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Long-term outcomes of submaximal activities of peptide receptor radionuclide therapy with 177Lu-DOTATATE in neuroendocrine tumour patients.

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Running title: efficacy of submaximal dosage of PRRT

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ABSTRACT

Rationale

In literature, up to 45% of the neuroendocrine tumour (NET) patients who are treated with peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE do not receive the intended cumulative activity of 29.6 GBq (800 mCi). The aim of this study was to analyse the efficacy of submaximal activities of PRRT in patients who discontinued for disease-unrelated reasons.

Methods

Retrospective inclusion of well-differentiated and advanced NET patients who underwent PRRT from 2000 until 2019 and did not receive 29.6 GBq ^{177}Lu-DOTATATE. For comparison, we selected control NET patients who received the intended cumulative activity of 29.6 GBq ^{177}Lu-DOTATATE between 2000-2012. Primary outcomes were progression-free survival (PFS) and tumour response, and the secondary outcome was overall survival (OS).

Results

In total 243 patients received 3.7-27.8 GBq. In 130 patients the submaximal activity was disease-unrelated (e.g. bone marrow and renal toxicity in 48% and maximal renal absorbed dose in 23%) and they were included. Patients receiving a reduced activity had more bone metastases, a lower BMI and albumin level, a higher alkaline phosphatase, and less grade 1 tumours than the 350 patients included in the control group. The disease control rate in the reduced activity group was 85% compared to 93% for the control group (P=0.011). The median PFS (95%CI) was 23 (21-26) months for the reduced activity group and 31 (27-35) months for the control group (P=0.001), and the median OS was 34 (28-40) months and 60 (53-67) months, respectively (P<0.0001). With adjustment for relevant confounders in the multivariable Cox regression analyses, cumulative activity was an independent predictor of both PFS and OS.

Conclusion

In NET patients treated with a cumulative activity less than 29.6 GBq ^{177}Lu-DOTATATE, PRRT was less efficacious in terms of tumour response and survival compared to patients who received 29.6 GBq.

Key words: cumulative activity, peptide receptor radionuclide therapy, neuroendocrine tumour

INTRODUCTION

Neuroendocrine tumours (NET) predominantly originate from neuroendocrine cells located in the bronchopulmonary system, the gastrointestinal tract, and the pancreas *(1)*. For patients with metastatic disease, peptide receptor radionuclide therapy (PRRT) is an established treatment option *(2)*. PRRT with radiolabelled somatostatin analogues targets somatostatin receptors (SSTRs) that are frequently present on the NET cell membrane. Currently, PRRT with [^{177}Lu-DOTA0,Tyr3]octreotate (^{177}Lu-DOTATATE) is approved for well-differentiated, progressive or advanced gastroenteropancreatic (by European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA)) and other foregut NET (by FDA only).

^{177}Lu-DOTATATE induced objective response (complete response or partial response) in 39% and disease control (objective response or stable disease) in 83% of the patients with gastroenteropancreatic, bronchial, other foregut, and unknown primary NET who were treated with 22.2-29.6 GBq *(3)*. The NETTER-1 trial in well-differentiated advanced midgut NET patients showed that ^{177}Lu-DOTATATE plus long-acting octreotide results in a longer progression-free survival (PFS) than treatment with high-dose octreotide. Here, the dosing schedule of ^{177}Lu-DOTATATE consisted of 4 cycles of each 7.4 GBq for a total cumulative activity of 29.6 GBq. However, 23% of the patients did not complete these 4 cycles. Activity reductions were required in 7% of the patients due to dose-limiting toxicities, but other causes for not completing the treatment and the outcomes in this subgroup have not been reported *(4)*. Other studies have reported that 5-45% of patients do not reach their intended full cumulative activity of PRRT *(5-9)*.

Most often, PRRT is discontinued due to progressive disease or death *(5,7-9)*, which evidently influences the response and survival outcomes. The aim of this study was to provide an analysis of the treatment response, PFS, and overall survival (OS) in patients who did not receive the full cumulative PRRT activity for reasons unrelated to the behaviour of the tumour.

PATIENTS AND METHODS

Patients

For this retrospective analysis, we selected all Dutch gastroenteropancreatic and other foregut NET patients who were treated between 2000 and March 2019 with ^{177}Lu-DOTATATE at Erasmus MC and did not receive 29.6 GBq (800 mCi). Patients were excluded for this study if they had a grade 3 NET or neuroendocrine carcinoma or if PRRT was administered in neoadjuvant setting for local disease or in an adjuvant setting. The patient files were searched for the reason of activity adjustment and the clinical and tumour characteristics. The follow-up scans after PRRT were assessed for the treatment response according to the Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1). A subselection was made for patients in whom the activity reduction was not related to death, disease progression, or other reasons directly related to their tumour burden. A group of patients who received the maximum PRRT dosage was collected for comparison. Here, we selected prospectively characterized Dutch NET patients who were enrolled in our phase 2 trial *(3)* from 2000 until May 2012, for a follow-up of at least three years for the PFS, and received 29.6 GBq of ^{177}Lu-DOTATATE. For this group, the same inclusion and exclusion criteria were applied as for the patients who received <29.6 GBq. The tumour grade before PRRT was retrospectively assessed for all patients by retrieving the mitotic index or Ki67% from pathology reports applying the WHO 2019 classification *(10)*. Our local institutional review board (IRB) approved the phase 2 study and all subjects signed an informed consent form or, for patients treated after 2015, the need for written informed consent was waived by the IRB.

PRRT

All inclusion and exclusion criteria and details of the preparation and administration of ^{177}Lu-DOTATATE were previously described *(3)*. The intended cumulative activity of ^{177}Lu-DOTATATE was 29.6 GBq, administered in 4 cycles with an interval of 6-10 weeks between the cycles. In case of dose-limiting toxicity, other adverse events or precautions, the administered radioactivity per cycle could be halved and the number of cycles could be adjusted. PRRT was discontinued, and the intended cumulative activity of 29.6 GBq was not reached, when dose-limiting toxicities recurred or persisted longer than 16 weeks. In

patients treated before 2008, the maximum cumulative activity was also reduced if the calculated renal dose exceeded 23 Gy.

Follow-up visits were scheduled at 4-6 weeks after each cycle, and at 6 weeks, 3 months, 6 months, and thereafter at 6-month intervals after the last treatment cycle. These visits included laboratory measurements (hematologic, hepatic, and renal function tests) and imaging (CT or MRI).

Outcomes

Primary endpoints were PFS and tumour response compared for patients who received the reduced activity for disease-unrelated reasons with patients who received the full PRRT activity. PFS was calculated from the start of PRRT until disease progression or death from any cause. The PFS was censored when patients were lost to follow-up. Tumour response was assessed according to RECIST 1.1 *(11)*. The secondary endpoint was OS, calculated from the start of PRRT until death from any cause. The survival status was updated until June 2021.

Statistics

The full activity and reduced activity groups were compared using χ^2 or Fisher exact test for categorical variables and Mann-Whitney U or t test for continuous variables. The PFS and OS were analysed with the Kaplan-Meier method and the Log-rank test. Cox proportional-hazards analysis was used to calculate the adjusted hazard ratio (HR) of cumulative activity for PFS and OS. We included the following known prognostic variables in the multivariable analyses with a full model approach *(12)*: age, sex, BMI, tumour origin (bronchial, pancreatic, gastrointestinal, unknown primary), tumour grade (grade 1, grade 2, unknown), Karnofsky index, months since diagnosis, prior treatments (somatostatin analogues, surgery, chemotherapy), progression before PRRT, liver metastases, bone metastases, tumour uptake on ^{111}In-DTPA-octreotide scintigraphy higher than the kidneys/spleen, extent of the disease (moderate, limited, extensive), albumin, alkaline phosphatase, and year of treatment with PRRT. A two-sided *P*-value <0.05 was considered statistically significant. All analyses were performed with use of IBM SPSS Statistics for Windows software (version 25, IBM Corp., Armonk, NY).

RESULTS

Between 2000 and 2019, 243 NET patients received a cumulative PRRT activity of less than 29.6 GBq. The median (range) administered activity was 18.5 (3.7-27.8) GBq administered in a median (range) of 3 (1-7) cycles. The main causes for discontinuing PRRT included bone marrow toxicity, death in the course of PRRT cycles, and maximum calculated renal absorbed dose (Table 1). Patients who received a reduced activity because of progression, death, and other reasons related to their tumour burden were excluded for further analysis, resulting in a cohort of 130 patients with reduced administered activity due to disease-unrelated causes (Figure 1). The control group of patients receiving the full PRRT activity of 29.6 GBq consisted of 350 patients.

Patient Characteristics

In Table 2, the baseline characteristics of the reduced and full activity groups are shown. The subjects in the reduced activity group received an average of 3 cycles with a median (IQR) cumulative activity of 22.2 (18.5-25.9) GBq. The patients in the reduced activity group had a significantly lower median BMI and albumin level, lower proportion of unknown primary tumour origins, more frequently bone metastases, and a higher alkaline phosphatase level than the patients in the full activity group. In the reduced activity group also a significantly lower proportion of grade 1 tumours was observed, although grade was not available in half of the subjects. In the reduced activity group, PFS and OS were not significantly different between patients treated before and after 2013.

Progression-free Survival

The median (95%CI) PFS of 23 (21-26) months for the reduced activity group was significantly shorter than the PFS of 31 (27-35) months for the full activity group (P=0.001). The PFS was further stratified according to the number of cycles. The PFS increased with each higher cumulative activity subgroup from 19 (10-29) months for ≤14.8 GBq, 23 (20-26) months for 16.7-22.2 GBq, and 28 (18-38) months for 25.9-27.8 GBq (P=0.038, Figure 2a). Cumulative activity was an independent predictor of PFS in the multivariable Cox regression analysis with an HR (95%CI) per 3.7 GBq of 0.84 (0.76-0.93, P=0.001).

Treatment Response

An objective response was reached in 39 (34%) patients of the reduced activity group and 141 (43%) patients in the full activity group (*P*=0.100). Disease control was observed in 97 (85%) patients of the reduced activity group compared to 305 (93%) in the full activity group (*P*=0.011), Table 3.

Overall Survival

During the follow-up, 115 (88%) patients in the reduced activity group and 287 (82%) patients in the full activity group died (*P*=0.088). The patients in the reduced activity group had a median (95%CI) OS of 34 (28-40) months, which ranged from 25 (20-30) months for the 3.7-14.8 GBq group, 34 (29-40) months for 16.7-22.2 GBq, and 51 (35-68) months for the 25.9-27.8 GBq group (*P*=0.018). The survival of the reduced cumulative activity subgroups was shorter than the median OS of 60 (53-67) months of the full activity group (*P*<0.0001, Figure 2b). The adjusted HR (95%CI) for all-cause death of cumulative activity per 3.7 GBq was 0.80 (0.73-0.87, *P*<0.0001) in the multivariable Cox regression.

DISCUSSION

^{177}Lu-DOTATATE is a systemic treatment option for advanced NET patients *(2)*. It has been demonstrated that this treatment induces disease control in the majority of patients *(3)* and prolongs the PFS compared to treatment with high-dose somatostatin analogue *(4)*. However, 23% of the patients in the NETTER-1 trial *(4)* and up to 45% of the patients in other studies *(6)* did not receive the optimum activity of ^{177}Lu-DOTATATE. To our knowledge, this is the only large analysis of the efficacy of submaximal dosages of PRRT with ^{177}Lu-DOTATATE as a result of PRRT toxicity and other NET-unrelated causes.

As described previously *(5,7-9)*, death or progressive disease (27%) and toxicity (26%) were the most prevalent reasons for submaximal PRRT dosage in our cohort of 243 NET patients. Since progression, death, and other NET-related adverse events influence the treatment outcome, we selected patients who received a lower activity for NET-unrelated reasons for the efficacy analysis. Most prevalent causes in the patients included in the reduced activity group were bone marrow toxicity, a maximum calculated renal dose and renal impairment, indicating that the bone marrow and kidneys are the dose-limiting organs *(13)*.

Although the treatment response and PFS of patients treated with a submaximal activity of PRRT were lower compared to the full activity group, still a disease control rate (DCR) of 85% and a median PFS of 23 months were observed. The median OS of 34 months, however, was significantly shorter than the OS of the full activity group (60 months). This substantial difference could potentially be explained by the observation that patients with presumably more severe disease (i.e. more grade 2 tumours and bone metastases, increased alkaline phosphatase, and lower BMI and albumin) seemed to be at risk for discontinuing PRRT. In literature, a higher tumour grade *(14)* and, possibly, presence of bone metastases *(5,15-17)* and lower BMI or worse nutritional status *(18)* negatively influence prognosis. There is no clear evidence for the association between bone metastases and the risk of PRRT-induced bone marrow toxicity *(19,20)*. Furthermore, no scoring system for the extent of bone metastases was implemented, so there might be a large variability in the extent of bone metastases. Nonetheless, the cumulative activity had a dosage-dependent effect on the PFS and OS, which in the multivariable Cox regression analyses was confirmed to be independent from other important confounders that potentially influence the cumulative activity as well as the outcomes. Therefore, our study indicates an independent, incremental, and causal relationship between prognosis and cumulative activity.

It has been demonstrated that tumour response after PRRT is correlated to the administered radioactivity *(5,21)*. Hamiditabar et al. reported a DCR of 59% in the total group of 132 patients who had at least 1 cycle (7-44 GBq) and a follow-up scan, and a DCR of 86% in the subgroup of 28 patients who completed at least 4 cycles (29-44 GBq). Patients who died or voluntarily withdrew during PRRT were excluded from their analysis *(6)*, but it is unclear what the reasons were for not completing PRRT. In the phase II studies of Sansovini *(22)* and Paganelli *(23)* et al., the administration of a cumulative activity of 18.5 or 25.9 GBq was based on the presence of potential risk factors for renal or haematological toxicity. In the 32 pancreatic NET patients treated with a reduced activity, a DCR of 78%, a median PFS of 22 months, and a median OS of 64 months were observed, compared to a DCR of 86%, a PFS of 53 months (P=0.353), and a median OS not reached (P=0.007) in the 28 patients in the full activity group *(22)*. The treatment response after 18.5 GBq was comparable to our observations in the reduced activity group, although the OS of 64 months was much longer than the 34 months in our cohort. However, in the 43 gastrointestinal NET patients aimed for treatment with 18.5 GBq, both the median PFS and OS were not reached after a

median follow-up of 38 months and the treatment response and OS were equal between the 18.5 GBq and 25.9 GBq groups *(23)*. In our study, power was insufficient to calculate differences stratified for primary tumour site. These studies are not fully comparable to our study, because the different administered cumulative activities were intentional prior to start of PRRT and patients who stopped PRRT for other reasons than progressive disease were excluded for their efficacy analyses.

Given the clear dose response observed until the current maximal activity, PRRT employing higher activities should be investigated in future trials. In two prospective trials, the efficacy of increasing the individual cumulative activities were studied. In the study of Del Prete et al., in which the activity per cycle was based on renal function and body surface area for the first cycle and subsequently on renal dosimetry, the activity was increased in 85% of the patients completing ≥3 cycles. A median 1.26-fold increase in the absorbed tumour dose was observed, without increased toxicity rates *(24)*. Garske et al. based the number of cycles on the bone marrow and renal dose. Half of the study population received 5-10 cycles and the treatment response was better when the renal dose of 23 Gy was reached. However, in 22% of the patients, PRRT was stopped because of bone marrow toxicity *(25)*. These personalized dosing strategies may help optimizing the efficacy of PRRT, but future research should also focus on preventing PRRT-related toxicities that are dose-limiting. A further interesting possibility emerging from the present analysis could be that after some recovery from toxicity, an increased activity might prognostically be of benefit in selected patients. However, this should be subject of future research.

Although the present findings are compelling, as with any retrospective study, there may be other, not immediately evident or unknown confounding issues that could not be adequately controlled for. One particular limitation of our study is the lack of tumour grade in half of the subjects, because until 2007 it was not common practice to consistently report the Ki67% or mitotic count. Moreover, although the majority of the patients were participants in the prospective phase II trial that included the main outcomes of this study, we retrospectively selected the patients and included patients for the reduced activity group who had PRRT after the phase II trial to increase the sample size. As a consequence, there may have been a selection of patients with different characteristics, because alternative treatment options for PRRT became available *(26-30)* and the availability of ^{68}Ga-DOTATATE PET-CT could have influenced the detection of metastases *(31)*. We tried to correct for this by adding the year of treatment with PRRT in the regression analyses.

Furthermore, another limitation caused by the retrospective nature of the present work, it would have been interesting to perform an explanatory dosimetric analysis in this patient group to clarify the influence of cumulative activity in more detail. Unfortunately, in the large majority of patients, only a single post-therapy scan was acquired, thus precluding accurate dosimetric evaluations.

In spite of the limitations of this study, the data compellingly show that patients are likely to benefit from striving towards completing a full 29.6 GBq PRRT regimen. In the light of these findings, it appears that only serious medical complications of PRRT or unwillingness of the patient to undergo further cycles would constitute appropriate grounds for discontinuation of PRRT. Whether such medical reasons can be expressed in a discrete or continuous classifier may be an interesting direction for future research.

CONCLUSION

The cumulative administered activity of ^{177}Lu-DOTATATE may have an important, incremental, and independent effect on the response to and survival after PRRT. Therefore, it appears eminently sensible to strive for achieving a cumulative therapeutic activity of 29.6 GBq ^{177}Lu-DOTATATE if medically possible.

KEY POINTS

Question:

What is the efficacy of submaximal doses of ^{177}Lu-DOTATATE as a result of NET-unrelated reasons?

Pertinent Findings:

In this retrospective analysis of 350 NET patients who received 29.6 GBq compared to 130 NET patients who received 3.7-27.8 GBq due to NET-unrelated adverse events (mainly bone marrow and renal toxicity), we observed statistically significant lower PFS, DCR, and OS for the patients receiving submaximal activities.

Implications For Patient Care:

Clinical practice and future research should focus on preventing PRRT-related dose-limiting toxicities in order to administer the optimal dose.

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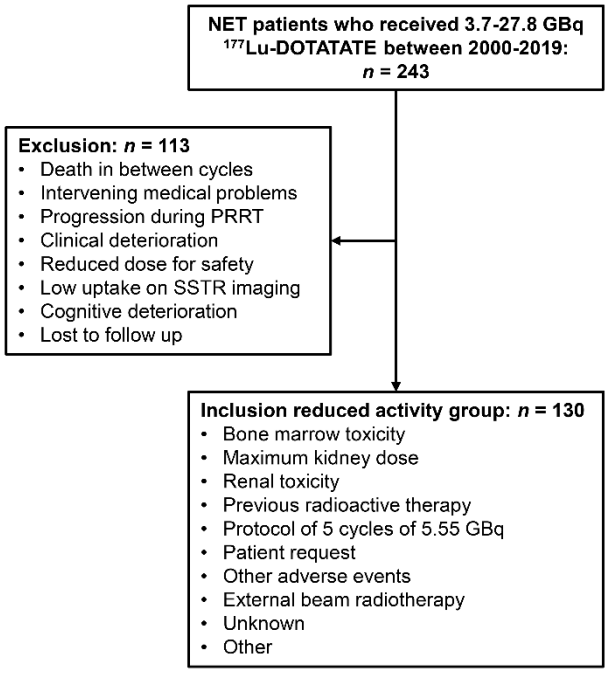
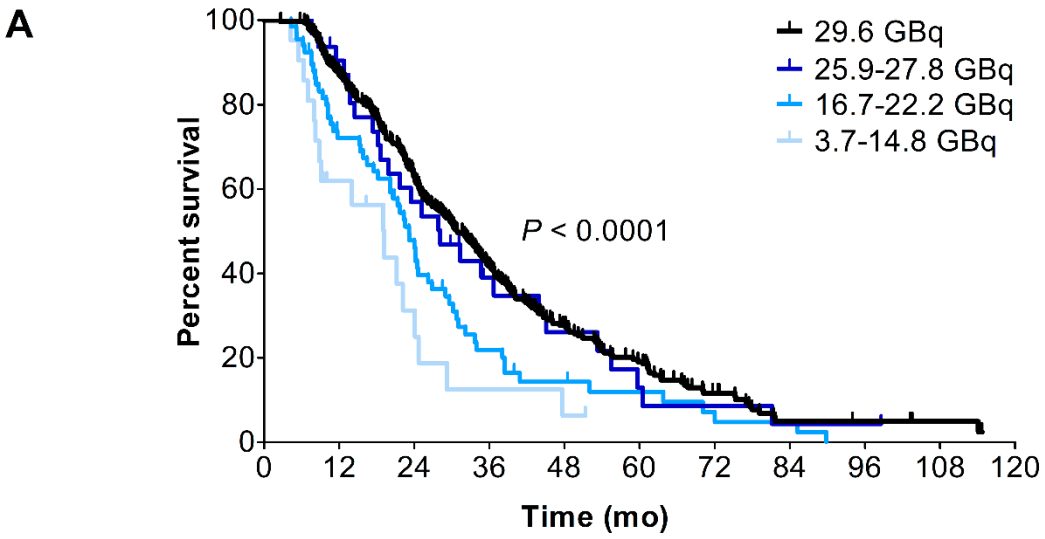
FIGURE 1. Flowchart

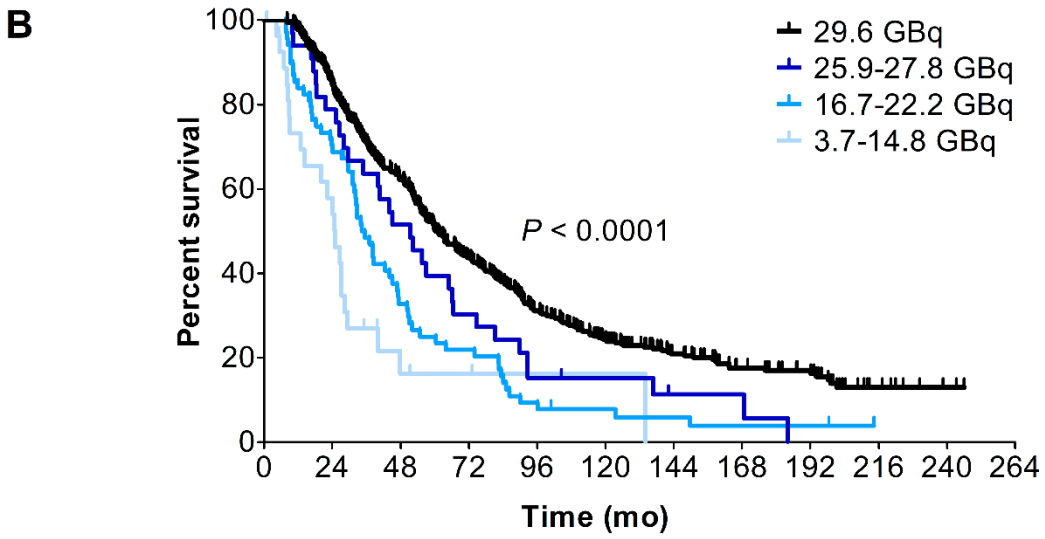


Legend. Flowchart of the inclusion and exclusion criteria for the selection of the patients for the reduced activity group. *NET, neuroendocrine tumour; SSTR, somatostatin receptor*

FIGURE 2. Survival Analyses



no. at risk											
29.6 GBq	350	270	173	102	57	37	17	5	4	2	0
25.9-27.8 GBq	33	27	17	9	6	3	2	1	1	0	0
16.7-22.2 GBq	69	44	28	12	7	5	3	2	0	0	0
3.7-14.8 GBq	28	11	5	2	1	0	0	0	0	0	0



no. at risk											
29.6 GBq	350	297	218	153	109	79	51	32	24	8	2	0
25.9-27.8 GBq	33	26	17	10	5	4	2	2	0	0	0	0
16.7-22.2 GBq	69	46	21	14	6	4	3	2	2	0	0	0
3.7-14.8 GBq	28	15	4	2	1	1	0	0	0	0	0	0

Legend. Progression-free survival (A) and overall survival (B) of the full activity group (29.6 GBq) compared to the reduced activity group (3.7-27.8 GBq), stratified for different cumulative activity categories. *P*-values were calculated with the log-rank test.

TABLES

TABLE 1. Reasons for submaximal activity for all patients who received <29.6 GBq (*n*=243).

	No. (%)	Number of cycles, median (range)	Cumulative activity, GBq, median (range)
Death in between cycles	52 (21%)	1 (1-4)	7.4 (3.7-25.9)
Bone marrow toxicity	49 (20%)	3 (1-6)	22.2 (3.7-25.9)
Maximum kidney dose	30 (12%)	3 (3-4)	22.2 (18.5-27.8)
Intervening medical problems*	28 (12%)	2.5 (1-4)	16.7 (3.7-25.9)
Renal toxicity	14 (6%)	3 (1-5)	22.2 (7.4-22.2)
Progressive disease during PRRT	14 (6%)	2.5 (2-3)	16.7 (14.8-22.2)
Previous radionuclide therapy	9 (4%)	3 (2-3)	22.2 (14.8-22.2)
Protocol 5 cycles of 5.55 GBq	7 (3%)	5 (5-5)	27.8 (25.9-27.8)
Reduced dose for safety†	6 (2%)	4 (4-7)	25.9 (22.2-25.9)
Clinical deterioration	5 (2%)	2 (2-5)	14.8 (11.1-25.9)
Patient request	5 (2%)	3 (1-3)	22.2 (7.4-22.2)
Low uptake on ^{111}In-DTPA-octreotide scan	4 (2%)	1 (1-2)	7.4 (7.4-14.8)
Cognitive deterioration	3 (1%)	2 (1-2)	14.8 (7.4-14.8)
Other adverse events‡	3 (1%)	3 (2-4)	22.2 (11.1-25.9)
External beam radiotherapy	1 (0.4%)	3	22.2
Lost to follow-up	1 (0.4%)	2	14.8
Other§	4 (2%)	1 (1-2)	7.4 (7.4-14.8)
Unknown	8 (3%)	4 (4-6)	25.9 (22.2-25.9)

**Ileus (n=6), infections (n=5), cardiac valve surgery (n=4), myocardial infarction (n=2), hypercalcemia due to PTHrp production (n=1), carcinoid crisis (n=1), carcinoid heart disease (n=1), analysis of a pulmonary nodule (n=1), breast carcinoma (n=1), gastrointestinal bleeding (n=1), cerebrovascular event (n=1), oedema due to hypoalbuminemia (n=1), admission elsewhere (n=1), multiple problems (n=2).*

†Reasons include: prevention of carcinoid crisis (n=2), prevention of tumour lysis (n=1), large tumour load in the liver (n=1), baseline thrombocytopenia (n=1), unknown (n=1).

‡Increased abdominal pain (n=2), nausea and hair loss (n=1).

§Unsafe administration due to radioactive contamination (n=2), incompliance regarding planned visits (n=1), aim of treatment was biochemical stabilisation (n=1).

TABLE 2. Baseline characteristics of all included patients.

Variables	Reduced activity *n*=130	Full activity *n*=350	*P*-value
Cumulative activity, GBq			
3.7-7.4	8 (6%)	0	**<0.0001**
11.1-14.8	20 (15%)	0	
16.7-22.2	69 (53%)	0	
25.9-27.8	33 (25%)	0	
29.6	0	350 (100%)	
Number of cycles	3 (3-4)	4 (4-4)	**<0.0001**
Age, years	60.6 ± 11.6	60.0 ± 10.3	0.562
Female sex	72 (55%)	163 (47%)	0.086
BMI, kg/m^2	23.4 (20.9-25.9)	24.7 (22.3-27.3)	**0.001**
Tumour origin			
Bronchial and thymus	11 (8%)	19 (5%)	0.131
Pancreatic	43 (33%)	98 (28%)	
Gastrointestinal	63 (48%)	172 (49%)	
Unknown primary	13 (10%)	61 (17%)	
Tumour grade			
Grade 1 NET	20 (16%)	91 (26%)	**0.048**
Grade 2 NET	39 (30%)	86 (25%)	
Unknown	70 (54%)	173 (49%)	
Karnofsky Performance Score	90 (80-95)	90 (80-100)	0.078
Months since diagnosis	22.8 (6.3-48.1)	14.9 (5.7-43.6)	0.253
Previous treatments			
Somatostatin analogues	75 (58%)	205 (59%)	0.862
Surgery	59 (45%)	151 (43%)	0.660
External beam radiotherapy	14 (11%)	24 (7%)	0.158
Chemotherapy	6 (5%)	27 (8%)	0.233
Progression before PRRT			
Yes	68 (52%)	202 (58%)	0.113
No	28 (22%)	48 (14%)	
Unknown	34 (26%)	100 (29%)	
Liver metastases	114 (88%)	318 (91%)	0.304
Bone metastases	38 (29%)	61 (17%)	**0.005**
Uptake on ^{111}In-DTPA-octreotide scan*			
Lower than liver	1 (1%)	3 (1%)	0.803
Equal to liver	7 (6%)	23 (7%)	
Higher than liver	79 (67%)	216 (62%)	
Higher than kidneys/spleen	31 (26%)	108 (31%)	
Extent of the disease†			
Limited	13 (11%)	37 (11%)	0.861
Moderate	83 (71%)	257 (73%)	
Extensive	21 (18%)	56 (16%)	
Creatinine, µmol/L	73 (61-90)	74 (63-85)	0.861
Albumin, g/L	42 (40-45)	43 (40-46)	**0.001**
Alkaline phosphatase, U/L	136 (87-214)	105 (77-160)	**0.001**
Chromogranin A, µg/L	445 (166-1859)	491 (143-2349)	0.972

Data are presented as number (%), median (interquartile range), or mean ± standard deviation.

**In 12 patients of the reduced activity group, a ^{68}Ga-DOTATATE PET-CT scan was performed.*

†Scored on ^{111}In-DTPA-octreotide scintigraphy: Limited, up to five sites in one part of the body (head/neck, chest, upper abdomen, lower abdomen); moderate, multiple sites in up to two parts of the body; extensive, multiple tumour sites in more than two parts of the body.

TABLE 3. Radiological tumour response according to RECIST 1.1.

Variables*	**Reduced activity *n*=130**	**Full activity *n*=350**	***P*-value**
Complete response	3 (3%)	9 (3%)	0.061
Partial response	36 (32%)	132 (40%)	
Stable disease	58 (51%)	164 (50%)	
Progressive disease	17 (15%)	23 (7%)	

Data are presented as number (%).

**The best response was not evaluable in 16 patients from the reduced activity group and 22 patients from the full activity group.*

GRAPHICAL ABSTRACT