Management of meningioma

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Summary

Meningiomas are the most frequent primary brain tumors, accounting for ~37% of central nervous systems tumors. Despite being largely benign, clinicians frequently face difficult treatment decisions in cases with complex morphology or localisation, near vital brain structures such as the optic nerve or in the case of incidental tumors. Here, we review current concepts of diagnosis, treatment and follow-up with clinical decision-making informed by multimodal imaging, histology, and molecular biology.

Introduction

Meningiomas are the most frequent primary brain tumors, accounting for ~37% of central nervous system (CNS) tumors [1]. Prognosis is mostly favorable with an overall recurrence rate of 20% within 20 years for benign meningiomas [2]. Anaplastic meningiomas, however, have a poor prognosis with a median overall survival of 1.5 years [3]. In addition, clinicians frequently face difficult treatment decisions in cases with complex morphology or localisation, near vital brain structures such as the optic nerve or in the case of incidental tumors.

Here, we review current concepts of diagnosis, treatment and follow-up with clinical decision-making informed by multimodal imaging, histology, and molecular biology. Where available, we reference evidence levels as laid out by the current European Association of Neuro-Oncology (EANO) or Response Assessment in Neuro-Oncology (RANO) guidelines [4,5]. In addition, advances in imaging, especially positron emission tomography (PET), and molecular profiling are imminent to impact current clinical practice and are expected to be integrated with current guidelines in the near future [5,6].
Molecular landscape

Meningiomas are extra-axial tumors that originate from arachnoid meningotheelial cells [7]. They are highly diverse tumors with respect to localization, histology and molecular biology. This has resulted in numerous and complex subtype definitions from clinical, histological and molecular perspectives. While some of these classifications result in overlapping groups, some of them seem to be non-redundant and independent of each other. For example, the 2016 WHO classification of central nervous system tumours distinguishes 15 histological variants of meningioma [37]. Some of them imply higher tumor grade, i.e. clear cell, chordoid and atypical (grade II), as well as papillary, rhabdoid and anaplastic (grade III) variants. However, even with grading, their clinical value is limited and there is suboptimal inter-observer agreement [38]. Refinement by genetic and other molecular markers is thus needed. Molecular profiling efforts of benign sporadic meningiomas have identified two large, molecularly and clinically divergent clusters [8-13]: a clinically heterogeneous group of tumors with mutations of the NF2 gene and/or loss of chromosome 22; and non-NF2 meningiomas with frequent alterations in the Sonic hedgehog (SHH) pathway, phosphatidylinositol-3-kinase (PI3K) signalling pathway, TRAF7, KLF4 or POLR2A genes who are clinically benign and often occur at the skull base (table 1). Mutations in multiple genes of the SHH signalling have been described. SMO-mutant meningiomas are predominantly located in the olfactory groove [8,14]. Two mutational hotspots exist (p.L412F, p.W535L) [8,15]. Prognosis might be poorer compared to other (grade I) olfactory groove meningiomas due to a higher recurrence rate [14], even though SMO-mutant cases were uniformly assigned to a methylation cluster with favorable outcome [13]. Mutations in the PRKAR1A and SUFU genes complement this group [9,16]. SUFU mutations might be associated with poor prognosis [13].

KLF4 mutations are confined to the p.K409Q hotspot and are both defining and exclusively seen in secretory meningiomas. KLF4-mutant meningiomas are localized to the skull base. Despite complications arising from peritumoral edema (see below), these tumors have a good outcome. AKT1 p.E17K hotspot mutations are unique to meningiomas among CNS tumors [10]. AKT-mutant meningiomas predominantly localize to the median skull base and are associated with a benign clinical course [13,14].

POLR2A mutations occur in skull base, non-NF2 meningiomas, frequently near the tuberculum sellae [9]. No data are currently available with respect to clinical outcome. Mutations in the above genes are largely mutually exclusive with each other as well as NF2 mutations and mainly confer a favorable prognosis. In contrast, NF2-mutant meningiomas, which account for 36% to 43% of all cases [8,13,15], are a clinically heterogeneous group. Within this group, TERT promoter mutations have been described as negative prognostic factor for risk of recurrence or progression-free survival (PFS) in several studies [13,17,18]. Importantly, TERT mutations occurred in meningiomas of all WHO grades [18].

**Table 1.** Molecular classification of meningiomas. The table summarizes findings of molecular characterization studies stratifying tumors by key mutations. Predominant phenotypes with respect to histology, clinical manifestation and methylation-based classification are given.

<table>
<thead>
<tr>
<th>Predominant histology</th>
<th>Predominant localization</th>
<th>Genetic alterations</th>
<th>Methylation class</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningotheelial</td>
<td>Skull base (anterior fossa)</td>
<td>AKT1 E17K, PIK3CA, PIK3R1, TRAF7</td>
<td>MC ben-2</td>
<td>Favorable</td>
</tr>
<tr>
<td>Transitional</td>
<td>Skull base</td>
<td>KLF4, TRAF7</td>
<td>MC ben-2</td>
<td>Favorable</td>
</tr>
<tr>
<td>Meningotheelial</td>
<td>Skull base (olfactory groove)</td>
<td>SMO, SUFU, PRKAR1A</td>
<td>MC ben-2</td>
<td>Favorable</td>
</tr>
<tr>
<td>Atypical</td>
<td>Skull base (tuberculum sellae)</td>
<td>POLR2A, NF2, SMARCB1, TERT</td>
<td>N/A</td>
<td>Mixed</td>
</tr>
<tr>
<td>Atypical</td>
<td>Convexity</td>
<td></td>
<td>All</td>
<td>Mixed</td>
</tr>
<tr>
<td>Transitional</td>
<td>Convexity</td>
<td></td>
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<tr>
<td>Fibroblastic</td>
<td></td>
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</table>

PI3K: phosphoinositol-3-kinase.
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On the other hand, molecular profiling of high-grade meningiomas has failed to identify highly recurrent somatic mutations besides NF2 [19,20]. Some mutations have been linked to specific WHO grade II/III histological subtypes, like SMARCE1 mutations in clear cell meningioma [21] and BAP1 mutation in a subset of rhabdoid meningiomas [22]. Mutations in chromatin modifier genes ARID1A and ARID1B have been reported in anaplastic meningiomas or were acquired at recurrence [13,23,24]. Irrespective of tumor grade, (homozygous) deletions of the CDKN2A/B locus have been associated with unfavorable prognosis [25,26] as well as progression to anaplasia [27] and occur mostly in cases that are TRAF7, SMO, KLF4 and AKT1 wildtype [13]. Of note, CDKN2A loss does not necessarily correlate with increased Ki-67 proliferation index and might thus identify cases with unfavorable outcome at an early clinical stage [26]. Exposure to ionizing radiation is the only exogenous risk factor that has been identified for meningiomas [28,29]. Molecularly, radiation-induced meningioma have recently been described to show structural rearrangements in the NF2 gene that lead to protein truncation (in contrast to the inactivating point mutations mostly observed in sporadic cases) [30]. Several lines of evidence suggest a role for sex hormones in meningioma biology, including increased incidence in females, expression of progesterone, estrogen and androgen receptors in meningiomas, effects of exogenous hormone administration on tumor growth and protective effects of breastfeeding [29,31]. Indeed, meningiomas arising in the context of long-term exposure to progestins are clinically and molecularly distinct [32]. They particularly harbor PIK3CA mutations more frequently and are less associated with NF2 mutations.

Prognosis

To date, no prospective evaluation of the prognostic value of any of the described alterations has been performed. Histological grading (WHO grade I to grade III) has traditionally been used to inform prognosis and clinical decision-making such as treatment or follow-up intervals. However, it seems reasonable to routinely determine these biomarkers to identify cases with a probable benign (KLF4, SMO, AKT1) or malignant (TERT, CDKN2A) clinical course to support clinical decision-making for follow-up intervals and treatment. For example, the reduced median PFS of TERT mutant vs. wildtype cases of 10.1 vs. 179 months [18] might justify routine screening for TERT alterations and shorter follow-up intervals in mutant cases. A different approach used methyleome profiling to identify six clusters with similar methylation signatures and clinical outcome [13]. Three of the six clusters identified conferred a good outcome and had a preference for female sex while the remaining clusters were associated with intermediate or poor prognosis. Importantly, these clusters predicted outcome better than histological grade. Recently, the transcription factor FOXM1 has been identified as a potential molecular target and (immunohistochemical) biomarker, but whether its prognostic value is independent of tumor grade and proliferation index needs to be confirmed in future studies [33].

Diagnosis

Imaging

Meningiomas typically present T1-isointense with homogenous contrast enhancement on MR imaging (Figure 1). Contrast agent uptake frequently enhances into the thickened adjacent leptomeninges, which is referred to as “dural tail”. T2-weighted MRI can demonstrate peritumoral edema, which can be disproportionate to tumor size. CT imaging often reveals widespread calcification of the tumor or hyperostosis of adjacent bone. Molecular imaging techniques are increasingly used for meningiomas. Positron emission tomography (PET) using gallium-conjugated peptides binding to the somatostatin receptor (SSR) subtype 2 provides additional specificity in the differential diagnosis between meningiomas and other primary and secondary
brain tumors or non-neoplastic lesions, as SSTTR expression is nearly ubiquitously present in meningioma and at considerably higher levels than most other entities. The RANO/PET group has developed recommendations on the use of in management of meningioma [5], mainly for differential diagnosis, tumor delineation in difficult localizations and target volume planning for radiotherapy.

Need for histological diagnosis
The preliminary diagnosis of suspected meningioma is usually made based on MRI or (less commonly) CT imaging. When typical imaging findings support the diagnosis of meningioma, histological verification is not mandatory according to EANO guidelines, but it is recommended to rule out metastasis (recommendation level: good practice point) [4]. Routinely, in cases where the clinical presentation can clearly be attributed to the tumor mass and a surgical resection is warranted, a final histological diagnosis will be made. Conversely, in asymptomatic tumors where only observation is indicated or symptomatic tumors where radiotherapy is the primary treatment method, it is critical to decide whether to enforce a histological diagnosis. Importantly, incidental meningiomas are found in about 1% of the healthy [34]. Molecular PET imaging using $^{68}$Ga-DOTATOC or $^{68}$Ga-DOTATATE may aid in the differential diagnosis (considered evidence level 2 [5]). Care must be taken in tumors close to the pituitary gland, which shows physiological enrichment of SSTTR radioligands [35] and with tumors known to express somatostatin receptors themselves, such as neuroendocrine tumors or breast cancer [36].

Treatment
Generally, surgery aiming for gross total resection is the primary treatment for intracranial meningiomas. It also serves to establish a histological diagnosis which guides all subsequent decision-making. Current guidelines recommend gradual treatment regimens depending on tumor grade and the extent of tumor resection as established by Simpson [39] (figure 2). Here, we report recommendation levels for treatment and follow-up intervals from the current EANO guidelines [4]. Grade I tumors that can be totally resected (Simpson grade I-III) should be followed by observation. When total resection cannot be achieved, stereotactic radiosurgery is the adjuvant treatment of choice (recommendation level C). In grade II tumors, fractionated radiotherapy is the adjuvant therapy of choice (recommendation level C). Whether Simpson grade I resected atypical tumors should be followed by observation or radiotherapy is subject of the on-going ROAM/EORTC 1308 trial (ISRCTN71502099) [40]. Follow-up interval should be every 6 months for 5 years, then annually. Grade III tumors require radical surgery and adjuvant radiotherapy due to their aggressive clinical course. Irrespective of surgical extent, fractionated radiotherapy ($\geq 54$ Gy in 1.8 to 2.0 Gy fractions) is indicated (recommendation level B). Follow-up intervals of anaplastic meningiomas should be 3–6 months. Metastasis of meningioma is rare even in WHO grade III tumors [41], but associated with the papillary histological variant where it occurs in 20% of cases [42].

Experimental therapies
Chemotherapy is considered experimental in the context of meningioma as only limited evidence or negative reports exist for most agents [43]. As such, their use is only recommended in anaplastic cases and preferentially in the context of clinical trials. Targeted treatment trials are underway for $\textit{SMO}$ and FAK inhibitors for $\textit{SMO}$- and $\textit{NF2}$-mutant meningiomas, respectively (NCT02523014). This trial is the only one that takes into account

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>extent of resection</th>
<th>adjuvant treatment</th>
<th>follow-up</th>
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<tbody>
<tr>
<td>WHO grade I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simpson grade I-III</td>
<td>Observation</td>
<td>3 months, annually for 5 yrs, then every 2 yrs</td>
<td></td>
</tr>
<tr>
<td>Simpson grade IV-V</td>
<td>Radiosurgery</td>
<td></td>
<td></td>
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<tr>
<td>WHO grade II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simpson grade I-III</td>
<td>Observation or fractionated radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simpson grade IV-V</td>
<td>Fractionated radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all Simpson grades</td>
<td>Fractionated radiotherapy (plus experimental therapy)</td>
<td>every 3-6 months</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2**
Treatment guidelines for meningioma with respect to WHO grade and extent of resections. Recommendations summarize the 2016 European Association of Neuro-Oncology (EANO) guidelines for the diagnosis and treatment of meningiomas. Adapted from Goldbrunner et al., 2016. *WHO, World Health Organization*
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possible driver mutations and stratifies patients depending on tumor genotype. The mTOR inhibitor vistusertib (AZD2014) is investigated in a phase II study irrespective of molecular background (NCT03071874), but especially in tumors with PI3K or AKT mutations, there might be a rationale for mTOR inhibition. Several immune checkpoint inhibitors (nivolumab, pembrolizumab), tumor treating fields and bevacizumab are also under investigation.

Challenges in meningioma management

Surgical challenges
The extent of surgical resection is the most important clinical predictor of recurrence. While many factors affect this surrogate marker, gross total resection remains the primary goal for most meningiomas. Surgery can be complicated due to difficult localisation in otherwise benign tumors, as for skull base meningiomas, or invasion of healthy brain, which reflects malignancy in the first place. While neurosurgical technique advances for the first group [44], adjuvant therapy is warranted for anaplastic tumors. Advanced preoperative and postoperative imaging techniques are increasingly used for tumor delineation, determination of residual tumor mass, and identification of bone or brain invasion and their use is encouraged (RANO evidence level 2) [5]. For example, $^{68}$Ga-DOTATATE shows superior signal to background ratio for delineation of meningiomas in regions with low MRI contrast (skull base, orbita, sinus or parafalcine region) [45] or to detect bone infiltration [46].

Radiotherapeutic challenges
Primary or adjuvant radiotherapy is often considered when (complete) surgical removal is impossible. This is usually the case for patients in poor clinical condition, in tumors with complex morphology or in difficult locations. All of these factors also affect planning of radiotherapy. In order to effectively target the tumor mass in its entity and to spare healthy brain tissue and vital structures such as the optic nerve, it is necessary to accurately determine tumor extent. PET imaging using SSR ligands (current data support $^{68}$Ga-DOTATOC) may aid in both volume definition and dose sparing (evidence level 2) [5] and has proven useful in planning of target volume in skull base tumors for stereotactic [47-49] or intensity-modulated [50] radiotherapy.

Peritumoral edema
Meningiomas present with peritumoral edema in 40–66% of cases [51,52]. Edema can be disproportionate with respect to the tumor size and seems to be associated with angiomatous, microcystic and secretory morphology [53]. Life-threatening courses of peritumoral edema have especially been described for the histological subtype of secretory meningiomas [54], which are non-NF2 tumors characterized by co-occurrence of KLF4 and TRAF7 mutations [8,11]. Edema occurs in 62–84% of secretory meningiomas [52,54,55]. Mast cells, which are frequently found in secretory meningiomas compared to other subtypes, have been discussed as possible mediators of edema formation, but evidence has not been conclusive [56,57]. Management of peritumoral edema largely relies on use of steroids (mainly dexamethasone), but antiangiogenic therapy can be considered in exceptional cases when (long term) side effects or insufficient efficacy is being faced [58,59]. Intensive care unit treatment with sedation, mechanical ventilation and intracranial pressure monitoring may be necessary in critical cases, especially those seen in secretory meningioma. Some authors thus suggest an intraoperative histological diagnosis to confirm or rule out secretory meningioma in cases with prominent preoperative edema [54]. Despite these life-threatening complications, it should be noted that secretory meningiomas have a favorable long-term outcome.

Meningioma en plaque
"En plaque" meningiomas are tumors with a sheet-like growth pattern along the dura. They predominantly occur at the sphenoid wing with frequent involvement of the orbit. They typically present with pronounced hyperostosis [60]. Their surgical removal is challenging with gross total resection in 56–83% of cases [61,62]. As such, aggressive resection might not be advisable and a combined primary approach with adjuvant radiosurgery might be preferred [61]. "En plaque" meningiomas may also present as diffuse midline skull base tumors with severe associated morbidity, including vision and hearing loss [63].

Optic nerve sheath meningioma
Optic nerve sheath meningiomas (ONSM) account for 1–2% of all meningiomas [64]. Biopsy is generally not recommended. However, when MRI findings are inconclusive, molecular imaging using $^{68}$Ga-DOTATATE-PET should be considered to rule out differential diagnosis (e.g. lymphoma, optic neuritis, metastasis) [65]. Especially intracanalicular ONSM may mimic optic neuritis [66]. Surgery is not an option in most cases, especially since tumor and optic nerve share the same blood supply. Stereotactic fractionated radiotherapy is the recommended treatment of choice (reviewed in [67]). Initial observation may be warranted in pediatric cases where vision is not compromised due to a possibly favorable clinical course [68].

Spinal meningioma
Spinal meningiomas are rare. Especially when multiple spinal tumors or other entities are encountered (ependymoma, meningioma, schwannoma and astrocytoma), neurofibromatosis type 2 should be considered [69]. Surgical resection and decompression of the spinal cord is routinely aimed for. The extent of resection should be adapted to the location of the tumors: for easily accessible, dorsally located meningiomas where dural repair is possible, Simpson grade I resection should be aimed for. In ventrally located tumors, when neurological
function is at risk or in case of calcified dural attachment, no resection but rather coagulation of involved dura should be performed due to an increased risk of complications [70]. Adjuvant treatment should be in analogy to cranial meningiomas.

**Multiple meningiomas**

Multiple meningiomas occur mostly in the context of neurofibromatosis type 2, which is defined by heterozygous germline inactivation of NF2 [69]. The disease follows autosomal dominant inheritance and typically presents with peripheral and central nervous system, ocular and cutaneous manifestations. Bilateral vestibular schwannomas are the most common CNS manifestation. When intracranial meningiomas occur in NF2, multiple tumors (median of 3 tumors) are common [71]. Meningiomas in neurofibromatosis type 2 are more likely to be atypical or anaplastic compared to sporadic cases [71,72], even though most evidence antedates the distinction between NF2-mutated and non-NF2 sporadic meningiomas. Young age (< 30 years) at initial presentation with meningioma should alert for a possible germline alteration and might warrant molecular testing [73]. Genetic counseling should be offered to those patients with suspected or confirmed neurofibromatosis as penetrance is high and the diagnosis may affect family planning.

Besides neurofibromatosis type 2, other genetic predispositions to meningioma have been described. Mutations in SMARCE1 predispose to clear cell meningioma of the spinal cord and intracranially [21,74]. First presentation was before age of 30 years in 15/16 symptomatic individuals. In addition to recurrent somatic mutations, germline mutations in the *SUFU* gene were observed by two studies [16,75].

Even a solitary meningioma in young patients should raise alertness to a genetic predisposition as one study identified a germline mutation in *NF2* or *SMARCE1* in 38% of patients with a meningioma before age of 25 years [76].

**Conclusion**

Overall prognosis of meningioma is good and despite the lack of a solid body of prospective and/or randomized treatment trials, current treatment regimens with surgery and/or radiotherapy allow for sufficient tumor control in many cases. In contrast, prospective studies are urgently needed to validate putative molecular prognostic markers (such a *TERT* mutations, *CDKN2A* deletion, chromosome 1p deletion and methylation classes). The aim must be to identify unfavorable clinical courses at an early timepoint and to initiate targeted treatment in a clinical trial setting.

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