSRT2 is the predominant receptor type in tumor cells, and have found it in > 68% of cases. SSRT3 was found in 31% of cases, SSRT5 in 44%, and SSRT1 and SSRT4 were not detected in any of the samples.

Forssell-Aronsson *et al*[59] have investigated tissue samples from 68 patients and have reported that all thyroid tumor types regularly express SSRT1, SSRT3, SSRT4 and SSRT5. Although SSRT2 is expressed in most medullary thyroid carcinomas, it is not detected in

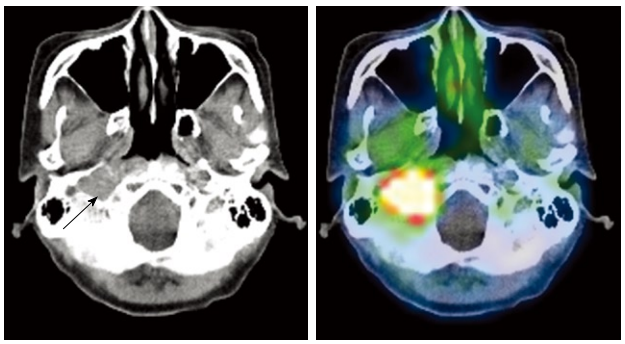

Figure 4 Malignant paraganglioma at the right jugular foramen. Axial CT and PET/CT of the base of skull. Soft tissue mass in the right jugular foramen showing intense tracer avidity, compatible with a somatostatin receptor expressing tumor.

follicular or papillary carcinoma subtypes. Ribonuclease protection assay however has detected SSRT2 expression in several samples deemed negative by northern blotting. In addition, despite the lack of SSRT2 expression detected by northern blotting, most tumors show uptake of radiolabeled octreotide analogues.

Ain *et al*[60] have reported that most thyroid cancer cell lines express SSRT3 and SSRT5, with varying SSRT1 expression and SSRT2 only faintly detectable. SSRT4 was found to be positive in only one of their samples. It has been suggested that SSRT5-specific analogues are the best suited for targeting, and that SSRT2-specific analogues are of little use.

The literature regarding somatostatin receptor expression on thyroid tumor lines is conflicting, and may be related to the different investigative methods used. SSRT expression in differentiated thyroid carcinoma may also be heterogeneous in nature, possibly accounting for the differences in the findings.

Nevertheless, the value of SRS in thyroid tumor imaging dates back to the mid 1990s, when ^{111}In-labeled octreotide was found to visualize non-medullary differentiated thyroid carcinoma[61]. Subsequently, several studies have followed that predominantly have focused on the clinical value of SRS in non-iodine-avid thyroid carcinoma, with sensitivities ranging from 19% to 100%[62]. Overall sensitivity by the largest group investigating 43 patients was reported to be 51%. The anatomical location of the tumor has a significant influence on tumor detection; mediastinal tumors had the highest detection rate, while small lesions in the neck and lung were missed[63]. The limitations of planar imaging and the inherent low-resolution capacity of earlier diagnostic modalities are likely contributors to the overall low sensitivity. With the advent of PET imaging and the development of newer somatostatin analogues, imaging sensitivity and specificity is expected to be significantly improved.

Similarly, ^{68}Ga SRS can be used clinically in patients with non-iodine-avid, non-medullary thyroid carcinoma for tumor localization, and assessment of suitability for PRRT and response to treatment. Our own experience of ^{68}Ga SRS for thyroid tumors is at an early stage, but current findings show promise, with imaging showing significant tracer uptake in non-iodine-avid lesions (Figure 5).

FDG PET/CT has demonstrated clinical utility in evaluating non-iodine-avid lesions, with sensitivity approaching 90%[64,65]. This peculiar phenomenon has been described by Feine *et al*[66] as the "flip-flop" mechanism, where the dedifferentiated tumors lose iodine trapping capability, but have increased glucose metabolism and *vice versa*.

To the best of our knowledge, there have been no studies comparing FDG with ^{68}Ga SRS PET/CT in the evaluation of non-iodine-avid lesions. It is possible that dedifferentiation of thyroid carcinoma results in sequential loss of function, starting from loss of iodine trapping to loss of somatostatin receptors, with an increase in glucose metabolic activity. This suggests the clinical utility of dual tracer PET/CT imaging for non-iodine-avid lesions for evaluating the proportion of somatostatin-receptor-avid lesions, which could have an impact on management decisions. Patients with somatostatin-receptor-avid lesions may benefit from PRRT[67], while those with solely FDG-avid lesions could benefit from trials of novel chemotherapy agents such as Sorafenib™[68]. Current studies concerning ^{68}Ga SRS for thyroid carcinoma are rare, and further investigations are needed.

MENINGIOMAS

Meningiomas are mesodermal type tumors, which represent a significant percentage (approximately 20%) of intracranial neoplasms, with an overall incidence of 2.3/100 000[69]. In general, surgical resection continues to be the mainstay of therapy, with complete removal providing the optimal chance for long-term remission. In patients for whom surgical options are not viable, external beam radiotherapy provides a safe palliative option[70]. Almost all meningiomas express a high SSRT2 density, and kinetic studies using ^{68}Ga-DOTA-TOC has demonstrated high uptake in such tumors as expected[71].

Clinical experiences are promising. Henze *et al*[72] have shown that ^{68}Ga DOTA-TOC PET/CT is able to demonstrate clear visualization of meningioma, even subcentimeter size lesions, with good sensitivity and specificity. They have concluded that ^{68}Ga SRS appears to be a promising modality for imaging meningioma, which offers excellent imaging properties and a high tumor-to-background ratio.

Aside from possible clinical use in surgical or radiotherapy planning, findings from ^{68}Ga SRS can be used to determine suitability for PRRT. Bartolomei *et al*[73] have found a promising response to ^{90}Y-DOTA-TOC therapy in 29 patients with histologically proven meningioma, and have alluded to the possible adjuvant role of PPRT.

OTHER ^{68}Ga-RADIOLABELED LIGANDS

Somatostatin receptor scintigraphy illustrates the archetypical use of ^{68}Ga in PET/CT imaging, but does not

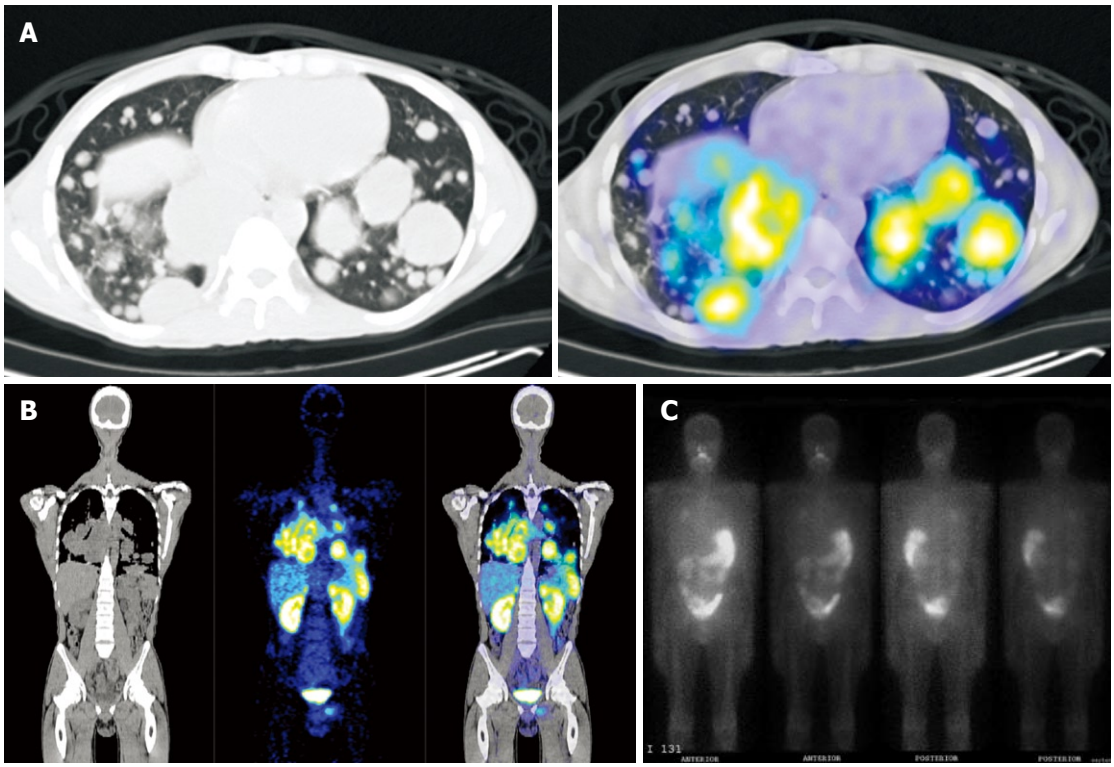

Figure 5 Metastatic non-iodine avid Hurthle cell thyroid carcinoma. A: Axial CT and PET/CT section of the thorax shows multiple pulmonary masses demonstrating avid tracer uptake; B: Coronal CT, PET and PET/CT images show somatostatin receptor rich pulmonary and mediastinal masses, and another discrete lesion projected over the left pelvis; C: I131 Whole body planar scan of the same patient shows only faint iodine uptake projected over the right upper lobe.

encompass its entire clinical spectrum. We thus discuss several promising ^{68}Ga-radiolabeled ligands and their potential clinical uses.

BOMBESIN

Bombesin was first described in 1970 by Erspamer *et al*. It was isolated from the skin of the *Bombina bombina* frog, and subsequently described in mammals by McDonald *et al* in 1979 and Minamino *et al* in 1983. Bombesin is a tetradecapeptide with a COOH terminus, which closely resembles gastrin-releasing peptide and neuromedin B[74].

These peptides elicit a variety of physiological actions in the nervous system and gastrointestinal tract, with current nomenclature describing three classes of receptors: BB1 (384 amino acids, neuromedin receptor), BB2 (390 amino acids, gastrin-releasing peptide receptor) and BB3 (399 amino acids, orphan receptor), each of which is a G-protein-coupled receptor with separate general characteristics[75].

Activation of the bombesin receptors is proposed to be important in the mediation of several disorders, as well as in the growth/differentiation of cancer. These receptors have been found to be overexpressed in a large number of tumors. For example, BB2 receptors have been found in tumors such as small cell lung cancer (85%-100%), non-small cell lung cancer (74%-78%) breast cancer (38%-72%), pancreatic cancer (10%), prostate cancer (62%-100%) and head/neck squamous cell carcinoma (100%) and neuroblastoma/ glioblastoma (72%-85%)[76]. In addition, these receptors have been found to have growth-promoting effects in several tumors[77].

Overexpression of these receptors allows for the targeted imaging and possible therapy of such tumors, with ongoing evaluation on the use of ^{68}Ga and other radioisotope-labeled bombesin analogues. Synthetic bombesin analogues can be categorized into two forms: type-A analogues are truncated peptides with only a portion retained, usually the BN (7-14) at the C terminus, and Type-B analogues, which are full-length synthetics. Type-A analogues are usually more accepted, as they are more stable *in vivo* and yet maintain acceptable receptor binding capability[77]. Examples of bombesin analogues include demobesin-1, AMBA, pesin, DOTABOM and RP527, all with altered amino acid sequences.

Dimitrakopoulou-Strauss *et al*[78] have investigated 17 patients with proven gastrointestinal stromal tumors (GISTs) using FDG- and ^{68}Ga-labeled bombesin analogue PET/CT. They found that, although FDG was superior in sensitivity and general tracer avidity, two false-positive lesions with FDG demonstrated uptake with the bombesin analogue. Thus, there is possibly a sub-group of GISTs that demonstrate enhanced bombesin receptor expression, but the clinical significance of this is still uncertain.

Prostate cancer is one of the most frequently diagnosed cancers in developed countries, and a significant cause of morbidity. Current non-invasive methods for imaging using MRI/CT/ultrasound have limitations and are of insufficient sensitivity in early tumor staging or

tumor recurrence. There have been prior investigations using predominantly ^{99m}Tc-labeled bombesin analogues, but the literature on PET imaging is scarce. Hofmann *et al*[79] have evaluated ^{68}Ga-labeled DOTABOM in 11 patients with prostate cancer. Peak tumor uptake was found at 15-25 min, with rapid renal excretion (> 75% injected dose recovered in the urine at 60 min). A transient reversible drop in systemic blood pressure was encountered in four patients. All tumor sites identified by the tracer was histologically proven, with the smallest tumor measuring 5 mm delineated, and it was concluded that ^{68}Ga-labeled DOTABOM appeared feasible in localizing the primary tumor and locoregional metastasis in patients with prostate carcinoma.

In addition to the above examples, radiolabeled bombesin analogues have shown promise in several other tumors such as breast[80] and colorectal cancers[81], using ^{99m}Tc as the radioisotope. Use of the ^{68}Ga PET tracer is being studied, and publications can be expected in the near future.

MELANOCYTE STIMULATING HORMONE (MSH) ANALOGUES

Melanomas are aggressive tumors arising from melanocytes, and can occur in any part of the body to which neural crest tissue migrates, with the skin being the most common primary site. There is an age-adjusted incidence rate of 19.6 per 100000 per year[82], with an estimated 70000 new cases encountered in the United States annually.

Prognosis and management depend on tumor staging, which is influenced by clinical and histological factors, as well as the presence of nodal and distant spread[83]. Although early-stage disease is curable in a significant proportion of patients, those with distant metastasis are rarely curable with standard therapy, and all such patients are considered candidates for clinical trials for new forms of therapy. Hence, accurate initial staging has a tangible clinical impact on prognosis and therapy stratification.

α-MSH peptides are tridecapeptides that are secreted by the pituitary gland, which target the melanocortin-1 receptor. This has been reported to have a > 80% expression rate in human melanoma[84], which indicates a potential clinical use of such peptide analogues in patients with melanoma.

In a preclinical study, Wei *et al*[85] have utilized DOTA-ReCCMSH (Arg11) as a melanocortin-1-receptor-targeting ligand, labeled with ^{68}Ga, for imaging B16/F1 melanoma tumor-bearing mice. They reported moderate receptor-mediated tumor uptake, fast non-target organ clearance, and high tumor to non-target tissue ratios.

Current strategies already include FDG PET/CT as part of the diagnostic workup for melanoma, with estimated 92% sensitivity and 90% specificity reported in a meta-analysis, and an overall FDG PET directed change in management value of 22%[86]. Hence, such ^{68}Ga-tagged α-MSH analogue ligands may be used for assessing suitability for PRRT in patients with advanced, non-curative malignant melanoma.

Table 2 Examples of FDA approved monoclonal antibodies

Generic name	Target	Type	Indication
Rituximab	CD20	Chimeric IgG1	Non-Hodgkins lymphomas
Trastuzumab	HER-2/neu	Humanized IgG1	Breast cancer
Alemtuzumab	CD52	Humanized IgG1	Chronic lymphaocytic leukaemia
Bevacizumab	VEGF	Humanized IgG1	Colorectal cancer Non-small cell lung cancer Breast cancer Glioblastoma Renal cancer
Cetuximab	EGFR	Chimeric IgG1	Colorectal cancer Head and neck cancer
Panitumumab	EGFR	Human IgG1	Colorectal cancer
Ofatumumab	CD20	Human IgG1	Chronic lymphocytic leukaemia
Gemtuzumab Ozogamicin	CD33	Humanized IgG4 conjugated to calicheamicin	Acute myeloid leukaemia
^{90}Y-Ibritumomab Tiuxetan	CD20	^{90}Y-radiolabeled murine IgG1	Non-Hodgkins lymphoma
^{131}I-Tositumomab	CD20	^{131}I-radiolabeled murine IgG2a	Non-Hodgkins lymphoma

FDA: Food and Drug Administration; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor.

IMMUNOSCINTIGRAPHY USING ^{68}Ga

Antibodies have been frequently utilized as targeting ligands for tumors and other lesions because of their ability to bind to specific targets on the intended tissue. Advances in cell biology and molecular techniques have also facilitated the discovery of novel new molecular targets on tumor cells, further spurring development of newer targeting monoclonal antibodies (mAbs). To date, there are multiple mAbs approved by the US FDA for use in the systemic treatment of cancer (Table 2).

The use of positron-emitting radiotracers such as ^{18}F- and ^{68}Ga-tagged mAb ligands is an attractive proposition that allows accurate localization of tumor tissues, with potential use in assessment of therapeutic suitability, prognosis, and response to treatment. We are possibly on the cusp of the "magic bullet" notion proposed by Paul Ehrlich, both in diagnostic and therapeutic applications.

mAbs are produced from a single B-cell clone, and it was the work of Köhler and Milstein in 1975, with the introduction of hybridoma technology, that led to the development of commercially and economically viable mAb production[87]. This is essentially the production of cell lines formed by the fusion of the specific antibody-

producing B cell with immortal myeloma cell lines, which results in a biological factory that produces a homogeneous and specific line of mAbs.

Immunoglobulins are designated IgG, IgM, IgE, IgA or IgD according to their general structure and can be further subdivided on basis of internal attributes. For example, IgG is a bivalent antibody that comprises two long and two short amino acid chains (heavy and light chains), with a total molecular weight of approximately 150 000 Da. Two antigen-binding Fab fragments contain the variable regions, which are unique for each mAb. The constant region of the antibody molecule is known as the Fc fragment.

An initial drawback in the early years was the immunogenic nature of such antibodies because of their murine origin. Immunogenicity attracted significant attention when such mAbs were utilized, with human anti-mouse antibody immunoreactions being encountered[88]. However, further developments in DNA recombination technology have led to development of partially and fully humanized antibodies, as well as antibodies with selected deletion of unfavorable domains (domain-deleted antibodies), which further diminishes the problems with immunogenicity[89].

Generally, whole mAbs have a long residence time *in vivo*, with optimal tumor-to-non-target tissue ratios at 2-4 d post administration. Conversely, mAb fragments reach optimal target tissue concentrations earlier and are cleared rapidly *in vivo*. This is because the smaller molecular size compared with whole antibodies allows for increased blood clearance and soft tissue penetration. However, absolute target concentrations are often lower.

The selection of a suitable mAb depends on several considerations: (1) serum half-life; (2) efficient tumor localization and general tissue penetration; and (3) immunogenicity.

At present, there are several FDA-approved immuniscintigraphic products available for clinical use. For example, OncoScint™, CEA-Scan™ and ProstaScint™, utilizing either ^{99m}Tc or ^{111}In as radiotracers[90].

In considering positron emission immunoscintigraphy, several issues have to be addressed. First, internalization of the selected mAb has implications for those positron tracers that degrade upon internalization (e.g. ^{124}I), which results in rapid cellular clearance. Hence, the appropriate positron emitter has to be selected with regard to the mAb ligand. Second, the biodistribution and clearance of the selected mAb has to be considered for diagnostic and therapeutic purposes. In general, mAb fragments are cleared by the kidneys while whole mAbs are cleared by the reticuloendothelial system. This has implications for diagnosis because physiological areas of uptake will be obscured, and it also has dosimetric and clinical implications in therapeutic applications. Third, the choice of delivery technique for the radioisotope is important. For a short-lived positron tracer such as ^{68}Ga, whole mAbs may be unsuitable due to the long interval required before optimal target tissue concentration is reached, therefore, mAb fragments may be the more suitable candidate. However, target tissue concentrations may not be optimal using such mAb fragments.

Several technological methods have been developed to address the problem of optimal radioisotope delivery, such as pre-targeting[91,92]. Pre-targeting is essentially the technique of giving the non-radioactive antibody first to allow optimal localization in the target tissue (pre-targeting), and subsequently administering the radiolabel that targets the pre-targeting antibody[93]. There are currently several techniques routinely used in pretargeting; bispecific mAbs constructed with one hapten-binding site and another target binding site; antibodies conjugated to streptavidin or avidin to enable binding of biotin ligands; biotinylated antibodies capable of forming a complex with avidin or streptavidin; antibodies conjugated to DNA to promote binding to complementary nucleotide sequences; and antibodies conjugated to enzymes to activate a pro-drug at the target site[94]. Specifically, techniques for ^{68}Ga PET that utilize bispecific antibody pre-targeting have been developed, possibly opening the door for routine clinical practice and targeted therapies[95].

Several studies have been carried out using ^{68}Ga as the positron tracer. Klivényi *et al*[96] in a preclinical study have demonstrated the feasibility of using ^{68}Ga chelates in the imaging of human colon carcinoma xenografts pre-targeted with bispecific anti-CD44$_{v6}$/anti-Ga chelate antibodies. Furthermore, Schuhmacher *et al*[97] have conducted a phase I trial of 10 patients with histologically proven breast carcinoma. Using mAb 12H12, a murine IgG$_1$ mAb that targets carbohydrate side chains of TAG12, which is overexpressed by most epithelial cell adenocarcinomas, and anti-Ga-chelate mAbs (designated 3A10, an IgG$_3$ mAb), the authors hybridized both mAbs to create a bispecific mAb towards Ga-chelate and TAG12. Next, ^{68}Ga was joined to the Ga-chelate ligand. Patients were then infused with the bispecific mAb, followed by a blocker to saturate hapten ligand sites in free floating bispecific mAbs, before the administration of the ^{68}Ga-labeled Ga chelate. Fourteen of 17 known lesions were visualized, with three false-negative results, with authors concluding that the technique provided better sensitivity for the detection of breast cancer at low tumor contrasts as compared with conventional immunoscintigraphy.

CONCLUSION

^{18}F-labeled FDG is currently the most widely used general PET tracer worldwide, but there are several limitations to its use. The emergence of ^{68}Ga provides promise of a logistically easy to manage PET tracer with broad applications, and current developments in both diagnostic and therapeutic areas show great clinical potential for this tracer. Further work and investigations are still required, but there is the promise that the long-awaited potential of ^{68}Ga might finally be realized.

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