Intraarterial Administration of Peptide Receptor Radionuclide Therapy in Patients with Advanced Meningioma: Initial Safety and Efficacy

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Peptide receptor radionuclide therapy (PRRT) is a treatment option for patients with advanced meningioma. Recently, intraarterial application of the radiolabeled somatostatin receptor agonists has been introduced as an alternative to standard intravenous administration. In this study, we assessed the safety and efficacy of intraarterial PRRT in patients with advanced, progressive meningioma. **Methods:** Patients with advanced, progressive meningioma underwent intraarterial PRRT with [^{177}Lu]Lu-HA-DOTATATE. The safety of PRRT was evaluated according to the Common Terminology Criteria for Adverse Events version 5.0. Treatment response was assessed according to the proposed Response Assessment in Neuro-Oncology criteria for meningiomas and somatostatin receptor–directed PET/CT. **Results:** Thirteen patients (8 women, 5 men; mean age, 65 ± 13 y) with advanced meningioma underwent 1–4 cycles (median, 4 cycles) of intraarterial PRRT with [^{177}Lu]Lu-HA-DOTATATE (mean activity per cycle, $7,428 \pm 237$ MBq; range, 6,000–7,700 MBq). Treatment was well tolerated with mainly grade 1–2 hematologic toxicity. Ten of 13 patients showed radiologic disease control at follow-up after therapy (1/10 complete remission, 1/10 partial remission, 8/10 stable disease), and 9 of 13 patients showed good control of clinical symptoms. **Conclusion:** Intraarterial PRRT in patients with advanced meningioma is feasible and safe. It may result in improved radiologic and clinical disease control compared with intravenous PRRT. Further research to validate these initial findings and to investigate long-term outcomes is highly warranted.

Key Words: somatostatin receptor; theranostics; peptide receptor radionuclide therapy; PRRT; meningioma

Meningiomas are the most common primary neoplasms of the central nervous system (CNS) and account for more than one third of all cases (*1*). Meningiomas are mostly classified as benign (CNS WHO grade 1), but 10%–15% of cases are higher grade tumors that are considered atypical (CNS WHO grade 2) or even malignant or anaplastic (CNS WHO grade 3) (*2*).

The preferred treatment is complete surgical resection, when feasible, with external beam radiotherapy serving as a common alternative or adjunctive, depending on the WHO grade (*3*). However, 30%–40% of lesions are skull-base meningiomas that can be ineligible for surgery because of tumor localization in close proximity to critical intracranial structures such as the cavernous sinus or the optic nerve (*4*). Furthermore, recurrence rates are notably high, with 10%–30% of benign meningiomas and up to more than 80% of anaplastic meningiomas recurring within 5 y after surgery or external beam radiotherapy (*5,6*). Therefore, various pharmacologic treatment options have been developed, which, however, often show an increased toxicity and poor efficacy (*7,8*).

Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin receptor (SSTR) agonists such as [^{177}Lu]Lu-DOTA-3-iodo-Tyr3-octreotate ([^{177}Lu]Lu-high-affinity [HA]-DOTATATE) and [^{177}Lu]Lu-(1,4,7,10-tetraazacyclododecane-N,N,N,N-tetraacetic acid)-Tyr3-octreotide ([^{177}Lu]Lu-DOTATOC) is an established second-line therapy in the therapeutic regimen for neuroendocrine tumors of gastroenteropancreatic origin that typically overexpress SSTR (*9*).

Given that approximately 90% of meningiomas highly express SSTR, predominantly receptor subtype 2a (*10*), PRRT is a therapeutic option for patients with refractory or recurrent meningioma (*11,12*). Previous reports have demonstrated the general feasibility and good tolerability of SSTR-directed radionuclide therapy in meningioma (*13–15*). The most frequently observed adverse effects of intravenous PRRT include low to moderate nephrotoxicity, hepatotoxicity, and hematotoxicity with exception of a few cases of severe transient lymphocytopenia (*11,13,16–20*). In a more recent study, which included a long-term observation period of 5 y after combined external beam radiotherapy and PRRT, no relevant chronic adverse effects were found (*15*). Disease stabilization was largely achieved after PRRT, especially in patients with CNS WHO grade 1 or 2 meningioma (*12,13*).

Since most meningiomas are highly vascularized (*21*) and previous studies have shown that SSTRs are highly expressed not only on the tumor cell surface but also on the endothelium of the peritumoral vessels (*22*), intraarterial administration of PRRT might be a reasonable therapeutic approach to further enhance the

therapeutic efficacy. In an initial case series, Vonken et al. observed a 2- to 4-fold increase in tumor uptake, and Braat et al. found an 11-fold increase through intraarterial administration of PRRT in comparison to intravenous procedures (23,24).

Most preliminary studies so far have investigated the safety of intraarterial PRRT in small patient cohorts during a short follow-up period. Reports of the radiologic and clinical outcome of intraarterial PRRT are largely limited as well, necessitating further investigations.

In this study, we assessed both the safety and efficacy of intraarterial PRRT in patients with advanced progressive meningioma during a long-term follow-up of up to 43 mo.

MATERIALS AND METHODS

Patients

Thirteen patients with locally advanced and progressive meningioma who were either ineligible for surgery, refractory to surgery or external beam radiotherapy, or declined surgery or external beam radiation therapy and underwent at least 1 cycle of intraarterially administered PRRT were included in this retrospective analysis. Patients with meningiomas located in close proximity to critical intracranial structures, such as the optic nerve, were included as well.

Each patient provided written informed consent following comprehensive medical information provided by a board-certified nuclear medicine physician. All procedures were performed in full compliance with the Declaration of Helsinki and its subsequent amendments and the legal considerations of clinical guidelines.

This study was approved by the Medical Ethics Committee of Ludwig-Maximilians-University of Munich, Munich, Germany (22-0907).

Preparations

Screening of patients included clinical assessment, laboratory tests, and ^{68}Ga-DOTATOC PET/CT (SomaKit TOC; Advanced Accelerator Applications) to assess sufficient tracer accumulation according to current guidelines (with target lesion uptake significantly higher than the uptake of intracranial reference structures such as, for example, the sagittal sinus) (25). In all patients, cardiac MRI (performed 68 ± 16 d before PRRT) was available. Renal scintigraphy was performed to rule out advanced kidney impairment before therapy.

Administration of [^{177}Lu]Lu-HA-DOTATATE

[^{177}Lu]Lu-HA-DOTATATE (7,400 MBq/cycle; peptide mass, 150 μg; maximum 4 cycles) was applied directly into the tumor-feeding vessel as identified by diagnostic digital subtraction angiography. If multiple tumor-feeding vessels were present, a single, more proximal site of injection was chosen to cover all tumor-feeding vessels. A single injection position was preferred to avoid microcatheter manipulation and contamination of the angiography suite. In case of multifocal disease, the dominant lesion causing the most clinical symptoms was selectively treated (defined as the target lesion). During the fourth treatment cycle, the dominant artery feeding the tumor was embolized with precipitating hydrophobic injectable liquid 25%.

PRRT was performed according to the practical guidance on PRRT in patients with neuroendocrine tumors of the International Atomic Energy Agency, the European Association of Nuclear Medicine, and the Society of Nuclear Medicine and Molecular Imaging (26), with injection of an amino acid solution of lysine (2.5%) and arginine (2.5%) in combination with antiemetic drugs over a 4-h period during each treatment cycle to reduce renal retention of the radiopeptide.

Therapy Response

Assessment of treatment response included imaging (cardiac MRI and SSTR-directed PET/CT) as well as monitoring of clinical symptoms and laboratory parameters.

The radiologic response was determined on the target lesions according to the proposed Response Assessment in Neuro-Oncology criteria for meningiomas, using volumetric measurements on gadolinium-enhanced cardiac MRI (27).

Clinical response was assessed by frequent assessments (median time interval, every 2 mo) including a detailed patient history (focusing on tumor-related neurologic symptoms and common treatment-related side effects such as fatigue, asthenia, or alopecia) and physical examinations.

Toxicity

All patients underwent frequent laboratory testing (every 14 d), including renal function (creatinine, glomerular filtration rate), liver function (γ-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, albumin, international normalized ratio, total bilirubin), and blood count (hemoglobin, leukocyte count, platelet count). Clinical evaluations were performed between and during the treatment cycles. Safety was assessed according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

Descriptive analysis was conducted including both qualitative and quantitative parameters. Quantitative parameters were assessed with consideration of mean, median, and SD.

RESULTS

Clinical Characteristics

Thirteen patients (8 women, 5 men; mean age, 65 ± 13 y) were included. The median time between primary diagnosis and the start of PRRT was 8 y (range, 0.5–20 y). All patients received SSTR-directed PET/CT (108 ± 12 MBq of [^{68}Ga]Ga-DOTATOC, imaging 60 min after intravenous tracer administration) before PRRT to confirm receptor expression on the tumor cell surface. The target lesions showed a median SUV_{max} of 21.9 and a median SUV_{peak} of 14.5.

Eight patients had undergone at least 1 surgical intervention before PRRT, with 4 of them received additional external beam radiotherapy. Only 1 patient had undergone external beam radiotherapy alone, and 4 patients had not undergone any treatment before PRRT either because of inoperability of the tumor or because the patient rejected any other therapy. Detailed patient characteristics are outlined in Table 1.

Treatment Characteristics

Each patient underwent at least 1 cycle of intraarterially administered PRRT with a median of 4 cycles (range, 1–4 cycles; 4 patients had less than 4 cycles because of clinical deterioration, death, or the patient refused another treatment cycle). The median time interval between consecutive cycles was 9 wk (range, 6–13 wk). The technical success rate of angiography was 100%. On average, $7,428 \pm 237$ MBq of [^{177}Lu]Lu-HA-DOTATATE was administered per cycle (range, 6,000–7,700 MBq). No dose reduction was required in any patient. The mean cumulative activity administered over all cycles was 25.7 ± 7.2 GBq of [^{177}Lu]Lu-HA-DOTATATE (range, 7.5–30.1 GBq; detailed information on the administered activities can be found in Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

Safety

The treatment was generally well tolerated by all individuals. Immediately after PRRT or during the therapy-free interval, the most common adverse effects considered to be treatment-related were fatigue and asthenia. Two individuals (15.4%) suffered from

TABLE 1
Patient Characteristics*

Patient	Age[†] (y)	Sex	Localization of tumor	CNS WHO grading	Previous therapy	Time interval[‡] (y)	Follow-up time (mo)
1	46	Female	Sphenoorbital (right hemisphere)	1	Surgery	7	43
2	78	Male	Parafalcine parietooccipital (right hemisphere)	2	Surgery/radiation	16	40
3	59	Female	Cavernous sinus (left hemisphere)	—	Radiation	4	38
4	95	Female	Posterior cranial fossa (right hemisphere)	—	None	9	34
5	77	Male	Parietal (right hemisphere)	—	None	1.5	14
6	73	Male	Parafalcine biparietal	2	Surgery/radiation	8	27
7	52	Male	Sphenoid wing (right hemisphere)	1	Surgery	10.5	24
8	64	Female	Frontal, temporooccipital and sphenoorbital (left hemisphere)	2–3[¶]	Surgery/radiation	3.5	8
9	52	Male	Frontobasal expanding to para-/sellar region (both hemispheres)	1	Surgery	17	24
10	60	Female	Sphenoid wing (right hemisphere)	—	None	0.5	18
11	55	Female	Posterior cranial fossa (left hemisphere)	1	Surgery	9	14
12	74	Female	Parafalcine parietal (right hemisphere)	—	None	2	13
13	67	Female	Multiple intracranial locations (meningiomatosis; both hemispheres)	2	Surgery/radiation	20	1

*Patient 5 passed away from unknown cause 11 mo after second treatment cycle; patient 8 passed away from progressive disease 4 mo after third treatment cycle; patient 13 passed away from heart failure 1 mo after first treatment cycle.
[†]Age at first PRRT cycle.
[‡]From primary diagnosis to PRRT.
[¶]Histologically confirmed increasing dedifferentiation to CNS WHO grade 3 meningioma.

severe nausea, which was attributable to the amino acid solution and subsided after completion of the infusion.

Other treatment-related adverse events included transient mild to severe headache (15.4%; 2/13) and minor alopecia (15.4%; 2/13).

All patients developed transient hematotoxicity at some point after therapy, including grade 3 anemia (7.7%; 1/13), thrombocytopenia (15.4%; 2/13), or lymphocytopenia (38.5%; 5/13), and 1 patient developed grade 4 lymphocytopenia (Supplemental Table 2). There were no cases of higher-grade hepatotoxicity or pathologic elevations of the international normalized ratio and total bilirubin in any patient (Supplemental Table 3).

One patient (7.7%) experienced transient grade 3–4 nephrotoxicity in the form of acute kidney injury of postrenal etiology, which was not directly attributable to PRRT (Supplemental Table 4; Supplemental Figs. 1–10). Another subject experienced progressive dizziness, facial paralysis, and painful limbs 3–6 mo after PRRT.

In patients with preexisting anemia or kidney impairment, there was no worsening of clinical condition during treatment, except for 1 patient who experienced first-stage chronic kidney failure before PRRT, who developed second-stage kidney failure at the end of follow-up.

One patient showed local necrosis and infection on a finger of the left hand, which might have been related to angiography. Apart from that, there were no severe angiography complications observed.

Efficacy

Radiologic treatment response was assessed according to the volumetric response criteria of the Response Assessment in Neuro-Oncology working group (27). At the end of treatment, 1 patient (7.7%) showed a complete remission (Fig. 1), 1 patient (7.7%) showed a partial remission, and 8 patients (61.5%) achieved stable disease. The pattern of tumor growth did not significantly change after therapy. Some larger tumors developed central necrosis, whereas smaller tumors diminished in size without altering their growth pattern. In cases in which the tumors remained stable in volume, no change in the growth pattern was observed. Follow-up imaging or end-of-therapy staging was not available in 3 patients because of either death or clinical deterioration.

In terms of clinical outcome, 2 patients (15.4%) showed improvement of tumor-related symptoms, and 7 subjects (53.8%) were clinically stable. Two patients (15.4%) experienced clinical deterioration, and 1 of them passed away after the third treatment cycle because of progressive disease. Another patient died of heart failure, and another one was lost to follow-up and passed away more than a year later of unknown cause. Response assessment regarding clinical and radiologic outcome is shown in Table 2.

Progression-Free Survival (PFS) and Overall Survival (OS)

The median follow-up period was 24 mo (range, 1–43 mo). At the time point of censoring, median PFS in our cohort was 18 mo (CNS WHO grade 1, 24 mo; grade 2, 4 mo; unknown grading, 18 mo). The 6-mo and 12-mo PFS for the entire cohort was 76.9% (10/13; CNS WHO grade 1, 100%; grade 2, 25%; unknown grading, 100%).

Overall, 3 of 13 patients (23.1%) experienced either clinical (2 patients) or radiologic (1 patient) progression during the
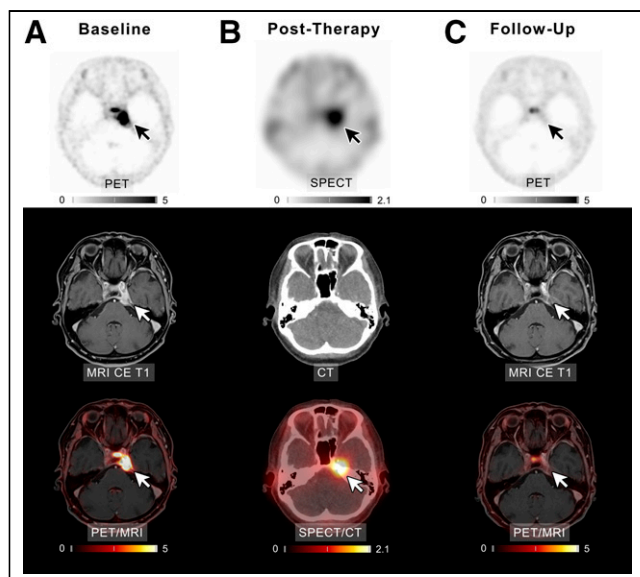
FIGURE 1. Example of patient 3 with meningioma of unknown grade undergoing intraarterial PRRT with [^{177}Lu]Lu-HA-DOTATATE. (A) Transaxial slices of baseline PET, contrast-enhanced (CE) T1-weighted MRI, and fused PET/MRI demonstrate SSTR-expressing meningioma in left cavernous sinus (white and black arrows). After 4 cycles of PRRT (posttherapeutic SPECT/CT imaging after the first cycle presented in B), complete remission according to RANO as well as PET criteria was recorded (C). In line with imaging, patient reported significant improvement of previous vertigo, headaches, and isolated unilateral abducens nerve palsy. Scale bars denote SUVs.

24 person-years of follow-up. Three patients (23.1%) passed away 1 mo (patient 13), 8 mo (patient 8), and 14 mo (patient 5) after the first treatment cycle of heart failure, tumor progression, and unknown cause, respectively.

The 6-mo OS was 92.3% (12/13; CNS WHO grade 1, 100%; grade 2, 75%; unknown grading, 100%), and the 12-mo survival rate was 84.6% (11/13; CNS WHO grade 1, 100%; grade 2, 50%; unknown grading, 100%). Median OS has not been reached yet. The PFS and OS rates are listed in Supplemental Table 5.

DISCUSSION

As about 10%–30% of benign meningiomas and up to more than 80% of anaplastic meningiomas recur within 5 y after conventional therapy (5,6), PRRT offers a potential therapeutic option because of the high SSTR expression of the tumors (10–12). Given that meningiomas are often highly vascularized and SSTRs are also highly expressed on endothelial cells of peritumoral blood vessels (21,22), it appears that intraarterial administration of PRRT has the potential to deliver higher radiation doses to the tumor, which has been suggested in initial case series (23,24). In this study, we report a long-term follow-up of 13 meningioma patients who received a maximum of 4 treatment cycles of intraarterial PRRT.

Safety

To the best of our knowledge, this study is the first to investigate the toxicity and response to treatment with intraarterial PRRT with a long-term follow-up of up to 43 mo in a population of more than 10 patients. We were able to show that intraarterial administration of PRRT is well tolerated with only transient hemato-, hepato-, and

TABLE 2
Outcome Including Imaging, Clinical Symptoms, and PFS

| Patient | CNS WHO grading | Outcome | | PFS (mo) | Cumulative number of cycles | Cumulative activity (GBq) |
		Imaging	Clinical symptoms			
1	1	Stable disease	Stable	41	4*	29.8
2	2	Stable disease after PRRT (complete remission after another tumor resection surgery)	Progressive frailty	4	4*	29.9
3	—	Complete remission	Improvement	38†	4*	30.0
4	—	Stable disease	Stable	34†	4*	28.3
5	—	—	Lost to follow-up	14	2*	14.9
6	2	Partial remission	Stable	27†	4*	29.7
7	1	Stable disease	Stable	24†	4*	29.8
8	2–3‡	—	Clinical progression	4	3	22.3
9	1	Stable disease	Improvement	24†	4	29.9
10	—	Stable disease	Stable	18†	4*	30.1
11	1	Stable disease	Stable	14†	4*	29.6
12	—	Stable disease	Stable	13†	3*	22.4
13	2	—	Death	1	1	7.5

*Patients who received an embolization of tumor-feeding artery during last treatment cycle.
†Not reached at time point of censoring.
‡Histologically confirmed increasing dedifferentiation to CNS WHO grade 3 meningioma.

nephrotoxicity being observed, except for higher-grade lymphocytopenia. Treatment-related clinical symptoms were transient and self-limiting in all cases.

Persistent deterioration of renal function occurred in 1 of our patients that experienced nephrotoxicity after PRRT (9.1%). In contrast, this rate was significantly higher (71%) in the previous study by Bodei et al. on intravenous PRRT in patients with neuroendocrine tumors (28). However, the comparability of the data is limited as the cohort of Bodei et al. was significantly larger than the one investigated in the current work (13 patients vs. 807 patients), and different tumor entities were analyzed. Furthermore, different radiopharmaceuticals had been used, and especially ^{90}Y-labeled somatostatin analogs are known to be associated with higher renal toxicity rates (28). In a review by Mirian et al. on intravenous PRRT in patients with meningioma, the rate of permanent nephrotoxicity in all patients was even lower than that in our cohort (7.7% vs. < 1%) (11).

The patient with increasing dizziness, facial paralysis, and painful limbs 3–6 mo after PRRT had undergone surgery before PRRT, which led to postoperative bleeding. Considering the tumor location and radiologic tumor control, the reported symptoms seem to be more likely attributable to the postoperative complications rather than to PRRT or tumor progression. In comparison to a study on PRRT in patients with neuroendocrine tumors by Kobayashi et al. and to the NETTER-1 trial, the number of lymphocytopenia of any grade was higher in our patient cohort (85% vs. 50% vs. 18%) (16,19). However, higher-grade lymphocytopenia was comparable to the results reported by Kobayashi et al. (grade 3, 39% vs. 33%) but higher than in the NETTER-1 trial (grade 3–4, 38.5% vs. 9%) (16,19). Again, it should be noted that different tumor entities are compared here, and the number of participants of the prospective NETTER-1 trial is significantly larger than our patient cohort (16).

In comparison to the review by Mirian et al., the rate of higher-grade anemia, lymphocytopenia, and thrombocytopenia was higher among our patients (grade 3: anemia, 7.7% vs. <1%; lymphocytopenia, 38.5% vs. 11%; thrombocytopenia, 15.4% vs. 2%; grade 4: lymphocytopenia, 7.7% vs. <1%) (11). However, it needs to be considered that Mirian et al. analyzed a significantly higher number of patients (13 patients vs, 111 patients) of different studies with different radiopharmaceuticals being used (not only [^{177}Lu]Lu-DOTATATE but also [^{177}Lu]Lu-DOTATOC and [^{90}Y]Y-DOTATOC) (11).

In contrast, a more recent study on intravenous PRRT in patients with meningioma by Minczeles et al. observed a higher rate of grade 3 and a comparable rate of grade 4 lymphocytopenia (grade 3: 38.5% vs. 53.3%; grade 4: 7.7% vs. 6.7%) (13). It is noteworthy that previous studies on PRRT in patients with neuroendocrine tumors demonstrated that high-grade therapy-associated lymphocytopenia did not lead to an increased incidence of severe infections (19,29).

One patient (7.7%) experienced local necrosis and infection on a finger of the left hand, possibly due to peripheral embolism after transfemoral catheterization, which is a rather rare complication of this procedure (30). There was no other possibly angiography-related complication observed.

Efficacy

In line with the existing literature on the results of intravenously administered PRRT (14,15,31,32), intraarterial PRRT also yielded a good therapeutic response in most of our patients. The disease control rate in our study was around 80%, with 1 patient achieving a complete remission and 1 patient a partial remission. Control of clinical symptoms was achieved in 9 of 13 patients (69%). In contrast, Minczeles et al. found a response rate of 40%, with no

patient achieving a partial or complete remission (13). In comparison to results from Mirian et al., the rate of stable disease was slightly higher in our cohort (69% vs. 58%) as well as the rates of partial and complete remission (7.7% vs. 2% and 7.7% vs. 0%) (11). Again, the limited number of subjects enrolled in our study needs to be acknowledged.

Overall improvement of clinical symptoms was observed in 2 patients (15.4%). Two patients (15.4%) experienced clinical deterioration. One of these patients experienced dedifferentiation from CNS WHO grade 2 to grade 3 meningioma, which was histologically confirmed after surgery between 2 PRRT cycles. The other patient showed progressive frailty that could not be explained by imaging results. Since another surgical tumor resection had been performed in the meantime, the cause of the patient's worsening condition could not be conclusively clarified.

One of our 13 patients (7.7%) experienced disease progression during treatment. Minczeles et al. reported a nearly 7-fold higher rate of progressive disease (53%) in their cohort, and the patients in the study by Mirian et al. showed a 5-fold higher rate (41%) (11,13).

According to the existing literature, patients with well-differentiated meningiomas appear to benefit more from PRRT (11). In their metaanalysis, Mirian et al. reported a 6-mo PFS rate of 94% for CNS WHO grade 1, 48% for CNS WHO grade 2, and 0% for CNS WHO grade 3 meningiomas. The 12-mo OS rates were 88%, 71%, and 52% (11). In comparison, the 6-mo PFS rate in our cohort was 100% in patients with CNS WHO grade 1 tumors, 25% in patients with CNS WHO grade 2 tumors, and 100% in patients with meningiomas of unknown grade. The 6-mo OS in our study was 100%, 75%, and 100% for patients with CNS WHO grade 1, grade 2, or unknown tumor grade, respectively, and the 12-mo OS was 100% (CNS WHO grade 1), 50% (CNS WHO grade 2), and 100% (unknown grading). At the time point of censoring, the median PFS was 18 mo, and the median OS has not yet been reached. In contrast, Bartolomei et al. reported a median PFS of 21 mo (32). However, it is noteworthy that their follow-up time ranged up to 77 mo, whereas our maximum follow-up time is limited to 43 mo, which could explain the lower median PFS in our cohort. Furthermore, 1 patient died from heart failure shortly after the first PRRT cycle, so she was not available for long-term follow-up.

In addition, intraarterially administered PRRT suggests promising efficacy compared with local therapy approaches such as surgical resection or external beam radiotherapy, with 6-mo PFS rates of 29% and a median OS of 10.6 mo (33).

Our findings suggest that intraarterial administration of PRRT may be a therapeutic option with favorable efficacy compared with local therapies and intravenous procedures. However, these are preliminary findings of a small patient cohort, and further prospective, multicenter studies are warranted.

Future Perspectives

In the future, individual dosimetry for each patient could further improve the results of intraarterial PRRT. Moreover, the therapeutic efficacy may be fostered using radiopharmaceuticals labeled with α-emitting radionuclides instead of the commonly used β-emitters. Another promising therapeutic option is the combination of external beam radiotherapy and intraarterial PRRT to further increase the achievable radiation doses to the tumor.

Limitations

The limitations of this study include its retrospective design and the limited number of patients with heterogeneous previous

treatments. Furthermore, most subjects received additional tumor embolization during the final treatment cycle, which may have led to an additional therapeutic effect. Currently, dosimetry data are not yet available for this patient cohort. Therefore, an analysis to this effect is planned as a future project to evaluate whether higher tumor uptake is associated with a better therapeutic efficacy. Despite these limitations, our study provides valuable information on the feasibility, tolerability, and efficacy of intraarterial administration of PRRT in patients with advanced progressive meningioma, a subject for which the existing literature is rather limited.

CONCLUSION

To the best of our knowledge, this retrospective analysis is the first to investigate the long-term toxicity and efficacy of intraarterially administered PRRT in a cohort of more than 10 patients with progressive meningioma. Intraarterial PRRT is feasible and safe without significant additional toxicity and can lead to better radiologic and clinical disease control compared with intravenous PRRT. Further research to validate these initial findings and to investigate long-term outcomes is highly warranted.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is the intraarterial administration of PRRT a feasible and safe therapeutic option with a superior therapeutic efficacy compared with intravenous PRRT for patients with meningioma?

PERTINENT FINDINGS: In our retrospective study, intraarterial PRRT was well tolerated in all individuals and showed good therapeutic efficacy. No chronic adverse effects were observed.

IMPLICATIONS FOR PATIENT CARE: Intraarterial PRRT is feasible and safe with no additional toxicity compared with intravenous PRRT, and it may lead to better disease control rates than intravenous procedures; however, further research to validate these initial findings is highly warranted.

REFERENCES

1. Ostrom QT, Price M, Neff C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2016–2020. *Neuro-oncol.* 2023;25:iv1–iv99.
2. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro-oncol.* 2017;19:v1–v88.
3. Goldbrunner R, Stavrinou P, Jenkinson MD, et al. EANO guideline on the diagnosis and management of meningiomas. *Neuro-oncol.* 2021;23:1821–1834.
4. Cornelius JF, Slotty PJ, Steiger HJ, Hanggi D, Polivka M, George B. Malignant potential of skull base versus non-skull base meningiomas: clinical series of 1,663 cases. *Acta Neurochir (Wien).* 2013;155:407–413.
5. van Alkemade H, de Leau M, Dieleman EM, et al. Impaired survival and long-term neurological problems in benign meningioma. *Neuro-oncol.* 2012;14:658–666.
6. Palma L, Celli P, Franco C, Cervoni L, Cantore G. Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. *J Neurosurg.* 1997;86:793–800.
7. Chamberlain MC, Barnholtz-Sloan JS. Medical treatment of recurrent meningiomas. *Expert Rev Neurother.* 2011;11:1425–1432.
8. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neuro-oncol.* 2014;16:829–840.
9. Pavel M, Oberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2020;31:844–860.
10. Menke JR, Raleigh DR, Gown AM, Thomas S, Perry A, Tihan T. Somatostatin receptor 2a is a more sensitive diagnostic marker of meningioma than epithelial membrane antigen. *Acta Neuropathol (Berl).* 2015;130:441–443.
11. Mirian C, Duun-Henriksen AK, Maier A, et al. Somatostatin receptor-targeted radiopeptide therapy in treatment-refractory meningioma: individual patient data meta-analysis. *J Nucl Med.* 2021;62:507–513.
12. Seystahl K, Stoecklein V, Schuller U, et al. Somatostatin receptor-targeted radionuclide therapy for progressive meningioma: benefit linked to ^{68}Ga-DOTATATE/-TOC uptake. *Neuro-oncol.* 2016;18:1538–1547.
13. Minczeles NS, Bos EM, de Leeuw RC, et al. Efficacy and safety of peptide receptor radionuclide therapy with ^{177}Lu-DOTA-TATE in 15 patients with progressive treatment-refractory meningioma. *Eur J Nucl Med Mol Imaging.* 2023;50:1195–1204.
14. Kreissl MC, Hanscheid H, Lohr M, et al. Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma. *Radiat Oncol.* 2012;7:99.
15. Hartrampf PE, Hanscheid H, Kertels O, et al. Long-term results of multimodal peptide receptor radionuclide therapy and fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma. *Clin Transl Radiat Oncol.* 2020;22:29–32.
16. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376:125–135.
17. Kwekkeboom DJ, Bakker WH, Kam BL, et al. Treatment of patients with gastroentero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. *Eur J Nucl Med Mol Imaging.* 2003;30:417–422.
18. Gupta SK, Singla S, Bal C. Renal and hematological toxicity in patients of neuroendocrine tumors after peptide receptor radionuclide therapy with ^{177}Lu-DOTA-TATE. *Cancer Biother Radiopharm.* 2012;27:593–599.
19. Kobayashi N, Takano S, Ito K, et al. Safety and efficacy of peptide receptor radionuclide therapy with ^{177}Lu-DOTA0-Tyr3-octreotate in combination with amino acid solution infusion in Japanese patients with somatostatin receptor-positive, progressive neuroendocrine tumors. *Ann Nucl Med.* 2021;35:1332–1341.
20. Traub-Weidinger T, Raderer M, Uffmann M, et al. Improved quality of life in patients treated with peptide radionuclides. *World J Nucl Med.* 2011;10:115–121.
21. Deibler AR, Pollock JM, Kraft RA, Tan H, Burdette JH, Maldjian JA. Arterial spin-labeling in routine clinical practice, part 3: hyperperfusion patterns. *AJNR Am J Neuroradiol.* 2008;29:1428–1435.
22. Dutour A, Kumar U, Panetta R, et al. Expression of somatostatin receptor subtypes in human brain tumors. *Int J Cancer.* 1998;76:620–627.
23. Braat AJAT, Snijders TJ, Seute T, Vonken EPA. Will ^{177}Lu-DOTATATE treatment become more effective in salvage meningioma patients, when boosting somatostatin receptor saturation? A promising case on intra-arterial administration. *Cardiovasc Intervent Radiol.* 2019;42:1649–1652.
24. Vonken EPA, Bruijnen RCG, Snijders TJ, et al. Intraarterial administration boosts ^{177}Lu-HA-DOTATATE accumulation in salvage meningioma patients. *J Nucl Med.* 2022;63:406–409.
25. Kim SH, Roytman M, Madera G, et al. Evaluating diagnostic accuracy and determining optimal diagnostic thresholds of different approaches to [68Ga]-DOTA-TATE PET/MRI analysis in patients with meningioma. *Sci Rep.* 2022;12:9256.
26. Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2013;40:800–816.
27. Huang RY, Bi WL, Weller M, et al. Proposed response assessment and endpoints for meningioma clinical trials: report from the Response Assessment in Neuro-Oncology working group. *Neuro-oncol.* 2019;21:26–36.
28. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging.* 2015;42:5–19.
29. Sierra ML, Agazzi A, Bodei L, et al. Lymphocytic toxicity in patients after peptide-receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC. *Cancer Biother Radiopharm.* 2009;24:659–665.
30. Karalis DG, Quinn V, Victor MF, et al. Risk of catheter-related emboli in patients with atherosclerotic debris in the thoracic aorta. *Am Heart J.* 1996;131:1149–1155.
31. Marincek N, Radojewski P, Dumont RA, et al. Somatostatin receptor-targeted radiopeptide therapy with ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC in progressive meningioma: long-term results of a phase II clinical trial. *J Nucl Med.* 2015;56:171–176.
32. Bartolomei M, Bodei L, De Cicco C, et al. Peptide receptor radionuclide therapy with ^{90}Y-DOTATOC in recurrent meningioma. *Eur J Nucl Med Mol Imaging.* 2009;36:1407–1416.
33. Preusser M, Silvani A, Le Rhun E, et al. Trabectedin for recurrent WHO grade 2 or 3 meningioma: a randomized phase II study of the EORTC brain tumor group (EORTC-1320-BTG). *Neuro-oncol.* 2022;24:755–767.