REVIEW

# Treatment of advanced neuroendocrine tumours with radiolabelled somatostatin analogues

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## Abstract

Neuroendocrine tumours (NETs) constitute a heterogeneous group of tumours that frequently express cell membrane-specific peptide receptors, such as somatostatin receptors (SSTRs), and of which gastroenteropancreatic (GEP), carcinoid and pancreatic islet cell tumours exhibit the highest expression of SSTRs. Radiolabelled receptor-binding somatostatin analogues (octreotide and lanreotide) act as vehicles to guide radioactivity to tissues expressing SSTRs, and can thus be used for their diagnosis and treatment. After the localization of NETs bearing SSTRs with $^{111}$In-octreotide (OctreoScan), a number of radioisotopes with different physical properties have been used for their treatment. The administration of high doses of the Auger electron and γ-emitter $^{111}$In-diethylenetriaminepenta-acetic acid (DTPA)$^0$,octreotide in patients with metastatic tumours has been associated with considerable symptomatic improvement but relatively few and short-lived objective tumour responses. The use of another radiolabelled somatostatin analogue coupled with $^{90}$Y, a pure β-emitter, $^{90}$Y-1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid (DOTA)$^0$,Tyr$^3$,octreotide ($^{90}$Y-DOTATOC, OctreoTher), was associated with 10–30% objective tumour response rates, and appears to be particularly effective in larger tumours. $^{111}$In- and $^{90}$Y-DOTA-lanreotide has also been used for the treatment of NETs although its therapeutic efficacy is probably inferior to that of octreotide-based radiopharmaceuticals. More recently, treatment with $^{177}$Lu-DOTA$^0$,Tyr$^3$octreotate ($^{177}$Lu-DOTATATE), which has a higher affinity for the SSTR subtype 2, resulted in approximately 30% complete or partial tumour responses; this radiopharmaceutical is particularly effective in smaller tumours. Furthermore, treatment using both $^{90}$Y-DOTATOC and $^{177}$Lu-DOTA$^0$,Tyr$^3$octreotate seems promising, as the combination of these radiopharmaceuticals could be effective in tumours bearing both small and large lesions. Tumour regression is positively correlated with a high level of uptake on $^{111}$In-octreotide scintigraphy, limited tumour mass and good performance status. In general, better responses have been obtained in GEP tumours than other NETs. The side effects of this form of therapy are relatively few and mild, particularly when kidney-protective agents are used. Treatment with radiolabelled somatostatin analogues presents a promising tool for the management of patients with inoperable or disseminated NETs, and particularly GEP tumours.

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## Introduction

Neuroendocrine tumours (NETs) constitute a heterogeneous group of tumours that originate from the diffuse endocrine system (DES). This system includes endocrine glands, such as the pituitary, the parathyroids and the adrenal medulla, as well as endocrine islets within glandular tissue (thyroid or pancreatic) and cells disseminated between exocrine cells, such as endocrine cells of the digestive and respiratory tracts (Arnold *et al.* 1994, Kaltsas *et al.* 2004*a*). The latter are usually known as 'carcinoid tumours', and, according to their anatomic site of origin, they have been classified as foregut, midgut and

hindgut carcinoid tumours (Solcia *et al.* 1999). Within these subgroups, the biological behaviour of the tumours can vary significantly (Oberg 2004*a*, Oberg *et al.* 2004). NETs occur either sporadically or as part of familial syndromes, and although some may show aggressive behaviour and become highly malignant (poorly differentiated NETs), the great majority are either benign or relatively slow growing (well-differentiated NETs), retaining many multipotent differentiation features (Kaltsas *et al.* 2001*a*). Such features include the possession of neuroamine uptake mechanisms and/or specific receptors at the cell membrane, such as somatostatin receptors (SSTRs), which can be used for the identification, localization and therapy of NETs (Oberg 2002, 2004*a*). Of the five major subtypes of SSTR, $SSTR_{1-5}$, $SSTR_2$ and $SSTR_5$ are the ones most commonly expressed in NETs; however, there is considerable variation in SSTR subtype expression among the different tumour types and among tumours of the same type (de Herder *et al.* 2003).

Radiopharmaceuticals are radiolabelled substances that can be utilized for the identification and localization of NETs by their ability to bind to suitable ligands (Kaltsas *et al.* 2001*b*). They form an imaging modality which is based on the physiological (the presence of functioning receptors) rather than the anatomical characteristics of the tumours (de Herder *et al.* 1996). As the majority of NETs express SSTRs they form an ideal target for treatment with somatostatin analogue (SST analogue)-derived radiopeptides (Krenning *et al.* 1999*a*, de Herder *et al.* 2003). SST analogues are synthetic peptides (octreotide, Novartis, Basel, Switzerland, and lanreotide, Ipsen, Paris, France) that exert most of the biological actions of the native peptide somatostatin, but have a longer half-life (2 min vs ~90 min), being resistant to plasma degradation (de Herder *et al.* 2003). The high affinity of these peptides for SSTRs (highest affinity for $SSTR_2$, moderately high for $SSTR_5$ and intermediate for $SSTR_3$) and the internalization of the receptor–peptide complex facilitate retention of the radiopeptide in receptor-expressing tumours, whereas their relatively small size facilitates rapid clearance from the blood (Reubi *et al.* 2004). In order to ensure the stability of the molecule, the peptide labelled with a radioisotope is bound to a chelator. Covalently linking ethylene-triamine-penta-acetic acid (DTPA) with octreotide results in DTPA-octreotide (pentetreotide); this tracer was initially labelled with ^{123}I, but it gradually became evident that it is more clinically effective in localizing NETs when labelled with [111]In (Kaltsas *et al.* 2004*a*) (Fig. 1). Subsequently, labelled lanreotide was also introduced,
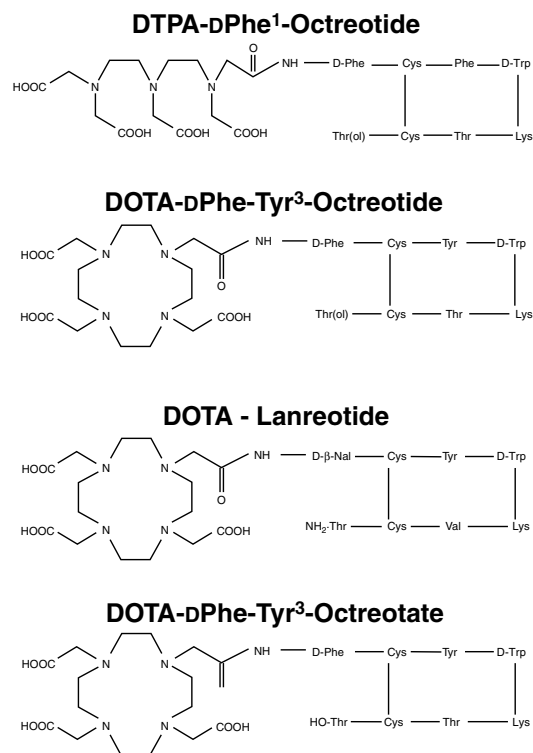


**Figure 1** Currently used ligands for treatment with radiopeptides based on somatostatin analogues.

but the images obtained with this radionuclide were generally inferior to those of octreotide (Virgolini *et al.* 2002*a,b*).

The injected activity of ^{111}In-pentetreotide is about 200 MBq (containing at least 10 µg of the peptide); approximately 80% of the i.v. administered ^{111}In-pentetreotide is eliminated via the urinary system (Krenning *et al.* 1999*b*). Due to its relatively long half-life, planar and single photon emission computerized tomography (SPECT) images can be acquired at 24 and 48 h when interfering background radioactivity is minimized by renal clearance. Normal scintigraphic features include visualization of the thyroid, spleen, liver, pituitary, urinary bladder and occasionally the bowel (Krenning *et al.* 1999*b*, de Herder *et al.* 2003). Scintigraphy with ^{111}In-octreotide represents the imaging modality of choice in the initial evaluation of gastroenteropancreatic (GEP) and islet cell tumours, exhibiting a sensitivity of 67–100%; it can identify clinically unsuspected lesions and optimize the overall staging of these tumours (Kaltsas *et al.* 2001*a,b*). Chromaffin cell tumours (phaeochromo-cytomas and paragangliomas) also express SSTRs, and scintigraphy with ^{111}In-octreotide can be used

**Table 1** Physical properties of β-emitting isotopes used for targeted radiotherapy

| Radioisotope | Maximum energy gamma emission (keV) | Physical half-life ($T_{1/2}$ days) | Maximum particle range (mm) | Mean particle range (mm) | Beta emission × 90 (mm in water) |
|---|---|---|---|---|---|
| [153]Sm | 103 | 1.93 | | | 1.01 |
| [90]Y | 2284 | 2.67 | 12 | 4.2 | 5.34 |
| [186]Re | 1037 | 3.78 | | | 1.8 |
| [177]Lu | 497 | 6.68 | 1 | 0.27 | – |
| [131]I | 606 | 8.04 | 2.4 | 0.45 | 0.83 |
| [32]P | – | 14.28 | 8.7 | | 3.61 |
| [89]Sr | – | 50.52 | | | |

Adapted from Wiseman and Kvols 1995 and Lewington 2003.

particularly in cases of ^{123}I-metaiodobenzylguanidine (MIBG)-negative lesions, whereas in cases of medullary thyroid carcinoma (MTC), scintigraphy with ^{111}In-octreotide has a sensitivity of 50–75% (Kaltsas *et al.* 2001b). Parathyroid and pituitary tumours also express SSTRs and can be imaged with ^{111}In-octreotide; however, this is not the imaging modality of choice for these tumours (Krenning *et al.* 2005).

After the introduction of radiolabelled octreotide for the diagnosis of lesions expressing SSTRs, the next step was to use this radiopharmaceutical to develop specific therapy, particularly for inoperable or multiple-site tumours showing diagnostic uptake of ^{111}In-octreotide (Lewington 2003). As SSTRs are mainly expressed in GEP tumours, these tumours represent the main target group for therapy with radiolabelled peptides (de Herder *et al.* 2003).

## Basic concepts of applying therapy with radiopharmaceuticals to NETs

The initial management of NETs is surgical excision of the primary tumour, unless specific medical therapy is available. This form of treatment usually suffices for the majority of benign tumours, but recurrent, malignant and disseminated tumours require further treatment; this is particularly relevant to the majority of GEP tumours (Oberg *et al.* 2004). SST analogues and interferon-alpha (IFN-α) can achieve disease stabilization but, eventually, further treatment will be required for primary and metastatic tumours that continue to grow; this has traditionally been in the form of systemic chemotherapy and external radiotherapy for local control (Kaltsas *et al.* 2004b, Oberg *et al.* 2004). Although systemic chemotherapy can be temporarily effective in the minority of patients with poorly differentiated NETs, the majority

of well-differentiated NETs are relatively chemoresistant (Kaltsas *et al.* 2004b, Oberg *et al.* 2004). Chemotherapy itself is also associated with considerable side effects, and thus its use must be weighed against potential adverse effects (Kaltsas *et al.* 2004b). Different forms of treatment with a more favourable side-effect profile are highly required for patients with well-differentiated metastatic NETs, particularly as such patients can experience prolonged survival in the presence of extensive disease (Oberg 2004b, Oberg *et al.* 2004).

The application of therapy with radiopharmaceuticals to NETs is dependent on the concept that coupling a radioisotope to a molecule which would specifically bind to tumour cells could deliver an effective radiation dose to the tumour without damaging healthy tissues, thus limiting adverse effects (Krenning *et al.* 1999a). The success of this approach depends upon the amount of radioligand that can be concentrated within tumour cells and the rates of internalization, degradation and recycling of both ligand and receptor (Wiseman & Kvols 1995). The radioisotope's physical properties are important for targeting radiation therapy because even though tumour heterogeneity can cause incomplete responses, crossfire from the radioisotope localized on target-positive tumour cells can kill the nearby tumour cells that are target negative (Krenning *et al.* 2004, Kwekkeboom *et al.* 2005, Pauwels *et al.* 2005, Reubi 2005). The radioisotope selection is based on the type of radiation emitted, the emission energies, the distance over which the energy is deposited, and the physical half-life of the radioisotope (Tables 1 and 2). According to this concept, β-, α- or Auger electron emitters can deliver a cytotoxic dose of radiation with a high linear energy transfer selectively to tumours expressing SSTRs; the β-emitter selected must have an appropriate path to reach the cell nucleus (probably the principal, although not the sole, target to achieve cell death)

**Table 2** Physical properties of currently used radioisotopes for targeted radiotherapy of neuroendocrine (gastroenteropancreatic, GEP) tumours in relation to $^{131}$I, the most widely used radioisotope for the treatment of differentiated thyroid carcinoma

| Radioisotope | Half-life (T/2) (days) | Maximum energy (keV) | Maximum range (mm) | Sphere diameter (mm) | % Energy absorption ($^{90}$Y/$^{177}$Lu)* | |
|---|---|---|---|---|---|---|
| | | | | | $^{90}$Y | $^{177}$Lu |
| $^{131}$I | 8 | 606 | 2.4 | 50 | 95 | 100 |
| $^{90}$Y | 2.7 | 2284 | 12 | 30 | 91 | 99.6 |
| $^{177}$Lu | 6.7 | 497 | 1 | 10 | 66 | 97 |
| | | | | 5 | 41 | 93 |
| | | | | 3 | 26 | 88 |
| | | | | 1 | 9 | 67 |
| | | | | 0.1 | 1 | 15 |
| $^{111}$In | 2.8 | 245 (IC) | 550 μm | | | |
| | | 25 (Au) | 10 μm | | | |

*High-energy β-particles are not efficient in small metastases, since only a small fraction of the energy will be deposited in such small targets. IC: Internal conversion. Au, Auger electrons.
Adapted from Kassis & Adelstein 2005 and Siegel JA & Stabin MG 1994.

depending upon the site of cellular radiopharmaceutical concentration (Siegel & Stabin 1994, Lewington 2003). Physical half-life directly relates to the rate at which the absorbed radiation dose is delivered; a higher dose rate is best suited to rapidly dividing tumours, whereas a longer physical half-life may be more effective for relatively slow-growing tumours such as the majority of NETs (Lewington 2003, Pauwels *et al.* 2005).

To date, the best paradigm for a radiopharmaceutical targeting agent is that for radioiodine ($^{131}$I) used for the treatment of thyroid disorders; this agent's favourable physical characteristic include a high target-to-non-target ratio, rapid clearance of the unbound radioisotope and a long residence time in the target tissue (Wiseman & Kvols 1995). Information derived from patients with differentiated thyroid carcinoma treated with $^{131}$I has proven its therapeutic efficiency and the absence of major side effects (Robbins & Schlumberger 2005) (Table 2). Information on the biodistribution of $^{111}$In-DTPA-D-Phe$^1$-octreotide after i.v. injection, including activity concentrations and absorbed doses in tumour and normal tissues, in patients with various tumour types demonstrated that carcinoid tumours exhibit the highest $^{111}$In activity concentration in tumour tissue and tumour-to-blood ratio, therefore making these tumours an ideal target (Forssell-Aronsson *et al.* 2004). In addition, radiopeptide uptake in metastases was higher than in primary tumours; this was attributed to the differential expression of SSTR subtypes and differences in total expression of SSTRs between primary and secondary tumours (de Jong *et al.* 2003). A major advantage of treatment with radiopharmaceuticals is that radiation can be delivered selectively not only to large primary

tumours and metastases but also to subclinical tumours and metastases that are too small to be imaged and identified for surgery or external beam radiotherapy (de Jong *et al.* 2003). Due to high individual variation between patients, when radiolabelled octreotide is to be used for therapy it is advisable to perform individual dosimetric calculations (Forssell-Aronsson *et al.* 2004).

Targeted radiotherapy for NETs (mainly GEP tumours) is mostly performed with radiopeptides based on SST analogues; the ligands that are currently in clinical use are shown in Fig. 1 (DTPA octreotide, DOTA-$_D$Phe-tyr$^3$-octreotide (DOTA TOC), DOTA-$_D$Phe-Tyr$^3$-octreotate (DOTATATE) and DOTA-lanreotide) (Krenning *et al.* 2005, Reubi *et al.* 2005). $^{111}$In-DTPA exhibits moderate binding affinity for SST$_2$ (negligible for SST$_{1,3-5}$), while $^{111}$In is mainly an Auger electron emitter exhibiting only short-range radiotoxicity. However, DTPA is not an ideal chelator for the currently used β-particle emitters such as yttrium-90 ($^{90}$Y) and lutetium-177 ($^{177}$Lu); for these radioisotopes, the macrocyclic chelator 1,4,7,10-tetra-azacyclododecane-*N,N',N'',N'''*-tetraacetic acid (DOTA) is better, as it forms stable complexes with the isotopes. The DOTA-coupled, somatostatin-based radiopharmaceuticals are $^{90}$Y-DOTA$^0$-Tyr$^3$-octreotide ($^{90}$Y-DOTATOC), $^{90}$Y-DOTA-lanreotide and $^{177}$Lu-DOTA-Tyr$^3$-Thre$^8$-octreotide ($^{177}$Lu-DOTA-TATE), shown in Fig. 2. These differ with regard to SST receptor affinity profile (Table 3), the DOTA-TATE derivative exhibiting the highest affinity to SSTR$_2$ and DOTA-lanreotide having the lowest affinity to SSTR$_2$ although demonstrating considerable SSTR$_5$ affinity (Krenning *et al.* 2005). The various factors that may determine the amount of uptake of
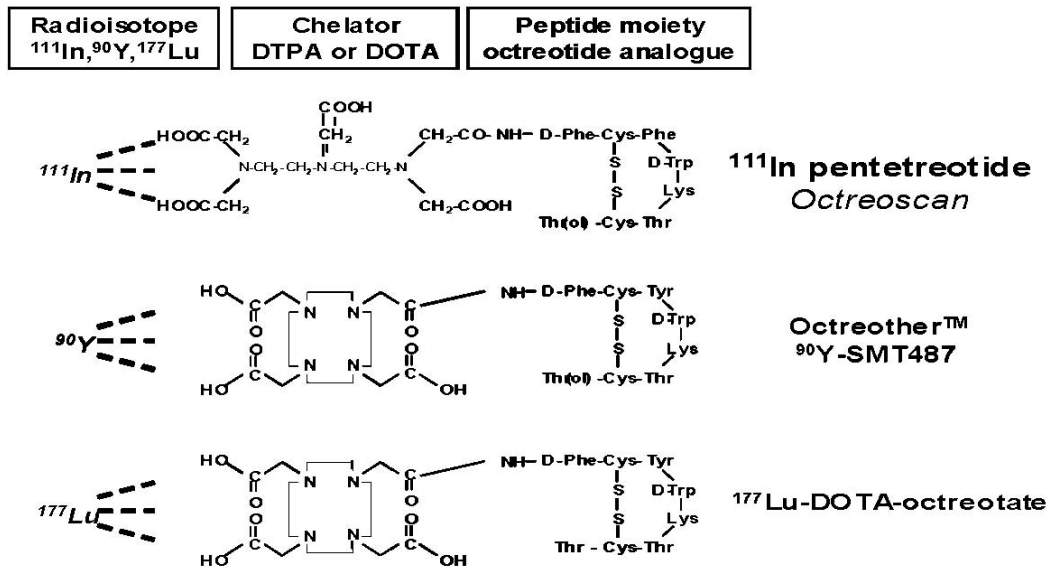
**Figure 2** Chemical structure of currently used octreotide-based radiopharmaceuticals for the treatment of gastroenteropancreatic and other neuroendocrine tumours (Octreother$^{TM}$ = $^{90}$Y-SMT487 = $^{90}$Y-DOTATOC).

radiolabelled SST analogues have been recently outlined as follows:

1. the stability of the radioligand
2. the density of SSTR expression on the tumour
3. the type of SSTRs expressed by the tumour
4. the affinity of the radioligand for the SSTRs
5. the efficiency of SSTR-mediated internalization and recycling
6. the final trapping of the radioisotopes within the tumour cells
7. the mass of the injected peptide (de Herder *et al.* 2003).

## Dosimetry

Radiopharmaceuticals are taken up by both tumour cells and normal tissues, and this form of therapy aims to deliver the highest possible dose to the tumour while sparing normal tissues from damage (Pauwels *et al.* 2005). As in other forms of treatment aiming at the elimination of neoplastic cells, critical dose-limiting organs in therapy with radiopharmaceuticals are the bone marrow and the kidneys, the latter due to interstitial irradiation derived from tubular peptide reabsorption (Bodei *et al.* 2004*a*). This was evident from preliminary clinical trials using $^{111}$In- and $^{90}$Y-labelled peptides in which the considerable therapeutic benefits noted in patients with progressive disease were associated with significant, mostly delayed toxicity leading to substantial morbidity (Otte *et al.* 2002, Valkema *et al.* 2002). Dosimetry methods can be used to provide reliable dose estimates to critical organs and to tumoral tissues before therapy, leading to individualized therapeutic regimes; dosimetry can help to identify patients who would benefit from therapy with radiopharmaceuticals while excluding unsuitable patients (Bodei *et al.* 2004*a*, Pauwels *et al.* 2005). These estimations require time-consuming and sophisticated methods, including pharmacokinetic,

**Table 3** Affinity profiles for somatostatin receptors of currently used octreotide-based radiopharmaceuticals (SSTR$_{1-5}$)

| Radiopharmaceutical | SSTR$_1$ | SSTR$_2$ | SSTR$_3$ | SSTR$_4$ | SSTR$_5$ |
|---|---|---|---|---|---|
| Native somatostatin SS-28 | 5.2 | 2.7 | 7.7 | 5.6 | 4.0 |
| $^{111}$In-DTPA-octreotide | >10 000 | 22 | 182 | >1000 | 237 |
| $^{90}$Y-DOTA-Tyr$^3$ octreotide | >10 000 | 20 | 27 | >10 000 | 57 |
| $^{177}$Lu-DOTA,Tyr$^3$ octreotate | 10 000 | 15 | >1000 | 453 | 547 |

DTPA: diethylenetriaminepentaacetic acid; DOTA: 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid.
Adapted from Reubi *et al.* 2000.

biodistribution and wash-out studies involving the selected radiopharmaceutical to be used for therapy (Kassis & Adelstein 2005, Pauwels *et al.* 2005).

## Selection of the radiopharmaceutical

The chemical structure of the radiopharmaceutical is important, as it influences tumour uptake, renal clearance and retention, and residence time in tissues (Reubi *et al.* 2000). Dosimetry with ^{111}In-octreotide can easily be performed when this same radiopharmaceutical is to be used for treatment (Cremonesi *et al.* 1999, Pauwels *et al.* 2005). However, this is not possible with ^{90}Y-radiopharmaceuticals, as the β-emission of ^{90}Y does not allow appropriate quantification from the γ-activity emitted by affected cells, necessitating the use of alternative approaches. Imaging with the peptide surrogate labelled with the positron emitter [86]Y was precise in measuring distribution and retention of the radiopharmaceutical over time, but a major drawback is the requirement of a positron emission tomography (PET) facility and a high-energy cyclotron (Pauwels *et al.* 2005). A different method to overcome the limitations of using [86]Y was based on the evaluation of the biodistribution and dosimetry of DOTATOC radiolabelled with [111]In (Cremonesi *et al.* 1999); however, biodistribution studies using ^{111}In-DTPA octreotide have demonstrated either under- or overestimation of renal doses of ^{90}Y-DOTATOC (Pauwels *et al.* 2005). Additional improvements in the determination of the kidney radiation dose can be obtained with the precise organ volume measurement (instead of a fixed volume) by computerized tomography (CT) or magnetic resonance imaging (MRI) (Barone *et al.* 2005). Patient-specific dosimetry requires quantitative imaging of the patient at different times points (according to the half-life of the radioisotope used) to evaluate the retention of activity in various organs over time. After integration of the measured activities, time integrals of activity are multiplied by energy-transport factors to obtain radiation dose estimates in target organs. Once these activities are measured, absorbed doses in target organs are calculated with dedicated software (Sgouros 2005). In cases where the absorbed dose is mainly related to self-irradiation, the energy transported per decay from the source tissue to the mass of the target tissue (S factor) depends on the target volume; improvements in the accuracy of measured doses may thus be achieved by organ volume estimation using CT or MR imaging (Pauwels *et al.* 2005, Sgouros 2005).

Although it is clear that accurate prediction of absorbed doses is required for internal radiotherapy, inaccuracies can occur even with the use of highly sophisticated techniques, leading to miscalculation of the absorbed doses: this will lead to either under- or overtreatment with unpredictable toxicity (Pauwels *et al.* 2005).

## Evaluation of response

Patients' responses to therapy should be evaluated by uniform criteria and divided into symptomatic, hormonal and tumour responses (Kaltsas *et al.* 2004*a*). Tumour responses are classified by WHO criteria as follows:

1. *complete response*, complete regression of all clinical and hormonal evidence of tumour, including radiological abnormalities
2. *partial response*, a 50% or greater reduction of all measurable tumour and no appearance of new lesions, along with hormonal and symptomatic improvement
3. *stable disease*, a less than 50% reduction or no greater than 25% increase of tumour size, hormonal measurements and symptoms
4. *progression*, appearance of new lesions or an increase of 25% or more of tumour size, and hormonal and symptomatic deterioration.

Patients are reviewed at 3–6-month intervals; review assessment comprises clinical, biochemical and radiological evaluation. The rationale of applying further treatment at these time intervals is contingent on the relatively prolonged replication period of these tumours (Kaltsas *et al.* 2004*b*).

## Pretreatment considerations

A large number of NETs, mainly GEP tumours (functioning or non-functioning), are being treated with SST analogues; this is particularly important, as many of these tumours are associated with severe humoral syndromes (functioning tumours) for the control of which treatment with SST analogues is continuously required (Kaltsas *et al.* 2004*b*, Oberg 2004*b*). During treatment with these drugs, the uptake of ^{111}In-DTPA-octreotide in SST-positive tumours and the spleen is diminished (similar to blocking the receptor binding of a labelled 'hot' peptide with an excessive amount of unlabelled 'cold' peptide). In practice, NETs may still remain visible during treatment with octreotide, although tumour uptake of ^{111}In-octreotide may be substantially reduced. In order

to maximize the uptake of radiolabelled compounds, patients on long-acting releasable (LAR) SST analogues should receive treatment with radiopharmaceuticals before the next LAR administration (4–6 weeks), or after they have been switched to s.c. octreotide, which has a much shorter half-life and can be discontinued 24 h before therapy (Kwekkeboom *et al.* 2005). Particular attention should be paid to patients with extensive hepatic involvement and high uptake on the diagnostic OctreoScan (Mallinckrodt Pelten, The Netherlands). These patients are at high risk of developing fulminant hepatic necrosis, as extremely high radiation may be delivered to the small number of normal liver cells from the increased uptake of the neighbouring metastatic foci (Kwekkeboom *et al.* 2005). In such cases, lowering the cycle dose is an alternative if treatment with radiopharmaceuticals is required (see below). In addition, when there is increased uptake in the bone marrow in patients with disseminated disease, it is important to exclude metastatic infiltration of the bone marrow, as treatment with radiopharmaceuticals may exacerbate the bone marrow failure after therapeutic radiation (Mukherjee *et al.* 2001). This is also important for patients who have previously undergone intensive chemotherapy (Bodei *et al.* 2004*b*).

## Peptide receptor radionuclide therapy with ^{111}In-octreotide

[111]In emits mainly γ-radiation, which passes through tissue relatively easily and can be imaged by a γ-scanner. [111]In also emits Auger and conversion electrons that exert an anti-proliferative effect in malignant tumours if their major target, the DNA of the cell, is within the particle range (de Jong *et al.* 2002). In a study by Krenning *et al.* (1999*b*), 30 end-stage patients with NETs, including 20 patients with GEP tumours, were treated with [^{111}In-DTPA]-octreotide, receiving a cumulative dose of 20 GBq (550 mCi). Seven patients who were treated with a total dose of less than 20 GBq ^{111}In-DTPA-octreotide had to stop therapy prematurely due to the extension of their disease despite treatment. Of the 21 patients who received adequate doses of ^{111}In-DTPA-octreotide (all had progressive disease), six demonstrated partial shrinkage of the tumour, while eight others showed stabilization of their disease; patients with higher tumour uptake tended to show better results (Krenning *et al.* 1999*b*). Similar results were obtained in a study that included 40 patients who received cumulative doses of 20–160 GBq. Therapeutic effects were seen in 21 patients: partial remission in one,

minor remissions in six and stabilization of previously progressive tumours in 14 (Valkema *et al.* 2002). Nevertheless, three of the six patients who received more than 100 GBq (2.7 Ci) developed a myelodysplastic syndrome or leukaemia, and the authors concluded that 100 GBq are the maximal tolerable dose. In another study, 27 patients were treated with two doses of 6.5 GBq (180 mCi) ^{111}In-pentetreotide: objective partial responses occurred in two (8%) patients and significant tumour necrosis in seven (27%) (Anthony *et al.* 2002). Symptomatic and hormonal response was obtained in 62% and 81% respectively, whereas median survival was 18 months compared with the 6 months expected, without any major side effects (Anthony *et al.* 2002). However, a more recent study has challenged the long-term efficacy of ^{111}In-pentetreotide therapy in patients with disseminated NETs (Buscombe *et al.* 2003). This is not surprising, as ^{111}In-coupled peptides are not ideal for therapy with radiopharmaceuticals because of the small particle range and therefore lower tissue penetration rate; short-lived responses have been attributed to the preferential survival of resistant clones (de Jong *et al.* 1997, 2003, Kwekkeboom *et al.* 2005). Moreover, its efficacy in large tumours and end-stage patients is limited, reflecting mainly heterogeneous radiopharmaceutical uptake due to poor tumour vascularity and central necrosis (Lewington 2003). It has been therefore been suggested that ^{111}In-octreotide should be given only with high-energy β-particle emitters in order to eradicate micrometastasis (de Jong *et al.* 2002), particularly as various studies with β-emitters alone have demonstrated better response rates (Valkema *et al.* 2002, de Jong *et al.* 2005, Kwekkeboom *et al.* 2005) (see below).

## Peptide receptor radionuclide therapy with (^{90}Y-DOTA [0]Tyr[3])-octreotide [[90]Y- DOTATOC]

Radiopeptides emitting β-radiation have superior therapeutic potential since the particles they emit have sufficient energy to cause cell damage without penetrating very far into surrounding tissue (Wiseman & Kvols 1995). A high-energy β-emitter attached to a SST analogue could potentially deliver a lethal dose of radiation to a SST-positive tumour with minimal damage to healthy tissue (Wiseman & Kvols 1995, de Jong *et al.* 2003). Despite its diagnostic use, DTPA-octreotide is not suitable for labelling with yttrium-90 (^{90}Y), a pure energetic β-emitter well suited for internal radiotherapy; this has led to the development of a new peptide chelator that can be stably labelled with ^{111}In and [90]Y (de Jong *et al.* 1997, Krenning *et al.* 1999*a*). The same SST analogue (Tyr[3]-octreotide) used
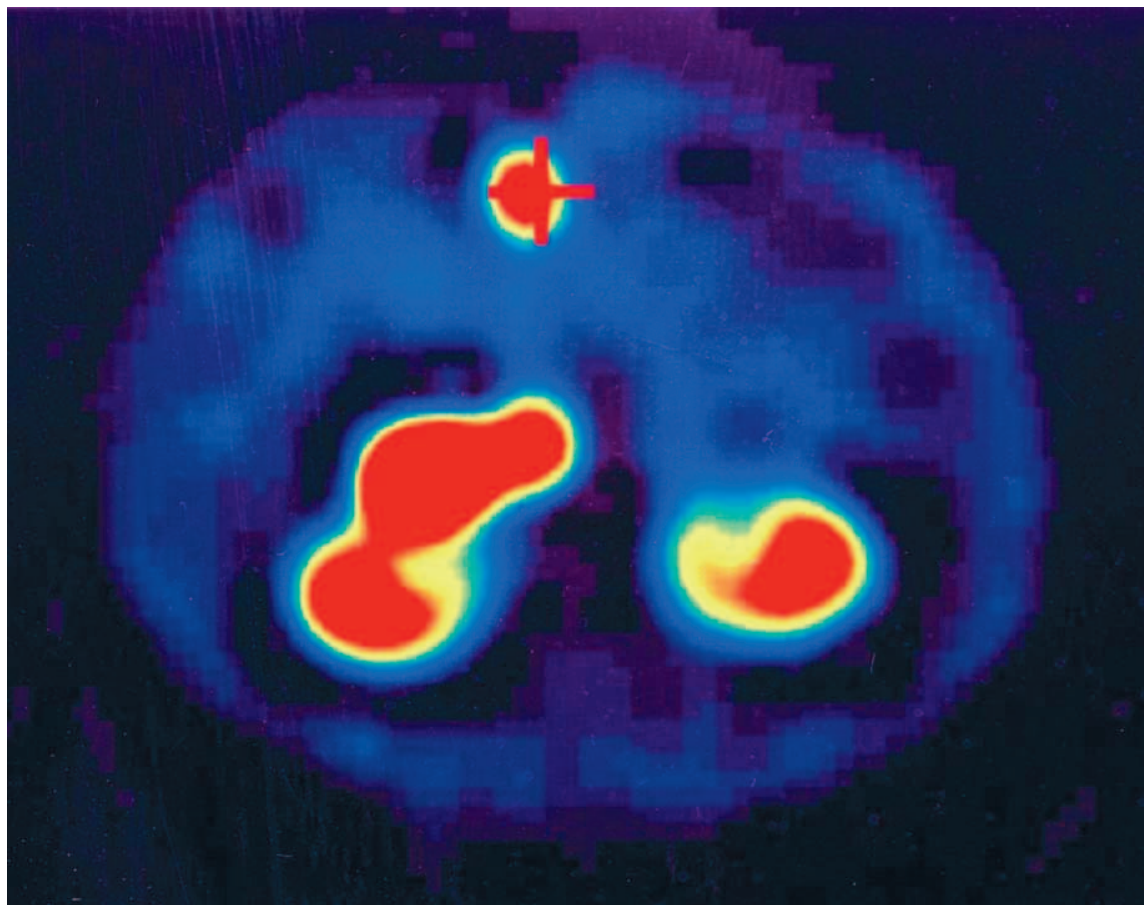
**Figure 3** Reconstructed SPECT image of a malignant insulinoma imaged with ^{90}Y-octreotide at 24 h. Note that the primary tumour is clearly shown (Indicated by the cross). The radiation from this predominantly β-emitter is secondary radiation, *Bremsstrahlung*.

for diagnosis has been coupled to the bifunctional chelating agent (1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid, DOTA[0]) for the complexing of [90]Y (de Jong *et al.* 1997, Krenning *et al.* 1999*a*) (Fig. 2). In contrast to ^{90}Y-DTPA-octreotide, ^{90}Y-DOTA-D-Phe[1]-Tyr[3]-octreotide (^{90}Y-SMT487, OctreoTher, ^{90}Y-DOTATOC) shows no dissociation from the DOTA-chelated peptide in serum and can deliver tumouricidal doses of radiation by targeting SST-positive tumours that have demonstrated uptake on a diagnostic ^{111}In-pentetreotide scan (OctreoScan) (de Jong *et al.* 1997). Furthermore, while, in general, ^{90}Y-DOTA-D-Phe[1]-Tyr[3]-octreotide is a non-γ-emitter, the β-particles can cause localized release of γ-activity from affected cells (*Bremsstrahlung*), making some imaging of the effectiveness of therapy possible (Kaltsas *et al.* 2004*a*) (Fig. 3).

Initial biodistribution studies indicated that the highest predicted absorbed doses were to the spleen,

the kidneys and the tumour, suggesting that high activities of ^{90}Y-DOTATOC could be administered with low risk of myelotoxicity, although with potentially high radiation doses to the spleen and kidneys (Cremonesi *et al.* 1999). In the first clinical results reported by Otte *et al.* (2002), ^{90}Y-DOTATOC was administered as single doses at 6-week intervals (cumulative dose $6120 \pm 1347 \, \text{MBq/m}^2$); five of their patients had non-NET tumours. When the study was concluded, 20 of the 29 patients showed disease stabilization; two, partial remission; four, a reduction in tumour mass of $< 50\%$; and three, progression of tumour growth. Renal and/or haematological toxicity developed in five patients, all of whom received a cumulative dose of $> 7400 \, \text{MBq/m}^2$ (Otte *et al.* 2002). In a phase II non-randomized study, 37 patients with GEP tumours, the majority of whom had resistant and progressive disease, were treated with four intravenous injections of ^{90}Y-DOTA-D-Phe[1]-Tyr[3]-octreotide, up

**Table 4** Tumour responses and side-effect profile of treatment using various radiopharmaceuticals based on somatostatin analogues in patients with GEP tumours

| Radiopharmaceutical | Reference | No. of patients | Tumour response | | | Toxicity* |
|---|---|---|---|---|---|---|
| | | | CR/PR | SD | PD | |
| [111]In | Valkema *et al.* 2002 | 26 | 0 | 16 (61%) | 10 (38%) | 3 (11%) AML/MDS |
| | Anthony *et al.* 2002 | 26 | 2 (8%) | 21 (81%) | 3 (12%) | 11 grades 3–4 haematologic, 3 liver, 1 renal |
| | Buscombe *et al.* 2003 | 16 | 5 (31%) | 7 (23%) | 4 (25%) | – |
| [90]Y | Waldherr *et al.* 2001 | 74 | 18 (24%) | 48 (65%) | 8 (11%) | 8% grades 3–4 1 renal |
| | Waldherr *et al.* 2002 | | | | | |
| | Valkema *et al.* 2003 | 54 | 4 (7%) | 40 (74%) | 10 (19%) | 38% grades 3–4 haematological, 1MDS, 1 liver, 1 renal |
| | Bodei *et al.* 2004*b* | 141 | (26%) | (55%) | (18%) | |
| [177]Lu | Kwekkeboom *et al.* 2005 | 131 | 35 (28%) | 68 (54%) | 22 (18%) | Up to 1.5% grade 3 haematological, 1 liver, 1 renal |

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease;
AML: acute myeloid leukaemia; MDS: myelodysplastic syndrome.
*Assessment followed WHO criteria (grades 3–4 toxicity is presented only).

to a total of 6000 MBq (160 mCi)/m$^2$ (Waldherr *et al.* 2001). An objective tumour response rate of 24% (36% for pancreatic tumours) was noted, without serious toxicity. The same group evaluated the response of GEP tumours to high-dose, targeted irradiation with 7.4 GBq/m$^2$ of the radiolabelled SST analogue, concluding that high-dose, targeted radiotherapy with $^{90}$Y-DOTATOC is a well-tolerated treatment, showing an objective tumour response of 23% according to WHO criteria (38% for pancreatic tumours) (Waldherr *et al.* 2002). A similar tumour response rate (28%, 5% of which were a complete response) was obtained in a study of 87 patients with NETs who were treated with a cumulative activity of 7.4–20.3 GBq/m$^2$; no major adverse effects were noted up to a dose of 5.55 GBq/ cycle (Paganelli *et al.* 2002). In different phase I trials involving the administration of $^{90}$Y-DOTA Tyr$^3$-octreotide in patients with NETs, an overall antimitotic effect with a 20% partial response and 60% disease stabilization was observed, even though the maximum cumulative dose (26 GBq) failed to reach the maximum tolerable dose (de Jong *et al.* 2002). Recent data presented by Bodei *et al.* (2004*a*) on $^{90}$Y-DOTATOC in 141 patients with mainly NETs, who were treated with a cumulative activity of 7.4–26.4 GBq, suggested an overall objective response rate (partial and complete) of 26%. When the authors subdivided patients according to the state of disease at the time of enrolment, an overall clinical benefit (complete

and partial response and stable disease) was observed in 76%, whereas complete and partial responses were evident in 32% of cases. The duration of response was 2–59 months, and the majority of responders had GEP tumours (Bodei *et al.* 2004*a*). Treatment with $^{90}$Y-DOTATOC was also associated with an improvement in patients' well-being and overall improved quality of life (QoL) (Bushnell *et al.* 2003*b*).

Despite differences between the several protocols used, most of the studies using $^{90}$Y-DOTATATE have demonstrated tumour responses of 10–30% (mean 25%), considerably higher than those obtained with $^{111}$In-DTPA (Table 4). These differences could be attributed either to differences in administered doses and dosage schemes between the various studies or, more likely, to differences in patient characteristics (percentage of radionuclide uptake, estimated total tumour burden and extent of liver involvement). In addition, several studies have included different types of NETs with considerable differences in the density of SSTRs and natural history. As already mentioned, when response is considered according to the various types of NETs, it becomes evident that patients with GEP tumours exhibit a more favourable response, 36–38%, than other NETs treated with the same radiopharmaceuticals (Waldherr *et al.* 2001, Bodei *et al.* 2004*a*, Kwekkeboom *et al.* 2005) (Table 4).

## Peptide receptor radionuclide therapy with ^{90}Y-lanreotide

In contrast to ^{111}In-DTPA-D-Phe[1]-octreotide, which binds to $SSTR_2$ and $SSTR_5$ with high affinity, binds to $SSTR_3$ with moderate affinity, and does not bind to $SSTR_1$ and $SST_4$, [111]In- and ^{90}Y-DOTA-lanreotide was found to bind to $SSTR_{2-4}$ and $SST_5$ with high affinity, and to $SSTR_1$ with low affinity (Virgolini et al. 2002a). Based on this unique binding profile, ^{111}In-DOTA-lanreotide was considered a potential radioligand for tumour diagnosis, and, consequently, ^{90}Y-DOTA-lanreotide was considered for receptor-mediated radionuclide therapy (Virgolini et al. 2002a,b). Leimer et al. (1998) initially reported a 25% regression of liver metastasis and substantial symptomatic improvement in a patient with a malignant gastrinoma after four infusions of 1 GBq ^{90}Y-lanreotide. Following that observation, the phase IIa Multicentre Analysis of a Universal Receptor Imaging and Treatment Initiative (MAURITIUS) European study was organized, in which 39 patients with GEP tumours (34 carcinoid tumours) were included (Virgolini et al. 2002a). After two cycles of ^{90}Y-DOTA-lanreotide, the treatment was discontinued in the presence of progressive disease; otherwise, a further two cycles were given. Over a 3-year follow-up period, 20.5% of patients achieved regression of their disease, whereas 43.6% demonstrated stable disease. However, the fact that ^{90}Y-DOTATOC exhibits higher tumour uptake in patients with NET lesions than lanreotide suggests that, where available, it should be the treatment of first choice (Virgolini et al. 2002b).

A few patients with malignant chromaffin cell tumours have been treated with ^{111}In-DTPA-octreotide and ^{90}Y-DOTATOC, some obtaining disease stabilization (Waldherr et al. 2001, Valkema et al. 2002). A few patients with medullary carcinoma of the thyroid (MTC) also received ^{111}In-octreotide or ^{90}Y-lanreotide in the MAURITIUS trial (Krenning et al. 1999a, Virgolini et al. 2002b, Buscombe et al. 2003). Although this was a heterogeneous group of patients, initial results were encouraging, supporting further prospective studies of the use of this therapy in patients with advanced MTC (Krenning et al. 1999a, Virgolini et al. 2002b, Buscombe et al. 2003).

## Peptide receptor radionuclide therapy with [^{177}Lu-DOTA-Tyr[3]]octreotide

In order to overcome the limitations of administering tumoricidal doses of radiotherapy to non-octreotide-avid lesions, and the lack of uptake to certain areas due to tumour heterogeneity, several β-emitters, in addition to ^{90}Y, such as [153]Sm, ^{177}Lu and [186]Re, have also been considered, usually in combination with Tyr[3]-octreotate (DOTATE), which exhibits the highest affinity for $SSTR_2$ (de Jong et al. 2002). Initial studies reported a ninefold increase in the affinity for $SST_2$ of DOTA Tyr[3]-octreotate compared with DOTA-Tyr[3]-octreotide, which remained six- to seven-fold higher when ^{90}Y was also added to the complex (Reubi et al. 2005). Besides the higher tumour uptake, Tyr[3]-octreotate exerts similar kidney uptake to Tyr[3]-octreotide, leading to a better tumour : kidney ratio; however, Tyr[3]-octreotide exhibits faster renal clearance, and this could in theory mean lower bone-marrow irradiation (de Jong et al. 2002). The relative advantages of ^{177}Lu over ^{90}Y include also the emission of γ-radiation, which makes it available for scintigraphy/dosimetry, and the shorter range of β-particles, by which higher radiation can be delivered to smaller tumours (de Jong et al. 2003). Therefore, ^{177}Lu-DOTA-Tyr[3]-octreotate may well represent a radiopharmaceutical advance, as it can achieve higher absorbed doses for most tumours with similar doses to dose-limiting organs because of the lower tissue-penetration range than ^{90}Y-DOTATOC, a feature particularly important for smaller lesions (de Jong et al. 2003).

An initial study assessed the effects of ^{177}Lu-DOTA-Tyr[3]-octreotate therapy on tumours of various sizes in 34 patients with GEP tumours (Kwekkeboom et al. 2003). Three months after the final administration, complete remission was found in one patient (3%), partial remission in 12 (35%) patients, stable disease in 14 (41%) patients and progressive disease in seven (21%) patients. The outcome of radionuclide therapy was positively correlated with a high uptake on the OctreoScan, limited hepatic tumour mass and high performance status (Kwekkeboom et al. 2003). The authors also noted that responding patients had a limited tumour load, thus indicating early employment of receptor radionuclide therapy in patients with GEP tumours, without waiting for tumour progression (Kwekkeboom et al. 2003). The same group have recently assessed the effect of ^{177}Lu-DOTA-Tyr[3]-octreotate on the self-reported QoL in patients with metastatic GEP tumours (Teunissen et al. 2004). The global health/QoL, as well as several function and symptom scales, was significantly improved after ^{177}Lu-DOTA-Tyr[3]-octreotate therapy even in patients with progressive disease (Teunissen et al. 2004). More recently, the results of 131 patients with GEP tumours treated with a cumulative dose of 22.2–29.6 GBq of ^{177}Lu-DOTA-Tyr[3]-octreotate became available: three

patients (2%) obtained complete remission; 32 (26%), partial remission; 24 (19%), a minor response (tumour diameter decrease of 25–50%); and 44 (35%), stable disease. Twenty-two (18%) patients developed tumour progression. Serious side effects were rare, only a single patient developing acute renal failure and one developing hepatorenal syndrome, whereas the median time to progression for patients who either responded or remained stable was 36 months (Kwekkeboom *et al.* 2005). Patients who obtained lower remission rates and/or progression of their disease had lower uptake on the diagnostic ^{111}In-octreotide scan, more extensive disease and hepatic involvement, and worse performance status. These results compare favourably to the ones obtained in patients treated with chemotherapy, and imply that treatment efficacy is probably related to early initiation of treatment when tumour load is limited (Kwekkeboom *et al.* 2005). A further finding of the latest study favours the early administration of treatment with radiopharmaceuticals, as disease stability or progression before the initiation of treatment did not affect the response to treatment (Kwekkeboom *et al.* 2003).

From these studies, where several different radiopharmaceuticals have been used for the treatment of NETs, it seems that ^{177}Lu-DOTA-Tyr[3]-octreotate represents a major advance in the field of treatment with radiopeptides. However, it must be emphasized that direct, randomized, comparative studies of the various forms of radiopharmaceuticals used are lacking.

## Combination treatment with ^{90}Y-DOTATOC and ^{177}Lu-DOTA-Tyr[3]-octreotate

When we consider the individual radiobiological features of the β-emitters ^{177}Lu and ^{90}Y, it becomes evident that each has specific potential advantages for tumour therapy (Tables 1 & 2). [90]Y particles have higher energies and longer ranges, leading to the deposition of more radioactivity in tumour cell per peptide molecule and to a better crossfire throughout the tumour; in addition, the relatively short half-life of ^{90}Y leads to a higher dose rate. These properties make it more favourable for the treatment of larger tumours and for tumours with heterogeneous receptor distribution (de Jong *et al.* 2005). However, smaller tumours are less suitable for treatment with ^{90}Y, as they will not absorb all the energy emitted from ^{90}Y in the tumour cells, whereas adjacent healthy tissue will absorb

relatively high doses and will be exposed to toxicity (Krenning *et al.* 2004). In contrast, ^{177}Lu particles that have lower energy and a smaller particle range are associated with better absorption in smaller tumours, and enable scintigraphy, as they emit γ-radiation (de Jong *et al.* 2005). Therefore, to treat patients with tumours of various sizes and non-homogeneous receptor distribution, the combination of the high-energy ^{90}Y for the larger lesions and the low-energy ^{177}Lu for the smaller lesions and metastases seems a reasonable approach. Animal studies have documented that this combination (^{90}Y and ^{177}Lu) provides different β-energies and particle ranges that achieve higher cure rates in tumours of various sizes than either radionuclide alone (de Jong *et al.* 2005). These results also agree with the prediction of a mathematical model that was used to assess tumoral response to different β-emitting particles in relation to tumour size, and that suggested an optimal tumour diameter of 34 mm for ^{90}Y and 2 mm for [177]Lu (O'Donoghue *et al.* 1995). Another interesting option is the sequential treatment of these tumours with these analogues, initially administering ^{90}Y-labelled analogues to treat larger lesions followed by ^{177}Lu-labelled analogues to treat smaller metastases (de Jong *et al.* 2005).

## Predictors of response

Despite variations of the protocols used, objective tumour size responses of approximately 25% (range 10–30%) have been obtained in studies using ^{90}Y-DOTATOC (Chinol *et al.* 2002, Waldherr *et al.* 2002, Bodei *et al.* 2003, Valkema *et al.* 2005), and approximately 30% in those using [177]Lu-^{177}Lu-DOTA-Tyr[3]-octreotate (DOTATATE) (Krenning *et al.* 2005, Kwekkeboom *et al.* 2005, Pauwels *et al.* 2005). This rather low response rate may be related to the relative radioresistance of NETs, but probably also reflects the absence of uniform criteria in patient selection (Bodei *et al.* 2004*b*, Pauwels *et al.* 2005). It is therefore important to establish predictive parameters to select patients likely to benefit from treatment with these radiopeptides and identify those not likely to respond. As shown from data derived from patients with NETs treated with ^{131}I-MIBG, important predictors of the outcome of therapy with this radionuclide are the extent of the disease and the total tumour load (Chatal *et al.* 2000, Mukherjee *et al.* 2001). Similarly, tumour regression was positively correlated with high level of uptake on OctreoScan imaging, limited hepatic tumour mass and high Karnofsky performance score (Kwekkeboom *et al.* 2003). There is also evidence of a significant correlation

**Table 5** Patient selection criteria for targeted radiotherapy

| Indications | Contraindications |
|---|---|
| Inoperable/metastatic GEP | Myelosuppression |
| Increased uptake at tumour sites | Bone-marrow metastatic disease |
| Haematological considerations* | Renal impairment |
| Hb >10 g/l | Extensive hepatic involvement |
| WBC >3.0 × 10⁹/l | Poor performance status |
| PLT >100 × 10⁹/l | |
| Biochemical considerations | Pregnancy/lactation |
| Urea <10 mmol/l | Previous therapy with radiopharmaceutical |
| Creatinine <160 μmol/l | Exceeding a dose limit |
| GFR >40 ml/min | |
| Good performance status | |

Hb, haemoglobin; WBC, white blood cells; PLT, platelets; GFR, glomerular filtration rate; GEP, gastroenteropancreatic tumours.
*Attention is required in patients previously treated with chemotherapy.

between dose estimates of tumours and tumour size reduction that is measured at the end of the treatment; the median absorbed dose was sixfold higher in responding than non-responding tumours (Pauwels *et al.* 2005). Although tumour dosimetry did not completely distinguish responders from non-responders, it may be useful in the management of patients with NETs. It has therefore been suggested that early treatment (particularly in patients with progressive disease) may be associated with better outcome (Kwekkeboom *et al.* 2003). The fact that progression during or after treatment was more frequent in patients with extensive tumour load, particularly in the liver, implies that a more aggressive approach may be more appropriate than a 'wait-and-see' approach, as this might be associated with worse outcome (Kwekkeboom *et al.* 2003). In addition, future studies should provide evidence-based information on the optimal time to treat with radiopeptides with respect to other forms of treatment, and whether disease stability should be regarded as response to treatment, particularly in the group of patients with progressive disease following other forms of treatment (Bodei *et al.* 2004*b*). However, we now have sufficient information to suggest rational indications for the possible use of this type of treatment (Table 5).

## Radioembolization

NETs show a particular predisposition for hepatic metastases that receive most of their blood supply from the hepatic artery (Kaltsas *et al.* 2004*a*). Radioembolization implies the administration of microspheres labelled with radioactive isotopes that induce hepatic artery occlusion and simultaneously local irradiation (brachyradiotherapy). In a preliminary phase I study, six patients with metastatic NETs were enrolled, and glass microspheres loaded with $^{90}$Y were administered for radioembolization (Andrews *et al.* 1994). Although some beneficial results were obtained, problems with dosimetry due to difficulties in calculating the exact volume of liver metastases and the inhomogeneous distribution of the microspheres have limited their use (Andrews *et al.* 1994). More recently, $^{111}$In-octreotide has been advocated as an alternative; direct intra-arterial injection achieves higher intratumoral concentrations and may be of value in treating isolated hepatic and/or cerebral lesions but is less helpful in the management of disseminated disease (Lewington 2003).

## Safety and side effects

Biodistribution studies demonstrated that the highest predicted absorbed doses were to the spleen, kidneys and the tumour. Preliminary studies showed that since no spleen toxicity was demonstrated, the kidneys are the critical organs, particularly as octreotide is mainly excreted by the kidneys (Bodei *et al.* 2003, Pauwels *et al.* 2005). After being filtered by glomeruli, radiopeptides are reabsorbed and retained from the proximal tubule; renal toxicity occurs because of irradiation of the radiosensitive glomeruli by activity retained in the relatively radioresistant tubular cells, the main histological finding being thrombotic microangiopathy (Otte *et al.* 2002, Pauwels *et al.* 2005). The cumulative absorbed dose to the kidney may cause renal damage when it exceeds the conventional threshold of 23–25 Gy; although this threshold is derived from experience obtained from external irradiation, cases of several renal failure have been found to follow treatment with radiopharmaceuticals (Cybulla *et al.* 2001, Otte *et al.* 2002). Adjustments of the threshold dose by the linear-quadratic method has estimated the renal threshold toxicity dose to be 35 ± 7 Gy for $^{90}$Y-DOTATOC (Konijnenberg 2003). Although renal uptake may vary considerably in patients undergoing dosimetry, this can be substantially improved when the actual kidney volume (as estimated by CT) is taken into consideration (Pauwels *et al.* 2005). Retrospective analysis of patients who have developed renal toxicity revealed that this occurred in patients who had the smaller kidneys (received higher radiation doses per ml) (Pauwels *et al.*

2005, Valkema *et al.* 2005). In addition, methods to reduce kidney uptake and thus avoid acute and/or delayed renal toxicity have been developed (Pauwels *et al.* 2005, Valkema *et al.* 2005). Positively charged amino acids, such as L-lysine and/or L-arginine, have been shown to completely inhibit proximal tubular reabsorption of the radiopeptides, thus resulting in a potential deduction in the renal dose. Different regimens of amino-acid co-infusion with a 27% mean reduction (range 20–40%) in the renal absorbed dose and no effect on tumoral uptake have been described; no further cases of renal insufficiency have been described in studies treating a considerable number of patients with NETs with this regimen (Bodei *et al.* 2004*a*, Pauwels *et al.* 2005, Valkema *et al.* 2005).

Renal toxicity was not the only parameter to be considered. Recent studies have shown that SST analogues are also taken up from the bone marrow, but not the trabecular cortical bone; although cases of bone-marrow toxicity were described in the initial studies, several subsequent studies treating a large number of patients failed to confirm these data (Bodei *et al.* 2004*a*, Pauwels *et al.* 2005). However, the possibility of a mild but progressive deficiency in bone-marrow reserves has to be considered, and this form of treatment should probably not be administered to patients with metastatic disease involving the bone marrow extensively (Bodei *et al.* 2004*a*). Following the development of acute hepatic toxicity in patients with extensive hepatic involvement, Bushnell *et al.* (2003*a*) studied 12 patients with extensive hepatic metastases (defined as 25% or more) who were treated with $^{90}$Y-DOTATOC. Only four patients developed a significant elevation of hepatic enzymes, suggesting that such patients can be treated with a cumulatively administered activity of 360 mCi of $^{90}$Y-DOTATOC with only a small chance of developing mild, acute or subacute hepatic radiation damage (Bushnell *et al.* 2003*a*). Neither endocrine dysfunction of the pituitary axis nor diabetes mellitus has been observed after treatment with radiopharmaceuticals (Bodei *et al.* 2004*a*); however, transient impairment of spermatogenesis has been described (de Jong *et al.* 2002).

## Future prospects

Targeting antigens or receptors that are overexpressed in tumour cells compared with the expression in normal cells, or exploiting uptake mechanisms, has been the basis for therapy with radiopharmaceuticals. To optimize their effect, this form of treatment should be used in patients with small tumour targets (not more than 1–2 cm in diameter) (de Jong *et al.* 2002).

For large, macroscopic targets, internal radiotherapy is probably inefficient because of the low, heterogeneous tumour uptake (Krenning *et al.* 2005). Combination therapy with both $^{131}$I-MIBG and $^{90}$Y-DOTATATE or the combinations of $^{111}$In/$^{90}$Y/$^{177}$Lu-octreotide remains an attractive theoretical option, after as complete a surgical resection as possible, to ensure good uptake of the radiopharmaceutical by the remaining tumour target (Krenning *et al.* 2005, Larson & Krenning 2005). If treatments are repeated regularly, it is likely that the disease can be at least stabilized for a period of several years, if not cured (Kaltsas *et al.* 2004*a*).

In addition, newer SST analogues in combination with different emitters are in development that might exhibit superior imaging and therapeutic properties. SOM230 (Novartis, Basel, Switzerland) is a newly developed SST analogue that binds with high affinity to $SSTR_{1-3}$ and $SSTR_5$, but not $SSTR_4$ (Bruns *et al.* 2002, de Herder *et al.* 2003). Its potential use as a radiopharmaceutical is awaited with interest. In addition, new drugs interacting with multireceptor family cross-talk, particularly SSTRs, are being developed; these SST subtype homo- or heterodimers may exert properties distinct from the individual receptors in terms of internalization and functional activity (de Herder *et al.* 2003). Hybrid somatostatin-dopamine molecules with high affinity to $SSTR_2$ and $D_2$ receptors have been developed and are expected to have a higher affinity than each receptor alone in NETs that express them (de Herder *et al.* 2003).

Apart from expressing SSTRs, GEP tumours can express several other receptors such as glucagon-like peptide 1 (GLIP-1) receptors, cholecystokinin receptors, and bombesin or vasoactive intestinal peptide (VIP) receptors (Reubi & Waser 2003). Thus, insulinomas have more GLIP-1 receptors than SSTRs whereas carcinoid tumours also express cholecystokinin 2, bombesin and/or VIP receptors (Reubi 2004). The concomitant expression of several of these peptide receptors in GEP tumours forms the basis for *in vivo* multireceptor targeting of those tumours, using a combination of radiolabelled compounds (de Jong *et al.* 2003, Reubi *et al.* 2005). Such an approach may increase the accumulation of radioactivity in these tumours, improving further targeting efficacy, and it may also allow different radioligands to be labelled with isotopes of different ranges in order to obtain optimal radiotherapy for lesions of various size. Radiolabelled minigastrin analogues have already been applied successfully in cholecystokinin 2 receptor-positive tumours, such as MTC (de Jong *et al.* 2003, Reubi 2005).

Compounds such as RGD (Arg-Gly-Asp) peptides have been described as antagonizing tumour angiogenesis by binding to $a_v\beta_3$ receptors on newly formed blood vessels. These compounds may be combined with DTPA-Tyr$^3$-octreotate and form hybrid peptides that can bind to both SSTR$_2$ and $a_v\beta_3$ receptors and can thus be used for both scintigraphy and radionuclide therapy (van Hagen *et al.* 2000). Co-administration of chemotherapeutic drugs with radiosensitizing properties may act synergistically with irradiation, improving the efficacy of therapy with radiopharmaceuticals (Chatal *et al.* 2000). Immune system activation for the control of micrometastatic disease may play an additional role in pursuit of complete control and cure. Finally, transfer of genes encoding for the expression of SSTR$_2$ and SSTR$_5$ to receptor-negative tumours may render them responsive to treatment with these agents, including radiolabelled compounds (de Herder *et al.* 2003, Kaltsas *et al.* 2004*b*).

## Multidisciplinary approach

Patients with cancer and particularly patients with GEP tumours (due to their prolonged survival in the face of extensive disease) greatly benefit from a multidisciplinary therapeutic approach. Such teams should include physicians with a special interest in NETs, pathologists, endocrinologists, gastroenterologists, interventional radiologists, surgeons, oncologists and nuclear medicine experts. Diagnostic procedures should be critically reviewed to help establish a consensus on the best evidence-based management, including invasive procedures such as chemoembolization or repeated surgical procedures. The integration of receptor therapy with SST analogue (octreotide and lanreotide)-based radiopharmaceuticals and biotherapy (long-acting SST analogues with or without IFN-$\alpha$), together with other therapeutic approaches, must be explored. As a rule, surgical debulking of the primary tumour and reduction of hepatic deposits should be the first-line treatment; the optimal approach must be considered in each patient in order to improve survival and maintain good QoL (Kaltsas *et al.* 2004*b*). Attempts to improve QoL should be sought, as patients with metastatic disease may still experience prolonged survival, and this should be weighed against the potential side effects of any systemic treatment. Since the majority of these tumours grow slowly and even patients with disseminated disease may have prolonged survival, early involvement in palliative team programmes may be helpful. In order to evaluate the results of current management, establish guidelines and develop new therapeutic trials, multicentre collaborations are particularly helpful.

## Summary

Treatment with radiolabelled SST analogues is an evolving therapeutic modality for the management of patients with inoperable or metastasized neuroendocrine, particularly GEP, tumours. Prerequisities for treatment success include demonstration of high tumour uptake relative to non-target tissues on quantitative, diagnostic radionuclide imaging (e.g. OctreoScan) and stable haematological and biochemical function. Although there is a need for more accurate prediction of the absorbed doses, treatment with all $^{111}$In-, $^{90}$Y- or $^{177}$Lu-labelled SS analogues has been associated with considerable symptomatic improvement with limited side effects that are mainly related to kidney function. Targeted therapies are better tolerated than other systemic treatments and deliver higher absorbed radiation doses to the tumour than can be achieved by external beam irradiation. The results obtained with [$^{90}$Y-DOTA$^0$,Tyr$^3$]-octreotide and [$^{177}$Lu-DOTA$^0$,Tyr$^3$]-octreotate have also exhibited substantial tumour regression, whereas the combination of these two radiopeptides may be even more effective than either alone. Future directions for improving this type of therapy include multireceptor targeting, attempts to upregulate SSTR expression on tumours and the use of radiosensitizers.

## Acknowledgements

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