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THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

Theranostics in neuroendocrine tumours: somatostatin receptor imaging and therapy

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ABSTRACT

Theranostics and its principles: pre-treatment selection of patients who are most likely to benefit from treatment by the use of a related, specific diagnostic test are integral to the treatment of patients with neuroendocrine tumours (NETs). This is due to NETs' important, but variable, somatostatin receptor (SSTR) expression, their heterogeneity and variation in site of primary and rate of progression. Only patients whose tumours have sufficient expression of SSTRs will benefit from SSTR-based radionuclide therapy and demonstrating this expression prior to therapy is essential. This article provides a relevant overview of NETs and the multiple facets of SSTR based theranostics, including imaging and therapy radionuclides; clinical efficacy and toxicity; patient selection and treatment and finally emerging radiopharmaceuticals and newer clinical applications.

INTRODUCTION

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours in which the cells display neuroendocrine characteristics. NETs can originate from pancreatic islet cells (pNETs), gastroenteric tissue [together: gastroenteropancreatic (GEP)] and respiratory epithelium.¹ Two of the strongest prognostic markers are tumour differentiation and proliferation. NETs can be well- or poorly-differentiated (depending on how closely the tumour resembles neuroendocrine cells). Tumour grade refers to the proliferative activity of the tumour, measured by the Ki-67 proliferative index and/or the mitotic rate and is divided into Grade 1 (G1): Ki-67 $\leq 2\%$, Grade 2 (G2): Ki-67 3–20% and Grade 3 (G3): Ki-67 $> 20\%$ ² with G1 being the least proliferative and G3 the most proliferative^{2–4}

Another characteristic of NETs is their ability to secrete a large number of bioactive substances, e.g. chromogranin A (CgA), serotonin, gastrin and insulin.¹ The classic carcinoid syndrome results predominantly in patients with liver metastases that produce serotonin which, when not broken down by the liver, produce symptoms including diarrhoea, wheezing and flushing which can have a significant negative impact on a patient's quality of life (QoL).⁵

When NET is suspected investigations include biochemical testing (e.g. for serum CgA and urinary 5-hydroxyindoleacetic acid, the breakdown product of serotonin) and imaging such as ultrasound, CT and MRI. In addition to conventional radiology, functional/molecular or nuclear imaging is of particular importance in the diagnosis, staging and treatment decisions of well differentiated NETs. A large percentage of NETs tend to retain the properties of neuroendocrine cells and express somatostatin receptors (SSTRs) on their surface. The well differentiated tumours typically express SSTRs, of which there are five different subtypes, in particular SSTR subtype 2 (SSTR2) is (over)expressed by NETs.⁶ The over expression of SSTRs is exploited by using radiolabelled somatostatin (SST) peptide analogues resulting in a highly sensitive and specific imaging modality.

There are several licenced and unlicensed therapeutic options for progressive metastatic NETs where no surgical cure is possible. Some of the more commonly employed treatments include long-acting somatostatin analogues (SSAs), local liver therapies, chemotherapy, molecular targeted treatments (everolimus and sunitinib), interferon and peptide receptor radionuclide therapy (PRRT). Of these therapies, PRRT appears to provide the greatest benefit in terms of progression-free survival (PFS) with

the recent NETTER 1 trial reporting a PFS of approximately 40 months in patients with progressive midgut NETs.⁷ In keeping with the principles of theranostics both imaging and therapeutic radionuclides can be bound to the SST analogue via the same mechanism allowing targeted treatment of the previously imaged disease. The diagnostic and therapeutic agents form a theranostic pair.

MOLECULAR IMAGING OF NETS

Somatostatin receptor Scintigraphy

There are a number of different SST peptide analogues which can be used to bind to SSTRs and image NETs. One of the first and most widely used radiopharmaceuticals was ¹¹¹In-DTPA-octreotide. Octreotide is a synthetic peptide that binds to SSTRs and ¹¹¹In is a gamma emitter. ¹¹¹In has a half-life of 67h and delayed imaging (24 or 48 h) is usually required to ensure reduction in background activity caused by clearance via the renal and hepatobiliary system. SST analogues have also been radiolabelled with ^{99m}Tc-Technetium (^{99m}Tc), which has imaging and logistic advantages (can be performed on a single day) over ¹¹¹In. These include ^{99m}Tc-EDDA/HYNIC-octreotate,⁸ or ^{99m}Tc-EDDA/HYNIC-octreotide.⁹ However, these tracers are currently less widely used than ¹¹¹In-octreotide.

Newer DOTA-coupled peptides which are bound to the positron emitter ⁶⁸Gallium (⁶⁸Ga) have been developed which have advantages over octreotide. DOTATOC (DOTA-Tyr3-octreotide) is lipophilic, with better affinity for SSTR2 and higher uptake in SSTR2 positive tumours than octreotide.¹⁰ Another analogue is DOTATATE (DOTA-D-Phe1-Tyr3-octreotide) and newer still is DOTANOC (DOTA, 1-Nal3-octreotide) which binds avidly to SSTR2 and also has higher affinity for

SSTR3 and SSTR5 than DOTATATE.¹¹ There are also pansomatostatin analogues which target multiple SSTR subtypes *e.g.* DOTA0-lanreotide.¹²

In addition to higher receptor affinity, there are other pharmacological advantages of the DOTA peptides over octreotide. These include maximum tumour activity occurring about 70 mins after injection and excretion almost entirely through the kidneys.¹³ This is in contrast to ¹¹¹In-pentetreotide where 2% is excreted through the hepatobiliary system and then via the bowel and 1% of injected activity remains in the blood pool 20 h after injection.¹⁴ These differences confer advantages both to scanning protocols and image interpretation. The chelating of the DOTA peptides to the positron emitter ⁶⁸Ga results in superior sensitivity and resolution of these images compared to images acquired with ¹¹¹In-octreotide. The characteristics of the commonly used ⁶⁸Ga labelled peptides for imaging NETs are displayed in Table 1.^{13,15–20}

Systematic reviews and meta-analyses have demonstrated SSTR PET-CT's high accuracy, high rates of change in patient management and its superiority to ¹¹¹In-octreotide. For example a meta-analysis of the use of ⁶⁸Ga-DOTATOC found it had a sensitivity of 92% and specificity of 82%. It demonstrated an impact on subsequent NET patient management in 51%. The sensitivity of DOTATOC on a per-lesion basis was 100%, and for ¹¹¹In-octreotide it was 78%.²¹ A systematic review and meta-analysis of ⁶⁸Ga-DOTATATE compared with ¹¹¹In-DTPA-octreotide found there were three studies which compared the two radiopharmaceuticals in the same patient, finding ⁶⁸Ga-DOTATATE had an estimated sensitivity of 90.9% and specificity of 90.6% and was more sensitive than octreotide.²²

Table 1. Common ⁶⁸Ga-labelled peptides for imaging NETs

	⁶⁸ Ga-DOTATOC	⁶⁸ Ga-DOTATATE	⁶⁸ Ga-DOTANOC
Half life	68 min	68 min	68 min
Production	Generator	Generator	Generator
Injected activity	Ranges from 100 to 150 MBq	Ranges from 100 to 150 MBq	Ranges from 100 to 150 MBq
Route of synthesis	Chelation of generator-produced ⁶⁸ Ga chloride by DOTATOC at elevated temperature. May be preceded or followed by purification step.	Chelation of generator-produced ⁶⁸ Ga chloride by DOTATATE at elevated temperature. May be preceded or followed by purification step.	Chelation of generator-produced ⁶⁸ Ga chloride by DOTANOC at elevated temperature. May be preceded or followed by purification step.
Radiation dosimetry	Effective dose equivalent (mSv/MBq): 0.021 (2 mSv/100 MBq) Organ doses (mGy/MBq): urinary bladder wall, 0.119; spleen, 0.108; kidney, 0.082; adrenal gland, 0.077	Effective dose equivalent (mSv/MBq): 0.021 (2 mSv/100 MBq) Organ doses (mGy/MBq): spleen, 0.109; urinary bladder wall, 0.098; kidney, 0.093; adrenal gland, 0.086	Effective dose equivalent (mSv/MBq): 0.025 (2.5 mSv/100 MBq) Organ doses (mGy/MBq): kidney, 0.090; urinary bladder wall, 0.084; spleen, 0.073; liver, 0.034
Normal biodistribution	Activity initially high in liver, spleen and kidneys.	Activity initially high in liver, spleen and kidneys.	Activity initially high in liver, spleen and kidneys.
Excretion	Gradual clearance with 16% urinary excretion over 4 h.	Gradual clearance with 12% urinary excretion over 4 h.	Gradual clearance with 25% urinary excretion over 4 h.
Affinity profile	⁶⁸ Ga-DOTA-TOC binds to SSTR2 also binds to SSTR5	⁶⁸ Ga-DOTA-TATE has a predominant affinity for SSTR2	⁶⁸ Ga-DOTA-NOC binds to SSTR2 also shows a good affinity for SSTR3 and 5
Clinical application	Assessment of SSTR status of NETs and selection of patients for PRRT	Assessment of SSTR status of NETs and selection of patients for PRRT	Assessment of SSTR status of NETs and selection of patients for PRRT

NETs, neuroendocrine tumours; PRRT, peptidoreceptor radionuclide therapy;

Another advantage of the PET tracers is that quantification of tumour uptake of tracer can be performed which is not possible with SPECT.²³ A close correlation has been found between maximum standardised uptake value (SUVmax) and quantitative assessment of the density of subtypes of SSTR using immunohistochemical scores.²⁴ Also, SUVmax of the tumour of uptake of ⁶⁸Ga-DOTATOC has been found to correlate with response to PRRT.²⁵

More recently, SSTR antagonists are starting to enter clinical use, these are discussed below.

FDG

¹⁸F-fludeoxyglucose (FDG) PET-CT does not have a therapeutic counterpart, however its role in imaging is still relevant when discussing SSTR theranostics. Typically, as Ki-67 and grade of tumour increases, the intensity/extent of FDG uptake in the tumour increases, although low grade and well differentiated NETs can still be FDG avid.²⁶

FDG positivity is a very strong negative prognostic factor. A prospective study of 38 patients found that patients with a negative FDG PET-CT had overall survival (OS) of 119.5 vs 15 months for those with positive FDG PET. Even in patients with a low grade GEPNET and a positive SSTR scintigraphy, PFS and OS were significantly lower for patients with a positive FDG PET.²⁷ A different study found that FDG positivity conferred a hazard ratio of 10.3 exceeding the prognostic value of Ki-67, CgA and liver metastases.²⁸

In terms of the current use of FDG PET-CT in NET: it is usually the preferred tracer for G3 NETs, as well as for some high-grade G2 tumours. Its use in G1 and low-grade G2 tumours is not yet fully defined, a Ki-67 >10% is often considered as a cut-off.²⁹ FDG-PET-CT should also be considered if lesions are identified on anatomical imaging (CT or MRI), which are not SSTR tracer avid or if they are progressing fast as these could represent de-differentiated disease.³⁰

Currently, the combination of FDG and ⁶⁸Ga somatostatin receptor scintigraphy (SRS) is often performed together in patients with G2/G3 tumours or if there has been relatively quick progression of disease to determine if there is discordant disease, *i.e.* FDG positive, SRS negative disease. The combination of these two scans helps plan treatment appropriately: if patients have lesions that are FDG-positive, SRS-negative, these patients should not be treated with PRRT as the first option, but treatment of the FDG-positive lesions should be prioritised (chemotherapy/local treatments). Figures 1 and 2 show two patients, one of which is suitable for PRRT (⁶⁸Ga DOTATATE+, FDG-), the second of which is not suitable for PRRT (⁶⁸Ga+; FDG+ but with discordant lesions). Figure 3 shows that tracer distribution on pre-therapy SRS (⁶⁸Ga-DOTATATE) and post-therapy imaging (¹⁷⁷Lu-DOTATATE) is the same.

There has been recent interest in the more systematic use of FDG PET-CT in patients with NET, this is due to the variable

Figure 1. A 64-year-old patient with G2 metastatic midgut NET who underwent staging with ¹⁸F-FDG and ⁶⁸Ga-DOTATATE. The ⁶⁸Ga-DOTATATE demonstrated multiple sites of avid disease within a mesenteric mass, abdominal nodes, liver and skeletal deposits. All of these lesions were not avid on ¹⁸F-FDG. ¹⁸F-fludeoxyglucose; NETs, neuro endocrine tumours.

outcome of patients within the same category of NET (*e.g.* grade and primary) and the recognition of the strong negative association between FDG avidity and prognosis described above. A “NETPET” score has been developed which combines the uptake on both SSTR and FDG PET-CT into a single reportable value which has prognostic significance.³¹ In future, more routine use of dual tracer imaging might be used to decide on when to use a watch and wait strategy vs SSTR analogues vs PRRT vs chemotherapy in addition to guiding sites for biopsy.²⁶

Selection of patients for PRRT based on molecular imaging

In line with the theranostic principle, compounds which bind to SSTRs can also be labelled with therapeutic radionuclides, allowing treatment of the previously imaged disease. This is often referred to as PRRT. The key factor in assessing suitability of a patient for PRRT is SRS. Sufficient uptake within tumours on the SSTR scan provides evidence that the tumours are likely to concentrate radioactivity in sufficient quantities to achieve tumour damage (the theranostic principle, illustrated in Figure 3). Based on SSTR imaging, the liver is commonly used as the reference point (the liver having tracer uptake related to hepatic peptide metabolism). Uptake greater than that seen in the background liver in the majority of disease (*i.e.* >90%) is generally considered sufficient to proceed with PRRT, this criterion is used by many centres^{32,33} and was used in a recently published randomised controlled trial (RCT) on the use of PRRT, the NETTER-1 trial.⁷ Partial volume effects and the resolution of the imaging system (*e.g.* single photon versus PET) should be

Figure 2. A 72-year-old gentleman with G2 pancreatic NET who had PD on CT, underwent staging with ^{18}F -FDG (a) and ^{68}Ga -DOTATATE (b), consideration for PRRT. There are several tracer avid liver metastases. The yellow arrows demonstrate two lesions that are DOTATATE avid and to a lesser degree FDG avid. The three red arrows demonstrate lesions that are FDG avid but ^{68}Ga negative. As this patient has discordant disease that is progressive, he is not suitable for PRRT. ^{18}F -fluorodeoxyglucose; NETs, neuroendocrine tumours; PRRT, peptide receptor radionuclide therapy.

taken into account when assessing small lesions as it can result in an underestimate of the true tracer uptake of the tumour.

As imaging with ^{68}Ga -DOTA-peptides is more sensitive than ^{111}In -octreotide, patients who do not show sufficient uptake within their tumour on ^{111}In -octreotide should ideally be re-imaged with ^{68}Ga -DOTA peptides. This is because there can still be sufficient uptake ($\geq$ liver) of the ^{68}Ga -DOTA peptides to make these patients eligible for PRRT.³⁴ Patients who still demonstrate only low-grade uptake on ^{68}Ga -DOTA peptides ($<$ liver) in their tumour sites are not suitable for PRRT as they are unlikely to concentrate sufficient radiation in their tumours. It has been shown that reduced tumoral uptake on SRS correlates with reduced response rates.²⁹

Additionally, SSTR expression within tumours and metastases can decline as the disease progresses and so, it is necessary to ensure there is up-to-date SRS if there has been a long time interval between the initial SRS and the decision to treat with PRRT or if there has been a marked change in tumour behaviour.

Treatment of NETs

PRRT is a treatment option for patients with metastatic, inoperable, well-differentiated NETs that show good uptake of the radio-labelled peptide on diagnostic imaging.^{35,36} For patients with localised disease or with resectable hepatic metastases, potentially curative surgical resection is offered when possible.^{1,3,36–38} There are other systemic treatments for metastatic or locally advanced disease which depend on factors including site of primary, grade

and differentiation. These include SSAs, cytotoxic chemotherapy, molecular targeted therapies including sunitinib or everolimus (particularly for pNET), interferon and liver targeted treatments (embolization, radioembolisation, radiofrequency ablation). Regarding chemotherapy, response rates are highly variable depending on site and grade of tumour. Poorly-differentiated G3 tumours are usually the most chemosensitive and well-differentiated midgut NETs the most chemoresistant.

Characteristics of the therapeutic radionuclides used in PRRT

The two most frequently used therapeutic radionuclides are ^{90}Y -Yttrium (^{90}Y) and ^{177}Lu -Lutetium (^{177}Lu). Both are β beta particle emitters with path lengths well-suited for killing tumour cells with restricted damage to neighbouring normal tissue. The half-lives are appropriate for molecular radiotherapy agents, allowing particle emission during the cell cycle of malignant cells and (hopefully) ensuring cell death. The other emissions can be used to image the distribution of the radionuclide. Since ^{177}Lu also emits gamma rays, these can be used for dosimetry and monitoring of tumour response. Table 2 below, describes the physical characteristics of ^{90}Y and ^{177}Lu .

Indications and patient selection for PRRT

The current timing of PRRT in the treatment of patients with incurable, well differentiated NET is not well defined and the European Neuroendocrine Tumour Society (ENETS) guidelines are not proscriptive on its use. In patients with positive

Figure 3. A 71-year-old male with midgut NET, small bowel resection, had pre-therapy ^{68}Ga -DOTATATE (a) and post-therapy ^{177}Lu -DOTATATE (b) imaging, demonstrating similar tracer distribution with avid liver and mesenteric node. NETs, neuro endocrine tumours.

SRS, SSAs should be considered as first-line treatment.^{35,39} In patients with midgut NET who require systemic therapy having progressed through SSAs, PRRT is usually the preferred next treatment option.³⁵ It is also considered in patients with NETs of other primary sites, particularly when there is extensive disease, extrahepatic disease and good uptake on functional imaging.³⁵ In pNET, there are more therapeutic options including cytotoxic chemotherapy, everolimus or sunitinib and PRRT. The treatment options for NETs, including suitability for PRRT, should be discussed in a multidisciplinary team meeting. Inclusion and exclusion criteria, below, are adapted from recent ENETS guidelines on PRRT.³⁰

INCLUSION CRITERIA

- (1) Inoperable/metastatic well-differentiated (G1/2) NET
- (2) Well-differentiated G3 NET can be considered if it shows sufficient uptake on SSTR imaging
- (3) Sufficient tumour uptake on the diagnostic SRS (defined as tumour uptake > liver) $\pm$ FDG PET/CT demonstrating no discordant sites of uptake.

- (4) Sufficient bone marrow reserves (Grades 1–2 haematological toxicity usually accepted)
- (5) Creatinine clearance >50 mL/min
- (6) Karnofsky Performance Status > 50 or ECOG 1 or 2
- (7) Expected survival >3 months
- (8) Following MDT discussion

EXCLUSION CRITERIA

- (1) Significant sites of active disease identified as contrast-enhancing lesions on CT or MRI that lack SSTR expression (*i.e.* negative SRS).
- (2) Moderate to severe renal impairment (*i.e.* creatinine clearance <50 ml min)¹
- (3) Impaired haematological function²
- (4) Severe hepatic impairment³
- (5) Severe cardiac impairment⁴
- (6) Moderate to severe right heart valvular disease (valve replacement is encouraged prior to PRRT)
- (7) Pregnancy or ongoing lactation

Table 2. The physical characteristics of ^{90}Y and ^{177}Lu

Radionuclide	Half life (days)	β -particle path length (mean, max) mm	Other emissions
^{177}Lu	6.75	0.23, 1.7	113keV and 208 keV gamma rays
^{90}Y	2.67	3.9, 11	Bremsstrahlung and positrons

Significant sites of active disease identified as contrast-enhancing lesions on CT or MRI that lack SSTR expression (*i.e.* negative SRS).

Moderate to severe renal impairment (*i.e.* creatinine clearance <50 ml min)¹

1 (patients on dialysis can be treated with a significantly reduced administered activity to account for lack of urinary excretion with dialysis delayed for 24 h after treatment, following liaison with the renal team)

2, *i.e.* Hb <5 mmol l⁻¹ (8 g dl⁻¹); platelets $<75 \times 10^9$ /l; white blood cell count $<2 \times 10^9$ /l

3, *i.e.* total bilirubin >3 . upper limit of normal or both an albumin <25 g l⁻¹ and prothrombin time increased >1.5 . upper limit of normal, indicating biosynthetic liver failure *

4 NYHA Grade 3 or 4

Clinical efficacy

⁹⁰Y-DOTATOC was first used in 1996.³⁶ Since then, multiple papers reporting on the outcomes of patients with incurable NET-treated with PRRT have been published, although the inclusion and disease response criteria are quite variable limiting direct comparison between studies. A recent meta-analysis of the use of ¹⁷⁷Lu-DOTATATE demonstrated a pooled effect disease objective response (OR) rate (which they defined as complete response (CR) and partial response (PR)) of 29% and an average disease control rate (OR and stable disease (SD)) of 81%.⁴⁰ Median PFS with PRRT has been reported as 33 months,³³ 26 months⁴¹ and 36 months.⁴²

Unfortunately, in the above studies, there has been no true control population, limiting assessment of the significance of these results. This changed with the publication of the NETTER-1 trial, an RCT of ¹⁷⁷Lu-DOTATATE vs high-dose SSAs⁷ in patients with incurable G1/2 midgut NET. It found that median PFS for the ¹⁷⁷Lu-DOTATATE group was not yet reached (estimated at 40 months) and was 8.4 months for the high-dose SSA group, giving a statistically significant hazard ratio of 0.21 and a 79% reduction in the risk of disease progression/death. Figure 4 demonstrates an example of an excellent response to ¹⁷⁷Lu-DOTATATE.

PRRT has also been shown to improve QoL which is an important measure given the severe symptoms which secretion

Table 3. Side effects from PRRT

Nausea and vomiting
Abdominal pain (after 10% of administrations)
Temporary mild hair loss in 60% of patients after ¹⁷⁷ Lu-DOTATATE
Grade 3/4 haematological toxicity ($<15\%$ of patients)
Hormonal crises due to release of bioactive substances ($<1\%$ of patients)

PRRT, peptidoreceptor radionuclide therapy;

¹⁷⁷Lu, Lutetium-177.

of the bioactive substances can cause. A study of 265 patients⁴³ found QoL, insomnia, appetite loss, and diarrhoea improved significantly in patients with inoperable or metastatic GEP or bronchial NET treated with ¹⁷⁷Lu-DOTATATE.

Toxicity

The critical organs are the bone marrow and kidneys.⁴⁴ The kidneys are usually the dose limiting organ, the radiopeptide is renally excreted and also reabsorbed in the proximal tubules⁴⁵ and therefore retained within renal parenchyma. Bone marrow is irradiated from circulating radiopeptide and irradiation from absorbed radiopeptide into bone metastases. The most common subacute side-effect of PRRT, occurring within 4–6 weeks after therapy, is haematologic toxicity.⁴⁴

Renal protection can be provided by administering intravenous lysine and arginine prior to PRRT which reduces reabsorption of the radiopeptide (competitive inhibition) but also causes nausea and, occasionally, vomiting. With adequate renal amino acid protection, Grade 3–4 renal toxicity occurs in $<3\%$ of patients.⁴⁴ There are currently no forms of myeloprotection available and myelodysplastic syndromes and leukaemia have been reported.⁴⁴ Table 3 (adapted from recent ENETS guidelines)³⁰ lists the acute and subacute side effects from PRRT.

There are no RCTs comparing optimal administered activity per treatment cycle, optimal cycle interval, or optimal cumulative administered activity for either ⁹⁰Y- or ¹⁷⁷Lu-labelled SST analogues. The NETTER-1 trial used up to four cycles of a fixed administered activity of 7.4 GBq per cycle, administering each cycle every 8 weeks. Renoprotection is provided with infused solutions containing lysine and arginine and intravenous fluids together with anti emetics. Blood counts, renal and liver function are checked before and between cycles. Post-treatment imaging of Bremsstrahlung for ⁹⁰Y or gamma rays for ¹⁷⁷Lu is often performed to confirm distribution of disease and uptake of PRRT and, when required, for dosimetry. Treatment is usually stopped after the pre-determined number of cycles (usually four)

Figure 4. A 67-year-old gentleman who had four cycles of ¹⁷⁷Lu-DOTATATE imaging. Pre-therapy ⁶⁸Ga-DOTATATE (a) imaging demonstrates multiple sites of tracer avid disease in the liver. Post-therapy ⁶⁸Ga-DOTATATE imaging (b) shows an excellent response to treatment with significant reduction in size and avidity in multiple lesions (including a target lesion shown).

Table 4. Comparison of the efficacy of different treatment options for metastatic NET

Study	Treatment	Patient group	Outcome
Strosberg et al ⁷ (NETTER-1 trial) <i>n</i> = 229	¹⁷⁷ Lu-DOTATATE versus SSAs	Advanced progressive midgut NET	PFS after 20 months: 65.2 in the ¹⁷⁷ Lu-Dotatate group and 10.8 in the SSA group. OR 18% in the ¹⁷⁷ Lu-Dotatate group versus 3% in the SSA group
Kwekkeboom et al ³³ (<i>n</i> = 310 2008)	¹⁷⁷ Lu-DOTA-peptides	Patients with metastatic GEP NET (not necessarily progressive)	Median PFS 33 months. Radiological response: 46% OR, 35% SD.
Imhof et al ⁴⁶ <i>n</i> = 1109 2011	⁹⁰ Y-DOTA-peptides	Progressive metastatic NET of any primary	Median survival 45 months in those who responded, 18 months in those who progressed. Radiological response: 34% OR, 5% SD. Biochemical response 15.5%.
Kong et al ⁴⁷ <i>n</i> = 68 2014	¹⁷⁷ Lu-DOTA-peptides with 5-FU	Patients with progressive or uncontrolled symptomatic, metastatic NET of any primary site	OS 72 and 52% at 2 and 5 years. PFS not reported. Radiological response: 68% OR. Biochemical response 56%
Ezziddin et al ⁴⁸ <i>n</i> = 68 2014	¹⁷⁷ Lu-DOTATATE	Metastatic inoperable Grade 1/2 pNET	Median PFS 34 months, OS 53 months. Radiological response 72% OR, 13% SD
Strosberg et al ⁴⁹ <i>n</i> = 30 2011	Capecitabine with temozolomide	Metastatic pNET	Median PFS 18 months. Radiological response 70% OR
Sun et al ⁵⁰ <i>n</i> = 249 2005	RCT of fluorouracil with either streptozocin or doxorubicin	Metastatic carcinoid tumours	PFS 4.5–5.3 months. Radiological response 16%
Yao et al ⁵¹ <i>n</i> = 410 2011	RCT of Everolimus v. placebo	Metastatic radiologically progressive pNET	PFS 11 months. Radiological response: 5% OR 73% SD
Raymond et al ⁵² <i>n</i> = 171 2011	RCT sunitinib v placebo	Metastatic progressive pNET	PFS 11.4 months. Radiological response: 8% OR 54% SD

¹⁷⁷Lu, Lutetium-177; 5-FU, 5 fluorouracil; GEP, gastro entero pancreatic; NET, neuroendocrine tumour; OR, objective response; PFS, progression-free survival; pNET, pancreatic neuro endocrine tumour; RCT, randomised controlled trial; SD, stable disease; SSAs, somato statin analogues.

or if the patient progresses during treatment, identified either by imaging or symptomatic deterioration. The recent ENETs guidelines³⁰ provide further, detailed guidance on PRRT administration requirements.

Comparison with other treatments

Table 4, below, shows that the reported PFS is better with PRRT than other treatments. Radiological response with PRRT is similar to chemotherapy, but much better than that seen in molecular targeted treatments. A study comparing ⁹⁰Y and ¹⁷⁷Lu-DOTA-peptides⁵³ showed them to be broadly similar in terms of overall efficacy although ¹⁷⁷Lu produces less nephrotoxicity and severe haematological toxicity than ⁹⁰Y.^{53,54}

In addition to patient selection, another important aspect of the theranostic approach is individualised patient dosimetry using pre- or post-therapy imaging. The goal of pre-therapeutic dosimetry is to maximise radiation dose to the tumour whilst ensuring the dose to the kidneys and bone marrow is kept below a toxic threshold.

For ¹⁷⁷Lu compounds, the emitted γ -rays allow individual imaging and dosimetry of the same compound using the first cycle of post-therapy images. Due to ⁹⁰Y's emission of Bremsstrahlung rather than gamma rays, post-therapy dosimetry for

⁹⁰Y is more challenging but can be performed, either with the use of complex corrections or simulations using ¹¹¹In-DOTATOC, the positron emitter ⁸⁶Y³⁶ or the (low rates of) positron emission from ⁹⁰Y.⁵⁵

Planar scans, SPECT imaging, blood and urine collections can all be used for dosimetry calculations and the dosimetric methods/calculations are described in multiple publications including those by Bodei et al³⁶ and Bison et al.⁵⁶ The calculation of internal dosimetry is complex for a number of reasons. These include that tumour cells are irradiated not for seconds or minutes, but continuously, over a long period of time with permanently changing dose rate. Additionally it can be difficult, or impossible, to always define relevant, accurate regions of interest, e.g. around bone marrow or around multiple different tumour sites with variable uptake

In practice, very few centres routinely follow dosimetry-guided administration but use a fixed activity scheme instead. This is at least, in part, because it is labour intensive and also because of the relatively low toxicity of PRRT. In clinical practice, dosimetry is usually performed in those with pre-existing renal impairment to help predict and limit renal toxicity, where the dosimetric results from the first cycle of treatment can help determine how many cycles can be safely administered.

In the future, particularly if the development of new software allows more efficient dosimetry calculations, it may be possible to deliver even more personalised therapy by routinely performing dosimetry thus ensuring that the radiation dose delivered to the tumour can be safely maximised for every patient.

PRRT variants

As described above, PRRT is typically used for patients with incurable NET, however, PRRT has been used in other circumstances, although generally in much smaller patient numbers and with less published evidence on its efficacy. These variants are outlined below.

Combination PRRT

In theory, ^{90}Y has advantages for larger tumours due to its longer β -particle path length whereas ^{177}Lu would be better suited to smaller lesions and there is some evidence combined PRRT may be more effective than either agent alone.⁵⁷ An analysis⁵⁸ of data from three previously published studies^{46,53,59} also found that combined therapy with ^{90}Y and ^{177}Lu PRRT may be associated with prolonged survival than treatment with either radiopeptide alone. More recent data using ^{90}Y -DOTA-octreotate followed by ^{177}Lu -DOTA-octreotate for patients with bulky disease demonstrated relatively high response rates and survival.⁶⁰ However, prospective, randomized controlled studies are needed to ultimately prove that PFS is better when using a combination of radionuclides.

Chemoradionuclide therapy

Chemotherapeutic agents particularly those with radiosensitising effects such as 5-fluorouracil (5-FU) and its prodrug capecitabine and have been combined with PRRT, sometimes referred to as peptide receptor chemoradionuclide therapy (PRCRT). A study of combined 5-FU infusion with ^{177}Lu -DOTATATE reported similar response and toxicity rates to PRRT alone.⁴⁷ A Phase 2 study evaluating capecitabine with Lu-177-octreotate in 33 patients demonstrated radiological regression or stabilisation in 94% with no significant increase in toxicity, survival at 1 and 2 years was 91 and 88% respectively.⁶¹ The same authors reported on the results of a Phase I-II study of ^{177}Lu -octreotate in combination with capecitabine and temozolomide in advanced low-grade NETs. This showed median PFS was 31 months, and median OS has not been reached with 90% surviving at 24 months, OR (regression or stabilisation) occurred in 94% of patients.⁶²

While apparently safe and efficacious, there is currently no data confirming whether PRCRT is superior to PRRT. Therefore, the use of PRCRT rather than PRRT alone could be more appropriate for those with higher grade NETs, the shorter survival associated with these tumours means the potential benefits of chemotherapy are more likely to outweigh the risks. As described above, a group of patients with known poorer prognoses are those with FDG avidity, therefore, this has been used as a criterion for selecting patients for PRCRT. This could be considered a different form of theranostic. A study of 52 patients with FDG avid NETs treated with 5-FU and ^{177}Lu DOTATATE reported radiological response rates of OR in 30%, SD in 68% and PD in only 2%, PFS was 48 months.⁶³

In vivo and *in vitro* studies have also been performed combining PRRT with a number of other chemotherapeutic agents including gemcitabine, camptothecin, mitomycin C, cisplatin, doxorubicin and everolimus.⁵⁶

Salvage

Repeat or “salvage” treatment in patients who have already received cycles of PRRT and later progress is also administered. A retrospective analysis of 33 patients who received salvage treatment reported radiological regression or stabilisation of disease in 77%. Median PFS from the start of salvage therapy was 13 months and patients with a history of a durable PFS after initial PRRT tended to have long-lasting PFS after salvage treatment ($p = 0.04$). There was no severe nephrotoxicity but reversible severe haematotoxicity was seen in 21% of patients.⁶⁴

Future directions

The scope for PRRT is growing, through the development of new SSTR agents and the introduction of new radionuclides. Additionally, the clinical indications for PRRT could expand and, as the results of randomised trials are published, better evidence regarding its current role in the treatment of NETs and its potential for combination with other therapies will emerge. These areas are outlined below.

SSTR antagonists

More recently SSTR antagonists have been developed and are entering clinical use. They have the advantages of higher tumour uptake and better tumour to background ratio than the agonists.⁶⁵ An antagonist named JR11 ((Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH₂) has been developed as a PET tracer labelled with ^{68}Ga using the chelator NODAGA (^{68}Ga -OPS202)⁶⁵ and as a therapeutic agent labelled with ^{177}Lu using the chelator DOTA (^{177}Lu OPS201).

A Phase I/2 trial comparing ^{68}Ga -OPS202 with ^{68}Ga -DOTATOC PET-CT found that the antagonist showed lower uptake than ^{68}Ga -DOTATOC in the normal liver, the pancreas and the gastrointestinal tract but similar uptake in malignant lesions, this significantly improved lesion contrast. On a lesion-basis, the diagnostic accuracy of ^{68}Ga -DOTATOC vs ^{68}Ga -OPS202 was 42 and 92% respectively.⁶⁶

Pilot studies have shown 1.7–10.6 times higher tumour dose with Lu-177-DOTA-JR11 when compared to Lu-177-DOTATATE.⁶⁷ Additionally, renal retention of SSTR antagonists is lower, resulting in a 5.2 times higher tumour-to-kidney ratio in favour of the receptor antagonist.⁵⁶ These characteristics mean that PRRT with SSTR antagonists could have significant advantages over the agonists. There is currently a clinical Phase I/II study underway to investigate the safety and tolerability, biodistribution, dosimetry and preliminary efficacy of ^{177}Lu -OPS201.⁶⁸

α emitters

Some radionuclides decay to release α particles (comprised of two protons and two neutrons). These have high energy, e.g. 8.32 MeV for Bismuth-213 (^{213}Bi) and a small particle range of 50–80 μm . This gives them a higher relative biological effectiveness and

potential to induce cell death. When alpha emitters are stably complexed to their SST analogue peptide and receptor density in normal tissue is low, radiotoxicity in non-targeted normal tissues should be minimal, based on the short path length of the emitted particle.⁵⁶

A pre-clinical study showed that, at the same absorbed dose, ²¹³Bi-DOTATOC is therapeutically more effective in decreasing survival of human pancreatic adenocarcinoma cells than is ¹⁷⁷Lu-DOTATOC.⁶⁹ A study in patients refractory to treatment with ⁹⁰Y/¹⁷⁷Lu-DOTATOC of intra arterial ($n = 7$) and systemic administration ($n = 1$) of ²¹³Bi-DOTATOC found that the biodistribution of ²¹³Bi-DOTATOC was evaluable with 440 keV gamma emission scans, and demonstrated specific tumour binding. Prolonged responses were observed in all treated patients, there was moderate chronic kidney toxicity but haematotoxicity was less severe than with the preceding β beta therapies.⁷⁰

Scandium

Scandium-44 (⁴⁴Sc) is a cyclotron produced positron emitting radionuclide with a half life of 3.97 h (vs 68 min for ⁶⁸Ga). It can therefore be more easily transported over long distances compared to ⁶⁸Ga. A report on ⁴⁴Sc-DOTATOC in four patients found that five additional metastases were detected in one patient, and one new metastasis was revealed in another patient, compared to the previous ⁶⁸Ga-DOTATOC PET/CT study. No adverse effects were observed in any of the patients. This tracer could be an excellent theranostic agent as pre-therapeutic imaging and dosimetry by ⁴⁴Sc-DOTATOC may be followed by radioreceptor therapy using the beta-emitting Scandium-47.⁷¹

Adjuvant and neo-adjuvant use

PRRT could, in future, be used as an adjuvant treatment after surgery, either to kill micrometastases already present or to prevent tumour development after spread during manipulation of the tumour during surgery. This potential use stems from an animal model where therapy with ¹⁷⁷Lu-octreotate prevented or significantly reduced the growth of tumour deposits in the liver after injection of tumour cells via the portal vein, mimicking preoperative tumour spill.⁷² Neo-adjuvant use is also a possibility as there have been a few case reports of the neo-adjuvant use of PRRT to render initially inoperable pancreatic and duodenal NETs^{73,74} and hepatic metastases⁷⁵ resectable.

Intra-arterial

Direct administration of radiolabelled DOTA peptides into hepatic arteries supplying liver metastases has been investigated. A study comparing standardised uptake values after intra-arterial administration of ⁶⁸Ga-DOTATOC vs intravenous administration in 15 NET patients found that SUVs were 3.75 times higher after intra-arterial administration.⁷⁶ The same authors performed a small study in which ⁹⁰Y- or ¹⁷⁷Lu-DOTATOC was infused via the hepatic artery in 15 patients with liver metastases arising from GEP-NETs. This resulted in a higher rate of objective radiological responses than typically reported for intravenous treatment (60 vs 30 %, respectively).⁷⁷ However long-term responses and toxicity are not available yet. There is an early

Phase 1 study currently underway where some study participants will receive a single dose of ⁹⁰Y-DOTATOC via the hepatic artery and other participants will receive ⁶⁸Ga-DOTATOC together with the ⁹⁰Y-DOTATOC dose and then have additional imaging and assessment.⁷⁸

Combined PRRT and other agents

The combination of PRRT with other agents, apart from just chemotherapy, is a potential area for development for example a Phase 1 study demonstrated that ¹⁷⁷Lu-octreotate could be combined with everolimus.⁷⁹

There has been also recent interest in the use of immunotherapy for NET. The results of pembrolizumab in patients with NET has been reported⁸⁰ and there is a clinical trial underway of nivolumab and ipilimumab⁸¹ in patients with NET. Given the emerging interest, efficacy and possible synergy of combining radiotherapy and immunotherapy^{82,83} combined PRRT and immunotherapy may be an additional future treatment option.

PRRT and RCTs

In the past, there has been criticism of PRRT that it was used in the absence of good quality evidence of its effectiveness, most data coming from observational or cohort studies. This is changing, both with the publication of the preliminary results of the NETTER-1 trial⁷ and because other randomised trials are underway. These include:

- (1) A randomized Phase II, parallel group study/trial of patients with GEP NET that is SRS and FDG positive. Patients will be randomly assigned to two different arms: ¹⁷⁷Lu PRRT either with or without capecitabine.⁸⁴
- (2) A Phase II randomised trial comparing PRCRT with CAPTEM (capecitabine plus temozolomide) with either CAPTEM for patients with pNET or PRRT for patients with midgut NET⁸⁵
- (3) A prospective randomised controlled open Phase 3 study of ¹⁷⁷Lu-Edotreotide (DOTATOC) compared to everolimus in patients with or GEPNET⁸⁵
- (4) The final outcomes of the NETTER-1 trial

In line with this move towards more trial based research of PRRT, the recent ENETs guidelines include a section on "recommendations to improve comparability of trials of PRRT".³⁰ However, until the results of these trials, and potentially others which may still be necessary, are known there is inadequate evidence to clearly define where in the treatment pathway PRRT should lie. Current guidelines place it as an option after other treatments have failed, however, in the future PRRT may be earlier in the treatment pathway and, in the further future still, may be able to cure patients who are currently deemed incurable.

CONCLUSION

NETs are a heterogeneous collection of tumours and the ability to apply the theranostic principle of appropriately identifying patients who are most likely to benefit from the therapeutic arm of SSTR-based therapy, by using the diagnostic arm of SSTR scintigraphy, is a key treatment strategy for patients with NETs.

There are multiple different imaging and therapeutic radionuclides available with newer generation ones entering clinical use or in development. Improving evidence in the form of clinical trials is consolidating PRRT's current place in the treatment of incurable NETs and it is likely this role will expand over time, either by PRRT moving earlier in the treatment algorithm or by combining it with other therapies.

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