Long-Term Outcomes of Submaximal Activities of Peptide Receptor Radionuclide Therapy with ^{177}Lu-DOTATATE in Neuroendocrine Tumor Patients

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In the literature, up to 45% of neuroendocrine tumor (NET) patients who are treated with ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) do not receive the intended cumulative activity of 29.6 GBq (800 mCi). The aim of this study was to analyze the efficacy of submaximal activities of PRRT in patients who discontinued treatment for non–disease-related reasons. **Methods:** We retrospectively included patients with well-differentiated and advanced NETs who underwent PRRT from 2000 until 2019 and did not receive 29.6 GBq of ^{177}Lu-DOTATATE. For comparison, we selected control NET patients who received the intended cumulative activity of 29.6 GBq of ^{177}Lu-DOTATATE between 2000 and 2012. Primary outcomes were progression-free survival (PFS) and tumor 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 unrelated to disease (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 body mass index and albumin level, a higher alkaline phosphatase level, and fewer grade 1 tumors than the 350 patients included in the control group. The disease control rate in the reduced-activity group was 85%, compared with 93% for the control group ($P = 0.011$). The median PFS (95% CI) was 23 mo (range, 21–26 mo) for the reduced-activity group and 31 mo (range, 27–35 mo) for the control group ($P = 0.001$), and the median OS (95% CI) was 34 mo (range, 28–40 mo) and 60 mo (range, 53–67 mo), 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 of less than 29.6 GBq of ^{177}Lu-DOTATATE, PRRT was less efficacious in tumor response and survival than in patients who received 29.6 GBq.

Key Words: cumulative activity; peptide receptor radionuclide therapy; neuroendocrine tumor

Neuroendocrine tumors (NETs) originate predominantly from neuroendocrine cells 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 radiolabeled somatostatin analogs targets somatostatin receptors that are frequently present on the NET cell membrane. Currently, PRRT with [^{177}Lu-DOTA[0],Tyr[3]]octreotate (^{177}Lu-DOTATATE) is approved for well-differentiated, progressive, or advanced gastroenteropancreatic NETs (by the European Medicines Agency and the U.S. Food and Drug Administration) and other foregut NETs (by the Food and Drug Administration only).

^{177}Lu-DOTATATE induced an 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 NETs who were treated with 22.2–29.6 GBq (*3*). The NETTER-1 trial on patients with well-differentiated advanced midgut NETs showed that ^{177}Lu-DOTATATE plus long-acting octreotide results in a longer progression-free survival (PFS) than treatment with high-dose octreotide. The dosing schedule of ^{177}Lu-DOTATATE consisted of 4 cycles of 7.4 GBq each, 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 because of 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 because of progressive disease or death (*5,7–9*), which evidently influences the response and survival outcomes. The aim of this study was to analyze the treatment response, PFS, and overall survival (OS) in patients who did not receive the full cumulative PRRT activity for reasons unrelated to the behavior of the tumor.

MATERIALS AND METHODS

Patients

For this retrospective analysis, we selected all Dutch patients with gastroenteropancreatic and other foregut NETs 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 if they had a grade 3 NET or neuroendocrine carcinoma or if PRRT was administered in a neoadjuvant setting for local disease or in an adjuvant setting. Patient files were searched for the reason for activity adjustment and the clinical and tumor characteristics. Follow-up scans after PRRT

TABLE 1
Reasons for Submaximal Activity for All Patients Who Received < 29.6 GBq (n = 243)

Reason	n	No. of cycles	Cumulative activity (GBq)
Death 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 of 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
Loss 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 pulmonary nodule (n = 1), breast carcinoma (n = 1), gastrointestinal bleeding (n = 1), cerebrovascular event (n = 1), edema due to hypoalbuminemia (n = 1), admission elsewhere (n = 1), multiple problems (n = 2).

†Reasons include prevention of carcinoid crisis (n = 2), prevention of tumor lysis (n = 1), large tumor load in liver (n = 1), or baseline thrombocytopenia (n = 1) or were unknown (n = 1).

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

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

Data are number and percentage or median and range.

were assessed for the treatment response according to RECIST, version 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 tumor burden. A group of patients who received the maximum PRRT dosage was collected for comparison. For that group, 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 3 y for PFS, and received 29.6 GBq of ^{177}Lu-DOTATATE. The same inclusion and exclusion criteria were applied as for the patients who received less than 29.6 GBq. The tumor grade before PRRT was retrospectively assessed for all patients by retrieving the mitotic index or Ki-67% from pathology reports, applying the WHO 2019 classification (10). Our local institutional review board approved the phase 2 study, and all subjects signed an informed-consent form; for patients treated after 2015, the need for written informed consent was waived by the institutional review board.

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 wk between cycles. In cases 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 wk. 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 wk after each cycle and at 6 wk, 3 mo, 6 mo, and thereafter at 6-mo 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 tumor response for patients who received the reduced activity for non–disease-related reasons compared with patients who received the full PRRT activity. PFS was calculated from the start of PRRT until disease progression or death from any cause. PFS was censored when patients were lost to follow-up. Tumor response was assessed according to RECIST, version 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 the χ^2 or Fisher exact test for categoric variables and the Mann–Whitney U test or the t test for continuous variables. PFS and OS were analyzed
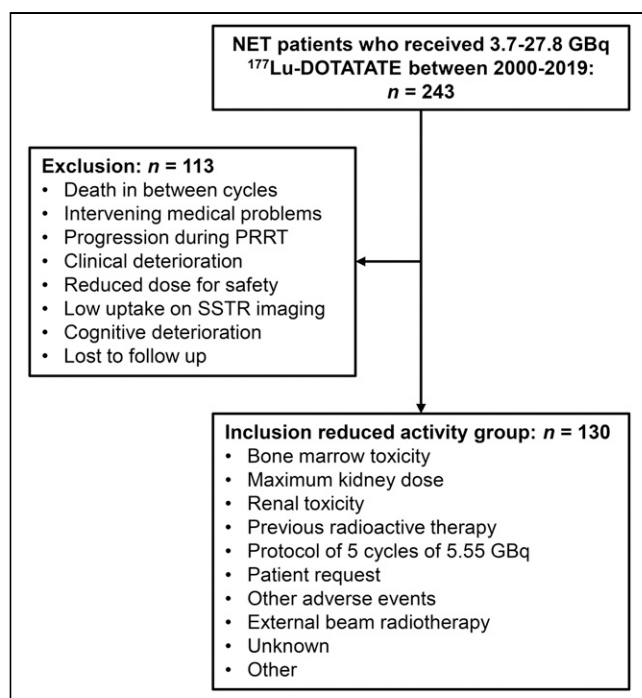
FIGURE 1. Inclusion and exclusion criteria for patients in the reduced-activity group. SSTR = somatostatin receptor.

with the Kaplan–Meier method and the log-rank test. Cox proportional-hazards analysis was used to calculate the adjusted hazard ratio 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, body mass index, tumor origin (bronchial, pancreatic, gastrointestinal, or unknown primary), tumor grade (grade 1, grade 2, or unknown), Karnofsky index, months since diagnosis, prior treatments (somatostatin analogs, surgery, or chemotherapy), progression before PRRT, liver metastases, bone metastases, tumor uptake on ^{111}In-diethylenetriaminepentaacetic acid (DTPA)–octreotide scintigraphy higher than kidney or spleen uptake, extent of disease (moderate, limited, or extensive), albumin level, alkaline phosphatase level, and year of treatment with PRRT. A 2-sided *P* value of less than 0.05 was considered statistically significant. All analyses were performed with SPSS Statistics (version 25, IBM Corp.) for Microsoft Windows.

RESULTS

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

Patient Characteristics

Table 2 shows the baseline characteristics of the reduced- and full-activity groups. The subjects in the reduced-activity group

received an average of 3 cycles with a median cumulative activity of 22.2 GBq (interquartile range, 18.5–25.9 GBq). The patients in the reduced-activity group had a significantly lower median body mass index and albumin level, a lower proportion of cases of unknown primary tumor origin, more frequent bone metastases, and a higher alkaline phosphatase level than the patients in the full-activity group. In the reduced-activity group, a significantly lower proportion of grade 1 tumors was also observed, although grade was not available in half the subjects. In the reduced-activity group, PFS and OS did not significantly differ between patients treated before and after 2013.

PFS

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

Treatment Response

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

OS

During 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 OS of 34 mo (95% CI, 28–40 mo), which ranged from 25 mo (95% CI, 20–30 mo) for 3.7–14.8 GBq to 34 mo (95% CI, 29–40 mo) for 16.7–22.2 GBq to 51 mo (95% CI, 35–68 mo) for 25.9–27.8 GBq (*P* = 0.018), and was shorter than in the full-activity group (60 mo [95% CI, 53–67 mo]) (*P* < 0.0001, Fig. 2B). The adjusted hazard ratio for all-cause death per 3.7 GBq of cumulative activity was 0.80 (95% CI, 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*). This treatment has been shown to induce disease control in most patients (*3*) and—compared with treatment with high-dose somatostatin analog—to prolong PFS (*4*). However, 23% of patients in the NETTER-1 trial (*4*) and up to 45% of patients in other studies (*6*) did not receive the optimum activity of ^{177}Lu-DOTATATE. To our knowledge, ours has been the only large analysis of the efficacy of submaximal doses of PRRT with ^{177}Lu-DOTATATE as a result of PRRT toxicity and other non–NET-related causes.

As described previously (*5,7–9*), death or progressive disease (27%) and toxicity (26%) were the most prevalent reasons for a submaximal PRRT dose 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 non–NET-related reasons for the efficacy analysis.

TABLE 2
Baseline Characteristics of All Included Patients

Variable	Reduced activity ($n = 130$)	Full activity ($n = 350$)	P
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 (y)	60.6 ± 11.6	60.0 ± 10.3	0.562
Female	72 (55%)	163 (47%)	0.086
Body mass index, kg/m^2	23.4 (20.9–25.9)	24.7 (22.3–27.3)	0.001
Tumor origin			
Bronchial and thymus	11 (8%)	19 (5%)	0.131
Pancreatic	43 (33%)	98 (28%)	
Gastrointestinal	63 (48%)	172 (49%)	
Unknown	13 (10%)	61 (17%)	
Tumor 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
Time since diagnosis (mo)	22.8 (6.3–48.1)	14.9 (5.7–43.6)	0.253
Previous treatments			
Somatostatin analogs	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 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 ()	136 (87–214)	105 (77–160)	0.001
Chromogranin A (μg/L)	445 (166–1,859)	491 (143–2,349)	0.972

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

†Scored on ^{111}In-DTPA-octreotide scintigraphy: limited = up to 5 sites in 1 part of body (head/neck, chest, upper abdomen, lower abdomen); moderate = multiple sites in up to 2 parts of body; extensive = multiple tumor sites in more than 2 parts of body.

Data are number and percentage, median and interquartile range, or mean ± SD.
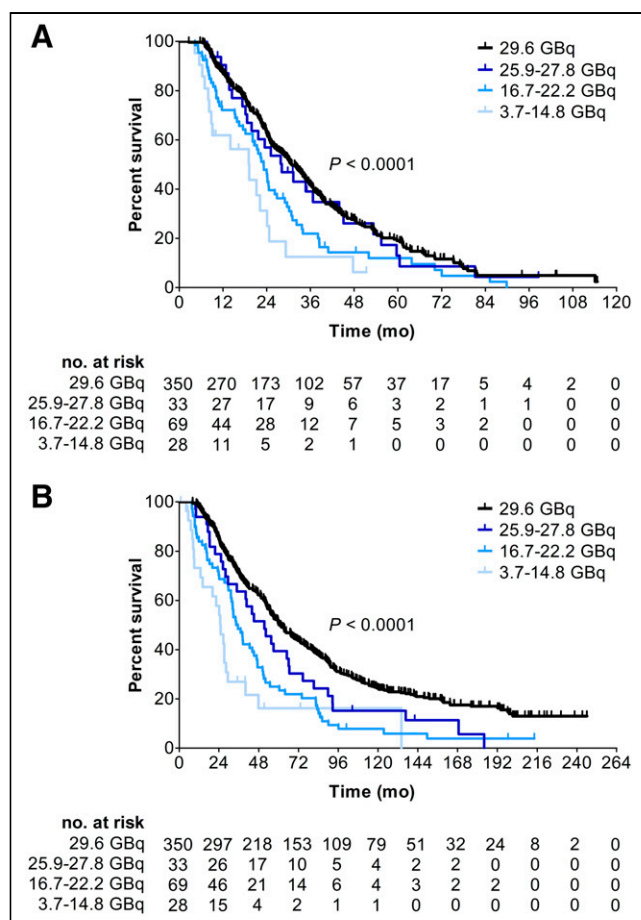
FIGURE 2. PFS (A) and OS (B) of full-activity group (29.6 GBq) compared with reduced-activity group (3.7–27.8 GBq), stratified for different cumulative-activity categories. *P* values were calculated with log-rank test.

The most prevalent causes for the patients included in the reduced-activity group were bone marrow toxicity, reaching the 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 than in the full-activity group, a disease control rate (DCR) of 85% and a median PFS of

TABLE 3
Radiologic Tumor Response According to RECIST 1.1

Variable*	Reduced activity (n = 130)	Full activity (n = 350)	P
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%)	

*Best response was not evaluable in 16 patients from reduced-activity group and 22 patients from full-activity group.
Data are number and percentage.

23 mo were still observed. The median OS of 34 mo, however, was significantly shorter than in the full-activity group (60 mo). This substantial difference could potentially be explained by the observation that patients with presumably more severe disease (i.e., more grade 2 tumors and bone metastases, increased alkaline phosphatase level, and lower body mass index and albumin) seemed to be at risk for discontinuing PRRT. In the literature, a higher tumor grade (*14*) and, possibly, the presence of bone metastases (*5,15–17*) and a lower body mass index or worse nutritional status (*18*) negatively influence prognosis. There is no clear evidence of an association between bone metastases and the risk of PRRT-induced bone marrow toxicity (*19,20*). Furthermore, because no scoring system for the extent of bone metastases was implemented, there might be a large variability in the extent of bone metastases. Nonetheless, the cumulative activity had a dose-dependent effect on 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 and the outcomes. Therefore, our study indicates an independent, incremental, and causal relationship between prognosis and cumulative activity.

Tumor response after PRRT has been shown to correlate with administered radioactivity (*5,21*). Hamiditabar et al. (*6*) 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, but it is unclear what the reasons were for not completing PRRT. In the phase II studies of Sansovini et al. (*22*) and Paganelli (*23*) et al., administration of a cumulative activity of 18.5 or 25.9 GBq was based on the presence of potential risk factors for renal or hematologic toxicity. In the 32 pancreatic NET patients treated with a reduced activity, a DCR of 78%, a median PFS of 22 mo, and a median OS of 64 mo were observed, compared with a DCR of 86%, a PFS of 53 mo (*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 mo was much longer than the 34 mo in our cohort. However, in the 43 gastrointestinal NET patients aimed for treatment with 18.5 GBq, both the median PFS and the median OS were not reached after a median follow-up of 38 mo, and the treatment response and OS were equal between the 18.5- and 25.9-GBq groups (*23*). In our study, power was insufficient to calculate differences stratified for primary tumor site. These studies are not fully comparable to our study because the different administered cumulative activities were intentional before the start of PRRT and patients who stopped PRRT for reasons other than progressive disease were excluded from efficacy analyses.

Given the clear dose response observed until the current maximal activity, PRRT using higher activities should be investigated in future trials. In 2 prospective trials, the efficacy of increasing the individual cumulative activities was studied. In the study of Del Prete et al. (*24*), 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 at least 3 cycles. A median 1.26-fold increase in absorbed tumor dose was observed, without increased toxicity rates. Garske et al. (*25*) based the number of cycles on the bone marrow and renal doses. Half 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. These personalized dosing strategies may help optimize 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 possibility should be the 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 tumor grade in half the subjects, because until 2007 it was not common practice to consistently report the Ki-67% or mitotic count. Moreover, although most 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 might 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 possibility by adding the year of treatment with PRRT to the regression analyses. Furthermore, regarding 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 most patients, only a single posttherapy scan was acquired, thus precluding accurate dosimetric evaluations.

Despite the limitations of this study, the data compellingly show that patients are likely to benefit from striving toward 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 of ^{177}Lu-DOTATATE if medically possible.

DISCLOSURE

Wouter W. de Herder has received speaker fees from Novartis and Ipsen and compensation from Novartis and Ipsen for service on advisory boards. Richard Feelders has received speaker and consultancy fees from Recordati, Corcept, and Ipsen. Johannes Hofland has received speaker fees from Ipsen and compensation from Novartis and Ipsen for service on advisory boards. Tessa Brabander has received speaker fees from Novartis and Ipsen and compensation from Novartis for service on an advisory board. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the efficacy of submaximal doses of ^{177}Lu-DOTATATE given for non–NET-related reasons?

PERTINENT FINDINGS: In this retrospective analysis of 350 NET patients who received 29.6 GBq, compared with 130 NET patients who received 3.7–27.8 GBq for non–NET-related adverse events (mainly bone marrow and renal toxicity), we observed a 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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