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Review

Peptide receptor radionuclide therapy for advanced gastroenteropancreatic neuroendocrine tumors — from oncology perspective

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Abstract

Peptide Receptor Radionuclide Therapy (PRRT) is a form of molecular targeted therapy which is performed by using a small peptide (somatostatin analogue — SSA) that is coupled with a radionuclide beta emitting radiation. PRRT is a nuclear medicine for the systemic treatment of non-resectable, metastasized well/moderately differentiated, neuroendocrine tumours (NET) with overexpression of somatostatin receptor. These types of tumours include gastroenteropancreatic neoplasm (GEP-NENs), e.g. arising from the small bowel (often called carcinoid tumours), the pancreas, duodenum or stomach, but also from the large bowel or the lung and many other tissues (so called diffuse neuroendocrine system). The goal of PRRT is irradiation of tumour cells, via direct binding into specific receptor, somatostatin receptors (SSTR) family, overexpressed on the cell membrane of the primary tumours as well as on the metastasis. Over many years of clinical use of PRRT with ^{90}Y and current with ^{177}Lu DOTA conjugated somatostatin analogues proved to be efficient therapy option for NETs, with tumour responses, base on radiological evaluation. Also, a clinical response with symptoms relief and improvement in quality of life based on standard EORTC questioners is seen. Additional, common NET biomarker reduction and, ultimately, an impact on overall survival (OS) of patients with advanced non-resectable often progressive NEN can be expected. PRRT with ^{90}Y or ^{177}Lu-labelled peptides is generally well tolerated by most of the patients. The acute side effects (Adverse Events — AEs) are usually mild; most of them are related to the co-administration of amino acids (AA), such as nausea and vomiting. Others are related to the radioisotopes, such as fatigue or the exacerbation of endocrine syndromes, which are very rarely and they occurs, only in patients with functional tumours and large tumours burden. Chronic and permanent damage has an effect on target organs, particularly the kidneys and the bone marrow, which are generally mild. Currently, when ^{177}Lu DOTATATE is used, the potential risk to kidney damage is significantly reduced, compared to the previous usage of ^{90}Y labelled analogues. Up to now, kidney and bone marrow toxicity limits the dose of radioactivity of PRRT.

KEY words: PRRT, NET, therapy, somatostatin receptor

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Introduction

PRRT with radiolabeled somatostatin analogues (SSTA) is a reasonable option for treatment of non-resectable and/or metastasized, well/moderately differentiated, NETs [1–7]. The main goal of PRRT is to deliver the high dose of radiation to the tumour cells and a cross-fire effect that targeted nearby receptor-negative tumour cells, thus limiting the dose of irradiation of normal tissues. Radioisotope labelled synthetic somatostatin analogues (SST) are used by systemic administration with fractionated dose and in sequential cycles (usually 4–5) every 6 to 9 weeks [1, 2]. Currently, the potential risk of kidney and bone marrow damage limits the cumulative dose of radioactivity that may be administered.

The volume reduction of tumour burden can be seen, when tumour masses are irradiated with adequate doses of high energetic electrons [3–9]. Tumour response is associated with high uptake of radioisotopes on somatostatin receptor scintigraphy with ^{99m}Tc or, more recently, with ^{68}Ga-labeled octreotide/tate using PET technology [1, 2]. The therapeutic efficacy is related to a high affinity for somatostatin receptors subtype 2 (sst2) and moderate affinity

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for subtype 5 (sst5). However, tumour dose does not depend directly only on the administered activity and the uptake versus time, namely on the amount of energy released. The response also depends on tumour mass and biology of cancer cells with potential high resistant rate of tumour, even a high absorbed dose of energy deposition within cancer cells, due to high SSTR expression. Potentially, smaller masses have higher chances of reduction, owing to a higher absorbed dose in the tumour. Another factor influencing tumour irradiation, and therefore, the response, is the choice of the radionuclide. Each of the β emitters currently used for therapy, ^{177}Lu and ^{90}Y, shows some potential advantages. In particular, ^{90}Y electrons are highly energetic (E_{max} 2.27 MeV, penetration range R_{max} 11 mm, half-life $T_{1/2}$ 64 hours) and penetrating, leading to better crossfire through the tumour, which is particularly valuable in larger tumours and when heterogeneous receptor and/or activity distribution exists. The shorter half-life of ^{90}Y allows a higher dose rate. ^{177}Lu, on the other hand, has lower energy and smaller particle range, allowing a better absorption probably in smaller tumours, also has less toxicity to bone marrow and kidney [1, 2].

^{90}Y-octreotide [DOTATOC] was the first radiopeptide with beta emission used in PRRT; therefore, has been the most widely used in the first years of experience. Others peptides like ^{90}Y DOTALAN (DOTA Lanreotide) or ^{90}Y DOTATAE (DOTA Octreotate) were less common used in clinical practice. Unfortunately, all of the published results come from different and non-homogeneous, but most prospective clinical phase I and II trails.

Therefore, a direct comparison between the data sets of different studies isdifficult. However, even with these limitations of clinical use of PRRT, objective responses to the radionuclide therapy are recorded from 10% up to 34% of patients. Consider usually advanced stage of disease (CS IV), this seems to be quite effective way to treat patients with advanced, non-resetable usually progressive neuroendocrine neoplastic disease [3–7].

Currently most centres used ^{177}Lu DOTATATE. ^{177}Lu is a medium-energy β-emitter with a maximum energy of 0.498 MeV, mean 0.133 MeV and a maximal tissue penetration of 1.7 mm and mean 0.23 mm. Its half-life is 162 hours. ^{177}Lu also emits low-energy γ-rays at 208 keV and 113 keV with 10% and 6% abundance, respectively, which allows somatostatin receptor imaging (SRI) and subsequently to assess an internal dosimetry with the same therapeutic radiopharmaceutic agent. The shorter β-range of ^{177}Lu provides potentially better irradiation of small tumours, in contrast to the longer β-range of ^{90}Y which provides more uniform irradiation in large volume tumours that may show heterogeneous uptake of radiotracer in both diagnostic somatostatin receptor imaging (SRI) and also post therapeutic scans. Currently the most widely used radiopharmaceutical is ^{177}Lu-DOTA-Tyr^3-octreotate (^{177}Lu-DOTATATE or ^{177}Lu-octreotate), less common ^{177}Lu DOTATOC [8, 9]. Also, only for ^{177}Lu-DOTATATE the clinical efficiency was proved in the NETTER-1 phase III randomized trial of ^{177}Lu- DOTATATE *vs.* high-dose Octreotide LAR in patients with non-resectable, progressive, midgut carcinoid tumours [10].

PRRT efficacy

Over past two decades, PRRT with ^{90}Y and ^{177}Lu DOTA SSTA proved to be efficient therapy of advanced, non-resectable and progressive NEN with tumour responses, based on radiological, evaluation, biomarkers reduction as well as clinical symptoms relief, improving quality of life (evaluating by standard EORTC quality of life questioners (EORTC QLQ C-30 and GI NET21) [11–13].

^{90}Y [DOTA^0, Tyr^3] octreotide (DOTATOC) has been the most widely used radiopeptide in the first decade of PRRT experience. The protocols were mostly based on empirical criteria [1–7]. Most of schemes, the injection of therapeutic activities, came from escalation studies and clinical experiences of the researchers, with big differences among protocols. Few centres used fixed dose, others used related to body weight or body surface. Also, there is discordant between number of cycles and time of intervals between each cycle of PRRT [3–8].

The first studies with ^{90}Y-DOTATOC/TATE or ^{177}Lu DOTATATE were conducted in patients with advanced disease, further studies demonstrated a higher efficacy of PRRT in those with less tumour burden stage. Some studies indicated that the tumour liver load, and patient clinical status (PS — performance status, WHO or ECOG) are the independent prognostic factor of overall survival and predicting factor of PRRT outcome [1, 5, 7, 8].

Recent studies have demonstrated that FDG is also a crucial parameter in predicting the duration of response to PRRT. Individuals with positive FDG exhibit a significantly shorter PFS, clear evidence that tumour glucose utilization represents a significant parameter in predicting therapeutic efficacy [5, 7, 14].

The current strategy of PRRT in advanced, non-resectable, often progressive NET indicated more frequent use of radioisotope therapy, which was provided by numerous factors including tumour volume and the biologic features of the neoplasm. Thus, more advanced (aggressive) tumours expressed less somatostatin receptors (SSTR) and are FDG-positive, increased genetic mutations, such as in p53, and are thus less responsive to treatment [14, 15].

A further consideration was the localisation of primary NET treated by PRRT. Thus, metastases of pancreatic NETs more frequently have radiological (RECIST, WHO or SWOG) response to PRRT compare to other types of NETs. Those patients with hormonal symptoms of NETs also relapse more rapidly [5–8, 13–15].

However, the only prospective trial proving PRTT efficacy is NETTER-1 phase III randomized trial of ^{177}Lu-DOTATATE *vs.* high-dose Octreotide LAR in patients with inoperable, progressive, midgut carcinoid tumours. This trial identified that ^{177}Lu-octreotate significantly improves PFS in patients with functional as well as non-functional tumours (PFS not reached *vs.* 8.4 months; hazard ratio 0.21, with a 79% reduction of the risk of progression). The overall number of deaths was also significantly lower in the PRRT group (14 *vs*. 26) [10].

PRRT clinical consideration

Candidates for therapy should be selected based on scintigraphy with ^{99m}Tc-HYNICTOC (Tektrotyd®, NCBJ, Polatom PL) — somatostatin receptor scintigraphy (SRS) or, more recently, using ^{68}Gallium-labeled synthetic SST analogues DOTATOC (Somakit®; AAA, CH) or DOTATATE (NETspot®; AAA, CH). Such images should indicate an adequate uptake (at least equal to the uptake of normal liver) as evidence of adequate expression of targetable somatostatin receptors. Somatostatin Receptor Imaging (SRI) evaluation of somatostatin receptor is the most accurate noninvasive method to identify and confirm the overexpression of

functioning SST receptors. Other methods like immunohistochemistry of SST receptors expression, which provides similar information at the time of biopsy, are not practical from clinical point of view. In fact, that immunohistochemistry, is not as quantitatively accurate as molecular analysis (real time polymerase chain reaction RT-PCR and Western blot), which can precisely define the level of somatostatin receptors (SSTR) and their functionality due to calculation of receptor protein amount [16, 17]. The use of in vivo functional SRI methods facilitates the simultaneous evaluation of the receptor density and the internalization capacity in real-time in all lesions base on single functional imaging approach. When evaluating images to determine PRRT selection, it is important to exclude false positives. False positives include uptake in the gall bladder (for example inflammation), accessory spleens, recent surgical scars (inflammatory infiltrate), previous radiotherapy and any other cause of granulomatous or lymphoid (sarcoidosis) infiltrate that can mimic the presence of NET tissue [1, 2].

The signal typically represents accumulation of inflammatory cells which express SST receptors. False negatives should also be considered. These are mainly represented by small, sub-centimeter lesions, below the resolution limit of the functional imaging technique (although this limitation is partially overcome by recent advance of PET/CT technology). In addition, certain tumors, such as the majority of highly malignant and high grade (Ki-67 > 55%) NENs do not express adequate numbers of detectable somatostatin receptors [17].

The practical consideration of PRRT in patients with advanced, non-resectable NET should include the goal of therapy: carcinoid syndrome control resistant to somatostatin analogues, reduction of progressive tumour mass or neoadjuvant treatment before surgery [1, 2, 5, 8, 12, 18, 19].

Another clinical issue is monitoring the results of the therapy. Currently, the clinical evaluation of the PRRT is used with evaluation of symptoms reduction, improvement in performance status (PS) using ECOG or WHO criteria. So far, there is no randomised control trails to unified inclusion criteria, except ones used in NETTER-1 protocol for midgut NET, evaluation form of clinical effect of this kind of treatment, through the different protocols are currently used in clinical practice [10]. Compare to other randomised trials in oncology the inclusion and exclusion criteria in most published reports of PRRT are not quite clear and often inhomogeneous including selection of patients, previous therapy, stage of disease etc. [3, 4, 6–8].

Additional question to be answer is the additional treatments with PRRT. Currently data from NETTER-1 trial shows concomitant use of "cold" SST analogues in patients with functional tumours. There is still doubt, if somatostatin analogues should be used between PRRT cycles also in patients with non-functional tumours [2, 12].

Some recent studies have examined the utility of PRRT using ^{177}Lu DOTATATE with concomitant chemotherapy (CapTem — capecitabine and temozolomide). The results indicated better objective response rate (ORR), than PRRT or chemotherapy alone with accepted toxicity [20]. The concept of simultaneously use of different drugs together with PRRT seems to be rational. In most clinical trials PFS is a primary end point of the study as a surrogate of the improvement of overall survival (OS). The other questions addressed is used of adjuvant therapy after PRRT as a supportive treatment with SST analogues or targeted therapy everolimus — mTOR inhibitors (mammalian target of rapamycin) or sunitynib — multitarget tyrosine kinase inhibitor particular in those patients with advanced non-resectable, progressive well or moderate differentiated pancreatic NET [21, 22].

The optimal sequence for using PRRT, chemotherapy, everolimus, and sunitinib will remain to be established in further clinical trials. There is only few reports indicated potential used of both techniques, so far not as subsequent therapy approach, but as additional option after relapse of PRRT [23, 24].

Just another point which is not clear so far is a decision of reasonable treatment courses using PRRT. At least two treatment cycles should be performed for more sufficient tumour killing by high energetic electrons from ^{90}Y or ^{177}Lu. Most centres used several injections up to 4 in their standard protocol [3, 4, 6–8, 13, 17, 24]. Also, 4 cycles were used in NETTER-1 trial [10]. However, from clinical experience we know that the number of courses depend on patient clinical status, concomitant disease previous therapy, which could influence renal and bone marrow function. In case of restricted bone marrow reserve or kidney deterioration the injected activity and number of therapy session should be reduced [2, 5, 12, 13, 17, 24–26].

Currently when ^{177}Lu DOTATATE is routinely used, the significant delayed adverse events consider kidney damage and myelosupression occur approximately only in 1.4% of patients. The meylosupression which is more dramatic in terms of patient survival, than kidney damage should be consider in those patients with initial cytopenia, which is contributed to significant haematological toxicity [24–26].

The rational use of several courses of PRRT at least 8–9 weeks each other is related to the recover of bone marrow after radioisotope therapy. There is additional need of clarification how fast we can back to repeat PRRT after relapse of initial therapy? Some reports indicated relatively safe repeat PRRT in patients with GEP-NETs after initial PRRT and response on this type of therapy. The PFS of repeat therapy was only 13 months (CI ± 95% 9.0–18.0), but there was no significant haematological and renal toxicity, based on Common Terminology Criteria of Adverse Events — NCI (CTCAE ver. 3.0) [26].

Before including cytotoxic agents and in case of well or moderate differentiated NET/NEN of pancreatic origin sunitynibe or everolimus another therapy option should be used. The way of administration is also important . In case of massive liver involvement and not significant outside of the liver tumour involvement should we prefer i.a. injection of the radiolabelled SST analogues [23].

There are only few reports considering intra-arterial PRRT. Initial report described use of ^{90}Y DOTALAN in therapy of bulky liver disease after relapse on standard therapy, another report described used of ^{90}Y DOATATE [27, 28] The optimal methods will remain to be established in clinical trials.

Technique of PRRT administration

PRRT consists of the several times of radiopeptide administration. The cumulative activity, fractionated in multiple cycles, is able to irradiate the tumour more efficiently, than single dose, without surpassing the conventional 25- to 27-Gy absorbed dose threshold to the kidneys, which are the dose-limiting organs. Recently, it has been reported that the biologic effective dose (BED)

as opposed to the absorbed dose provides a dose threshold value that is slightly higher [29].

The rhythm of administration, every 6 to 9 weeks, is based on the time that has been determined as necessary to recover from potential haematological toxicity [2, 5, 12, 24, 25]. To reduce the renal dose of irradiation, patients are prepared to an intravenous infusion of positively charged amino acids — AA (lysine and arginine), usually at least 25 g AA per therapy. This infusion is started 1–3 hours before the radioisotope administration and is maintained until 4 to 6 hours after the radioisotope administration [1, 2, 12, 13]. The infusion has the objective of simultaneously hydrating the patients and reducing the renal radioactivity dose by providing competitive inhibition of the proximal tubular reabsorption of the radiopeptide. The radiopeptide is intravenously administered slowly over 20–30 minutes in approximately 50–60 mL of saline using infusion pump. In some cases, mild adverse events (AEs) are experienced during the administration [2, 5, 12, 17, 24]. These mild adverse events (AE) include gastrointestinal symptoms, such as a slight nausea, and occasionally, vomiting. These symptoms may be related to the AA co-administration, but are controlled with appropriate medication (antyemetics) [1, 2].

Tumour response on ^{90}Y DOTA SST analogues PRRT

A number of phase I and II trails, retrospective, and most prospective oriented at defining the objective response using ^{90}Y DOTATOC. In specific classes of diseases, mostly GEP-NET, were published in the past 15 years [1, 3, 4]. Most of these trails consider very advanced disease after relapse of standard therapy. In this clinical advanced disease led to use PRRT in earlier phases of disease because it was evident that with decreased tumor burden radiopeptides exhibited a greater efficacy [1, 2, 5, 17].

In an initial study, 39 patients with NENs, mostly of gastroenteropancreatic (GEP-NET) origin, were treated with 4 cycles of ^{90}Y DOTATOC with a cumulative activity of 7.4 GBq. Objective responses, based on advanced disease radiological response according to WHO criteria, were as follows: complete remission in 2 patients (CR), partial response in 7 patients (PR) and disease stabilization in 27 (SD). Pancreatic NETs (13 patients) showed a better objective response (38% PR and CR) than the other classes did [3].

In another multicentre phase I study, including 60 patients affected by GEP NETs were treated with 4 cycles and administered 6–9 weeks apart. In an initial evaluation of the results published in 2002 in 32 evaluable patients, objective responses, according to Southwest Oncology Group (SWOG) criteria, consisted in about 9% of partial responses and 9% of minor responses [30]. In a later analysis of the same population published in 2006 on 58 assessable patients who were treated with cumulative activities of 1.7–32.8 GBq, a 57% clinical benefit, including stabilization and minor responses, was observed, according to SWOG criteria. A true objective response was described in 5% of the patients. The most relevant finding of the study was the observed overall survival (OS), with a median 37 months and a median progression-free survival (PFS) of about 29 months [30]. Characteristically, patients stable at baseline had a better overall survival than those who were progressive at baseline. The extent of disease at baseline was also a predictive factor for survival.

The Milan group reported results of two phase I/II studies and an evaluation of therapy 141 patients with different NENs. All patients were treated with a cumulative activity of 7.4–26.4 GBq of ^{90}Y DOTATOC. The OR rate was 26%, including CR and PR, according to SWOG criteria. Stabilization was seen in 55% of them and DP in 18%. The median progression free survival (PFS) was 18 months. The study indicated that if treated patients had better PS (WHO or ECOG) or/and had stable disease before PRRT, those patients had better OR and outcome (PR and CR in 32%) compared to those who had DP or worse PS (PR and CR in 24%) [31]. Most who responded had GEP-NETs.

A significant observation was the assessment of the objective response according to the basal status indicated that individuals stable at baseline demonstrated a better outcome (partial and complete responses in 32%) than individuals with progressive disease (partial and complete responses in 24%).

American multicentre study of the role of ^{90}Y DOTATOC in symptomatic, midgut, advanced, non-resectable NEN conducted in 90 patients showed stabilization of tumour mass, according to SWOG criteria in 74% of patients, as well as, a significant clinical response, including most of the symptoms related to the tumour burden and the hormone related clinical symptoms of carcinoid syndrome, PFS in this group of subjects was 16 months and OS 27 months [32].

The one of the pioneers of PRRT, the Basel group published the results of their open-label phase II trial in 1,109 patients treated with ^{90}Y DOTATOC, divided into multiple cycles of 3.7 GBq/m^2 each. Objective responses (CT), according to RECIST criteria, were observed in 378 (34.1%), biochemical response in 172 (15.5%) and symptomatic response in 329 (29.7%). Improvement in overall survival (OS) was related to tumour and symptomatic response. The best predictor of OS was the tumour uptake at baseline [33].

There are only few reports about the use of ^{90}Y-DOTATATE in one of them a group of 60 patients with histologically proven GEP-NETs were treated with 4.1–16.2 GBq per patient (mean 3.7 GBq per therapy). Six months after PRRT completion, partial response was registered in 13 patients (23%), while the remaining patients showed stable disease (77%). Median progression-free survival was 17 months, while the median overall survival was 22 months. Haematological AEs WHO grade 3 and 4 was noted during therapy in 10% of patients and persisted in 5%. After 24 months of follow-up, renal toxicity grade 2 was seen in seven patients, and the authors pointed out the need for careful renal monitoring [7]. Summarized data of outcome after PRRT using ^{90}Y DOTATOC is presented in Table 1, after PRRT using ^{90}Y DOTATATE [7, 34] and additional clinical use of ^{90}Y DOTALAN [6] are presented in Table 2.

The evaluation of results of many trails using PRRT indices that treatment in a phase of "early" progression rather than a "wait-and-watch" approach was more efficacy [1, 2, 5, 12, 13]. Overall, it was apparent that PRRT treatment in advanced stage disease was substantially less effective. A further consideration was the type of disease being treated. Thus, metastases of pancreatic NET/NENs were frequently more amenable to therapy compared with other types of NENs. Active secretors tumours with bioactive substance production (functional NEN) also tended to relapse very rapidly [1, 2, 8, 13, 17].

Table 1. Outcome of PRRT using ^{90}Y DOTATOC, selected publications

Study	Type of the tumour	No pts	Overall response rate	OS (median & range, months)	PFS (median & range months)
Waldherr et al. JNM 2002	Varius NET, progressive CS IIIB & IV	39	23% CR & PR	24 M	N.R.
Bodei et al. EJNM 2004	Various type of NET	141	26% CR & PR; 55% SD	N.R.	18 M
Valkema et al. Semin Nucl Med. 2006	Various type CS IIIB & IV	58	21% CR & PR	37 M (19–54)	14 M
Bushnell et al. JCO 2010	Various „carcinoid" CS IV	90	4% — CR & PR; 74% — SD	27 M	16 M
Imhof et al. JCO 2011	Various NET, CS unclear	1109	34% CR & PR	26 M	N.R.

Table 2. Outcome of PRRT using ^{90}Y DOTATOC, selected publications

Study	Type of the tumour	No pts	Overall response rate	OS (median & range, months)	PFS (median & range months)
Virgolini et al. Sem Nucl Med. 2002	Carcinoid, CS unclear	34	18% CR & PR	24 M	N.R.
Sowa-Staszczak et al. Endo Pol 2011	Varius NET, progressive CS IV	32	44% CR & PR	N.R.	N.R.
Cwikla et al. Ann Oncol 2010	GEP-NET, progressive 85% CS IV	57	23% PR	22 M all 39 M PR & SD 10 M in DP	17 M all 24 M PR & SD 5 M in DP

Peptide receptor radionuclide therapy using analogues labeled with ^{177}Lu

Currently most clinical work about PRRT are focused on ^{177}Lu [DOTA^0, Tyr^3] octreotate (DOTATATE). This radioisotope is a medium-energy β-emitter with a maximum energy of 0.5 MeV and a maximal tissue penetration of 2 mm. Its half-life is 6.7 days. ^{177}Lu also emits low-energy γ-rays at 208 and 113 keV with 10% and 6% abundance, respectively, which allows scintigraphy and subsequent internal dosimetry with the same therapeutic compound [8, 12, 35–38]. The shorter β-range of ^{177}Lu provides better irradiation of small tumours, in contrast to the longer β-range of ^{90}Y which allows more uniform irradiation in large tumours that may show heterogeneous uptake. In a comparison in patients, it was found that the uptake of radioactivity, expressed as a percentage of the injected dose of ^{177}Lu-DOTATATE, was comparable with the use of ^{177}Lu-DOTATOC in the kidneys, spleen and liver, but was three to four times higher in four out of five tumours [35]. Therefore, ^{177}Lu-DOTATATE has a potential advantage because of the higher absorbed doses that can be achieved in most tumours without increases in the doses to potentially dose-limiting organs [35, 38]. Also, in tumours in the same patients in a therapeutic setting, was found that the residence times are in favour of ^{177}Lu-DOTATATE in comparison with ^{177}Lu-DOTATOC by a factor of 2.1. [35].

The initial report of using ^{177}Lu DOTATATE was published by Kwekkeboom et al. in 2003. This study consists of 35 patients with GEP-NETs all patients treated with 3.7, 5.6, or 7.4 GBq of ^{177}Lu-octreotate, up to a final cumulative dose of 22.2 to 29.6 GBq, with complete and partial responses in 38% (WHO criteria). No serious side effects were observed [36].

The next study the same group analysed responses to ^{177}Lu-DOTATATE therapy according to tumour type at 3 months after the last therapy cycle in 310 patients [8]. Patients were treated up to an intended cumulative activity of 22.2–29.6 GBq. The overall objective tumour response rate including complete remission 2% (CR), PR 28% and minor response (MR) 16%, overall there was 46% subjects with ORR. SD was noted in another 16% of subjects. Prognostic factors for predicting tumour remission (CR, PR or MR) as the treatment outcome were high uptake on diagnostic Somatostatin Receptor Scintigraphy (^{111}In Octreoscan®, NL) and a Karnofsky performance score of over 70. A small percentage of patients who had either stable disease (SD) or MR at their first two evaluations after therapy, i.e. 6 and 12 weeks after the last treatment cycle, had a further improvement in categorized tumour response at 6 and 12 months, occurring in 4% and 5% of patients, respectively [8]. The most important information from this trail was the impact of PRRT on survival, with a median OS over 48 months and a median PFS of 33 months [8].

A direct comparison with data obtained from similar patients (in the literature) showed a substantial 40-month to 72-month survival benefit for PRRT-treated subjects [17]. Although these data are not derived from robust/rigorous prospective randomized phase III trials, (RCTs) this substantial survival difference in all probability reflects a real impact of PRRT as a very efficacy therapeutic approach in advanced non-resectable NET/NENs. These PRRT data compare favorably with other treatments, such as chemotherapy, from both the cost/benefit and the tolerability point of view. A categorization of ORR once again indicated that pancreatic NETs tended to respond better than other GEP- NETs, although functioning tumors (eg, pancreatic gastrinomas) tended to relapse in a shorter interval (median time to progression 20 months vs. > 36 in the remaining GEP-NETs) [8].

Next prospective trail including 51 patients with advanced non-resectable mostly GEP-NETs presented by Milan group. Patients were treated in a phase I–II study aimed at defining toxicity

and efficacy of ^{177}Lu-octreotate. Patients were divided into 2 groups, receiving escalating activities, from 3.7 to 5.18 GBq and from 5.18 to 7.4 GBq, with cumulative activities up to 29 GBq, based on dosimetry. PR and CR were observed in 15 patients (32.6%). The median time to progression was 36 months, with an overall survival of 68% at 36 months. Non-responders and patients with extensive tumor involvement had a lower survival [37].

There is also recent trail in patients with "poor responding" tumors, including bronchial and gastric NENs. Patients were treated with standard 22.2 GBq to 29.6 GBq activities. Despite the limited numbers of subjects observed ORR (SWOG criteria) was comparable to GEP-NETs. The broncho-pulmonary NETs results were 5 partial responses, 1 minor response, and 2 stabilizations in 9 patients. In the gastric tumor group, there was 1 complete response, 1 minor response, and 2 stabilizations (5 patients). In thymic tumors, the series were too small to draw any conclusions [39]. The authors concluded that, contrary to previous findings, PRRT was as effective in bronchial and gastric NETs as in GEP-NETs [37, 39]. In a small group of 21 patients treated with ^{177}Lu-DOTATATE by Garkavij et al., 12 were evaluated for objective response using RECIST criteria. PR was found in 5 subjects and SD in another 5 [38].

NETTER-1 phase III randomized control trial (RCT) of ^{177}Lu--DOTATATE *vs.* high-dose Octreotide LAR in 221 patients with non-resectable, progressive, midgut carcinoid tumors identified that ^{177}Lu-octreotate significantly improves PFS in patients with functional as well as non-functional tumours (PFS not reached *vs.* 8.4 months; hazard ratio 0.21, with a 79% reduction of the risk of progression) [10]. The overall number of deaths was also significantly lower in the PRRT group (14 *vs*. 26). The response rates of 18% in the ^{177}Lu-DOTATATE group and 3% in the control group were observed ($P < 0.001$) [10]. Moreover, consistent treatment benefits associated with ^{177}Lu-DOTATATE were observed irrespective of stratification factors and prognostic factors, which included levels of radiotracer uptake on somatostatin receptor scintigraphy, tumor grade, age, sex, and tumor marker levels NETTER-1 data showed that < 10% of patients developed myelosuppression [10].

There are few reports using a salvage protocol with ^{177}Lu-DOTATATE. Patients in progression were enrolled after an initial response to PRRT with ^{177}Lu-octreotate, administered using standard cumulative activities (22.2–29.6 GBq). In this series, 32 patients with bronchial or GEP-NETs received 2 additional cycles of ^{177}Lu-octreotate, with a cumulative activity of 15 GBq. A new objective response occurred in 8 patients (2 PR and 6 MR), whereas stabilization was identified in another 8 patients. Median time to progression (TTP) was 17 months. Both, response rate and duration over time appeared lower than during the primary treatment [26]. An example of patient with progressive, non-resectable NETG2, Ki-67 = 15%, cancer of unknown primary (CUP), after relapse of previous therapy including i.v. and i.a. PRRT, current salvage PRRT using ^{177}Lu DOTATATE is present on Figure 1.

In second trail the mean cumulative activity was 44.3 GBq (30.0–83.7 GBq) consider initial and next PRRT. ORR with CR noted in 1 patient (3.0%), PR in 6 patients (18.2%), MR in 1 patient (3.0%), SD in 14 patients (42.4%), and PD in 11 patients (33.3%). Median PFS from the start of salvage therapy was 13 months. None of the patients developed severe nephrotoxicity (grade 3/4) or a myelodysplastic syndrome during follow-up [25].

Protocols combining ^{177}Lu-peptides and ^{90}Y-peptides have been considered to take advantage of the different physical properties of both 2 radionuclides. In theory, the combination of the 2 radioisotopes would allow simultaneous treatment of both larger lesions (based on the higher energy and penetration range of the particles emitted by ^{90}Y) and small lesions (based on the lower energy and penetration range of ^{177}Lu) [40]. Some new algorithms are used like sequential use of ^{90}Y and ^{177}Lu DOTATATE (duo) [41] or mix of both radioisotopes (tandem). In the study using mix (tandem) PRRT (^{90}Y/^{177}Lu DOTATATE) provided longer overall survival than with a single radioisotope (^{90}Y DOTATATE), the weak point of this study this was not RCT, and initial group of patients treated with ^{90}Y DOTATATE was compare to second group those treated with mix [42].

Other study using mix ^{90}Y and ^{177}Lu DOTATATE (tandem) was reported on limited number of patients, only 26, induced objective responses was in 42.3% of patients with metastatic NET with a median PFS over 24 months. Patients with carcinoid syndrome in 90% showed a symptomatic response or a reduction in tumour-associated pain [43]. This relatively new strategy, however, have been still be validated in clinical practice in larger series and optimal RCT. Furthermore, the previously published studies include treatment schemes wherein ^{177}Lu and ^{90}Y were administered using empirically designed protocols rather than being based on individualized dosimetric analyses [17].

Another option for more efficient therapy using PRRT is combination of radioisotopes and chemotherapy. The initial report comes from Rotterdam. Keeping with recent tendencies in oncology, PRRT experiences have been focused toward combination therapies. In particular, combinations of the radiosensitizer chemotherapy agent, capecitabine, with ^{177}Lu-octreotate have been undertaken. An initial study in a small group (*n* 57) with progressive GEP-NETs reported encouraging results [44]. Patients were treated with 4 cycles of standard activities of ^{177}Lu-octreotate followed by capecitabine (1650 mg/m^2) for 2 weeks. No severe toxicity, particularly hand-foot syndrome or hematological/renal-associated toxicity was evident. Objective responses were observed.

A phase II study of progressive NETs with combining chemotherapy and PRRT was performed by Australian group. In their initial study ^{177}Lu DOTATATE (7.8 GBq) was used together with capecitabine in case of progressive disseminated NEN. The results of such approach were as follows 24% of complete response (CR) and partial response (PR), 70% of stable disease (SD) and 6% progressive disease (PD). Median progression-free survival and median overall survival had not been reached at a median follow-up of 16 months (range 5–33 months). Survival at 1 and 2 years was 91% (95% CI 75–98%) and 88% (95% CI 71–96%) [45]. The next study of the same Australian team shows even better results using combination of standard activity and protocol including mean 4 times administration of ^{177}Lu DOTATATE (7.8 GBq each dose) and chemotherapy using capecitabine and temozolomide in treating advanced low-grade neuroendocrine tumors (NETs). Overall, complete response (CR) was achieved in 15% (95% CI 3–27); partial response (PR), in 38% (95% CI 22–55); stable disease (SD), in 38% (95% CI 22–55); and 3 patients failed to respond to the treatment.

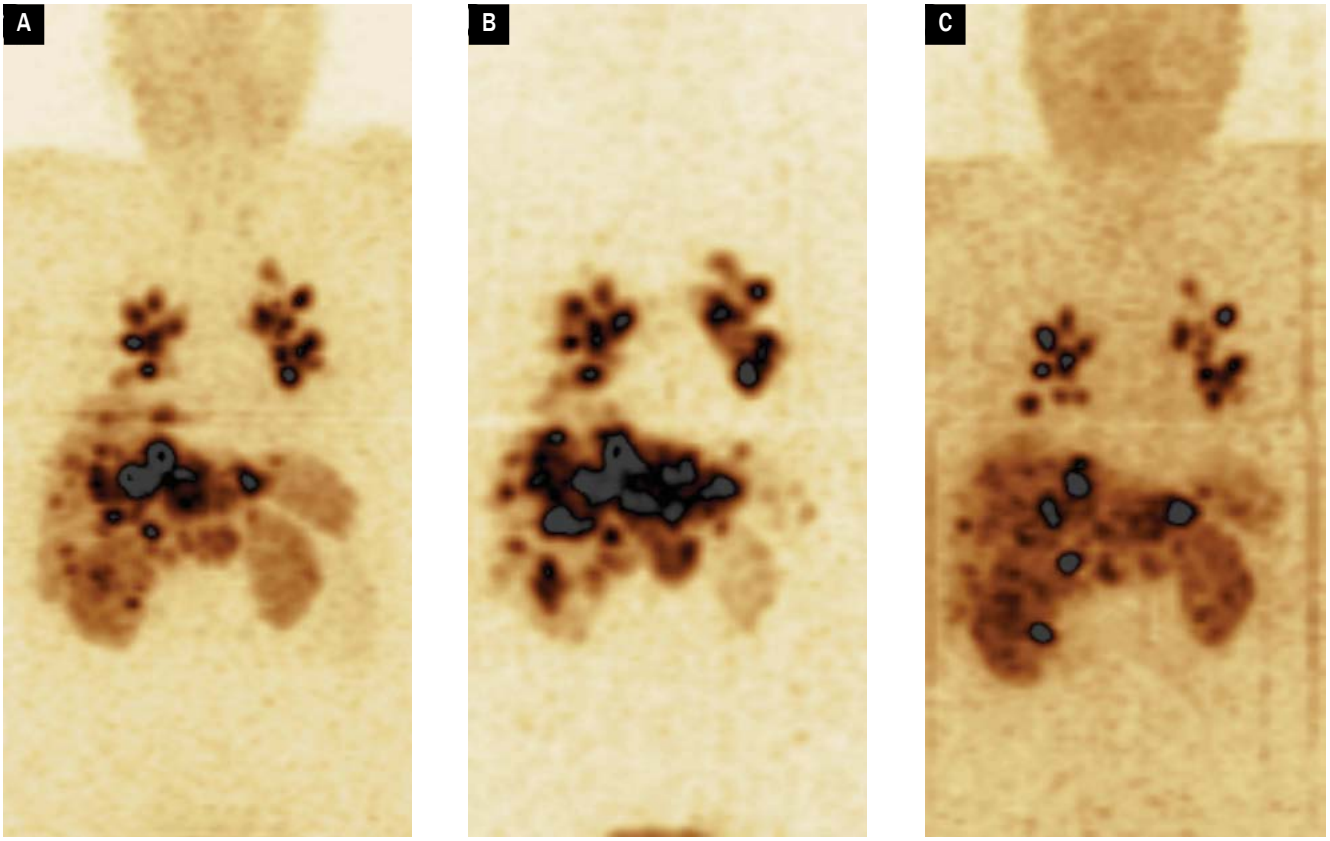

Figure 1. A 62-year-old male with NETG2 (Ki-67 = 15%) cancer of unknown primary (CUP). After relapse of several treatment approaches including chemotherapy, analogues SST therapy, initial i.v. and i.a. PRRT using 90Y DOTATATE, currently, with liver and chest relapse and further progression salvage therapy. **A.** Initial (before present PRRT) Somatostatin Receptor Scintigraphy using ^{99m}Tc HYNICTOC (Tektrotyd®; NCBJ, Polatom, PL). WB-SPECT (whole body SPECT) image with multiple liver and chest metastasis with high uptake of the radiotracer evaluated as Krenning 4; **B.** PRRT post-therapeutic scan after infusion of 5.55 GBq of ^{177}Lu DOTATATE. Acquired after 12 h, using the same WB-SPECT technique to compare with initial SRS scan. There is further liver progression, seen in first post-therapy scan, all lesions with high uptake of radiotracer with similar distribution as diagnostic scan; **C.** Next diagnostic SRS scan 3 months after second PRRT (5.55 GBq ^{177}Lu DOTATATE), using ^{99m}Tc HYNICTOC (Tektrotyd®; NCBJ, Polatom, PL), WB-SPECT shows at least metabolic stabilization, clinical PR

Median progression free survival (PFS) was 31 months (95% CI 21–33), and median overall survival (OS) has not been reached with 90% surviving at 24 months follow-up (range 21–30). Overall objective response rate (ORR) in patients with gastroenteropancreatic NETs showed CR 16% (95% CI 3–28), PR 41% (95% CI 24–58), SD 37% (95% CI 21–54), and PD 6% (95% CI 0–15). Response rates were higher in patients with gastro-pancreatic NETs than in those with bowel primaries (enteric-NETs); CR 18% versus 13%, PR 64% versus 13%, SD 12% versus 67% [46].

Summarized data of selected studies with outcome after PRRT using ^{177}Lu DOTATATE and also selected papers consider outcome after PRRT using mix ^{90}Y and ^{177}Lu DOTATATE, also ^{177}Lu DOTATATE with capecitabine and temozolamide (CAPTEM) is presented on Table 3.

Just another option is used locoregional therapy together with PRRT, which potentially lead to higher efficacies. Radioembolisation (RE) using resin or glass spheres loaded with ^{90}Y is high effective way to destroy cancer cells, due to hypervascularity of the NEN tumours. Selective internal radiation therapy (SIRT) is kind of intravascular brachytherapy. This concept of therapy is rational in case of liver dominant disease and heterogenous SST expression [47].

There is an only single report using RE after relapse after PRRT, performed as salvage option of therapy. A retrospective analysis of 23 advanced NENs patients, the overall response rates for radiologic, biochemical, and symptomatic responses were 30.4%, 53.8%, and 80%, respectively [48]. The median overall survival was 29 months (95% CI ± 95% 4.0–54.0) from the first radioembolization session and 54 months (95% CI ± 95% 47.0–61.0) from the first PRRT cycle. The key point of this option was the safe use of RE after initial PRRT. The mean previous cumulative activity of ^{177}Lu-DOTATATE was 31.8 GBq. The mean cumulative treatment activity of RE with ^{90}Y microspheres was 3.4 ± 2.1 GBq. It should be mentioned that any previous external radiotherapy is contraindicated to RE, except of PRRT. In clinical settings probably RE could be used before PRRT, in those cases with bulky liver disease with heterogeneous receptor expression to kill cancer cells without SST expression, potentially select clones with overexpression of SST [14].

Table 3. Outcome of PRRT using ^{177}Lu DOTATATE, mix ^{90}Y and ^{177}Lu DOTATATE and combination therapy PRRT (^{177}Lu DOTATATE) and CAPTEM (capecitabine and temozolomide)

Study	Type of the tumour	No pts	Overall response rate	OS (median & range, months)	PFS (median & range months)
Kwekkeboom et al. JCO 2008	GEP-NET CS IV	310	46% all 40% carcinoid CR, PR & MR	46 M	33 M
Van Essen et al. JNM 2010 (retreatment)	Various DP, CS IV	33	24% CR, PR & MR	15 M	N. R.
Bodei et al. EJNM 2011	GEP-NET	51	55% CR, PR & MR	36 M –68%	36 M
Kunikowska et al. EJNM 2011	NETG1/NETG2	50 (25 ^{90}Y) (25 mix)	16 % PR 20 % PR 12 % PR	N.R. 26.2 M 24 M (89%)	N.R. 21.4 M 29.4 M
Turner et al. Cancer Bio. Radio. 2012	NETG1/NETG2	35 + capecit. & temozol.	15% CR 38% PR	24 M –90%	31 M

Conclusion

Radiolabeled somatostatin analogues provide a means of delivering targeted radiation with a high therapeutic index to tumors that overexpress somatostatin receptors. The clinical data from nonrandomized multiple trials, as well as, from the NETTER-1 randomized control trial have shown high response rates and long durations of median progression-free survival in heterogeneous patient populations with gastro-entero-pancreatic neuroendocrine tumors (GEP-NET) with limited adverse events effects (AEs).

Radionuclide therapies with radiolabeled somatostatin analogues provide symptomatic benefit and increase survival in patients with metastatic NEN, particular GEP-NETs and are a reasonable option for treatment NEN patients.

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