REVIEW ARTICLE

RADIONUCLIDE IMAGING AND THERAPY OF NEUROENDOCRINE TUMOURS

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Abstract

The incidence and prevalence of neuroendocrine tumours (NETs) are on the rise. Although NETs are a heterogeneous group of tumours, they have some similar properties, for example, that they can concentrate neuroamines and tend to have a high degree of somatostatin receptor (SSR) expression. These mechanisms can be exploited and this article discusses the important role of radionculide imaging and radionculide therapy in the management of NETs based on these mechanisms. This article reviews the current literature and discusses the role of radionuclide imaging in NETs both in terms of SSR imaging and neuroamine (metaiodobenzylguanidine [MIBG]) imaging. We discuss state-of-the-art 68Ga-radiopeptide imaging and indications for it use. We also discuss the role of 18F-FDG and other tracers in the management of NETs. The second half of the article focuses on radiotargeted treatment of NETs, discussing I-131 MIBG therapy and focussing on the emergence of peptide receptor radionuclide therapy. We discuss the clinical results, toxicities and patient selection for PRRT.

Key words: DOTA octreotide, DOTATATE, Ga-68, Lu-177, metaiodobenzylguanidine, neuroendocrine tumours, peptide receptor radionuclide therapy, Y-90

Introduction

Neuroendocrine tumours (NETs) are perceived to be rare tumours. However, the incidence is on the rise from 1973 (1.09/100,000) to 2004 (5.25/100,000).[1] There are several possibilities for this increase such as increased (a) awareness and diagnosis by clinicians, (b) detection due modern imaging and immunohistopathological techniques and (c) possibly a true increase in incidence.[2] In general, NETs tend to be slow growing. However, the prevalence of people with NET is increasing: 35/100,000 and is currently reported to be the second most prevalent gastrointestinal neoplasm (second to colon cancer).

NETs are a heterogeneous group of tumours graded histologically according to their proliferative activity and number of mitoses/high-power field into low-, intermediate- and high-grade (G3) tumours. NETs have similar properties in that the majority of well-differentiated and some high-grade tumours can concentrate neuroamines and tend to have a high degree of somatostatin receptor (SSR) expression. This high degree of SSR expression and neuroamine concentration can be exploited both in terms of imaging and therapy using radiolabelled somatostatin analogues and radiolabelled metaiodobenzylguanidine (MIBG) (catecholamine analogue). This article explores the important role of nuclear medicine in both the diagnosis and treatment of NETs.

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Diagnosis

The diagnosis of NETs is based on clinical assessment, biochemical evaluation, topographic including radiological investigations and, finally, histological confirmation.

Cross-sectional imaging (computed tomography/ magnetic resonance imaging [CT/MRI])

Cross-sectional imaging is generally the first-line imaging modality, which is often used to stage/restage patients with NETs and to assess response to treatment. A triple-phase CT study is essential (non-contrast scan and 2 contrast-enhanced studies: An arterial phase and a portovenous phase), as liver metastases may be isodense on portovenous phase and often show characteristic

arterial enhancement. Arterial and portovenous phase CT is particularly good at demonstrating vascular involvement (evaluate potential resectability of a primary tumour/mesenteric mass). In general, MRI is superior to CT in diagnosing liver metastases.

Functional imaging

Functional imaging with nuclear medicine techniques in NETs includes MIBG imaging (I-123, 131I), SSR imaging (111 in-pentetreotide, 68 Gallium-DOTA), Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) and F-18-FDG PET/CT.

I-123/I-131-MIBG imaging

MIBG is an alkylguanidine (catecholamine analogue) concentrates by 1 active amine uptake mechanism in the cell membrane of sympathomedullary tissues and is stored within cytoplasmic catecholamine storage vesicles.[3-5] Radioiodinated MIBG is well established in the scintigraphic detection of catecholamine-secreting tumours (pheochromocytoma and paraganglioma), with overall sensitivity around 90%. MIBG imaging has also been used in NETs, with rates of positivity at around 70%.[6] In several studies comparing 123I-MIBG and 111Indium (111In)-pentetreotide, 111In-pentetreotide was found to be more sensitive for the detection of disease in NETs.[7-9] The majority of NETs thus are imaged not with MIBG but with SSR scintigraphy (SSR). Although MIBG imaging may not be useful in staging a patient, it may be useful determine therapeutic options in some patients i.e. I-131 MIBG radionuclide therapy [Figure 1].

SSR scintigraphy (SRS)

SSRs are expressed in a number of normal cells including the pituitary, thyroid, spleen, kidney and peripheral nervous system. In addition, several tumours have been found to express SSRs, with a high incidence and density of receptors found particularly in NETs.[10] SSR subtype-2 is relatively overexpressed SSR in NETs.[10]

When to use SSR imaging

The main application of SSR imaging is to accurately stage disease, follow up and restage patients with known disease, determine SSR receptor status so that patients can be selected for "cold" or radiotargeted therapy and assess response to treatment.

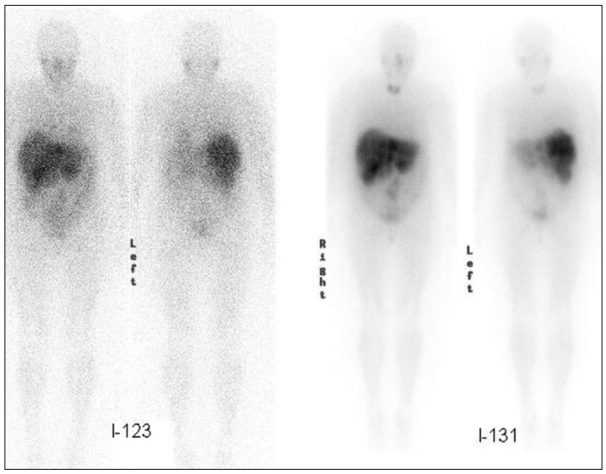

Figure 1: Patient with midgut NET: I-123 metaiodobenzylguanidine (MIBG) study demonstrating good uptake at sites of diseases in the liver and abdomen. This, therefore, allowed patient to be treated with I-131 MIBG (shows similar distribution of disease)

Single-photon emission tomography SRS imaging

SSR imaging was first introduced in the late 1980s.[2] The first somatostatin analogue used for imaging of NETs was octreotide (having a predominant affinity for SSR subtypes 2 and 5 [SSR-2 and SSR-5] with lesser affinity for SSR subtype 3 [SSR-3]) and remains as a most popular analogues used for imaging NETs. Octreotide was subsequently labelled with 111In. It has a half-life of 68 h and delayed imaging (24 or 48 h) is usually required to ensure a reduction in background activity caused by clearance through the renal and hepatobiliary system. Labelling of somatostatin analogues with the most commonly used radionuclide in nuclear medicine (Tc-99m) has also been achieved.[11] 99mTc-hydrazinonicotinyl-Tyr3-octreotide (99mTc-HYNIC-TOC) and 99mTc-hydrazinonicotinyl-Tyr3-Thr8-octreotide (99mTc-HYNIC-TATE) have a predominant renal excretion (hepatobiliary excretion being negligible),[11] which make this agent suitable and attractive for imaging abdominal NETs.

Uptake of 111In-pentetreotide and Tc-99m-HYNIC-peptides is seen in majority of patients (>75%) with gastroenteropancreatic NETs (GEPNETs), and major exceptions include insulinomas with a reduced sensitivity of 50–70% (probably due to small tumour size or poor expression of SSR-2 receptor) and poorly differentiated GEPNETs due to a lower expression of SSR-2.[12] More recent studies have showed that the use of hybrid SPECT/

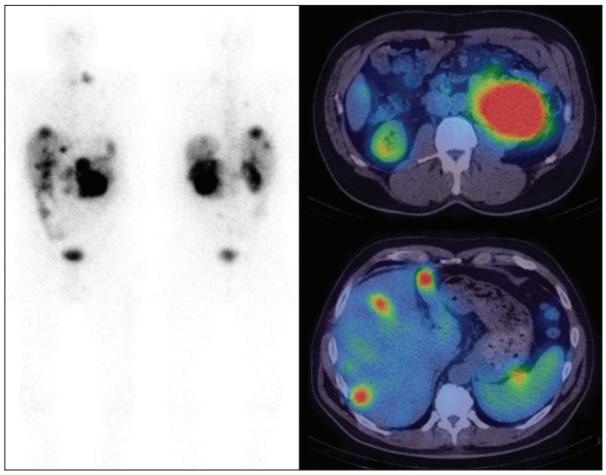

Figure 2: 111In-DTPA-octreotide whole-body and single-photon emission computed tomography/computed tomography (SPECT/CT) study in a patient with metastatic pancreatic neuroendocrine tumour. The whole-body study demonstrates uptake in the left supraclavicular fossa, liver, and abdomen. SPECT/CT images demonstrate pancreatic primary and liver and splenic metastases

CT cameras/system may improve accuracy (>90%) and is reported to have clinical impact on patient management ranging from 14% to 64%.[13-17] Figure 2 demonstrates an example of an 111In-pentetreotide study.

PET SRS imaging

Gallium-68 (68Ga) imaging has become increasingly more popular recently in centres where PET/CT imaging is available. 68Ga has a convenient physical half-life of 68 min and decays by positron emission, giving the advantages of increased sensitivity and resolution that modern PET imaging allows. As it is produced by a 68Ge–68Ga generator, it has the advantage of being independent of a cyclotron and each generator lasts for 7–9 months. The short half-life allows completion of the study within 2–3 h of administration of tracer. In addition, the patient effective radiation dose is less than half (0.0167mSv/MBq) of 111In-DTPA-octreotide.[18] 68Ga-linked somatostatin analogues have shown affinity towards SSRs and have been evaluated *in vivo* with several DOTA-related labelled somatostatin peptides including DOTA-TATE, DOTA-NOC, DOTA-TOC, DOTA-OC and DOTA-BOC (the first three of which being the most extensively studied/used clinically).[19] The main differences between these compounds are small changes in the peptide side chain, which result in different affinities to the SSR subtypes. DOTA-TATE has the highest affinity for SSR-2. In addition to expressing high affinity for SSR-2, DOTA-TOC has affinity for SSR-5, whereas DOTA-NOC has an additional affinity for SSR-3 and SSR-5 as well.[20]

There is no doubt that 68Ga-DOTA-peptides represent a significant evolution in SSR imaging over 111In-DTPA-octreotide imaging. The advantages of improved resolution and sensitivity of PET and the stronger binding affinity for the SSR expressing tumour with DOTA-TATE have been demonstrated. In a recent study, it was shown that 68Ga-DOTA-TATE changed the management in 36 of the 51 (70%) patients who had either no uptake (35 patients) or low-grade uptake (15 patients) of 111In-octreotide. These patients were found to have a positive 68Ga-DOTA-TATE scan as part of their staging, enabling them to be treated with 'cold' or radiolabeled somatostatin analogue.

68Ga-DOTA-peptides may also be used to restage patients after peptide receptor radionuclide therapies (PRRT), with a reduction in uptake suggestive of a response to therapy. Rarely, a reduction in uptake on PET SRS may be as a result of tumour dedifferentiation (less expression of SSR), which may result in a false report of a response despite an increase in size of tumour. Correlation with the CT component of the study (or contrast-enhanced cross-sectional imaging) helps to minimise this error.

18F-FDG PET/CT

Patients with NETs generally do not take up FDG due to the majority of PNETs having relatively low metabolic activity. In general, only tumours that are dedifferentiated or have a high proliferative index (i.e. G3 tumours) show marked uptake on 18F-FDG-PET/CT. 18F-FDG-PET/CT may thus have a role in staging and determining response to therapy (e.g., chemotherapy) in patients with high-grade tumours. Similarly, 18F-DOPA (precursor of dopamine) is less frequently used (selected cases) and is reported to be useful patients with insulinoma.

18F-DOPA and 11C-5-HTP

NETs have the ability to take up amine precursors. Amine precursors, for example, 5-hydroxy-L- tryptophan (5-HTP) and L-DOPA are incorporated and decarboxylated by the tumour cells by aromatic amino acid decarboxylase enzyme and stored in cytoplasmic secretory granules.

18F-DOPA enters the catecholamine metabolic pathway of endogenous L-DOPA, both in the brain and peripherally. As NETs demonstrate increased activity of L-DOPA decarboxylase, they show a high uptake of 18F-DOPA. 18F-DOPA is useful in imaging pheochromocytomas and paragangliomas with studies showing superiority to 123I-MIBG imaging.[21,22] It is particularly useful in head and neck paragangliomas (sensitivity >90%). This is in part due to the high tumour:background ratio, with the absence of physiological uptake in adjacent structures.[23]

11C-5-HTP may also be useful in NETs, but due to it being labelled with 11C (half-life of 20 min, its use is restricted to only a few centres with an on-site cyclotron.

Radionuclide Therapy in NETs

131I-MIBG therapy

I-131-MIBG therapy for NETs has become less popular gradually over the past 10 years, with increased availability and relatively better uptake and wider indications of SSR therapies. However, it may still play an important role in patients, where their tumours do not express SSR and demonstrate good uptake on pre-uptake I-123-MIBG scan.

131I-MIBG efficacy

A summary of the most relevant studies in NETs is shown in Table 1. Approximately 40–50% of patients develop good symptomatic response to treatment. Not only many studies demonstrated progression-free survival (PFS) but also most studies showed an overall survival (OS) of over 40 months following MIBG therapy [Table 1]. Interestingly, Sywak *et al*.[24-29] compared two groups of 58 and 59 patients, respectively, with midgut NET. The first group was treated in a centre were 131I-mIBG was available, whilst the second group had no access to 131I-mIBG (or other radio-targeted treatments). The 5-year survival rate in Group A was 63%versus 47% from Group B ($P = 0.1$).

131I-MIBG toxicity

The main toxicities are bone marrow suppression and myelodysplasias. Grade 3/4 bone marrow toxicity was seen in approximately 8% of patients (range 2–25%) with some relationship between the administered activity and the degree of toxicity. The most common form of bone marrow toxicity was thrombocytopaenia (11%) followed by leucopaenia (10%). Myelodysplasia is another possible rare side effect, which may occur in patients heavily pre-treated with chemotherapy or radiotherapy.[24-29]

PRRT

PRRT is the term commonly used to describe treatment with β-emitting radiolabeled somatostatin analogues. PRRT has been performed with various somatostatin analogues labelled with 111Indium, 90Yttrium and 177Lutetium. From these, three main agents have been developed: 90 Yttrium-DOTA octreotide (90Y-DOTATOC), 90 Yttrium-DOTA octreotate (90YDOTATATE) and 177 Lutetium-DOTA octreotate (177Lu-DOTATATE). The radionuclides used have different physical characteristics/properties, which may reflect on their efficacy and toxicity, for example, 90Yttrium has a higher energy beta particle emission than 177 Lutetium and may be suited to treating larger tumour masses but has some relatively increased toxicity.

The first radiolabelled PRRT was performed with 111In-DTPA-octreotide. Although γ-rays (173 +247 KeV) of 111In are useful for diagnostic imaging of NETs, the decay of 111In also produces Auger and conversion electrons. These electrons have a path length of 0.02–10 and 200–500 mm, respectively.[30] *In vitro* PRRT studies have shown that the Auger electrons are responsible for the

Table 1: Summary of major studies using 131I-MIBG in metastatic NET radionuclide therapy

First author	CT responders (CR and PR)	CT SD	Biochemical responders	Symptomatic responders (%)	Median OS (months)	5-Year survival (%)
Safford (24)	10/75	-	15/52	35/72 (49)	28	22
Nwosu (25)	11/40	-	11/29	24/48 (56)	46	-
Gedik (26)	8/17	6/17	8/12	16/18 (89)	42	-
Gonias (27)	12845	24/45	24/34	-	-	64
Navalkissoor (28)	3/37	22/37	3/20	15/34 (44)	48	33

reported tumour responses with 111In-labelled somatostatin analogues. However, as 111In emits Auger electrons have mean particle ranges of <1 cell diameter, radiation emitted from a receptor-positive tumour cell is, therefore, unlikely to kill neighbouring receptor-negative cells. High activity 111In-DTPA-octreotide was the first radiolabelled somatostatin analogue to be used in humans but did not subsequently have widespread popularity with published studies not showing significant objective responses.[31,32]

90Y-based therapies

90Y-Lanreotide, 90Y-DOTATATE and 90Y-DOTATOC have been used. One multicentre trial (MAURITIUS) has been reported[33] in which targeted therapy was performed with 90Y-lanreotide (29). 8/39 (21%) patients with GEP NETS had an objective response to therapy, with a further 17/39 (44%) having stable disease. This agent has also not found significant popularity. 90Y-DOTATATE and 90Y-DOTATOC have been the most commonly used 90Y-based radiopeptides in the treatment of NETs. A summary of the major studies using 90Y and 177Lu-labeled radiopeptides is shown in Table 2.

90Y-90 DOTATATE/DOTATOC antitumour effects

Complete responses are rare. However, partial responses to treatment have been reported at between 9% and 37%, with disease progression reported only in 0%–13% of patients.[34-41] Patients treated are those with baseline progressive disease; thus, overall disease response/stabilisation is seen in approximately 70–80% of patients.[34-41] In addition, the majority of studies have shown an excellent symptomatic response in >70% of patients.[34-41] Time to progression in reported studies ranged from 13 to 29 months. On multivariate analysis, Valkema *et al*. showed that the best predictors for OS are related to the baseline extent of disease (i.e., presence/absence of liver metastases and the absence/presence of end-stage disease).

The Basel group found factors predicting longer survival which include morphologic response, clinical response and high tumour uptake of the radiopeptides.[35] Factors associated with worse survival include presence of bone or liver metastases and previous chemotherapy.

Toxicity

The main toxicities in these studies were bone marrow and renal impairment. The rate of permanent renal toxicity showed variation (range 1–9%). The highest recorded significant permanent renal toxicity was 9% from a Swiss study of over 1000 patients.[32] However, a recent multinational phase 2 trial reported renal toxicity at 2%.[38]

Table 2: Summary of the major studies using 90Y and 177Lu-labeled radiopeptides for radionuclide therapy

First author	Number	Place	CR/PR (%)	PD (%)	Symptom response (%)	Time to progression	Median OS (months)
*Paganelli (34)	87	Milan	28	24	-	14 months	-
*Imhof (35)	1109	Basel	34	26	30	12.7 months	56% alive at 23 months
*Valkema (36)	58	Rotterdam	9	29	58	29 months	37
*Gabriel (37)	60	Innsbruck	22	20	-	-	
*Bushnell (38)	90	Multicentre	4	21	88	16.3 months	27
**Baum (39)	75	Germany	37	11	85	-	-
**Cwikla (40)	60	Poland	23	0	72	17 months	22 months
**Toumpanakis (41)	85	London	9	13	73	-	53% alive at 39 months
Kwekkemboom (42)	310 (504)	Rotterdam	91/301 (29)	61/310 (20)	-	33	46
Bodei (43)	51	Milan	15/51 (29)	9/51 (18)	-	36 months	68% at 36 months
Claringbold (Plus capecitabine) (44)	33	Perth	24	6	-	-	88% at 24 months

The predictors for severe renal toxicity by the Swiss study were advancing age, baseline glomerular filtration rate and high uptake of tracer by the kidneys on the baseline 111In-DTPA-octreotide scans.

Bone marrow toxicity is seen in approximately 12% of patients overall and is usually transient, presenting as either thrombocytopaenia or leucopaenia. Mild-to-moderate liver toxicity has also been recorded in 1% of patients, all of whom had extensive bilobar liver metastases.

177Lu-PRRT

The Rotterdam group is the largest institution to have published single centre outcomes using 177Lu-DOTATATE. In this group's most recent publication,[42] 504 patients were treated (the majority with four cycles), with a maximum cumulative activity of 29.6 GBq.

Antitumour effects

In response analysis of 310 evaluable patients, 2% had a CR, 28% had a PR and a further 16% had a MR (using the Southwest Oncology Group Criteria). The median OS from treatment in these 310 patients was 46 months, whilst the median PFS was 33 months. On a Cox regression analysis, factors associated with poorer survival include progressive disease following treatment, the presence of liver/bony metastases, KPS score <70 and baseline weight loss. The Milan group has also reported similar response rates.[43]

Toxicity

The WHO grade 3/4 haematological toxicity occurred in 9.4% of 504 patients. 2/504 patients developed renal insufficiency. There were three patients with serious liver toxicity. One of these patients (with diffuse liver metastases) died of hepatic failure. Four patients developed myelodysplastic syndrome, one of which was likely to be related to previous alkylating chemotherapy. 6/504 patients were hospitalised soon after treatment with hormonal crisis. All six patients had extensive metastases and developed the hormonal-induced crisis after the first cycle of treatment.

Combination therapies

Combination therapies have been used in PRRT, either combining different radionuclides (i.e., 90Y and 177Lu-labelled peptides) or combining PRRT with radiosensitising chemotherapy.

Treatment with radiosensitising chemotherapy has also been reported, with disease stabilisation seen in 96% of patients.[44]

Combination radiopeptide therapies have been performed as tandem therapies (i.e. administrating a combination of 90Y and 177Lu-radiopeptides at a single sitting) or sequential therapies with 90Y and 177Lu-radiopeptides.

Kunikowska *et al*. compared 90Y-DOTATATE to tandem treatment with 90Y- and 177Lu-DOTATATE in patients with NET.[45] They demonstrated a statistically significant increase in OS (median OS 26 months vs. not reached $P = 0.027$). This was achieved with no increase in toxicity.

Villard *et al*. compared 237 patients who had 90Y-DOTATOC versus 249 patients with 90Y-DOTATOC and 177Lu-DOTATOC sequentially.[46] They found that the combination therapy provided a significant increase in OS (47 months vs. 66 months $P = 0.006$). Significant renal toxicity was reported to increase from 8.9% to 11.2%.

Randomised controlled trials

PRRT has often been criticised due to the lack of RCT data. However, there is a multicentre phase III randomised controlled study of 177Lu-labelled DOTATATE versus high-dose Octreotide LAR in patients with inoperable, progressive, SSR positive, midgut carcinoid tumours. This study is currently recruiting patients in Europe and the United States. Hopefully, this may provide more robust data for the efficacy of Lu-177 DOTATATE in the near future.

Patient selection for PRRT in NETs

The therapeutic options in NETs should be discussed in a multidisciplinary setting, with the choice of the most appropriate technique made. In the majority of patients, surgical resection offers the only realistic possibility of cure, and thus, this should be considered the preferred option if curative surgery is feasible and the patient is fit enough.

In patients with unresectable metastatic disease, there are various therapeutic options available. These include surgical debulking, chemotherapy, molecular targeted therapies (e.g., sunitinib and everolimus), interferon, somatostatin analogues, local therapies (e.g., radiofrequency ablation or embolisation) and PRRT.

Patient selection for PRRT in NETs should include histologically proven NET, who are SSR positive and have no surgical cure possible or patients are unsuitable for surgery. Patients should not have sufficient bone marrow reserve i.e., platelets >90,000/μL for 90Y and >75,000/μL for 177Lu.[47]

In addition, significant renal impairment is a relative contraindication, particularly if 90Y-radiopeptides are being used.

Those with too extensive disease, for example, extensive liver and bone metastases tend not to do as well with PRRT. Similarly, it has been shown that significantly poorer outcomes occur in patients with poor baseline functional status (i.e., Karnofsky performance score >70 or ECOG <3–4).[42] Grading of the tumour also has a role in treatment with PRRT, as patients with G3 tumours should have cisplatin-based chemotherapy rather than PRRT as first line if they have progressive disease.

As NETs can be slow growing, the timing of treatment can be debatable. Patients with progressive disease or patients who are symptomatic despite cold somatostatin analogues should be the patients considered for therapy.

Conclusion

Nuclear medicine imaging and therapy have a vital role to play in the management of NETs. SSR imaging provides increased accuracy in staging patients with accuracies of >90% in well-differentiated tumours and allows a change in management compared with conventional imaging. Radionuclide therapies with radiolabeled somatostatin analogues and radioiodinated MIBG provides symptomatic benefit and increases survival in patients with metastatic NETs.

Conflict of Interest

The authors declare that they have no conflict of interest.

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