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EXPERT REVIEW

Current status of SSR-directed imaging and therapy in meningioma

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Abstract

Background Meningiomas are the most common tumours of the central nervous system in adults. In clinical routine, their diagnostic workup prior to subsequent therapies such as resection and radiotherapy usually consists of contrast-enhanced MRI and CT of the brain. However, there are several diagnostic uncertainties in the clinical workup, which standard morphological imaging fails to resolve. Molecular imaging has an emerging role for the diagnosis of meningiomas, which characteristically show high expression of the somatostatin receptor subtype 2 (SSR). PET imaging with selective ligands can visualize and quantify this expression against low background signal in healthy brain. Moreover, SSR-directed radioligands labeled with beta-emitters can be effective for radiopeptide therapy (RPT) in patients with recurrent or refractory meningioma.

Methods A literature search on the PubMed literature database was conducted using the terms "meningioma", "PET", "somatostatin receptor", "SS(T)R", "DOTATATE", "DOTATOC", "Radiopeptide therapy", "imaging", "therapy" alone and in combination, extending until February 2019. The search results were augmented by the authors' own literature files.

Results We summarize the current state of SSR-directed imaging in patients with meningioma regarding the distinct clinical applications for initial diagnosis, differential diagnosis, surgery and radiotherapy planning. Our review also summarizes SSR imaging for the differentiation of recurrent meningioma tissue from post-therapeutic changes within the individual follow-up. Moreover, we discuss the clinical value and place of SSR-directed RPT in patients with refractory or recurrent meningioma.

Conclusion Molecular imaging with SSR-directed radioligands contributes to the diagnostic work-up of meningioma patients by providing information that is absent from structural MR or CT imaging. Targeted SSR RPT offers well-tolerated treatment options in patients with refractory or recurrent meningioma.

Keywords Meningioma · Somatostatin receptor · PET · Radionuclide therapy

Meningioma—the most common CNS tumour

What is meningioma?

The meninges are membranes that envelope the brain as well as the spinal cord, therefore, constituting a protective encasement of the central nervous system (CNS). The embryonic precursor cells of the adult meninges derive from the neural crest and the mesodermal structures [1–3], which can undergo neoplastic transformation later in life, leading to the development of meningeal tumours, known collectively as the meningiomas (see also 2016 WHO classification of brain tumours [4]). With an annual incidence of 8/100,000, meningiomas represent the most common primary CNS tumour, comprising around 36% of all CNS tumours [5]. This WHO classification names 15 meningioma subtypes (e.g. meningothelial meningioma, transitional meningioma,

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etc.) within three grades of malignancy, i.e. WHO grade I meningioma, WHO grade II meningioma (atypical meningioma) and WHO grade III meningioma (anaplastic meningioma) [4, 6]. In analogy to other CNS tumours such as glioma [7], medulloblastoma [8] or ependymoma [9], molecular genetic profiling is increasingly used for meningioma characterization, enabling the identification of subtypes with characteristic properties in relation to optimal treatment and clinical outcome [10]. By way of example, mutations of the telomerase reverse transcriptase (TERT) promoter are an important molecular risk factor for tumour recurrence, therefore, bringing a shorter progression free survival of meningioma patients [11, 12].

Standard imaging of meningioma

The clinical gold standard for meningioma structural imaging is represented by contrast-enhanced MRI of the brain, and likewise of the spine in case of spinal meningiomas [6, 13]. Due to its excellent soft-tissue contrast and the lack of ionizing radiation exposure, this imaging technique is indispensable for delineation of the meningioma boundaries, the consecutive treatment planning, follow-up treatment monitoring, and especially for the diagnostic evaluation of tumour recurrence. Contrast-enhanced CT serves as an alternate imaging modality in meningioma workup, e.g. in case of contraindications for MRI. Whereas cerebral angiography can provide additional information with regard to the vascularization of meningiomas, it is not applied on a routine basis [6, 14].

On morphologic imaging, meningiomas mostly present as a broad-based dural lesion, most frequently occurring at a supratentorial location, or along the falx, but occasionally at unusual locations such as the optic nerve sheath or even within the ventricles [15]. Most meningiomas present on CT as predominantly isodense with healthy brain. On the other hand, CT detects more sensitively than MRI psammomatous calcifications, which occur in around 25% of meningiomas. Moreover, CT is even more sensitive for osseous involvement possibly indicative of atypical or anaplastic meningiomas [16]. On MRI, meningiomas usually present hypointense to isointense on T1-weighted images and isointense to hyperintense on T2-weighted sequences compared to healthy brain, but present an extraordinarily high and homogenous contrast enhancement after intravenous injection of gadolinium-based contrast agent. Another typical feature on MRI is the enhancing dural-tail, which is mostly a hypervascular, non-neoplastic reaction of the dura mater adjacent to the lesion [17].

Nonetheless, morphological imaging techniques, are of limited use for tumour delineation, particularly when a meningioma occurs at unusual locations such as the skull base, and are unsuited for the evaluation of osseous involvement. Moreover, the treatment follow-up can be challenging with structural imaging due to its limited diagnostic power for the differentiation of residual vital tumour from scan tissue, or post-therapeutic changes [18]. For additional information on meningioma imaging see also [6, 15, 19].

Treatment of meningioma

Surgical resection is the primary, potentially curative therapy in patients suffering from meningioma. The main goal of gross and total resection is often achievable; consequently, the histological features of the resected tumor and its molecular genetic features can be obtained in considerable detail, which can contribute importantly to the clinical management and treatment in the follow-up regimen. When surgery resolves clinical symptoms and there is initially no residual tumor mass on MRI, an observational strategy can be pursued with follow-up MRI scans. After surgery, the current EANO guidelines recommend subsequent treatment strategies, which depend on the individual histological features and the extent of resection as classified by the Simpson grade [20].

After total meningioma resection (i.e. Simpson grade I–III), patients suffering from WHO grade I meningioma can undergo direct follow-up with an observational strategy, whereas adjuvant stereotactic radiotherapy followed by annual MRI control scans is indicated in cases when the gross tumour resection could not be obtained (i.e. Simpson grade IV–V). Adjuvant fractionated radiotherapy is indicated in patients suffering from atypical meningioma WHO grade II, in whom the follow-up MRI is performed at 6 months intervals for 5 years, and thereafter with annual scans. Of note, there is a discussion of the need for adjuvant therapy in patients with atypical meningioma after undergoing total tumour resection including osseous and dural structures (i.e. Simpson grade I). This issue will be addressed within the ongoing ROAM/EORTC 1308 study [21]. In patients suffering from anaplastic meningioma WHO grade III, adjuvant radiotherapy is recommended, irrespective of the individual extent of resection/Simpson grade. Moreover, experimental chemotherapies or RPT can be considered as additional treatment options due to the poor clinical course of patients suffering from anaplastic meningioma. In these cases, follow-up MRI should be performed at intervals of 3–6 months [6]. Of note, chemotherapies are generally considered as experimental treatments for meningioma, given their mainly limited therapeutic effect [22]. There are currently several novel experimental therapies underway, e.g. targeting SMO and FAK (NCT02523014), targeting mTOR using vistusertib (NCT03071874), but also immune checkpoint inhibitors such as nivolumab (NCT02648997). For further information, see also [6, 19, 23].

PET imaging of meningioma

PET tracers for meningioma imaging

Despite its widespread availability and use for oncologic imaging, ^{18}F-FDG is of limited value for meningioma imaging. As meningiomas are predominately slow-growing tumours, they do not exhibit markedly high glucose metabolism [24–26]. Also considering the high physiological glucose metabolism of underlying cortical structures, meningiomas tend to have low target-to-background contrast to PET with ^{18}F-FDG, which is, therefore, of limited value for the identification, delineation, and characterization of meningioma tissue. Moreover, ^{18}F-FDG uptake is generally enhanced in inflammatory processes, resulting in low specificity for meningioma tissue [27]. PET examination of tumoural phospholipid synthesis with ^{11}C-choline [29] provides a higher target-to-background contrast compared to ^{18}F-FDG, but has not found widespread use for meningioma, being reported with small sample sizes [28]. This is in line with the decreasing clinical use of ^{11}C-choline in the context of prostate cancer, due to the great success of ligands targeting the prostate-specific membrane antigen (PSMA). These agents are considered superior to PET imaging with ^{11}C-choline in patients with prostate cancer [30–32] and also show high uptake in meningioma [33, 34].

Whereas ^{11}C-choline images phospholipid synthesis, ^{11}C-acetate is marker of fatty acid and cholesterol synthesis [27, 35], which shows high target-to-background contrast and clear superiority over ^{18}F-FDG in hepatocellular carcinoma [36]. However, there is only limited experience with this tracer in patients suffering from meningioma [35], or indeed any routine indications of ^{11}C-acetate PET. Another potential tracer for meningioma imaging is the bone specific tracer ^{18}F-fluoride, which might be suitable for detecting osseous involvement of meningiomas [37, 38]. Interestingly, high tracer uptake in meningioma has been reported as an incidental finding in patients suffering from neurodegenerative disorders while undergoing amyloid PET using ^{11}C-PIB and dopamine transporter PET using ^{18}F-FP-CIT [39].

SSR-directed PET imaging

While the metabolism tracers noted above have had little penetration into clinical routine, somatotstatin receptor (SSR)-directed PET imaging has had a burgeoning impact on meningioma imaging due to its several favorable properties. The SSR subtype 2 binding site has high expression in meningiomas, making SSR a promising target for meningioma imaging [40–42]. The most commonly used SSR-ligands are ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC, which are predominantly used for PET imaging of neuroendocrine neoplasms, which also comprise a strong overexpression of SSR [43]. The distinct advantages of these chelated ligands arise from the potential in-house production using a ^{68}Ge/^{68}Ga generator, which facilitates clinical handling and scheduling. Moreover, due to their low physiological uptake in osseous structures and healthy brain, there is an excellent target-to-background contrast. Only the physiologically high uptake of SSR-ligands by the pituitary gland can hamper the delineation of skull base meningiomas, especially those with infiltration of the pituitary gland [44–46]. Of note, ^{68}Ga-DOTATATE has shown superior imaging properties compared to ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC in a rodent meningioma model [47], whereas there is no direct comparison of these tracers as is far available in humans with meningioma.

Clinical applications of SSR-directed PET imaging

Initial diagnosis/differential diagnosis

SSR-directed PET imaging does not represent a standard approach at initial diagnosis of meningiomas, as meningiomas usually present with a typical appearance on conventional imaging such as MRI or CT. However, SSR-directed imaging can contribute importantly to differential diagnosis at initial diagnosis, as lymphomas, metastases, inflammatory processes or even infectious diseases of the central nervous system can involve the meninges with a ‘meningioma-like’ appearance on standard MRI [48]; these lesions do not typically show any overexpression of SSR and, therefore, no pathological uptake on SSR PET. Furthermore, the high target-to-background contrast of meningiomas on SSR PET increases the method`s sensitivity for meningioma detection. In a comparative study, contrast-enhanced MRI detected 90% of meningiomas, whereas 100% were detectable on ^{68}Ga-DOTATOC PET [44]. Along the same lines, another comparative study reported that numerous meningiomas that were invisible on contrast-enhanced MRI could be detected by ^{68}Ga-DOTATATE PET/CT [45]. At initial diagnosis, SSR-directed PET can, therefore, facilitate the detection of multifocality and particularly the detection of small meningioma lesions, which would usually remain undetected on standard imaging. Furthermore, SSR PET is useful for the initial evaluation of meningiomas with difficult assessment on MRI due to challenging localizations such as the skull base or at the optic nerve sheath (see Fig. 1). In uncertain cases with regard to the differential diagnosis, PET can

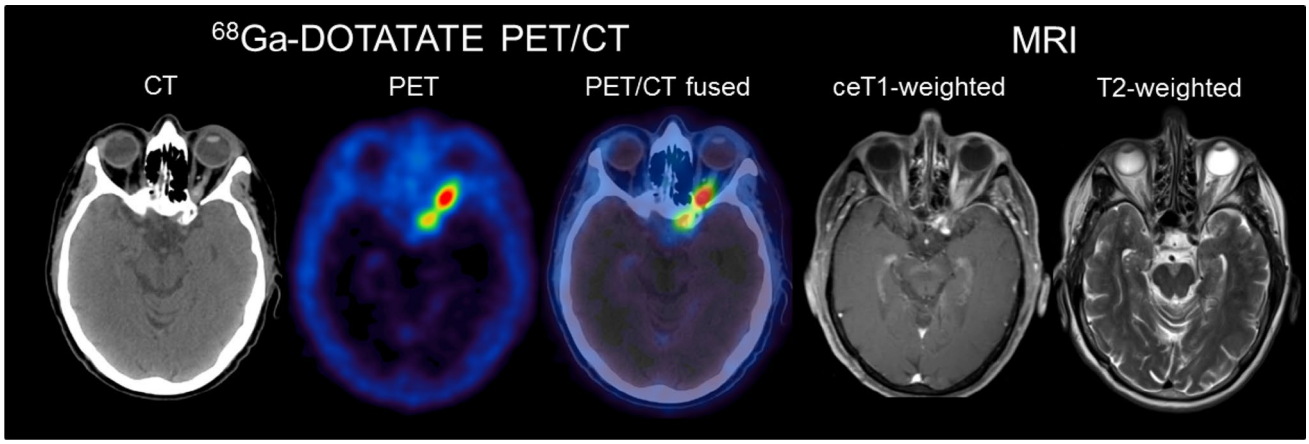

Fig. 1 A patient with optic nerve sheath meningioma and unclear extension. On ^{68}Ga-DOTATATE-PET/CT a high SSR-expression is detectable along the optic nerve (SUV_{max} 6.3), but also along the optic canal and additional meningioma tissue at the entry of the optic canal

contribute to the non-invasive diagnosis of meningioma. For example, metastases from extracranial malignancies can also affect the meninges and lead to a meningioma-like appearance on MRI [49]. As most malignancies show little or no SSR expression, SSR-directed PET can be particularly valuable for the differentiation of leptomeningeal metastases from meningiomas [50], see also Fig. 2.

However, the expression of SSR is not exclusively limited to meningiomas and neuroendocrine tumors. Low to intermediate SSR expression can also be found in pituitary tumours, gliomas, fibrous dysplasia, and Paget's disease, although these lesions usually present with lower uptake, and with morphological appearance and locations that are not typical of meningiomas [18]. Nonetheless, certain lesions with extraordinarily high SSR expression can mimic meningiomas on MRI and PET and, hence, can be hardly distinguishable from meningiomas, e.g. metastases of neuroendocrine origin (e.g. follicular thyroid cancer) [51, 52], Epstein-Barr associated nasopharyngeal carcinoma [53, 54], and neurosarcoidosis [55].

Besides its utility in resolving differential diagnosis, SSR-directed PET imaging may also contribute to tumour grading or even estimation of the tumour aggressiveness. Although SSR-directed PET using ^{68}Ga-DOTATATE could not reliably predict the histological WHO grade of a meningioma in a study by Sommerauer et al., the tracer uptake intensity on SSR PET correlated well with the tumoural growth rate in WHO grades I and II meningiomas. However, this association did not hold for WHO grade III anaplastic meningioma. To the contrast, Sommerauer et al. concluded SSR PET

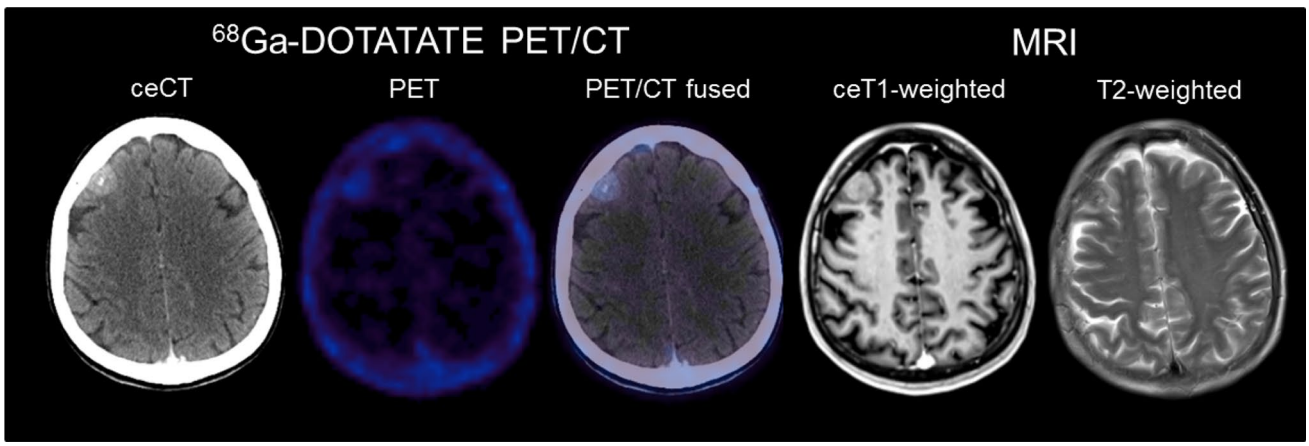

Fig. 2 A female patient with partly contrast-enhancing tumour with broad dural attachment at the right frontal lobe. In the light of the individual medical history of breast cancer the main clinical differential diagnoses were dural metastasis from breast cancer and meningioma. On ^{68}Ga-DOTATATE-PET/CT no elevated uptake exceeding the physiological uptake of the osseous structures was observed (SUV_{max} 0.8). Thus, ^{68}Ga-DOTATATE-PET/CT lead to the clinical diagnosis of distant dural metastasis from breast cancer and excluded meningioma tissue

could predict tumour growth rate irrespective of the WHO grades [56]. The key points on differential diagnosis with SSR PET are highlighted in Table 1.

Delineation of meningioma extent

As mentioned above, SSR-directed PET ligands provide an excellent target-to-background contrast, due in part to the characteristically high SSR expression of meningiomas against a near absence in healthy brain tissue or osseous structures. ^{18}F-FDG, the most commonly used tracer for oncologic imaging, is less suitable because of its physiologically high uptake in grey matter directly under the meninges. This features of ^{18}F-FDG PET gives a significantly lower target to background contrast in patients with meningioma, compounded by the inherently low uptake in meningiomas due to their less aggressive biology and low glucose consumption [26]. A study by Rachinger et al. correlating the meningioma uptake in ^{68}Ga-DOTATATE PET with histological and MRI findings revealed that tracer to give more precise tumour delineation compared to contrast-enhanced MRI. This emphasizes the superior diagnostic power of SSR-directed imaging compared to stand along MRI for estimating the tumour extent [46]. This present distinct advantages for tumours at particular locations, such as the optic nerve sheath, orbita or skull base [57–59]. In addition, the osseous extension/trans-osseous growth of a meningioma can be delineated with higher diagnostic reliability using SSR-directed PET compared to contrast-enhanced MRI alone [60], which also guides further surgical or radiotherapeutic procedures (see Fig. 3). Moreover, in the rare case of suspected distant metastases from meningioma, SSR-directed PET imaging can distinctly contribute in the clinical workup of these patients [61, 62]. These key points pertaining to tumour delineation are highlighted in Table 2.

Therapy planning and follow-up

In case of newly diagnosed brain lesions suggestive of meningioma, surgery is indicated in patients in good clinical

Table 1 Key points: Initial diagnosis/differential diagnosis of meningioma

Initial diagnosis/differential diagnosis of meningioma
^{68}Ga-DOTATOC PET has a higher sensitivity than MRI for meningioma detection
^{68}Ga-DOTATATE PET detects a higher number of meningioma sites than contrast MRI
SSR-directed PET can contribute to the differentiation of leptomeningeal metastases from meningioma
Uptake intensity on SSR-directed PET correlates with the tumoural growth rate in meningiomas

Table 2 Key points: Delineation of meningioma extent

Delineation of meningioma extent
^{68}Ga-DOTATATE PET allows more precise tumour delineation compared to contrast-enhanced MRI
Better delineation of tumours at particular localizations such as the optic nerve sheath, orbita, or skull base
Higher diagnostic accuracy for the detection of osseous extension/trans-osseous growth using SSR-directed PET compared to MRI

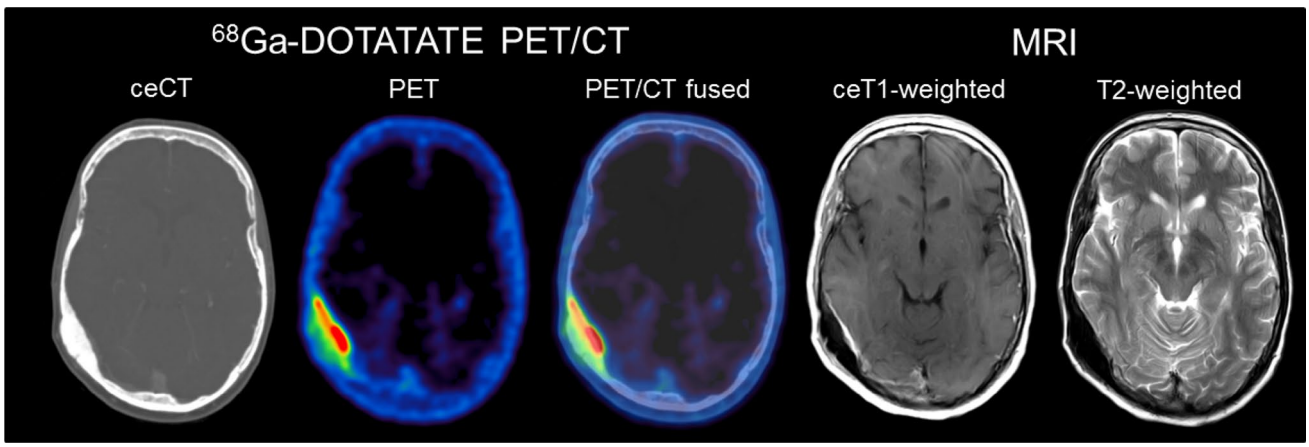

Fig. 3 A patient with predominant intra-osseous meningioma and only faint extra-osseous extent. The CT scan using the bone window indicates a certain osseous thickening at the right parietal lobe, but only a small longitudinal contrast-enhancing part can be detected on MRI. On ^{68}Ga-DOTATATE-PET/CT, the primary osseous involvement can be estimated more precisely due to the high SSR-expression of meningioma tissue (SUV_{max} 9.5)

condition who have significant mass effect, extensive symptoms, or an explicit wish for surgery. This procedure usually consists of total surgical resection of the lesion along with affected dural structures, and followed by histological and molecular genetic workup of the specimen [6]. Moreover, radiotherapy using techniques such as stereotactic radiotherapy or even radiosurgery plays a key role in the clinical management of patients with meningioma at all stages of their disease. The planning of radiotherapy is commonly based on imaging information from contrast-enhanced MRI, identifying the gross-tumour-volume (GTV) together with additional margin as the target for initial and subsequent treatments.

In cases with characteristic meningioma appearance on MRI, the radiotherapy procedure seems quite straightforward, but difficulties arise when the tumor is located at challenging locations such as the skull base, the sphenoid wing, or the orbita. These locations distinctly interfere with the specific detection of meningioma tissue, potentially leading to relevant residual tumour masses after resection, or omission of tumour tissues from the GTV selected for radiotherapy planning. Furthermore, the physiological behavior of gadolinium-based MR contrast-agents impedes the delineation of meningiomas and the subsequent GTV-delineation, as both the skull and healthy dural structures show some physiological contrast-enhancement on MRI.

SSR-directed PET has superior diagnostic value with regard to the evaluation of osseous involvement, the delineation of the tumour extent, and the differentiation of viable residual tumour masses from post-therapeutic changes (Fig. 4). SSR-directed PET, therefore, facilitates the planning of further treatments such as radiotherapy and resection by including tumor-specific information extending beyond mere visualization to morphological MRI. PET-derived information, in conjunction with structural MRI, can be implemented into radiotherapy planning and neuro-navigation systems for surgery planning [18]. Concerning radiotherapy planning, a study by Milker-Zabel et al. showed that ^{68}Ga-DOTATOC PET in addition to MRI and CT imaging optimizes the target volume delineation for radiotherapy planning in meningiomas. This held irrespective of the underlying WHO grade, as PET added additional information about tumour extent for every patient in the study [58], which is in line with a body of additional research dealing with radiotherapy planning [59, 63–65]. For further indications and the respective levels of evidence see also [18]. The key points on therapy planning with SSR PET are highlighted in Table 3.

SSR-directed radiopeptide therapy (RPT)

Throughout the last two decades, SSR-directed radioligands labeled with beta-emitting isotopes (predominantly [^{177}Lu] and [^{90}Y]) have been increasingly used with high clinical effectiveness and safety margin in terms of side effects and long-term toxicity [66, 67]. This emerging trend towards targeted radiotherapies was driven by the success od RPT in

Table 3 Key points: Therapy planning and follow-up

Therapy planning and follow-up
PET derived information can be used for radiotherapy planning and neuro-navigation for surgery planning in addition to MRI
^{68}Ga-DOTATOC PET imaging can optimize the target volume delineation for radiotherapy planning in addition to MRI and CT
SSR-directed PET can be used for differentiation of viable tumour masses from post-therapeutic changes

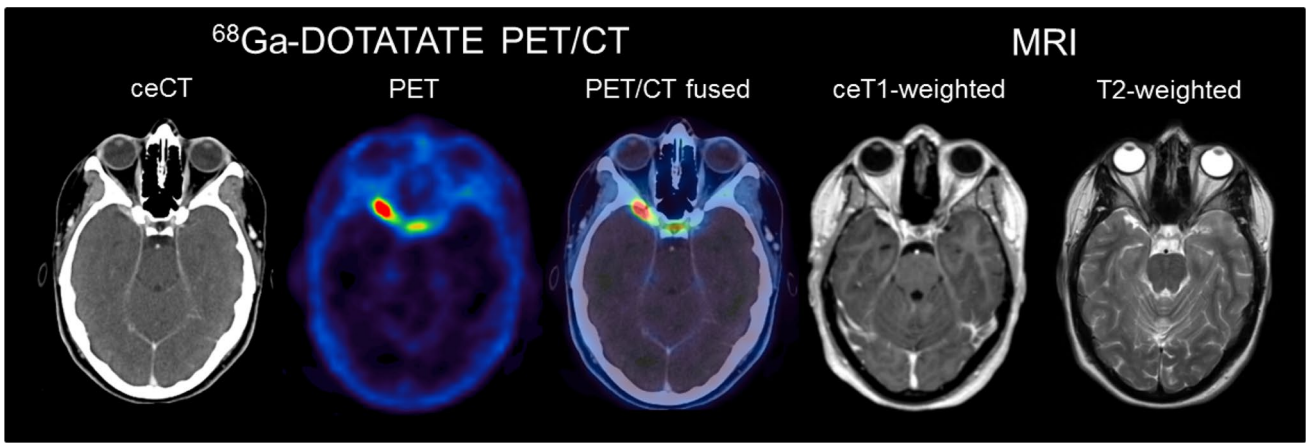

Fig. 4 A patient with residual contrast-enhancement on a follow-up MRI 16 months after meningioma resection at the right sphenoid wing suggestive of postoperative scar tissue without clinical significance. However, a high SSR-expression was detectable on ^{68}Ga-DOTATATE-PET/CT (SUV_{max} 15.3) leading to the diagnosis of recurrent/residual meningioma masses after initial resection and omitting the differential diagnosis of scar tissue

Table 4 Key points: SSR-directed radiopeptide therapy

SSR-directed radiopeptide therapy
Radiopeptide therapy shows a good risk profile and clinical response in pre-treated meningioma patients
Six-month progression free survival rates range from 57–100%
Further harmonization of treatment regimens and controlled, randomized trials are needed

neuroendocrine tumours. This was followed by the greatly successful NETTER-1 trial, which was the first controlled, randomized trial comparing SSR-directed RPT with the standard of care (high-dose octreotide long-acting repeatable) in patients with advanced midgut neuroendocrine tumours [68]. After its conclusion, the NETTER-1 trial resulted in the FDA-approval of [^{177}Lu]-DOTATATE for the therapy of advanced midgut neuroendocrine tumours [69]. In analogy to this experience in neuroendocrine tumours, SSR-directed RPT is effective and safely in patients with meningioma, especially those with recurrent, unresectable disease.

So far, use of SSR-directed RPT in patients with meningioma lags behind the comprehensive use or RPT in patients with NET, and there are few such studies in the meningioma literature [70–77]. These predominantly retrospective studies from different European centers report approximately 120 cases in total. Nonetheless, it can be confidently stated that SSR-directed RPT, such as NET, also shows a good risk profile and clinical response in these patients with extensive pre-treatment histories. The six-month progression free survival rates ranged from 57 to 100%, indicating a significant benefit. In addition, a concurrent treatment with external radiotherapy seems feasible and clinically tolerated [71].

Nonetheless, there are major drawbacks of the currently published studies, as also recently stated by Guedj et al. [78]. First, included patients significantly differed in terms of clinical stage, neuropathological diagnosis, pre-treatments, and molecular genetics (when applicable). Moreover, among the above-mentioned studies there is no consistent treatment regimen in terms of administered activities, radioisotopes (^{177}Lu and ^{90}Y), and radioligands (DOTATATE and DOTATOC), nor was there a comprehensive use of objective treatment response criteria such as 'Response Assessment in Neuro-Oncology (RANO)' criteria for meningioma [13]. Hence, drawbacks of the studies to date distinctly hamper the comparability and generalizability of their conclusions. Despite this limitation, results and clinical experience underline the potential effectiveness of SSR-directed RPT and are highly encouraging for the further comprehensive use.

Developing a standard RPT approach requires further steps in the direction of personalized medicine, taking into account the individual pre-treatment history, SSR-expression (as assessed by histology and imaging), histological features, but also dosimetry aspects. These factors should contribute to the individual decision-making, as some patients might experience an unfavorable ratio of absorbed doses in meningioma vs. absorbed doses in organs-at-risk such as the kidneys. There is no study yet evaluating the influence of the individual dosimetry on the clinical outcome in terms of progression-free survival and overall survival. As mentioned above, the molecular genetic profile and DNA-methylation status is rapidly gaining importance in the characterization of meningiomas [10, 12, 15]; these features should enter consideration in defining an algorithm for the optimal use of RPT in conjunction with synergistic treatments.

Moreover, future studies must seek to identify the particular markers indicating systemic therapies in recurrent meningioma [79]; on the one hand, the current RANO criteria for meningioma should be applied as the standard for follow-up evaluation [13], but little is known about the benefits of SSR-directed PET imaging within the individual follow-up. The key points pertaining to SSR-directed therapy are highlighted in Table 4.

Summary

Extending beyond the morphological imaging using CT or contrast MRI, SSR-directed PET imaging can distinctly contribute to resolving diagnostic uncertainties within different clinical settings. SSR-PET is proven effective in the evaluation of uncertain brain lesions suggestive for meningioma, especially at particular locations such as the skull base. The molecular imaging approach enables improved tumour delineation, with special emphasis on the detection of osseous involvement, which a crucial issue insufficiently addressed by morphological imaging. In addition, the intensity of SSR-PET uptake may eventually allow estimation of the individual tumour aggressiveness. These properties in baseline imaging particularly contribute to the subsequent resection and radiotherapy planning, with improved tumour delineation and sparing of organs at risk. Importantly, SSR-directed imaging is of high clinical relevance for differentiating viable tumour tissue due to tumour progression from post-therapeutic and reactive changes seen in the individual follow-up scan. SSR-directed RPT is emerging as a well-tolerated treatment option in patients with recurrent or refractory meningioma, offering stabilization or deceleration of tumour growth. Hence, SSR-directed PET imaging may contribute to the individual clinical workup, and support RPT as treatment option.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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