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ORIGINAL ARTICLE

Efficacy and safety of peptide receptor radionuclide therapy with [^{177}Lu]Lu-DOTA-TATE in 15 patients with progressive treatment-refractory meningioma

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Abstract

Purpose There is no evidence-based systemic therapy for patients with progressive meningiomas for whom surgery or external radiotherapy is no longer an option. In this study, the efficacy and safety of peptide receptor radionuclide therapy (PRRT) in patients with progressive, treatment-refractory meningiomas were evaluated.

Methods Retrospective analysis of all meningioma patients treated with [^{177}Lu]Lu-DOTA-TATE from 2000 to 2020 in our centre. Primary outcomes were response according to RANO bidimensional and volumetric criteria and progression-free survival (PFS). Overall survival (OS) and tumour growth rate (TGR) were secondary endpoints. TGR was calculated as the percentage change in surface or volume per month.

Results Fifteen meningioma patients received [^{177}Lu]Lu-DOTA-TATE (7.5–29.6 GBq). Prior to PRRT, all patients had received external radiotherapy, and 14 patients had undergone surgery. All WHO grades were included WHO 1 (n=3), WHO 2 (n=5), and WHO 3 (n=6). After PRRT, stable disease was observed in six (40%) patients. The median PFS was 7.8 months with a 6-month PFS rate of 60%. The median OS was 13.6 months with a 12-month OS rate of 60%. All patients had progressive disease prior to PRRT, with an average TGR of 4.6% increase in surface and 14.8% increase in volume per month. After PRRT, TGR declined to 3.1% in surface (p=0.016) and 5.0% in volume (p=0.013) per month.

Conclusion In this cohort of meningioma patients with exhaustion of surgical and radiotherapeutic options and progressive disease, it was shown that PRRT plays a role in controlling tumour growth.

Keywords Peptide receptor radionuclide therapy · [^{177}Lu]Lu-DOTA-TATE · Meningioma

Introduction

Meningiomas originate from the arachnoid meningothelial cells [1] and account for approximately one-third of all primary brain and central nervous system tumours [2]. Most meningiomas have a benign behaviour, but can cause serious morbidity and mortality depending on the location and growth pattern [1]. Neurosurgical resection with or without adjuvant external radiotherapy (e.g. stereotactic radiosurgery, conventionally fractionated external beam radiotherapy (EBRT)) is the first therapeutic approach for symptomatic or expanding meningiomas [3]. Reported recurrence rates after surgery vary and depend on the extent of resection [4–6], but recurrence was described in

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7–23% of WHO grade 1, 38–55% of WHO grade 2, and 78% of WHO grade 3 meningioma patients 5 years after gross total resection [7]. For patients with recurrent meningiomas without surgical options and who are refractory to or have a contra-indication for repeat external radiotherapy, no established systemic therapies are available [3]. Various medical therapies (e.g. cytotoxic chemotherapy, immunotherapy, tyrosine kinase inhibitors, nonradioactive "cold" somatostatin analogues, progesterone receptor (ant) agonists, and anti-angiogenic agents) have been investigated in exploratory arms, pilot studies, retrospective analyses, and mostly uncontrolled phase II studies, without undisputed efficacy for an antineoplastic response [8].

PRRT with [177Lu-DOTA0,Tyr3] octreotate ([^{177}Lu]Lu-DOTA-TATE) is a registered second-line therapy for advanced low-grade gastroenteropancreatic neuroendocrine tumours [9]. With PRRT, the radiolabelled somatostatin analogues bind to the somatostatin receptors (SSTR), predominantly SSTR subtype 2 ($SSTR_2$), that are present on the tumour cell membrane, which is followed by internalization of the radioligand-receptor complex into the tumour cell. Similar to neuroendocrine tumours, the majority of meningiomas express SSTR, with a predominance for $SSTR_2$ [10–12], and display high uptake on SSTR imaging [13–15].

In a meta-analysis of patients with recurrent or progressive meningiomas, PRRT resulted in disease control in 63% of the meningioma patients and a 6-month progression-free survival (PFS) proportion of 61% [16]. The study populations were small and the treatment protocols differed regarding the response criteria, amount of administered activity, and the radiopharmaceutical (i.e. [^{177}Lu]Lu-DOTA-TATE, [^{177}Lu]Lu-DOTA-TOC, [^{90}Y]Y-DOTA-TOC, and [^{111}In]In-Pentetreotide, or combinations thereof) [17–21]. Four studies reported on [^{177}Lu]Lu-DOTA-TATE, but in two studies, [^{177}Lu]Lu-DOTA-TATE was combined with EBRT [22, 23], and in one study, [^{90}Y]Y-DOTA-TOC or the combination was included [19]. Muther et al. reported solely on [^{177}Lu]Lu-DOTA-TATE, but the study consisted of only seven patients [24]. In this study, we report the efficacy of PRRT with [^{177}Lu]Lu-DOTA-TATE in patients with treatment-refractory meningiomas according to the recent response criteria proposed by the Response Assessment in Neuro-Oncology (RANO) working group. In addition, exploratory analyses of tumour growth rate before and after treatment were performed.

Patients and methods

Patients and treatment

From 2000 to 2020, all patients who received [^{177}Lu]Lu-DOTA-TATE for meningiomas in our centre were selected for retrospective analysis. Patients treated before 2015 were included in a phase II trial which investigated the efficacy and toxicity of [^{177}Lu]Lu-DOTA-TATE in SSTR-positive tumours, mainly consisting of neuroendocrine tumours [25]. The phase II trial was approved by our local institutional review board, and all subjects signed an informed consent form. For patients treated after 2015, the need for written informed consent was waived by the medical ethical committee of the Erasmus MC.

Patients were considered ineligible for (repeat) surgery or external beam radiotherapy. Other requirements for PRRT were creatinine ≤150 µmol/L (or a measured creatinine clearance ≥40 ml/min), haemoglobin ≥6.0 mmol/L, leucocytes ≥2×10^9/L, thrombocytes ≥75×10^9/L, total bilirubin ≤2× upper limit of normal, albumin ≥30 g/L, and a Karnofsky performance status >50.

[^{177}Lu]Lu-DOTA-TATE was administered with a maximum activity of 7.4 GBq (200 mCi) per cycle with a maximum of 4 cycles. In this cohort, the interval between the cycles was a median of 9 weeks (range 6–14 weeks). An amino acid combination (lysine 2.5% and arginine 2.5% in 1 litre NaCl) was intravenously given for renal protection and a selective serotonin (5-HT3) receptor antagonist for nausea prophylaxis. Additional treatment details were described previously [25].

Definitions and outcomes

The primary study outcomes were treatment response after completion of PRRT and PFS. Radiological response was evaluated by MRI. MRI imaging included post contrast T1-weighted imaging in all patients and in the majority also T2 images, with slice thicknesses ranging 1 to 5 mm. All available MRI scans at baseline and after the last cycle of PRRT were reassessed for the response evaluation, for which the criteria proposed by the RANO working group [26] were applied. PFS was defined as the time from start of PRRT to progression according to the RANO criteria or to death by any cause. Other endpoints were overall survival (OS), defined as the time between start of PRRT to death by any cause, and treatment-related toxicity. Renal, hepatic, and haematological toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [27], and the highest occurring grade was counted provided that the grade increased compared to baseline. The follow-up of the patients was updated until April 2021.

Volume measurements

The tumour volumes of all target lesions were calculated using Brainlab Elements software using semi-automatic segmentation of tumours on post-contrast T1-weighted

MRI images using SmartBrush 4.0. All segmentations were checked in three planes for accuracy.

Tumour growth rate

The tumour growth rate of each target lesion was calculated as the percentage change in tumour volume divided by the time in months between the scans. In 3 patients, new target lesions were detected on the baseline scan. For the analysis of the TGR of the individual lesions, the size of the new lesions on the scans before the baseline was based on the slice thickness and therefore the detection limit of the MRI scans (4 mm^2 and 0.008 cm^3 for MRI scan with 2 mm slice thickness and 9 mm^2 and 0.027 cm^3 for MRI scan with 3 mm slice thickness).

Dosimetry

The absorbed doses to the tumours were calculated according to the Medical Internal Radiation Dose (MIRD)-scheme [28]. Planar whole body and spot view scans were used to quantitate the activity in region of interests (ROIs) drawn over the tumour regions, using the Hermes Hybrid Viewer (version 4.0, Hermes Medical solutions, Sweden), using the count rate in ROI drawn over a reference standard with known activity to determine the planar calibration factor in cps/MBq. When SPECT imaging was available, the image was reconstructed using the Hermes SUVSPECT software, as described in Peters et al. [29]. When tumour imaging data was available at multiple time points, the time-activity curve was determined and fitted with a single exponential curve, which was used to determine the time-integrated activity. In most patients, only one time point imaging was available, and in those cases, it was assumed that the tumour showed equal kinetics as the spleen, also with $SSTR_2$-mediated uptake. When the spleen was also imaged at one time point, the effective half-life of tumour clearance was set at 60 h. The absorbed doses per time-integrated activity or S-values for tumours were based on the IDAC-spheres S-values for lymphatic node tissue, obtained with the IDAC-Dose 2.1 software [30]. The tumour volumes were obtained as described above.

Histopathology and immunohistochemistry

All available histological samples of the included patients were retrieved and reassessed by an expert pathologist for the WHO 2016 grade [31], the Ki67 index, and the $SSTR_{2a}$ expression level. For all $SSTR_{2a}$ and for the Ki67% if it was not yet available, the immunohistochemistry (IHC) was performed in our centre on 4-µm-thick FFPE sections by automated IHC using the Ventana Benchmark ULTRA (Ventana Medical Systems Inc.) according to the protocol, using the rabbit polyclonal antibody (BioTrend, Köln, Germany) at a dilution of 1:25 for the $SSTR_{2a}$ and the rabbit MIB-1 antibody (clone 30-9, Ventana) at a dilution of 2.0 ug/ml for the Ki67%.

Statistical analysis

IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, NY) was used for the statistical analysis, which consisted of the Kaplan Meier method with the log-rank test for the survival analyses and the Wilcoxon signed rank test for the paired analyses of the TGR. Two-sided *p* values of below 0.05 were considered statistically significant.

Results

Baseline characteristics

Between 2000 and 2020, 15 meningioma patients were treated with PRRT (Table 1). Revision of the histology showed WHO grade 1, 2, and 3 in 3, 5, and 5 patients before PRRT, respectively. The median (IQR) percentage of Ki67-positive tumour cells was 10% (4–20). Revision of the histology was unavailable in one patient with a grade 3 meningioma, and the grade was unknown in one patient whose tumour was not amenable to surgery and/or biopsy. The 14 other patients had undergone neurosurgical resection at least once, and all patients had received external radiotherapy prior to PRRT. Multiple lesions were present in 11 (73%) patients. In two patients, lesions were located in the spinal canal. Tumour uptake on SSTR imaging was higher than the normal liver uptake in 9 (60%) patients, and the median (IQR) number of tumour cells expressing $SSTR_{2a}$ on histology, regardless of intensity, was 100% (90–100). One patient (Fig. 1, subject 6) was treated with PRRT despite tumour uptake lower than the liver uptake due to the absence of alternative treatment options. Based on tumour uptake on the post-therapeutic scintigraphy, PRRT was completed in this patient. Fourteen patients had symptoms related to the meningioma (Table 2).

All patients had progressive disease according to RANO prior to start of PRRT (defined as ≥25% increase in surface, ≥40% increase in volume or detection of a new lesion), which was within a median (IQR) of 7.4 (4.2–13.1) months and within 12 months in 11 patients.

Peptide receptor radionuclide therapy and dosimetry

The intended cumulative activity of 29.6 (28.9–30.5) GBq was administered in 8 of the 15 patients (Table 3).

Table 1 Baseline clinical and tumour characteristics

Variables	All patients, *n*=15
Age (years)	51.6 ± 11.7
Female sex	8 (53%)
Body mass index (kg/m^2)	23.5 (21.7–37.0)
Karnofsky performance score	80 (68–83)
Time since diagnosis (months)	75.3 ± 43.1
Prior treatments	
External radiotherapy	15 (100%)
Number	1 (1–5)
Surgery	14 (93%)
Number	2 (1–5)
Cytotoxic chemotherapy	3 (20%)
Somatostatin analogues	2 (13%)
Tyrosine kinase inhibitor	1 (7%)
Mifepristone	1 (7%)
Embolization	1 (7%)
Highest histological grade before PRRT	
WHO grade 1	3 (20%)
WHO grade 2	5 (33%)
WHO grade 3	6 (40%)
Unknown	1 (7%)
Histological subtype	
Meningothelial	10 (67%)
Transitional	3 (20%)
Fibrous	1 (7%)
Unknown	1 (7%)
Ki67-index	10 (4–20)
Highest percentage of $SSTR_{2a}$-positive cells before PRRT	
100	8 (53%)
50–90	5 (33%)
Unknown	2 (13%)
Multifocal disease	11 (73%)
Number of lesions	5 (1–16)
Number of target lesions[a]	3 (1–4)
Largest diameter of the largest lesion (mm)	64 (33–74)
Volume of all target lesions (cm^3)	38.3 (16.3–61.2)
Volume of largest lesion (cm^3)	26.5 (14.1–49.5)
Uptake on [^{111}In]In-DTPA-octreotide scintigraphy[b]	
Lower than the liver	1 (7%)
Equal to the liver	2 (13%)
Higher than the liver	9 (60%)

Data are presented as numbers (%), median (IQR), or mean ±SD. Abbreviations: $SSTR_{2a}$, somatostatin receptor subtype 2a

[a]Not exactly known for 2 patients

[b]Uptake was assessed on planar imaging. A [^{68}Ga]Ga-DOTA-TATE PET-CT was performed in 3 patients, in whom the tumour uptake was equal to (*n*=1) or higher than the liver uptake (*n*=2)

The patients who discontinued PRRT for radiological progressive disease, clinical deterioration, death, and patient's own request received a median (range) of 15.1 (7.5–26.1) GBq.

In 8 patients, absorbed doses to 14 target tumours could be calculated. After completion of PRRT, the cumulative absorbed dose to the lesions ranged 7 to 404 Gy with a median (IQR) of 36 (13–90) Gy per lesion. In 7 of the 14

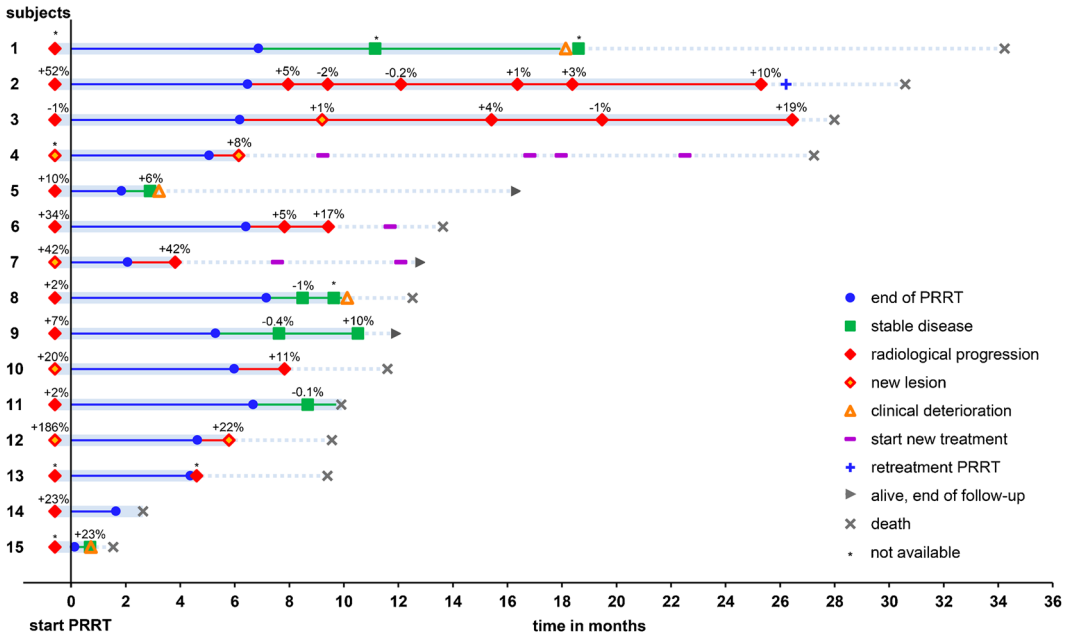

Fig. 1 Swimmer plot of treated patients. Each bar represents one study subject with a follow-up period from the baseline scan before PRRT until death or last known date alive. Follow-up MRI scans with response assessment according to RANO and compared to the baseline scan or nadir are shown with green squares (stable disease) and red diamonds (progressive disease) if available and until new treatment modalities were started. Percentages at each follow-up mark indicate the tumour growth rate (TGR) in percentage volume change per month since the previous measurement. Other treatment modalities included surgery, external radiotherapy, hydroxyurea, cisplatin, and tamoxifen

tumours, the cumulative absorbed dose exceeded 50 Gy (Supplementary Table 1 and Table 2).

Tumour response

In 11 patients, reassessment of both the volumetric and bidimensional RANO response criteria was available. In one patient, only the bidimensional RANO was evaluated because the baseline scan could not be digitalized for the volumetric measurement. In two patients, only reports of the scans were available. After completion of PRRT, stable disease was observed in 6 (40%) patients and progressive disease in 8 (53%) patients. One (7%) patient died after two cycles (Fig. 1, Supplementary Fig. 1). No patient had a minor, partial, or complete remission after PRRT. RANO surface and volumetric assessments were concordant regarding best overall response.

Progression-free survival

During a median (IQR) follow-up of 13 months (10–27), 8 patients demonstrated radiological progression and one patient still had stable disease according to RANO. Two patients died and 4 patients clinically deteriorated before radiological progression occurred (Fig. 1). The median (95% CI) PFS was 7.8 (5.3–10.3) months after start of PRRT with a 6-month PFS rate of 60% (Fig. 2a). The median PFS of 9.9 (1.6–18.2) months for the subjects with stable disease after PRRT was longer than the PFS of 6.1 (5.1–7.2) months for those with progressive disease (p=0.045). Moreover, the median PFS for WHO grade 1, 2, and 3 tumours was 10.1, 7.8, and 3.8 months, respectively (p=0.097). One patient received one additional retreatment cycle of PRRT 26 months after the first four PRRT cycles, since the response was considered prolonged tumour growth stabilization by the treating physicians (Fig. 1, subject 2).

Overall survival

Twelve (80%) patients died during the study period (Fig. 1). The median (95% CI) OS was 13.6 (10.3–17.0) months with a 12-month OS rate of 60% after start of PRRT (Fig. 2b) and 91.2 (80.9–101.4) months after diagnosis. The median OS was similar for the patients displaying progressive disease and stable disease after PRRT (13.6 and 12.5 months, respectively). Patients with WHO grade 3 showed the shortest median OS (9.4 months), while patients with WHO grade 1 had a median OS of 12.5 months and patients with WHO grade 2 27.2 months (p=0.022).

Tumour growth rate

Surface and volumetric TGR measurements were available for both the baseline and follow-up scans in 11 and 10 patients,

Table 2 Symptoms at baseline

Variables	All patients, *n*=15
Asymptomatic	1 (7%)
Symptomatic	14 (93%)
Pain (head, neck)	6 (43%)
Seizures	6 (43%)
Fatigue	6 (43%)
Paresis/paralysis	5 (36%)
Sensory disorders	5 (36%)
Cranial nerve impairment	10 (71%)
Vision loss/blindness	5 (36%)
Visual field loss	4 (29%)
Diplopia	4 (29%)
Hearing loss	2 (14%)
Anosmia	1 (7%)
Dysphagia	1 (7%)
Dysarthria	1 (7%)
Cognitive disorders[a]	8 (57%)
Impaired memory	5 (36%)
Impaired orientation	2 (14%)
Aphasia	2 (14%)
Impaired organization	1 (7%)
Impaired concentration	1 (7%)
Change in behaviour	1 (7%)
Apraxia	1 (7%)
Other	4 (29%)
Balance disorder	4 (29%)
Obstructive hydrocephalus	1 (7%)

Data are presented as numbers (%)

[a]In one patient, the cognitive disorder was not specified

Table 3 Details of peptide receptor radionuclide therapy with [^{177}Lu]Lu-DOTA-TATE

Variables	All patients, *n*=15
Completion of PRRT	8 (53%)
Cumulative activity (GBq)	28.9 (7.5–30.5)
No. of cycles of PRRT	4 (1–4)
Reasons for stopping PRRT	
Radiological progressive disease	3
Clinical deterioration	2
Death	1
Patient request	1
Prophylactic corticosteroid use[a]	8 (53%)

Data are presented as numbers, numbers (%), or median (range). Abbreviations: PRRT, peptide receptor radionuclide therapy

[a]Corticosteroid use in other patients: at baseline for symptomatic control (*n*=1), suppletion for hypopituitarism (*n*=1), and unknown (*n*=1)

respectively. After PRRT, tumour growth declined in 10 of the 11 patients according to the surface TGR and in 8 of the 10 patients according to the volumetric TGR (Fig. 1). The median (IQR) percentage increase was 4.6 (2.4–15.6) in surface and 14.8 (2.3–44.4) in volume per month before PRRT, which declined to 3.1% (1.3–9.8) in surface (p=0.016) and 5.0% (−0.2 to 13.6) in volume (p=0.013) per month on the first follow-up scan after PRRT. Patients who had progressive disease after PRRT had a higher median pre-therapeutic TGR (+14.6% in surface and +38.1% in volume per month) than those who had stable disease (+2.9% in surface and +4.6% in volume per month) after PRRT.

After PRRT, tumour growth declined in 19 of the 27 tumours that were available for the surface TGR and in 21 of the 23 tumours that were available for the volumetric TGR assessments. The median (IQR) TGR of all individual target lesions before PRRT was 7.3 (2.4–26.4) percentage increase in surface per month and 14.4 (2.5–52.1) percentage increase in volume per month, which was 3.1 (1.2–14.3) percent in surface (p=0.002), and 6.4 (1.5–17.6) percent in volume (p=0.002) change per month after PRRT.

Toxicity

At least one type of sub-acute hepatic or haematological toxicity was observed in 13 (87%) patients: grade 1 in 10 (67%) patients, grade 2 in 4 (27%) patients, grade 3 in 8 (53%) patients, and grade 4 in one (7%) patient. Severe grade 3 or 4 toxicity consisted only of lymphocytopenia (Table 4), and no secondary haematological malignancies occurred in this cohort. No renal toxicity was found. Ten patients reported increase in one or more neurological symptoms following PRRT or at the first follow-up after the last cycle. In the majority of cases, this concerned worsening of pre-existing neurological symptoms over time, which partly responded to dexamethasone.

Discussion

Although meningiomas are generally considered benign, recurrence, and progression after resection and/or external radiotherapy is not uncommon [7]. For patients who fail surgical and radiotherapeutic approaches, no registered systemic treatment option is available [3]. In the current study, we report our experience with [^{177}Lu]Lu-DOTA-TATE in patients with progressive treatment-refractory meningiomas. In 6 of the 15 patients (40%) who were treated in our centre from 2000 to 2020, stable disease was achieved after the last treatment cycle resulting in a median PFS of 7.8 months and a median OS of 13.6 months. The 6-month PFS and 12-month OS proportions of our cohort were both 60%. To compare, local standard of care of grade 2–3 meningiomas that were progressive

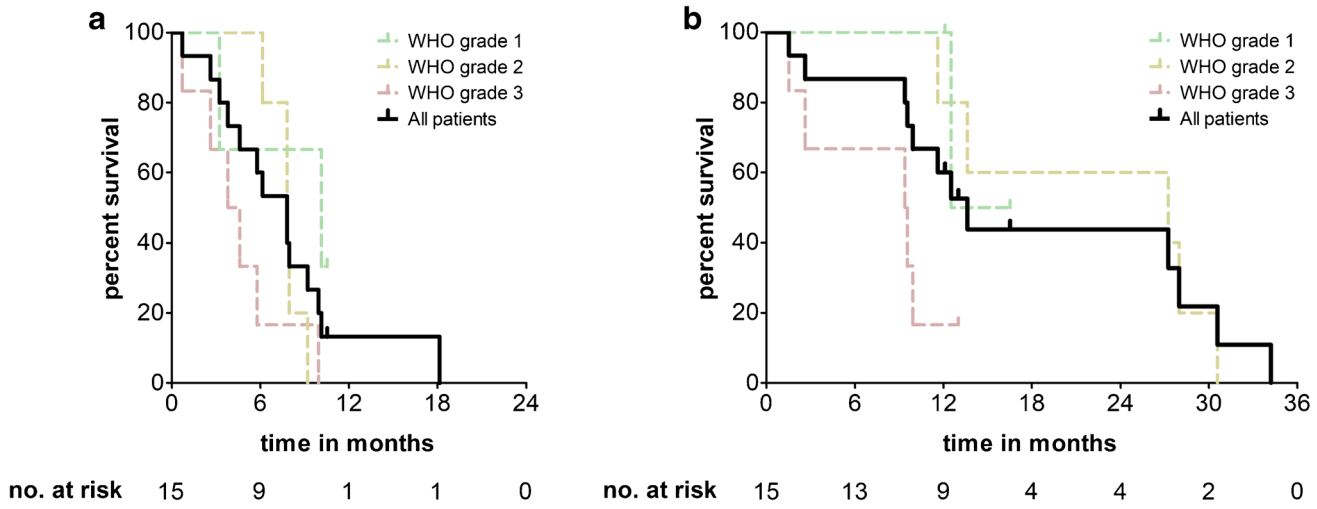

Fig. 2 Survival analyses of meningioma patients undergoing PRRT. Kaplan Meier curves of the progression-free survival (**a**) and overall survival (**b**), calculated from the first treatment of PRRT

Table 4 Sub-acute toxicity according to CTCAE 4.03

Adverse event	Total	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	5 (33%)	5	0	0	0
Thrombocytopenia	5 (33%)	5	0	0	0
Leukopenia	2 (13%)	1	1	0	0
Neutropenia	1 (7%)	0	1	0	0
Lymphocytopenia	10 (67%)	0	1	8	1
Increased alanine transaminase	2 (13%)	1	1	0	0
Increased alkaline phosphatase	1 (7%)	1	0	0	0

Data are presented as numbers or numbers (%)

after local treatment resulted in a 6-month PFS rate of 29% and a 12-month OS rate of 43% in a randomized phase II multicentre study [32]. In line with preceding analyses [17–21], the treatment-induced toxicity was mild in our cohort. Severe toxicity only consisted of lymphocytopenia, which has not been associated with an increased risk of infectious complications in PRRT-treated neuroendocrine tumour patients [25, 33, 34].

Several other studies with small numbers of patients have reported results of PRRT in meningioma patients, with disease control in 50–88% of patients [17–21, 24] and PFS or time to progression ranging 5–24 months after treatment [18–20]. In a pooled analysis, the disease control rate was 63%, the 6-month PFS rates 94%, 48%, and 0% for WHO grade 1, 2, and 3, respectively, and the 12-month OS rates 88%, 71%, and 52% for WHO grade 1, 2, and 3, respectively [16]. The outcomes in this pooled analysis have a large variability because of the heterogeneity in patient and tumour characteristics and treatment protocols, which makes it difficult to perform a meaningful comparison with our study. Furthermore, we present a meningioma population with progressive, severe, end-stage disease, which is illustrated by the high number of pretreatments, 12 (80%) patients with WHO grade 2–3, large tumour volumes, 11 (73%) with multifocality, and neurological sequelae in 14 (93%) patients. In the largest prospective study by Marincek et al. [17], stable disease was achieved in 66% of the 34 patients treated with [^{90}Y]Y-DOTA-TOC, and the mean overall survival was 9 years. The better response in this study might be attributed to the use of ^{90}Yttrium, as this radionuclide has a higher energy and longer tissue penetration range than ^{177}Lutetium [35]. However, in their study, 91% of patients had unifocal tumours, and only 26% WHO grade 2 and 3 lesions, and in more than half of cases unknown histological grade. Before PRRT, 74% had surgery, and only 3% underwent external radiotherapy. Consequently, it can also be hypothesised that the extensive pretreatment with external radiotherapy in our cohort has led to resistance to ionizing radiation [36]. On the other hand, the total advised doses of fractionated radiotherapy range 50–60 Gy for meningiomas [37, 38], while a total dose >50 Gy was

reached in only 7 out of 14 measured tumour regions after PRRT. However, dosimetry analysis was only possible in 8 patients, which included single-time point imaging in 4 of these patients. Due the limited availability of the data, the dosimetric calculations may be less accurate.

Furthermore, achieving partial response after PRRT [16] or other systemic therapies [8] in meningiomas is rare. It might therefore be better to start PRRT timely before patients develop treatment-refractory, progressive, and extensive disease. This was not the case in our cohort, where 6 patients died or clinically deteriorated because of tumour progression before the effect of PRRT could have been instigated or lasted.

In the previous studies, different response criteria (SWOG [18, 21], RECIST 1.1 [17, 20], RANO [22, 24], modified Macdonald [19], PERCIST [24], others [23]) were used. To our knowledge, this is the first study that demonstrates that the bidimensional and volumetric RANO best response on MRI are concordant for meningiomas treated by PRRT. Response assessment in meningioma trials can be challenging, because of the variation in the baseline progression rate. In more slowly growing tumours, stable disease might be an acceptable outcome if the TGR declines after therapy. Since the volumetric TGR was previously found to be predictive of antitumour activity in meningiomas [39], we assessed the TGR before and after PRRT. We were limited by the retrospective nature of this study, as the TGR calculation was not possible in all patients and this analysis might have been more reliable when the scans had been performed with a similar follow-up schedule in all patients. Nevertheless, we did notice a significant decline in the TGR after PRRT in the majority of our patients, indicating that PRRT was able to reduce the growth potential of the tumours. Additionally, Seystahl et al. [19] reported a ≥25% reduction in the volumetric TGR in half of their patients. However, there is no consensus yet on how to calculate the TGR, since it is debated whether the growth pattern is exponential or linear [39–42].

Limitations of this study were the retrospective design, the long period of patient inclusion, and the small sample size. However, we provided a detailed analysis of the response including the recommended RANO criteria, adding evidence to the limited existing literature of PRRT for high-grade, progressive, and treatment-refractory meningioma.

In conclusion, the currently available data indicate that PRRT can inhibit tumour growth in a subset of meningiomas, warranting a multicentre controlled prospective clinical trial with clearly defined response criteria. Preferably, such a clinical study should be performed in meningioma patients at earlier disease stages and making use of tumour growth rate measurements as additional outcome measure.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-022-06044-9.

Author contribution Concept and design: NSM, EMB, JECB, JH, and TB
Acquisition, analysis, and/or interpretation of data: all authors
Drafting of the manuscript: NSM
Critical revision of the manuscript for important intellectual content: all authors
Statistical analysis: NSM, JH, and TB.

Data availability The datasets generated during and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics approval The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Erasmus Medical Centre.

Consent to participate Informed consent was obtained from all subjects involved in the study, or the need for written informed consent was waived by the medical ethical committee of the Erasmus MC.

Consent for publication Informed consent was obtained from all subjects involved in the study, or the need for written informed consent was waived by the medical ethical committee of the Erasmus MC.

Conflict of interest E.M.B has received consultancy fees from BrainLab A.G. W.W.D.H has received speaker fees from AAA-Novartis and Ipsen, compensation from AAA-Novartis and Ipsen for service on advisory boards, and research support from AAA-Novartis. J.H. has received speaker fees from Ipsen and compensation from AAA-Novartis and Ipsen for service on advisory boards. T.B. has received speaker fees from AAA-Novartis and Ipsen, compensation from AAA-Novartis for service on advisory board, and research support from AAA-Novartis. The other authors have no disclosures.

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