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Authors
Galldiks, Norbert
Albert, Nathalie L
Wollring, Michael
et al.

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Advances in PET imaging for meningioma patients

Norbert Galldiks, Nathalie L. Albert, Michael Wollring, Jan-Michael Werner, Philipp Lohmann, Javier E. Villanueva-Meyer, Gereon R. Fink, Karl-Josef Langen, and Joerg-Christian Tonn

Department of Neurology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany (N.G., M.W., J.-M.W., G.R.F.); Institute of Neuroscience and Medicine (INM-3, -4), Research Center Juelich, Juelich, Germany (N.G., M.W., P.L., G.R.F., K.-J.L.); Center of Integrated Oncology (CIO), Universities of Aachen, Bonn, Cologne, and Düsseldorf, Germany (N.G.); Department of Nuclear Medicine, University Hospital of Munich (LMU), Munich, Germany (N.L.A.); German Cancer Consortium (DKTK), Partner Site Munich, German Cancer Research Center (DKFZ), Heidelberg, Germany (N.L.A., J.-C.T.); Department of Stereotactic and Functional Neurosurgery, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany (P.L.); Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, California, USA (J.E.V.-M.); Department of Nuclear Medicine, University Hospital RWTH Aachen, Aachen, Germany (K.-J.L.); Department of Neurosurgery, University Hospital of Munich (LMU), Munich, Germany (J.-C.T.)

Corresponding Author: Norbert Galldiks, MD, Institute of Neuroscience and Medicine (INM-3), Research Center Juelich, Leo-Brandt-St. 5, 52425 Juelich, Germany (n.galldiks@fz-juelich.de) and Department of Neurology, University Hospital Cologne, Kerpener St. 62, 50937 Cologne, Germany (norbert.galldiks@uk-koeln.de).

Abstract

In patients with meningioma, diagnosis and treatment planning are predominantly based on anatomical imaging using MRI or CT. Constraints of these imaging modalities include precise meningioma delineation—especially at the skull base, in the case of *trans*-osseus growth, and in tumors with complex geometry—and the differentiation of post-therapeutic reactive changes from meningioma relapse. Advanced metabolic imaging using PET may help to characterize specific metabolic and cellular features providing additional information beyond the information derived from anatomical imaging alone. Accordingly, the use of PET in meningioma patients is steadily increasing. This review summarizes recent advances in PET imaging helpful for improving the clinical management of patients with meningioma.

Keywords

amino acid PET | DOTATATE | FDG | FLT | SiTATE | somatostatin receptor-expression

Structural contrast-enhanced MRI is indispensable in neuro-oncology at all stages of the disease, i.e., the initial diagnosis, resection and radiotherapy planning, and follow-up evaluation, including treatment response and the diagnosis of tumor relapse. Besides, structural contrast-enhanced MRI is readily available at relatively low cost and offers outstanding spatial resolution, particularly at 3T or more.

Notwithstanding, various PET tracers for brain tumor imaging provide valuable additional information beyond the information derived from structural MRI.[1–3] In detail, a higher sensitivity and specificity for detecting neoplastic tissue may help to solve inconclusive diagnostic situations as well as to plan tumor resection or radiotherapy. Furthermore, improved planning of tumor resection and radiotherapy to the tumor's true extent may help improve tumor resection while sparing healthy tissue. Importantly, the possibility to identify early progression or distinguish treatment-related changes can avoid either a delay of therapy or else a potentially harmful and unnecessary overtreatment.

Since these advantages of PET imaging constitute an added value also for meningiomas, we here summarize the current advances of PET imaging for the clinical management of meningioma patients.

Imaging of Somatostatin Receptor-Expression in Meningiomas Using Ligands Labeled with ^{68}Ga

Owing to the over-expression of somatostatin receptors (SSTR) in meningiomas,[4–6] radiolabeled SSTR ligands allow

the visualization of meningiomas using PET. It has been demonstrated that the SSTR subtype 2 is the most abundant isoform, with pronounced expression in meningioma tissue.[4] For PET imaging, SSTR ligands are typically labeled with ^{68}Ga, which has a physical half-life of 68 min. These radiotracers can be produced using a ^{68}Ge/^{68}Ga radionuclide generator without the need of an on-site cyclotron unit.

Various SSTR ligands such as ^{68}Ga-DOTA-Tyr3-octreotide (DOTATOC), ^{68}Ga-DOTA-D-Phe1-Tyr3-octreotate (DOTATATE), or ^{68}Ga-DOTA-I-Nal3-octreotide (DOTANOC) have been used for the diagnostic evaluation of meningiomas, either in clinical routine or for research purposes.[7] Since several years, SSTR imaging is already being used to visualize neuroendocrine tumors, which also express high levels of SSTR.[8] Thus, this imaging modality is widely distributed within the clinical routine of nuclear medicine.[9] The ^{68}Ga-labeled tracers DOTATATE and DOTATOC are the most common clinically applied tracers in patients with meningioma.[7] These tracers provide an improved lesion contrast relative to the background due to a negligible uptake in both osseus structures and the unaffected brain parenchyma.[10,11] Of note, the pituitary gland shows increased physiological uptake serving as internal positive control, but may also hamper the evaluation of meningioma extent in close proximity to the sellar region.[12]

In clinical practice, the most common indications for PET imaging using SSTR ligands are the delineation of meningioma extent for treatment planning, the differential diagnosis of meningioma-mimicking lesions, and the diagnosis of meningioma relapse.

Delineation of Meningioma Extent for Treatment Planning

Cross-sectional structural imaging modalities such as MRI or CT have constrains in delineating meningiomas, especially at the skull base, in case of *trans*-osseus growth, and in meningiomas with complex geometry.[13] More specifically, in meningiomas located at the skull base (i.e., approximately one-third of cases), it is challenging to delineate tumor tissue from both normal dura, vascular structures, and bone due to similar signal intensities and contrast enhancement on MRI. Besides, in case of *trans*-osseous tumor growth it is difficult to precisely define the degree of infiltration even with bone reconstruction kernel on CT images.[14,15] Furthermore, artifacts and calcifications may lead to equivocal findings on conventional MRI, which may negatively affect the evaluation of meningioma extent.

In comparative studies with neuropathological validation of imaging findings, DOTATATE PET proved to allow a more precise delineation of meningioma extent compared to contrast-enhanced MRI.[10,15] In addition, in intra-osseous meningiomas as well as in complex anatomical regions such as the skull base, orbits, and along dural venous sinuses, using DOTATATE and DOTATOC PET were superior to structural MRI in terms of tumor delineation.[12,16–18]

These advantages of SSTR PET in terms of meningioma delineation are beneficial for radiosurgery or fractionated radiotherapy planning (Table 1). Several studies suggested that ^{68}Ga-DOTA-conjugated PET ligands coregistered to structural CT and MR imaging provide valuable additional information in terms of both meningioma extent[16,17,19,20] and the detection of distant or residual meningioma remnants[11,21–24] for the planning of subsequent therapy including radiotherapy. Moreover, it has been demonstrated that areas without binding of SSTR PET ligands can be excluded from the radiation field and eloquent structures such as the optic nerves, optic chiasm, or the pituitary gland, which helps to spare these organs at risk from unnecessary radiation exposure.[25] Another study suggested that the addition of PET imaging including SSTR ligands for target volume definition in patients with WHO grade I meningioma led to a significantly improved local control.[26]

The concept of theranostics, i.e., the combination of therapeutics and diagnostics, allows the exact application of radiation to meningiomas. The same PET tracer can be used for focal radiotherapy by exchanging the frequently used radionuclide ^{68}Ga for diagnostic PET with β-emitters such as ^{90}Y or ^{177}Lu. This technique, also called peptide receptor radionuclide therapy, is primarily of clinical value when in patients with progressive meningioma after surgery and conventional radiotherapy have failed. More recent studies suggested that this concept is effective in a subset of patients resulting in improved progression-free survival (> 6 months).[28–30] Importantly, peptide receptor radionuclide therapy is well established in patients with neuroendocrine tumors,[31] therefore widely available and applicable for meningioma treatment.

Differential Diagnosis of Meningioma

In case of lesions suspicious of meningioma, SSTR PET imaging can help to overcome diagnostic uncertainties (Table 2). This is especially important whenever surgical intervention would only be done for obtaining a histologic diagnosis and non-surgical therapies exist. In case of contrast-enhancing lesions affecting the optic nerve, DOTATATE PET has proven to distinguish optic nerve sheath meningiomas from of non-tumoral lesions, partially with neuropathological validation.[32–35] In tumors restricted to the cavernous sinus, radiation is nowadays considered as a valid treatment option especially in non-space occupying tumors.[13] In meningiomas in this particular region, SSTR PET imaging serves as a tool with high specificity to both confirm the diagnosis and to delineate the target volume of radiation.[27] Furthermore, dural brain metastases can be distinguished from meningioma which might be helpful in patients with a medical history of cancer.[36,37] However, more histology-validated data are needed to establish reliable thresholds for tracer uptake in order to avoid diagnostic pitfalls. This is of considerable clinical relevance because not all meningiomas express high levels of the SSTR subtype 2. Increased SSTR subtype 2 expression has also been reported in other intracranial tumors such as brain metastases, medulloblastoma, and cerebral lymphoma.[38–40]

Diagnosis of Meningioma Relapse

In case of suspected residual or relapsed meningioma, it may be challenging to distinguish viable tumor tissue from

Table 1. Studies using SSTR PET imaging for the delineation of tumor extent and treatment planning in meningioma patients

References	Study design and number of patients	PET tracer	Main finding(s)
Hadi et al.[27]	Retrospective study, 85 patients with WHO grade I meningioma involving the cavernous sinus	DOTATATE	SSTR PET improves target volume delineation for radiotherapy planning and may help to reduce radiation dose for organs at risk
Milker-Zabel et al.[16]	Prospective study, 26 patients with primary or recurrent meningiomas	DOTATOC	
Nyuyki et al.[17]	Prospective study, 42 patients with WHO grade I–III meningiomas	DOTATOC	
Gehler et al.[19]	Retrospective study, 26 patients with skull base meningioma	DOTATOC	
Graf et al.[20]	Retrospective study, 48 patients with 54 skull base meningiomas	DOTATOC	
Pelak et al.[21]	Retrospective study, 30 patients with WHO grade I meningioma	DOTANOC DOTATOC DOTATATE	
Mahase et al.[25]	Retrospective study, 29 meningioma patients after surgery or at progression	DOTATATE	
Henze et al.[12]	Case series, 3 patients with WHO grade I intraosseous meningioma	DOTATOC	SSTR PET improves detection of meningiomas with *trans*-osseous growth compared to MRI
Kunz et al.[15]	Retrospective study, 82 meningioma patients with *trans*-osseous growth	DOTATATE	
Kessel et al.[26]	Retrospective study, 332 patients with 339 WHO grade I meningiomas evaluated with various tracers (SSTR PET, $n = 104$; FET PET, $n = 26$; MET PET, $n = 73$)	DOTATOC DOTANOC FET MET	SSTR PET-based planning of target volume for radiotherapy improves local control

Table 2. Studies using SSTR PET for the detection of meningioma tissue and differential diagnosis in meningioma patients

References	Study design	PET tracer	Main findings
Afshar-Oromieh et al.[11]	Retrospective study, 134 patients with 190 meningiomas	DOTATOC	SSTR PET improves detection of meningiomas compared to MRI, especially at the skull base or falx cerebri
Pelak et al.[21]	Retrospective study, 30 patients with WHO grade I meningioma	DOTANOC DOTATOC DOTATATE	
Einhellig et al.[18]	Comparative study, MRI alone vs. MRI/SSTR PET, 57 patients with 112 meningiomas	DOTATOC	PET/MRI combined revealed highest sensitivity and specificity for small or difficult located meningiomas
Rachinger et al.[10]	Prospective study, 21 patients with primary or recurrent meningiomas	DOTATATE	SSTR PET helps to differentiate between meningioma from tumor-free tissue
Klingenstein et al.[32]	Retrospective study, 13 patients with symptomatic lesions of the optic pathway	DOTATATE	SSTR PET helps to distinguish optic nerve sheath meningiomas from non-tumoral lesions
Yarmohammadi et al.[33] Vay et al.[34] Mairot et al.[35]	Case report	DOTATATE DOTATOC	
Nyuyki et al.[17]	Prospective study, 42 patients with WHO grade I–III meningiomas	DOTATOC	SSTR PET allows detection of additional lesions in patients with multiple meningiomas
Bashir et al.[22]	Prospective study, 37 patients with histologically confirmed meningiomas	DOTATOC	SSTR PET improves detection of postoperative residual meningioma tissue
Salgues et al.[23]	Case report	DOTATOC	
Purandare et al.[37]	Retrospective study, 42 patients with dural lesions	DOTANOC	SSTR PET helps to differentiate between meningioma and dural metastasis
Unterrainer et al.[36]	Case report	DOTATOC	

Table 3. Studies using SSTR PET for the diagnosis of meningioma relapse and other indications

References	Study design	PET tracer	Main findings
Rachinger et al.[10]	Prospective study, 21 patients with primary or recurrent meningiomas	DOTATATE	SSTR PET differentiates residual or recurrent meningioma from treatment-related changes
Slotty et al.[42]	Case report in a patient with recurrent spinal meningioma	DOTATATE	DOTATATE PET was able to differentiate noninvasively between tumor and scar tissue; imaging findings were validated histologically
Sommerauer et al.[43]	Retrospective study, 23 patients with 64 WHO grade I–III meningiomas with aggressive behavior (i.e., *trans*-osseous growth, multiple meningiomas)	DOTATATE	SSTR PET correlates significantly with growth rate in WHO grade I–II meningiomas

post-treatment-related changes or scar tissue by structural imaging alone, particularly after radiotherapy or several surgeries. Especially in patients with incomplete meningioma resection, adjuvant radiotherapy is frequently applied to reduce the risk of relapse.

It has been demonstrated that SSTR PET adds essential clinical information for the differentiation of meningioma relapse from posttreatment-related changes (e.g., scars related to prior treatment), usually presenting as equivocal radiologic findings on contrast-enhanced MRI[10,11,41] (Table 3). For example, it has been demonstrated that DOTATATE PET has superior sensitivity compared to conventional MRI (90% vs. 79%).[10]

For patient management, an earlier identification of meningioma patients with increased relapse risk is also of significance for clinical decision-making. It has been demonstrated that DOTATATE binding in PET correlates significantly with the growth rate in patients with WHO grade I and II meningioma, but is not present in WHO grade III anaplastic meningiomas.[43] Therefore, this technique may help in selecting an earlier time point for treatment initiation. In that study,[43] the majority of patients had either meningiomas with aggressive behavior (i.e., multiple meningiomas or with *trans*-osseus growth) or had concurrent treatment underlining the clinical importance to further examine patients with untreated and solitary meningioma to evaluate the growth rate in this groupmof patients using SSTR PET.

Imaging of Somatostatin Receptor-Expression in Meningiomas Using Ligands Labeled with ^{18}F

The tracer ^{18}F-SiTATE (also known as ^{18}F-SiFAlin-TATE) is a novel ^{18}F-labeled SSTR targeting peptide providing high tumor uptake, excellent image quality, and economic and logistic advantages of ^{18}F- over ^{68}Ga-labeled compounds. In particular, a cost-intensive ^{68}Ge/^{68}Ga generator is no longer necessary for tracer radiosynthesis. Furthermore, the labeling approach of ^{18}F-SiTATE is straightforward and automated.[44] An initial report in a meningioma patient suggested that tumor delineation of ^{18}F-SiTATE PET is equivalent to ^{68}Ga-DOTATOC PET but with higher resolution.[45] A similar example is presented in Figure 1. Further studies in meningioma patients using ^{18}F-SiTATE PET imaging are warranted.

Imaging of Meningiomas Using PET Tracers not Targeting Somatostatin Receptor-Expression

[^{18}F]-2-Fluoro-2-Deoxy-D-Glucose (FDG)

FDG is the most widely used PET tracer and it has also been the most commonly used in meningiomas to date.[46] The uptake of FDG into tissue reflects both transport and phosphorylation of glucose by viable

cells.[47]The increased FDG uptake in tumor tissue is caused by a high energy demand leading to an increased glycolysis.[48,49] A recent meta-analysis analyzed the use of FDG PET in meningiomas.[46] The authors reported that after pooling the data of 302 patients from 13 studies, FDG PET seems useful to differentiate noninvasively benign (WHO grade I) from atypical (WHO grade II) or anaplastic meningiomas (WHO grade III).[46] It was concluded that for patients in whom an atypical or anaplastic tumor is suspected because of rapidly progressive growth with neurological deficits and the resection is expected to be difficult, FDG PET could be useful in the preoperative planning.

A threshold of 1.05 of the tumor-to-gray matter ratio of FDG uptake has been recommended in primary meningiomas for differentiating WHO grade I from WHO grade II or III meningiomas and a ratio of 0.85 in tumor relapses. These ratios yielded a specificity of 88% and a negative predictive value of 98%.[50] Specificity increased to 96% in patients who had fastened overnight before the PET was performed.

However, FDG PET is of limited value in detecting and delineating meningiomas because the tumors are primarily slow-growing, and their glucose metabolism might be low.[49–51] Furthermore, the normal brain tissue shows high FDG uptake leading to a low tumor-to-background contrast.[52] Another limitation of FDG PET is the fact that tracer uptake is not tumor-specific, and uptake may also be increased in inflammatory tissue.[52] While FDG PET is therefore rarely used for the investigation of meningiomas, whole-body FDG PET may serve as a useful screening tool for extracranial meningioma metastases in select patients.[53]

Radiolabeled Amino Acids

Unlike FDG, radiolabeled amino acids offer a better tumor-to-background contrast because of lower tracer uptake in the normal brain tissue.[54] The uptake of amino acid tracers such as *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET), [^{11}C]methyl-L-methionine (MET), and 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine (FDOPA) is mediated by the L-amino acid transporter system, and increased uptake is also frequently seen in slow-growing tumors such as low-grade gliomas[55–57] and meningiomas.[58,59] FET, MET and FDOPA are widely used for glioma imaging and recurrent brain metastases and part of routine diagnostics in many centers.[1,2] A correlation of MET uptake with proliferative activity in meningiomas has been reported,[60] but there is some controversy concerning its role for noninvasive meningioma grading.[61,62] For FET PET, a more recent study observed that static and dynamic FET parameters might provide additional information for noninvasive grading of meningiomas.[59] Since FET does not accumulate in the pituitary gland in contrast to MET and SSTR ligands, it may be helpful to differentiate intrasellar meningioma invasion.[63]

Studies in meningiomas using MET or FET PET reported differences in tumor size compared to MRI, which, however, were not confirmed histologically.[58,64,65] Some authors integrated MET PET in radiation treatment planning in meningiomas[66] and reported a significant influence on target volume definition. In patients with skull

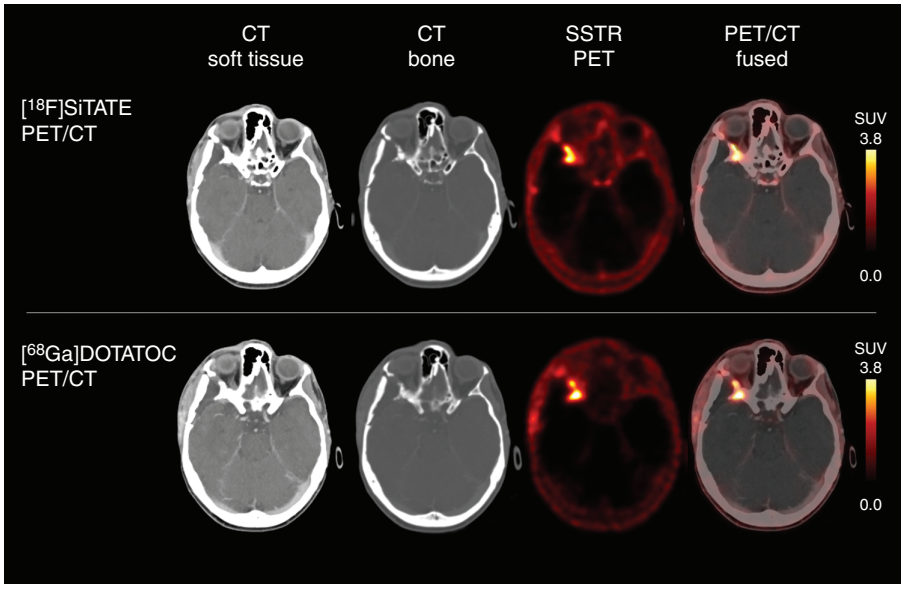

Figure 1. ^{18}F-SiTATE (top row) and ^{68}Ga-DOTATATE PET/CT (bottom row) of a patient after resection of a WHO grade I sphenoid wing meningioma show residual tumor laterally located to the right orbit. Visually, tumoral uptake on ^{18}F-SiTATE was highly comparable to ^{68}Ga-DOTATATE PET/CT. Note the lower spatial resolution of the ^{68}Ga-labeled peptide DOTATATE compared to ^{18}F-SiTATE PET.

base meningioma treated with fractionated radiotherapy, the addition of MET PET changed the target volumes in the most patients.[58] MET PET detected tumor areas, that were not visible on CT or MRI, which increased the target volume by approximately 9%. Moreover, areas without tumor infiltration were identified and excluded from the target volume. Furthermore, anatomical structures at risk such as the optic nerves, optic chiasm, or pituitary gland could be better considered in radiation planning.[58]

In summary, amino acid PET offers some advantages in meningioma imaging compared with FDG PET, but compared with SSTR ligands, its use is limited.

3′-Deoxy-3′-[^{18}F]-Fluorothymidine

The radiolabeled pyrimidine analogue 3′-deoxy-3′-[^{18}F]-fluorothymidine (FLT) allows noninvasively evaluating proliferative tumor activity.[67,68] FLT is trapped intra-cellularly after being phosphorylated by the cytoplasmatic enzyme thymidine kinase-1 that is expressed during cell proliferation.[69,70] For glioma imaging, the diagnostic use of FLT is limited due to the presence of a disrupted blood-brain barrier for tracer uptake.[71,72]Therefore, FLT PET is clinically not valuable in detecting and delineating brain tumors such as WHO CNS grade 2 gliomas, which usually show no contrast enhancement. In addition, a meta-analysis showed no superiority of FLT compared to FDG for the diagnosis of glioma relapse.[73,74]

Two studies by Bashir and colleagues have investigated FLT PET in patients with meningioma in recent years. In the first study, static and dynamic FLT PET parameters of 17 patients with meningioma were correlated with cellular biomarkers of proliferation and angiogenesis.[75] FLT PET parameters differentiated WHO grade I from WHO grade II meningiomas with a high accuracy of 99%, showed a significant correlation with important biomarkers of proliferation such as the Ki-67 index, and identified aggressive meningiomas with a high accuracy of 80%.[75] Subsequently, the value of FLT PET for the prediction of tumor progression in 46 patients with asymptomatic meningioma was evaluated.[76] Prediction of patients with an early meningioma progression was achieved with a diagnostic accuracy of 78%, indicating that this technique might be helpful in the selection of high-risk meningioma patients already after initial diagnosis.[76]

Other PET Tracers

^{11}C- or ^{18}F-labeled choline is a radiotracer to detect an increased phospholipid synthesis in tumor cells, initially developed for prostate cancer diagnostics.[77] Since the choline uptake in healthy brain tissue is low, it has a high lesion-to-background contrast for brain tumor imaging. Besides incidental findings of ^{11}C-choline uptake in patients with meningioma,[78–80] there is only one study comparing ^{11}C-choline with ^{18}F-FDG PET in seven meningioma patients, suggesting that ^{11}C-choline provides an improved tumor delineation due to the higher tumor-to-background contrast.[81] ^{11}C-choline was largely replaced by prostate-specific membrane antigen (PSMA) PET ligands more recently. Several case reports have described incidental findings of increased ^{68}Ga-PSMA uptake in meningiomas.[82–87] The increased uptake of ^{68}Ga-PSMA in patients with meningioma might be caused by the neovasculature of the tumor tissue.[88]

^{11}C-acetate is a PET tracer that targets the cell membrane lipid synthesis and is used in extracranial tumors that are difficult to detect using FDG PET (e.g., renal cell carcinoma, hepatocellular carcinoma).[89,90] Experience with ^{11}C-acetate in patients with meningioma is limited to one study in 22 patients, which reported the advantage of ^{11}C-acetate over FDG PET for detecting and delineating meningiomas for treatment response assessment and radiosurgery planning.[52]

The detection of bone invasion of meningiomas might be assessed by ^{18}F-fluoride PET, which is commonly used for imaging of bone metastases. Besides incidental findings of increased ^{18}F-fluoride uptake in meningioma patients,[91–94] 2 studies described that ^{18}F-fluoride PET detects osseous involvement and hyperostosis in meningioma patients better than CT and MRI, which might be valuable for treatment planning.[95,96]

^{11}C-labeled Pittsburgh compound B (PiB) is a benzothiazole derivative initially designed to bind to amyloid-beta plaques in the brains of patients with Alzheimer's disease. In addition to incidental findings with increased uptake of amyloid tracers such as ^{11}C-PiB and ^{18}F-florapronol in meningioma patients,[97–100] a more extensive study evaluated the role of ^{11}C-PiB in 45 patients with intracranial tumors, including 29 meningiomas. In that study, meningiomas had an increased tracer uptake, and the authors suggested a yet unknown ^{11}C-PiB binding target other than beta-amyloid within these tumors.[101]

Further observations of incidentally increased PET tracer uptake in patients with meningioma have been reported for ^{68}Ga-NOTA-PRGD2, an integrin-targeting radiotracer,[102] ^{18}F-AV1451, a tracer that binds to the paired helical tau filament in patients with Alzheimer's disease,[103] ^{13}N-ammonia, targeting glutamine synthetase expression,[104–106] ^{18}F-FMAU, a synthetic pyrimidine analog,[107] and, ^{18}F-FP-CIT targeting dopamine transporters in patients with Parkinson's disease.[108] Overall, the clinical relevance of these tracers for meningioma imaging remains to be elucidated.

Summary and Outlook

The current literature provides strong evidence that several PET tracers are of diagnostic benefit in patients with meningioma. Especially PET using SSTR ligands offers a variety of supplementary information with the potential to overcome the constraints of conventional MRI or CT. Thus, this added value justifies a more widespread use of this diagnostic method. Of note, the necessary PET infrastructure including SSTR ligands, which are routinely used for diagnostics in patients with neuroendocrine tumors, are widely available with comparable costs to standard tracers such as FDG. Novel SSTR ligands labeled with ^{18}F are currently under evaluation and its additional clinical value compared to standard SSTR ligands labeled with ^{68}Ga is still to be determined.

Regarding theranostics for focal radiotherapy using β-emitters such as ^{90}Y or ^{177}Lu in patients with progressive meningioma after failure of standard treatment options, future studies should include an adequate sample size with clear inclusion and outcome criteria to evaluate the role of theranostics in the management of meningioma patients.

Furthermore, since meningiomas comprise a number of subtypes and typical genetic and epigenetic features (e.g., methylation profiles), the correlation of these with PET imaging features need to be elucidated in more detail.

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