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Somatostatin receptor-targeted radiopeptide therapy in treatment-refractory meningioma: an individual patient data meta-analysis

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ABSTRACT

Background: Somatostatin receptor (SSTR)-targeted peptide receptor radionuclide therapy (PRRT) represents a promising approach for treatment-refractory meningiomas.

Methods: We performed an individual patient data (IPD) meta-analysis including all published meningioma patients treated with SSTR-targeted PRRT. Main outcomes were toxicity, response to treatment, progression-free survival (PFS), and overall survival (OS). We applied the Kaplan-Meier method to estimate survival probabilities and report incidence rates per 100 person-years. We applied Cox proportional hazards models to determine the effect of covariates.

Results: We screened 537 papers, and identified six eligible cohort studies. We included a total of 111 patients with treatment-refractory meningioma who received SSTR-targeted PRRT. Disease control was achieved in 63% of patients. Six-month PFS was 94%, 48% and 0% for WHO (World Health Organization)-I, -II, & -III, respectively. The risk of disease progression decreased by 13% per 1000 MBq increase in the total applied activity. One-year OS was 88%, 71%, and 52% for WHO-I, -II & -III, respectively. The risk of death decreased by 17% per 1000-MBq increase of the total applied activity. Main side effects comprised transient hematotoxicities such as anemia in 22%, leukopenia in 13%, lymphocytopenia in 24%, and thrombocytopenia in 17% of patients.

Conclusion: This IPD meta-analysis represents the most comprehensive analysis of benefits and adverse events of SSTR-targeted PRRT for treatment-refractory meningioma. The treatment was well tolerated, achieved disease control in most cases, and showed promising PFS and OS.

INTRODUCTION

Meningiomas constitute the most common intracranial nonglial primary neoplasm (*1*). Low-grade meningiomas (WHO (World Health Organization)-I) are usually benign and typically display indolent behavior (*2*), while high-grade meningiomas (WHO-II and WHO-III) have higher rates of recurrence (*1*,*3*). Meningiomas of all grades may show multiple recurrences and become refractory to treatment (*4*).

Therapeutic options for recurrent and progressive meningiomas are limited to high-dose radiation and repeated surgery, often with unsatisfactory results. Several approaches with targeted therapy and cytotoxic chemotherapy have been investigated during the past decades but failed to demonstrate significant efficacy (*2*). Thus, new treatment modalities are urgently needed.

The majority of meningiomas express a high density of somatostatin receptor (SSTR) subtypes, making them susceptible to SSTR-targeted peptide receptor radionuclide therapy (PRRT), such as DOTA-Tyr^3-octreotide (DOTATOC) and DOTA-Tyr^3-octreotate (DOTATATE), labeled with the β^--emitting radioisotopes yttrium-90 and lutetium-177 (*5*,*6*).

The present work aims to systematically evaluate evidence for SSTR-targeted PRRT by analyzing toxicity, response to treatment, PFS, and OS via an IPD meta-analysis of all published patients subjected to SSTR-targeted PRRT.

MATERIALS AND METHODS

The study adhered to the PRISMA-IPD (Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data) Statement (*7*).

Literature Search

We searched PubMed, Embase, Cochrane Library, and ClinicalTrials on June 17th, 2019 using two different search strings: first, the MeSH-terms "octreotide" or "somatostatin" in combination with "meningioma"; and second, "meningioma" in combination with either "radiopeptide", "radionuclide", "octreotide", or "somatostatin". Two authors (CM and TM) independently screened abstracts and full-texts, settling all disagreements by consensus.

Study Selection

We included studies investigating patients treated with any radiolabeled somatostatin analogue in otherwise treatment-refractory or inoperable meningiomas. We excluded case reports and abstracts but did not impose restrictions on language. "Treatment-refractory meningioma" was defined as recurrent or progressive meningioma that failed control despite multiple attempts with conventional treatment modalities including surgery, fractioned or stereotactic radiotherapy, and/or chemotherapy. Hence, therapeutic options were considered to be exhausted by the treating physicians prior to initiation of SSTR-targeted PRRT. The fraction of patients with progressing tumors on time of PRRT initiation is unknown, however eligibility criteria in one study comprised tumor progression within 12 months prior to PRRT (n=34) (*8*). Tumors were considered "inoperable" due to anatomical location, comorbidity, or patient's refusal.

Outcomes and Data Extraction

We contacted the authors of each study (n=6) and obtained the following IPD: age, WHO tumor grade, total activity applied (in MBq), the number of treatment cycles, best obtained radiologic treatment response, PFS, and OS.

As data were either completely accessible online or received in a completely anonymized form, i.e. that data cannot be tracked to any patient, it is not required by Danish Law to obtain IRB Approval.

Quality of Evidence and Risk-of-Bias

We rated the quality of evidence according to GRADE (Grading of Recommendations, Assessment, Development and Evaluations) and applied ROBINS-I, a tool developed by Cochrane for assessing Risk Of Bias In Non-randomized Studies of Interventions (*9*) (Supplementary Table 1 and 2, respectively).

Data Synthesis & Statistical Analysis

We pooled data into one cohort for simultaneous analysis, thus applying the 'one-stage' approach according to the PRISMA-IPD Statement (*7*). We extracted adverse events as reported in the original studies. All studies addressed hematotoxicity but applied different assessment schemes: Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, version 4.0, and WHO criteria for hematotoxicity from 1979 (*10–12*). CTCAE v. 3.0 and v. 4.0 were identical in terms of hematotoxicity, thus comparable. Two studies that applied WHO criteria for hematotoxicity (1979), and reported grade 1 hematotoxicities exclusively. Since WHO criteria for hematotoxicity (1979) and CTCAE v. 4.0 utilize identical laboratory data points (levels of hemoglobin, granulocytes, leukocytes and thrombocytes), we allocated all patients with WHO hematotoxicity grade 1 to CTCAE v. 4.0 grade 1.

We generated a weighted estimate of the radiological treatment response. Despite different radiological assessment schemes, each radiological evaluation constituted stable disease, progression of disease, and partial response. We applied a random-effects model, and quantified heterogeneity as "low", "moderate", and "high" corresponding to I^2-values of 25%, 50%, and 75% (*13*).

We estimated the probabilities of PFS and OS at 6, 12, 18, and 24 months using the Kaplan-Meier method. End of follow-up was either the date of death, loss to follow-up, or the individual study termination. We estimated progression and mortality rates per 100 person-years for each WHO grade and subsequently compared all incidence rates as ratios. A uni- and multivariate Cox regression model estimated the association between risk of progression or death, and the covariates age (at diagnosis), total applied activity, and WHO grade (-I/-II/-III and Unknown). The univariate

estimates were adjusted only for the effect from each individual study center ("center effect"), while the multivariate estimates were adjusted for all covariates including the center effect.

We tested for non-linear effects of the continuous covariates age and total applied activity with restricted cubic splines regression and found that a linear relationship was adequate in both cases (Chi squared (sq.) $p>0.05$). We evaluated the assumption of proportionality for all models with visual inspection of Schoenfeld residuals, concluding that all covariate effects were proportional.

Results from a subgroup (n=82) analysis of yttrium-90-DOTATOC (n=47, 57%) *versus* lutetium-177-DOTATATE plus yttrium-90-DOTATOC (n=35, 43%) on OS is provided in the online Supplementary Table 3.

Finally, we applied a likelihood-ratio test (Chi-sq.) to evaluate for potential effect modification.

RESULTS

Study Selection

The search yielded 537 publications (Figure 1). We identified and reviewed nine studies for eligibility. Two studies were considered duplicates as they were based on the same patients and used data from included studies (*5*,*14*). Two studies combined SSRT-targeted PRRT with fractionated external beam radiotherapy, and were excluded from analysis (*15*,*16*). Thus, we identified six eligible studies (*5*,*6*,*8*,*17–19*).

Study Characteristics

We contacted all corresponding authors. All specific IPD of interest were accessible from the publication of three studies (*5*,*6*,*17*), and three authors provided original raw data from their respective studies (*8*,*18*,*19*).

Two studies were phase II clinical trials (*6*,*8*). One study examined the effect of SSTR-targeted PRRT prospectively over a 6-year period (*18*), whereas two evaluated the effect retrospectively over a 6-year (*5*) and a 2-year period (*17*), respectively. Finally, one study followed patients prospectively with routine scans every sixth month (*19*). The SSTR-targeted PRRT were either yttrium-90-DOTATOC, lutetium-177-DOTATOC, lutetium-177-DOTATATE, or combinations thereof (*5*,*6*,*8*,*17–19*). Patient inclusion criteria were similar across the studies and comprised a confirmed histological diagnosis, tumor uptake in SSTR scintigraphy and/or Positron Emission Tomography/Computer Tomography, disease progression or recurrence despite treatment, and a lack of further therapeutic options.

We included 111 patients who received SSTR-targeted PRRT between 1998 and 2015. Thirty-seven patients (33%) had WHO-I, 29 patients (26%) WHO-II, and 19 patients (17%) WHO-III. For the remaining 26 patients (23%), the grade could not be assessed (hereinafter labelled *Unknown*). Nineteen (17%) out of 111 patients were inoperable (five from Gerster-Gilliéron et al. (*6*), nine from Marincek et al. (*8*), three from Bartolomei et al. (*18*) and two from van Essen et al. (*20*)).

The median total applied activity was 12,950 MBq (range: 1,688 – 29,772) for the entire cohort. Figure 2 depicts the range and median total applied activity per WHO grade. The total applied activity was independent of WHO grades (Chi-sq. p=0.16).

Data on PFS could not be retrieved on 35 patients (*8*,*19*) Therefore, PFS analysis was based on 76 patients. Data on OS could not be retrieved on one patient (*19*). Thus, the OS analysis comprised 110 patients. Study and patient characteristics are listed in Supplementary Table 4.

Toxicity

The most frequently observed adverse events were grade 1 or 2 transient hematotoxicities (anemia (22% of patients), leukopenia (13%), lymphocytopenia (24%), and thrombocytopenia (17%)) (Supplementary Table 5).

Other transient adverse events, based on CTCAE v. 4.0, comprised: one grade 4 renal toxicity (*8*), one seizure, one cerebral edema, and one grade 2 renal toxicity that occurred 14 months after the treatment (*6*). Permanent AE: comprised one case each of grade 1 renal toxicity (*18*), alopecia and pituitary insufficiency (*5*).

Treatment Response

Three distinct radiological assessment protocols were applied to assess radiological treatment response (SWOG (*17–19*), RECIST v. 1.1 (*6*,*8*), Macdonald (*5*)). Sixty-four patients (58%) achieved stable disease, 45 patients (41%) experienced progression, and two patients (2%) had partial remission (Figure 3A**)**. A random-effects model estimated 63% of patients (95% CI: 0.45 – 0.81) experienced disease control. However, the model showed considerable and significant heterogeneity (I^2=77.3%, p<0.001, Figure 3B). Subsequently, we stratified for the different radiological assessment protocols, revealing moderate (I^2=60.9%) and non-significant (p=0.11) heterogeneity for RECIST v. 1.1 (*6*,*8*), and high (I^2=83.0%) and significant (p<0.001) heterogeneity for SWOG (*17–19*).

Progression-Free Survival

In total, 34 of 76 patients (45%) experienced progression during 117 person-years of follow-up. The cohort received a median of 3 (range: 1 – 6) treatment cycles. The PFS rates are listed in Supplementary Table 6. The 6-month (PFS6) and 12-month PFS (PFS12) were 61% (95% CI: 50 – 72) and 53% (95% CI: 42 – 65) for all grades combined, respectively (Figure 4A). We subsequently stratified based on WHO-grade, and found PFS6 of 94% (95% CI: 85 - 100), 48% (95% CI: 27 - 68) and 0% for WHO-I, -II & -III meningiomas, respectively (Figure 4B-D).

We estimated progression rates per 100 person-years (Figure 5A**)** and observed gradually increasing rates corresponding to higher WHO grades (Figure 5C). In the multivariate analysis, the rate of progression was significantly associated with total applied activity with HR of 0.87 (95% CI: 0.79 – 0.95) per 1,000 MBq increase, indicating the rate of progression decreased by 13% per 1,000 MBq increase. (Table 1). Figure 6A predicts the adjusted correlation between PFS and total applied activity. Reference was set to the median total applied activity of 12,540 MBq (Supplementary Table 4), and each HR must be interpreted relative to this reference.
There was no significant interaction between total applied activity and WHO grade, indicating the effect of SSTR-targeted PRRT on PFS was not modified by WHO grade (Chi-sq. p=0.7).

Overall Survival

Forty-five of 110 (41%) patients died during 263 person-years of follow-up. The cohort received a median of 2 (range: 1 – 6) treatment cycles. Survival times are summarized in Supplementary Table 6. The 6-month (OS6) and 12-month OS (OS12) for all tumors were 89% (95% CI: 83 – 95) and 78% (95% CI: 70 – 86), respectively (Figure 4A). Stratifying by WHO-grade, we found an OS12 of 88% (95% CI: 77 - 99), 71% (95% CI: 53 - 88), and 52% (95% CI: 28 - 77) for WHO-I, -II & -III, respectively (Figure 4B and Figure 4C).

The mortality rate for cases with unknown tumor grades was 11.4 per 100 person-years, which was slightly higher than the 8.1 deaths per 100 person-years observed in WHO-I, but markedly lower than the 31.1 and 43.1 deaths per 100 person-years observed in WHO-II and -III tumors (Figure 5B).

The mortality rate ratio of WHO-I versus Unknown was 0.73 (95% CI: 0.29 – 1.84) and the mortality rate ratio of WHO-II versus WHO-III was 0.72 (95% CI: 0.34 – 1.64), indicating no significant difference between these groups (Figure 5C). The mortality rate increased with increasing grades. Thus, the lowest mortality rate ratio was 0.19 (95% CI: 0.08 – 0.46) for WHO-I versus WHO-III (Figure 5C). In the multivariate analysis, risk of death was significantly associated with total applied activity with HR of 0.83 (95% CI: 0.76 – 0.90) per 1,000 MBq increase, indicating that risk of death decreased by 17% per 1,000 MBq increase (Table 1). Figure 6B predicts the adjusted correlation between OS and total applied activity. Reference was set to the median total applied activity of 12,950 MBq (Supplementary Table 4), and each HR must be interpreted relatively to this reference.
There were no interactions between total applied activity and WHO grade, suggesting the effect of SSTR-targeted PRRT on OS was not modified by WHO grade (Chi-sq. p=0.09).

DISCUSSION

The present IPD meta-analysis represents a comprehensive analysis on benefits and adverse events of SSTR-targeted PRRT for treatment-refractory meningioma. The results can be summarized as follows: First, SSTR-targeted PRRT is well tolerated in patients with treatment-refractory meningioma. All included studies concluded good overall tolerability of PRRT. The vast majority of patients experienced mild transient hematotoxicity, which was manageable in all cases. Second, SSTR-targeted PRRT resulted in disease control in most patients with treatment-refractory meningioma. Nevertheless, the respective random-effects model was associated with considerable and significant heterogeneity. Third, SSTR-targeted PRRT resulted in favorable PFS (for low-grade primarily) and OS in patients with treatment-refractory meningioma. Specifically, PFS6 was 94%, 48% and 0% for patients with WHO-I, -II &-III meningiomas, whereas the corresponding OS12 was 88%, 71%, and 54%. Finally, we established a prediction model of total applied activity and the correlation to progression or death, both indicating clinical benefits.

Strength and Limitations

The primary strength of this study is the 100% inclusion rate of original data on hitherto published cases of SSTR-targeted PRRT in treatment-refractory meningioma. We pooled the studies through the 'one-stage' method for IPD meta-analysis, thus making it possible to adjust and explore the data differently from a meta-analysis of aggregated data.

The study also has limitations. First, none of the included studies were randomized. However, our primary objectives were not to compare different treatments, but to analyze toxicity, response to treatment, PFS, and OS after PRRT, which are typical objectives of phase I or II trials (*21*). The relevance of this approach is supported by a meta-analysis of 61 cancer drugs where phase III-IV studies did not significantly increase detection of toxicities if the original phase I trial included more than 60 patients (*22*). Thus, this study, which included 111 patients, should be adequately sized to detect relevant toxicities.

Second, the studies applied three different radiological assessment protocols. Three studies used SWOG, two used RECIST v. 1.1, and one used Macdonald. The radiological protocols are not completely comparable. One study found a 21% discordance when SWOG and RECIST v. 1.1

criteria were applied to the same 80 patients (*23*). Different radiological assessment protocols along with evaluation of tumors at inequivalent time points might partially explain heterogeneity observed in the weighted estimate of 63% disease control. Consensus on assessment methods would improve external validity in future studies. There is already consensus in neuro-oncological and neuroimaging societies that the RANO (Response Assessment in Neuro-Oncology) criteria should serve as standard response criteria (*24*,*25*).

Third, included studies used different β^--emitting radionuclides and somatostatin analogues. We did not aim for a comparative analysis, since comparative efficacy can only be established in larger trials (20). The feasibility to pool different PRRTs is supported by experience from neuroendocrine tumors. Both yttrium-90-DOTATOC and lutetium-177-DOTATOC improved survival in neuroendocrine tumors, with no significant difference in the median OS (25).

Finally, some prognostic covariates were not accessible (*4*,*26*). The extent of surgery is often prognostically important but was not included in the IPD (*27*). Given our highly selected cohort of treatment-refractory meningiomas with uniformly progressive behavior, we would not assume this parameter to markedly affect the results. Patients with treatment-refractory meningiomas have dismal prognoses, and it is unlikely that co-morbidities such as cardiovascular disease, diabetes, or other cancers would have significantly affected the estimated OS.

Comparison With Results From the Literature

Our results on toxicity are in agreement with accumulating evidence from studies that validate SSTR-targeted PRRT as well tolerated therapies for neuroendocrine tumors with only transient and manageable adverse events (*20*,*28–30*).

The pooled findings of an anti-tumoral response are in agreement with those of the excluded study (*15*) that combined PRRT with external beam radiation with seemingly even better effects. Kreissl et al. included 10 treatment-refractory meningiomas (seven WHO-I, two WHO-II, and one Unknown) (*15*). Six patients received yttrium-90-DOTATOC, four received lutetium-177-DOTATATE, and all patients received external beam radiotherapy ranging between 40 and 60 Gy. All

patients had stable disease, including one partial remission, and one complete remission (*15*). These results suggest better disease control than for PRRT alone, and indicate a potential of combining PRRT with external beam radiotherapy.

The present results of PFS are promising in comparison with other therapies. A RANO review of 47 studies of surgery- and radiation-refractory meningioma reported a weighted PFS6 after treatment(s) with a variety of different agents (*2*). WHO-I meningiomas had a PFS6 of 29% (95% CI: 20.3 - 37.7) for all treatments combined, whereas the weighted PFS6 for WHO-II and -III meningiomas combined was 26% (95% CI: 19.3 – 32.7). The RANO review proposed that therapies achieving a PFS6 of at least 50% for WHO-I meningioma and at least 35% for WHO-II and -III meningiomas combined would be of potential clinical interest (*2*). This current study found PFS6 of 94%, 48%, and 0% for WHO-I, -II, & -III, respectively, and 37.7% for WHO-II and -III combined, which compare favorably to the RANO-proposed criteria for treatment-refractory WHO-I, -II and -III meningiomas.

Furthermore, the current results on OS are also promising. The RANO review observed that OS was less commonly reported and varied greatly between the included studies (*2*). For treatment refractory WHO-I meningioma, median OS ranged from 7 to 13 months. For WHO-II and -III meningioma, median OS ranged between 6 and 33 months. The highest OS was achieved with erlotinib and gefitinib (*2*). A phase II trial of antiangiogenic sunitinib for recurrent and progressive WHO-II (n=30) and -III (n=6) meningioma reported a median OS of 24 months (*31*). Similarly, another phase II trial of bevacizumab and Everolimus with mixed WHO-I, -II, -III, meningioma patients reported a median OS of 23 months (*32*). This current study found OS12 of 88%, 71%, and 52% for WHO-I, -II, & -III. Median OS was 43 months – again, indicating that SSTR-targeted PRRT compared favorably for management of treatment-refractory meningioma.

Implications

The findings of this study have implications for clinical practice, the drafting of guidelines, health insurance reimbursement, and further research. To clinicians, SSTR-targeted PRRT represents a promising approach for treatment-refractory meningioma when all other therapies have failed. Thus, future guidelines should mention this therapeutic option for such patients. Our results

warrant controlled studies to validate the adverse effects and benefits of SSTR-targeted PRRT for treatment-refractory meningioma prospectively. Our data on response and survival will help to determine expected effects and sample sizes. Finally, future studies should adhere to one common radiological assessment protocol to minimize heterogeneity and improve external validity.

CONCLUSIONS

The present IPD meta-analysis represents the presently most comprehensive analysis of benefits and adverse events of SSTR-targeted PRRT for treatment-refractory meningioma. The treatment is well tolerated, achieves disease control in most of cases, and shows promising results regarding PFS and OS. This treatment should be considered when other therapies have failed.

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None

Key points

Question

SSTR-targeted PRRT in treatment-refractory meningioma is conceptual attractive but hitherto previous published studies by necessity report small numbers of selected patients.

Pertinent findings

The present IPD meta-analysis represents the most comprehensive analysis of benefits and adverse events of SSTR-targeted PRRT for treatment-refractory meningioma. Its results demonstrate that the treatment is well tolerated, achieves disease control in the majority of cases, and shows promising results regarding PFS and OS.

Implications for patient care

SSTR-targeted PRRT should be considered when other therapies have failed.

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Figure 1. Flow diagram of study selection

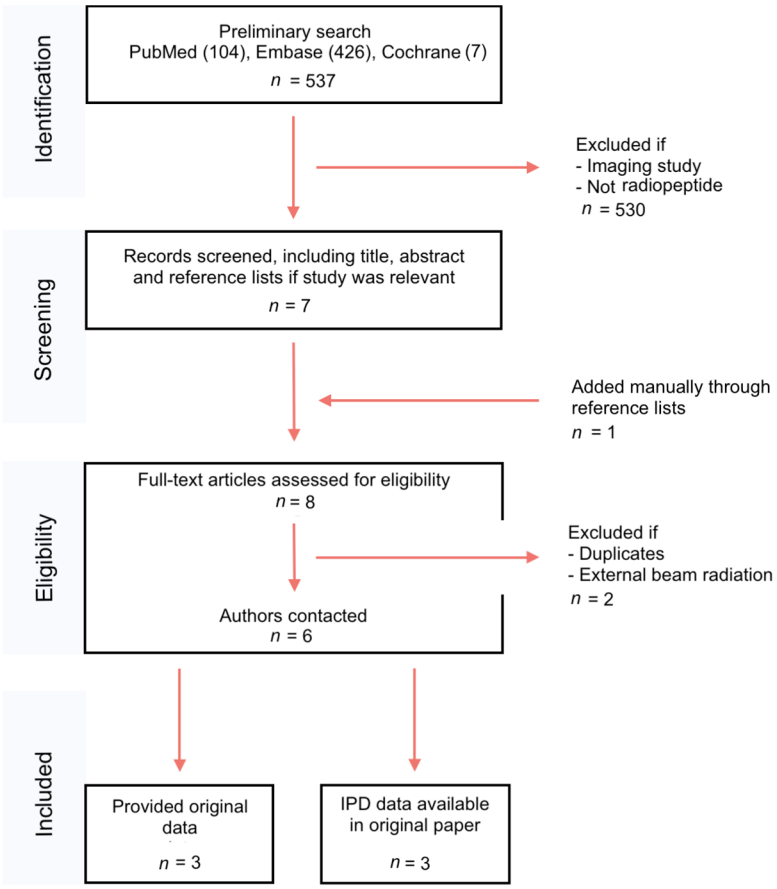


Figure 2. Boxplots of individual total applied activity per WHO grade of patients included in PFS and OS analysis.

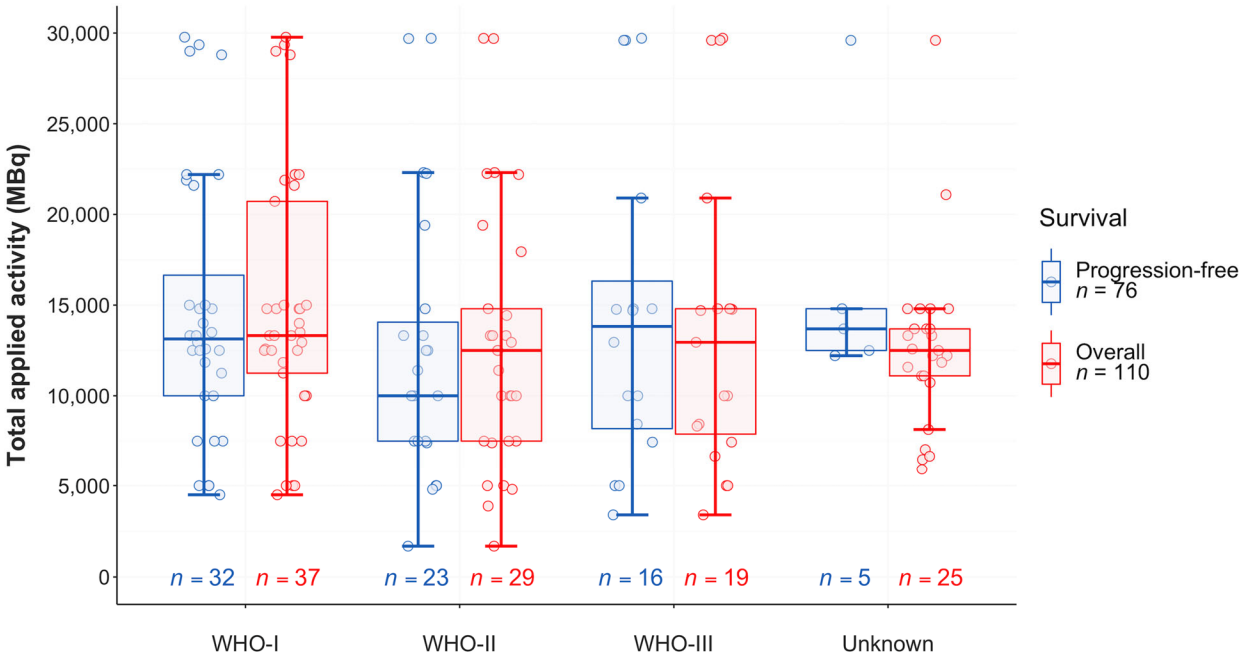


Figure 3AB. **A:** Cross-sectional observations of the best radiological treatment response obtained by each individual study and all studies combined. **B**. Forest Plot of the random-effects model estimating the weighted proportion of patients achieving stable disease or better. Overall and subgroup estimates based on the radiological assessment scheme applied.
Abbreviations: SD, stable disease. PR, partial remission.

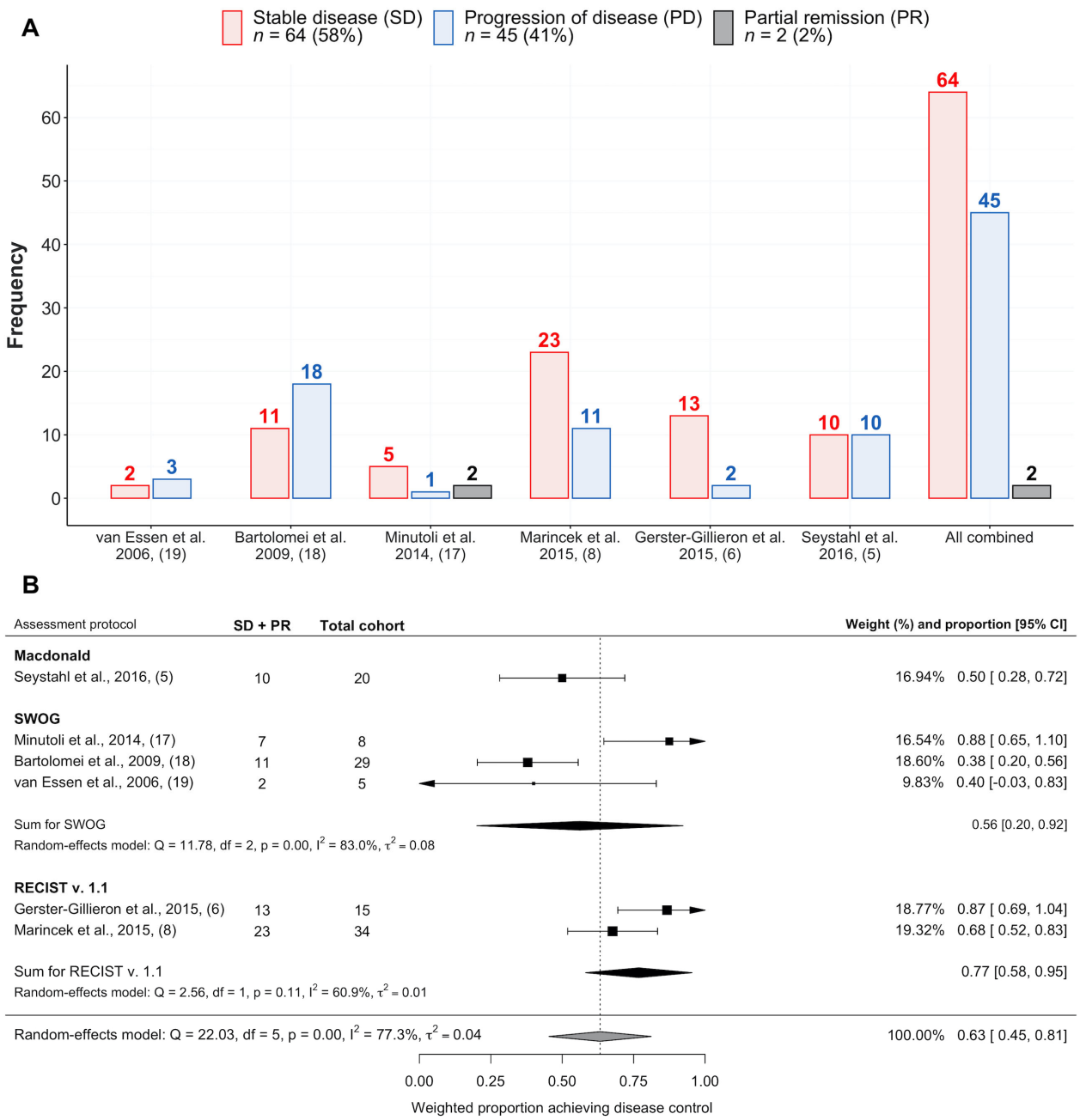


Figure 4AD. Kaplan Meier Curves. A: PFS and OS of all cases; **B:** PFS and OS for WHO-I meningioma; **C:** PFS and OS for WHO-II meningioma; **D:** PFS and OS for WHO-III meningioma.

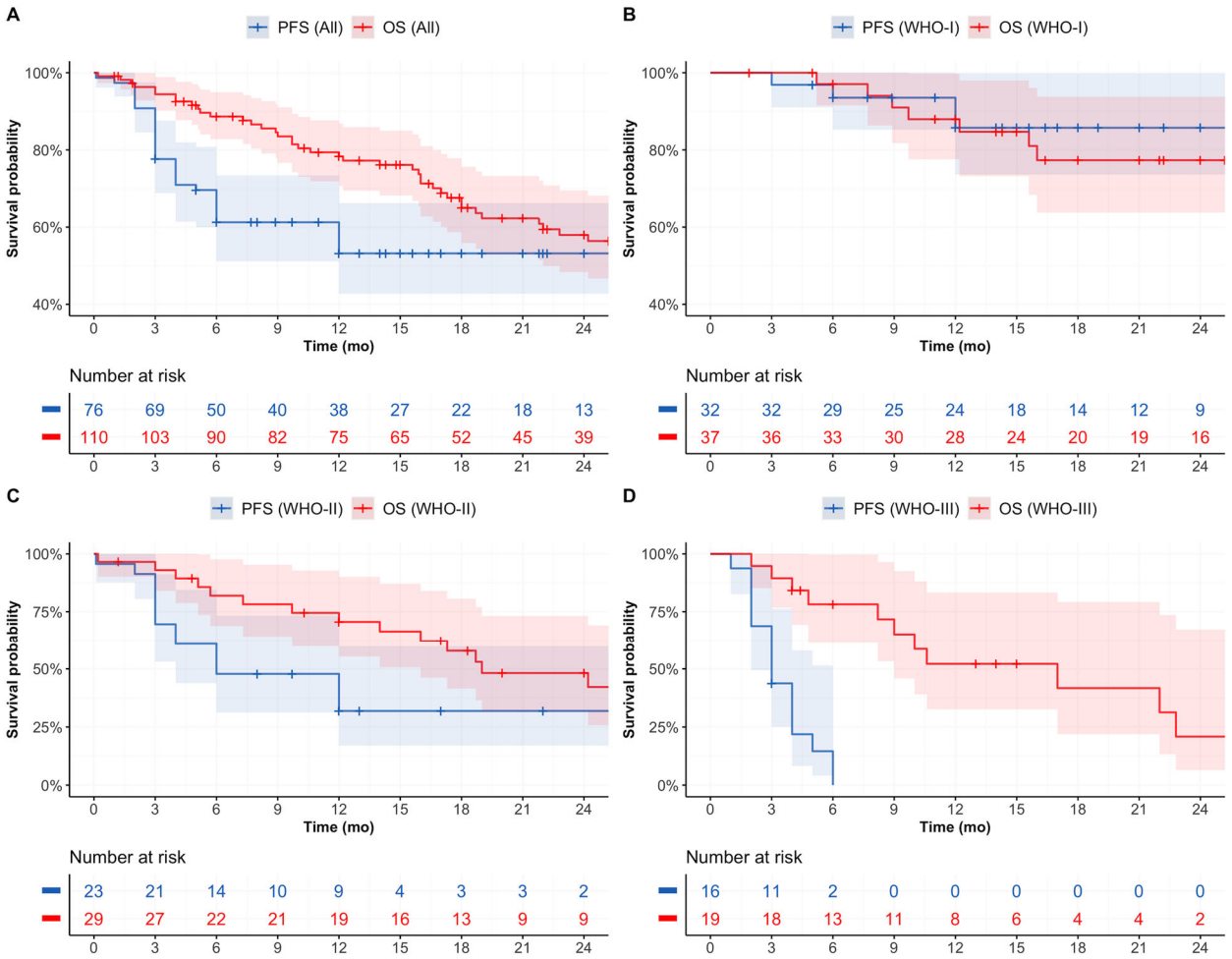
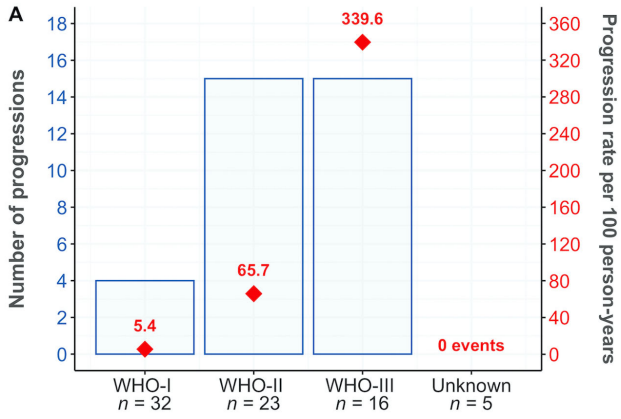
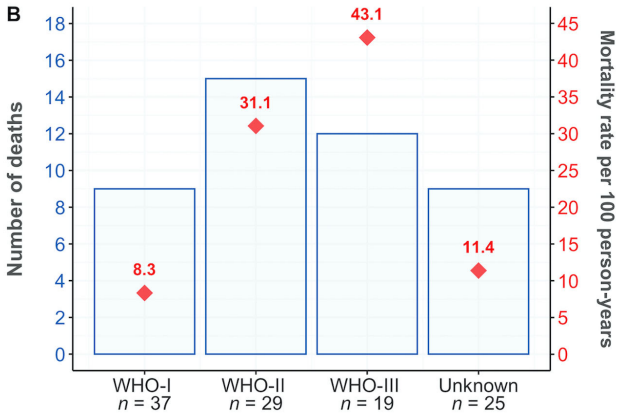


Figure 5AC. A: Progression per WHO grade. Number of progressions (left-hand y-axis) and progression rate per 100 person-years (right-hand y-axis). **B:** Mortality per WHO grade. Number of deaths (left-hand y-axis) and mortality rate per 100 person-years (right-hand y-axis). **C:** Incidence rate ratios (IRR) of progression and mortality.





C	Events per total	Person-years	IR	Events per total	Person-years	IR	Rate ratio [95% CI]
Progression rates							
WHO-I versus WHO-II	4/ 32	74.7	5.4	15 /23	22.8	65.7	0.08 [0.03, 0.25]
WHO-I versus WHO-III	4/ 32	74.7	5.4	15 /16	4.4	339.6	0.02 [0.01, 0.05]
WHO-II versus WHO-III	15/ 23	22.8	65.7	15 /16	4.4	339.6	0.19 [0.09, 0.39]
Cohort: 76 patients included							
Mortality rates							
WHO-I versus WHO-II	9/ 37	108.1	8.3	15 /29	48.3	31.1	0.27 [0.12, 0.61]
WHO-I versus WHO-III	9/ 37	108.1	8.3	12/19	27.9	43.1	0.19 [0.08, 0.46]
WHO-I versus Unknown	9/ 37	108.1	8.3	9 /25	79.1	11.4	0.73 [0.29, 1.84]
WHO-II versus WHO-III	15/ 29	48.3	31.1	12/19	27.9	43.1	0.72 [0.34, 1.54]
WHO-II versus Unknown	15/ 29	48.3	31.1	9/ 25	79.1	11.4	2.73 [1.19, 6.24]
WHO-III versus Unknown	12/ 19	27.9	43.1	9/ 25	79.1	11.4	3.78 [1.59, 8.97]
Cohort: 110 patients included							

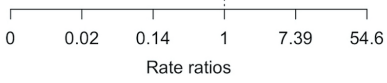
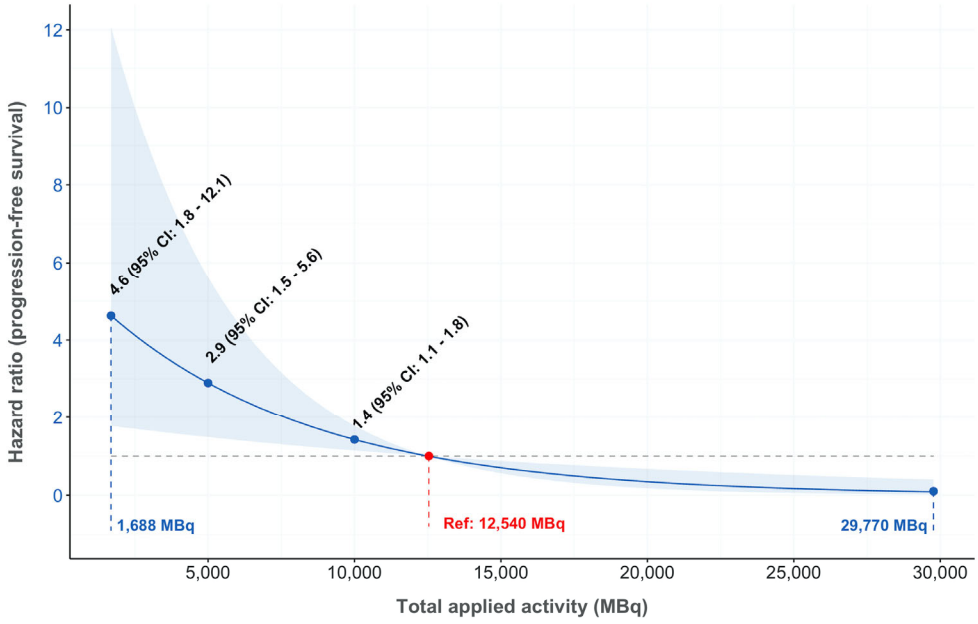


Figure 6AB. A: Correlation between total applied activity and the risk of progression. The model was adjusted to the median total applied activity (12,540 MBq), age at diagnosis, WHO grade (reference set to WHO-I), and center effect. Unknown grade (n=5) was omitted from the model. **B:** Correlation between total applied activity and the risk of death. The model was adjusted to the median total applied activity (12,950 MBq), age at diagnosis, WHO grade (reference set to WHO-I), and center effect.



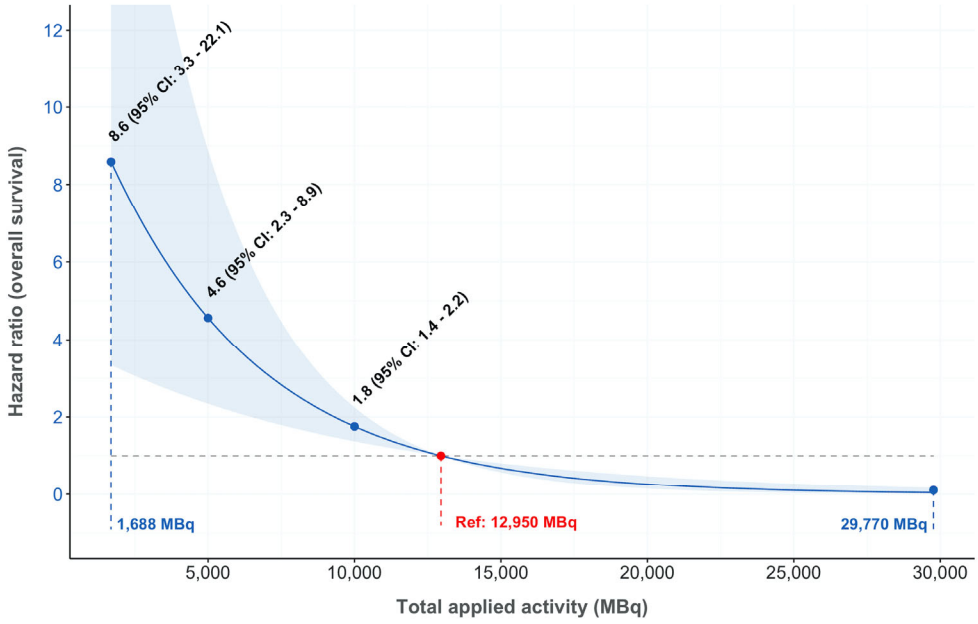


Table 1. PFS and OS according to total applied activity, age at diagnosis, and WHO grade.

Abbreviations: HR, hazard ratio.

Covariate	PFS (n=76)		OS (n=110)	
	Univariate	Multivariate*	Univariate	Multivariate*
	HR (95% CI)		HR (95% CI)	
Total applied activity, per 1000 MBq increase	0.84 (0.77 – 0.91)	0.87 (0.79 – 0.95)	0.83 (0.77 – 0.90)	0.83 (0.76 – 0.90)
Age at diagnosis, per 10-yrs increase	1.11 (0.86- 1.44)	1.08 (0.79 – 1.47)	1.29 (1.00 – 1.66)	1.47 (1.07 - 2.00)
WHO-I	Ref.	Ref.	Ref.	Ref.
WHO-II	9.06 (2.85 – 28.80)	8.09 (1.50 – 26.11)	2.45 (1.05 – 5.72)	2.32 (0.95 – 5.63)
WHO-III	31.17 (8.50 – 114.34)	25.78 (6.76 – 98.40)	4.61 (1.78 – 11.95)	2.28 (0.78 – 6.72)
Unknown grade	NA**	NA	2.58 (0.86 – 7.71)	2.45 (0.73 – 8.24)

*Adjusted for age at diagnosis, total applied activity, WHO grade, and center effect.

** Unknown grade (n=5) was omitted from the model.

Supplementary Table 1. The GRADE assessment: quality of evidence

	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Judgment of quality
Seystahl et al. *(5)*	No adjusted time-to-event analysis. No control population. Prognostic imbalance: no adjustment to competing risks.	Considerable heterogeneity determined by I^2 with corresponding p-value of 0.0 (Figure 3B, main text)	No head-to-head comparison; only reporting of SSTR-targeted PRRT, e.g. controls or other treatment groups	Time interval between resection of lesions and SSTR-targeted PRRT was median 13 mo (ranging 1 and 97 mo). There were no 95% confidence bands accompanying the estimates	Small study sample	Very low
Gerster-Gillieron et al. *(6)*	No adjusted time-to-event analysis. No control population. Prognostic imbalance: no adjustment to competing risks.	5/15 inoperable and 3/15 was not histopathological WHO graded Considerable heterogeneity determined by I^2 with corresponding p-value of 0.0 (Figure 3B, main text)	No head-to-head comparison.	There were no 95% confidence bands accompanying the estimates. No immunohistochemistry was applied. No Standard Uptake Volume was calculated.	Small study sample	Very low
Marincek et al. *(8)*	Cox regression not adjusted to WHO grade, thus unsuccessfully controlling confounding. The majority of patients had Unknown WHO grade. No control population. Prognostic imbalance: no adjustment to competing risks.	9/34 inoperable and 20/34 was not histopathological WHO graded. The assumption of proportionality was not tested for the Cox Regression. Considerable heterogeneity determined by I^2 with corresponding p-value of 0.0 (Figure 3B, main text)	No head-to-head comparison.	There were no 95% confidence bands accompanying the survival time estimates, but only for the Cox Regression model.	Small study sample	Very low
Bartolomei et al. *(18)*	No adjusted time-to-event analysis. No control population. Prognostic imbalance: no adjustment to competing risks.	Considerable heterogeneity determined by I^2 with corresponding p-value of 0.0 (Figure 3B, main text) One case was not histopathological WHO graded	No head-to-head comparison	PRRT started a median of 6 years (range: 4 months to 26 years) after primary diagnosis. There were no 95% confidence bands accompanying the estimates.	Small study sample	Very low

Minutoli et al. *(17)*	No adjusted time-to-event analysis. No control population. Prognostic imbalance: no adjustment to competing risks.	Considerable heterogeneity determined by I^2 with corresponding p-value of 0.0 (Figure 3B, main text)	No head-to-head comparison	There were no 95% confidence bands accompanying the estimates.	Small study sample	Very low
van Essen et al. *(19)*	No adjusted time-to-event analysis. No control population.	Two cases were not histopathological graded. Considerable heterogeneity determined by I^2 with corresponding p-value of 0.0 (Figure 3B, main text)	No head-to-head comparison	It was uncertain if patients were evaluated at equivalent times	Small study sample	Very low

Supplementary Table 2. The ROBINS-I assessment: risk of bias in non-randomised studies of intervention *(9)*.

Bias due to	confounding	selection of participants	classification of intervention	deviations of indented interventions	missing data	in measurement of outcome	in selection of reported results	Judgement
Seystahl et al. *(5)*	Moderate	Serious	Low	Low	Low	Moderate	Moderate	Moderate risk of bias
Gerster-Gillieron et al. *(6)*	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate to serious risk of bias
Marincek et al. *(8)*	Serious	Moderate	Low	Low	Critical	Moderate	Moderate	Serious to critical risk of bias
Bartolomei et al. *(18)*	Serious	Serious	Low	Low	Low	Moderate	Moderate	Moderate to serious risk of bias
Minutoli et al. *(17)*	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Moderate to serious risk of bias
Van Essen et al. *(19)*	Serious	Serious	Low	Low	Low	Moderate	Moderate	Moderate to serious risk of bias

The judgement was based on Supplementary Table A, B, C and D from *(9)*.

Supplementary Table 3. A subgroup multivariate Cox regression with focus on the effect of yttrium-90-DOTATOC *versus* lutetium-177-DOTATATE plus yttrium-90-DOTATOC on OS, exclusively.

Covariate	**OS (n=82)**	
	Univariate	Multivariate*
	HR (95% CI)	
Total applied activity, per 1000-MBq increase	0.78 (0.72 – 0.85)	0.81 (0.73 – 0.89)
Age at diagnosis, per 10-yrs increase	1.20 (0.94 – 1.53)	1.18 (0.86 – 1.64)
WHO-I ***n=27***	Ref.	Ref.
WHO-II ***n=21***	2.71 (1.15 – 6.38)	2.65 (1.10 – 6.39)
WHO-III ***n=10***	3.94 (1.50 – 10.30)	3.41 (1.24 – 9.42)
Unknown grade ***n=24***	0.99 (0.28 – 2.56)	2.34 (0.73 – 7.57)
Yttrium-90-DOTATOC ***n=47***	Ref.	Ref.
Lutetrium-177-DOTATATE plus yttrium-90-DOTATOC ***n=35***	0.34 (0.16 – 0.74)	0.43 (0.15 – 1.17)

*Adjusted to age at diagnosis, total applied activity, WHO grade, and center effect. The cohort comprised patients from four of the six studies (5, *6, 8, 18, 19).* In total, 16 patients from one study received lutetium-177-DOTATATE and were consequently excluded due to the small number of cases receiving this therapy exclusively *(5)*. The remaining study applied indium-111-pentetreotide and was excluded *(17).*

Supplementary Table 4. Study and patient characteristics.

MBq; megabecquerel. a) Includes embolization, Sandostatin, and one case of PRRT.

	van Essen et al. *(19)* **2006**	**Bartolomei et al.** *(18)* ***2009***	**Minutoli et al.** *(17)* ***2014***	**Marincek et al.** *(8)* ***2015***	**Gerster-Gilliéron et al.** *(6)*, ***2015***	**Seystahl et al.** *(5)*, ***2016***	**Included for PFS**	**Included for OS**
	N=5	N=29	N=8	N=34	N=15	N=20	N=76	N=110
Median age at diagnosis	55.0 (41 – 67)	53.8 (22 - 75)	54.5 (50 - 81)	54.4 (2 - 83)	56 (41 - 78)	42.5 (18 - 68)	53.4 (18 – 81)	53.9 (2 – 83)
WHO-I	0	13	5	5	9	5	32	37
WHO-II	0	11	3	6	2	7	23	29
WHO-III	3	4	0	3	1	8	16	19
Unknown grade	2	1	0	20	3	0	5	25
Prior surgery	3	26	6	25	10	18	63	88
Prior radiotherapy	5	18	1	11	4	18	46	57
Prior chemotherapy + othera	2	2	1	1	1	14	20	21
No treatment prior to PRRT	0	0	2	7	5	0	7	14
Median cumulative MBq	29600 (14800 – 29600)	10000 (5000 - 15000)	18200 (4800 - 29000)	13320 (3885 - 22200)	12950 (1688 - 14800)	20150 (3400 - 29770)	12540 (1688 – 12540)	12950 (1688 – 29772)
Mean treatment cycles	3.4	3.7	2.9	2.2	2.2	2.7	3.1	2.8
Median follow-up, months	5 (3 – 18)	15 (0.2 - 76)	11.5 (4 - 50)	21.8 (1 - 137)	48 (12 - 137)	16 (2 - 43)	16.2 (0.2 – 137)	17.2 (0.2 – 137)
Radiological criteria for progression	SWOG	SWOG	SWOG	RECIST 1.1	RECIST 1.1	Macdonald	-	-
Definition of progression	> 50% increase or an increase of 10 cm^2	> 50% increase or an increase of 10 cm^2	> 50% increase or an increase of 10 cm^2	> 20% increase	> 20% increase	> 25% increase	-	-

Supplementary Table 5. Transient hematotoxicity. Number of patients with adverse events observed in absolute numbers (proportion of the entire cohort). The definition for each specific grade is indicated below the cumulative number (and percentage). We report hematotoxicity according to CTCAE v. 4 (*34*) .

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Anemia ***24/111 (22%)***	20 (18%) (LLN – 6.2 mmol/L)	3 (3%) (6.2 - 4.9 mmol/L)	1 (<1%) (4.9 - 4.0 mmol/L)	0
Leukopenia ***14/111 (13%)***	5 (5%) (LLN – 3 x 10^9 /L)	7 (6%) (3 x10^9 - 2 x10^9 /L)	2 (2%) (2 x10^9 - 1 x10^9 /L)	0
Lymphocytopenia ***27/111 (24%)***	6 (5%) (LLN – 0.8 x10^9 /L)	8 (7%) (0.8 x10^9 - 0.5 x10^9 /L)	12 (11%) (0.5 x10^9 - 0.2 x10^9 /L)	1 (<1%) (<0.2 x10^9 /L)
Thrombocytopenia ***19/111 (17%)***	16 (14%) (LLN - 75 x10^9 /L)	1 (<1%) (75 x10^9 - 50 x10^9 /L)	2 (2%) (50 x10^9 - 25 x10^9 /L)	0

LLN; lower limit of normal, CTCAE v. 4; Common Terminology Criteria for Adverse Events version 4.

Supplementary Table 6. PFS and OS according to WHO grade.

Survival	WHO-I	WHO-II	WHO-III	Unknown	All
PFS (n=76)					
PFS6	94% (85 – 100)	48% (27 – 68)	0%	100%	61% (50 – 72)
PFS12	86% (73 – 99)	32% (12 – 52)	0%	100%	53% (42 – 65)
PFS18	86% (73 – 99)	32% (12 – 52)	0%	100%	53% (42 – 65)
PFS24	86% (73 – 99)	32% (12 – 52)	0%	100%	53% (42 – 65)
Median PFS	Not reached	6 months (4 – not reached)	3 months (2 – not reached)	Not reached	Not reached (12 – not reached)
OS (n=110)					
OS6	97% (91 – 100)	82% (68 – 96)	78% (59 – 97)	92% (81 – 100)	89% (83 – 95)
OS12	88% (77 – 99)	71% (53 – 88)	52% (28 – 77)	92% (81 – 100)	78% (70 – 86)
OS18	77% (62 – 92)	58% (39 – 77)	42% (15 – 68)	71% (51 – 91)	65% (55 – 75)
OS24	77% (62 – 92)	48% (28 – 68)	21% (0 – 45)	66% (45 – 87)	58% (47 – 69)
Median OS	Not reached (57 – not reached)	19 months (16 – not reached)	17 months (9 – not reached)	Not reached (22 – not reached)	43 months (22 – not reached)