



A look ahead: future directions of SSR-directed imaging and therapy in meningioma

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Abstract

Background Meningiomas, which are the most common of CNS tumours in adults, show a high expression of the somatostatin receptor subtype 2 (SSR). Visualization of these receptors with specific PET ligands augments contrast-enhanced MRI and CT of the brain in resolving several clinical issues related to differential diagnosis, evaluation of meningioma extent, and therapy planning or follow-up. Moreover, SSR-directed radioligands labeled with beta-emitters serve for radiopeptide therapy (RPT) in patients with recurrent or refractory meningioma. In the light of recent developments in radiochemistry, neuropathology/molecular genetics, and emerging systemic treatments, we present our perspective on future directions of SSR-directed imaging and therapy in meningioma.

Methods We conducted a search in the PubMed literature database until June 2019 using the terms “meningioma”, “PET”, “somatostatin receptor”, “SS(T)R”, “DOTATATE”, “DOTATOC”, “radiopeptide therapy”, “imaging”, “therapy”, “classification” alone and in combination, compiled with relevant literature from the authors’ own files.

Results/conclusion Our review identifies important emerging applications of SSR-directed imaging and therapy in patients with meningioma. We summarize the state of development novel SSR-directed radio-ligands, meningioma classifications and systemic treatment options.

Keywords Meningioma · Somatostatin receptor · PET · Radiopeptide therapy

Current status of SSR-directed imaging and therapy

Meningiomas are the most common category of tumours of the central nervous system in adults. Clinical work-up of suspected meningiomas is vulnerable to several diagnostic uncertainties, which are not easily resolved by standard morphological imaging methods such as contrast-enhanced MRI and CT [1]. Consequently, molecular imaging by modalities

such as positron emission tomography (PET) has an emerging role for diagnosis of meningiomas, by exploiting their characteristically high expression of the somatostatin receptor subtype 2 (SSR). PET imaging with selective SSR ligands can visualize and quantify this expression in tumours against a low background signal in healthy brain structures. This pharmacologically selective PET imaging of SSR can contribute importantly to the clinical workup. For example, SSR PET has higher sensitivity for meningioma detection at initial diagnosis, revealing larger numbers of lesions than are evident to structural imaging methods [2, 3]. Although current SSR PET methods are unfit to distinguish between the different WHO grades of meningioma, the intensity of lesional uptake does correlate with the tumoural growth rate [4]. Moreover, PET can contribute to the differentiation of leptomeningeal metastases from meningioma [5]. These features also enable better tumour delineation, even at diagnostically difficult locations, such as the optic nerve sheath or the skull base [6–8], where diagnosis is particularly challenging on standard imaging such as MRI. Particularly, PET is significantly superior to contrast enhanced

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MRI for evaluating the extent of osseous involvement of meningiomas [9], a feature of PET that can inform the planning of subsequent surgery or radiotherapy [8, 10–12]. Post therapy SSR PET follow-up examinations are useful for the differentiation of recurrent/residual tumour tissue and post-therapeutic scar tissue [13].

Besides these diagnostic uses of SSR-directed PET radioligands, labelling with high energy beta-emitters (predominantly [^{177}Lu] and [^{90}Y]) gives effective agents for targeted radiopeptide therapy (RPT) in patients with recurrent or refractory meningioma. RPT shows a good risk profile and clinical response rates in previously treated meningioma patients, often evoking stabilization or deceleration of tumour growth [14–21]. However, international harmonization of treatment regimens and results from controlled, randomized trials are needed to further foster the use of RPT in meningioma. We have recently presented a dedicated review article on the current status of SSR-directed imaging and therapy in meningioma [22], which we now augment with an account of future prospects for SSR-directed imaging and therapy in the light of current developments in radiochemistry, neuropathology/molecular genetics, and novel systemic treatments.

Novel radioligands

Currently, there are several promising radioligands targeting SSR, including not only somatostatin structural analogs (with agonist action), but also SSR antagonists, which might be suitable for improved diagnostic or theranostic approaches in patients with meningioma. By way of example, we note some promising agents (see also [23] for a detailed overview of novel SSR-ligands with emphasis on neuroendocrine tumors (NET)):

[^{68}Ga]-OPS202/[^{177}Lu]-OPS201 (a.k.a [^{68}Ga]-DOTA-JR-11/[^{177}Lu]-DOTA-JR11) is a novel theranostic pair of SSR-antagonists; PET studies with [^{68}Ga]-OPS202 ([^{68}Ga]-DOTA-JR-11) show significantly higher uptake and distinctly improved detection rate of tumour lesions in patients with NET compared to [^{68}Ga]-DOTATOC [24]. Moreover, evaluation of the therapeutic twin [^{177}Lu]-OPS201 ([^{177}Lu]-DOTA-JR11) in murine NET models gave up to 4.4-fold higher tumour dosimetry per injected activity (1.8 ± 0.7 Gy/MBq vs. [^{177}Lu]-DOTATATE, 0.36 ± 0.07 Gy/MBq) [25, 26], without increased exposure to healthy organs. Ongoing studies evaluating this theranostic SSR-ligand pair have given promising preliminary data with regard to the efficacy and safety in human patients with NET [27, 28].

[^{177}Lu]-DOTA-EB-TATE is a structural modification of the commonly applied radioligand [^{177}Lu]-DOTATATE incorporating a special Evans blue derivatization, which imparts higher efficacy by favouring its binding to serum albumin. This interferes with renal clearance, thus resulting

in a longer half-life in the blood, and consequently higher intra-tumoural retention in animal models [29]. In humans, [^{177}Lu]-DOTA-EB-TATE had nearly eightfold higher delivered doses to the tumours compared to conventional [^{177}Lu]-DOTATATE [30]. In a comparative therapy setting, a group of ($n=8$) NET patients received a single dose of up to 0.7 GBq of [^{177}Lu]-DOTA-EB-TATE only. Their response rates to this treatment as assessed with [^{68}Ga]-DOTATATE PET were comparable to those achieved with [^{177}Lu]-DOTATATE. However, the whole body radiation exposure with [^{177}Lu]-DOTA-EB-TATE was only about a sixth of that obtained with [^{177}Lu]-DOTATATE [31].

Besides the commonly applied therapeutic radioligands labeled with beta-emitters, there are also therapeutic approaches targeting the SSR-bearing tumors with alpha-emitting isotopes such as [^{213}Bi] and [^{225}Ac]. The novel radioligand [^{213}Bi]-DOTATOC had significant tumoural response rates and a moderate side effect profile after intra-arterial application in patients ($n=7$) with predominantly liver metastases from NET. Radiopeptide therapy with this and other alpha-emitters might be of particular interest in patients previously treated with beta-emitting radioligands, who showed insufficient clinical response or even refractory disease [32]. Modifications with other labeling agents might further improve their efficacy and therapeutic effects [33]. Despite promising experience with NET, there are so far no reports of SSR-directed therapy with alpha-emitters in patients suffering from meningioma.

In sum, emerging SSR-directed radioligands show promising benefits compared to the currently applied, standard theranostic ligands for NET such as DOTATOC or DOTA-TATE. However, there is limited data about these novel radioligands in meningioma animal models or indeed in patients suffering from meningioma. Nonetheless, their well-documented imaging or therapeutic properties in animal models and humans suffering from NET bode well for the effectiveness of new SSR ligands in future studies of meningioma.

Novel meningioma classifications

In clinical routine, risk stratification of meningiomas takes into account the individual histology, clinical presentation, localization, and the individual extent of resection. However, prediction models are imperfect instruments for reliable prognostication of tumour behavior and the individual risk of tumour recurrence. Patients typically undergo MRI based follow-up to assess the status of individual residual tumours. Besides established clinical factors, there is increasing evidence that certain features of tumoral molecular biology and genetics might contribute to an individualized and “patient-tailored” approach in patients suffering from meningioma [34]. The relevant molecular genetic profiles comprise genomic alterations

such as copy number alterations [35–37], but also extend to changes of the gene mutation signature, which drive meningiomagenesis and aggressive tumour behaviour. In brief, these mutations can be designated as neurofibromatosis type 2 (NF2) or non-NF2 based changes [34], in addition to numerous additional mutations of genes with varying diverging individual relevance such as tumour necrosis factor (TNF), receptor associated factor 7 (TRAF7), and the hedgehog signaling pathway (Hh) [38]. Besides specific gene mutations, the regulation of gene transcription through DNA-methylation is also increasingly implicated in meningioma classification, evaluation of tumour recurrence and prognostication, which is a matter extending beyond the current WHO classification, as it relies on histopathological criteria for meningioma classification [39]. For a more detailed overview see also [34].

PET examination of gliomas using radiolabelled amino acids such as [¹⁸F]fluoroethyltyrosine has already been evaluated in relation to different molecular genetic tumour classes, which delivers additive prognostic value along with molecular genetic information [40, 41]. It remains unknown whether this shall also hold for SSR-directed imaging in meningioma. Irrespective of any potential prognostic value of parameters such as tracer uptake intensity or volume in SSR-directed PET, patients identified as having an unfavourable molecular genetic profile and aggressive tumoural behaviour might profit from an optimized PET-based staging at initial diagnosis. Such an approach could help to exclude the presence of additional tumour sites, tumour remnants, or undetected osseous involvement.

In analogy to the recent glioma studies establishing the value of amino acid PET for the non-invasive prediction of molecular genetic parameters, future meningioma studies should test the potential value of SSR-directed PET imaging to identify high-risk patients with currently indolent course and absent symptoms, despite unfavourable molecular genetic features such as TERT-promoter methylation [42]. Importantly, novel classifications such as the DNA-methylation profile might also identify meningioma patients apt to enjoy the greatest benefit from radioligand therapy. This might include patients with a certain molecular genetic profile predicting a good response to RPT at an earlier disease stage. Conversely, molecular genetic analyses might eventually identify meningioma patients likely to benefit more from an experimental therapy other than RPT. Thus, we suppose that combining molecular genetic meningioma classification and molecular imaging/therapy may be a promising approach for additional tumour characterization, potentially contributing to individualized clinical management of meningioma patients.

Novel systemic treatments

Systemic treatment in meningioma may be beneficial in patients with recurrent or progressive disease after failure or unsatisfactory response to conventional treatment options such as radiotherapy and surgery. Unfortunately, systemic cytostatic treatments such as temozolomide and irinotecan show only limited benefits or palliative effects [43]. Systemic treatment with trabectedin, an antiproliferative agent derived from the mangrove tunicate, is finding some success in sarcoma patients [44]. This agent has also shown efficacy in meningioma studies conducted *in vitro* [45], and is currently being evaluated in a randomized multicenter trial of patients with recurrent meningioma WHO grade II/III (EORTC-1320-BTG). However, preliminary findings with trabectedin do not indicate clear superiority over current standards of care in human meningioma patients [46]. Moreover, there are numerous potential novel targets and treatments arising from the comprehensive understanding of the underlying molecular genetic changes involving signaling pathways (SMO, AKT1, and NF2) occurring in meningiomas (NCT02523014/A071401). For a more detailed overview, see also [43].

As is established for the treatment of numerous cancer entities, immunotherapy is also under investigation in patients suffering from meningioma. Current literature suggests a high expression of programmed death ligand 1 (PD-L1) in anaplastic meningioma WHO grade III [47, 48]. These observations inspired several clinical studies investigating the efficacy of checkpoint inhibitors such as nivolumab or pembrolizumab in atypical WHO grade II and anaplastic WHO grade III meningiomas (NCT03279692, NCT02648997).

In considering the effectiveness of novel drugs and treatments, one must take into account the question of “what constitutes activity of systemic therapy in [...] meningioma?” [49]. The RANO Working group previously stated that “No standard criteria exist for assessing response and progression in clinical trials involving patients with meningioma, and there is no consensus on the optimal endpoints for trials currently under way.” [50]. Moreover, it is often rather technically difficult even to assess or estimate the ‘real morphological extension’ of meningiomas by MRI, particularly at inaccessible localizations, such as the skull base. Therefore, the correct evaluation of the size and extent of meningiomas as an endpoint in experimental therapies is even more challenging. Therefore, molecular imaging with PET is a promising instrument for assessment of treatment response, which is particularly important for the evaluation of novel systemic treatments.

With regard to the application of SSR-directed RPT in patients with meningioma, novel antineoplastic drugs such as those mentioned above might also show synergistic

effects in combination with RPT. Pretreatment may prove to have radiosensitizing effects in addition to inherent antineoplastic properties, as is reported for capecitabine and temozolomide in patients with NET/paraganglioma [51, 52], or nutlin-3 and topotecan in patients with neuroblastoma [53]. In light of the emerging systemic treatment options mentioned above, there is scope for exploring potentially synergistic effects with SSR-directed RPT. i.e. a two-hit approach targeting vulnerable aspects of the meningiomas.

Summary

Extending beyond morphological imaging using MRI and CT, SSR-directed molecular PET imaging of meningiomas distinctly contributes to diagnostic uncertainties arising due to uncertainties in tumor boundaries and extent. Moreover, RPT using beta-emitting radioligands is a well-tolerated therapy option in patients with recurrent meningioma. Starting from the knowledge base established in NET investigations with ligands such as DOTATOC or DOTATATE, several new theranostic ligands with improved binding properties as well as therapeutic SSR ligands using alpha-emitters are under investigation. Augmentation of histological classification of meningiomas by molecular genetic classifications is proving effective for risk stratification and prognostication in clinical routine. Thus, SSR PET can bring additional diagnostic information in high-risk patients, and might contribute to the clinical prognostication. Due to the well-known inadequacy of structural imaging as an endpoint for meningioma therapy, SSR PET may be instrumental in the assessment of novel systemic treatments such as immune therapy. Promising initial results with RPT in patients with meningioma call attention to the need randomized controlled trials of this approach, either alone, in a theranostic setting, or in conjunction with potentially synergistic therapy options, especially keeping in mind the radiosensitizing effects of certain systemic treatments.

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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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