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Review Article

Somatostatin receptor PET-guided treatment and artificial intelligence applications in meningioma: a comprehensive review

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Abstract: Meningiomas are the most common primary intracranial tumors, with treatment involving resection and radiation therapy. However, therapeutic options are limited for recurrent or progressive disease, particularly in higher World Health Organization (WHO) grade tumors. Somatostatin receptor (SSTR) expression in meningiomas has opened new therapeutic opportunities as the differential SSTR2 overexpression permits molecular targeting using radiolabeled somatostatin analogs. PRRT offers promising therapeutic efficacy in select meningioma patients, with clinical responses strongly correlated to WHO tumor grade and SSTR expression levels. Combining SSTR PET imaging, to evaluate receptor density, with radiomic analysis can reveal tumor heterogeneity patterns and quantitative imaging features that can guide clinical decision-making and monitor treatment response. Integrating machine learning and artificial intelligence (AI) into clinical workflows offer novel approaches to apply quantitative SUV parameters, image texture features, and histopathologic data in order to identify patients with WHO grade II and III meningiomas at greater risk of tumor recurrence. Given the heterogeneity in imaging and treatment protocols across institutions and the limited number of PRRT-treated meningioma cohorts, future research should prioritize prospective, multicenter studies that integrate histologic and molecular imaging data to refine patient selection strategies and establish PRRT's role within personalized, precision cancer treatment paradigms.

Keywords: Artificial intelligence, DOTANOC, DOTATATE, DOTATOC, meningioma, peptide receptor radionuclide therapy, pet imaging, somatostatin receptor

Introduction

Meningiomas are the most common primary brain tumor, accounting for approximately 36% of all central nervous system neoplasms. These tumors arise from meningothelial cells and show significant heterogeneity in location, histological features, and molecular profiles [1, 2]. The World Health Organization (WHO) classification divides meningiomas into three grades: Grade I (benign, 80-85% of cases), Grade II (atypical, 10-15%), and Grade III (anaplastic or malignant, 1-3%). Each classification level is associated with distinct prognostic outcomes and guides clinical decision making accordingly [3].

The clinical presentation of meningiomas is largely driven by their anatomical location and resulting mass effect rather than intrinsic tumor biology. Convexity meningiomas, for example, typically present with seizures (reported in up to 50% of cases), headaches, focal neurological deficits, and disturbances in visual fields [4]. Parasagittal and falcine tumors often lead to bilateral lower extremity weakness, cognitive impairment, and personality changes due to compression of the parasagittal motor cortex [5-7]. Sphenoid wing meningiomas produce a distinct syndrome including proptosis, visual impairment, diminished facial sensation, and seizures originating from the temporal lobe [8, 9]. Tumors which cause lesions at the olfactory groove often follow a more insidious course, presenting with anosmia and subtle neurocognitive defects. In contrast, posterior fossa meningiomas may manifest with cerebellar dysfunction, ataxia, and potentially life-threatening obstructive hydrocephalus [10-12].

Seizures are reported in approximately 25-30% of all meningioma cases, with the highest incidence rising to nearly 50% in convexity tumors, particularly those located adjacent to eloquent cortical regions [13-15]. The slow-growing nature of most meningiomas, often seen with doubling times ranging from 2-10 years, often delays diagnosis. This underscores the need for maintaining heightened clinical suspicion for intracranial pathology when evaluating patients who present with new-onset focal neurological deficits or seizures.

Maximal safe surgical resection remains the foundational approach to meningioma treatment, with gross total resection (GTR) achieving up to 90% five-year progression-free survival for patients with WHO Grade I tumors [14, 16]. The Simpson grading scale quantifies the extent of resection and has a well-established association with

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recurrence risk. Simpson Grade I resection, which involves complete tumor excision along with resection of dural attachment and any involved bone, is linked to the lowest rates of recurrence [17-21]. Complete resection is frequently limited by anatomical constraints, particularly in skull based meningiomas located adjacent to vital neurovascular structures, and this often requires use of adjuvant therapies. External beam radiation therapy (EBRT) is the primary adjuvant treatment for managing residual tumor following subtotal resection, as well as for managing meningiomas of higher histologic grade. Meta-analyses have indicated that adjuvant radiotherapy following GTR of atypical meningiomas can reduce five-year recurrence rates from 50-71% to approximately 20-30% [22-25]. Despite these multimodal approaches, treatment failures remain a significant challenge. Grade II meningiomas recur in 50% of cases even after Simpson Grade I resection, and in up to 71% after following subtotal resection [24-26]. Outcomes are more unfavorable for Grade III tumors, with five-year progression-free survival rates of only 28% following GTR and 0% following subtotal resection without adjuvant therapy [27]. A summary of standardized treatment plans for meningiomas based on WHO grade is described in **Figure 1** [28].

Multiple challenges have hindered the development of effective systemic therapies for meningiomas. Conventional cytotoxic agents, such as temozolomide and dacarbazine, have demonstrated poor efficacy, with objective response rates consistently below 10%. This limited efficacy is likely due to the inherently low proliferative index of most meningiomas and the selective nature of blood-brain barrier [29-31]. Efforts to implement targeted agents, including hydroxyurea, bevacizumab, and mTOR inhibitors, have similarly failed to demonstrate clinically meaningful benefits; Hydroxyurea offers limited disease stabilization, antiangiogenic agents like bevacizumab show response rates below 15%, and mTOR inhibitors, such as Everolimus, have failed to meaningfully impact disease progression despite frequent PI3K/AKT pathway activation in meningiomas [32-48]. Treatment resistance in meningiomas is multifactorial. Tumor heterogeneity enables resistant cellular subpopulations to persist and drive tumor recurrence [49-53]. Anatomical constraints often limit both surgical and radiation interventions, especially in tumors near vital neurologic structures [54, 55]. Moreover, intrinsic resistance to radiation therapy is reinforced by the inherently slow growth rate of these tumors, robust DNA repair mechanisms, hypoxic tumor microenvironments, and need to restrict radiation doses to preserve surrounding neurologic tissue [56-59].

The discovery of elevated somatostatin receptor (SSTR) expression in meningiomas has opened new opportunities for novel therapeutic strategies. Somatostatin receptors (SSTRs) are seven-transmembrane G-protein-coupled receptors that normally bind the endogenous neuropeptide somatostatin, which regulates physiological processes including hormone secretion and cell proliferation. Although there are five SSTR subtypes (SSTR1-5), SSTR2 is most commonly expressed in meningiomas. Since SSTR2 is expressed in the vast majority of meningiomas, it makes a compelling target for peptide receptor radionuclide therapy (PRRT) [60]. This high-density SSTR2 expression has made somatostatin receptor PET a highly valuable imaging modality for diagnosing, prognosticating, and monitoring meningiomas [60-67]. The differential SSTR2 overexpression serves as a molecular target for radiolabeled somatostatin analogs used in PET imaging. The most used somatostatin tracers are the DOTA peptides labeled with gallium-68, a positron-emitting radioisotope that has a half-life of 68-minutes ([^{68}Ga]Ga-DOTATATE, [^{68}Ga]Ga-DOTATOC, and [^{68}Ga]Ga-DOTANOC). This approach combines integrated molecular imaging using ^{68}Ga-labeled somatostatin analogs with targeted therapies using β-emitting radionuclides, such as lutetium-177 (^{177}Lu) or yttrium-90 (^{90}Y), conjugated to somatostatin receptor-binding ligands [68] forming the theranostic twins. Highly specific SSTR-targeted therapies deliver concentrated radiation directly to meningioma cells while sparing healthy tissue, offering a novel and more efficacious approach to systemic treatment that addresses some of the aforementioned limitations of conventional therapies. We have highlighted a theranostic workflow for SSTR2-targeted meningioma management in **Figure 2**.

This comprehensive review synthesizes current evidence for SSTR-targeted PET imaging and peptide receptor radionuclide therapy (PRRT) in meningioma management, with a focus on clinical efficacy across WHO grades, patient selection criteria, and treatment optimization strategies. We examine the role of quantitative SSTR PET imaging biomarkers in predicting therapeutic response, discuss technical considerations including combination therapies and novel delivery methods, and explore the emerging applications of artificial intelligence and radiomics in enhancing patient selection and treatment monitoring. Additionally, we highlight current limitations including small cohort sizes, institutional variability in protocols, and the need for prospective validation, while outlining future directions for integrating AI-enhanced molecular imaging into personalized meningioma care.

SSTR peptide receptor radionuclide therapy

Clinical efficacy and patient selection

The therapeutic potential of SSTR-targeted peptide receptor radionuclide therapy (PRRT) in meningiomas has been established through systematic evaluation across WHO grades (**Table 1**). The most comprehensive evidence comes from a meta-analysis, which evaluated 111 patients with treatment-refractory meningiomas and reported disease control in 63% of cases following [^{90}Y]Y-DOTATOC, [^{177}Lu]Lu-DOTATOC, [^{177}Lu]Lu-DOTATATE, or

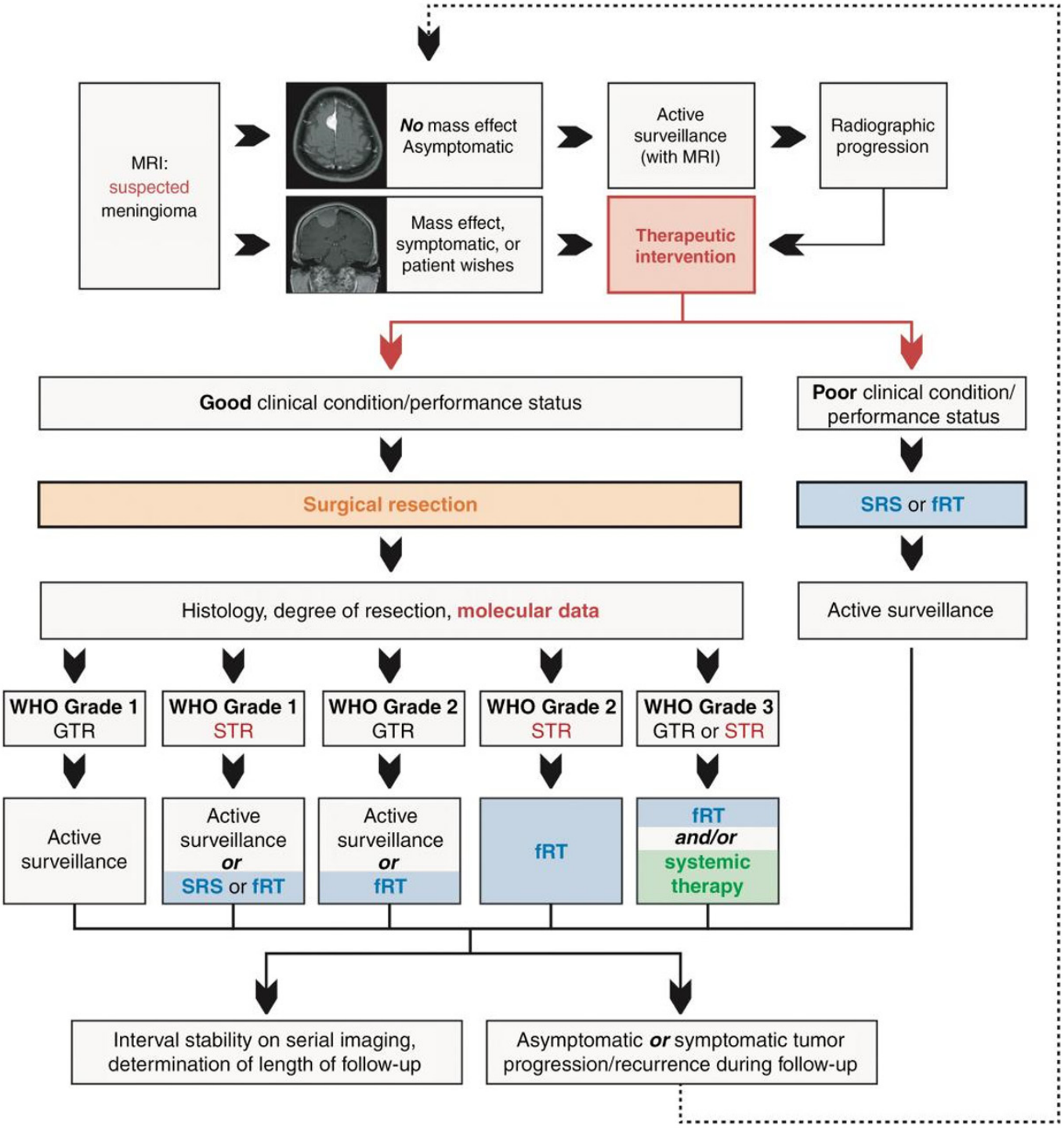

Figure 1. Summary of current treatment recommendations for management of meningiomas based on WHO tumor grade, extent of surgical resection, and the incorporation of molecular data when available. Abbreviations: MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery; fRT, fractionated external beam radiotherapy; GTR, gross total resection; STR, subtotal resection. Adapted from Wang J. et al. Neuro Oncol. 2024 Oct 3;26(10):1742-1780, with permission under Creative Commons Attribution 4.0 International Public License (https://creativecommons.org/licenses/by/4.0/legalcode) [28].

combination regimens [69]. **Figure 3** highlights the durable efficacy of [^{90}Y]Y-DOTATOC therapy, with follow-up MRI at 72 months showing stable disease in a WHO grade II meningioma initially extending from the cerebellopontine angle to the upper cervical spine [70].

The study revealed a pronounced grade-dependent response to therapy with six-month progression-free survival rates of 94% for Grade I, 48% for Grade II, and 0% for Grade III meningiomas. The corresponding one-year overall survival rates were 88%, 71%, and 52%, respectively

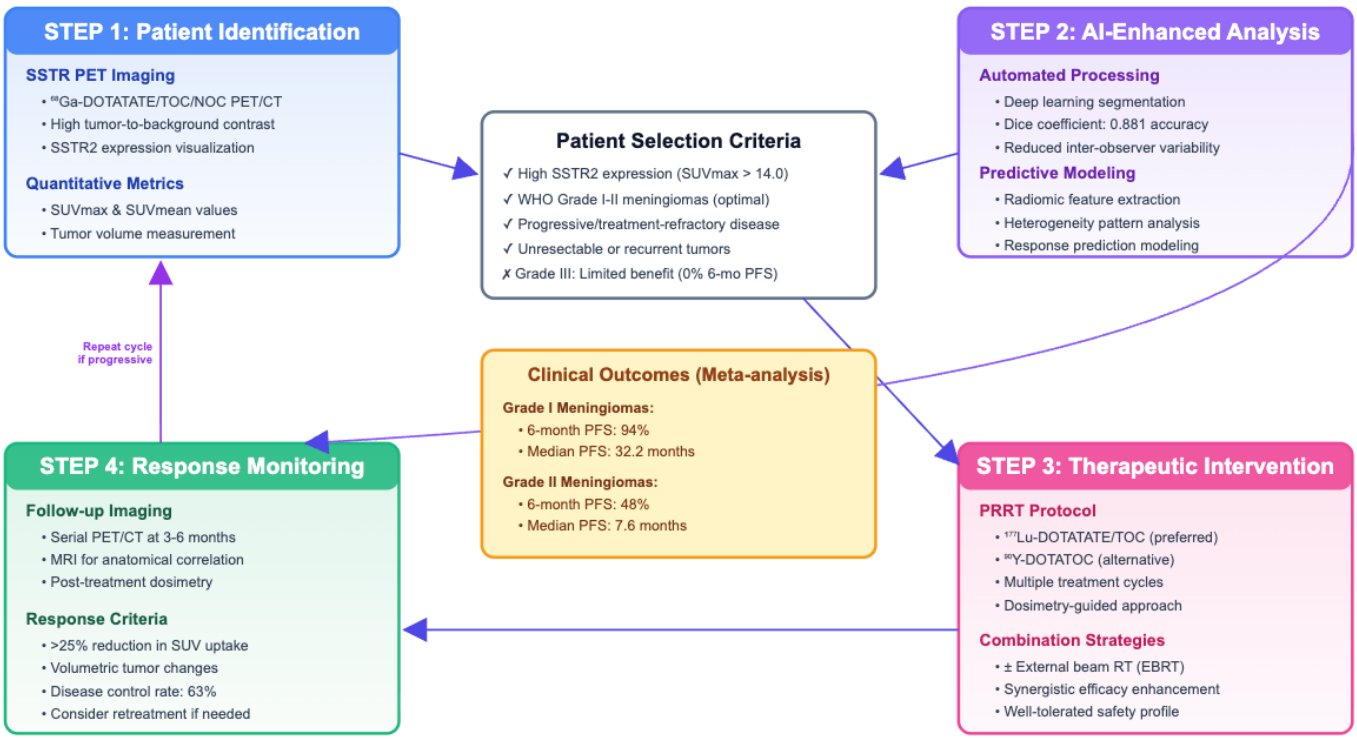

Figure 2. Integrated theranostic workflow for SSTR2-targeted meningioma management. The cycle encompasses patient identification via SSTR PET imaging (Step 1), AI-enhanced radiomic analysis with deep learning segmentation (Step 2), peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE/TOC ± external beam radiotherapy (Step 3), and serial PET/CT response monitoring (Step 4). Central panel displays meta-analysis outcomes showing 6-month progression-free survival of 94% (Grade I) and 48% (Grade II meningiomas). Progressive disease triggers workflow re-initiation, establishing a continuous precision medicine feedback loop. Made with Claude Sonnet 4.5 (claude-sonnet-4-5-20250929) and R version 4.3.2.

[66]. These findings reinforce the importance of histologic grade as a predictor of therapeutic response and have provided the foundation for subsequent studies that have confirmed this pattern in separate cohorts. Another similar study reported a median progression-free survival of 32.2 months for Grade I, compared to 7.6 months for Grade II, and just 2.1 months for Grade III tumors [71]. Adding to the body of evidence, Bartolomei et al. observed a median progression-free survival of 61 months for Grade I cases compared to 13 months for Grade II and III tumors [72]. This consistent trend seen across studies confirms that PRRT efficacy declines significantly as tumor grade increases, likely due to greater biological aggressiveness and diminished somatostatin receptor expression in higher-grade meningiomas.

Variations in therapeutic response by tumor grade highlight the need for imaging biomarkers to identify patients who are optimal candidates for PRRT. Reflecting on this need, SSTR imaging has emerged to be crucial for patient selection. Higher SUV_{max} and SUV_{mean} values on [^{68}Ga]Ga-DOTATOC PET were associated with prolonged progression-free survival, whereas early progression, within six months, correlated with lower levels of radiotracer uptake [71]. In the multicenter phase II trial (NCT03971461) a reduction of greater than 25% uptake of [^{68}Ga]Ga-DOTATATE PET was identified as a potential therapeutic biomarker [73]. Further validation for using this approach, as this study demonstrated increased SSTR-positive tumor volume on follow-up PET was a predictor of shorter progression-free survival [74].

Long-term outcomes and treatment optimization

Extended follow-up studies have demonstrated that PRRT can achieve disease control (**Table 1**). Interestingly, the longest-term outcomes to date were 65.6% of 32 patients achieving stable disease and a mean overall survival of 8.6 years following initial PRRT [75]. High tumor radionuclide uptake and stable disease response emerged as significant predictors of survival benefit. Notably, one study reported that the disease control rate in a cohort of 42 patients was 57% with a median progression-free survival of 16 months and overall survival of 36 months. Additionally, the study demonstrated the feasibility of PRRT retreatment feasibility in six patients [76]. Gerster-Gillieron et al. documented exceptionally prolonged responses, including stable disease for 87 months in a Grade I skull base tumor [70]. Together, these outcomes point to the long-term effectiveness of PRRT indicate that timing of administration may influence outcomes.

There is growing support to integrate PRRT earlier in clinical management, ideally before patients experience substantial treatment failure. One study proposed initiating

Table 1. Core clinical efficacy studies of peptide receptor radionuclide therapy in meningiomas

Author, Year [Ref]	n	WHO Grade Distribution	Agent(s)	Disease Control Rate	Median PFS	Median OS/ Survival	Key Findings
Mirian et al., 2021 [69]	111	Grade I-III (meta-analysis of treatment-refractory)	[^{90}Y]Y-DOTATOC, [^{177}Lu]Lu-DOTATOC, [^{177}Lu]Lu-DOTATATE	63% overall	6-mo PFS: Grade I 94%, Grade II 48%, Grade III 0%	1-yr OS: Grade I 88%, Grade II 71%, Grade III 52%	Meta-analysis demonstrating pronounced grade-dependent response; established foundation for patient selection
Seystahl et al., 2016 [71]	16	Grade I: 31%, Grade II: 50%, Grade III: 19%	[^{68}Ga]Ga-DOTATOC/-TOC	Progressive meningioma cohort	Grade I: 32.2 mo, Grade II: 7.6 mo, Grade III: 2.1 mo	Not reported	Higher SUV_{max}/SUV_{mean} on [^{68}Ga]Ga-DOTATOC PET associated with prolonged PFS; lower uptake correlated with early progression
Bartolomei et al., 2009 [72]	26	Grade I-II: 77%, Grade III: 23%	[^{90}Y]Y-DOTATOC	Recurrent meningioma	Grade I: 61 mo, Grade II-III: 13 mo	Not reported	Confirmed grade-dependent therapeutic response pattern
Gerster-Gillieron et al., 2015 [70]	8	Complex recurrent/progressive (includes Grade I and II)	[^{90}Y]Y-DOTATOC	Not reported	Stable disease up to 87 mo (Grade I skull base)	Not reported	Demonstrated exceptionally prolonged responses; Grade II case showed stable disease at 72 mo follow-up
Marincek et al., 2015 [75]	32	Progressive meningioma	[^{90}Y]Y-DOTATOC and [^{177}Lu]Lu-DOTATOC	65.6% stable disease	Not reported	Mean OS: 8.6 years	Longest-term outcomes to date; high tumor uptake and stable disease response predicted survival benefit
Severi et al., 2024 [76]	42	Advanced refractory	[^{177}Lu]Lu-DOTATATE	57%	16 mo	36 mo	Demonstrated PRRT retreatment feasibility in 6 patients with long follow-up
Graillon et al., 2024 [78]	15	Multirecurrent non-anaplastic	[^{177}Lu]Lu-DOTATATE with Lutathera	86.7% disease stabilization	Not reported	Not reported	Supports earlier PRRT integration in slowly progressing tumors rather than salvage-only use
Kreissl et al., 2012 [79]	10	Advanced symptomatic	[^{177}Lu]Lu-DOTATATE/DOTATOC + EBRT (42-60 Gy)	90% (1 CR, 8 SD)	Not reported	Not reported	Combination therapy achieved tumor volume reduction 21-81%; demonstrated synergistic efficacy
Hartrampf et al., 2020 [80]	10	Advanced symptomatic	PRRT + fractionated EBRT	Not reported	Responders: 107.7 mo, Non-responders: 26.2 mo	Not reported	Long-term follow-up (median 105 mo) confirmed durability of combination approach without severe toxicity
Kurz et al., 2024 [73]	14	Progressive intracranial	[^{177}Lu]Lu-DOTATATE	Not reported	Not reported	Not reported	Phase II trial (NCT03971461): >25% reduction in [^{68}Ga]Ga-DOTATATE uptake identified as potential therapeutic biomarker
Hasenauer et al., 2025 [74]	32	Relapsing/recurrent	[^{177}Lu]Lu-DOTATATE/DOTATOC	Not reported	Not reported	Not reported	Increased SSTR-positive tumor volume on follow-up PET predicted shorter PFS

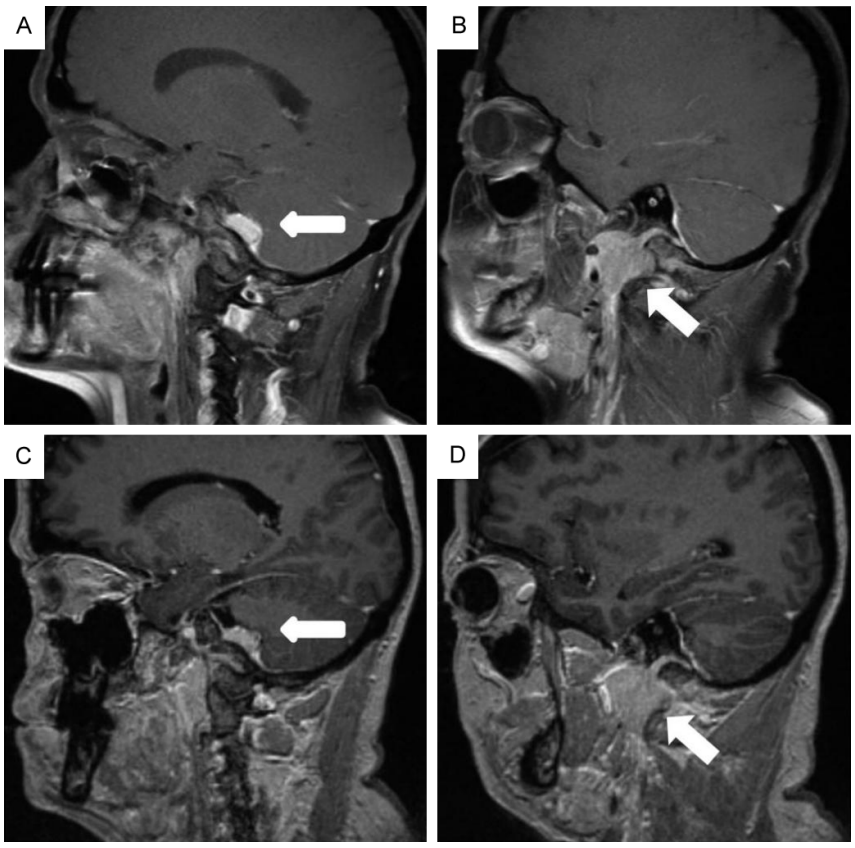

Figure 3. MRI demonstrating treatment response in a patient with WHO grade II meningioma after [^{90}Y]Y-DOTATOC treatment. (A, B). Contrast-enhanced T1-weighted MR images at initiation [^{90}Y]Y-DOTATOC therapy show enhancing tumor at the cerebellopontine angle extending into the upper cervical spine, with intracranial (A) and vertebral (B) involvement (arrows). (C, D) Follow-up MR imaging 72 months after [^{90}Y]Y-DOTATOC therapy demonstrates sustained tumor control with stable appearance of the treated lesions (arrows). This research was originally published in JNM. Gerster-Gilliéron K et al. [^{90}Y]Y-DOTATOC as a Therapeutic Option for Complex Recurrent or Progressive Meningiomas. J Nucl Med. November 2015, 56 (11) 1748-1751; © SNMMI [70].

PRRT in slowly progressing tumors may yield better patient outcomes compared to reserving PRRT for salvage therapy [77]. Disease stabilization in 86.7% of patients for progressive, unresectable meningiomas, supports PRRT's utility outside of salvage therapy [78].

Integrating PRRT with external beam radiation therapy (EBRT) has shown enhanced, synergistic efficacy. In a cohort of 10 patients, [^{177}Lu]Lu-DOTATATE/DOTATOC was administered along with EBRT (42-60 Gy), with one patient achieving complete response and eight cases of stable disease, with tumor volumes reduced by 21-81% compared to baseline [79]. Long-term follow up further supported the durability of combination therapy demonstrated durability with median follow-up of 105 months in 10 patients, reporting a median progression-free survival of 107.7 months among responders compared to 26.2 months in non-responders, without severe toxicity or adverse effects throughout the follow-up period [79, 80].

These studies reinforce the ability of PRRT to achieve durable disease stabilization in meningiomas, particularly when applied in carefully selected patient populations. A consistent theme across these studies is that high tumor uptake along with early stage sustained stabilization correlate with longer survival, however, this benefit varies across cohorts. Differences in outcomes is likely due to variations in timing of treatment and disease biology, with several reports suggesting that earlier integration of PRRT, rather than salvage use, may optimize clinical responses. The ability to achieve durable disease control, even with retreatment in some cases, reinforces PRRT's value as a long-term treatment option. Furthermore, combining PRRT with EBRT enhances tumor control and prolongs progression-free survival, without the evidence of additional toxicity reported in the studies.

Technical considerations and special applications of PRRT in meningiomas

Intra-arterial delivery has been investigated to improve tumor-specific targeting and radiotracer uptake (**Table 2**). In a small cohort of patients (n=8) with high grade meningiomas, intra-arterial PRRT delivered a greater mean-absorbed dose than intravenous administration (3.62 Gy vs. 2.86 Gy). Furthermore, the dose per unit activity was greater in the intra-arterial route compared to intravenous administration (1.72 Gy/GBq vs. 0.86 Gy/GBq) [81]. Similarly, Vonken et al. achieved 100% technical success using intra-arterial delivery of [^{177}Lu]Lu-DOTATATE, resulting in increasing tracer accumulation without procedure-related complications [82]. While technically viable, the selection of therapeutic isotope is another key consideration in PRRT. Among available isotopes, clinical experience favors [^{177}Lu]Lu over [^{90}Y]Y for meningioma therapy due to its dual beta and gamma emission, which allow for post-treatment dosimetry, favorable toxicity profile, and superior tumor-to-normal tissue dose distribution. Treatment with [^{177}Lu]Lu is generally well-tolerated, with hematologic toxicity being the most observed adverse effect. Clinically meaningful benefits have also been observed including improvements in quality of life, reductions in tumor-related pain, and enhanced performance status.

PRRT has also shown promise in difficult to treat patient populations. In a cohort of 11 individuals with neurofibro-

Table 2. Special applications and technical considerations in PRRT for meningiomas

Author, Year [Ref]	n	Population/Application	Agent(s)	Route	Key Findings
Puranik et al., 2024 [81]	8	High-grade meningiomas	[^{177}Lu]Lu-DOTATATE	Intra-arterial vs. intravenous	Mean absorbed dose: 3.62 Gy (IA) vs. 2.86 Gy (IV); Dose per unit activity: 1.72 Gy/GBq (IA) vs. 0.86 Gy/GBq (IV); improved tumor-specific targeting
Vonken et al., 2022 [82]	Salvage meningioma patients	Treatment-refractory	[^{177}Lu]Lu-HA-DOTATATE	Intra-arterial	100% technical success; increased tracer accumulation without procedure-related complications
Kertels et al., 2021 [83]	11	Neurofibromatosis type 2 with multifocal meningiomas	[^{177}Lu]Lu-DOTATATE	Standard	6 patients (55%) achieved disease stabilization; demonstrated therapeutic activity in difficult-to-treat NF2 population
Parghane et al., 2019 [84]	Cohort with incidental findings	Neuroendocrine tumor patients with incidentally detected meningiomas	[^{177}Lu]Lu-DOTATATE	Standard	Mean PFS: 26.25 months in treated cases; demonstrated proof-of-concept for dual-targeting approach
Minutoli et al., 2014 [85]	8	Unresectable meningiomas	[^{111}In]In-pentetreotide	Standard	Early proof-of-concept: 2 partial responses, 5 stable disease; demonstrated feasibility of SSTR-targeted therapy

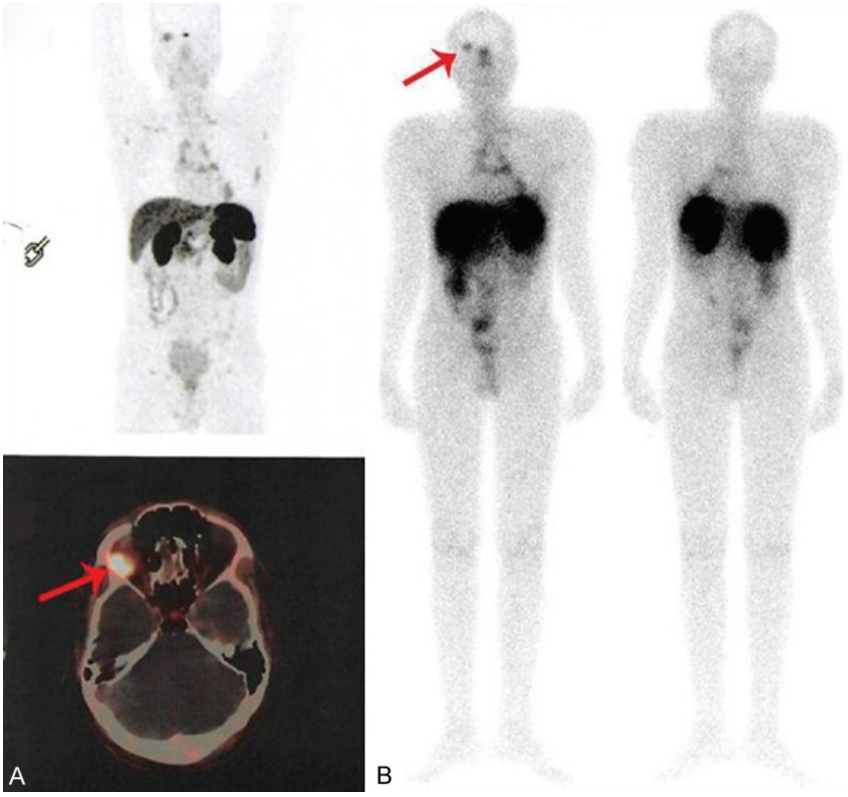

Figure 4. [^{68}Ga]Ga-DOTATATE PET/CT and treatment response in a patient with meningioma. A. [^{68}Ga]Ga-DOTATATE PET/CT demonstrates tracer uptake in the primary thymic neuroendocrine tumor and abnormal focal uptake at the right retrobulbar region adjacent to the optic nerve (red arrows), subsequently confirmed as a meningioma using MRI. B. Post-therapy [^{177}Lu]Lu-DOTATATE scan following four treatment cycles shows radiotracer accumulation within the meningioma (red arrow). At 26-month follow-up, the patient exhibited complete resolution of neurological symptoms with durable disease control, highlighting the potential of peptide receptor radionuclide therapy (PRRT) in meningioma management. Reproduced from Parghane RV et al. World J Nucl Med. 2019 Apr-Jun;18(2):160-170 with permission [84].

matosis type 2 (NF2) and multifocal meningiomas, PRRT demonstrated therapeutic activity, with six patients achieving disease stabilization [83]. PRRT was applied in patients with neuroendocrine tumors, who also had incidentally detected meningiomas, observing a mean progression-free survival of 26.25 months in treated cases [84]. Interestingly, there was evidence of early proof-of-concept using [^{111}In]In-pentetreotide therapy in eight patients with unresectable meningiomas. Treatment with [^{111}In]In-pentetreotide led to partial responses in two patients and disease stabilization in five others [85]. **Figure 4** below presents an example of meningioma imaging using [^{68}Ga]Ga-DOTATATE PET/CT and [^{177}Lu]Lu-DOTATATE, highlighting diagnostic utility SSTR2-directed imaging.

Data reported supports using PRRT as an effective treatment to manage progressive, treatment-refractory meningiomas, particularly in cases classified as WHO Grades I and II. When optimizing patient recruitment future prospective studies exploring this area should incorporate quantitative evaluation of SSTR expression using functional imaging. Early integration of PRRT in clinical management may lead to better clinical outcomes, and concurrent treatment with EBRM has shown potential value in select cases.

Artificial intelligence, radiomics, and machine learning in SSTR PET

The application of artificial intelligence in SSTR PET imaging addresses specific technical challenges in meningioma management while harnessing the unique properties of somatostatin receptor targeting.

Manual delineation of meningiomas on SSTR PET is subject to significant interobserver variability, especially in cases involving complex skull-based tumors where anatomical boundaries cannot be clearly defined. Deep learning models have improved measures of consistency in segmentation. SegResNet-based modelling in a cohort of 326 patients with meningiomas have demonstrated high segmentation accuracy, achieving a mean Dice coefficient of 0.881 (95% CI: 0.851-0.981). Additionally, radiomic features derived from manual and automated contours had strong agreement with an intraclass correlation (ICC) reaching 0.804. Semi-automated, threshold-based approaches, tailored to SSTR PET leverage its inherently high tumor-to-background contrast. A study implemented such methods in a cohort of 16 patients with meningiomas and identified SUV_{max} 14.0% to be the optimal threshold, achieving a mean Dice coefficients of 0.50 ± 0.19 compared to expert consensus, representing a practical approach for clinical implementation given SSTR PET's superior contrast compared to conventional imaging [86-88].

Beyond segmentation, the grade-dependent response patterns seen with PRRT, highlighted by six-month progression free survival rates of 94% Grade I, 48% for Grade II, and 0% for Grade III, provide a compelling basis to develop predictive clinical algorithms. Machine learning models have the potential to integrate pre-treatment SUV_{max}, SUV_{mean}, and volumetric SSTR uptake parameters with clinical variables to refine patient selection. In a lesion-based analysis of 16 patients diagnosed with treatment-refractory meningiomas, elevated values of pre-therapeutic SUV_{max} and SUV_{mean} on [^{68}Ga]Ga-DOTATOC PET imaging correlated with absence of disease progression at six months, whereas lower [^{68}Ga]Ga-DOTATOC uptake was associated with early progression [71]. However, current analyses are limited to simple univariate correlations. Multi-parametric models that incorporate spatial uptake heterogeneity, kinetic parameters, and tumor volume may enhance predictive accuracy in identifying cases of Grade II meningiomas that are likely to demonstrate the prolonged responses typically seen in Grade I tumors. By moving towards quantitative evaluation, these data-driven approaches may allow for more accurate selection of patients who are likely to respond favorably to PRRT.

Radiomic analysis of SSTR PET allows quantitative assessment of tumor heterogeneity to identify patterns that correlate with treatment resistance. Treatment failure often results from resistant cellular subpopulations. Automated evaluation of uptake variability within lesions may identify tumors at higher risk for early progression despite high overall SSTR expression. Hasenauer et al. reported that, in a cohort of 32 patients with relapsing meningioma, increased SSTR-positive tumor volume on follow-up PET was associated with shorter progression-free survival, suggesting that variability in SSTR expression may hold prognostic information in predicting disease course [74]. Algorithms designed to systematically analyze texture patterns may help identify heterogeneity signatures associated with long-term benefit as seen in studies like that of Marincek et al. where mean overall survival in meningioma reached 8.6 years in 34 patients [75].

Recent studies have started to link molecular tumor profiles with noninvasive imaging biomarkers. Radiomic models using diffusion-weighted MRI can predict [^{68}Ga]Ga-DOTATOC PET uptake values (correlation coefficient 0.42, $P<0.05$), with SUV_{max} showing significant associations with specific SSTR subtypes 2A, 2B, and 5 [89].

Radiomic approaches show promise for risk stratification. MRI-based radiomic models combined with clinicopathologic variables outperform clinical variables alone for predicting Grade II meningioma recurrence (AUC 0.78 vs. 0.67), with high-risk patients demonstrating improved five-year progression-free survival when treated with adjuvant radiotherapy [90]. However, several current models remain limited by single-center designs and lack of key histopathologic markers like MIB-1 and mitotic index, highlighting the need for multicenter validation and standardized molecular profiling [90, 91].

Current assessment of PRRT response primarily relies on anatomical imaging and subjective interpretation of changes in SSTR uptake. Kurz et al. established, in their cohort of 14 patient diagnosed with progressive meningioma, that a >25% reduction in [^{68}Ga]Ga-DOTATATE uptake correlated with adequate therapeutic response [73]. However, this binary threshold may overlook subtle response patterns. Machine learning algorithms offer the ability to detect complex changes in uptake distribution, intensity, and spatial configurations, potentially identifying treatment effects earlier than conventional criteria. The delayed antitumor activity of PRRT, which typically becomes evident at six months as noted by Graillon et al. creates a window where predictive imaging biomarkers can guide clinically adaptive treatment strategies [78]. Automated analysis of serial SSTR PET scans may identify specific patterns of response or treatment-resistance patterns that precede clear changes in anatomy, enabling timely intervention in complex meningioma cases.

Collectively, these investigations highlight the potential of AI and radiomics to transform SSTR PET from mainly a visual modality into a quantitative and predictive tool that can be used to manage for meningiomas. Deep learning models have shown promise in reducing interobserver variability and delivering reliable volumetric assessments, while threshold-based methods take advantage of the intrinsically high tumor-to-background contrast of SSTR imaging. Aside from image segmentation, radiomic and machine learning approaches are starting to integrate uptake metrics, spatial heterogeneity, and clinical variables to improve risk stratification and predict therapeutic response for patients. Importantly, preliminary studies that have linked imaging-derived features with histopath-

ologic markers suggest that multiparametric models could refine patient selection for PRRT, particularly in Grade II meningiomas where treatment outcomes are variable and not as clear.

Existing AI applications in SSTR PET face several challenges. Most validation studies are limited by small sample sizes, which is an inherent challenge given the rarity of PRRT-treated meningioma cohorts, as these cohorts typically include fewer than 50 patients. The heterogeneity in SSTR tracers, imaging protocols, and treatment regimens across institutions also limits generalizability of these predictive models. Furthermore, the relationship between SSTR PET findings and underlying molecular characteristics remains poorly understood. Unlike other brain tumors, where AI has successfully linked imaging features to genetic profiles, the molecular drivers of SSTR expression patterns in meningiomas are still not well characterized. This lack of molecular insight limits the development of truly personalized, precision-medicine approaches.

Aside from biological constraints, several practical barriers curb broad clinical adoption of AI and machine learning in SSTR PET. Data standardization is critical, since there is variability in scanners, reconstruction methods, and radiotracers which all limit generalizability of computational models. Interpretation of AI models also remains a significant challenge as deep learning models often have the "black box" issue in which there is a lack of transparent clinical rationale and input [92]. Furthermore, computational demands for model training further restricts widespread use of AI and machine learning, as advanced infrastructure may not be routinely available in many centers due to financial constraints. Adopting consistent imaging protocols, interpretable algorithms, and scalable platforms are essential to routinely integrate AI tools in meningioma care.

Limitations and future directions

The integration of AI, radiomics, and deep learning models with SSTR PET imaging offers promising avenues for precision medicine approaches in meningioma management. However, clinical implementation remains constrained by small cohort sizes, institutional variability in imaging protocols, and limited molecular characterization of SSTR expression patterns. There were limitations in determining recurrence probabilities, and the benefit of adjuvant radiotherapy was only evaluated in the test set due to oversampling in the training set. which limited the study's statistical power.

Researchers have aimed to enhance PRRT outcomes, which has led to the development of targeted alpha therapies (TAT). These new radiopharmaceuticals emit high-energy but short-range alpha particles, inducing cell death by double-stranded DNA breaks, thereby minimizing systemic side effects [93]. There have been several therapeutic radionuclides, such as Bismuth-213 (^{213}Bi), Actinium-225 (^{225}Ac), Terbium-149 (^{149}Tb), and Lead-212 (^{212}Pb) that have been investigated in other tumor types, but not in meningiomas [94]. Recently, there has been evidence from the phase II LUMEN trial suggesting that quantitative dosimetry and volumetric somatostatin receptor PET imaging may have a role in helping to predict outcomes of PRRT in 37 patients with gastroenteropancreatic neuroendocrine tumors. Notably, it was reported that achieving a minimum absorbed dose of 35 Gy in the first cycle and a reduction of more than 10% in somatostatin receptor tumor volume after the first cycle were both strongly associated with longer progression free survival. The major findings from the LUMEN trial suggest that personalized, dosimetry-based therapies, in conjunction with, early PET based response approaches could help optimize treatment strategies for patients with meningiomas undergoing PRRT [95]. The promising phase II results from this study are foundational for novel clinical trials that focus on [^{177}Lu]Lu-DOTATATE used to treat meningioma, such as the currently on-going LUMEN-1 study (NCT06326190) [96].

Future prospective, multicenter trials should be designed with several key features to maximize clinical impact. First, standardized imaging protocols across centers are essential to ensure reproducibility of SSTR PET metrics and facilitate pooled analyses. Second, integrating molecular profiling and histopathologic subtyping will help enable correlative studies linking imaging phenotypes with tumor biology. Third, AI-driven algorithms should be prospectively validated as part of clinical trial endpoints, both for automated lesion segmentation and for when models are used to predict responses to treatment. Finally, study designs should include predefined therapeutic sequencing arms, such as peptide receptor radionuclide therapy versus external beam radiation, to better clarify the role of SSTR-targeted approaches in relation to current treatment standards. Collectively, these features would provide high-quality evidence to inform standardized clinical practice.

Conclusion

SSTR-targeted PRRT is an effective treatment option for patients with progressive, treatment-refractory meningiomas, with efficacy directly related to WHO tumor grade and SSTR expression levels. Grade I and II meningiomas respond favorably to PRRT, while Grade III tumors show limited benefit, making patient selection using quantitative SSTR PET imaging parameters essential, particularly SUV_{max} and SUV_{mean} values which correlate with progression-free survival. Integrating of PRRT earlier into treatment paradigms, rather than reserving PRRT solely for salvage therapy, optimizes outcomes. Using combination approaches with external beam radiation therapy enhance efficacy without increased toxicity and adverse side effects. Incorporating artificial intelligence and radiomics with SSTR PET imaging offers potential improvements in patient stratification and treatment monitoring, though

current applications remain limited by small cohort sizes and institutional protocol variability. Future prospective, multicenter studies should incorporate standardized molecular imaging protocols with histopathologic characterization to establish PRRT's role in personalized precision medicine approaches for meningioma management.

Disclosure of conflict of interest

None.

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