Role of radiopharmaceuticals in the diagnosis and treatment of neuroendocrine tumours

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Introduction

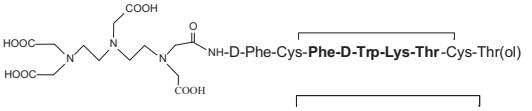
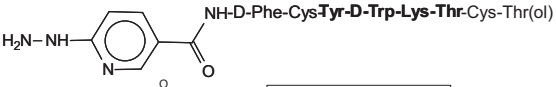
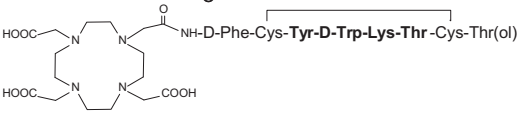
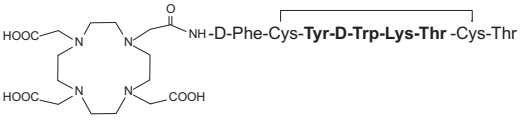
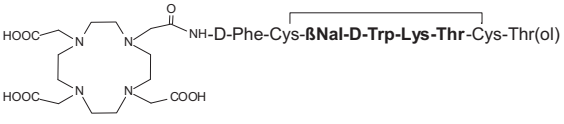
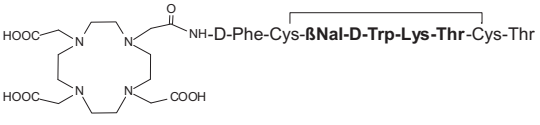
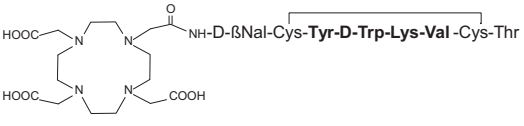
Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms characterised by their endocrine metabolism and histological pattern, originating mainly from the gastroenteropancreatic tract (GEP NETs). As opposed to other tumour entities GEP NETs are relatively rare tumours and their diagnosis requires a high index of suspicion. NETs characteristically synthesise, store and secrete a variety of peptides and neuroamines which may lead to clinical syndromes such as the carcinoid syndrome, the Zollinger Ellison syndrome, or the Verner Morrison syndrome [1,2]. However, most GEP NETs are clinically silent until late presentation with metastases. In fact, a delayed diagnosis of NET is typical, resulting in excessive morbidity and mortality and increased probability of metastatic disease. A multidisciplinary approach for therapeutic intervention is necessary. On initial clinical presentation, NETs may be difficult to diagnose because of the large variability in tumour location and the high frequency of small lesions. The proliferation marker Ki-67 (MIB-1) is important in determining tumour grade and prognosis. Once metastasised, the therapeutic options for patients with NETs are limited. Treatment with long-acting somatostatin (SST) analogues results in reduced hormonal (over)production, and thus, relief of symptoms. Surgery is the therapy of choice in localised disease. Chemoembolisation of primary tumour/liver metastases can be attempted in order to reduce the tumour mass for subsequent therapy with radiolabelled peptide analogues in patients with slow-growing tumours. In patients with poorly differentiated tumours chemotherapy may be considered [3]. However, the management options are manifold, and there are only a few evidence-based controlled studies available. Furthermore, formal guidelines are required. One should be aware that not all centres have the same treatment approach. For example, some believe that the long-acting SST analogues exert a beneficial effect even when the patient does not have symptoms. Positive effects of long-acting octreotide on tumour progression were assessed in the PROMID study recently [4]. In addition, there is not a general agreement as to the scope and timing of tumour debulking surgery and/or chemoembolisation [1].

The assessment of the location and extent of NETs is crucial for clinical management. Although being a heterogeneous group of neoplasms, NETs are characterised by their ability to over-express SST receptors (SSTR) at the cell surface. For localisation, conventional SSTR scintigraphy/positron emission tomography (PET), computed tomograhpy (CT)/magnetic resonance imaging (MRI), fused PET/CT or PET/MRI imaging, endoscopic ultrasound, arterial stimulation and venous sampling are used [5–8]. Other nuclear medicine techniques are also available for rare NETs. Here, we give an overview of the clinical value of radiopharmaceuticals used for diagnosis and treatment of NET patients.

Peptide receptor (R) expression on NETs as possible targets

In initial studies we have shown that the expression of peptide receptors on NET cells is significantly higher as compared to normal tissues and cells [9,10]. Over the past decade such receptors have become recognised targets for molecular imaging and therapy, because they are expressed on the cell surface and, upon binding of a ligand, the R-receptor-ligand complex is partly internalised [11]. SST and its analogues inhibit the growth of normal as well as malignant cells [12,13]. These effects of SST are mediated via a specific cell surface receptor. The vast majority of NETs over-express one or the other of five known SSTR subtypes (hSSTR1–5) [14–20]. Other peptide receptors expressed on the cell

Table 1
Selection of somatostatin analogues used in neuroendocrine tumour patients

Peptide-conjugate	Abbreviation	Formula	Radio-nuclides	Affinity to SSTR-subtype*	Ref.
DTPA-Octreotide	DTPA-OC		^{111}In	2, (3,5)	[26]
HYNIC-[Tyr^3]-Octreotide	HYNIC-TOC		^{99m}Tc	n.a.	
DOTA-[Tyr^3]-Octreotide	DOTA-TOC		^{111}In ^{90}Y ^{177}Lu ^{68}Ga	2, (3,4,5) 2, (3,5) n.a. 2, (5)	[27] [26] [26]
DOTA-[Tyr^3]-Octreotate	DOTA-TATE		^{111}In ^{90}Y ^{177}Lu ^{68}Ga	n.a. 2, (5) n.a. 2, (4,5)	 [26] [26]
DOTA-[Nal^3]-Octreotide	DOTA-NOC		^{111}In ^{177}Lu ^{68}Ga	2,3,(4),5 2,3,5 2,(3,4),5	[28] [28] [28]
DOTA-[Nal^3]-Octreotate	DOTA-NOCATE		^{111}In ^{90}Y ^{177}Lu ^{68}Ga	2,3,(4),5 2,(3),5 2,(3),5 2,(3,4,5)	[27] [28] [28] [28]
DOTA-Lanreotide	DOTA-LAN		^{111}In ^{90}Y ^{68}Ga	2,3,4,5 (2,3),5 n.a.	[29] [26]

*Affinity: Estimates of the inhibitory constant (IC_{50}) for the binding of radioligand are <20 nM and present high affinity binding for the subtypes as listed. Subtypes in brackets are estimates for the IC_{50} in the range of 50–500 nM and present moderate to lower affinity binding. The representation is based on data published in the literature (references as listed).

surface, such as those for vasoactive intestinal peptide (VIP) [9,21], bombesin [22,23], substance P [24], and neurotensin [25], have also been suggested as possible molecular targets.

Peptide radiopharmaceuticals as molecular agents

On the basis of SSTR-expression, a variety of SST-based radiopharmaceuticals have been synthesised and comparatively investigated for their *in vitro* binding properties to the five SSTR subtypes (Table 1).

^{111}In-DTPA-D-Phe^1-octreotide, which binds preferentially to the SSTR subtype 2, was the first radiopharmaceutical available on the market (OctreoScan®). This radiopharmaceutical was further improved to yield **^{111}In-DOTA-D-Phe^1-Tyr^3-octreotide** (^{111}In-DOTA-TOC), which shows a similar *in vitro* and *in vivo* binding capacity, but a higher affinity and increased internalisation rate [30]. In this molecule, Phe^3 was replaced with Tyr leading to increased hydrophilicity of the radiolabelled peptide.The purpose of this development was to create a ligand which can be stably labelled with ^{90}Y and ^{177}Lu for peptide receptor radionuclide therapy (PRRT) [31–34]. DOTA is a universal ligand for labelling with trivalent metal ions, which also provided the basis for the development of the PET-tracer **^{68}Ga-DOTA-Tyr^3-octreotide** (^{68}Ga-DOTA-TOC) [35]. Interestingly, exchange of ^{111}In by ^{68}Ga also leads to an improved biodistribution and increased tumour uptake [28]. Several other SST peptide analogues have consequently been developed. Among these,

DOTA-Tyr^3-octreotate (DOTA-TATE) shows a higher binding affinity exclusively to the SSTR subtype 2, whereas **DOTA-lanreotide (DOTA-LAN)** [36], **DOTA-1-Nal^3-octreotide** (DOTA-NOC) and **DOTA-1-Nal^3-octreotate** (DOTA-NOC-ATE) bind to a higher variety of SSTR subtypes [28]. DOTA-NOC showed a 3–4 times higher binding affinity for SSTR2 than DOTA-TOC together with a good affinity for SSTR3 and SSTR5, leading to an improved tumour uptake and kidney to tumour ratio [37–39]. The enhanced tumour uptake of these ligands seems to be related to improved SSTR2 and SSTR3 internalisation, evidenced by the demonstration that even highly potent SSTR5 agonists, such as KE108, BIM-23244, and L-817,818 are not able to induce SSTR5 internalisation [11].

The ligands mentioned above have been labelled with ^{111}In and ^{68}Ga for diagnosis, as well as with ^{90}Y or ^{177}Lu for PPRT.

In addition, **^{64}Cu-TETA-octreotide** (where TETA is 1,4,8,11-tetraazacyclotetradecane-N,N′,N″,N‴-tetra-acetic acid) has also been described as possessing a high sensitivity, favourable dosimetry and pharmacokinetics in NET patients [40] for potential use both for PET and PPRT. Furthermore, several efforts have been made to label octreotide-derivatives with ^{99m}Tc for single photon emission computed tomography (SPECT) applications [37,41]. **^{99m}Tc-N-α-(6-hydrazinonicotinoyl)-Tyr^3-octreotide** (HYNIC-TOC, Tectrotyd®) shows excellent image quality in NET patients [41–43].

Radiolabelled VIP [44–46], bombesin [47–49], gastrin, gastrin-releasing peptide (GRP), cholecystokinin (CCK) [50–52], neurotensin [53–55], and substance P [56], among other peptides, have also been implemented for clinical use.

Non-peptide molecular targets

Metaiodobenzylguanidine (mIBG) is the combination of the benzyl group of bretylium and the guanidine group of guanethidine. Since mIBG structurally resembles norepinephrine, it enters neuroendocrine cells by an active uptake mechanism and is stored in the neurosecretory granules [57]. Radioiodinated (^{123}I, ^{131}I) mIBG is used to image and treat NETs, particularly those of the sympatho-adrenal system (pheochromocytomas, paragangliomas and neuroblastomas), although other NETs (e.g. carcinoids, medullary thyroid carcinoma (MTC), etc.) are also candidates for diagnosis and treatment with ^{131}I-mIBG. mIBG was shown to be less sensitive for detecting metastatic lesions of NET patients [58,59].

In addition, **^{11}C-5-Hydroxy-tryptophan (^{11}C-HTP)-PET** [60] and **^{18}F-fluoro-L-3,4-dihydroxy-phenyl-alanine (^{18}F-DOPA)-PET** [61,62] also hold promising results in NET patients. ^{18}F-DOPA is usually prepared by an electrophilic pathway using fluorodemetallation of a stannylated derivative of levodopamine in a reaction with molecular [^{18}F]fluorine followed by hydrolysis of protecting groups and final purification. It is cyclotron-dependent in contrast to ^{68}Ga-labelled tracers and has a limited commercial availability. The synthesis of ^{11}C-HTP, starting from ^{11}C-CO_2, is a highly complex multi-step procedure. With the short half-life of C-11 of 20 min this tracer is only available at a few highly specialised cyclotron centres in the Netherlands and Sweden.

The high rate of positive DOPA-PET scans has also promoted the development of new chimeric molecules combining the binding to the dopamine D2 receptor as well as the SSTR subtypes 2 and 5 (i.e. BIM-23A760).

^{18}F-Fluorodeoxyglucose (FDG)-PET is another widely accepted imaging approach in clinical oncology, reflecting increased expression of glucose transport in malignant tissue. It is widely commercially available and prepared using ^{18}F-fluoride by nucleophilic substitution of the precursor mannose triflate, followed by hydrolysis and purification in automated synthesis modules. In combination with CT the functional findings can be morphologically correlated which results in a high-confidence image interpretation. Although ^{18}FDG-PET shows high spatial resolution it is not, unlike the case for many other malignancies, primarily indicated for NET because of its poor sensitivity to detect tumours with low metabolic activity and slow growth [63]. However, recent data have shown that ^{18}F-FDG PET, together with ^{68}Ga-DOTA-TOC PET, has considerable impact in the follow-up of patients treated by PRRT, and may change the management in approximately one third of NET patients [64].

Diagnosis

Peptide radiopharmaceuticals

Today, SSTR scintigraphy using the above mentioned radiolabelled peptide radiopharmaceuticals, in particular long-acting octreotide analogues, is established in clinical practice. Since its implementation in the late 1980s [65,66], SSTR scintigraphy has improved the ability to diagnose, detect, stage and review the response to therapy in patients with NETs. Clinical studies with ^{111}In-DTPA-OC have clearly shown that this radiopharmaceutical is effective in diagnosing and

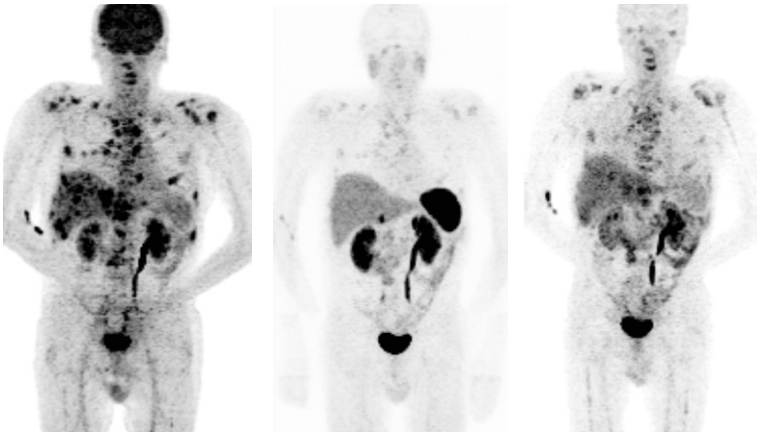


Fig. 1. Comparative SSTR PET scans in a 70-year-old man with poorly differentiated neuroendocrine carcinoma (primary tumour in the rectum). Whereas ^{68}Ga-DOTA-TOC did not indicate significant uptake of the tracer, ^{18}F-FDG and ^{68}Ga-DOTA-LAN indicated metastatic disease spread.

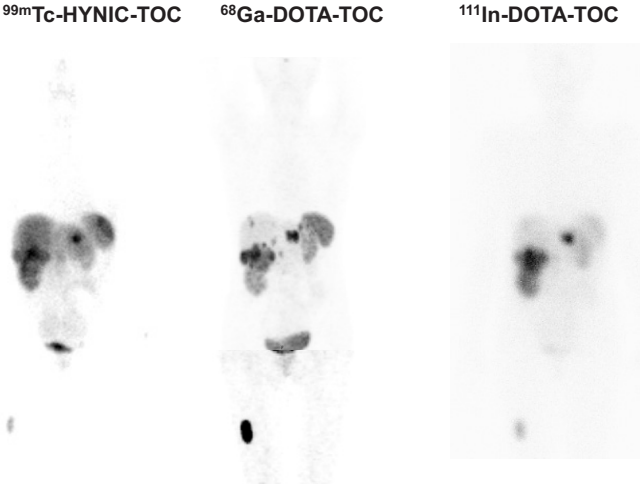


Fig. 2. Comparative somatostatin receptor scintigraphy. Comparative scintigraphy with three different SST receptor tracers in a 48-year-old woman. After surgery of the primary tumour (small bowel carcinoid) multiple liver metastases and a single bone metastasis (right femur) were depicted by all three radiotracers. Left: ^{99m}Tc-HYNIC-TOC whole body scan (a.p.) at 4 h postinjection of 400 MBq. Middle: ^{68}Ga-DOTA-TOC whole Body PET at 90 min postinjection of 200 MBq. Right: ^{111}In-DOTA-TOC whole body scan (a.p.) at 24 h postinjection of 200 MBq.

staging tumours and their metastases, due to binding to hSSTR2 [67,68]. The use of a germanium-68/gallium-68 generator provides the basis for convenient, easy production of ^{68}Ga-DOTA-TOC, and other peptides, which can be completed within 30 min using the DOTA-derivatised octreotide analogue [69]. This also guarantees a high flexibility and availability for clinical routine in contrast to the ^{11}C- or ^{18}F-labelled compounds which are cyclotron-dependent.

A comparative study of ^{111}In-DOTA-LAN and ^{111}In-DTPA-OC or ^{11}In-DOTA-TOC has shown discrepancies in the tumour uptake pattern in approximately one third of patients [70]. Similar discrepancies were found for the ^{68}Ga-labelled octreotide and lanreotide analogues (Fig. 1 [71]). SSTR-PET/CT with ^{68}Ga-DOTA-TOC [7,72,73] or ^{68}Ga-DOTA-NOC [74]) is superior in the detection of NET lesions as compared to conventional SPECT/CT (Fig. 2). The higher sensitivity for tumour detection of PET/CT has a clinical impact in a considerable number of patients. Furthermore, in clinical applications performed with the ^{111}In and ^{68}Ga radiolabel, more

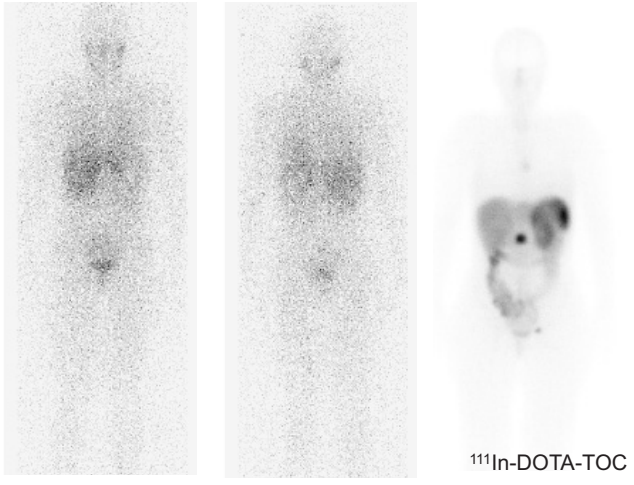


Fig. 3. Comparative scintigraphy with ^{123}I-mIBG and ^{111}In-DOTA-TOCT in a 35-year-old woman with a poorly differentiated NET of the upper abdomen. After removal of the primary tumour, a single bone metastasis in the thoracic spine was clearly depicted only by the SSTR tracer at 24 h postinjection.

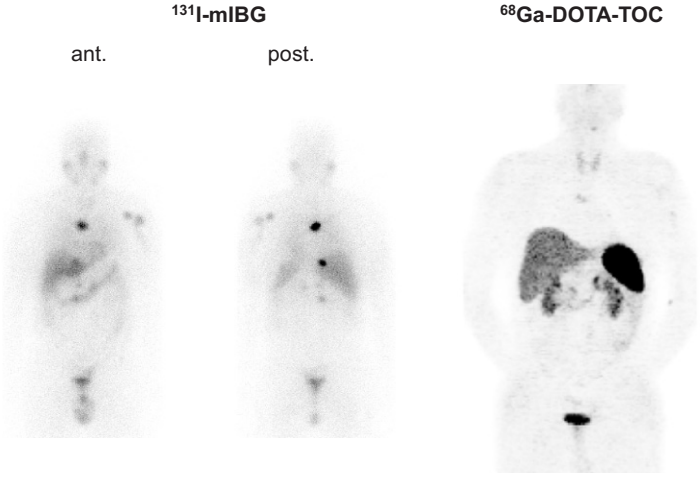


Fig. 4. Comparative scintigraphy with ^{131}I-mIBG and ^{68}Ga-DOTA-TOC in a 59-year-old man with metastatic pheochromocytoma. After removal of the primary tumour in the area of the right adrenal gland, several larger bone metastases were clearly indicated only by the mIBG tracer (postherapeutic scan postinjection of approx. 4 GBq ^{131}I-mIBG).

lesions could be detected with ^{68}Ga-DOTA-NOC in comparison to ^{111}In-DOTA-NOC and ^{99m}Tc-EDDA-HYNIC-TOC [74]).

Similar to lanreotide, the newer analogue 1-Nal3-octreotide (NOC) shows a broader receptor binding profile with higher binding affinities for hSSTR3 and hSSTR4, resulting in a higher whole body dose. Therefore, ^{90}Y-DOTA-TOC or ^{177}Lu-DOTA-TOC should be considered as first choice radiopharmaceuticals for experimental SSTR-based therapy in patients with NETs. Furthermore, a recent direct dosimetry comparison of ^{177}Lu-DOTA-TOC and ^{177}Lu-DOTA-TATE [75]) in a small number of patients showed a longer residence time of DOTA-TATE in tumour and kidneys, therefore suggesting a superiority in comparison with DOTA-TOC. Further studies are necessary to determine not only which peptide analogue is preferable for PRRT but also for which specific NET entity.

Other radiolabelled peptides, as mentioned above, have not found their way into broad clinical use.

Non-peptide molecular targets

MIBG can be radioiodinated with either ^{131}I or ^{123}I (Figs. 3,4). Theoretical considerations and clinical experience indicate that the ^{123}I-labelled agent is considered to be the radiopharmaceutical of choice, at

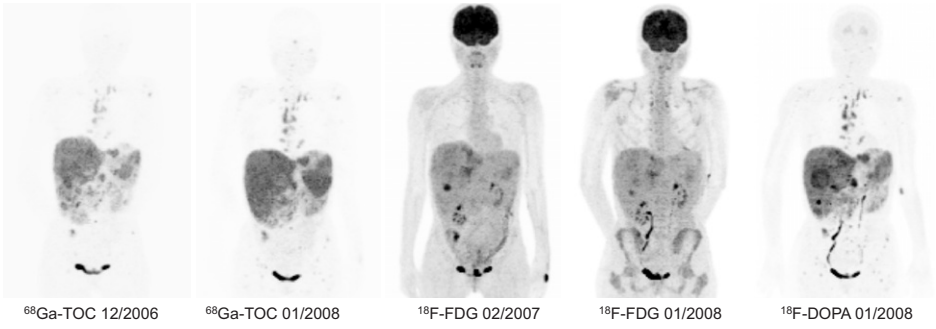


Fig. 5. Follow-up of PRRT (six cycles ^{90}Y-DOTA-TOC; 12.6 GBq, acc. dose) with ^{68}Ga-DOTA-TOC PET. The patient is a 44-year-old woman with a neuroendocrine carcinoma of the terminal ileum. Despite multiple metastases in the liver, peritoneum, bone and lymph nodes, the patient remained relatively stable. In this patient the ^{18}F-L-DOPA-PET scan showed a similar update pattern as ^{68}Ga-DOTA-TOC.

least in children, as it has a more favourable dosimetry and provides better image quality.

In small groups of patients with a variety of NETs, **^{18}F-L-DOPA** PET [62,76] and **^{11}C-5-HTP**-PET have shown promising results, and in some reports have proved better than conventional SSTR SPECT. Imaging results, however, are not directly comparable as no study has yet been published in which the imaging capability of these two PET tracers has been compared. PET with ^{11}C-5-HTP [60] visualised NET lesions in 95% of patients, compared to 84% using SPECT and 79% using CT. ^{18}F-L-DOPA-PET also holds promising results in NET patients with a sensitivity of at least 95% versus 79% for SPECT/CT and 57% for CT alone [29]. The high rate of positive L-DOPA-PET scans in patients with NETs has promoted the development of new chimeric molecules combining binding to the dopamine D2 receptor as well as the SSTR subtypes 2 and 5 (i.e. BIM-23A760). However, the clinical significance of positive SSTR- and L-DOPA-PET scans, and their relationship to each other remains to be determined (Fig. 5 [61]). Although the reports with these PET tracers are encouraging, additional comparative studies in a larger number of patients are needed. While ^{18}F-FDG-PET is not indicated for the primary staging of NET patients it has potential together with the SSTR PET radiopharmaceuticals, or the radiolabelled amine precursors, in the follow-up of patients under PRRT [63].

Somatostatin receptor-based peptide receptor radionuclide therapy

General approaches

Evaluation of the type of peptide radiopharmaceutical used for SSTR-targeted therapy, based on the scintigraphic pattern and dosimetric studies, should always be performed for the individual NET patient because of the above mentioned discrepancies concerning both tumour uptake and detection of tumour lesions between the different radiopharmaceuticals.

Patient selection and timing

In principle, all patients with NETs known to express SSTR are eligible for high-dose therapy, provided that the tumours demonstrate sufficient uptake of the radiolabelled peptide upon imaging. In general, the clinical protocols available were designed such that tumour uptake is controlled by dosimetry, or at least by repeated scintigraphic studies which score the tumour uptake prior to, as well as during, the whole treatment and follow-up period. It is a general understanding that patients with low proliferating tumours with a Ki-67 <3% should receive biotherapy, SST analogues, alpha interferon, or combinations of both. Patients with high proliferating tumours with a Ki-67 above 10% are usually first treated with cytotoxic treatment, streptozotocin plus 5-fluorouracil (5-FU), or cisplatin plus etoposide [77]. At progression, tumour-targeted radiotherapy is considered. In fact, so far, mostly patients with an advanced stage of disease have been treated with peptide receptor-mediated radionuclide therapy. Usually, patients who were included in therapeutic trials had multiple sites of disease as evidenced by scintigraphic and dosimetric evaluation with ^{111}In-/^{99m}Tc-labelled peptides [42,43,78] and/or by imaging with PET performed with ^{86}Y-/^{68}Ga-labelled peptide analogues [35]. The various response rates reported for PRRT may at least be in part due to differences in patient selection. It is still a matter of discussion at which stage of the disease treatment should be started. Most of the NET patients treated so far had no other treatment option, were refractory to conventional treatment strategies and/or were at a progressive stage upon the first treatment. In fact, a "*wait and watch*"

attitude is not justified any longer as results from larger trials are nowadays available [2].

Discontinuation of treatment

Usually, treatment is discontinued if the patient shows progressive disease (PD) under treatment, or in case of dose-limiting toxicity (mostly regarded as failure of kidney function).

Dosimetric evaluation

Adequate dosimetry prior to peptide therapy is mandatory and the most effective surrogate should be used, i.e. for instance ^{86}Y-DOTA-TOC for ^{90}Y-DOTA-TOC therapy. However, such isotopes are limited to only a few centres and a more widely feasible method should be used. In fact, recent data have shown that there exists only minimal difference in the pharmacokinetics of ^{111}In-DOTA-TOC and ^{177}Lu-DOTA-TATE [79]. Practically, if individual dosimetry is performed and if several treatment cycles are planned, dosimetry would be most adequate when being performed during the first treatment cycle by adding the ^{111}In-labelled substance.

The primary critical organ with PRRT is the kidney because small peptides are filtered through the glomerular capillaries and are reabsorbed by the proximal tubular cells. From external beam radiation, the critical dose to the kidneys is set in most protocols to about a 30 Gray (Gy) (or below) accumulative dose of the radiopeptide. It is thus recommended to use positively charged amino acids such as L-lysin or L-arginine to reduce renal uptake of the radiopeptide [80,81]. No definitive data are available on the relationship between absorbed dose and irreversible renal toxicity for internal radiotherapy. Therefore, patients should not be excluded from a beneficial treatment due to strict settings which are not proven and which can be overcome. The therapeutic situation is best displayed by the reality that most of the patients have already undergone potentially nephrotoxic or haematotoxic therapies such as ^{131}I-mIBG or cisplatin.

Dose and administration of radiolabelled peptide

Route of administration

The administration of radiolabelled peptides was done either intravenously, intra-arterially or intra-tumourally.

Cumulative dose

In most protocols an estimated kidney dose of about 30 Gy (critical dose derived from external beam radiation) is considered as maximum for the accumulated administered dose. Therapeutic applications are repeated if the patient does not show dose-limiting toxic reactions (i.e. World Health Oranisation (WHO)-grade IV haematological toxicity or grade III non-haematological toxicity), has stable disease (SD) or tumour regression (partial response (PR), minor response (MR)) with measurable persistent disease, and if the blood count, levels of hepatic and renal function, and performance status are in the range of that originally required for patient entry into the study.

Therapeutic response

Response of tumour lesions – disease burden

Evaluation of the tumour response is performed according to WHO standard criteria. As with other treatment modalities, CT and/or MRI are performed repeatedly to measure tumour burden and to document response to therapy. A tumour size to dose-response relationship is documented in most studies. In general, the smaller the tumour lesions at study entry were, the better the response to PRRT was. Patients with less liver involvement seem to respond better than those with extensive liver burden.

^{111}In-DTPA-D-Phe^{1}-octreotide (OctreoScan®)

The Rotterdam group pioneered radionuclide treatment with ^{111}In-DTPA-OC (OctreoScan®). Initial results published for the first time in 1994 indicated a significant therapeutic potential for patients with SSTR-expressing tumours [31,32]. Subsequent studies [82,83], despite improved clinical status, showed a low rate of side effects. However, CT-measurable tumour decrease was rare. Improved outcome was seen when 5-FU chemotherapy was added as a radiosensitising agent [84].

^{90}Y-DOTA-D-Phe^{1}-Tyr^{3}-octreotide (^{90}Y-DOTA-TOC)

Despite differences in the protocols used since its first application by the Basel group, complete remission (CR) was rarely reported. PR or MR in most of the studies were around 25%, the SD rate was around 50%, which gives an overall response rate to PRRT of about 75%. These results are better than those obtained with the ^{111}In-DTPA-OC as mentioned above [82–84].

The Basel group was the first to report the *in vivo* administration of ^{90}Y-DOTA-TOC in patients with

NETs [33,34,85–87]. In their first group of patients a dose-escalating treatment scheme was applied with a cumulative dose of 6 giga-becquerel (GBq)/m^2 [86]. Later, in four treatment cycles [87] or two treatment cycles [88], the treatment substance was given up to a cumulative dose of 7.4 GBq/m^2. Tumour response was found in 23% [87] and 33% [88], respectively. Whereas the first applications were done without renal protection, all later studies were performed under amino acid infusion, and there were differences in patient selection and histopathology of the NET, respectively.

The Milano group injected up to 5.2 GBq per cycle which they defined as the maximum tolerated dose per cycle [89,90]. The group reported a response rate of 29% in patients with 21 GEP tumours after two treatment cycles with a cumulative dose of 5.9–11.1 GBq [91]. The Milano summary [92] includes 141 patients from whom 114 patients were affected by NETs, and 59 patients had GEP tumours. An overall objective response was observed in 26% (PR, CR) of patients. Considering the progressive status of disease in 80% of patients, an overall clinical benefit was observed in 76% (CR, PR, SD). Stable patients showed a response (CR,PR) in 32% of patients. The duration of response was 2–59 months with a median of 18 months overall, and a median of 13 months in progressing patients, and 16 months in stable patients.

The Rotterdam group together with centres in Brussels (Belgium) and Tampa (Florida, US) injected escalating doses up to 14.8 GBq in four cycles, or up to 9.3 GBq in a single administration [93]. These administrations were done upto a cumulative radiation dose to the kidneys limited to 27 Gy and all 54 patients received amino acids concomitantly for kidney protection. PR was measured in 7% and MR in 13%. The median time to progression in 44 patients who had stable disease was 30 months.

The group of Iowa City [94] reported an overall clinical response of 66% in 21 patients with GEP allowing a total cumulative dose of 13.3 GBq in three cycles.

The Bad Berka group [95] summarised results from 57 patients treated with 3.25 GBq up to six times within a 3–6 month time interval between each treatment cycle. Despite that, no CR was seen, 20% of patients had PR and 60% had SD, providing an overall clinical benefit of 85%.

Since 1997 Innsbruck has treated patients with ^{90}Y-DOTA-TOC (Fig. 6 [96]). In general, our current treatment schedule foresees three to four cycles with 3.7 GBq, given under kidney protection with amino acids, up to a cumulative kidney dose of 28 Gy. If the patient shows response to therapy in terms of MR, PR or SD, a further one to three treatment cycles are added individually according to the clinical status of the patient. Radioactive treatment is usually applied every 10 weeks with long-acting octreotide, or lanreotide, respectively, (two injections) between the radioactive treatments. Restaging is done in all patients with ^{68}Ga-DOTA-TOC-PET and repeated dosimetry with ^{111}In-DOTA-TOC. All patients also undergo repeated ^{18}F-FDG-PET scanning during the follow-up period. The response rates have not changed over the last decade with about 50% stabilisation of disease and 25% PR or MR. CRs, as shown in Fig. 6, over a longer period of time, have rarely been seen.

^{177}Lu-DOTA-Tyr^3-octreotate (^{177}Lu-DOTA-TATE)

Reports with larger numbers of patients in treatment protocols with ^{177}Lu-DOTA-TATE are limited to the Rotterdam [97,98] and Bad Berka [99] groups. Remission rates were higher in patients with high pre-therapeutic uptake and a limited number of liver metastases, whereas PD was more frequent in patients with a low performance score and extensive disease. In 131 patients, cumulative doses of 22.2–29.8 GBq were applied, and CR was observed in 2%, PR in 26%, MR in 24%, and SD in 35% of patients. In 504 patients, 458 with GEP NETs [98], the Rotterdam group recently reported an update of their initial treatment applications: a survival benefit of 40–72 months from diagnosis, compared with historical reports, with a median time to progression of 40 months was observed. Furthermore, only a few adverse effects were seen. CR or PR occurred in 2% or 28%, respectively, and MR in 16% of patients.

Also, the Basel group [100] reported on 27 patients pre-treated with ^{90}Y-DOTA-TOC. Patients received a fixed dose of 7.4 GBq ^{177}Lu-DOTA-TATE. Restaging after 8–12 weeks showed PR in two patients, MR in five patients, and SD in 12 patients, suggesting a safe and efficacious form of retreatment modality. The time of remission ranged from 4–13 months. These authors suggested that a positive prognostic factor for further radionuclide treatment with ^{177}Lu-DOTA-TATE obviously exists in a good response to ^{90}Y-DOTA-TOC.

At Innsbruck, we have involved in this kind of PRRT mainly patients who had previously already undergone yttrium-90-labelled PRRT (Fig. 7 [96]) and who were showing PD at the time of referral.

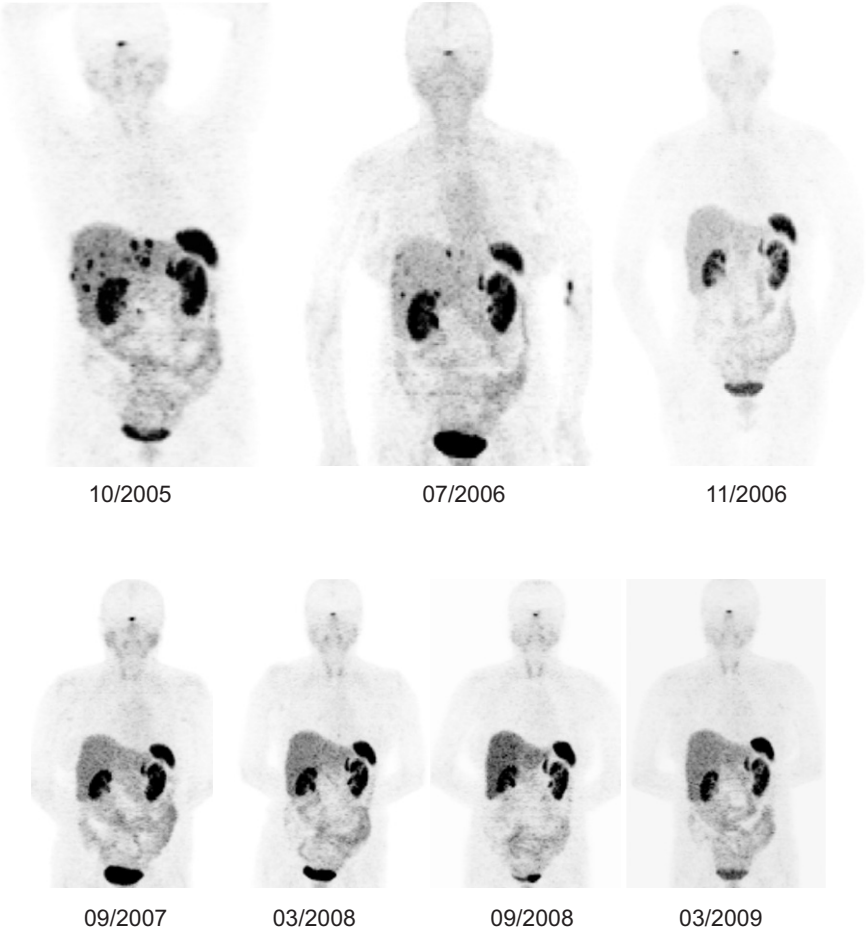


Fig. 6. Long-term follow-up of PRRT (nine cycles ^{90}Y-DOTA-TOC, 10 GBq, acc. dose; four cycles ^{177}Lu-DOTA-TATE; 29 GBq acc. dose) with ^{68}Ga-DOTA-TOC PET. The patient is a 59-year-old woman with NET of the pancreas with liver metastases. In addition to PRRT, the patient received long-acting octreotide over the years. CR has been documented in this patient over the last 2 years now.

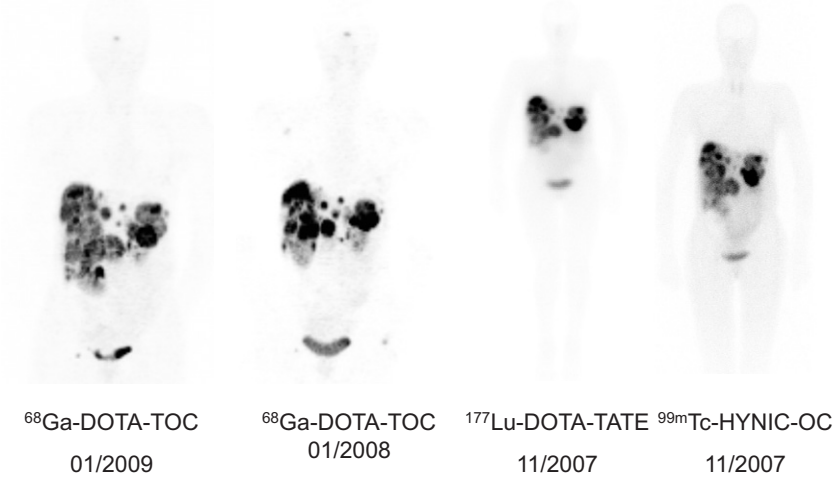


Fig. 7. Follow-up of PRRT (six cycles ^{177}Lu-DOTA-TATE; 26.9 GBq, acc. dose) with ^{68}Ga-DOTA-TOC PET. The patient is a 39-year-old woman with a carcinoid of the pancreas and partial pancreas resection and splenectomy in 07/2007. The patient was staged with ^{99m}Tc-HYNIC-TOC in 11/2007 prior to PRRT which resulted in stable disease over 1 year follow-up.

^{90}Y-DOTA-Tyr^3-octreotate (^{90}Y-DOTA-TATE)

Among others, the Bad Berka group reported objective tumour response in 85% of the patients. Beside tumour shrinkage, significant clinical response was seen in terms of symptom reduction, low toxicity and few adverse effects. The Bad Berka group [101] reported in 75 patients a rate of 37% PR and SD in 52%; thus objective clinical benefit was seen in 85% of the patients. In this study the mean activity applied was 3.6 GBq, and the time between the cycles ranged from 3–6 months. Beside tumour shrinkage, significant clinical response was seen in terms of symptom reduction, low toxicity and few adverse effects.

^{90}Y-DOTA-NOC and -NOC-ATE, ^{177}Lu-DOTA-NOC and NOC-ATE

These new SST analogues were recently used for treatment in patients in whom a higher ^{111}In-DOTA-NOC uptake, as compared to OctreoScan, was measured [102]. As with lanreotide analogues (see below), due to binding to a broader spectrum of SSTR, especially hSSTR3, a higher background activity is observed, as well as higher doses to normal organs. In-line with this observation, despite higher tumour uptake, the Bad Berka group [103] discontinued treatment with this substance.

^{90}Y-DOTA-lanreotide

The first applications of a low dose of ^{90}Y-DOTA-LAN (1 GBq) for PRRT have already indicated tumour size reduction and improved quality of life in advanced NET patients [104]. About 10% of all NETs exhibit higher uptake when compared to octreotide analogues, and thus implicate a more successful treatment option. These tumour types include MTCs, thymomas, neuroendocrine carcinomas and small cell lung cancer (SCLC). Subsequently, the results of the European study "MAURITIUS" (Multicenter Analysis of a Universal Receptor Imaging and Treatment Initiative, a eUropean Study) confirmed the potential usefulness of ^{111}In/^{90}Y-DOTA-LAN for diagnosis/therapy in 154 patients with different tumour entities expressing hSSTR [104]. The 5-year follow-up of the MAURITIUS trial [105] analysed the data of 235 patients with NETs, thymoma, thyroid cancer, brain tumours, lymphoma, intestinal adenocarcinoma and some rare tumours. Patients received an accumulated dose of up to 8.5 GBq of ^{90}Y-DOTA-LAN which was applied in up to seven treatment applications, given either intravenously (121 patients), intra-arterially (21 patients) [106], or by local intratumoural injection (93 patients). Patients had PD when entering treatment. The 5-year follow-up of intravenously treated patients showed that 37% (40/109) of the patients treated with ^{90}Y-DOTA-LAN had SD, and 18% (18/109) showed a PR. Objective response of quality of life measurements was documented in 10–20% of patients, and subjective response was found in 30–50% of patients. The new tracer ^{68}Ga-DOTA-LAN may provide helpful information in the pre-therapeutic work-up of patients suitable for therapy with ^{90}Y-DOTA-LAN (Figs. 1,8 [107]).

Time of progression of disease

In addition to evaluation of tumour disease response to treatment, the time to disease progression and the survival time are usually recorded.

Under therapy with ^{177}Lu-DOTA-TATE the median time to progression in 103 patients who had either SD or tumour regression was more than 36 months and thus is more beneficial as compared with chemotherapy [97]. In a recent report [98] the median time to progression was 40 months [98].

For ^{90}Y-DOTA-TOC, the Rotterdam group documented, in 44 patients with MRs, PRs or SD, a median time to progression of 30 months [93]. The Milano group reported a median duration of response of 9 months for a group of 21 patients [91].

Long-term and survival results of patients treated with ^{90}Y-DOTA-LAN therapy are available in form of a 5-year follow-up in patients with radioiodine-negative thyroid cancer including MTC [105]. An improved progression-free and overall survival was also reported by the London group [108].

Response of biochemical parameters

Several circulating or urinary markers can be used for the diagnosis and follow-up of functioning and clinically non-functioning NETs. Among the specific markers are serotonin and its metabolites in carcinoid tumours and the carcinoid syndrome, insulin and its precursors in insulinomas, and gastrin in gastrinomas. Of the non-specific tumour markers the most used are chromogranin A (CgA) and neuron-specific enolase (NSE). Indeed, CgA is currently the most sensitive marker in patients with metastatic gastrointestinal NETs and, in general, plasma CgA levels correlate with GEP-NET bulk. Changes in tumour marker serum levels (such as in serotonin, gastrin, CgA, NSE, VIP, or thyreoglobulin) have frequently been reported. We have shown correlation of response to PRRT with CgA levels [109].

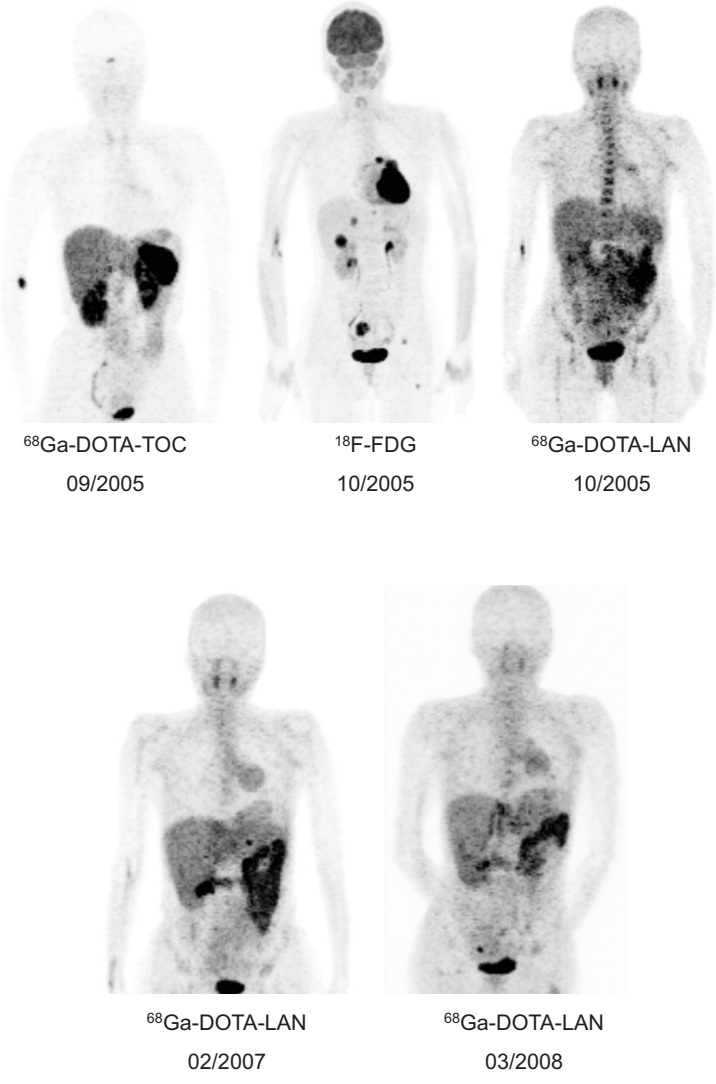


Fig. 8. Follow-up of PRRT (seven cycles ^{90}Y-DOTA-LAN; 12.6 GBq, acc. dose) with ^{68}Ga-DOTA-LAN PET. The patient is a 45-year-old woman with an atypical lung carcinoid. After recurrence of disease in the right thoracic region, peritoneal metastases, metastases adjacent to the stomach, as well as bone, liver and cerebellar metastases, were also found. In addition to PRRT, the patient also received polychemotherapy and external beam radiation due to compression of the spinal cord in 12/2007. The follow-up I^{68}Ga-DOTA-LAN PET scans indicated stable disease, despite a relatively good quality of life. In this patient the ^{68}Ga-DOTA-TOC PET was negative at primary staging in 2005.

PRRT and "quality of life"

In symptomatic patients, treatment with long-acting SST analogues is the therapy of choice and is highly effective in these patients for symptom reduction. Following treatment with radiolabelled SST analogues in patients with metastatic disease, with or without systemic therapy with long-acting SST analogues, and regardless of its effects on tumour shrinkage, an improved quality of life was repeatedly reported. By using the generally accepted European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30) [110] we have evaluated the impact of radionuclide treatment in patients undergoing PRRT. A reduction of general pain, bone pain reduction or relief, reduction of headache, and improvement of sleeping behaviour, appetite, weight and general well-being were found. Most patients with subjective improvement reported this after a single injection. The response of improved quality of life was not dependent on the tumour response, and was also observed in patients with PD.

In a more recent study, significantly improved global health and quality of life parameters were also reported for treatment with ^{177}Lu-DOTA-TATE in patients with metastasised GEP tumours [111]. The score significantly increased 6 weeks after therapy.

Furthermore, significant improvement was observed in the role, emotional and social function scales. The symptom scores for fatigue, insomnia and pain were significantly decreased. Most significantly, patients with PD also indicated an improvement in their global health score.

Side effects

Side effects of PRRT mainly concern the critical organs, the kidneys and bone marrow. Acute toxicity consists of a transient reduction in blood cells, with the nadir occurring 3–5 weeks after therapy. Nausea and vomiting frequently reported by the patients appear to be related to the co-administration of renal protective agents.

Renal toxicity

Using octreotide derivatives (^{90}Y-DOTA-TOC or ^{177}Lu-DOTA-TATE) a few patients were seen with reduced renal function, and over years, with chronic renal failure. Several alternative amino acid regimens have been investigated showing a large inter-patient variation [80,81,91,92,112]. It is likely that the maximal tolerated dose can be increased in the future by more individually tailored dosimetry models and also by the introduction of new protective agents and different treatment schedules.

Bone marrow toxicity

Using octreotide derivatives (^{90}Y-DOTA-TOC or ^{177}Lu-DOTA-TATE) grade 3 and 4 haematological toxicity were reported in a small number of patients (roughly 10% of all patients treated) throughout the various clinical trials (for review see [113]).

Impact of concomitant therapy with long-acting SST analogues

Tumour shrinkage was repeatedly reported following the application of long-acting analogues (for review see [2]). However, the doses used in many of the trials seem to be far too low for exerting a marked tumour response. In our patients, we are following a treatment schedule that changes between cold and radiolabelled SST analogue. In fact, the PROMID study (30 mg intramuscular every 4 weeks) showed that long-acting octreotide improves the time to tumour progression in patients with metastasised, well-differentiated midgut NETs [4].

Non-somatostatin receptor-based peptide receptor radionuclide therapy

Besides SSTR, receptors for other regulatory peptides are also frequently over-expressed in NETs [114]. Among them gastrin/CCK analogues binding to CCK receptors are garnering increasing interest especially in the diagnosis and therapy of metastatic MTC. Gastrin analogues showing a superior selectivity and affinity for CCK-2 receptors, the receptor subtype mainly expressed in tumours, have been extensively investigated for possible applications in nuclear medicine [115].

The first generation of minigastrin (MG) analogues based on D-Glu^1-minigastrin (MG0) radiolabelled with ^{111}In and ^{90}Y display a very high kidney uptake *in vivo* [116,117] and severe nephrotoxic side effects have been reported in first therapeutic applications in humans [118]. Kidney uptake was related to the pentaglutamic chain in the peptide sequence [119] and was successfully reduced in the second generation of minigastrin analogues missing this sequence (MG11) [120]. However, decreasing the number of glutamic acid residues, besides increasing the tumour-to-kidney ratio, was shown to progressively decrease enzymatic stability of the peptide conjugate [121].

The recent finding that minigastrin and CCK analogues also bind to a splice variant of the CCK-2 receptor, CCK-2i4svR, over-expressed in colorectal and pancreatic cancer opens up new perspectives for gastrin receptor (GR) scintigraphy and PRRT [122].

Considering the low kidney retention of the second generation of MG analogues and potential further stabilisation strategies, this new class of peptide analogues targeting CCK-2 receptors holds promise for new developments for PRRT in the near future.

In clinical trials GR scintigraphy with ^{111}In-DTPA-MG0 proved a higher tumour detection rate in comparison with SSTR scintigraphy and ^{18}F-FDG PET [123]. GR scintigraphy can also provide additional information in the detection of neuroendocrine tumours, especially if SSTR scintigraphy is negative, and may possibly also allow the detection of small cell lung cancer [124].

Non-peptide molecular targets (^{131}I-mIBG)

Radioiodinated mIBG is indicated for the treatment of neural crest tumours such as inoperable malignant pheochromocytoma, paraganglioma, carcinoid tumour, Stage II or IV neuroblastoma and MTC following whole body and tumour dosimetry [125]. In general, several therapeutic doses (3.7–11.2 GBq) may be required to achieve an objective response to treatment.

Treatment may be repeated in 4–6 week intervals, and activity reduction should be considered in patients with myelosuppression and impaired renal function. It is supposed that the administration of a higher activity of mIBG will result in a higher radiation-absorbed dose, and a greater likelihood of response. However, owing to difficulties with image quantification, the relationship between administered activity and tumour-absorbed dose, and response to treatment, is under debate [126,127]. Recent treatment strategies proposed myelo-ablative combinations such as the combination of high-dose mIBG with topotecan in neuroblastoma patients [128,129] which requires stem cell support. For pheochromocytoma patients, for example, in a recently published literature review [130] CR or PR was found in 26% of 116 patients, while 57% of patients showed no relevant change. Obviously, prospective multicentre studies are required to evaluate the overall outcome of treatment with different mIBG doses in the various patient groups with neuronal crest tumours. Insufficient mIBG uptake can be identified in advance by diagnostic scintigraphy, and such patients are eligible for chemotherapy. Whether the reported responses to mIBG treatment have an overall impact on survival, or quality of life, is unclear since no randomised studies have been published.

Furthermore, it has to be mentioned that discordant results have been found between mIBG uptake and uptake of SST analogues in NET patients evaluated for therapy with one or the other radiopharmaceutical, making the treatment strategy even more difficult.

Future aspects

Combination of different radiopharmaceuticals

Because of the differences in biodistribution and critical organs, targeted therapy in NET patients such as combined therapy could provide a significant increase in the delivered tumour dose over either agent alone. The magnitude of increase depends on the relative dose delivered by each agent.

Therapy might be improved by a combination of ^{177}Lu- and ^{90}Y-labelled SST radiopharmaceuticals. The ^{90}Y gives a high dose to the tumour lesions and also to areas with low SSTR expression, in heterogeneous tumour tissue. Because of the strong crossfire effect, parts of the tumour that are either poorly differentiated, and therefore have a low density of SSTR2 subtypes, or poorly vascularised, can thus be reached.

A potential advantage of combined ^{131}I-mIBG and ^{90}Y-DOTA-TOC therapy was recently proposed by the Iowa group [131] suggesting that the optimal tumour dose for the combined agents may be achieved when the dose per activity delivered to the tumour by ^{90}Y-DOTA-TOC is 2–3 times that of ^{131}I-mIBG.

Combination of PRRT with novel molecular target therapies

With the growing advance in genomic and proteomic research our understanding of the basic mechanisms underlying the development and progression of the various NET entities will improve. Further developments may include new multimodal concepts, maybe leading to pathway-specific therapeutic strategies tailored to the individual biological background of the patient.

Targeted therapy combinations have demonstrated unique promise and also provide challenges related to timing, and dosage necessary to enhance efficacy and reduce overlapping toxicities. There exists emerging interest, in the oncological community and industry, in combining therapeutic radiopharmaceuticals with other modalities such as immunotherapy, radiotherapy or chemotherapy. Incorporation of PRRT into clinical protocols in combination with chemotherapy, immunotherapy or external beam radiation is an evolving new treatment option of future targeted therapy protocols (Fig. 9). In the field of neuroblastoma [132] the feasibility of ^{131}I-mIBG in combination with chemotherapy or myeloablative chemotherapy has been demonstrated. Many other combination possibilities are evolving and finding their way towards clinical trials.

Among many possibilities, the expression of tyrosine kinase receptors on NETs provide the basis for new tyrosine kinase inhibitors such as imatinib [133] or sunitinib [134] concomitantly used in future treatment protocols.

Other molecules include angiogenesis inhibitors (such as bevacizumab which may alone, or in combination with cytotoxic agents, have some significance). Rapamycin (RAD001), an inhibitor on the mTOR signalling pathway alone, or in combination with cytotoxic treatment, might become of value for treatment in NETs [135].

Our own early results [136] have indicated that chemotherapeutic agents may modulate SSTR expression on tumour cells. Such combination strategies have already found entrance into clinical trials [3]. Some beneficial effects were reported for the combination of temozolomide and thalidomide [137] or of irinotecan and cisplatin [138]. Capecitabine, a pro-drug of 5-FU, in low dose is being used together with ^{177}Lu-DOTA-TATE in an ongoing trial [139].

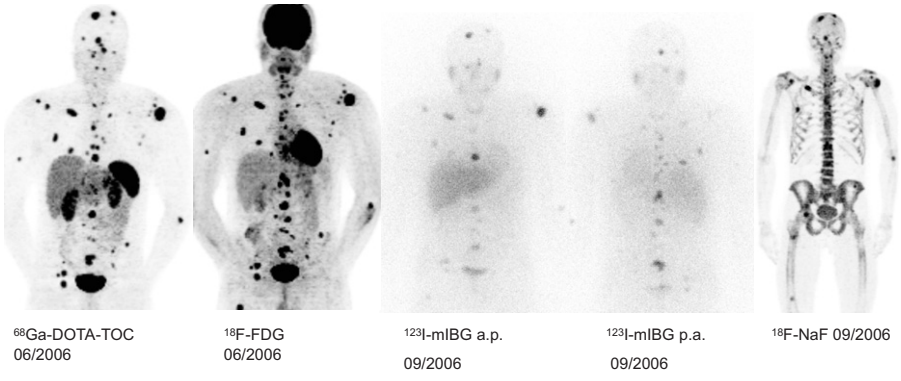


Fig. 9. Comparative scintigraphy with ^{68}Ga-DOTA-TOC, ^{18}F-FDG, ^{131}I-mIBG, and ^{18}F-NaF in a 30-year-old man with metastatic pheochromocytoma. In this patient, the uptake of both tracers was comparable, suggesting beneficial results of a combination therapy.

Conclusions

The highly variable natural course of the disease should always be considered. According to the results obtained so far, there can be no doubt about the wide therapeutic index and the high efficacy of SST analogues in the symptomatic management of NETs. In addition, the results of PRRT with long-acting SST analogues indicate that these molecular therapies have their place in the treatment of patients with SSTR-positive NETs for size reduction, improvement of quality of life and overall prognosis. Serious side effects are rare, especially when used in combination with amino acids for kidney protection. Patients should always be evaluated by preceding SSTR scintigraphy and dosimetry using respective octreotide or lanreotide analogues, preferably the ^{68}Ga-labelled ones for PET. ^{18}FDG-PET scanning shows a poor sensitivity to detect NETs with a low metabolic activity and slow growth rate, while together with the ^{68}Ga-labelled SST-analogues, ^{18}FDG-PET has clinical potential for the restaging of patients undergoing PRRT. The role of other PET radiopharmaceuticals, ^{11}C-5-HTP and ^{18}F-L-DOPA, for patients with NETs has to be comparatively assessed, and tumours may show unbelievable variation.

In general, there is a need for randomised trials in order to establish which treatment scheme and which radiolabelled SST analogue, or combination of analogues, is optimal for PRRT. There is also a great demand evolving for multi-institutional trials on the concomitant use of molecular therapeutics, but the availability of adequate facilities, and legislation, are restricting progress. One of the major problems is still the availability of these radiopeptides in general, and the request for new and cheaper therapeutic radionuclides in particular. For certain tumour entities ^{131}I-mIBG therapy is appropriate, and combination therapies with SST analogues are discussed.

The future treatment of NETs will be more individualised where the tumour biology and molecular genetics will play a major role. Future therapeutic trials should discuss the possibility of inclusion of patients at an earlier stage of disease, thereby enabling the evaluation of the possible potential of PRRT at an earlier stage of the tumour disease.

Conflict of interest statement

None declared.

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