Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours

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Abstract
Nuclear medicine plays a pivotal role in the imaging and treatment of neuroendocrine tumours (NETs). Somatostatin receptor scintigraphy (SRS) with [¹¹¹In-DTPA₀]octreotide has proven its role in the diagnosis and staging of gastroenteropancreatic NETs (GEP-NETs). New techniques in somatostatin receptor imaging include the use of different radiolabelled somatostatin analogues with higher affinity and different affinity profiles to the somatostatin receptor subtypes. Most of these analogues can also be labelled with positron-emitting radionuclides that are being used in positron emission tomography imaging. The latter imaging modality, especially in the combination with computed tomography, is of interest because of encouraging results in terms of improved imaging quality and detection capabilities. Considerable advances have been made in the imaging of NETs, but to find the ideal imaging method with increased sensitivity and better topographic localisation of the primary and metastatic disease remains the ultimate goal of research. This review provides an overview of the currently used imaging modalities and ongoing developments in the imaging of NETs, with the emphasis on nuclear medicine and puts them in perspective of clinical practice. The advantage of SRS over other imaging modalities in GEP-NETs is that it can be used to select patients with sufficient uptake for treatment with radiolabelled somatostatin analogues. Peptide receptor radionuclide therapy (PRRT) is a promising new tool in the management of patients with inoperable or metastasised NETs as it can induce symptomatic improvement with all Indium-111, Yttrium-90 or Lutetium-177-labelled somatostatin analogues. The results that were obtained with [⁹⁰Y-DOTA₀,Tyr³]octreotide and [¹⁷⁷Lu-DOTA₀,Tyr³]octreotate are even more encouraging in terms of objective tumour responses with tumour regression and documented prolonged time to progression. In the largest group of patients receiving PRRT, treated with [¹⁷⁷Lu-DOTA₀,Tyr³]octreotate, a survival benefit of several years compared with historical controls has been reported.

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Introduction
The first description of the in vivo visualisation of somatostatin receptor-positive tumours in patients was based on the use of a radioiodine (¹²³I) labelled somatostatin analogue (Krenning et al. 1989). In the years that followed an Indium-111 (¹¹¹In) labelled somatostatin analogue, chelated with diethylenetriaminepentaaceticacid (DTPA), was successfully developed. Subsequently, [¹¹¹In-DTPA₀]octreotide (OctreoScan, Covidien, Petten, The Netherlands), was introduced worldwide and became commercially available. Despite the development of several radio-labelled somatostatin analogues for scintigraphy, [¹¹¹In-DTPA₀]octreotide is the only registered radio-pharmaceutical for somatostatin receptor scintigraphy (SRS) of gastroenteropancreatic neuroendocrine tumours (GEP-NETs).

In the last decade, with the increasing use of positron emission tomography (PET) imaging, somatostatin
analogue have been labelled with various positron-emitting isotopes, such as Gallium-68 ($^{68}$Ga) and Copper-64 ($^{64}$Cu) (Lewis et al. 1999, Schottelius et al. 2004, Gabriel et al. 2007). Scintigraphy with these investigational compounds display encouraging good imaging quality that might result in an improved sensitivity in tumour site detection compared with $^{[111}$In-DTPA$^{b}$]octreotide scintigraphy. Also, other PET radiopharmaceuticals were developed, such as $^{18}$F-dihydroxy-phenyl-alanine ($^{18}$F-DOPA) and $^{11}$C-labelled 5-hydroxytryptophan ($^{11}$C-5-HTP) with encouraging results in terms of visualisation of GEP-NETs (Koopmans et al. 2008).

After the successful introduction of SRS in the diagnosis and staging of NETs, the next logical step was to increase the administered activity so that the radiopharmaceutical can induce tumour shrinkage in patients who had inoperable and/or metastasised NETs. Therefore, the first peptide receptor radionuclide therapy (PRRT) was performed with high administered activity of $^{[111}$In-DTPA$^{b}$]octreotide (Krenning et al. 1994a). However, besides encouraging results with regard to symptom relief, the reported number of objective responses was rather disappointing with relative low number of patients with tumour shrinkage.

To make significant advancements in the treatment of somatostatin receptor-positive metastatic disease, more efficient radiolabelled somatostatin analogues were developed with higher affinity to the somatostatin receptor. Also, more stable conjugation with high-energy β-emitters, such as Yttrium-90 ($^{90}$Y) and Lutetium-177 ($^{177}$Lu), was made possible with the introduction of the chelator 1,4,7,10-tetraazcyclododecane-1,4,7,10-tetraacetic acid (DOTA). These developments, together with the introduction of protective measures to limit the radiation dose to the kidneys and maximisation of the total cumulative administered activity respecting the currently international accepted dose limit to the bone marrow, were important to make PRRT a valuable therapeutic modality in the complete arsenal of treatment options in patients with encouraging results in terms of tumour shrinkage, quality of life (QoL) and survival.

This review covers the whole spectrum of the imaging of GEP-NETs with the emphasis on somatostatin receptor imaging and summarises the results of the therapeutic options within the field of nuclear medicine.

**Imaging**

To detect the exact location and subsequent staging of GEP-NETs, which is crucial for further patient management, a sensitive imaging modality is important. Commonly used imaging modalities include conventional radiology (computed tomography (CT), magnetic resonance imaging (MRI) and transabdominal ultrasonography (US)), selective angiography, nuclear imaging techniques (e.g. somatostatin receptor imaging) and endoscopic US (EUS). In most patients, however, more than one modality is needed to gather enough information to establish the exact localisation of the often small biochemically active tumours. Beside the increasing number of interesting new modalities, modalities are combined to increase the overall sensitivity and specificity.

**Conventional imaging**

The exact localisation of the primary tumour in patients diagnosed with a GEP-NET, especially gastrinomas and carcinoids of the small intestine, is often difficult to establish. The detection frequency with the conventional imaging modalities CT and MRI in pancreatic NETs is about 22–45%, which is higher than the reported sensitivity of abdominal US (13–27%; Modlin et al. 2008). For endoscopic US the percentages are mostly dependent on suspected tumour localisation with detection of 45–60% of the duodenal lesions and 90–100% of the pancreatic lesions (Anderson et al. 2000).

As most NETs are already metastasised at diagnosis, imaging of (liver) metastases is important. To visualise these metastases the use of specific acquisition protocols for CT and MRI is of vital importance. Owing to variability of appearance it is recommended to use a triple-phase (early/late arterial and portal venous) CT and a multiphasic (arterial, portal venous and delayed) dynamic and T2 weighted MRI protocol (Sheth & Fishman 2002). Even when these protocols are followed, the reported detection rate varies widely. For identification of metastasised disease, reported sensitivities of the modalities ranges from 60 to 80% visualisation with CT, 55–70% for MRI and 14–63% for US (Sugimoto et al. 1995, Gibril et al. 1996, Gibril & Jensen 2004, Tamm et al. 2007).

**Somatostatin receptor-based radionuclide imaging**

All somatostatin receptor-based radionuclide imaging is based on the principle of the binding of a radiolabelled ligand to the somatostatin receptor. Somatostatin receptors, which are structurally related membrane glycoproteins, are expressed in various normal tissues, including central nervous system (CNS), anterior pituitary, thyroid, pancreas, gastrointestinal tract, spleen and adrenals (Kwekkeboom et al. 2009).
The first report of overexpression of somatostatin receptors on tumour tissue was published in 1984. (Reubi & Landolt 1984) High density of somatostatin receptors on pituitary tumours in acromegaly patients was demonstrated. Five different subtypes of somatostatin receptors (ssst1–ssst5) are currently known and was demonstrated. Five different subtypes of somatostatin receptors on pituitary tumours in acromegaly patients (Rohrer et al. 1993, Patel & Srikant 1994). However, the expression of the various subtypes and their density on the tumour cell surface differs among the various tumours. Reubi et al. (2001), who used autoradiography to study the sstr subtype profile of numerous human tumours, reported a predominance of sst2 and/or somatostatin sst1 in GEP-NETs. The first report of the in vivo imaging of these NETs expressing somatostatin receptors with 123I-labelled [Tyr3]octreotide was published in 1989 (Krenning et al. 1989). However, an important drawback considering routine use of this compound for scintigraphy was the relatively high non-receptor-based uptake in the liver and intestinal uptake, which both can obscure occult pathology. Therefore, a radiolabelled somatostatin analogue with better characteristics, [111In-DTPA0]octreotide, was developed. Since then, [111In-DTPA0]octreotide is regarded as the gold standard in nuclear imaging for patients with GEP-NETs (Krenning et al. 1993). The somatostatin analogue octreotide binds with high affinity to receptor subtypes 2 and 5. Several authors demonstrated that a positive [111In-DTPA0]octreotide scintigraphy is mainly due to the sst2, whereas sst1–ssst5 are less important. Therefore, the presence of sst2 is essential for imaging tumours with SRS (John et al. 1996, Hofland et al. 2003).

The use of an optimal protocol for [111In-DTPA0]octreotide scintigraphy in the diagnosis of GEP-NETs is important to ensure good image quality and performance (Kwekkeboom et al. 2009). The preferred administered activity of [111In-DTPA0]octreotide (with at least 10 μg of the peptide) is about 200 MBq. Besides planar imaging, single photon emission computed tomography (SPECT) has to be included because of the increased sensitivity compared with planar imaging and should, be performed of the upper abdomen, including the liver, and of other regions with suspicion of disease. Also, besides increased sensitivity, SPECT imaging allows better anatomical delineation than planar views. If available, it is recommended to use hybrid SPECT/CT imaging for even better anatomical delineation. Timing and sufficient counts per view are also important acquisition characteristics. Any change in the protocol might influence the quality and therewith the sensitivity of the SRS performed. In more detail, these recommendations are available as procedure guidelines for somatostatin receptor imaging, published by the Society of Nuclear Medicine (SNM; Balon et al. 2001). Furthermore, the most important acquisition protocol recommendations have also been adapted by the European Association of Nuclear Medicine (EANM) and European Neuroendocrine Tumour Society (ENETS; Bombardieri et al. 2010, Kwekkeboom et al. 2009).

Normal scintigraphic findings with SRS with [111In-DTPA0]octreotide include visualisation of thyroid, spleen, liver, kidneys and in a proportion of patients the adrenals and/or pituitary gland. Also, the urinary bladder and the bowel are usually visualised to a variable degree (Krenning et al. 1992, Jacobsson et al. 2003). The visualisation of the pituitary, thyroid, adrenals and spleen is due to receptor binding. The uptake in the kidneys is mainly due to reabsorption of the radiolabelled somatostatin analogue in the renal tubular cells after glomerular filtration. Clearance of the radiopharmaceutical is primarily via the kidneys and some clearance is via the hepatobiliary pathway. Because of the latter, the use of laxatives and 48 h scanning is sometimes necessary to differentiate between non-specific bowel uptake and somatostatin receptor-positive abdominal pathology. Also, because of possible competition between cold octreotide and radiolabelled octreotide at the receptor site, temporary discontinuation of the therapeutic use of somatostatin analogues is recommended before imaging; at least 24 h in case of short-acting somatostatin analogues and 6 weeks when long-acting forms of somatostatin analogues are used. Unwanted competition may negatively affect the sensitivity for the detection of somatostatin receptor-positive pathological lesions, and therewith can results in false negatives.

**Imaging results of [111In-DTPA0]octreotide scintigraphy**

The sensitivity of somatostatin receptor imaging with [111In-DTPA0]octreotide scintigraphy for detecting NETs, including NETs of the pancreas (functioning and non-functioning) and carcinoids, has been well-documented. The overall reported sensitivity is high with 80% to almost 100% sensitivity for carcinoids and 60–90% for pancreatic NETs, mostly depending on tumour type and lesion size (Krenning et al. 1993, Kwekkeboom et al. 1993, Westlin et al. 1993, de Kerviler et al. 1994, Kalkner et al. 1995, Gibril et al. 1996, Zimmer et al. 1996, Lebtahi et al. 1997, Virgolini et al. 2005).

The sensitivity of histologically or biochemically proven neuroendocrine pancreatic tumours or
carcinoids was evaluated in a European multi-centre trial (Krenning et al. 1995). The highest success rates were observed with glucagonomas (100%), VIPomas (88%), gastrinomas (72%), non-functioning islet cell tumours (82%) and carcinoids (87%). These excellent imaging characteristics have made $^{111}$In-DTPA$^0$octreotide scintigraphy essential in the clinical work-up of GEP-NETs.

In contrast, the sensitivity to detect insulinomas with $^{111}$In-DTPA$^0$octreotide scintigraphy is lower than for most GEP-NETs with a sensitivity of 20–60% (Krenning et al. 1993, Schillaci et al. 2000, Vezzosi et al. 2005, de Herder et al. 2006). The variability in sensitivity may be caused by the low number of patients included in each study and an inferior scanning protocol, such as low administered activity or short acquisition time (Schillaci et al. 2000). Furthermore, in malignant insulinomas, the expression and density of somatostatin receptor subtypes is different from benign insulinomas so that a higher rate of scan positivity with $^{111}$In-DTPA$^0$octreotide scintigraphy can be expected in malignant insulinomas (Bertherat et al. 2003). Most of the reported patients with malignant insulinoma who had an $^{111}$In-DTPA$^0$octreotide scintigram, demonstrated uptake in the primary and metastatic lesions (Bokenkamp et al. 2003, Hirshberg et al. 2005, Vezzosi et al. 2005, Baldelli et al. 2007). However, the reported numbers of patients within these studies are too low to establish a reliable sensitivity of $^{111}$In-DTPA$^0$ octreotide scintigraphy in malignant insulinoma.

Of interest for the detection of insulinomas is the recently introduced $^{111}$In-labelled (Lys$^{40}$[Ahx-DOTA]NH$_2$)exendin-4 ($^{111}$In-DOTA-exendin-4) which displays a high sensitivity for insulinomas. It targets specifically the glucagon-like peptide 1 receptor (GLP1R), which is expressed in very high density in almost all insulinomas (Christ et al. 2009). Although the results with this compound are promising, most of the insulinomas are benign and localised (90%). Therefore, the need for staging with GLP1R imaging in the preoperative setting for benign insulinoma is questionable. Also, because of the already proven high sensitivity of endoscopic ultrasound (de Geus-Oei et al. 2002) in these tumours (Zimmer et al. 1996), the need for this new imaging modality in clinical practice warrants further studies.

$^{111}$In-DTPA$^0$octreotide scintigraphy versus other radiolabelled somatostatin receptor analogues

After the successful introduction of $^{111}$In-DTPA$^0$ octreotide scintigraphy developments focused on new analogues that would have a better affinity profile with higher sensitivity or a wider somatostatin receptor subtype affinity profile compared with $^{111}$In-DTPA$^0$octreotide. Some of the newly developed $^{111}$In-labelled somatostatin analogues use the macrocyclic chelator DOTA instead of DTPA. The most important advantage of the use of DOTA is the stable conjugation with the $\beta$-emitting radionuclides such as $^{90}$Y and $^{177}$Lu, which are used in PRRT. DTPA-labelled counterparts are not stable enough in vivo to be used in a therapeutic setting (de Jong et al. 2002a). Therefore, in view of selecting patients for PRRT with diagnostic scintigraphy, the use of the same (DOTA conjugated) somatostatin analogue is preferable. Examples of such analogues that are used in clinical studies include $^{111}$In-DOTA]lanreotide (Virgolini et al. 2002) and $^{111}$In-DOTA$^0$octreotide (Kwekkeboom et al. 1999, Gabriel et al. 2007). Furthermore, the somatostatin analogues $^{111}$In-DOTA [1-NaI$^3$]octreotide ($^{111}$In-DOTANOC; Wild et al. 2003), $^{[111}$In-DOTA[NaI$^8$Thr$^8$]octreotide ($^{111}$In-DOTANOCATE) and $^{[111}$In-DOTA$^0$,BzTh$^3$,Thr$^8$] octreotide ($^{111}$In-DOTABOCATE) demonstrated...
promising affinity profile characteristics (Table 1; Ginj et al. 2005). [111In-DOTA]lanreotide is a somatostatin receptor imaging agent with a slightly different affinity profile than [111In-DTPA]octreotide (Reubi et al. 2000). In comparison with [111In-DTPA]octreotide, it has a lower sensitivity to demonstrate NETs. However, the use of [111In-DOTA]lanreotide may have advantages in other tumours, for instance in differentiated thyroid carcinoma (Virgolini et al. 2002). In a direct comparison with [111In-DTPA]octreotide, [111In-DOTA]octreotide demonstrated a distribution and excretion pattern that resembled that of [111In-DTPA]octreotide. However, the interstitial background was higher, which could be disadvantageous in therapy, thereby exposing a higher absorbed dose to the dose-limiting organs (Kwekkeboom et al. 1999). Although 111In-DOTANOC, 111In-DOTATATE, 111In-DOTANOCATE and 111In-DOTATOCATE are promising analogues in terms of biodistribution and receptor affinity profile, in vivo human studies are scarce.

Besides the various 111In-labelled somatostatin analogues, metastable Technetium-99 (99mTc) has been coupled to somatostatin analogues for imaging. The most important advantages of the use of 99mTc compared with 111In-labelled based somatostatin analogues includes no expense of producing 111In in a cyclotron and no need to wait 24–48 h after injection for optimal detection of tumours. 99mTc-labelled somatostatin analogues used in a clinical setting include [99mTc-EDDA–HYNIC–D-Phe1,Tyr3]octreotide (99mTc-HYNIC-TOC; Gabriel et al. 2005, 2007), [99mTc-EDDA/HYNIC0,Tyr3]octreotate (99mTc-HYNIC-TATE; Hubalewska-Dydejczyk et al. 2006) and 99mTc-Depreotide (Lebtahi et al. 2002). As [111In-DTPA]octreotide scintigraphy is regarded as the gold standard in SRS, several of these new somatostatin analogues have been compared with

<table>
<thead>
<tr>
<th>Radioligand (references)</th>
<th>Setting</th>
<th>Comparison with [111In-DTPA]octreotide</th>
<th>Other reported results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[111In-DOTA0,Tyr3]octreotide (Kwekkeboom et al. 1999)</td>
<td>Clinical</td>
<td>Yes; equal to [111In-DOTA0]octreotide</td>
<td>Higher background radioactivity</td>
<td></td>
</tr>
<tr>
<td>[111In-DOTA0,Tyr3]octreotide (Gabriel et al. 2007)</td>
<td>Clinical</td>
<td>Not performed</td>
<td>Inferior to [68Ga-DOTA0,Tyr3]octreotide</td>
<td></td>
</tr>
<tr>
<td>[111In-DOTA]lanreotide (Virgolini et al. 2002)</td>
<td>Clinical</td>
<td>Not performed</td>
<td>Inferior to [111In-DOTA0]octreotide</td>
<td></td>
</tr>
<tr>
<td>[111In-DOTA][1-NaI3]octreotide (Wild et al. 2003)</td>
<td>Preclinical</td>
<td>Not performed</td>
<td>High affinity to hsst2, 3 and 5</td>
<td>No clinical studies published</td>
</tr>
<tr>
<td>[111In-DOTA][NaI8Thr8]octreotide (Ginj et al. 2005)</td>
<td>Preclinical</td>
<td>Not performed</td>
<td>Superior to [111In-DOTA0]octreotide</td>
<td></td>
</tr>
<tr>
<td>[111In-DOTA0,BzThi3,Thr8]octreotide (Ginj et al. 2005)</td>
<td>Preclinical</td>
<td>Not performed</td>
<td>High affinity to hsst2, 3 and 5</td>
<td>No clinical studies published</td>
</tr>
<tr>
<td>99mTc-depreotide (Lebtahi et al. 2002)</td>
<td>Clinical</td>
<td>Yes; inferior to [111In-DTPA0]octreotide</td>
<td>High lung and bone marrow uptake</td>
<td>Both registered radio-pharmaceuticals</td>
</tr>
<tr>
<td>[99mTc-EDDA/HYNIC0,Tyr3]octreotate (Hubalewska-Dydejczyk et al. 2006)</td>
<td>Clinical</td>
<td>Yes; superior to [111In-DTPA0]octreotide</td>
<td>No 24/48 h p.i. imaging possible</td>
<td></td>
</tr>
<tr>
<td>[99mTc-EDDA/HYNIC0,Tyr3]octreotate (Gabriel et al. 2003)</td>
<td>Clinical</td>
<td>Yes; superior to [111In-DTPA0]octreotide</td>
<td>No 24/48 h p.i. imaging possible</td>
<td></td>
</tr>
<tr>
<td>[99mTc-EDDA/HYNIC0,Tyr3]octreotate (Bangard et al. 2000)</td>
<td>Clinical</td>
<td>Yes; equal to [111In-DTPA0]octreotide: liver lesions superior to [111In-DTPA0]octreotide: extrahepatic</td>
<td>No 24/48 h p.i. imaging possible</td>
<td></td>
</tr>
</tbody>
</table>

NA, not applicable; hsst2, human somatostatin receptor subtype 2; p.i., post-injection.

Table 1 111In- and 99mTc-radiolabelled somatostatin analogues compared with [111In-DTPA]octreotide for scintigraphy
Metaiodobenzylguanidine (MIBG) is an aryl-guanidine derivative, structurally similar to noradrenaline, which utilises the vesicular monoamine transporters and is incorporated into vesicles or neurosecretory granules in the cytoplasm of neuroendocrine cells (Wafelman et al. 1994). However, it is not significantly metabolised. MIBG shows little binding to post-synaptic receptors and causes little or no pharmacological response (Sisson & Wieland 1986).

$^{123}\text{I}$ radiolabelled MIBG has been used for many years to visualise carcinoid tumours as it is concentrated in endocrine cells (Hoefnagel et al. 1987). The use of radiolabelled MIBG was initially concentrated on detecting tumours arising from chromaffin cells such as phaeochromocytomas, paraganglioma and neuroblastoma with overall reported high sensitivity of $\sim 90\%$ and specificity as high as 99% (Hoefnagel et al. 1987, Shapiro 1995). Although with lower sensitivity, MIBG scintigraphy was thereafter utilised to detect NETs. MIBG scintigraphy in carcinoid tumours, including the diagnostic scintigraphy with $^{131}\text{I}$-labelled MIBG, has shown lower sensitivity than the more frequently used $^{111}\text{In-DTPA}^0$octreotide scintigraphy. In a review of 10 years experience with MIBG, including MIBG scintigraphy, a median detection rate and sensitivity of 50 and 76%, respectively, was reported (Modlin et al. 2006). In contrast, the largest review, that included pooled imaging data from 35 centres with in total more than 1200 patients with carcinoid tumours, $^{111}\text{In-DTPA}^0$octreotide scintigraphy demonstrated a higher sensitivity of 84% (57–93%; Modlin et al. 2005). Furthermore, imaging with $^{123}\text{I}$-MIBG has a poor sensitivity in identifying islet cell tumours (Kaltsas et al. 2001a). Interestingly, within the few studies that compared $^{123}\text{I}$-MIBG and $^{111}\text{In-DTPA}^0$octreotide scintigraphy in carcinoid tumours, despite the in general lower uptake of $^{123}\text{I}$-MIBG, a complementary role of $^{123}\text{I}$-MIBG scintigraphy has been noted as either a different intensity or a different pattern of uptake in non-octreotide avid regions (Taal et al. 1996a, Kaltsas et al. 2001a). In one report in which a direct comparison between these two imaging modalities was performed, comparable results with sensitivities of about 84% were demonstrated, whereas the combination of these scans increased the sensitivity to 95% (Taal et al. 1996a).

Considering these two imaging modalities, it was concluded that $^{111}\text{In-DTPA}^0$octreotide scintigraphy is more sensitive in detecting metastatic lesions from GEP-NETs than with $^{123}\text{I}$-MIBG scintigraphy, with the latter imaging modality useful in the occasional patient who has MIBG-avid lesions, which do not show up with the initially performed $^{111}\text{In-DTPA}^0$octreotide scintigraphy (Kaltsas et al. 2001b). Also, differential uptake of $^{123}\text{I}$-MIBG and $^{111}\text{In-DTPA}^0$octreotide in different metastases within one subject has been reported and may be important in view of further clinical management (Quigley et al. 2005).

**Imaging results of PET**

PET using $^{18}\text{F}$-fluorodeoxyglucose ($^{18}\text{F}$-FDG) is a powerful functional modality for oncological imaging, especially in tumours with high proliferative activity and low differentiation grade. Unfortunately, since most GEP-NETs are well-differentiated, $^{18}\text{F}$-FDG is not accumulated in GEP-NETs except in the case of less differentiated tumours with high proliferative activity (Adams et al. 1998). Therefore, in general, it is not used as the initial imaging modality in the early diagnostic phase. However, a recently published study reported a negative correlation of $^{18}\text{F}$-FDG uptake and...
the prognosis of the disease (Binderup et al. 2010a). Furthermore, in a recent study by the same group, the combination of \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy and \(^{18}\text{F-FDG PET}\) yielded an overall sensitivity of 96% compared with 89% with \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy alone, indicating that \(^{18}\text{F-FDG PET}\) provides complementary diagnostic information (Binderup et al. 2010b). \(^{18}\text{F-FDG PET}\) was especially of value in GEP-NET patients with negative \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy or a high proliferation index (Ki-67 > 15%). Also, in pathology proven NETs that do not visualise on somatostatin receptor imaging, it is recommended to perform FDG-PET in staging, since these tumours show often more aggressive behaviour and faster growth. (Belhocine et al. 2002).

Other PET radiopharmaceuticals are also used to visualise these relatively slow growing tumours. In line with the commonly used \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy, somatostatin analogues labelled with a positron-emitting radionuclide are the most obvious radiopharmaceuticals to use for imaging.

Currently, several \(^{68}\text{Ga}\) labelled somatostatin analogues have been evaluated. \(^{68}\text{Ga}\) is a generator-produced radionuclide that can be chelated with DOTA to form a stable complex with somatostatin analogues. \([^{68}\text{Ga-DOTA}^0,\text{Tyr}^3]\)octreotide (\(^{68}\text{Ga-DOTATOC}\)) was the first \(^{68}\text{Ga}\)-labelled somatostatin analogue that was studied in patients. The results were promising (Hofmann et al. 2001, Mæcke et al. 2005, Gabriel et al. 2007). Consequently, other clinically applicable \(^{68}\text{Ga}\)-labelled somatostatin analogues were developed to increase their sensitivity or widen their affinity profile, including \(^{68}\text{Ga-DOTANOC}\) (Wild et al. 2005, Ambrosini et al. 2008, Fanti et al. 2008, Krausz et al. 2010) and \([^{68}\text{Ga-DOTA}^0,\text{Tyr}^3]\)octreotate (\(^{68}\text{Ga-DOTATATE}\); Kayani et al. 2008).

All these positron-emitting radionuclide labelled somatostatin analogues share the excellent image quality with better spatial resolution compared with the imaging with the \(\gamma\)-emitting analogues. Comparison of \(^{68}\text{Ga}\)-labelled somatostatin analogues with \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy and other imaging modalities has been performed in several studies (Table 2; Hofmann et al. 2001, Buchmann et al. 2007, Ambrosini et al. 2008, Fanti et al. 2008, Krausz et al. 2010). Unfortunately, however, inadequate protocols for \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy were used in many studies and therefore the comparison often inappropriate.

In clinical practice, PET imaging with the \(^{68}\text{Ga}\)-labelled somatostatin analogues has some more advantages compared with \([^{111}\text{In-DTPA}^0]\)octreotide scintigraphy besides the already mentioned higher spatial resolution with excellent image quality. These advantages include the easy accessibility and availability of the \(^{68}\text{Ga}\) generator, favourable acquisition protocol, with relative short scanning time, and low radiation exposure to the patient (Krausz et al. 2010). It is likely that, if available, PET/CT with \(^{68}\text{Ga}\)-labelled somatostatin analogues will become the image modality to be used for SRS in the future.

Also in SRS with the use of \(^{68}\text{Ga}\)-labelled somatostatin analogues in GEP-NET patients, \(^{18}\text{F-FDG PET}\) might have its place in the diagnostic work up with an increased overall sensitivity of 92% with the combination of \(^{68}\text{Ga-DOTATATE}\) PET/CT and \(^{18}\text{F-FDG PET/CT}\) especially in intermediate- and high-grade NET (Kayani et al. 2008).

### Table 2 Results of \(^{68}\text{Ga}\) labelled positron emission tomography ligands in clinical imaging compared with other imaging modalities

<table>
<thead>
<tr>
<th>Radioligand (references)</th>
<th>Compared with</th>
<th>Reported results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>([^{68}\text{Ga-DOTA}^0,\text{Tyr}^3])octreotide (Hofmann et al. 2001)</td>
<td>([^{111}\text{In-DTPA}^0])octreotide</td>
<td>Superior</td>
<td>Scan protocol ([^{111}\text{In-DTPA}^0]) octreotide inadequate</td>
</tr>
<tr>
<td>([^{68}\text{Ga-DOTA}^0,\text{Tyr}^3])octreotide (Buchmann et al. 2007)</td>
<td>([^{111}\text{In-DTPA}^0])octreotide</td>
<td>Superior to SPECT</td>
<td>Scan protocol ([^{111}\text{In-DTPA}^0]) octreotide inadequate</td>
</tr>
<tr>
<td>([^{68}\text{Ga-DOTA},1\text{-nal}^3])octreotide (Fanti et al. 2008)</td>
<td>CT</td>
<td>Useful additional information</td>
<td>No comparison with other radioligands</td>
</tr>
<tr>
<td>([^{68}\text{Ga-DOTA},1\text{-nal}^3])octreotide (Ambrosini et al. 2008)</td>
<td>(^{18}\text{F-DOPA})</td>
<td>Superior</td>
<td>Case report</td>
</tr>
<tr>
<td>([^{68}\text{Ga-DOTA},1\text{-nal}^3])octreotide (Wild et al. 2005)</td>
<td>([^{111}\text{In-DOTA}^0])octreotide</td>
<td>Superior</td>
<td></td>
</tr>
<tr>
<td>([^{68}\text{Ga-DOTA},1\text{-nal}^3])octreotide (Kayani et al. 2008)</td>
<td>(^{18}\text{F-FDG})</td>
<td>Superior: low-grade tumours Inferior: high/intermediate-grade tumours</td>
<td></td>
</tr>
<tr>
<td>([^{68}\text{Ga-DOTA},1\text{-nal}^3])octreotide (Krausz et al. 2010)</td>
<td>([^{111}\text{In-DTPA}^0])octreotide</td>
<td>Comparable, if not superior</td>
<td></td>
</tr>
</tbody>
</table>
Besides, the $^{68}$Ga-labelled somatostatin analogues, a glycosylated $^{18}$F-labelled somatostatin analogue, $N^2$-(1-deoxy-o-fructosyl)-$N^6$-(2-[18F]fluoropropionyl)-Lys$^0$-Tyr$^3$-octreotate (Gluc-Lys[$^{18}$F]FP)-TOCA), has been introduced for PET with a diagnostic performance superior to $^{[111}$In-DTPA$^0$]octreotide scintigraphy and probably comparable with $^{68}$Ga-DOTATOC (Meisetschlager et al. 2006). However, the preparation of Gluc-Lys($^{18}$F)FP)-TOCA requires a time-consuming multistep synthesis that will probably hamper its future clinical use.

Other interesting, not somatostatin analogue-based, PET imaging agents in GEP-NETs include $^{18}$F-DOPA and $^{11}$C-5-HTP.

PET with $^{18}$F-DOPA is based on the fact that DOPA is a catecholamine precursor, which is taken up by neuroendocrine cells (Becherer et al. 2004), whereas 5-HTP is a direct precursor for the serotonin pathway and therefore a potentially sensitive universal method for NET detection (Orlefoes et al. 2005).

In a recent comparison on the diagnostic sensitivity of PET scanning with both $^{11}$C-5-HTP and $^{18}$F-DOPA as tracers, it was concluded that $^{18}$F-DOPA PET is an ideal imaging modality for staging in carcinoid patients and $^{11}$C-5-HTP PET in patients with NET in the pancreas. Furthermore, the anatomical information obtained by the (almost) simultaneously performed CT increases the sensitivity of the PET in both studies even more (Koopmans et al. 2008). Examples of $^{18}$F-DOPA PET and $^{11}$C-5-HTP images in the same patient are shown in Figs 1 and 2.

Both new tracers, especially in combination, are promising for more accurate staging of patients with NETs. However, for selecting patients for PRRT, the radiopharmaceutical for imaging has to be of the same family as for PRRT and therefore SRS the imaging method of choice.

**Therapy**

Peptide receptor scintigraphy is important in staging as it may detect resectable GEP-NETs that could be missed with conventional imaging techniques. Furthermore, it may prevent surgery in patients whose tumours have metastasised to a greater extent than could be detected with conventional imaging alone. Besides staging it may also be used to select patients for PRRT with $^{111}$In-$^{90}$Y- or $^{177}$Lu-labelled peptide analogues.

The outcome of several phases 1 and 2 PRRT studies have been published in which different somatostatin analogues labelled with on of these three radionuclides were used (Tables 3 and 4).

$^{[111}$In-DTPA$^0$]octreotide

The initial studies on radiolabelled somatostatin analogue therapy in GEP-NET patients were performed in the early 1990s and were based on the administration of high administered activities of $^{[111}$In-DTPA$^0$]octreotide (Krenning et al. 1994b). At that time no other chelated analogue was available for therapeutic purposes (Table 3; Anthony et al. 2002, Valkema et al. 2002, Buscombe et al. 2003, Delpassand et al. 2008). Overall, the reported outcome of these treatments was encouraging in terms of reduced symptomatology and biochemical response.

Despite reported partial remissions (PRs) were few, patients with stable disease (SD) and minor remission might be considered to have had a beneficial therapeutic effect as 92% or more patients had documented progressive disease at study entry.

Recently, a study reported high-activity PRRT with cumulative administered activities up to 37.3 GBq given in two cycles (Delpassand et al. 2008). On an intention to treat basis, two out of 29 (7%) patients had PR, 16/29 (55%) had SD and 11/29 (37%) of the patients were either deceased ($n=4$) or withdrawn from the study without any clear reason mentioned ($n=7$). Eighteen out of 29 (62%) patients had the intended therapy of two cycles of $^{[111}$In-DTPA$^0$]octreotide. In this group, 2/18 (11%) had PR and 16/18 (89%) had SD 3 months after the last therapy. Although the number of PRs was few, the remainder of patients ($n=16$) that could be analysed had SD. In addition, a significant decrease in the tumour marker chromogranin A (CgA) or hormone levels from pretreatment observations was observed with a 50% reduction from pretreatment levels in CgA or at least one hormone in eight patients (44%). Change of biomarkers, such as CgA in GEP-NETs might, besides objective responses, be important in these relative indolent growing tumours as morphological assessment alone might underestimate the therapeutic efficacy. Unfortunately, biomarkers as secondary outcome parameters are often not available and moreover difficult to compare with other studies.

When therapeutic toxicity of PRRT is considered, transient bone marrow suppression was the most often encountered toxicity after $^{[111}$In-DTPA$^0$]octreotide therapy. More serious side effects included leukaemia and myelodysplastic syndrome (MDS), which were discovered during follow-up in three out of six patients who had received more than a total administered activity of 100 GBq with estimated bone marrow radiation dose of more than 3 Gy (Valkema et al. 2002). One of the patients had chemotherapy before
Figure 1 (a) $^{18}$F-dihydroxy-phenyl-alanine ($^{18}$F-DOPA, 180 MBq) positron emission tomography (PET) of a 64-year-old male patient diagnosed with carcinoid disease with multiple abdominal lesions and one possible small lesion in the supraclavicular region (black arrows). (b) $^{11}$C-5-hydroxy-tryptophan ($^{11}$C-5-HTP, 200 MBq) PET in the same patient with almost similar uptake pattern. $^{18}$F-DOPA PET in this patient appears to be slightly more sensitive, with a better tumour-to-background ratio and a possible left supraclavicular lesion. Note also the clearance of both radiopharmaceuticals via the kidneys. (c) From left to right: coronal thoracoabdominal images of $^{18}$F-DOPA PET, CT and $^{18}$F-DOPA PET/CT in the same patient.
[111In-DTPA\textsuperscript{0}]octreotide therapy, which could have contributed or caused this severe complication. Renal insufficiency was reported by Anthony et al. (2002) in one patient and was probably related to retroperitoneal fibrosis already present before therapy. Three patients with tumour replacement of more than 75% of their hepatic parenchyma and with treatment-associated necrosis on CT experienced transient grade 4 hepatic toxicity.

From the clinical studies with [111In-DTPA\textsuperscript{0}]octreotide, it can be concluded that [111In-DTPA\textsuperscript{0}]octreotide therapy is not the ideal radiolabelled peptide for PRRT, at least not for metastatic GEP-NETs. Experimental data in rats have shown that high absorbed doses of [111In-DTPA\textsuperscript{0}]octreotide can inhibit the growth of liver metastases after injection of somatostatin receptor ss\textsubscript{T2} tumour cells into the portal vein. Therefore, [111In-based PRRT might be efficacious in the treatment of micro-metastases or in the prevention of metastatic spread during initial surgery (Slooter et al. 1999). However, clinical studies that confirm these preclinical observations are lacking.

\[111\text{In-DTPA}^{0}\text{]octreotide therapy, which could have contributed or caused this severe complication.}

\textbf{Figure 2} (a) \textsuperscript{18}F-dihydroxy-phenyl-alanine (\textsuperscript{18}F-DOPA) positron emission tomography (PET) of a 56-year-old female patient diagnosed with an endocrine tumour of the pancreas extending towards the spleen with liver metastases. Note the known physiological uptake in the gallbladder (Balan 2005). (b) \textsuperscript{11}C-5-hydroxy-tryptophan (\textsuperscript{11}C-5-HTP) PET in the same patient indicating more tumour mass and a higher number of liver metastasis in comparison with the \textsuperscript{18}F-DOPA PET. Note also the clearance of both radiopharmaceuticals via the kidneys.

\textbf{90Y-labelled somatostatin analogues}

The next generation of radiolabelled somatostatin analogues was coupled to the β-emitting radionuclide \textsuperscript{90}Y. DOTA-chelated somatostatin analogues were used for more stable conjugation of analogue and radionuclide. The different somatostatin analogues have different affinities for the somatostatin receptor subtypes, which can have accounted for the difference in reported outcome as is shown in Table 4. However, since no randomised trial has been performed, other differences, such as used protocol, selected patient population and the total administered activity, could have been responsible for the observed differences. In a small group of patients, Otte et al. (1998). Reported two PRs out of ten patients with somatostatin receptor-positive tumours treated with \textsuperscript{90}Y-DOTA\textsuperscript{0},\textsuperscript{Tyr}\textsuperscript{3}]octreotide (\textsuperscript{90}Y-DOTATOC), whereas six patients had SD. In the studies that followed, response rates (complete response (CR) and PR) in patients with GEP-NETs, who were either treated with up to 6.0 GBq/m\textsuperscript{2} (dose-escalating study of four cycles) or 7.4 GBq/m\textsuperscript{2}, were 10/37 (27%) and 8/37 (22%) respectively (Waldherr...
In a preliminary subsequent study the same total administered activity of 7.4 GBq/m² was given in two cycles to determine whether a decrease in the number of treatments could increase PRRT efficacy in terms of objective responses (Waldherr et al. 2002b). Twelve out of 35 patients (34%) had CR or PR, which indicated a higher percentage of tumour regression. No increase in side effects was reported. Unfortunately, published randomised clinical studies to indicate a therapeutic benefit of less cycles in PRRT are lacking.

Reported clinical studies of PRRT from Milan, also used the radiolabelled somatostatin analogue 90Y-DOTATOC to treat patients with various somatostatin receptor-positive tumours (Paganelli et al. 2001, 2002, Chinol et al. 2002, Bodei et al. 2003, 2004). Objective tumour responses, including CR and PR varied from 26 to 29%. Unfortunately, a clear description of the tumour response in relation to a specific tumour type on a per-patient basis was not always given. Instead, it was reported that most of the patients who had a favourable outcome, had GEP-NETs.

In a multi-centre (Rotterdam, The Netherlands; Brussels, Belgium; Tampa, USA) dose escalation phase I study, also with 90Y-DOTATOC, escalating administered activities up to 14.8 GBq/m² in four cycles or up to 9.3 GBq/m² in a single cycle were given to a total of 58 GEP-NET patients (Valkema et al. 2006). The maximum tolerated single dose was not reached. The total administered activity was limited according to a maximum estimated dose of 27 Gy to the kidneys. Furthermore, concomitantly with the therapy, an amino acid (lysine 2.5%/arginine 2.5%) solution was administered for kidney protection. Five out of 55 (9%) evaluable patients had PR, seven (13%) had minimal response (MR) and 29 (53%) had SD. Although a detailed QoL assessment was not performed, 21 of the 36 patients (58%) had improvement in Karnofsky performance score (KPS) or symptoms.

In a recently published study, 90 GEP-NET patients were treated with a fixed dose regimen of three cycles of 4.4 GBq 90Y-DOTATOC (90Y-dotreotide, Onalta, Molecular Insight Pharmaceuticals, Cambridge, MA, USA; Bushnell et al. 2010). The maximum cumulative administered activity of 13.3 GBq was chosen as it is regarded as both safe and effective (Smith et al. 2000, Valkema et al. 2006). Four out of 90 (4%) evaluable patients had PR and 63 (70%) had SD. Median progression-free survival was 16.3 months. The number of patients who had PR and SD is comparable with the results of the second largest (multi-centre)
Table 4 Peptide receptor radionuclide therapy clinical trials with ⁹⁰Y- or ¹⁷⁷Lu-labelled somatostatin analogues in patients with gastroenteropancreatic neuroendocrine tumours

<table>
<thead>
<tr>
<th>References</th>
<th>No. of evaluable patients</th>
<th>Progression at inclusion (%)</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
<th>CR + PR</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>[⁹⁰Y-DOTA³,Tyr³]octreotide</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>20</td>
<td>0/28 (100%)</td>
<td>SWOG</td>
</tr>
<tr>
<td>Otte et al. (1999)</td>
<td>16</td>
<td>N/I</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>7</td>
<td>2/16 (12%)</td>
<td>WHO</td>
</tr>
<tr>
<td>Waldherr et al. (2001)</td>
<td>37</td>
<td>30% reduction of tumour size</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td>0/33 (0%)</td>
<td>SWOG</td>
</tr>
<tr>
<td>Waldherr et al. (2002a)</td>
<td>37</td>
<td>25% reduction of tumour size</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>0/33 (0%)</td>
<td>WHO</td>
</tr>
<tr>
<td>Waldherr et al. (2002b)</td>
<td>36</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>0/33 (0%)</td>
<td>WHO</td>
</tr>
<tr>
<td>Bodei et al. (2003)</td>
<td>21</td>
<td>25% reduction of tumour size</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>0/33 (0%)</td>
<td>WHO</td>
</tr>
<tr>
<td>Valkema et al. (2006)</td>
<td>58</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>0/33 (0%)</td>
<td>WHO</td>
</tr>
<tr>
<td>Bushnell et al. (2010)</td>
<td>90</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>0/33 (0%)</td>
<td>WHO</td>
</tr>
<tr>
<td>[¹⁷⁷Lu-DOTA³,Tyr³]octreotate</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>20</td>
<td>0/28 (100%)</td>
<td>SWOG</td>
</tr>
<tr>
<td>Virgolini et al. (2002)</td>
<td>39</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>20</td>
<td>0/28 (100%)</td>
<td>WHO</td>
</tr>
<tr>
<td>[¹⁷⁷Lu-DOTA³,Tyr³]octreotate</td>
<td>75</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>20</td>
<td>0/28 (100%)</td>
<td>WHO</td>
</tr>
<tr>
<td>Baum et al. (2004)</td>
<td>89</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>20</td>
<td>0/28 (100%)</td>
<td>WHO</td>
</tr>
<tr>
<td>[¹⁷⁷Lu-DOTA³,Tyr³]octreotate</td>
<td>310</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>20</td>
<td>0/28 (100%)</td>
<td>WHO</td>
</tr>
<tr>
<td>Kwekkeboom et al. (2008)</td>
<td>12</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>20</td>
<td>0/28 (100%)</td>
<td>WHO</td>
</tr>
<tr>
<td>Garkavij et al. (2010)</td>
<td>12</td>
<td>30% reduction of tumour size</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>14</td>
<td>20</td>
<td>0/28 (100%)</td>
<td>WHO</td>
</tr>
</tbody>
</table>

N/I, not indicated or not specified to the number of evaluable patients.  
⁹CaModification of the Southwest Oncology Group (SWOG) criteria including MR (minor remission), between 25 and 50% reduction of tumour size.  
βCriteria of tumour response: SWOG: PR (partial remission), ≥30% reduction of tumour size; MR (minor remission), 30% reduction or increase of SD (stable disease), <30% reduction or increase of <20% of tumour size; PD (progressive disease), ≥20% increase of tumour size or new lesion(s), measurements: bidimensional. WHO: PR, ≥50% reduction of tumour size; SD, <50% reduction or increase of <25% of tumour size; PD, ≥25% increase of tumour size or new lesion(s), measurements: bidimensional. Response evaluation criteria in solid tumours (RECIST): PR, ≥50% reduction of tumour size; SD, <25% reduction or increase of tumour size; PD, >50% increase of tumour size, measurements: unidimensional.

PRRT phase I study with ⁹⁰Y-DOTATOC (Valkema et al. 2006). Furthermore, in this study, a subgroup analysis of 19 patients who received a cumulative activity between 9.9 and 13.3 GBq ⁹⁰Y-DOTATOC was performed to mimic the cumulative activity administered in the phase II studies. Median overall survival (OS) in these 19 patients was 21.3 months, which is in line with the reported OS of 26.9 months in the larger group of 90 patients (Bushnell et al. 2010).

Also clinically used, is the ⁹⁰Y-labelled somatostatin analogue [DOTA³,Tyr³]octreotide (DOTATATE). DOTATATE is formed by replacing the C-terminal threoninol in DOTATOC with threonine. This small change of molecular structure improved the binding to somatostatin receptor-positive tissues in animals (de Jong et al. 1998). Furthermore, a ninefold increase in affinity for the sst₂ for DOTATATE if compared with DOTATOC was reported (Reubi et al. 2000). After coupling of Yttrium to both analogues, an almost sevenfold increase was preserved.

Preliminary results of the therapeutic efficacy of ⁹⁰Y-DOTATATE in patients with somatostatin receptor-positive tumours was reported by Baum et al. (2004) Twenty-eight out of 75 (37%) patients had PR and 39/75 (52%) had SD after therapy. Therefore, ⁹⁰Y-DOTATATE might also be a promising ⁹⁰Y-labelled somatostatin analogue. In analogy with [¹¹¹In-DTPA⁰]octreotide therapy, transient, but mild bone marrow suppression was the most often observed side effect in patients treated ⁹⁰Y-labelled somatostatin analogues. Acute grades 3 and 4 haematologic toxicity was observed for platelets in 3–12% of the patients, 1–7% for haemoglobin and 2–7% for white blood cells (Otte et al. 1999, Waldherr et al. 2002a, Bodei et al. 2003, Valkema et al. 2006) The latter toxicity has recently been addressed in a study by Sierra et al. (2009) in which it was concluded that the toxicity regarding the lymphocytic subpopulation is mainly directed to the B-cell subpopulation.

Despite the current use of kidney protection which consists of coinfusion of an amino acid solution during PRRT, the kidneys are often found to be dose-limiting. Especially in patients treated with ⁹⁰Y based somatostatin analogues with and without kidney protection renal toxicity has been reported in a limited number of patients.

In an intra-patient dose-escalating study renal toxicity was seen in four out of 29 (14%) treated patients after administration of cumulative activities of 7.6–8.9 GBq/m² ⁹⁰Y-DOTATOC (Otte et al. 1999). None of these four patients received coinfusion of an amino acid solution during and after PRRT. Two of them needed haemodialysis treatment. No renal...
toxicity was observed in the other patients who received a maximum of administered cumulative activity of 7.4 GBq/m². A cumulative administered activity of 7.5 GBq/m² was, therefore, suggested to be dose-limiting for the kidneys in PRRT with ⁹⁰⁰⁰Y-DOTATOC. However, a case report of a patient treated with 5.6 GBq/m² ⁹⁰⁰⁰Y-DOTATOC, who developed end-stage renal disease, suggests that this limit is not completely reliable to exclude renal toxicity (Cybulla et al. 2001).

In a more detailed study focusing on renal function, 28 patients who had a cumulative radiation dose to the kidneys up to 38.7 Gy and a median follow-up 2.9 years, had a median decline of creatinine clearance of 7.3%/year (Valkema et al. 2005). Furthermore, a decline of >15% was reported in a subgroup of nine patients of which five had hypertension and/or diabetes. In this and another study by Bodei et al. (2008), it was concluded that cumulative renal radiation dose, per-cycle renal radiation dose, age, hypertension and diabetes are probable contributing factors responsible for the high rate of decline in creatinine clearance after PRRT demonstrated in a subgroup of patients.

All the clinical trials with ⁹⁰⁰⁰Y-labelled somatostatin analogues, despite the differences in analogues and protocols used, report favourable outcome in terms of percentages of patients with complete or PR ranging up to 37% (Table 4) and, therefore, compare favourably with [¹¹¹In-DTPA⁰]octreotide based PRRT. Furthermore, survival data are encouraging in terms of a longer documented OS. In the multi-centre study comprising a group of 58 patients treated with ⁹⁰⁰⁰Y-DOTATOC, the OS compared favourably with a historical group of patients treated with [¹¹¹In-DTPA⁰]octreotide with a median time of survival of 3 years (versus 12 months; Valkema et al. 2002, 2006). Limitation of this comparison is the fact that both were separate phase I studies and thus without randomisation. However, the observed difference in median survival can probably not be solely explained by this.

**¹⁷⁷⁰⁰⁰Lu-labelled somatostatin analogues**

In preclinical studies by de Jong et al. (2002b), different radiolabelled somatostatin analogues were evaluated for future clinical therapeutic use. Besides [¹¹¹In-DTPA⁰]octreotide and ⁹⁰⁰⁰Y-DOTATOC, the β-emitting radionuclide ¹⁷⁷⁰⁰⁰Lu coupled to DOTATATE (¹⁷⁷⁰⁰⁰Lu-DOTATATE) was used. ¹⁷⁷⁰⁰⁰Lu-DOTATATE demonstrated the highest tumour uptake together with excellent tumour-to-kidney ratios compared with [¹¹¹In-DTPA⁰]octreotide and ⁹⁰⁰⁰⁰Y-DOTATOC. Furthermore, in a clinical study by Esser et al. (2006) was compared with ¹⁷⁷⁰⁰⁰Lu-DOTATOC in a therapeutic setting. A mean residence time ratio of 2.1 in favour of ¹⁷⁷⁰⁰⁰Lu-DOTATATE for PRRT was reported. Therefore, in our view for GEP-NETs ¹⁷⁷⁰⁰⁰Lu-DOTATATE is the radiolabelled somatostatin analogue of choice for PRRT.

The first reports on the results of the clinical use of ¹⁷⁷⁰⁰⁰Lu-DOTATATE were promising with CR and PR in 30%, MR in 12% and SD in 40% of the treated GEP-NET patients (Kwekkeboom et al. 2003a). In a more recent analysis these results were confirmed in a large group of a total of 310 GEP-NET patients (Kwekkeboom et al. 2008). Patients were treated up to a total administered activity of 27.8–29.6 GBq, usually in four treatment cycles, with treatment intervals of 6–10 weeks. Complete and partial tumour remissions occurred in 2 and 28% of patients respectively. Factors predictive of a favourable response with tumour shrinkage (CR, MR and PR) were high uptake on pre-PRRT [¹¹¹In-DTPA⁰]octreotide scintigraphy and a KPS higher than 70. Interestingly, a reduced tumour uptake after the third or fourth treatment in comparison with the scan after the first treatment was frequently seen in patients who eventually had a tumour regression during follow-up (Kwekkeboom et al. 2005). This phenomenon is illustrated in Fig. 3. In line with these observations on post-PRRT scintigraphy, similar results of reduced somatostatin receptor mediated uptake after PRRT was recently published by Haug et al. (2010). In their study, decreased ⁶⁸⁰⁰⁰Ga-DOTATATE uptake in tumours after the first cycle of PRRT predicted the time to progression (TTP) after completion of PRRT (one, two or three cycles) and was correlated with improvement in clinical symptoms. Most obvious cause of the observed decrease in uptake is a decreased amount of viable somatostatin receptor-expressing tumour cells and thereby reflecting the cytotoxic therapeutic effect of PRRT. Other suggested causes included the induction of dedifferentiating of NET cells within the tumour as somatostatin expression depends on the grade of differentiation of NET (Miederer et al. 2009). However, dedifferentiation is less likely because the observed favourable effect on tumour response, TTP and clinical symptoms in tumours with reduced uptake in the tumours after PRRT. Also, the effect of PRRT on receptor expression and density on a single tumour cell is not know and has to be elucidated in further studies.

Four patients who were judged inoperable by the surgeon, became operable after adequate reduction of tumour mass, 6–12 months after PRRT. Three of these
patients were successfully operated upon, whereas one died of unfortunate postoperative complications.

Median TTP in the GEP-NET patients who did not have PD ($n = 249$) was 40 months from start of the first cycle. Median OS was 46 months and median disease-related survival was > 48 months. Median progression-free survival was 33 months (Kwekkeboom et al. 2008). Not surprisingly, the most important factor predicting increased survival was treatment outcome. Patients with PD had significantly shorter survival compared with patients with SD or tumour shrinkage. Survival between other treatment outcomes did not differ significantly (Fig. 4).

Furthermore, patients with a low KPS or extensive tumour load within the liver had a less favourable survival.

In 42 patients with metastasised bronchial or GEP-NETs who had an objective tumour response of tumour remission or SD with clearly clinical benefit after the regular $^{177}$Lu-DOTATATE therapy, salvage therapy, with two additional cycles of 7.4 GBq, was evaluated (van Essen et al. 2010). On radiological evaluation, eight (24%) out of 33 eligible patients had tumour remission (MR or PR), ten (31%) had SD and 15 (45%) had PD 3 months after the last therapy. The additional treatments were well tolerated with acceptable haematological toxicity and without any serious delayed toxicity. A similar study was performed by Forrer et al. (2005) in patients with NETs previously successfully treated with $^{90}$Y-DOTATOC. Twenty-seven patients received an additional treatment of 7.4 GBq $^{177}$Lu-DOTATATE. On radiological evaluation, seven (26%) had tumour remission (MR or PR) and 12 (44%) had SD 8–12 weeks after therapy.

Published reports of PRRT with $^{177}$Lu-DOTATATE in other clinical centres are in a small group of patients or anecdotal. In the study by Muros et al. (2009), PRRT with $^{177}$Lu-DOTATATE was performed in two patients with advanced NETs in addition to previously given treatments of $^{90}$Y-DOTATOC. In both patients disease stabilisation was the maximum achieved objective tumour response. In a recently published study, which was mainly focused on dosimetric issues instead of the therapeutic efficacy of PRRT, two out of 12 (17%) patients, who were evaluable and had completed the treatments (three and four cycles of 7.4 GBq) with $^{177}$Lu-DOTATATE, had PR, 3/12 (25%) had MR and 5/12 (42%) had SD (Garkavij et al. 2010). Although a limited number of patients studied, the results are in line with the large series by Kwekkeboom et al. (2008).

Clinical PRRT studies with other $^{177}$Lu-labelled somatostatin analogues are limited. The use of

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**Figure 3** (a) Posttherapy scans (anterior/posterior, abdominal spot view images) after each cycle of PRRT with 7400 MBq ($^{177}$Lu-DOTA$^{0}$,Tyr$^{3}$)octreotate (top to bottom row indicates the first to last cycle) in a patient with rectal carcinoid with metastases who eventually had partial remission as tumour outcome. Note the decrease of uptake in the liver lesions compared to physiological liver uptake with every post-therapy scan. (b) CT of the abdomen of the same patient before (left panel) and 3 months after (right panel) the last cycle.
DOTANOC is interesting because it has a high affinity to the sst2, sst3 and sst5 (Wild et al. 2003). Therewith, a broader affinity profile than DOTATATE, which has predominantly high affinity to the sst2. In theory, the broader affinity profile can be beneficial for patients with tumours that express not only the sst2. In a recent study, eight patients were treated with one cycle of 3600–7400 MBq $^{177}$Lu-DOTANOC (Wehrmann et al. 2007). PRRT was continued in three patients with $^{177}$Lu-DOTATATE (Wehrmann et al. 2007). Because the report was primarily conducted for dosimetric comparison of $^{177}$Lu-DOTATATE with $^{177}$Lu-DOTANOC, no tumour response outcome was reported. From the results it was concluded that DOTANOC coupled to $^{177}$Lu leads to a higher uptake in normal tissue, and therefore an increase in the whole-body dose. Together with the observed high inter-patient variability this outcome indicates that individual patient dosimetry is important to decide whether to treat a patient with $^{177}$Lu-DOTATATE or $^{177}$Lu-DOTANOC. In a preliminary report from Rotterdam, four patients with thyroid carcinoma were treated with 6.7–32.5 GBq $^{177}$Lu-DOTANOC (Valkema et al. 2007). One patient with follicular thyroid carcinoma had PR, one patient with Hürthle cell thyroid carcinoma (HCTC) had clinical improvement whereas the other two patients (HCTC and medullary thyroid carcinoma) had PD. Studies that report tumour responses in patients with NETs with $^{177}$Lu-DOTANOC therapy are lacking.

Side effects after PRRT with $^{177}$Lu-DOTATATE were analysed in a total of 504 patients. Acute side effects within 24 h after administration were reported and included nausea (25%) and vomiting (10%) and abdominal pain/comfort (10%). However, it is not clear whether both nausea and vomiting are purely related to the PRRT since both side effects can be caused by the coinfusion of renal protective amino acid solutions (Rolleman et al. 2003).

Acute haematological toxicity was often mild and transient with grade 3 or 4 toxicity (WHO criteria) in 3.6% calculated on a per-cycle basis or 9.5% on a per-patient basis (at least one of several cycles). Patients had an increased risk of grade 3 or 4 haematological toxicity when older than 70 years of age at the start of PRRT, previous chemotherapy, low creatinine clearance (<60 ml/min; Cockcroft’s formula estimation) or the presence of bone metastases. Temporary mild hair loss was noticed in 62% of the patients.

Serious late toxicity in the group of 504 patients included MDS in four patients of which in three probably PRRT-related, two patients with renal insufficiency, both probably unrelated, and three patients with serious liver toxicity.

Similar to PRRT with $^{90}$Y-labelled somatostatin analogues, the kidneys are one of the dose-limiting organs with $^{177}$Lu-DOTATATE. However, the study by Valkema et al. (2005) indicated that the impact on creatinine clearance rate is less pronounced than with $^{90}$Y-DOTATOC with a median decline in creatinine clearance of 3.8%/year.

Prolonged or (re-)hospitalisation after therapy because of probably PRRT-induced hormonal crises occurred in six (1%) patients (de Keizer et al. 2008). All patients recovered after adequate care including fluid infusion, high-dose i.v. administered somatostatin analogue, corticosteroids and correction of electrolyte disturbances.

PRRT-induced hormone disturbances such as transient inhibitory effect on inhibin that suggests an effect on the spermatogenesis and mild decrease in gonadotropin hormones in postmenopausal women have been described (Teunissen 2009). This could have clinical relevance, especially in those patients with a favourable durable response. These endocrine effects are similar with the reported experience of the use of $^{131}$I treatment in men with differentiated thyroid carcinoma (Wichers et al. 2000).
Quality of life

Another study evaluated the QoL in patients with metastatic somatostatin receptor-positive GEP-NETs treated with $^{177}$Lu-DOTATATE (Teunissen et al. 2004). Fifty Dutch patients completed the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (Aaronson et al. 1993) before therapy and at follow-up visit 6 weeks after the last cycle. A significant improvement in the global health status/QoL scale was observed after therapy with $^{177}$Lu-DOTATATE. Furthermore, significant improvement was observed in the role, emotional and social function scales. The symptom scores for fatigue, insomnia and pain decreased significantly. Patients with proven tumour regression most frequently had an improvement of QoL domains. However, because of the lack of a control group in this study, some placebo effect cannot be ruled out completely.

Comparison of the various radiolabelled somatostatin analogues used for PRRT

Treatment with $^{90}$Y- and $^{177}$Lu-labelled somatostatin analogues is very encouraging in terms of tumour shrinkage. However, studies that compare the different radiopharmaceuticals in a direct randomised manner, are lacking. Even comparison of studies using the same compound (e.g. $^{90}$Y-DOTATOC, Table 4) is difficult because of differences in the used PRRT such as the amount of administered activity, number of cycles, selection of patients and the tumour response criteria used. These among other causes can be responsible for the observed differences in treatment outcome. Therefore, randomised controlled trials are necessary to define the optimal PRRT and treatment scheme for future use. It may be kept in mind, however, that 50 years of experience of $^{131}$I treatment for thyroid disease, has not lead to a general accepted consenses on treatment protocols.

Comparison of PRRT with conventional therapy

At this moment the opportunity for a prospective randomised comparison of PRRT with no further treatment has passed. It seems unethical to perform such a trial with the impressive reported results of PRRT to date. Of interest is the use of ‘cold’ somatostatin analogues and interferon-α. In a group of 80 progressive therapy-naive GEP-NET patients, somatostatin analogues and/or interferon-α was started (Faiss et al. 2003). Four (5%) patients had a tumour remission and 19 (24%) had SD. In another recently published prospective randomised trial, patients with metastatic mid-gut NET (carcinoids) were assigned to either placebo or octreotide LAR 30 mg/month (Rinke et al. 2009). Octreotide LAR significantly lengthened the TTP compared with placebo with 8–9 months, with the most favourable effect in patients with low hepatic tumour load and resected primary tumour. The next logical step would be a similar randomised trial with octreotide LAR versus PRRT.

Studies in which a direct comparison of PRRT with chemotherapy was performed are lacking. However, in a recent article (Kwekkeboom et al. 2005) the outcome of historical studies with single or combination chemotherapy regimens was used as a surrogate for the comparison with the outcome of PRRT with $^{177}$Lu-DOTATATE (Kwekkeboom et al. 2005).

Compared with these historical control groups, a survival benefit of 40–72 months was observed. Although comparison with historical controls always has to be interpreted with caution, the consistent differences with these studies is at least suggestive for a better survival after $^{177}$Lu-DOTATATE therapy.

Options to improve PRRT

Various methods to improve the efficacy of PRRT have been proposed. The combination of $^{90}$Y- and $^{177}$Lu-labelled somatostatin analogues, which demonstrated more favourable tumour responses in animal experiments than either analogue tested as a single agent, might be more effective (de Jong et al. 2002b). However, an adequate prospective randomised trial has not yet been performed.

Currently, locoregional administration of radio-labelled somatostatin analogues administered via the hepatic artery to increase the uptake in liver lesions is studied. This therapeutic approach could be especially effective when the major tumour bulk is within the liver. Selective hepatic intra-arterial administered $^{[90}Y$-DOTA]lanreotide proved to be both safe and effective, resulting in PR in 3/19 (16%) and SD in 12/19 (63%) of patients. Comparison with the same therapy i.v. administered, however, was impossible, because of the absence of randomisation, limited number of patients included and because locoregional administration was performed with and without embolisation (McStay et al. 2005).

Another study reported the results in 17 patients after multiple cycles (maximum of 15 per patient) of intra-arterially administered $^{[111}In$-DTPA]octreotide (Limonis et al. 2008). An average of 6.3 ± 2.3 GBq per cycle was administered. The use of $^{[111}In$-DTPA]octreotide in this therapeutic setting resulted in CR in 1/17 (6%), PR in 8/17 (47%) and SD in 3/12 (25%)
considering acute and subacute side effects (van Essen et al., 2004) of capecitabine, indicated that treatment with this combination was feasible and safe per day for 2 weeks) of capecitabine, which was performed in analogy with radioimmunotherapy (Wong et al., 2003) and (fractionated) external beam radiotherapy (Rich et al., 2004), could also be more effective than PRRT with a single agent. A phase 1 feasibility study with the combination of $^{177}$Lu-octreotate and relatively low doses (1650 mg/m$^2$ per day for 2 weeks) of capecitabine, indicated that treatment with this combination was feasible and safe considering acute and subacute side effects (van Essen et al., 2008). Subsequently, a randomised, controlled clinical trial to compare this combination with $^{177}$Lu-octreotate as a single agent was started.

As mentioned, the kidneys and bone marrow are the dose-limiting organs in PRRT. To widen its therapeutic window, both the reduction of the absorbed radiation dose to these organs and a tumour-specific increase in somatostatin receptor density are subjects of research. Lastly, individualised tailored dosimetry for each patient is the ideal method of treating patients with PRRT, combining the highest possible radiation dose to the tumour and a maximally well-tolerated dose to the dose-limiting organs. Both kidneys and bone marrow absorbed radiation dose vary widely between patients (Kwekkeboom et al., 2001, Forrer et al., 2009). Therefore, the administration of fixed activities to our patients with relatively few side effects implicate that some patients had suboptimal administered activities and thus suboptimal doses to the tumours. This means that with fixed dose regimens that show relatively few side effects, a proportion of patients is undertreated. The currently used method of tailored dosimetry includes urine collection, repeated imaging and blood sampling and is time-consuming. However, although practically difficult, tailored dosimetry could indicate the maximum cumulative activity that can be safely administered to the patient and thereby increase the effectiveness of PRRT. Studies into more accurate and, if possible, simplified individualised dosimetry are necessary to address this method of tailored PRRT.

**MIBG therapy**

Except for the diagnosis and staging of GEP-NETs, $^{123}$I-MIBG scintigraphy can also be used to select patients for $^{131}$I-MIBG therapy. In a similar approach as with PRRT, $^{131}$I-MIBG therapy has the advantage that the treatment targets all sites of disease, including distant metastases, that were visible on $^{123}$I-MIBG scintigraphy. Visualisation of disease on $^{123}$I-MIBG scintigraphy is therefore a prerequisite for the initiation of treatment. Treatment protocols vary between different centres. The usual prescribed activities range between 7.4 and 11.2 GBq, administered at 3–6 months intervals. Reported tumour responses after $^{131}$I-MIBG therapy in patients with metastatic carcinoid disease range from 13 to 35% (Hoefnagel 1994, Bomanji et al., 2003, Safford et al., 2004), with objective tumour shrinkage (WHO criteria), evaluated with CT or MRI, in 13 and 15% of patients in the two largest studies comprising 75 and 52 evaluable patients respectively.

In general, biochemical response, which was defined as >50% reduction in the tumour marker levels such as CgA or 5-hydroxyindoleacetic acid (5-HIAA), was demonstrated in 37–46% (Bomanji et al., 2003, Safford et al., 2004). However, biochemical responses do not correlate well with objective tumour responses.

Symptomatic control was reported in a higher proportion of patients, being present in 49–87% $^{131}$I-MIBG treated patients (Taal et al. 1996b, Pathirana et al. 2001, Bomanji et al. 2003, Safford et al. 2004). Reports on survival in patients with NETs (including carcinoids) treated with $^{131}$I-MIBG are few. Recently, two studies reported survival benefit when patients with carcinoid tumour were treated with at least 15 GBq $^{131}$I-MIBG given in a period of 6 months (Safford et al. 2004, Sywak et al. 2004).

In general, $^{131}$I-MIBG treatment is well tolerated with side effects limited to nausea or vomiting 24–72 h after administration, mild hepatic dysfunction with spontaneous recovery and temporary myelosuppression 4–6 weeks posttherapy. Only incidentally patients may develop significant side effects such as severe myelosuppression, especially when extensive metastatic spread within the bone marrow is present, or hepatic failure in patients with widespread liver metastases (Bongers et al. 1997). Furthermore, the frequency and severity of most haematological side effects is clearly dependent on the (cumulative) administered activity (Bomanji et al. 2003, Safford et al. 2004).

In conclusion, in patients with GEP-NETs who have low tumoural uptake on SRS and do not qualify for PRRT, but have uptake on MIBG scintigraphy, $^{131}$I-MIBG therapy can be an alternative treatment option to offer possible tumour size reduction and/or effective palliation. Furthermore, survival analyses after $^{131}$I-MIBG suggest that there may be a survival benefit.

**Summary**

Conventional imaging techniques such as CT, MRI and US to image NETs have been improved over the years.
Nonetheless, to image the small primary tumours and metastases that can be encountered during the initial diagnostic work up, nuclear medicine imaging with SRS continues to play a pivotal role with \([^{111}\text{In-DTPA}]\text{octreotide}\) scintigraphy, including the acquisition methodology of planar imaging, SPECT and SPECT–CT as the gold standard. Different alternative somatostatin analogues labelled with \(\gamma\)-emitting radionuclides have been proposed, and although some of them are encouraging in terms of imaging quality and sensitivity to detect GEP-NETs, none of them is approved by the European Medicines Agency (Daly et al. 2006) and/or FDA.

The same holds true for the very promising somatostatin analogue-based PET radiopharmaceuticals, such as \(^{68}\text{Ga-DOTATOC}\), \(^{68}\text{Ga-DOTATATE}\) and \(^{68}\text{Ga-DOTANOC}\). Other interesting and promising PET imaging modalities includes metabolic imaging of GEP-NETs with \(^{18}\text{F-DOPA}\) and \(^{11}\text{C-HTP}\).

Treatment with radiolabelled peptides or PRRT is a promising new therapeutic option in the management of inoperable or metastasised NETs. Symptomatic control can be achieved with all \(^{111}\text{In-},\ 90\text{Y-}\) and \(^{177}\text{Lu-labelled somatostatin analogue-based PRRT}\). For objective response and long-lasting duration of response, \(^{90}\text{Y-DOTATOC}\) and \(^{177}\text{Lu-DOTATATE}\) are the most promising radiopharmaceuticals. Side effects of PRRT are few and mild, if adequate kidney protective measures are taken and dose-limits are respected. In a minority of patients, when SRS fails to identify neuroendocrine disease, MIBG scintigraphy and subsequent \(^{131}\text{I-MBG}\) therapy might be an alternative treatment option.

**Declaration of interest**

E P Krenning is a member of the advisory board of BioSynthema, and a consultant of Biosynthema and Coviden. He receives research or material support from Coviden, Novartis and BioSynthema, and is a shareholder in BioSynthema. D J Kwekkeboom is a shareholder in BioSynthema.

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**References**


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