Peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumours

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Abstract
Neuroendocrine neoplasms are a rare type of tumour that typically have a slow growing pattern. Most neuroendocrine tumours express high levels of somatostatin receptors type 2 (SSTR-2) on their cell surface. These receptors are a potential target for radiolabelled somatostatin analogues. Since 2017, peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lu-DOTATATE is EMA and FDA approved for treatment of metastatic and/or advanced gastroenteropancreatic neuroendocrine tumours (GEPNETs). Along with a reported good objective response, both increased survival and improved quality-of-life are the most important outcomes. Subacute toxicity to the kidneys and bone marrow is usually mild and self-limiting. Reported long-term adverse events include myelodysplastic syndrome and acute leukaemia in up to 2-3%. Renal failure is rare. Hence, PRRT is now a generally accepted effective and safe therapeutic option for patients with inoperable neuroendocrine tumours and/or metastases. Provided that SSTR-2 receptor expression is sufficient, PRRT is now well established in the treatment algorithm from the neo-adjuvant to salvage setting.

Introduction
Neuroendocrine neoplasms (NENs) are a rare type of tumours that can arise almost anywhere in the body, but most often originate in the digestive tract and lungs. The typical relatively slow-growing nature of NENs and relatively good prognosis make it the second most prevalent gastrointestinal tumour (1). In 2018 in The Netherlands, approximately 1000 patients were diagnosed with a neuroendocrine tumour (NET) and 400 patients with a more aggressive neuroendocrine carcinoma (NEC) (2). In the majority of patients, the primary tumour was found in the gastrointestinal tract.
NETs can be hormonally active. This excessive hormonal secretion can cause a variety of symptoms, based on the type of hormone produced (e.g. serotonin, gastrin, insulin). The typical symptoms of the carcinoid syndrome (i.e. flushing, diarrhoea and bronchospasm) are, however, not specific for a NEN of the small intestine and may also be attributed to e.g. menopause, irritable bowel disease, asthma. Consequently, the possibility of a NEN as a differential diagnosis is oftentimes not recognized by primary care physicians and non-specialized internal medicine physicians, resulting in a significant diagnostic delay. The median time between symptoms until the initial diagnosis is 36 months for a small intestinal NEN and 24 months for a pancreatic NEN (3). In 31% of patients the diagnosis is made in an emergency care setting. If not hormonally active, NETs can present with symptoms due to local growth and development of metastases. At diagnosis, 21-30% of NETs present with distant metastases, as do 50% of the NECs, however this may be an underestimation due to inadequate diagnostic testing (1). Metastases are most often found in regional lymph nodes and the liver (4). Metastatic spread limits therapeutic options, with surgery being the only potentially curative treatment (5).
For most metastatic NETs, treatment with somatostatin analogues (SSAs) (e.g. octreotide) is prescribed as first line treatment (4). In addition to a minor cytostatic effect, SSAs can also significantly decrease hormonally induced symptoms (6,7). Also, targeted therapies such as protein kinase inhibitors (e.g. everolimus and sunitinib) are being approved for NETs from various origins (8).
One of the major breakthroughs in the therapeutic management of metastatic and/or inoperable NETs in the past decades has been the development of peptide receptor radionuclide therapy (PRRT). PRRT with [^{177}Lu]Lu-[DOTA0,Tyr3]octreotate ([^{177}Lu]Lu-DOTATATE) is now a well-established second- or third line treatment for patients with progressive, advanced gastroenteropancreactic neuroendocrine tumours (GEPNETs). It is also the first "theranostic" with an FDA and EMA registration in the field of NENs.
This review will give an overview of the clinical use and the current evidence for the efficacy and safety of PRRT.

Background of PRRT
The vast majority of NENs overexpress a high number of the somatostatin

receptors (SSTRs) on their cell surface. SSTRs are G-protein coupled receptors and at this moment there are five main subtypes of the receptor known (SSTR1-5). Subtype 2 is found most frequently on NENs. Radiolabelled SSAs, such as the beta-particle emitting ([^{177}Lu]Lu-DOTATATE, can bind to the receptor and become internalised within the tumour cell. This results in an internal irradiation in highly specific target locations.

The technique of tumour targeting with radionuclide-labelled SSAs was first applied in the late 1980's using ^{123}I-Tyr3- octreotide for scintigraphic localisation of NETs (9). Soon thereafter a switch was made to ^{111}In-diethylenetriamine pentaacetic acid0-octreotide ([^{111}In]In-DTPA-octreotide) for use in imaging and since 1992 in therapy at Erasmus MC Rotterdam, using the Auger and conversion electron emission of the radionuclide (9,10). With the development of the chelator 1,4,7,10-tetraazacyclotetradecane-1,4,7,10-tetraacetic acid (DOTA), SSAs could be linked to beta emitters resulting in a higher radiation dose on the tumours. With modification of the SSA octreotide into octreotate (threonine substitutes C-terminal threoninol), a nine-fold higher affinity for SSTR2 was achieved (11,12).

At the start of PRRT both Yttrium-90 and Lutetium-177 were used as beta emitting radionuclides. Yttrium-90 is a pure beta emitter with a half-life of 2.7 days, decay energy of 2.28 MeV and a maximum tissue penetration of 12 mm; but is not well suited for imaging as it produces only a few positron- and Bremsstrahlung emissions in its radioactive decay. Contrary, Lutetium-177 emits both beta-particles (half-life 6.7 days, decay energy 0.5 MeV, maximum tissue penetration 2 mm) and sufficient gamma rays of 113 and 208 keV useful for scintigraphic imaging. Lutetium-177 has less side-effects than Yttrium-90, and better post-therapy imaging possibilities for treatment evaluation and dosimetry. For these reasons Lutetium-177 is now the radionuclide of choice for PRRT. In 2017, therapy with [^{177}Lu]Lu-DOTATATE was approved by the FDA and EMA for treatment of NETs based on the data of the NETTER-1 trial and the phase-2 Erasmus MC data (13,14).

Selection for PRRT

One of the major selection criteria for PRRT is the imaging evaluation of the SSTR expression in the tumour. Formerly, this was based on uptake on [^{111}In]In-DTPA-octreotide scintigraphy using the "Krenning score". This semiquantitative score relates the visual uptake in the tumour to that in normal organ tissue, particularly the liver and spleen. However, the emergence of ^{68}Ga-SSA positron emitting tomography (PET) imaging, with a better diagnostic performance and a higher patient comfort, has made the use of [^{111}In]In-DTPA-octreotide and the traditional Krenning score obsolete. In the Netherlands both [^{68}Ga]Ga-DOTATATE and [^{68}Ga]Ga-DOTATOC are used for imaging of NENs. To be eligible for PRRT, the uptake in the tumour should be higher than in normal liver parenchyma (considered by some to be equivalent to the traditional Krenning 3 score). During treatment patients should be self-supporting and therefore a Karnofsky performance status (KPS) of at least 60 is required. To prevent severe toxicity, the following pre-treatment laboratory values are required: creatinine clearance >40 mL/min, haemoglobin levels ≥6 mmol/L, leucocytes >2 x 10^9/L, platelet count >75 x 10^9/L, bilirubin, alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) <3 times the upper limit of normal and albumin >30 g/L. Contra-indications are severe cardiac impairment (NYHA III or IV), pregnancy or breastfeeding and a life expectancy of less than 3 months (14).

Efficacy of PRRT

Tumour response

The effect of PRRT on tumour growth and survival was proven in several phase-2 studies and the phase-3 NETTER-1 study (15). In the latter study, the effect of four cycles of 7.4 GBq [^{177}Lu]Lu-DOTATATE plus long-acting octreotide 30 mg was compared to a control group that was treated with high dose of 60 mg long-acting octreotide. Patients had a grade 1 or 2 midgut NET and were all progressive on long-acting octreotide. Results of PRRT were impressive. The rate of progression free survival (PFS) after 20 months as well as the over-all response rate were about six times higher for patients treated with [^{177}Lu]Lu-DOTATATE (20 months PFS 65%, ORR 18%) than in the control group (20 months PFS 11% and ORR 3%). Moreover, the risk of progressive disease (PD) or death was 79% lower in the [^{177}Lu]Lu-DOTATATE group than in the control group. Recently, an update of the overall survival (OS) data was published (16). After a follow-up of 76 months in the intention-to-treat population, the median OS was 48 months in the [^{177}Lu]Lu-DOTATATE group, which did not significantly differ from the median OS of 36 months in the control group. However, 36% of the patients in the control group switched to the PRRT treatment during follow-up, which probably had a major effect on the results. Data for the different types of GEPNETs and bronchial NETs were provided by the large prospective phase-2 study from the Erasmus MC (14). This study included patients with GEPNET, bronchial NET and NET of unknown primary origin, and all patients were treated with [^{177}Lu]Lu-DOTATATE. A median PFS of 29 months and a median OS of 63 months were observed in 443 patients with bronchial- and GEPNET who received

a cumulative activity of 22.2-29.6 GBq (600-800 mCi) [^{177}Lu]Lu-DOTATATE. An ORR of 39% after PRRT was found, whereas stable disease (SD) was observed in 43% of the patients. Results of PRRT in the largest phase 2/3 studies are presented in table 1.

Quality of life

In addition to tumour response and survival, PRRT can influence quality-of-life. In a group of 265 patients with metastatic or inoperable NETs, receiving 22.2-29.6 GBq [^{177}Lu]Lu-DOTATATE (completed by 241/265), European Organisation for Research and Treatment of Cancer quality of life questionnaire scores were prospectively registered, to measure global health status quality of life (GHS/QoL), as well as several clinical symptoms and several domains of functioning (20). Independent of tumour response, there was an increase in GHS/QoL, emotional and social functioning and a decrease of insomnia, appetite loss and diarrhoea. In patients who reported decreased GHS/QoL at baseline, clinically relevant improvements were seen in 36%, in patients who reported fatigue, in 49%; for nausea/vomiting, in 70%; for pain, in 53%; for dyspnoea, in 44%; for insomnia, in 59%; for appetite loss, in 63%; for constipation in 60%; and for diarrhoea in 67% (21). The effect on QOL was confirmed in the phase-3 NETTER-1 study, which demonstrated a longer time to deterioration (TTD) in the domains of global health, physical functioning, diarrhoea, pain, body image, disease-related worries and fatigue (22).

By reducing disease activity and hormone hypersecretion, PRRT can have an effect on levels of circulation hormones and correlating symptoms. In patients with a carcinoid syndrome the effect of PRRT was especially significant regarding both flushing and bowel movements. Two-thirds of the patients who had at least two episodes of flushing per day had a minimal decrease of 50% of these episodes. The bowel movement frequency of patients with diarrhoea at least four times a day, 47% experienced more than 30% decrease in frequency of diarrhoea, and 29% experienced even more than 50% decrease (21). Also, positive effects of PRRT on hormonal levels and symptoms have been observed in patients with functioning pancreatic NET syndromes, such as insulinoma, gastrinoma, glucagonoma and VIPoma (23).

Toxicity

(Sub)acute toxicity

Acute and subacute side effects of PRRT are generally mild. Nausea and vomiting are mostly related to the co-infusion of amino acids, administered for renal protection by preventing tubular uptake of [^{177}Lu]Lu-DOTATATE and consequent radiation of the renal parenchyma. Other side effects include fatigue, mild hair loss and mild abdominal pain in a minority of patients. Bone marrow toxicity mainly affects red blood cells, platelets and white blood cells, with the nadir to be expected 4-6 weeks after each therapy. However, the bone marrow toxicity is usually self-limiting. Large series report grade 3/4 hematotoxicity in 3.1-11.3% for [^{177}Lu]Lu-DOTATATE. In general, blood counts restore within 3-6 months after treatment (24-26). The most commonly found predictors for subacute hematotoxicity are poor renal function, low blood cell counts at baseline and previous chemotherapy (25-29). Long-term adverse events relate mainly to the kidneys and the bone marrow.

Long-term nephrotoxicity

PRRT can lead to a yearly decline of renal function due to radiation damage. An important part of the dose to the kidneys is due to reabsorption of the radiolabelled peptide in the proximal renal tubular cells. This can partially be prevented

Table 1. Results of the largest phase 2 and phase 3 studies including different types of neuroendocrine tumour patients.

	No patients	ORR (%)	SD (%)	PD (%)	Median PFS (months)	Median OS (months)
Strosberg et al (15,16)	117	18	60	23	28	48
Brabander et al (14)	443	39	43	12	29	63
Hamiditabar et al (17)	132	9	50	41	NR	NR
Roman et al (18)	200	24	38	4	27	43
Demirci et al (19)	160	50	22	28	36	55

by co-infusion of positively charged amino acids (30-33). A combination of lysine and arginine has shown to be safe and effective, resulting in a dose reduction of up to 40%, allowing for escalation of administered activity. Currently, the use of amino acids is standard of care and implemented in all guidelines. The most commonly found risk factors for nephrotoxicity are old age, hypertension, diabetes mellitus, high renal dose, impaired renal function at baseline and previous chemotherapy (25,26,34-37). In the NETTER-1 study and in the data from the Erasmus MC (13,38), there was no therapy related long term kidney failure established. PRRT in combination with co-infusion of amino acids is therefore considered a safe treatment for the kidneys.

Long-term hematological toxicity

A known risk of PRRT is the induction of secondary myelodysplastic syndrome (MDS) and acute leukemia (AL). These events are considered stochastic and are observed in the years after PRRT (39). In the studies where patients were only treated with [^{177}Lu]Lu-DOTATATE, the combined incidence of MDS/AL was approximately 2-3%, with AL being the least common (about 0.7%) and generally occurring after several years (at least 12 months) (38,40). An unusual high incidence was reported by Brieau et al., however (41). In 20 patients, heavily pre-treated with alkalizing chemotherapeutic agents and receiving [^{177}Lu]Lu- DOTATATE (intended dose 22.2–29.6 GBq), 3 (15%) patients developed MDS and one (5%) patient developed AL. These patients were pre-treated with 6–20 cycles chemotherapy with alkalizing agents; the high incidence of this alarming effect most likely reflects the natural course after treatment with myelotoxic chemotherapies. Therefore, PRRT should preferably be given prior to these therapies or at the point no alternative therapeutic option is left.

PRRT in the international guidelines

Several major randomised controlled trials have led to the registration of systemic, targeted approaches for the treatment of advanced and inoperable grade 1 and 2 NETs. For intestinal and pancreatic NETs with a Ki-67 index of <10%, treatment with non-radionuclide labelled ('cold') SSAs is now the standard first line treatment. For NETs of the small intestine PRRT with [^{177}Lu]Lu-DOTATATE is the preferable second line treatment in both the ENETS and ESMO guidelines (4,42), as the NETTER-1 study was performed in patients with midgut NETs. At this moment, there is no phase-3 evidence for the treatment of pancreatic NETs. However, there is abundant data from phase-2 studies and meta-analyses demonstrating the excellent effect of PRRT in panNETs. The results of several phase-3 studies in panNETs are to be expected in the coming years. Until then, the recommended second-line treatments for panNETS are targeted drugs such as everolimus (an inhibitor of mammalian target of rapamycin) and sunitinib (a tyrosine kinase inhibitor). The RADIANT trials support the use of everolimus in advanced NETs associated with carcinoid syndrome (RADIANT-2) (43), advanced P-NETs (RADIANT-3) (44) and advanced non-functioning NETs from the lung and gastrointestinal tract (RADIANT-4) (45). The effect of sunitinib was shown in a randomised trial in 2011, with a median PFS of 11.4 months in the sunitinib group versus 5.5 months in the placebo group (46).

Salvage therapy

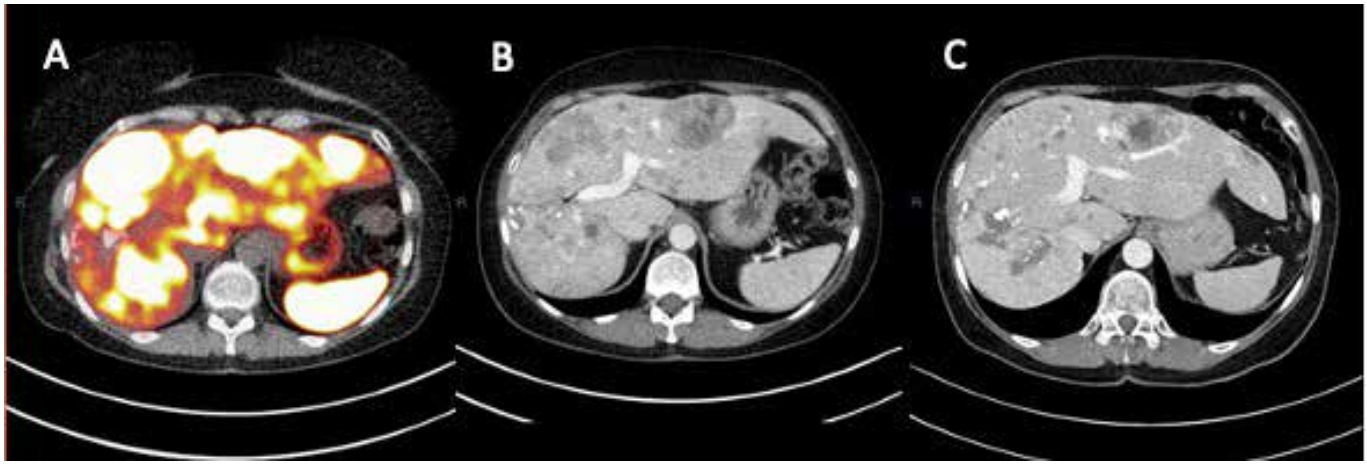
For patients who initially had benefit from PRRT (i.e. a tumour response of at least 18 months after the first cycle of PRRT), salvage treatment can be considered in case of disease progression. In a meta-analysis on the effect of re-PRRT (R-PRRT), the pooled median PFS was 14 months with a pooled median OS of 27 months. Similarly, the pooled ORR was 17% with a disease control rate of 77% (47). These results are not as good as initial treatment, however only two cycles of 7.4 GBq are administered to these patients (instead of four cycles of 7.4 GBq). Also, the increase in tumour burden might be an explanation for the results. Toxicity rates are in line with primary treatment and no additional cases of MDS/AL were reported (48). Moreover, no additional kidney toxicity was reported in the largest study in retreatment. It is therefore considered safe to treat patients with two, four, or occasionally, providing blood counts and kidney parameters are in good order, even six additional cycles of [^{177}Lu]Lu -DOTATATE.

Neo-adjuvant treatment

With surgery being the only treatment with curative intent, PRRT can be applied in a neo-adjuvant setting. Due to involvement of adjacent vascular structures and organs of advanced panNETs, surgery may be complex or accompanied with an increased risk of recurrence and surgery-related morbidity. The ORR in panNETs is 13-57% (17,38,49,50) and could be therefore an option for downstaging of neo-adjuvant treatment. The largest study in 49 patients who were treated with a neo-adjuvant intent, eventually 26 patients underwent surgery (51). Downstaging of the tumour-vessel interface was observed in 38% of patients. The median OS was 14.7 years in the group patients who underwent surgery and 5.5 years in the group who received only PRRT. These results demonstrate that the neo-adjuvant use of PRRT is a valuable option for patients with locally advanced panNETs and can be considered for selected patients.

PRRT for other SSTR positive tumours

Several malignancies other than NETs can overexpress SSTRs, including meningiomas, paragangliomas, small cell lung carcinomas, melanomas and



Images of a partial response after re-re-re-PRRT (cycle 9 and 10) in a patient with a NET of unknown origin with extensive metastases in the liver. A: Axial slice of [^{68}Ga]Ga-DOTATATE PET-CT before PRRT demonstrating multiple SSTR positive metastases in the liver. B and C: Axial slice of contrast enhanced CT before (B) and after (C) PRRT demonstrating a partial response.

thyroid cancer. However, even high expression of SSTRs (and thus a high effective dose) may not be enough to be effective, since the tumour cell type must be radiosensitive as well. Moreover, tumours with a high growth rate, such as small cell lung carcinomas, may not be sufficiently treated in an 8 weeks interval schedule (52). A recent retrospective study including 15 patients with progressive, treatment-refractory meningiomas was published (53). Currently, no established systemic therapy is available for this subgroup of patients. Although the median PFS after PRRT was limited, it seemed to be longer than the current standard of care. Also, treatment with [^{177}Lu]Lu-DOTATATE reduced the tumour growth rate in the majority of patients and resulted in disease stabilization in approximately half of the study population. A review on PRRT used in thyroid cancer identified 88 patients (in 15 publications) treated with four different radiopharmaceuticals (54). Best outcome was PR in 4.5% and SD in 43%. Though in the latter study the fraction of disease progression at baseline is unknown and unsuccessful cases may be unreported, it shows that treatment with radiolabelled SSAs can be a viable option for patients with non-NET SSTR positive tumours, especially when alternative therapeutic options are lacking.

PRRT with alpha emitting radionuclides

The use of alpha emitting radionuclides in radioligand therapy for both prostate cancer and NETs has emerged in the last decade. Alpha emitters offers advantages over beta emission due to the high linear energy transfer (LET) and limited range in tissue. This results in the selective radiation of tumours cells through double strand DNA breaks while sparing healthy tissue. In NETs the use of Actinium-225, Lead-212 and Bismuth-213 are being studied (55-57). For [^{225}Ac]Ac-DOTATATE most publications come from India (56). The largest study including 32 patients that were treated with 100 kBq/kg demonstrated a PR in 15/24 patients (63%) and a SD in 9/24 patients (38%). The optimal amount of activity is not yet known and a phase-1 dose-escalation study with [^{225}Ac]Ac-DOTATATE will start in 2023 in the Erasmus MC. For Lead-212 a recent dose-escalation study was published (57). This study included 20 patients that received four cycles of [^{212}Pb]Pb-DOTAMTATE. A radiological response was found in 80% of patients and no severe side effects were reported. The use of alpha emitting radionuclides will probably increase in the upcoming years; however, much research is needed to establish the optimal amount of activity and the best place in the treatment sequence.

Conclusion

PRRT with [^{177}Lu]Lu-DOTATATE is a safe and effective treatment option for patients with metastatic or inoperable NETs. In terms of radiographical response, patients' quality-of-life and progression free survival, the results of PRRT are outstanding. With appropriate patient selection, side effects from PRRT are typically mild and self-limiting. After the EMA and FDA approval of this radiopharmaceutical, the use in clinical practice has emerged and implementation in the international guidelines is accomplished. Ongoing research will determine the role in other SSTR positive tumours and new strategies to improve this treatment even further.

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