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PET imaging in patients with meningioma—report of the RANO/PET Group

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Abstract

Meningiomas are the most frequent nonglial primary brain tumors and represent about 30% of brain tumors. Usually, diagnosis and treatment planning are based on neuroimaging using mainly MRI or, rarely, CT. Most common treatment options are neurosurgical resection and radiotherapy (eg, radiosurgery, external fractionated radiotherapy). For follow-up after treatment, a structural imaging technique such as MRI or CT is used. However, these structural imaging modalities have limitations, particularly in terms of tumor delineation as well as diagnosis of posttherapeutic reactive changes. Molecular imaging techniques such as PET can characterize specific metabolic and cellular features which may provide clinically relevant information beyond that obtained from structural MR or CT imaging alone. Currently, the use of PET in meningioma patients is steadily increasing. In the present article, we provide recommendations for the use of PET imaging in the clinical management of meningiomas based on evidence generated from studies being validated by histology or clinical course.

Key words

MRI | positron emission tomography | ligand | somatostatin | meningiomas

Meningiomas are the most common primary brain tumors and represent approximately 30% of intracranial tumors. According to the classification of the World Health Organization (WHO), the majority of meningiomas are benign (WHO grade I), exhibit slow growth, and have a low recurrence rate (5-y overall recurrence rate of ~5% following complete resection).[1] In contrast, WHO grade II (atypical) and WHO grade III (malignant) meningiomas may show a more aggressive clinical behavior.[2] Atypical and malignant meningiomas have 5-y overall recurrence rates of 40% and 80%, respectively.[3] Molecular factors with strong prognostic information[4,5] and potential value

Importance of the study

This paper seeks to summarize all data published thus far on PET imaging in meningiomas, which account for levels 1–3 evidence according to the Oxford Centre for Evidence-Based Medicine in order to provide recommendations for its use as a guideline for clinicians.

as predictive markers for targeted therapies have recently emerged.[6–10] Most common treatment options are neurosurgical resection and various radiotherapy options such as radiosurgery and external fractionated radiotherapy.[6]

Contrast-enhanced structural imaging techniques such as MRI and CT (to delineate bony structures) are routinely used for defining the extent of the meningioma, treatment planning, and monitoring, as well as for follow-up after treatment, especially diagnosis of tumor recurrence. However, these structural imaging techniques have limitations in delineating meningiomas, especially at the skull base and in the case of bony involvement as well as in tumors with complex geometry.[6] Furthermore, in the case of suspected residual or recurrent tumor, it can be challenging to distinguish viable tumor from scar tissue or posttherapeutic changes by CT or MRI alone, particularly after radiotherapy.

Molecular imaging modalities, which are not routinely used yet, may provide further diagnostic information. PET has meanwhile gained considerable importance for diagnostic purposes in general oncology. In neuro-oncology, particularly cerebral gliomas have been extensively studied using initially ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) and more recently amino acid PET tracers.[11,12] In meningiomas, several tracers have been used, including specific somatostatin receptor (SSTR) ligands such as gallium-68 (^{68}Ga)-DOTA-Tyr3-octreotide (^{68}Ga-DOTATOC), ^{68}Ga -DOTA-D-Phe1-Tyr3-octreotate (^{68}Ga-DOTATATE), and ^{68}Ga-DOTA-1-Nal3-octreotide (^{68}Ga-DOTANOC). Currently, the number of PET examinations in meningioma patients is steadily increasing. The Response Assessment in Neuro-Oncology (RANO) Working Group and the European Association for Neuro-Oncology recently published guidelines for the use of PET in gliomas[11]; here we have prepared evidence-based recommendations for the use of PET imaging in the diagnosis and follow-up of patients with meningiomas to guide clinicians from all disciplines involved in the management of patients with these tumors.

Search Strategy, Selection Criteria, and Levels of Validation

A PubMed search was performed of the published literature with the combination of the search terms "meningioma," "PET," "FDG," "amino acid," "somatostatin," "DOTATOC," "DOTATATE," "DOTANOC," "grading," "delineation," "radiotherapy," and "extent" until September 2016. Additionally, articles identified through searches of the authors' own files were included in the search. Results of the search were evaluated by the working group with respect to the level of evidence and the grade of validation of the PET studies examined. As described previously,[11] any study that correlated the PET findings with histopathology was considered to represent the highest degree of validation. Next, correlation with MRI and with the patient's clinical course was used for the second level of validation. Only papers constituting levels 1–3 evidence according to the Oxford Centre for Evidence-Based Medicine ("The Oxford 2011 Levels of Evidence") were included.

Tracers for PET Imaging in Meningioma Patients

Several tracers addressing different molecular structures or pathophysiological pathways in meningioma cells are available for PET imaging and will be summarized in the following paragraphs.

Glucose PET

^{18}F-FDG represents the most widely used tracer in oncological PET imaging.[13] With a half-life of the ^{18}F isotope of 110 minutes, the tracer does not need in-house production, which facilitates supply. Therefore, ^{18}F-FDG is available at all PET centers independently of the presence of a cyclotron. Due to an increased glycolysis in neoplastic tissue, uptake of ^{18}F-FDG is generally higher than in nonneoplastic tissue.[14,15] However, there are several limitations for the use of ^{18}F-FDG in meningioma. Meningiomas are mostly slow-growing tumors and their glucose metabolism might be only moderately elevated[15–17] (Fig. 1). Furthermore, high physiological glucose uptake of the normal cerebral cortex leads to a low tumor-to-background ratio and therefore limits the sensitivity for the detection of meningioma tissue and its delineation from adjacent brain parenchyma.[18] Moreover, ^{18}F-FDG uptake is not tumor specific but may be increased in inflammatory tissue.[18]

PET Ligands for Somatostatin Receptors

Because of the overexpression of SSTRs in meningiomas,[19–21] radiolabeled SSTR ligands can be used for the visualization of meningioma tissue. Somatostatin receptor subtype 2 has been found to be the most abundant isoform, with almost 100% expression in meningiomas.[19] The most commonly applied SSTR ligands for PET imaging are ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC. These tracers are also frequently used for imaging of neuroendocrine tumors, which likewise express high levels of SSTR.[22] ^{68}Ga has a physical half-life of 68 minutes and can be produced with a ^{68}Ge/^{68}Ga generator system, which enables in-house production without need of an on-site cyclotron. PET ligands to SSTR

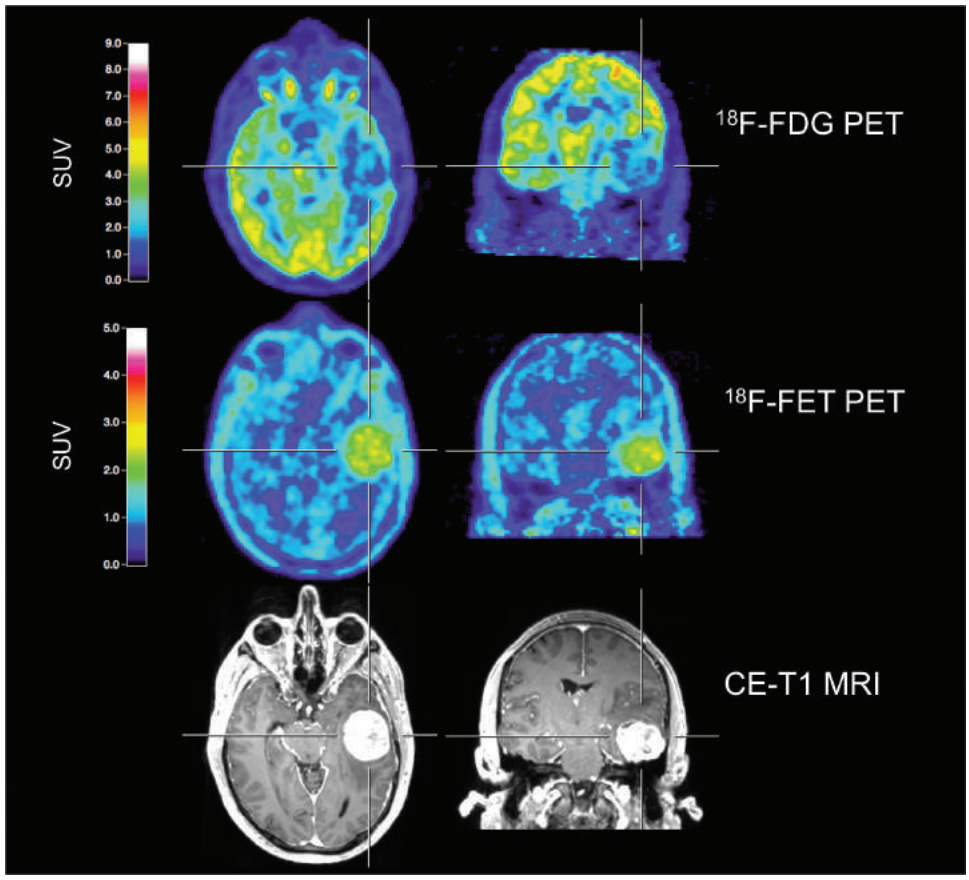

Fig. 1 A 43-year-old male patient with a newly diagnosed left temporal meningioma (WHO grade I), preoperatively examined by multimodal imaging. Both contrast-enhanced MRI and ^{18}F-FET PET allow a precise tumor delineation. Conversely, ^{18}F-FDG PET shows decreased metabolic activity, indicating its limitation for the evaluation of meningioma extent.

provide high sensitivity with excellent target-to-background contrast due to low uptake in bone and healthy brain tissue.[23,24] However, the pituitary gland shows high physiological uptake which serves as a positive control but limits the exact delineation of meningioma extent in its close proximity.[25] Up to now, a comparative study of ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC in meningioma patients is not available. An animal study with nude mice bearing xenografts of a human meningioma cell line (CH-157MN) revealed similar uptake kinetics of the 3 tracers, but tumor uptake ratios were higher with ^{68}Ga-DOTATATE, suggesting a higher diagnostic value of ^{68}Ga-DOTATATE for detecting meningiomas.[26] However, the uptake of all these tracers is relatively high compared with normal brain; thus, these differences are of less importance. Procedure guidelines for PET imaging with ^{68}Ga-DOTA–conjugated peptides have been published previously.[27]

Amino Acid PET Tracers

Uptake of radiolabeled amino acids or their analogues, such as [^{11}C-methyl]-methionine (^{11}C-MET) and O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET), is mediated by the L-amino acid transporter system, and increased uptake is already seen in slow-growing tumors such as low-grade gliomas[28–30] and meningiomas.[31,32]

Amino acid PET tracers are widely used for glioma imaging as well as for the assessment of brain metastases after radiotherapy and have been integrated in many centers in clinical routine.[11,12] Even though amino acid PET exhibits a better tumor-to-background contrast than ^{18}F-FDG PET,[33] the availability of specific SSTR ligands with even higher tumor-to-background contrast led to a limited use of amino acid PET in meningioma imaging.[34,35] For the use of ^{11}C-MET, an on-site cyclotron is needed due to the short half-life (20 min) of ^{11}C. In contrast, ^{18}F-FET is (like ^{18}F-FDG) labeled with ^{18}F (half-life, 110 min) and can therefore be purchased and delivered independently of a local radiopharmaceutical setting. Interestingly, ^{18}F-FET does not accumulate in the pituitary gland in comparison with ^{11}C-MET and SSTR ligands; it may be superior in detecting intrasellar invasion of meningioma.[36] For therapeutic procedures such as boron neutron capture therapy, boronated amino acid PET probes have been used in meningiomas.[37,38]

Other PET Tracers

^{11}C-choline can be used as a marker of increased phospholipid synthesis in tumor cells.[39] Over the last years, it has been mostly used in prostate cancer and is currently being replaced by prostate-specific membrane antigen (PSMA) ligands.[39,40] As choline exhibits low uptake in the healthy brain tissue, the target-to-background contrast is good as well, but the experience in meningioma patients is limited to case reports so far, and only one small study on 7 patients compared the value of ^{11}C-choline with ^{18}F-FDG PET in meningiomas, indicating a higher target-to-background contrast for ^{11}C-choline than for ^{18}F-FDG.[41]

^{11}C-acetate is another possible PET tracer used in extracranial tumors which are difficult to detect by ^{18}F-FDG PET, such as renal carcinoma, prostate cancer, and hepatocellular carcinoma.[42–44] Uptake of ^{11}C-acetate in tumor cells depends on the activation of anabolic pathways of fatty acids and sterol synthesis.[18,45] The experience with this tracer for meningioma imaging is also very limited. So far, only one study on 22 patients has been published, stating that the tracer is superior to ^{18}F-FDG for the detection of meningioma and delineation of tumor extent for radiosurgery planning and the evaluation of treatment response.[18]

^{18}F-fluoride, which is used in imaging of bone metastasis of neoplastic tissue, might facilitate detection of bone invasion of meningiomas. There are 2 studies reporting superior detection of bone involvement with ^{18}F-fluoride compared with CT and MRI, which might assist in planning of surgery.[46,47]

Aside from PET imaging with the specific purpose of meningioma imaging, meningiomas might be detected incidentally on PET scans using ^{11}C-PIB (Pittsburgh compound B) in patients with Alzheimer's disease,[48] ^{68}Ga-labeled PSMA ligand PET,[49] or dopamine transporter imaging in patients with Parkinson syndromes.[50]

Clinical Applications for PET Imaging

Diagnosis/Differential Diagnosis

Mostly, meningiomas are well-defined, extra-axial masses, which may displace the adjacent brain. Furthermore, the cerebrospinal fluid (CSF) cleft sign can be present, representing a thin rim of CSF between tumor and brain parenchyma. Sometimes, however, meningiomas may become very large before causing clinical symptoms, and furthermore the distinction between an intra-axial and extra-axial origin may be difficult.[51] Several other disease processes have a propensity for primary involvement of the dura mater or subdural space, giving a meningioma-like appearance, including lymphomas, brain metastases, other benign tumors (eg, schwannomas), inflammatory lesions (eg, neurosarcoidosis, Wegener's granulomatosis), and infections of the central nervous system (eg, tuberculosis).[52]

Although PET plays no major role in the primary diagnosis of meningiomas, SSTR imaging may be helpful in terms of definition of gross target volume (GTV) and clinical target volume (CTV). A study comparing contrast-enhanced MRI and ^{68}Ga-DOTATOC PET/CT prior to radiotherapy reported that all meningiomas (n = 190) were detected by PET/CT. In contrast, only 171 meningiomas were detected by contrast-enhanced MRI (90%), indicating an improved sensitivity for ^{68}Ga-DOTATOC PET in meningioma detection compared with contrast-enhanced MRI.[24] Particularly difficult to detect by standard MRI alone were tumors adjacent to the falx cerebri, tumors located at the skull base, tumors infiltrating bony structures, and tumors obscured by imaging artefacts or calcification (Fig. 2). The authors concluded that ^{68}Ga-DOTATOC PET/CT may provide additional information in patients with uncertain or equivocal results on MRI or could help to confirm a diagnosis of meningioma based on MRI. Moreover, ^{68}Ga-DOTATATE PET/CT helps to discriminate optic nerve sheath meningiomas in the differential diagnosis of other lesions being associated with the optic nerve[53] (Fig. 3). In a comparative study between MRI and ^{68}Ga-DOTATATE PET/CT, additional meningiomas were detected by PET, some of them even in retrospect not being visible yet in MRI.[23]

However, expression of SSTRs may also be observed in esthesioneuroblastomas, leukocytes accumulating in chronic inflammatory tissue, pituitary tumors, gliomas, fibrous dysplasia of the bone, Paget's disease, and brain metastases originating from various extracranial tumors (eg, breast cancer).[24,27] Such lesions, however, usually present with a lower uptake and with a distinct morphology and location that differ from meningiomas.

- PET ligands for SSTRs may add valuable diagnostic information to standard MRI in newly diagnosed brain lesions suspicious for meningiomas, especially concerning differential diagnosis and sensitivity to detect lesions (evidence level 2).

Tumor Grading

The uptake of ^{18}F-FDG correlates significantly with the WHO grade in meningiomas,[14,15] but as a major limitation its uptake is not tumor specific and may be increased in inflammatory tissue.[18] ^{11}C-choline may overcome this limitation and may be helpful for meningioma grading as well,[41] but the present results are preliminary. Regarding PET ligands to SSTR, ^{68}Ga-DOTATATE binding correlates with tumor growth rate in WHO grades I and II meningiomas but is abolished in anaplastic (WHO grade III) meningiomas.[35] Data on the amino acid tracer ^{11}C-MET suggest a correlation with proliferative activity in meningiomas[54] but are controversial for noninvasive meningioma grading.[34,55] Furthermore, its use is strictly limited to centers with an on-site cyclotron unit. Preliminary findings revealed that static and dynamic ^{18}F-FET parameters may provide additional information for noninvasive grading of meningiomas.[32] The tracer ^{11}C-acetate seems not to be helpful for meningioma grading.[18]

- Up to now, only preliminary evidence for a potential benefit of PET for noninvasive meningioma grading is present (evidence level 3).

Delineation of Tumor Extent

A prerequisite for an improved delineation of tumor extent is a high tumor-to-background ratio derived from

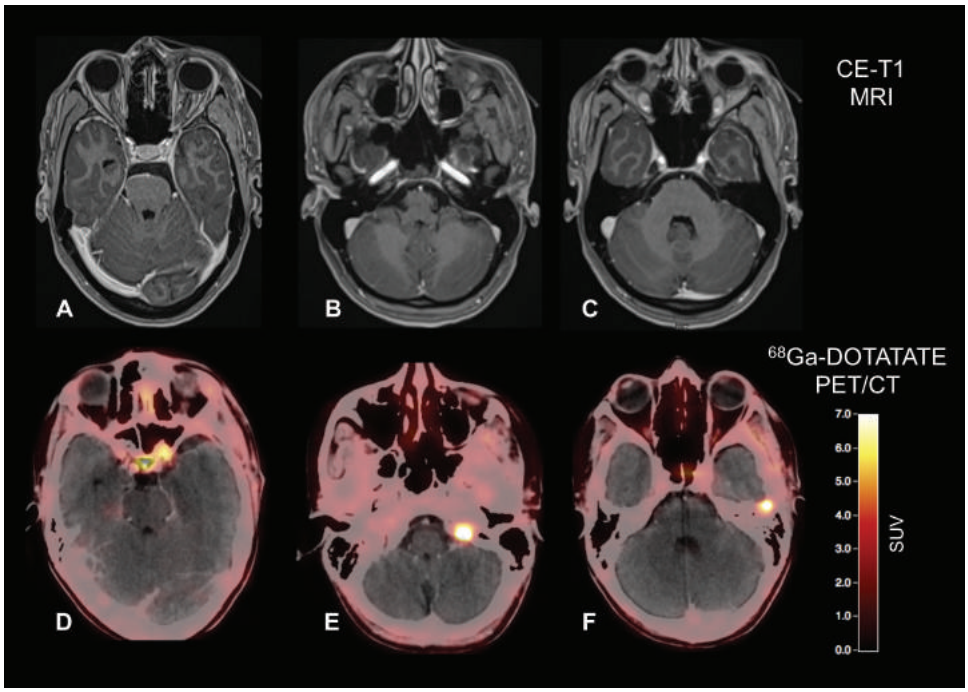

Fig. 2 Postoperative contrast-enhanced MRI and ^{68}Ga-DOTATATE PET/CT of a 32-year-old patient after resection of a WHO grade I meningioma show residual tumor located at the left internal carotid artery and at tumor at the tip of the left orbit (A, D). Surprisingly, 2 additional meningiomas were also visible on the ^{68}Ga-DOTATATE PET/CT (E, F), without corresponding contrast enhancement on MRI (B, C).

the administered PET tracer, preferably higher than the contrast that can be achieved by contrast-enhanced MRI (Fig. 4). Furthermore, regarding meningioma delineation, several different tissues are to be respected as background (eg, brain, bone, blood, fibrotic tissue, inflammatory lesions). Due to usually high levels of glucose in healthy brain parenchyma causing a poor tumor-to-background contrast, the tracer ^{18}F-FDG is not suitable for precise tumor delineation.[17] On the other hand, PET ligands to SSTR and radiolabeled amino acids generally elicit high tumor-to-background ratios. In a comparative study using neuronavigated tissue sampling with histological confirmation, in various tumor locations ^{68}Ga-DOTATATE revealed a more precise delineation of tumor extent than contrast-enhanced MRI.[23] Furthermore, in meningiomas with osseous infiltration as well as in regions such as the skull base, orbita, and cavernous sinus, PET using ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC was also reported to provide a better tumor delineation than MRI.[25,56,57] In the latter studies, however, histological confirmation of imaging findings was not performed. Similarly, studies using ^{11}C-MET or 2-[^{18}F]-fluoro-L-tyrosine reported an improved tumor delineation compared with MRI, but again without histological confirmation.[31,58,59] In one retrospective study with histological evaluation, ^{18}F-fluoride improved preoperative detection of bone infiltration.[46]

- Different PET tracers might facilitate tumor delineation in meningiomas, especially in regions with low MR and CT contrast such as the skull base, orbita, parafalcine area with involvement of the sagittal sinus, cavernous sinus, and any transosseous growth; best evidence exists currently for ^{68}Ga-DOTATATE (evidence level 2).

Value for Treatment Planning

Resection

Whenever treatment is considered in newly diagnosed meningiomas, surgical resection is the mainstay of therapy in the majority of locations. The surgical goal should be total excision of the lesion, including the involved dura.[6,60] In order to achieve this goal, the exact delineation of the tumor has to be fully visualized prior to surgery, since bony involvement and extended dural infiltration might not be recognizable, even with the use of an operating microscope. This is especially the case for regions with low MR and CT contrast, such as the skull base, orbita, parafalcine area with involvement of the sagittal sinus, cavernous sinus, and any transosseous growth. Histology-controlled and imaging-guided resection studies using both ^{68}Ga-DOTATATE PET and MRI showed that ^{68}Ga-DOTATATE PET better delineates the extent of meningiomas than does contrast-enhanced MRI alone.[23,61] Equally important, ^{68}Ga-DOTATATE PET helps to discriminate between recurrent tumor and scar tissue after previous surgery or radiotherapy with higher sensitivity and equal specificity compared with MRI.[23] This is of additional value to tailor

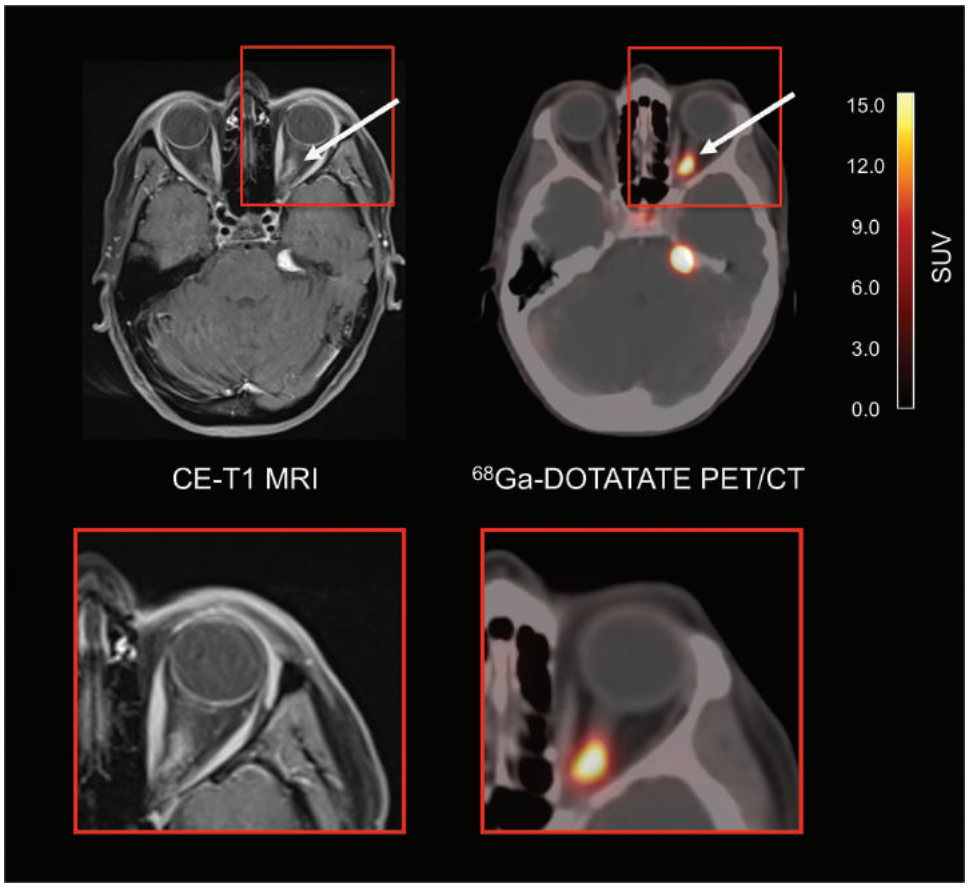

Fig. 3 A 43-year-old female patient with a history of a meningioma of the left optical sheath treated with surgery and radiotherapy 8 years ago. At follow-up, ^{68}Ga-DOTATATE PET/CT reveals multiple meningioma lesions, including meningioma recurrence at the optical sheath (arrows).

the resection, especially in recurrent, pretreated tumors. Thus, ^{68}Ga-DOTATATE PET provides additional valuable information regarding extent and localization of meningioma tissue, especially when this information is being integrated into neuronavigation systems.[62]

- ^{68}Ga-DOTATATE PET improves the delineation of tumor extent in meningiomas with potential benefits for tumor resection (evidence level 2).

Radiation treatment planning

Target volume delineation plays a crucial role in the planning of high precision radiation therapy such as radiosurgery and stereotactic fractionated radiotherapy. In meningiomas, the GTV and CTV are delineated based on image fusion of contrast-enhanced CT and MRI. Usually, contrast-enhanced MRI visualizes the GTV very well. However, in a considerable number of cases, especially in tumors located at the skull base (meningiomas of the suprasellar region and the sphenoid wings are ~30% of cases), it is difficult to differentiate between normal dura tissue and tumor tissue, because both normal dura as well as bone show a high contrast enhancement. Moreover, in tumors infiltrating the bone it is difficult to define the infiltration depth with high precision, despite using the bone window on CT images. In these cases, PET imaging may add helpful information. Furthermore, in postoperative MRI with inconclusive findings (eg, reactive changes), PET may aid in the identification of active tumor remnants in the planning of adjuvant radiotherapy after subtotal or partial tumor resection. For radiotherapy planning, it is necessary to fuse PET with MRI/CT due to the lower spatial resolution of PET alone.

^{11}C-MET PET can be integrated into radiation treatment planning[63] and significantly influence GTV delineation in meningiomas. Astner and colleagues demonstrated that in 32 patients with benign skull base meningiomas treated with stereotactic fractionated radiotherapy, the addition of ^{11}C-MET PET changed the GTV in all but 3 patients.[31] In that study, ^{11}C-MET PET detected tumor areas with a mean volume of 1.6 mL which were not visualized on CT or MRI, leading to an enlargement of GTV of approximately 9%. At the same time, areas without tumor infiltration could be excluded from the GTV, and critical structures like optic nerves, the chiasm, and the pituitary gland could be spared more effectively.[31] Furthermore, regarding the GTV definition, the addition of ^{11}C-MET PET to CT and MRI helps to significantly lower

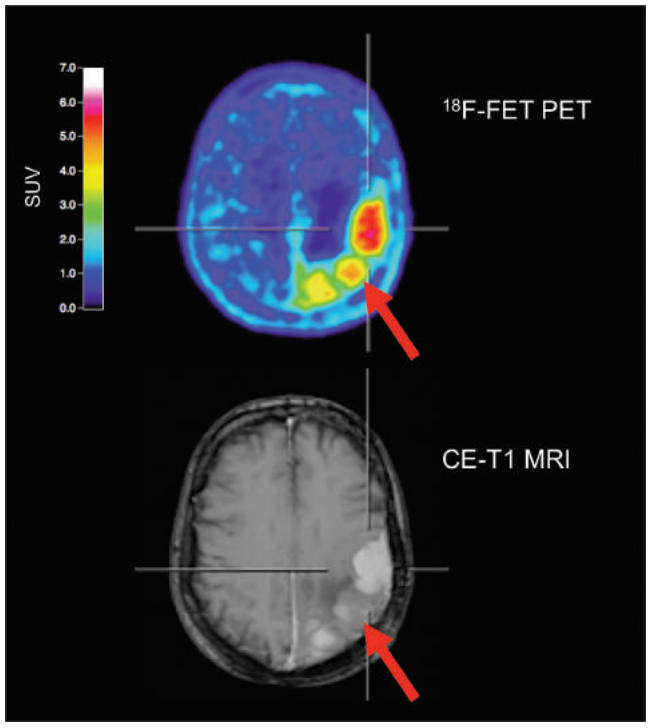

Fig. 4 Amino acid PET with ^{18}F-FET and contrast-enhanced MR images of a 68-year-old female meningioma patient (WHO grade I) with suspected recurrence 9 years after tumor resection at initial diagnosis. ^{18}F-FET PET identifies 3 hypermetabolic lesions, consistent with meningioma recurrence. In contrast, MRI shows prominent contrast enhancement in only 2 of 3 lesions. In that lesion (arrow, bottom), contrast enhancement is subtle and not well defined. ^{18}F-FET PET allows an improved delineation of this lesion (arrow, top).

the interobserver variability in comparison to MRI and CT alone.[59] Subsequently, other groups have confirmed these findings using other radiolabeled amino acids.[58]

Milker-Zabel et al demonstrated an optimized target volume delineation for stereotactic fractionated radiation therapy in grades I–III meningiomas using ^{68}Ga-DOTATOC PET coregistered to CT and MRI.[56] In all patients, ^{68}Ga-DOTATOC PET delivered additional information concerning meningioma extent for fractionated stereotactic radiotherapy target definition. These results are supported by data reported subsequently by other groups[57,64,65] (Figs. 5, 6).

- Amino acid PET and ^{68}Ga-DOTATOC PET add valuable diagnostic information for meningioma delineation, particularly helpful for radiotherapy planning by improving both GTV definition and dose sparing of organs at risk (evidence level 2).

Follow-up: Treatment Response, Progression

In a prospective study with 19 meningioma patients, serial ^{11}C-MET PET scans were used to evaluate the effect of stereotactic high-energy proton beam treatment (24 Gy in 4 consecutive daily 6-Gy fractions).[66] The authors observed no significant reduction of tumor size but an average tumor/brain ratio reduction of 19% in the total patient group, suggesting that ^{11}C-MET PET may enable an earlier evaluation of treatment effects than CT or MRI. The long-term evaluation over 10 years of the same patient cohort revealed that in the majority of patients, MET uptake ratios showed a further decrease, whereas tumor size was predominantly unchanged throughout the follow-up.[67] As ^{68}Ga-DOTATOC PET is superior in both discriminating meningioma tissue from scars related to pretreatment and detecting meningiomas not (yet) seen in MRI, it is useful in cases of unclear differential diagnosis between tumor progression and posttherapeutic reactive changes.[23,24,52] For the discrimination of scar tissue from vital tumor, Rachinger and colleagues demonstrated that standard MRI has a lower diagnostic performance than ^{68}Ga-DOTATATE PET: sensitivity, 79% versus 90%; specificity, 65% versus 74%; and positive predictive value, 84% versus 89%.[23] In line with this, a more recent ^{68}Ga-DOTATATE PET study with focus on transosseous growing meningiomas showed an even better diagnostic performance for pretreated lesions than standard MRI (sensitivity, 97% versus 54%; specificity, 100% versus 83%; positive predictive value, 100% versus 95%; and negative predictive value, 86% versus 23%).[61]

- Up to now, only preliminary evidence for a potential benefit of amino acid PET for treatment monitoring of radiotherapy is present (evidence level 3).
- ^{68}Ga-DOTATOC PET can be useful in cases of unclear differential diagnosis between tumor progression and posttherapeutic reactive changes (evidence level 2).

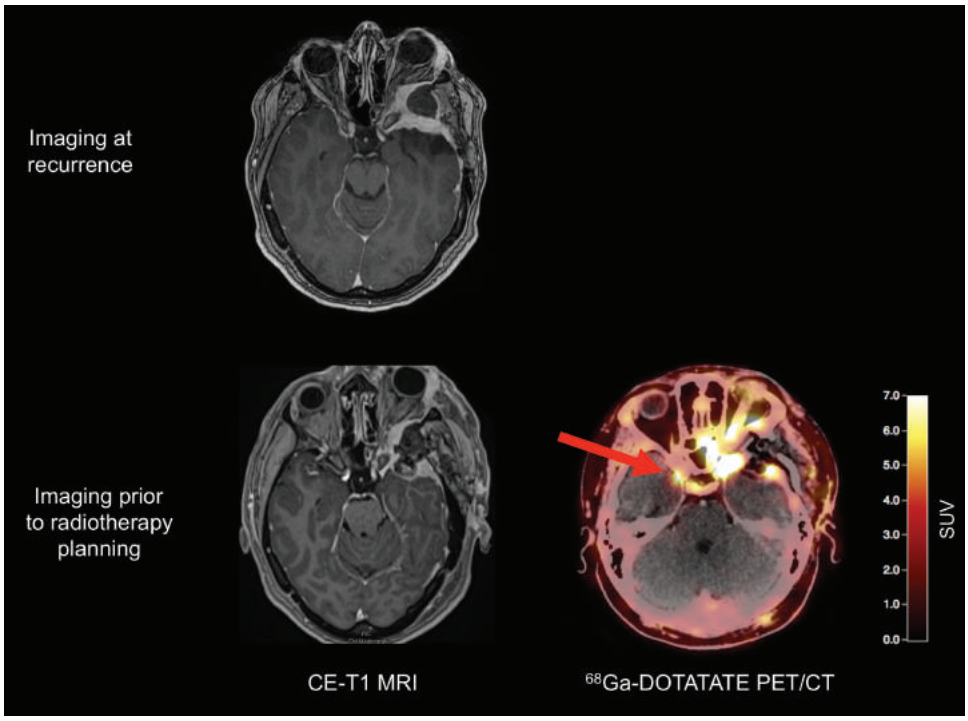

Fig. 5 A 42-year-old patient with exophthalmos and a history of a left sphenoid wing meningioma. Preoperative MRI shows tumor recurrence (top). Postoperative MRI (bottom left) shows an incomplete resection of the tumor, necessitating adjuvant radiotherapy. For radiotherapy planning, ^{68}Ga-DOTATATE PET/CT reveals an additional tumor located at the tip of the right sphenoid wing (arrow, bottom right).

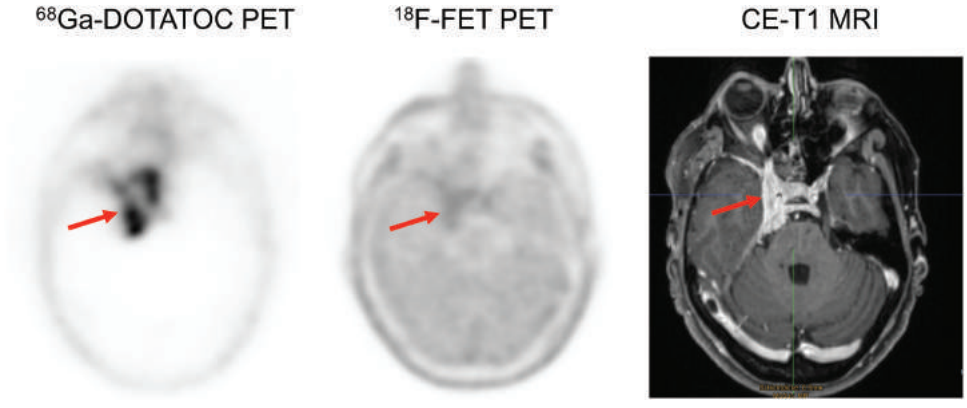

Fig. 6 Patient with a WHO grade I meningioma (arrows). In contrast to structural MRI, particularly ^{68}Ga-DOTATOC PET delineates meningioma extent more precisely. For radiotherapy planning, the contralateral unaffected side can be spared.

Current Limitations

PET data in relation to the clinical management of meningioma patients have predominantly been reported for small, retrospectively assembled patient series, and data were usually obtained in monocentric studies. Recent encouraging findings in this field should therefore be validated in larger clinical prospective multicenter cohorts and trials. Moreover, further studies evaluating the correlation between PET imaging findings and histology are necessary and essential to define more accurately the impact of PET in this group of patients. Importantly, it has still to be demonstrated that a better tumor delineation

Table 1 Overview of the most relevant indications for PET imaging in meningioma patients

Clinical Indication	PET Ligands for Somatostatin Receptors	Amino Acid PET Tracers	Other PET Tracers
Detection of meningioma tissue/ differential diagnosis	^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE PET may add valuable diagnostic information[24,53]	na	na
Meningioma grading	^{68}Ga-DOTATATE binding correlates with tumor growth rate in WHO grades I and II meningiomas[35]	^{11}C-MET correlates with proliferative activity,[54] but data on grading are controversial.[34,55] Static and dynamic ^{18}F-FET PET may provide additional information for meningioma grading[32]	^{11}C-choline seems to be helpful for meningioma grading.[41] ^{11}C-acetate seems not to be helpful[18]
Delineation of tumor extent for resection planning	^{68}Ga-DOTATATE PET delineates the meningioma extent better than standard MRI[23,61]	na	na
Delineation of tumor extent for radiation treatment planning	^{68}Ga-DOTATOC PET delivers additional information on tumor extent for radiotherapy target definition[56,57,64,65]	^{11}C-MET PET significantly influences GTV delineation in meningiomas[31,59]	na
Treatment monitoring	na	^{11}C-MET PET allows an earlier evaluation of treatment effects than standard imaging.[66,67] Boronated amino acid PET probes may help to evaluate treatment effects[38]	na
Diagnosis of tumor progression/differentiation of tumor progression from posttreatment changes	^{68}Ga-DOTATOC/^{68}Ga-DOTATATE PET is useful for differentiation between progression and posttreatment changes[23,24,52]	na	na

na = not available.

allows better long-term tumor control. Another methodical concern of using PET for planning radiotherapy of meningioma is the definition of threshold values defining the radiation volumes (eg, GTV). Because meningiomas may have microscopic tumor growth and PET has a limited spatial resolution, empirical margins have to be added.

Outlook Perspective

Radiopeptide Therapy

By exchanging the radionuclide, the same tracer can be used either for diagnostics or for therapy ("theranostics"). The principle of peptide receptor radionuclide therapy (PRRT) is well established in the management of neuroendocrine tumors[68] and, more recently, has been introduced into meningioma treatment. An exchange of the short-lived positron emitter gallium-68 used for PET with a longer-lived β-emitter like lutetium-177 or yttrium-90 allows for receptor-targeted therapy. Due to the wide application in neuroendocrine tumors, the safety profile of SSTR-based PRRT is known and therapy is generally well tolerated.

Eight studies and one single-case study on PRRT treatment in meningioma have been published, reporting on ^{90}Y-DOTATOC, ^{177}Lu-DOTATATE, and ^{111}In-pentetreotide therapy in 124 patients.[69–77] However, due to retrospective and prospective study designs, mixed patient populations, differences in administered doses, and varying response assessments as well as follow-up interval, pooling of the present data is complex. Nevertheless, the high rate of reported disease stabilization and the possibility of a patient- or lesion-tailored therapy make PRRT a promising tool; however, future studies should include an adequate sample size with clear inclusion criteria, preferably a comparator to PRRT, and rigorous response assessment to determine the role of PRRT in meningioma management. In the future perspective, PRRT may be further optimized by a change to α-emitters and local application of the substance to increase the locally administered dose.[78,79]

Conclusion

Compared with standard MRI, particularly PET ligands to SSTR (receptor subtype 2) add valuable additional diagnostic information. Based on the current levels of evidence, the most relevant indications for this group of tracers are differential diagnosis of newly diagnosed brain lesions suspicious for meningiomas, the delineation of meningioma extent in regions with low MR and CT contrast (eg, osseous infiltration) and complex anatomy (eg, skull base) for resection or radiotherapy planning, and the differentiation of tumor progression from a posttherapeutic reactive change such as scar tissue or radiation necrosis (Table 1). The evidence in this field justifies therefore a further validation in larger prospective multicenter clinical cohorts and trials for which standardized technical guidelines for imaging and readout procedures will now be developed.

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