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68Gallium-DOTATATE PET in meningioma: A reliable predictor of tumor growth rate?

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Background. DOTATATE-based radionuclides have added new options in the diagnosis and treatment of meningiomas; however, a reliable predictor of tumor growth has still not been established.

Methods. We analyzed 64 meningiomas imaged with ^{68}Ga-DOTATATE PET. Tumor growth rates were calculated by volumetric analysis of sequential MRI scans. Maximums of standardized uptake values (SUV_{max}) were correlated with tumor growth and co-variates.

Results. World Health Organization (WHO) grades I and II meningiomas showed a correlation of SUV_{max} and tumor growth rate (meningiomas limited to the intracranial compartment: $r = 0.757$, $P < .001$, and transosseous growing meningiomas: $r = 0.819$, $P = .024$). SUV_{max} was significantly higher and the slope of the linear regression significantly steeper in transosseous compared with intracranial meningiomas (both $P < .001$). The association remained significant in multivariate analysis, and the prediction of tumor growth rate was independent of WHO grade. Anaplastic meningiomas showed no significant correlation of SUV_{max} and tumor growth.

Conclusions. ^{68}Ga-DOTATATE PET is a reliable predictor of tumor growth in WHO grades I and II meningiomas and provides additional information to conventional cross-sectional imaging modalities. Hence, ^{68}Ga-DOTATATE PET can assist in selecting the time point for treatment initiation. Furthermore, meningiomas with fast tumor growth and transosseous expansion elicit the highest DOTATATE binding; therefore, they might be especially suited for DOTATATE-based therapy.

Keywords: DOTATATE-PET, DOTATOC-PET, meningioma, SSTR2.

Meningiomas, with an annual incidence of 2.3 per 100 000, are the most common primary CNS tumors and comprise nearly 34% of all CNS tumors.[1–3] According to the World Health Organization (WHO), ~94% of meningiomas are classified as benign (grade I), 5%–7% as atypical (grade II), and 1%–3% as anaplastic (grade III).[4–7] WHO grade I tumors have a good prognosis, with a recurrence rate of ~5% after 5 years following gross total resection. WHO grades II and III meningiomas, however, remain challenging to treat and show 5-year overall recurrence rates of ~40% and 80%, respectively.[1,2] Multiple simultaneous meningiomas are recognized, especially in the context of neurofibromatosis II, and usually display a uniform histology.[8,9]

The cross-sectional imaging modalities CT and MRI are commonly applied for the identification and assessment of meningiomas.[10] In meningioma management, the assessment of tumor growth rate (TGR) is critical to select an appropriate time point for therapy initiation and type of treatment, with surgery as the mainstay of primary treatment. However, surgery is challenging in meningiomas located in the skull base region, due to frequent transosseous growth and the close relationship to cranial nerves and other delicate anatomical structures.[11]

Positron emission tomography with specific radiotracers is an imaging modality that adds molecular information. As

meningiomas generally express somatostatin receptor subtype 2 (SSTR2),[12] octreotide-based radiotracers with high affinity to these receptors are suitable tumor-imaging tracers.[13] Primarily, gallium-68 (^{68}Ga)–labeled dodecanetetraacetic acid–tyrosine-3-octreotate (DOTATATE) and DOTA-(Tyr^3)-octreotide (DOTA-TOC) tracers are used to determine the extent of SSTR2-positive meningiomas.[14–18] Using ^{68}Ga-DOTATOC, Afshar-Oromieh and colleagues[17,19] showed that PET has superior sensitivity in meningioma detection. Rachinger et al[18] demonstrated better tumor-to-nontumor discrimination of PET/CT over contrast-enhanced MRI. Furthermore, ^{68}Ga-DOTATOC PET/CT information may strongly complement MRI and CT for intensity-modulated radiation therapy planning in patients with complex meningiomas of the skull base region.[20]

In recent years, initial studies have described use of yttrium-90 or lutetium-177 radiolabeled somatostatin analogs to treat SSTR2-positive meningiomas. Bartolomei and colleagues[21] demonstrated disease stabilization in 66% of patients with meningiomas after peptide receptor radionuclide therapy (PRRT), which was confirmed in a recent study that reported a high percentage of patients with disease stabilization.[22] Accordingly, binding of the therapeutic radionuclide correlates with the pretherapeutic standardized uptake value (SUV) in PET, and ultimately with SSTR2 expression of meningiomas.[18,23] However, these results are conflicting, since SSTR2 expression itself is supposed to lead to growth inhibition in neoplastic and non-neoplastic tissue.[24,25] Alternatively, binding may reflect only a more benign tumor behavior rather than beneficial response to therapy.

We aimed to study the SUV reflecting SSTR2 expression as measured by ^{68}Ga-DOTATATE PET and its correlation to tumor growth in subsequent MR scanning. We hypothesized that SSTR2 uptake in ^{68}Ga-DOTATATE PET not only accurately delineates meningiomas as previously reported but also provides critical information on tumor behavior for further treatment planning.

Materials and Methods

Patient Population

All patients who received a ^{68}Ga-DOTATATE PET scan for meningioma imaging from January 2011 to December 2014 ($n = 45$) were included in this study. Twenty-two patients were excluded because of insufficient MRI follow-up data, cerebral radiation therapy within the last 2 years, or incomplete histological work-up. In patients with multiple meningiomas, we assessed up to a maximum of 5 separate lesions and analyzed the tumors with the highest volumes, resulting in 64 meningiomas from 23 patients. The study was approved by the local ethics committee (KEK-ZH 2014-0605).

PET and MR Data Acquisition

PET imaging was performed on a full-ring PET/CT system (Discovery VCT, GE Healthcare). For attenuation correction purposes, a low-dose CT scan of the head was initially performed (10 mA, 120 kV, pitch = 0.984:1, collimation = 64 × 0.625 mm). The PET scan was initiated directly after the injection of 150 MBq ^{68}Ga-DOTATATE, and emission data were acquired over 60 min (axial field of view = 153 mm covering the entire brain with one bed position). Emission data were corrected for randoms, dead time, scatter, and attenuation and iteratively reconstructed (3 iterations, 18 subsets) using CT.

We selected one brain MRI examination before ^{68}Ga-DOTATATE PET and another afterwards, resulting in at least 4 months of temporal difference between both images (median 11, minimum 4, maximum 20 mo). All MRI examinations included axial T1- and T2-weighted images and axial, coronal, and sagittal T1-weighted images after the injection of gadolinium contrast media (T1Gd).

PET and MR Image Analysis

A board-certified nuclear medicine physician analyzed the PET images using PMOD v3.4 and measured the maximal SUV (SUV$_{max}$) in all meningiomas. For the quantitative evaluation of the PET data, frames acquired between 40 and 60 min were averaged. In the PET dataset, volumes of interest were adjusted in 3 planes so that the entire meningioma was included.

A second independent reader, blinded to the SUV, determined TGR of meningiomas in each patient. Meningiomas "en plaque" were not assessed, as they are prone to measurement inaccuracies. As all other intracranial meningiomas corresponded approximately to a rotational ellipsoid, volume was calculated by multiplying the product of the 3 diameters by 0.523 (according to the formula $4/3 * \pi * a * b * c$, where a, b, c are the lengths of each radius). The volumes of all transosseous meningiomas were determined by 3D volumetric measurements (contour outline on all axial slices) on T1Gd images. Finally, the monthly growth rate was calculated by dividing the percentage change in size by the numbers of months between the 2 examinations.

Grading and Histological Assessment

Histological grading according to WHO classification was performed in at least one of the meningiomas by a board-certified neuropathologist blinded to clinical and radiographic details.[4] Median time interval between histology and PET imaging was 5.9 months. Since the majority of simultaneously occurring multiple meningiomas show a uniform histology,[8,9] all meningiomas from a given patient, even those that were not surgically sampled, were assigned the same WHO grade. To assess for potential bias when analyzing multiple meningiomas per patient, an additional evaluation with only one biopsied meningioma per patient was performed. For this additional assessment, we selected the largest meningioma when histology of multiple meningiomas was available.

Concomitant Therapy

We assessed concomitant therapy during MR follow-up; 5 patients received focal therapy (all WHO grade I or II), including stereotactic radiation (protons or photons) and embolization (total of 6/57 meningiomas), and 1 patient with WHO grade III meningioma received systemic therapy with interferon alpha 2a. As all treatments aimed at tumor volume reduction or growth inhibition, we pooled treatments in statistical analysis.

Statistical Analysis

Statistical analyses were performed using SPSS v21. We calculated Pearson's r and linear regression analysis, with values of R^2 below 0.4 considered weak, between 0.4 and 0.6 moderate, and above 0.6 strong. We calculated significance of differences in regression slopes using the Chow test. In multivariate linear regression, SUV_{max}, age, sex, WHO grade, time between histology and PET, duration of follow-up, initial volume, and concomitant therapy during follow-up were set as independent variables, and TGR as the dependent variable. Differences in mean values were tested with Student's t-test. Significance was defined as $P < .05$.

Results

Sixty-four meningiomas in 23 consecutive patients were analyzed (29 WHO grade I, 28 grade II, and 7 grade III). TGR in relation to SUV_{max} of ^{68}Ga-DOTATATE PET is summarized in Fig. 1. Meningiomas were separated into 3 different clusters: transosseous growth, intracranial meningiomas of WHO grades I and II, and meningiomas of WHO grade III, which were analyzed separately. Examples of PET and MR imaging of meningiomas are shown in Fig. 2.

Eighteen patients with 50 meningiomas of WHO grades I and II had tumor growth limited to the intracranial compartment. TGR of these meningiomas strongly correlated with SUV_{max} of ^{68}Ga-DOTATATE PET ($r = 0.757$, $P < .001$) and SUV_{max} correlated weakly with initial tumor volume in intracranial meningiomas ($r = 0.316$, $P = .025$) (Fig. 1). In the patient analysis of biopsied meningiomas, correlation did not change ($r = 0.907$, $P < .001$). Both TGR and SUV_{max} did not differ in meningiomas with concomitant therapy during follow-up ($n = 4$) versus nontreated meningiomas ($n = 46$) (TGR: 9.8 ± 6.4 vs 9.8 ± 8.1, $P = .998$ and SUV_{max}: 10.5 ± 3.4 vs 11.2 ± 7.4, $P = .728$). Correlation coefficient of TGR and SUV_{max} was stable when calculated for medicated meningiomas only but, because of low patient numbers, not to a significant degree ($r = 0.770$, $P = .23$). In multivariate linear regression, SUV_{max} remained a strong predictor for TGR ($\beta = 0.863$, $P < .001$; only covariate: initial tumor volume $\beta = -0.335$, $P < .001$, $R^2 = 0.7$). Patients with intracranial meningiomas are summarized in Table 1.

Seven meningiomas from 5 patients showed transosseous growth into the skull base or temporal squama (all WHO grade I; 3 patients had meningiomas with transosseous growth as well as tumors limited to the intracranial compartment) (Table 2). SUV_{max} of these meningiomas were remarkably higher, with a mean SUV_{max} of 43.3 g/mL (range 18–70.7 g/mL) compared with a mean SUV_{max} of 11.2 g/mL (range 2.6–32.0 g/mL) for meningiomas without transosseous growth ($P < .001$). Additionally, the slope of the linear regression coefficient was steeper in meningiomas with transosseous growth compared with meningiomas restricted to the intracranial compartment ($a = 5.5$ and $a = 0.70$, respectively; $P < .001$). Again, TGR of transosseous meningiomas correlated significantly with SUV_{max} of ^{68}Ga-DOTATATE PET ($r = 0.819$, $P = .024$) (Fig. 1). The correlation coefficient remained stable at a high level in per patient analysis of biopsied meningiomas, but because of low patient numbers, not to a significant degree ($r = 0.789$, $P = .113$). TGR and SUV_{max} were concordantly lower in transosseous meningiomas ($n = 2$) with treatment during follow-up versus nonmedicated meningiomas ($n = 5$) (TGR: 5.8 ± 4.4 vs 7.6 ± 2.9, $P = .667$ and SUV_{max}: 34.1 ± 2.7 vs 45.5 ± 24.6, $P = .361$). SUV_{max} did not correlate with initial tumor volume in these meningiomas ($P = .251$) and it was the only predictor of TGR in multivariate linear regression analysis ($\beta = 0.818$, $P = .024$, $R^2 = 0.7$).

WHO grade III meningiomas showed no significant correlation between TGR and SUV_{max} ($P = .518$) (Fig. 1). The monthly growth was remarkably high, with relatively low SUV_{max} (Table 3).

Discussion

Our study provides convincing evidence that high expression of SSTR2 as measured by SUV_{max} in ^{68}Ga-DOTATATE PET predicts faster growth in WHO grades I and II meningiomas, whereas WHO grade III meningiomas did not show an association of TGR with tracer binding. Meningiomas with transosseous growth elicited considerably higher ^{68}Ga-DOTATATE binding.

These data are surprising, since SSTR2 expression itself is supposed to lead to growth inhibition in various neoplastic tissues.[24,25] The (patho)physiological relevance of SSTR2 overexpression in meningiomas is not well understood,[26] and growth stimulation in the presence of somatostatin and its
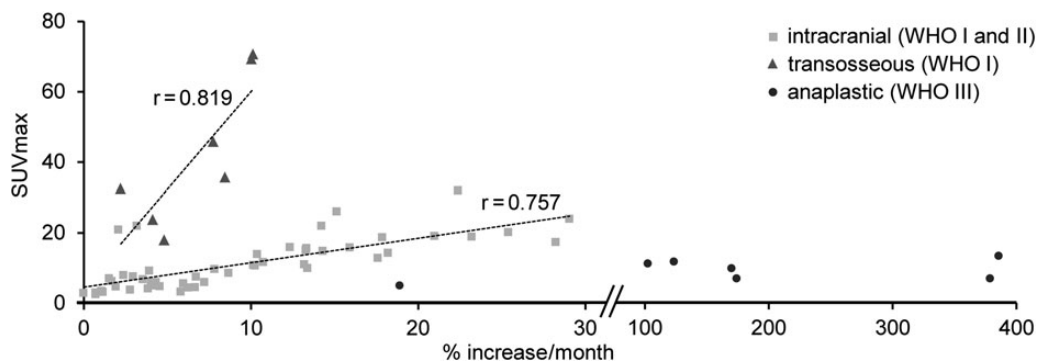

Fig. 1. Correlation between TGR and SUV_{max}. Meningiomas separated into 3 different clusters (intracranial growth, transosseous growth, and anaplastic).
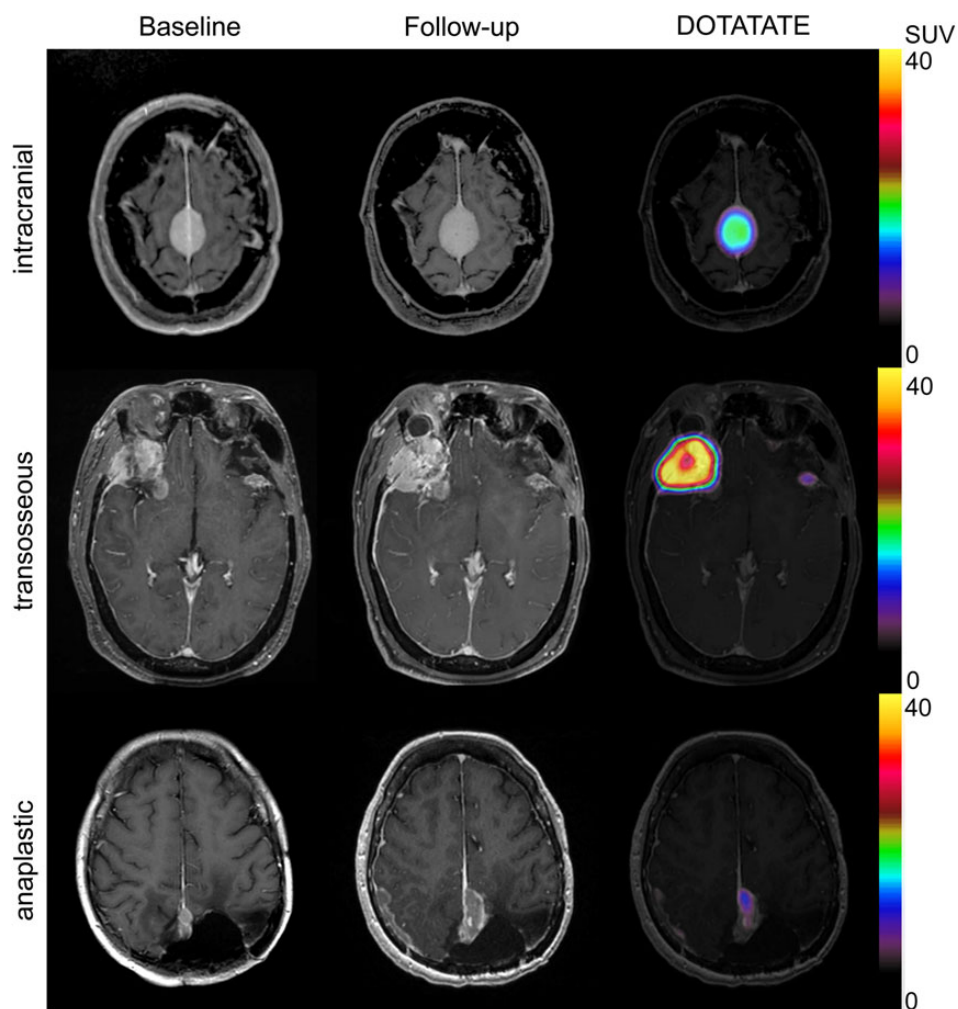
Fig. 2. Examples of intracranial, transosseous, and anaplastic meningiomas. From left to right: baseline MRI, follow-up MRI, and ^{68}Ga-DOTATATE PET.

analog octreotide has been reported.[27] The inhibitory effect of somatostatin in meningiomas is further challenged by the disappointing results of current treatment trials using somatostatin analogs.[28,29]

The predictive value of TGR with ^{68}Ga-DOTATATE PET may be especially informative in meningiomas adjacent to delicate structures such as cranial nerves or arteries. Specifically, TGR with ^{68}Ga-DOTATATE PET may help in planning the optimal time point for surgery and for follow-up imaging. This is especially valuable for newly diagnosed meningiomas in such critical locations. SUV_{max} remains an independent predictor of TGR estimation in multivariate analysis, including tumor size and WHO grade, providing additional information to these estimates. Further studies have to assess the potential changes in management by the treating physician or the advisory tumor board in order to establish corresponding recommendations.

Our results also support further development of PRRT in meningiomas. As noted, Rachinger and colleagues showed a strong congruence of SUV_{max} in ^{68}Ga-DOTATATE PET with SSTR2 expression in the histological preparations. In addition, ^{68}Ga-DOTATATE PET SUV_{max} correlates with radionuclide uptake

in PRRT in meningiomas.[23] This information taken together with the physical properties of ^{177}Lu or ^{90}Y with a very limited maximal tissue penetration of the emitted β particles of 2 mm (maximum energy = 0.5 MeV) and 12 mm (max energy = 2.3 MeV), respectively, allows for radiation dose estimation and consequently high tumor radiation doses while minimizing the total radiation dose to normal brain parenchyma. As faster growing meningiomas have higher SUV_{max}, they will potentially also have higher radiation doses in PRRT. Accordingly, this treatment option might be particularly target oriented. Furthermore, transosseous meningiomas elicited considerably high DOTATATE binding; therefore, PRRT appears especially suited to complement surgery or external radiation therapy for skull base and spheno-orbito-maxillar meningiomas.

Finally, PET generates functional and morphological information that enhances treatment planning and dose calculation for intensity-modulated radiation therapy.[20] Notably, PET morphometry facilitates more accurate delineation of skull base meningiomas compared with contrast-enhanced MRI alone.[18]

WHO grade III meningiomas showed no correlation between SUV_{max} and TGR. Furthermore, the monthly growth

Table 1. Intracranial meningiomas

ID	Age (y)	Sex	WHO Grade	Lesion with Histology	Time between MRI Scans (mo)	Initial Volume (mm^3)	Growth Rate (%)	SUV$_{max}$ (g/mL)
1	42.0	Male	I	x	16	5726	14.58	22
						3107	15.51	26.1
						460	8.92	8.6
						431	22.88	32
2[a]	29.6	Female	I/II		10	2561	1.87	6.3
			I/II			2312	3.77	6.8
			II	x		1689	21.51	19.1
			I/II			952	13.79	10
			I/II			795	7.51	6
3[b]	44.3	Female	I		11	759	10.47	10.9
						544	13.67	15.1
						483	11.09	11.7
4	68.2	Male	I		11	4142	14.71	14.9
						435	13.58	11.1
				x		345	10.58	10.7
				x		251	4.26	6
5	49.7	Female	I		8	1841	12.76	16
				x		1054	18.38	18.8
						748	26.05	20.2
						483	16.40	15.9
						460	29.76	24
6	45.2	Female	I	x	5	8186	4.33	9.3
7	42.5	Female	II	x	6	483	4.91	4.8
						408	18.81	14.3
8	73.4	Female	II		12	259	6.05	3.3
						157	6.92	4.6
				x		146	6.20	5.6
						94	6.50	4.5
9	62.0	Female	II		13	314	8.09	9.7
				x		167	4.53	6
10	37.2	Male	II		20	1849	0.82	3
						1657	28.81	17.4
				x		598	1.24	3.2
						366	0.81	2.6
						362	1.16	3.5
11	28.4	Female	II	x	13	226	2.96	3.8
				x		176	4.04	4.2
						75	4.48	5
12	7.0	Male	II	x	10	925	2.12	4.7
13	63.1	Female	II	x	7	1255	7.08	7.5
14	68.1	Female	II	x	6	316	1.83	7.1
						774	18.18	12.9
15	52.2	Female	II		12	10 632	3.38	22
						1245	2.24	20.9
				x		322	2.57	8
16	75.1	Male	II		10	2457	10.72	14
				x		1809	3.18	7.6
17	64.5	Female	II	x	11	63	0.16	2.9
18[c]	68.7	Male	II		5	264	23.96	18.9
						188	13.91	15.7

[a]Patient with ID #2 had meningiomas with WHO grades I and II in histology (intracranial and transosseous); therefore, meningiomas without biopsy were not allocated to a specific WHO grade (as indicated by "I/II").
[b]Patient with ID #3 had intracranial and transosseous meningiomas; the latter was operated on and histology was obtained.
[c]Patient with ID #18 received total resection of another meningioma from which histology was obtained.

Table 2. Transosseous meningiomas

ID	Age (y)	Sex	WHO Grade	Lesion with Histology	Time between MRI Scans (mo)	Initial Volume (mm^3)	Growth Rate (%)	SUV$_{max}$ (g/mL)
1[a]	42.0	Male	I	x	16	23 995	10.32	69.3
						1271	7.98	45.8
						1391	4.31	23.8
2[a]	29.6	Female	I	x	10	941	10.42	70.7
3[a]	44.3	Female	I	x	11	1640	5.06	18
19	46.5	Female	I	x	5	565	8.93	35.7
20	52.2	Female	I	x	4	7362	2.67	32.5

[a]These patients elicited intracranial and transosseous meningiomas.

Table 3. Anaplastic meningiomas

ID	Age (y)	Sex	WHO Grade	Lesion with Histology	Time between MRI Scans (mo)	Initial Volume (mm^3)	Growth Rate (%)	SUV$_{max}$ (g/mL)
21	39.0	Female	III	x	7	31 777	19.48	5
22	78.2	Female	III	x	7	2921	104.42	10.7
23	61.8	Female	III		7	1486	126.02	11.2
				x		205	173.29	9.4
						377	392.60	12.8
						78	177.53	6.6
						59	385.33	6.6

was remarkably high with relatively low SUVs. This observation implies advanced dedifferentiation of the meningioma cells and limits the accuracy of predicting the growth rate with ^{68}Ga-DOTATATE PET. The clinical role of the other PET tracers, like the widely used ^{18}F-fluorodeoxyglucose (FDG), in patients with dedifferentiated meningioma is still not clear. Arita and colleagues[30] did not find any correlation between ^{18}F-FDG uptake and WHO grading or tumor-doubling time. On the other hand, Lee et al[31] reported that FDG uptake was a significant prognostic factor regarding tumor recurrence. Regarding ^{18}F-fluoro-tyrosine and C11-methionine, markers of L-amino acid transport and protein synthesis, only small numbers of dedifferentiated meningiomas have been assessed in recently published studies,[32,33] thus their value as biomarkers for TGR or prognosis has not yet been established. Importantly, WHO grade III meningiomas show morphological features on MRI which help to diagnose this entity and guide PET use.[10] In meningiomas with an unclear tumor–brain interface, irregular tumor margins, heterogeneous contrast enhancement, and missing capsular enhancement, the probability of high-grade histology was 98%.[34] However, the present study does not allow any conclusion on the effect of PRRT on grade III meningiomas, as dedifferentiated cells may react differently to this therapy.

The study design was retrospective, and therefore a selection bias cannot be ruled out. Another potential limitation is the relatively high percentage of patients with multiple meningiomas; at least one lesion from these patients was histologically evaluated, but not all lesions were subjected to histological assessment. Previous studies revealed that multiple meningiomas usually display a uniform histology, and anaplastic meningiomas (WHO grade III) were rare among these.[9,35] Therefore, we analyzed meningiomas of WHO grades I and II together.

Standardized uptake value, reflecting the SSTR2 density measured by ^{68}Ga-DOTATATE PET, is a reliable predictor of TGR in WHO grades I and II meningiomas. This finding underlines its clinical importance for surgical planning and radiation therapy, since meningiomas with high SUV$_{max}$ are at risk for progression and require either local or systemic treatment. Our study suggests that patients with high SUV$_{max}$ might benefit from PRRT treatment, not only regarding dosimetric considerations but also with respect to risk for progression. This holds especially true for transosseous meningiomas eliciting very high SSTR2 density. However, further studies are indicated to evaluate the therapeutic effect of PRRT in different histological types of meningiomas and according to their SSTR2 expression.

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