Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues
Bodei, Lisa

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2009

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 2

PEPTIDE RECEPTOR THERAPIES IN NEUROENDOCRINE TUMOURS

Lisa Bodei, Diego Ferone, Chiara M. Grana, Marta Cremonesi, Alberto Signore, Rudi A. Dierckx, Giovanni Paganelli.

Divisions of Nuclear Medicine and Medical Physics, European Institute of Oncology, Milano, Italy
1Department of Endocrinological & Medical Sciences (DISEM), University of Genova, Italy;
2Sapienza University of Roma, Italy;
3University Medical Center Groningen, University of Groningen, The Netherlands.

Journal of Endocrinological Investigations 2009 in press

Introduction

Neuroendocrine tumours (NETs) are relatively rare tumours, mainly originating from the digestive system, able to produce a number of specific bioactive amines and hormones.
Since 2000, the WHO classification of endocrine tumours has clearly defined the neuroendocrine phenotype.
Treatment of NETs is typically multidisciplinary and should be individualised according to the tumour type, burden, and symptoms. Therapeutic tools in NETs include surgery, interventional radiology and medical treatments such as somatostatin analogues, interferon, chemotherapy, new targeted drugs and peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues.

NETs usually over-express somatostatin receptors on their cell surface, thus enabling the therapeutic use of somatostatin analogues, one of the basic tools for NETs. Somatostatin analogue biotherapy is able to reduce signs and symptoms of hormone hypersecretion, to improve quality of life and to slow tumour growth. Interferons, and particularly α-interferon, have been used in NETs, with similar therapeutic effects. Presently, the combined use of α-interferon and somatostatin analogues as first-line therapy is not justified by data in literature, while it could be indicated after progression to a single agent.

Diagnosis

The localisation of a NET and the assessment of the extent of disease are crucial for management. Nowadays, commonly used diagnostic techniques include conventional radiology with transabdominal ultrasound, computerized tomography (CT), and magnetic resonance (MRI), selective angiography with hormonal sampling, and functional imaging with widely available techniques like 111In-octreotide (OctreoScan) or, more recently, somatostatin receptor PET with 68Ga-octreotide, as well as experimental methods available only in some centres, such as 99mTc-EDDA/HYNIC-Tyr³-octreotide scintigraphy, or PET with ¹⁸F-levo-DOPA, ¹¹C-5-hydroxytryptophan, or ⁸⁶Y-DOTATOC. No technique is the gold standard, and specific sequences of exams might be needed for each tumour type. Only a
combination of two or more imaging techniques, usually leads to diagnosis and staging. Despite all efforts, a consistent number of NETs (up to 50%) remains with an unknown primary site. Usually, radiological techniques (such as ultrasound, CT, or MRI) are useful in the localisation of the primary tumour, particularly if non-functioning, while nuclear medicine aids in the evaluation of the extent of disease, staging and therapy decision making. In functioning tumours, receptor scintigraphic techniques may also allow the localisation of the primary tumour when it is placed in anomalous sites, such as the described cardiac septum gastrinoma, or in difficult areas, such as the mesenteric region or peripheral bronchia.

In pancreatic NETs, contrast-enhanced three-phase CT or MRI are able to localise 60-94% of the primaries, angiography up to 75%, and $^{111}$In-octreotide scintigraphy up to 77-85% of the primary lesions [1]. Sensitivity of OctreoScan is usually less for insulinomas due to a variable somatostatin receptor expression, but this technique is able to explore the whole body and gives important therapeutic indications for somatostatin analogue therapy. Endoscopic ultrasound is useful in the diagnosis and staging of intramural lesions of the duodenum, pancreas, stomach and rectum, and can detect up to 60% of duodenal and up to 100% of pancreatic lesions. For liver metastases, MRI proved to be the best technique, showing the highest number of lesions, followed by CT and $^{111}$In-octreotide scintigraphy. The latter has the lowest sensitivity for liver metastases because of low spatial resolution (about 1 cm) and physiological liver metabolism of the radiopharmaceutical. Nevertheless, it has been published that $^{111}$In-octreotide scintigraphy is able to modify therapeutic strategy in up to 53% of cases. None of the imaging techniques is able to give prognostic information, but a high tumour burden and a negative $^{111}$In-octreotide are associated with a poor prognosis. Moreover, a high $^{111}$In-octreotide uptake is associated to a higher probability of response to radiolabelled somatostatin analogues [2,3-7].

In thoracic tumours, CT, OctreoScan and flexible optic fibre (echo)bronchoscopy with biopsy or cytology, are the techniques of choice and have therapeutic implications. For example, $^{111}$In-octreotide can indicate somatostatin analogue therapy, while bronchoscopy may allow a laser dis-obstruction. Recently, the introduction of PET tracers other than $^{18}$FDG, which simply assesses metabolic activity, and is useful only in aggressive NETs, prompted a new era in the receptor imaging of these tumours. The use of $^{11}$C-5-hydroxytryptophan and $^{18}$F-levo-DOPA first, and, more recently, $^{68}$Ga-labelled octreotide ($^{68}$Ga-DOTANOC and –DOTATOC), allows the scintigraphic detection of NETs with dedicated PET/TC hybrid tomographs, thus increasing the lesion sensitivity to about 4-5 mm, and with CT fusion imaging to give an anatomical correlation to the areas of uptake. Nevertheless, these latter techniques are still under evaluation and not yet validated [8-10].

Nowadays, developments involve also radiological techniques. Ultrasound, with the use of intravenous “microbubble" contrast media, can better detect liver metastases and primary pancreatic tumours. CT, with the recording of dynamic contrast-enhanced three-phase images, can detect liver lesions as small as 3 mm. Dynamic MRI with the new liver specific contrast agents, such as those exploiting the super-paramagnetic effect of iron oxide particles distributed in the reticuloendothelial system, can improve the detection of liver and lymph node
metastases. Finally, videocapsule and double-balloon enteroscopy can identify otherwise undetectable small intestine tumours [11-14]. It must be considered that different kind of tumours may pose different diagnostic dilemmas. For example, an insulinoma will often be a small lesion not expressing somatostatin receptors, and therefore it will be best imaged by endoscopic and even intraoperative ultrasound. On the other hand, gastrinomas can present as large lesions, usually expressing somatostatin receptors, and receptor imaging techniques, exploring the whole body, will have a pivotal role [15,2]. Furthermore, medullary thyroid carcinomas often express somatostatin receptors and imaging with $^{111}$In-ocreotide or, even better, $^{99m}$Tc-EDDA/HYNIC-Tyr$^3$-octreotide scintigraphy is the most sensitive imaging modality for diagnosis but also for staging and follow-up [16].

**Therapy**

Treatment of NETs is typically multidisciplinary and should be individualised based on the tumour type and burden, as well as symptoms. Being NETs relatively new clinico-pathological entities, different algorithms have being proposed and applied by various centres. Consensus conferences have taken place to unify these schemes. Considering these limitations, the therapeutic tools in NETs include surgery, interventional radiology and medical treatments such as somatostatin analogues, interferon, chemotherapy, new targeted drugs and peptide receptor radionuclide therapy (PRRT) [2]. Surgery is fundamental in many phases, from the eradication of the primary, to the debulking of metastatic lesions, in view of other therapies, in order to control debilitating symptoms due to hormone overproduction or with a pure palliative intent. The main limitation of surgery is the frequent presence of synchronous metastatic disease, thus relegating the role of curative surgery only to 20% of cases [17]. Metastatic disease is classically considered as a contra-indication, although surmountable in selected situations within a multidisciplinary approach, when surgery represents a step of debulking in view of other loco-regional and/or systemic treatments.

Each tumour site has specific features and therefore specific surgical techniques apply to it. For example, tumours located in the head of pancreas or in the duodenum are treated with the Whipple pancreatico-duodenectomy, while ileal carcinoids are usually treated with ileal resection plus right hemicolectomy. For oncological radicality, regional lymph node dissection should be performed as well [18]. In case of bronchial carcinoids, surgery, including lymphoadenectomy, is the option of choice, with varying resection modalities, from atypical resections to pneumonectomy, according to oncological radicality criteria. For the more aggressive categories of thoracic NETs (LCNEC and SCLC), surgery is seldom feasible and the outcomes are, anyhow, quite poor [19]. Liver transplantation for GEP NETs remains controversial and can be proposed in selected patients (low Ki-67, intestinal NET) [20].

The rationale of interventional radiology techniques in NETs relies in their common spread to the liver. Liver metastases from NETs are typically hypervascular and (chemo)embolization of the hepatic artery, performed mechanically by microspheres or also chemically with cytotoxic agents, can lead to significant
necrosis. Recently, radioembolization of liver metastases with $^{90}$Y-labelled microspheres has recently been tested in several clinical trials with excellent preliminary results [21]. Other techniques still to be validated in NETs include "umbrella" radiofrequency ablation and the newest high-intensity focused ultrasound (HIFU) ablation [22].

Medical therapy is aimed at treating symptoms and/or reducing tumour growth. Traditional chemotherapy has little place in well-differentiated NETs, since most of them are slow growing tumours. A rigorous assessment of the efficacy of chemotherapy in literature is hampered by the prevalence of retrospective studies on limited and heterogeneous series of patients, where toxicity is relevant, and the responses are short-lived and sporadic, particularly in "midgut carcinoids". Many schemes, including single or multiple agents, have been attempted. Streptozotocin-based schemes in pancreatic tumours yielded significant objective responses, but none of the schemes used in "midgut carcinoids" showed any activity [23]. Usually, schemes based on platinum derivatives and etoposide are considered in poorly differentiated and/or rapidly progressive NETs, but generally the choice of the particular regimen is based on the site of the primary and the histopathological differentiation. In well-differentiated tumours, the Ki-67 proliferation index can be helpful in selecting tumours suitable for chemotherapy.

One of the basic tools for NETs is somatostatin analogue biotherapy, combined or not with interferon, which will be discussed in details below. Survival is reduced in patients with a clinical syndrome such as the carcinoid one (21% of 5-year survival, 38 months median survival from the first facial flushing, 23 from the biological diagnosis). In this respect, a therapy able to reduce signs and symptoms of hormone hypersecretion, to improve quality of life and to slow tumour growth, appears fully justified [24].

Somatostatin analogues are generally well tolerated and long acting formulations are used successfully to control tumour hypersecretion and symptoms in up to 70% of patients, although tachyphylaxis frequently and early occurs [25]. Antiproliferative activity is scarce, with objective responses encountered in less than 10% of patients, while stabilisation of disease occurs in about 50% [26]. Interferons, and particularly α-interferon, have been used in the management of NETs, with therapeutic effects similar to those of somatostatin analogues, although the onset is delayed, but with more pronounced side effects. Presently, the combined use of α-interferon and somatostatin analogues as first-line therapy is not justified by data in the literature, while it could be indicated after progression to a single agent [27].

Nowadays, new molecular drugs, targeting small cellular proteins or messengers involved in proliferation, are being experimented in phase II and III studies. The peculiar growth characteristics of NETs make them attractive targets for molecular targeted therapies, since the longer period needed to progress allow drugs hitting the stromal or subcellular targets to demonstrate activity. The scenario is particularly ebullient, with many pharmaceuticals reaching the clinical phase. The most efficient and studied are vascular endothelial growth factor (VEGF) and mTOR inhibitors.

VEGF expression has been demonstrated in NETs. Among VEGF inhibitors, the most active one appears to be bevacizumab, a monoclonal antibody against VEGF, which has been experimented in a phase II study combined with octreotide,
determining an improvement on progression-free survival vs. the combination of PEG-interferon plus octreotide.

The mammalian target of rapamycin, mTOR, is an intracellular protein that is central in the control of cell growth. Abnormalities in the mTOR pathway have been demonstrated in NETs. Phase II clinical studies using mTOR inhibitors, such as everolimus (RAD001) or temsirolimus (CCI-779), in the treatment of low-grade NETs demonstrated antitumour activity (13% objective responses). New phase II pathology oriented protocols have been designed and are presently ongoing [28].

**Peptide receptor therapies**

Neuroendocrine cells are typically regulated by numerous hormones, acting via specific receptors on the membrane surface. These receptors are usually 7-transmembrane-domain G-protein–coupled receptors. The presence of a suitable density of internalising receptors on the cell surface of NETs poses the basis for a peptide receptor-targeted therapy. The most exploited and known ligand-receptor system in clinical practice, including nuclear medicine, is the somatostatin. Somatostatin receptors are known in 5 subtypes, the role of which is still to be completely elucidated. Agonists binding to somatostatin receptors are internalised into endosomes and activate post-receptor mechanisms, such as adenyl cyclase, phospholipase and ion channels, that are responsible for the pharmacological effect. The receptor is either recycled on the membrane surface or entrapped into lysosomes for degradation. This retention into the lysosomes allows a radionuclide-based peptide diagnosis and/or therapy, depending on the radionuclide used [29]. Tumours over-expressing somatostatin receptors, and candidate for radionuclide therapy, typically include pituitary adenomas, gastrointestinal and pancreatic endocrine carcinomas (the so-called GEP tumours), paragangliomas, pheochromocytomas, small cell lung cancers, medullary thyroid carcinomas, breast cancers, and malignant lymphomas. Somatostatin receptors are expressed in a tissue- and subtype-selective manner in both normal and cancerous cells. Most of the above tumours express multiple receptor subtypes simultaneously, subtype 2 being the subtype most frequently detected. The presence of somatostatin receptors enables the treatment of tumour hypersecretion and of primary and metastatic lesion growth by somatostatin and its analogues, owing to post-receptor signalling, triggered by the receptor-ligand internalisation [30].

**Somatostatin analogues**

All five somatostatin receptor subtypes (sst) bind with high affinity native somatostatin (both 14- and 28-amino acid isoforms). Somatostatin has an extremely short plasma half-life (about 2 minutes) and cannot be used for clinical purposes. Somatostatin-28 was firstly labelled with $^{123}$I, showing *in vivo* the rapid cleavage and metabolism that poorly allowed visualizing and therefore treating tumours [31]. In the same years, beginning of 1980s, the octapeptide analogue octreotide was synthesised. Presently, octreotide, together with lanreotide, is the analogue approved for therapeutic clinical use. Both these analogues are mainly sst$_2$ preferring agents, showing therefore high affinity for sst$_2$ receptor, moderately high affinity for sst$_5$ and intermediate affinity for sst$_3$ [32].

**“Cold” somatostatin analogues in clinical use**

To date, the main clinical use of octreotide or lanreotide is limited to the symptomatic control of hypersecretory syndromes. Nevertheless, it has been used
in various trials with the aim of testing its antiproliferative efficacy [33]. In NETs of various origin the use of octreotide (0.5 - 1 mg t.i.d.) yielded symptomatic and biochemical responses in 73% and 77% of patients, respectively, with only 3% objective responses in carcinoids, in the evaluation of the Italian multicentre trial [34]. The use of ultra high-dose lanreotide (up to 15 mg/day) gave slightly higher tumour responses as well as biochemical and symptomatic responses (more than 6 %) [35]. In the medical treatment of advanced small-cell lung cancer, both octreotide and lanreotide were able to reduce growth factors, such as IGF-1, but did not show any antitumour efficacy [36].

**Somatostatin radio-analogues for peptide-receptor radionuclide therapy**

111In-labelled octreotide was approved by the FDA in 1994 as a diagnostic agent for scintigraphy of patients with NETs. Once octreotide was radiolabelled for diagnostic imaging in order to localise tumour lesions over-expressing somatostatin receptors [37], the next logical step was to develop PRRT. The theoretical basis of such therapy is principally to convey radioactivity inside the tumour cell, owing to the internalisation of the somatostatin receptor and radiolabelled analogue complex. The first attempts to perform PRRT with radiolabelled octreotide began in the 1990s in a multicentre trial using high activities of 111In-octreotide. The results obtained, in terms of clinical benefit and overall responses are due to the Auger and conversion electrons emitted by Indium-111, decaying in close proximity to the cell nucleus, once that peptide/receptor complex has been internalised. Despite these premises, partial remissions were exceptional [38].

Higher-energy and longer-range emitters, such as pure β emitter Yttrium-90 (E_{max} 2.27 MeV, R_{max} 11 mm, T_{1/2} 64 hrs) seemed more suitable for therapeutic purposes. Therefore a new analogue, Tyr³-octreotide, with a similar pattern of affinity for somatostatin receptors, was developed for its high hydrophilicity, simple labelling with 111In and 90Y, and tight binding to the macrocyclic chelator DOTA (1,4,7,10-tetra-azacyclododecane-N,N',N'',N'''-tetraacetic acid), to form 90Y-[DOTA]³-Tyr³-octreotide or 90Y-DOTATOC [39]. Recently, a newer analogue, named octreotate (Tyr³,Thr⁸-octreotide) with 6- to 9-fold higher affinity for sst₂ was synthesised. The chelated analogue [DOTA]⁰-Tyr³-octreotide or DOTATATE can be labelled with the β⁻ emitter Lutetium-177 (E_{max} 0.49 MeV, R_{max} 2 mm, T_{1/2} 6.7 days) and has been experimented in clinical studies. Theoretically, Auger-electron emitters represent an attractive alternative to β-particle emitters for cancer therapy if they can be placed intracellularly, especially in close proximity to (or within) the nuclear DNA. Incorporation of Auger-electron emitters into the DNA is a particularly efficient source of irradiation, capable of inducing cell death with virtually no damage to the surrounding cells. Experience in this field comes from a radiolabelled thymidine analogue, IUdR, which represents the most extensively explored radiobiologic model for cancer therapy with Auger-electron emitters. Upon incorporation of iodine-125 into DNA, the disintegration of this Auger–electron-emitting isotope has a relative biologic effectiveness (RBE) 7- to 8-fold greater than equivalent amounts of β or γ emission. There is now sufficient evidence that generally the intra-nuclear localisation and specifically intercalation or at least the proximity of Auger-electron emitters to the double-stranded nuclear DNA determine their cytotoxicity. Coming to somatostatin analogues, it has been extensively discussed whether 111In-octreotide locates targets placed inside the cell nucleus. Studies in literature are scant and contradictory, nonetheless nuclear uptake is
likely to be scarce, and this seems to be the explanation of such poor results in clinical trials. Since the beginning of new century, PRRT was performed only with β-emitters [40].

Several new peptides have been introduced in nuclear medicine for therapeutic and diagnostic purposes, such as new sst₂ agonists DOTA-TATE, DOTA-NOC, and DOTABOC-ATE (where NOC is [1-NaI³]-octreotide; and BOC-ATE is [BzThi³,Thr⁸]-octreotide). Each one can be labelled with either therapeutic radiometals, such as Yttrium-90 or Lutetium-177, or with positron-emitters, such as Gallium-68, for PET-receptor imaging, thus giving rise to different radiopeptides as to their biological and clinical properties, and many of them are already used in diagnostic and therapeutic trials [41].

**Other potential receptors and (radio)peptides for therapy**

Somatostatin receptor system represents an actual treatment pathway and a model for future tumour therapies. Many ligand–receptor systems have been discovered in different human tissues, such as dopamine, bombesin, cholecystokinin, vasoactive intestinal peptide, substance-P and others, which could represent adjunctive targets for “cold” and radiolabelled analogue therapy (Table 1). Regarding dopamine receptors, the first intuitions of their possible presence in NETs started from the observation that ¹²³I-epidepride, a D₂ dopamine receptor antagonist, could be used in pituitary imaging in substitution of an iodinated benzamide, ¹²³I-IBZM, known also to accumulate in melanomas. ¹²³I-epidepride was then demonstrated to accumulate in human melanomas, and dopamine D₂ receptors were therein demonstrated, also by means of other techniques. Subsequently D₂ receptors were demonstrated also in NETs, such as those associated with ectopic ACTH syndrome. Furthermore, cabergoline, a new D₂-receptor synthetic analogue demonstrated efficacy in controlling cortisol excesses in some patients [48,49]. Cabergoline seems also to increase the efficacy of somatostatin analogs in controlling ectopic Cushing syndrome [50].

Moreover, recent observations have shown that internalisation of human somatostatin receptors (ssts) could be determined by functional homo- and heterodimerization with somatostatin receptors or other G-protein–coupled receptors, such as dopamine D₂ receptor, with resulting properties that differ completely from those of the individual receptors as to ligand-binding affinity, signalling, agonist-induced regulation, and internalisation. The effects of newer analogues, such as sst₂/sst₅, sst₂/D₂ and sst₂/sst₅/D₂ (dopastatin) bi- or tri-hybrid chimerical analogues have been explored in vitro in primary cultures of GH-secreting pituitary adenomas partially responding to conventional somatostatin analogues, and are being experimented also in NETs [51-53].

For the moment, the lack of selectivity for basal ganglia and tumour shown by D₂ receptor ligands and possibly by chimeras, make them unsuitable for designing a radionuclide therapy.

Presently, a somatostatin analogue binding 4 out of 5 ssts, the so-called pan-agonist SOM-230 (pasireotide), which binds with high affinity sst₁,₂,₃ and sst₅, is being experimented in clinical trials for the therapeutic control of NETs, but, given the wide systemic expression of the receptor subtypes other than sst₂, pan-agonists are far from being used in radionuclide therapy [54].
Finally, the demonstration, in animal models, of a far superior tumour targeting by non-internalising somatostatin receptor antagonists is revolutionizing the paradigm of the internalization of the receptor-ligand complex as the basis for PRRT [55].

**PRRT with radiolabelled somatostatin analogues**

Nowadays, tumour candidates for PRRT with radiolabelled somatostatin analogues are basically sst₂ expressing NETs, mainly of the GEP and bronchial tract, but also pheochromocytomas, paragangliomas, medullary thyroid carcinomas, and, at least theoretically, any other tumour histotype known and documented as over-expressing sst₂. Among the inclusion criteria, a high expression of functioning, namely internalising somatostatin receptors is critical for an efficient therapy. Somatostatin receptor scintigraphy is presently the most accurate method to check for the presence of functioning somatostatin receptor over-expression. Immunohistochemistry for sst₂ can be also performed, but, being it a sort of photograph taken at the moment of bioptic sampling, the actual internalising capacity and the possible evolution in time of receptor density cannot be assessed. A correlation between immunohistochemical profile in NETs and the in vivo scintigraphy features has been explored in a recent study [56]. However, larger cohorts of patients are warranted to draw conclusive results. Moreover, the receptor status in the remainder of tumour sites cannot obviously be assessed and cannot always be assumed presumably homogeneous. Somatostatin receptor scintigraphy has indications in the localisation, staging and follow up of a NET, but indeed, the ability of selecting patients to be submitted to “cold” or radiolabelled somatostatin analogues, is the most peculiar. When analysing a scan, it is important to exclude possible false positives, such as gallbladder, accessory spleens, recent surgical scars, and any other cause of granulomatous-lymphoid infiltrate that may mimic a tumour lesion. In addition, possible cases of false negatives must be excluded, particularly sub-centimetre lesions under the resolution power of the method, recent chemotherapy, or de-differentiated disease.

PRRT consists in the systemic administration of the radiopeptide, such as ⁹⁰Y-DOTATOC or ¹⁷⁷Lu-DOTATATE, the most used ones, divided in sequential cycles, administered 6-9 weeks apart, up to a cumulative activity that is calculated basing on renal irradiation.

**PRRT efficacy**

Before considering the clinical outcome of PRRT, the theoretical principles at the basis of the efficacy must be summoned up, namely the radiosensitivity and the radioactive concentration on tumour site. Actually, NETs are not particularly radiosensitive [57], and this is an intrinsic characteristic involving the growth pattern and the DNA repair capability. On the other hand, the radioactive concentration at the tumour site is crucial and can be modulated. In fact, the higher is the concentration of radioactivity in the tumour, the higher is the probability of its shrinkage. In order to increase the amount of radioactivity at the target, and therefore the so-called target-to-background ratio, the kinetics characteristics of the radiopeptide used, its affinity for the receptor, and the receptor density on tumour cells, must be taken into account.

The pharmacokinetics profile of DOTATOC, and similarly of DOTATATE, is remarkably favourable, with a rapid plasma clearance after administration (less than 9%±5% of i.d. within the first hour to less than 0.9%±0.4% within 10–12 h after
injection) and the renal excretion is relevant (73%±11%. i.d. in urine after 24 hours) [58].

The various octreotide derivatives available possess variable affinity profiles for sst$_2$, sst$_3$ and sst$_5$. Peptides such as DOTATOC and even more DOTATATE and DOTANOC possess a high affinity for sst$_2$, the most widely expressed receptor in NETs (11, 1.5 and 3.3 IC$_{50}$ nM, respectively). Analogues showing high affinity for sst$_3$ and sst$_5$, such as DOTANOC (26 and 10 IC$_{50}$ nM for sst$_3$ and sst$_5$, respectively), can also be exploited in tumours, such as thymic tumors or follicular thyroid carcinomas, presenting a relatively higher expression of these subtypes [59].

Finally, the receptor density on tumour versus normal organs must be considered as well. The higher is the density, the greater the amount of radiopeptide that may be conveyed inside the tumour cells. In clinical practice, the density is evaluated by means of receptor scintigraphy, according to a visual scale, named the “Rotterdam scale”, where tumours candidate to PRRT are those with an uptake on planar images at least equal to the one of the normal liver (grade 1), higher than that (grade 2) or higher than the one of kidneys and spleen, the “hottest” organs at $^{111}$In-octreotide scintigraphy (grade 3). Tumour remission, in fact, is positively correlated with a high uptake at receptor scintigraphy [60]. Nevertheless, tumour radiation dose does not only depend directly on the administered activity and the uptake versus time, but also on the tumour mass. Smaller masses have higher chances of mass reduction, owing to a higher absorbed dose in the tumour. This is confirmed by clinical data regarding the characteristics of response: patients with limited number of liver metastases responded to PRRT, whilst patients with a high tumour load do not [61]. Considering PRRT with the two most exploited radiopeptides, $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATATE, mathematical models showed that $^{177}$Lu is better in small tumours (optimal diameter 2 mm), whilst $^{90}$Y in larger ones (optimal diameter 34 mm). Very small masses, in fact, are likely not to absorb all the β-energy released in the tumour cells by $^{90}$Y, while larger tumours will suffer from the lack of uniformity of activity distribution of $^{177}$Lu. Finally, differences in dose-rate must be taken into account: the longer physical half-life of $^{177}$Lu means a longer period needed to deliver the same radiation dose as $^{90}$Y. This may allow more time for tumour re-population. Therefore, a combination therapy with $^{90}$Y and $^{177}$Lu, either simultaneously or in distinct settings, has been suggested to overcome the difficulties of real clinical situation of different sized lesions [62].

**PRRT safety**

Due to their marked radiosensitivity, the kidneys are the critical organs in PRRT, particularly after $^{90}$Y-DOTATOC administration. Proximal tubular reabsorption of the radiopeptide and the subsequent retention in the interstitium results in renal irradiation. Nephrotoxicity is accelerated by risk factors, such as pre-existing hypertension or diabetes. Given the high kidney retention of radiopeptides, positively charged molecules, such as L-lysine and/or L-arginine, are used to competitively inhibit the proximal tubular re-absorption of the radiopeptide. This leads to a reduction in the renal irradiation dose ranging from 9 to 53% [63-65]. Renal doses are further reduced up to 39% by prolonging infusion over 10 hours and up to 65% by prolonging it over two days after radiopeptide administration, thus covering more extensively the elimination phase through the kidneys [66,67].
Despite kidney protection, renal function loss may become clinically evident years after PRRT. A median decline in creatinine clearance of 7.3% per year was reported in patients treated with $^{90}$Y-DOTATOC and of 3.8% per year in patients treated with $^{177}$Lu-DOTATATE. Cumulative and per-cycle renal absorbed dose, age, hypertension, and diabetes are considered as contributing factors to the decline of renal function after PRRT [68].

Kidney radiation toxicity is typically evident several months after irradiation, due to the slow repair characteristics of renal cell. According to studies on renal toxicity derived from external radiotherapy (those referred to by the nuclear medicine community, up to a few years ago), the accepted renal tolerated dose is in the range of 23-25 Gy. As stated by the National Council on Radiation Protection and Measurements –NCRPM- in fact, a dose of 23 Gy to the kidneys causes detrimental deterministic effects in 5% of patients within 5 years) [69,70]. Nevertheless, clinical experience and dosimetric studies clearly indicate that this renal dose threshold does not accurately correlate with the renal toxicity observed in patients undergoing PRRT [71].

PRRT is a form of continuous radiation delivery with a decreasing dose-rate with time. The irradiation produces both lethal and sub-lethal damage that can be repaired during the irradiation itself but the differential between creating new damage and the repairing depends on the specific dose-rate at any particular time and on the repair capability ($T_{\text{rep}}$) of the tissue. Low dose-rates, as in PRRT, will spare normal tissues more than the tumour and this may allow benefits as in fractionation in external radiotherapy [72].

The linear quadratic model interprets mathematically this differential sparing and the biological effective dose (BED) concept is used to quantify the biological effects induced by different patterns of radiation delivery. This model has been recently revised for radionuclide therapy and has been applied in particular to PRRT with the intent of increasing the dose-response correlation [73]. Focusing on the kidney concern, the BED has proven to be a reliable predictor of renal toxicity, helpful in the implementation of individual treatment planning [71]. However, BED is a relatively young concept applied to nuclear medicine and has still to be fully validated with a wider series of data.

The main radiobiological parameter required in such assessment is the tissue $\alpha/\beta$ ratio, which gives an indication of the sensitivity of a tumour or normal tissue cell to the effect of dose-rate (and/or fractionation), and is generally higher for tumours (5-25 Gy) than for late-responding normal tissues (2-5 Gy), such as the kidneys.

Renal toxicity is not the only parameter to be considered. Although it appears not to be the principal dose-limiting factor, bone marrow involvement must be taken into account as well. Usually, PRRT is well tolerated and severe, grade 3 or 4, haematological toxicity does not account for more than 13% of patients treated with $^{90}$Y-DOTATOC and 2-3% of those treated with $^{177}$Lu-DOTATATE (Table 3). The possibility of a mild, but progressive impoverishment in bone marrow reserves has to be considered in repeated cycles, particularly after $^{90}$Y-DOTATOC, while the recover appears to be virtually complete after $^{177}$Lu-DOTATATE. In addition, the possibility of MDS or overt leukaemia in patients receiving high bone marrow doses, especially in those previously treated with alkylating agents, must be considered [67,74]. Fertility can be temporarily impaired in males, due to damage to Sertoli cell, as testified by a drop in inhibin-B and a contemporary increase in
FSH. Usually, fertility is restored within 12-18 months from the end of therapy [61]. Finally, it must be considered that treating functioning NETs with PRRT may result in acute cell rupture and hence exacerbation of clinical syndromes, such as hypoglycaemia, carcinoid or Zollinger-Ellison syndromes, sometimes to severe degrees, requiring further hospitalisation [75].

**PRRT clinical results**

Several clinical phase I-II trials indicated that PRRT with radiolabelled somatostatin analogues is amongst the promising newly developed targeted tools in NETs, with registered objective responses in up to 30% of patients (Table 2) [74]. Initial studies were performed with the administration of high doses of the radiopeptide used in diagnostics, $^{111}$In-octreotide. The rationale is based on the emission of Auger and conversion electrons by Indium-111, decaying in close proximity to the cell nucleus after the internalisation of the peptide/receptor complex. Objective responses were rare due to the short range of the emission (0.0025 μm) of the particles. Amongst 40 patients treated with cumulative doses of 20 to 160 GBq, 1 partial remission, 6 minor remissions, and 14 stabilisation of disease were reported. Mild haematological toxicity was observed, but 3 cases of MDS or leukaemia occurred in the patients treated with high activities (>100 GBq) and high estimated bone marrow doses (about 3 Gy). In another study in 27 patients with GEP NETs, partial responses occurred in 2 of 26 patients with measurable disease. Renal insufficiency was reported in one patient, although possibly not treatment-related [38,76].

The radiopeptide that has been most extensively studied is $^{90}$Y-DOTATOC. All the published results derive from phase I-II trials, and were inhomogeneous as to patient selection, inclusion criteria, treatment schemes and dosages (cumulative activities ranged from 2 to 32 GBq). Therefore, an inter-study comparison is virtually impossible. Nevertheless, despite differences in clinical phase I-II protocols from various centres, complete and partial remissions were registered in 10 to 30% of patients, a rate undoubtedly higher than that obtained with $^{111}$In-octreotide. In a first report, 29 patients were treated with a dose-escalating scheme consisting in 4 or more cycles of $^{90}$Y-DOTATOC with cumulative activities of 6.12±1.35 GBq/m$^2$. Twenty of these patients showed disease stabilisation, 2 had partial remission, 4 minor remission and 3 progressed [77]. In a subsequent study, 39 patients were treated with 4 equal intravenous injections, for a total of 7.4 GBq/m$^2$ of $^{90}$Y-DOTATOC. The objective response rate was 23%, with complete remission in 2 patients, partial remission in 7, and stabilisation in 27. Pancreatic NETs (13 patients) showed a higher objective response rate (38%). A significant reduction of clinical symptoms was recorded [78]. Toxicity was generally mild and involved the kidney and the bone marrow. However, renal insufficiency was reported in 5 patients not receiving renal protection during the therapy, while severe haematological toxicity occurred in those patients treated with high cumulative activities. Dosimetric and dose escalating studies with $^{90}$Y-DOTATOC, with and without renal protection with amino acids, showing no major acute reactions were observed up to an administered dose of 5.55 GBq per cycle [79]. Reversible grade 3 haematological toxicity was found in 43% of patients injected with 5.18 GBq, which was defined as the maximum tolerated dose per cycle. None of the patients
developed acute or delayed kidney toxicity, although follow-up was short. Partial and complete responses were reported in 28% of 87 patients with NETs. In the multicenter phase 1 study, 60 patients received escalating doses up to 14.8 GBq/m² in 4 cycles or up to 9.3 GBq/m² in a single dose, without reaching the maximum tolerated single dose. All patients received renal protection. Three patients had dose-limiting toxicity: 1 had liver toxicity, 1 had grade 4 thrombocytopenia, and 1 had MDS. Four of 54 patients (8%) treated with the maximum allowed dose had partial response, and 7 patients (13%) had minor responses. The median time to progression in the 44 patients showing stable disease, minor or partial response was 30 months [80].

Genuine phase II studies with ⁹₀Y-DOTATOC are still lacking, but experiences in selected series of patients, mostly retrospective, are reported in literature. A tentative categorisation of the objective response according to the tumour type has been attempted in a metanalysis of results in GEP tumours. Pancreatic NETs resulted the ones responding better to PRRT [74]. Other limited experiences in medullary and follicular thyroid carcinomas, lympho-proliferative disorders, pheochromocytomas and parangangliomas are reported.

⁹₀Y-DOTATOC (7.5–19.2 GBq in 2–8 cycles) has been administered in 21 patients affected by metastatic medullary thyroid carcinoma with positive OctreoScan, progressing after conventional treatments. Two patients (10%) obtained a complete response (CR), as evaluated by CT, MRI and/or ultrasound, while a stabilisation of disease (SD) was observed in 12 patients (57%); seven patients (33%) did not respond to therapy. The duration of the response ranged between 3 and 40 months. Using biochemical parameters (calcitonin and CEA), a complete response was observed in one patient (5%), while partial response in five patients (24%) and stabilisation in three patients (14%). Twelve patients had progression (57%). Complete responses were observed in patients with lower tumour burden and calcitonin values at the time of the enrolment. This retrospective analysis is consistent with the literature, regarding a low response rate in medullary thyroid cancers treated with ⁹₀Y-DOTATOC. Nevertheless, patients with smaller tumours and higher uptake of the radiopeptide tended to respond better [81].

An interesting perspective of PRRT in lympho-proliferative disorders is opened by the presence of ssts in B-lymphocytes, but today no data are available regarding their use as targets for therapy. Sporadic observations are reported in literature, such as the case report of successful PRRT with ⁹₀Y-DOTATOC in B-chronic lymphocytic leukaemia in a patient affected by Binet A-chronic lymphocytic leukaemia and advanced neuroendocrine Merkel carcinoma. The presence of somatostatin receptors both in normal and neoplastic B cells, and the usual drop of lymphocytes normally observed after ⁹₀Y-DOTATOC, constitutes the basis for setting up PRRT specifically in B-cell lymphoma and leukaemia [82].

As to the survival after ⁹₀Y-DOTATOC, a phase I-II study on 58 patients with GEP NETs treated with 1.7-32.8 GBq reports a clinical benefit (including stabilisation and minor response) in 57% (with true objective response in 20%), a median overall survival of 36.7 months (vs 12 months in the historic group treated with ¹¹¹In-octreotide), and a median progression-free survival of 29 months. Characteristically, patients stable at baseline had a better overall survival than had patients progressive at baseline, and the extent of disease at baseline was a predictive factor for survival [83].
The newer somatostatin analogue [DOTA\(^0\),Tyr\(^3\),Thr\(^8\)]-octreotide or DOTATATE has a nine-fold higher affinity for the sst\(_2\) compared with [DOTA\(^0\),Tyr\(^3\)]octreotide in vitro. Radiolabelling with the \(\beta/\gamma\)-emitter Lutetium-177 yielded tumour regressions and prolonged animal survival in a rat model [84,85]. In a preliminary report by the Rotterdam group, 35 patients with GEP NETs were treated with 3.7, 5.6, or 7.4 GBq of \(^{177}\)Lu-DOTATATE, up to a final cumulative dose of 22.2–29.6 GBq, with complete and partial responses in 38%. No serious side effects were observed [86].

In a subsequent larger study, 131 patients with somatostatin receptor–positive tumours were treated with up to a cumulative dose of 22.2 to 29.6 GBq of \(^{177}\)Lu-DOTATATE. One patient developed renal insufficiency, and another patient developed hepato-renal syndrome. Severe haematological toxicity occurred after less than 2% of the administrations. In the 125 evaluated patients, complete remission was observed in 3 patients (2%), partial remission in 32 (26%), minor response in 24 (19%) and stable disease in 44 patients (35%), while 22 patients (18%) progressed. Better responses were more frequent in case of a high uptake on baseline octreotide scintigraphy and in case of a limited number of liver metastases were present, while progression was significantly more frequent in patients with a low performance score and extensive disease at enrolment. Median time to progression was more than 36 months, comparing favourably to chemotherapy. In addition, \(^{177}\)Lu-DOTATATE significantly improved the global health/QoL and various function and symptom scales in patients with metastatic GEP tumors. The effect was more frequent in patients obtaining tumour regression, but, surprisingly, was observed also in progressing patients [60,61].

A categorisation of objective response showed once more that pancreatic tumours tended to respond better than other GEP tumours, although pancreatic gastrinomas tended to relapse in a shorter interval (median TTP 20 months vs. >36 in the rest of GEP tumours) [61]. In another study, traditionally poor responding tumours, such as bronchial and gastric neuroendocrine carcinomas, were included. Despite the limited number of patients studied, the observed objective response was comparable to the one observed in GEP NETs [87].

Recently, an evaluation of the enlarged series of 504 patients treated with \(^{177}\)Lu-DOTATATE, 310 of which evaluated for efficacy, along with the confirmation of the occurrence of complete and partial remissions in 2 and 28% of cases, demonstrated a survival benefit of 40 to 72 months, compared to historical controls. Even with the limitations of such a comparison, the huge difference in survival is most likely to be caused by a real impact of PRRT [88].

In conclusion, PRRT with \(^{90}\)Y-DOTATOC or \(^{177}\)Lu-DOTATATE proved to be effective, with up to 30% objective responses, and reasonably safe up to 25-27 Gy to the kidneys, with an acceptable toxicity to kidneys and bone marrow. Nevertheless, some open questions remain, such as the most correct timing of PRRT. PRRT is a relatively young treatment, the majority of the results derive from phase I-II studies, and therefore the exact place of PRRT in the therapeutic work-up of NETs remains to be established. The first studies, in fact, were carried out in relatively advanced phases of disease, while further trials demonstrated a higher efficacy of PRRT in earlier phases of disease. This is supported by numerous reasons, primarily radiobiological, since the smaller is the tumour mass, the higher is the dose, and then biological, since more advanced tumours bear many genetic
mutations, such as p53, which make them less prone to respond to any treatment. Previous studies have indicated that the tumour load, especially in the liver, and the performance status would influence the outcome of PRRT. Therefore, early treatment rather than a “wait and see” approach could be advantageous. In addition, the type of disease has to be taken into account, as e.g. pancreatic NETs tend to respond better. Uniform pathology-oriented phase II trials are required to assess the potential of peptide receptor radionuclide therapy.

Another open question is which is the optimal radio-peptide and, even before that, which of the two experimented is the optimal radionuclide. Theoretical considerations and animal studies showed the better suitability of Yttrium-90 for bigger lesions (optimal diameter 34 mm) and of Lutetium-177 for smaller lesions and micrometastases (optimal diameter 2 mm) [62]. Nevertheless, the demonstration of high rates of objective responses with \( ^{177}\text{Lu-DOTATATE} \) in patients not selected for lesion’s size impairs these pre-clinical observations and beseeches further comparative studies between \( ^{90}\text{Y-DOTATOC} \) and \( ^{177}\text{Lu-DOTATATE} \). However, some considerations can be made in the meantime. The analysis of the residence times for DOTATATE and DOTATOC, calculated by means of the \( ^{177}\text{Lu-labelled} \) peptides, showed that residence times for DOTATATE are significantly longer in kidney and tumour (ratios DOTATATE: DOTATOC = 1.4 and 2.1, respectively), allowing higher tumour doses but also higher renal doses [89]. Therefore, considering the higher tumour dose, \( ^{177}\text{Lu} \) appears more beneficial when labelling DOTATATE, while, in view of the higher renal dose, \( ^{90}\text{Y} \) appears more convenient to label DOTATOC. From dosimetric projections, we can infer that, for peptides such as DOTATATE, switching the radiolabel from \( ^{177}\text{Lu} \) to \( ^{90}\text{Y} \) can increase the doses by a factor 2 to 4 to the tumour, depending on the tumour size, but also to normal organs, kidneys in particular. Therefore, the benefit/risk balance remains to be established for each patient [Cremonesi EANM congress 2006, personal communication].

In conclusion, from a dosimetric point of view \( ^{177}\text{Lu-DOTATATE} \) appears handier than \( ^{90}\text{Y-DOTATOC} \), as regards safety. Anyhow, \( ^{90}\text{Y-DOTATOC} \) is more powerful than \( ^{177}\text{Lu-DOTATATE} \), as regards the tumour dose. The choice of the radiopptide depends on the particular clinical scenario of the patient. Bigger lesions may benefit from \( ^{90}\text{Y-DOTATOC} \) while smaller ones from \( ^{177}\text{Lu-DOTATATE} \). Especially when using \( ^{90}\text{Y-DOTATOC} \), particular attention has to be paid to risk factors for renal toxicity, that should suggest caution (lower doses, hyper-fractionation) or switching to \( ^{177}\text{Lu-DOTATATE} \). Anyhow, in order to establish which treatment scheme and which radiolabelled somatostatin analogue or combination is optimal, a clinical randomised study comparing the two treatments is needed.

Future perspectives include studies addressed at exploring the effects of the combined use of PRRT with other drugs, such as radiosensitising chemotherapeutic agents like capecitabine, which showed some adjunctive antitumour activity without major side effects, or anti-angiogenetic drugs [90]. As GEP NETs may also express cholecystokinin 2, bombesin, neuropeptide Y, or vasoactive intestinal peptide receptors, even simultaneously, the potential availability and biological stability of radio-analogues of these peptides, will improve in the future the multireceptor targeting of the neuroendocrine cell [91].
Conclusions
Many different somatostatin receptor binding analogues have now been described being radiolabelled with $^{123}$I, $^{111}$In, $^{99m}$Tc, $^{68}$Ga or $^{18}$F for diagnostic purposes. These proved to be an excellent tool for the clinical management of patients with NET. Not only diagnosis has been eased with these radiopharmaceuticals together with radiological techniques but also useful information for staging and therapy decision making has been provided. When radiolabelled with beta-emitting isotopes, such as $^{90}$Y and $^{177}$Lu, the same peptides have been successfully used for peptide-based radio-therapy (PPRT), with few serious adverse effects, important tumour responses and long progression-free survival rates. This field is rapidly growing and improving; new agonist and antagonist peptides have been described that can soon be tested in clinical trials.

Acknowledgements
The Authors would like to thank Mrs Deborah Console for her precious help in editing the manuscript.

References


<table>
<thead>
<tr>
<th>Target</th>
<th>Ligand</th>
<th>Diagnostic radiopharmaceutical</th>
<th>Therapeutic radiopharmaceutical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin receptors</td>
<td>Somatostatin analogues</td>
<td>$^{111}$In-DTPA-D-Phe$_1$-Octreotide (Octreotide)</td>
<td>$^{111}$In-Pentetreotide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{111}$In-DOTA-Lanreotide</td>
<td>$^{99m}$Tc-DOTA-Lanreotide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{111}$In-DOTA-Tyr$_2$-Octreotide (-DOTATOC)</td>
<td>$^{90}$Y-DOTATOC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{99m}$Tc-Degreotide (FB25)</td>
<td>Not available (n.a.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{99m}$Tc-EDDA/HYNIC-Tyr$_3$-Octreotide</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{99m}$Tc-Vapreotide (RC186)</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{111}$In-DOTA-Tyr$_3$,Thr$_6$-Octreotide (-DOTATATE)</td>
<td>$^{177}$Lu-DOTATATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{68}$Ga-DOTA-I-NaP-octreotide (-DOTANOC)</td>
<td>$^{90}$Y-DOTANOC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{68}$Ga-DOTATOC</td>
<td>$^{90}$Y-DOTATOC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{84}$Cu-TETA-octreotide</td>
<td>n.a.</td>
</tr>
<tr>
<td>CCK2-gastrin receptors</td>
<td>CCK-gastrin analogues</td>
<td>$^{111}$In-DTPA-D-Asp$_2$,Nle$_9$,31-leucine</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{111}$In-DTPA-d-Glu$_1$,minigastrin</td>
<td>$^{99m}$Tc-DOTA-D-Glu$_1$,minigastrin</td>
</tr>
<tr>
<td>VIP receptors</td>
<td>VIP analogues</td>
<td>$^{123}$I-VIP</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{99m}$Tc-T-9954</td>
<td>n.a.</td>
</tr>
<tr>
<td>GRP-receptors</td>
<td>Bombesin analogues</td>
<td>$^{99m}$Tc-RP527</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{111}$In-DTPA-Pro$_1$Tyr$_2$-bombesin</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{88}$Tc-Dermobesin</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{177}$Lu-AMBA (or BENB)</td>
<td>$^{177}$Lu-AMBA</td>
</tr>
<tr>
<td>NK-1 receptors</td>
<td>Substance P analogues</td>
<td>$^{111}$In-DTPA-Substance P</td>
<td>$^{99m}$Tc-DOTAGA-Substance P</td>
</tr>
<tr>
<td>GLP-1 receptors</td>
<td>GLP-1 analogues</td>
<td>$^{111}$In-exendin-4</td>
<td>n.a.</td>
</tr>
<tr>
<td>NT-1 receptors</td>
<td>Neurotensin analogues</td>
<td>$^{99m}$Tc-NT-37</td>
<td>n.a.</td>
</tr>
<tr>
<td>Oxytocin receptors</td>
<td>Oxytocin analogues</td>
<td>$^{111}$In-DOTA-Lys$_2$-vasoactive</td>
<td>n.a.</td>
</tr>
<tr>
<td>Catecholamine transport and storage</td>
<td>Catecholamine</td>
<td>$^{18}$F-DOPA</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{123}$I-MIBG</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{18}$F-dopa</td>
<td>n.a.</td>
</tr>
<tr>
<td>Serotonin receptor</td>
<td>Serotonin</td>
<td>$^{11}$C-5-HTP</td>
<td>n.a.</td>
</tr>
<tr>
<td>GLUT (glucose transporter)</td>
<td>Glucose</td>
<td>$^{18}$FDG</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Table 1. Ligands used in clinical practice for diagnosis of neuroendocrine tumours and their relative therapeutic counterparts (ligands in development are shown in italic) [42-47].
Table 2. Major features of safety and efficacy in PRRT with $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATATE in the main published studies (modified from 74).

<table>
<thead>
<tr>
<th></th>
<th>EFFICACY</th>
<th>SAFETY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>CR+PR (%)</td>
</tr>
<tr>
<td><strong>$^{90}$Y-DOTATOC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milan (67)</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Basel (78)</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Rotterdam (83)</td>
<td>58</td>
<td>20</td>
</tr>
<tr>
<td><strong>$^{177}$Lu-DOTATATE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotterdam (61)</td>
<td>125</td>
<td>28</td>
</tr>
</tbody>
</table>

* Renal failure and MDS or overt leukemias have been reported by the various groups, mainly as personal communications; published data are still lacking and studies are ongoing. Therefore, an exact calculation of the incidence of these adverse events is not possible, although, especially in case of MDS, the incidence does not seem to be higher than in the normal oncological population and the estimate is frequently hampered by the occurrence of previous myelotoxic chemotherapies.