Current Surgical Strategies in the Treatment of Intracranial Meningiomas

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Introduction

Epidemiology/Aetiology
Being the most common primary brain tumour, meningiomas account for approximately 35% of all CNS tumours. In most cases, meningiomas are primarily diagnosed in the elderly population. Mean age at the time of diagnosis is 63 years and the overall incidence for meningiomas is 7.10 per 100,000. Among the patients developing a meningioma, there is a marked female preponderance with a female : male ratio of 1.7–2:1. In meningiomas located along the spinal cord, the female preponderance is even stronger approaching 90% of all cases [1–4].

In autopsy studies, the prevalence of meningiomas is as high as 2.3–2.8% [1–5]. Arachnoid cap cells are assumed to be the cells of origin as they compose a single fibroblast-like cell layer that can show thickened epitheloid nests of several layers with increasing age [5].

Due to their slow growth in general, nearly ¾ of meningiomas are asymptomatic and are found incidentally on neuroradiologic imaging for other reasons. Symptoms that can occur are mostly due to the space-occupying effect and depend on the specific location of the tumour. Other general symptoms that can occur are headache, visual impairment, and seizures [2, 3].

Currently, the best- evaluated risk factor is exposure to radiation. Low-dose exposition to radiation in nuclear bomb survivors or following treatment for tinea capitis as well as high-dose radiotherapy for brain tumours or haematopoeticologic diseases has been associated with meningioma formation besides other diseases in various follow-up studies [6–8].

Because of the fact that women show a higher incidence than men, hormonal factors as elements influencing the development of meningiomas have been studied and expression of progesterone, oestrogen, and androgen receptors has been identified in a number of tumours. The functional status of these receptors remains to be studied and meningioma is far from being dependent on hormonal stimulation [4, 9].

Hereditary susceptibility has been discussed as a major risk factor. Genetic mutations associated with meningioma development are neurofibromatosis type 2 (NF2), Li-Fraumeni syndrome, Cowden syndrome, and Gorlin syndrome. With NF2, there is a penetrance of almost 100% at the age of 60 years. Especially spinal meningiomas are frequent findings in patients with NF2. On the other hand, most cases of NF2 are spontaneous mutations without a family history. On the contrary, neurofibromatosis type 1 does not show a higher incidence of meningiomas [5, 10].

Pathology/Biological Behaviour
Currently, meningiomas are classified into 3 groups according to the WHO (World Health Organization) classification of 2007. Benign lesions account for approximately 80–92% of all meningiomas [2]. In 2007, brain invasion was implemented into the current classification as a feature of WHO grade-II and -III tumours. Therefore, the number of atypical meningiomas classified as WHO grade-II has risen. Currently, the proportion of atypical and anaplastic meningiomas is approximately 20–25% with 5–20% accounting for WHO grade-II tumours and 1–5% accounting for WHO grade-III meningiomas [4, 5, 11, 12].

Besides brain invasion, further characteristics of WHO grade-II tumours are chordoid and clear-cell histological subtypes as well as frequent mitoses (≥ 4 per high-power field) or 3 aspects of the following: hypercellularity, prominent nucleoli, small cells, and foci of spontaneous necrosis. For WHO grade-III anaplastic meningiomas, histopathological characteristics are excessive mitoses (≥ 20 per high-power field) or frank anaplasia and differentiation resembling sarcoma, carcinoma, or meningioma. Furthermore, histological subtypes of papillary or rhabdoid meningiomas are classified as grade III [13].
Various signalling pathways have been studied concerning the growth pattern of meningiomas, disruption of the arachnoid layer, as well as the great variability of peritumoral brain oedema formation. Vascular endothelial growth factor (VEGF) is probably the best-studied angiogenic factor in association with biological behaviour and clinical outcome of meningiomas.

Other investigated factors upstream or downstream of the angiogenic pathway associated with VEGF are hypoxia-induced factor 1α (HIF-1α), carboanhydrase (CA-IX), and glucose transporter 1 (Glut-1). In a recent analysis, higher-grade meningiomas have shown a correlation with a significant higher expression of CA-IX, VEGF, and HIF-1α [11, 12, 14].

Location
Meningiomas growing on the convexity form the biggest group followed by tumours growing along the falx and parasagittal meningiomas. Up to 25 % of all intracranial meningiomas show involvement of structures of the skull base. Of those, lesions in the anterior cranial fossa form the biggest group. Spinal meningiomas account for approximately 12 % of all meningiomas and form the largest group of spinal intradural tumours [15–18].

Treatment
The primary treatment of meningiomas is surgery and little has changed since the publication of the monograph by Harvey Cushing and Louise Eisenhardt in 1938 except for meningiomas arising in the central skull base [19]. In 1957, Donald Simpson published a hallmark paper on the significance of complete surgical resection for the rate of recurrence. He gradually classified surgical outcome and could demonstrate a gradual increase of recurrences in tumours that have not been completely resected. Regarding skull base meningiomas, Simpson stated that reaching macroscopically complete removal is hardly possible [20]. Due to refined techniques in surgery, this is not true in all locations [21, 22].

Ever since, macroscopically complete tumour resection with excision of altered dura and bony structures should be the goal of surgical treatment if achievable without significant morbidity [23–26].

In a study by Hasseleid et al, the importance of complete removal was shown again regarding recurrence rates of patients undergoing Simpson grade-I versus -II resections in convexity meningiomas [23].

In recent years, a number of other studies have also re-evaluated the outcome of more aggressive surgical strategies [24, 25]. In 2010, Sughrue et al showed that recurrence rates for Simpson grade-I resections did not differ significantly compared to Simpson grade-II, -III, or -IV resections. Nevertheless, they found a gradual decrease in 5-year progression-free survival (PFS) from 95 % in Simpson grade-I to 85 % in Simpson grade-II, 88 % and 81 % in Simpson grade-III and Simpson grade-IV removal, respectively [24].

Radiotherapy or stereotactic radiosurgery (SRS) has proven its value in treating residual tumour tissue. In anaplastic tumours following subtotal resection (STR) or partial resection (PR), broad agreement about the need for radiotherapy exists. The necessity of radiotherapy following resection of an atypical meningioma is still a matter of discussion and a consensus has not been found yet [13, 27]. In recent studies investigating these results, a trend towards a decreased rate of recurrence in patients receiving postoperative radiotherapy was noted. However, sample sizes were too small to detect statistical significance [27–29].

Depending on their location, various treatment strategies have been developed over the last decades.

Convexity Meningiomas
In convexity meningiomas, the primary form of treatment remains complete surgical resection since it is the easiest location to achieve Simpson grade-I resection with acceptable morbidity. New neurological deficits occurred in only 3 patients postoperatively in a study performed by Morokoff et al including 163 convexity meningiomas [23–25, 30, 31]. Although Morokoff et al included only patients undergoing Simpson grade-I resection, the rate of recurrence was as high as 4.3 % [31]. Various additional factors besides extent of resection and histological grade have been investigated to be responsible for tumour recurrence. In 1986, Borovich et al showed the existence of satellite lesions up to 3 cm in distance from the primary tumour at the time of initial treatment. To achieve gross total resection (GTR), they postulated a modified Simpson grade-“0” resection with excision of adjacent dura up to 4 cm if feasible [18, 32]. Besides these satellite lesions, the focus of interest was also directed towards the importance of a cleavage plane to completely resect meningiomas. A study performed by Alvernia et al showed a higher rate of recurrence in tumours that showed a subpial cleavage plane as a sign for pial vascular supply and brain-invasive growth pattern compared to meningiomas with an extrapial cleavage plane. A further modification of the Simpson classification was contemplated with respect to small tumour remnants due to cortical invasion or invasion of cortical blood vessels [33].

Parasagittal and Falcine Meningiomas
Difficulties in resecting parasagittal and falcine meningiomas occur with involvement of the superior sagittal sinus (SSS) and large bridging veins. Due to the deep localization within the interhemispheric fissure, achieving GTR is a surgical challenge. In case of parasagittal meningiomas with a stenotic or an obstructed sinus, complete surgical resection with excision of the occluded sinus is possible in the frontal region, but not always possible in central and parietal localizations. With the advent of stereotactic radiosurgery (SRS), treatment strategies for parasagittal meningiomas with a patent sinus have changed. For large tumours involving a patent sinus, GTR is attempted. If a residual tumour is present adhering to large bridging veins or the sinus, conservative treatment with serial magnetic resonance (MR) imaging can be performed in case of benign tumours. Postoperative SRS can be performed in small tumours involving a patent sinus and residual tumours that show progression on MR imaging, and tumour control rates as high as 89 % can be achieved [34–36].
Our policy for meningiomas invading the SSS is to resect the tumour together with the SSS anterior to the coronal suture. In case of a meningioma behind the coronal suture, the tumour is resected to the lateral wall of the sinus leaving all bridging veins intact. No efforts are made to incise or remove tumour from within the SSS. Resection and reconstruction of the sinus have been advocated but result in an unacceptably high risk of complications [35, 37]. In those cases with residual tumour within the SSS or its walls, radiosurgery is a given option.

Skull Base Meningiomas
As mentioned, up to 25 % of all tumours involve structures of the skull base, where complete removal is hardly possible without significant morbidity due to the close relationship to cranial nerves or large vessels supplying or draining blood from the brain [20, 26, 38–40].

Various treatment strategies exist for different regions of the skull base. For tumours arising in an accessible localization, surgical resection remains the modality of choice.

Olfactory Groove Meningiomas
In case of olfactory groove meningiomas, complete surgical resection can be achieved with modest morbidity. At the time of presentation, these tumours can already have reached an imposing size and mental changes represent the most common symptoms. A typical combination in olfactory groove meningiomas is the Foster-Kennedy syndrome consisting of anosmia, ipsilateral optic atrophy, and contralateral papilloedema. In a series of 82 olfactory groove meningiomas by Nakamura et al, complete resection (Simpson grades I and II) was achieved in 92 % using a unilateral frontolateral or bifrontal approach [41]. The preferred approach at our institution is pterional because of a lesser surgical trauma compared to a bilateral approach as well as early identification of the optic nerve and internal carotid artery.

**Tuberculum Sellae Meningiomas**
In contrast to olfactory groove meningiomas, due to early compression of the optic nerve or the chiasm, tuberculum sellae meningiomas are usually smaller at the time of diagnosis and visual impairment (Figure 1) is the typical first symptom. The combination of primary optic atrophy and bilateral hemianopsia occurring in cases of tuberculum sellae meningiomas has been termed chiasmal syndrome. Due to the close relationship to neurovascular structures, their surgical resection can be challenging. Nevertheless, gross total removal and improvement of visual function should be the aim of surgical resection. Nakamura et al published a series of 72 tuberculum sellae meningiomas resected via a transcranial approach and

![Figure 1. Tuberculum sellae meningioma found due to blurred vision operated via a right-sided subfrontal approach.](image)
GTR (Simpson grades I and II) was achieved in 66 patients (91.7%). Visual impairment was present in all of these cases. Postoperative visual examination was performed in 56 of these patients. Improvement of visual function was noted in 38 of 56 patients (67.9%) while in 11 patients (19.6%) visual function remained stable. Deterioration of visual impairment was found in 7 patients (12.5%).

As an alternative to transcranial resection of tuberculum sellae meningiomas, an endoscopic transsphenoidal approach can be a suitable alternative in selected cases without lateral extensions [42–44].

Sphenoid Wing Meningiomas
According to their location on the lesser wing of the sphenoid bone, sphenoid wing meningiomas are subclassified into lateral, middle, and medial meningiomas. Besides headaches, symptoms vary according to their location. In a series of 59 patients by Sughrue et al, seizures were the most common symptoms in lateral and middle sphenoid wing meningiomas, whereas visual impairment was the most common symptom for medial sphenoid wing meningiomas. Regarding surgical outcome, a trend towards a lower rate of GTR for medial meningiomas was shown but differences were not statistically significant. Nevertheless, for lateral and middle sphenoid wing meningiomas, complete surgical resection remains the treatment of choice.

Due to the close relation and involvement of the cavernous sinus as well as encasement of the internal carotid artery, subtotal resection with postoperative SRS can be a viable option for treatment of selected cases of medial sphenoid meningiomas [45].

Meningiomas of the Cavernous Sinus
In the past, large efforts have been made in surgical resection of meningiomas involving the cavernous sinus. Sekhar et al stated in a report about the surgical treatment of intracavernous neoplasms that meningiomas are probably most difficult to remove. In his series of 42 patients, neurological outcome of cranial nerves (CN) was stated as follows: loss of olfaction occurred in 3 patients due to the chosen subfrontal surgical approach. Dramatic loss of vision occurred in one patient and the loss of corneal sensation due to invasion of the ophthalmic nerve (V1) was found in 4 patients. Furthermore, permanent paralysis of the abducens nerve was found in 4 cases [46].

In a series by DeMonte et al, results of surgical resection of 41 cases of benign meningiomas were published. Complete removal was achieved via an orbito-zygomatic approach in 31 patients (76%). In 3 cases, cerebral ischaemia occurred postoperatively due to injury of small perforating vessels or the middle cerebral artery. Furthermore, episodes of transient diabetes insipidus and non-fatal pulmonary embolism occurred in another 3 patients. A cerebrospinal fluid (CSF) leak was reported in another 2 cases [22].

In a series of 29 meningiomas of the cavernous sinus at our institution, deterioration of preoperative oculomotor paralysis did occur in 14% of patients. Improvement of oculomotor function was noted in 43%. Deterioration of trochlear nerve function was seen in 4 patients. Impairment of the abducens nerve was noted in 55% of patients preoperatively and improvement was noted in half of them. The other half remained unchanged. Additionally, a new abducens nerve deficit was found in one patient who had good abducens nerve function preoperatively [38].

Due to these higher morbidity rates and with further technological development, stereotactic radiosurgery has become the treatment of choice for cavernous sinus meningiomas. In 2000, Roche et al presented a series of 80 patients undergoing SRS and a tumour control rate of 92.7% could be achieved [39, 40].

Current treatment standards for cavernous sinus meningiomas consist of primary SRS or radiotherapy (Figure 2) in case of close proximity to the optic nerves and reported tumour control rates in the current literature reach up to 96% [40, 47].
Petroclival Meningiomas

Due to its location in the posterior fossa and close proximity to cranial nerves and other vital neurovascular structures, treatment of petroclival meningiomas can be challenging and the best treatment strategy is still a matter of discussion. A higher risk of developing new cranial nerve deficits, either transient or permanent, has to be seen alongside the potentially curative aspect of surgical resection. Early intraoperative visualization of neurovascular structures is regarded as a major requirement to preserve neurological function, therefore extensive approaches have been developed. However, complete surgical removal also highly depends on the existence of a dissection plane. In cases without such a dissection plane or with infiltration of neurovascular structures or the brainstem, subtotal removal can be reasonable. For small asymptomatic tumours, SRS can represent a viable option given the lack of an exact histological diagnosis [47–49].

Foramen Magnum Meningiomas

In case of a meningioma arising at the foramen magnum, surgical resection remains the primary treatment modality. Borba et al published a series of 15 tumours arising at the foramen magnum – in 2 cases complications occurred related to surgery. One patient suffered from transient XII cranial nerve (CN) palsy and a cerebrospinal fluid (CSF) leak and one patient showed transient worsening of a motor deficit with improvement after 6 months. Especially ventral or ventrolateral tumours can pose surgical challenges and as for petroclival meningiomas, various surgical approaches have been developed to optimize operative exposure in order to protect vital neurovascular structures. Talacchi et al recently presented their results in 64 cases of ventral and ventrolateral foramen magnum meningiomas. A dorsolateral surgical approach was chosen in each patient and GTR could be achieved in 52 patients (81%). Pre-existing cerebellar deficits and long-tract signs improved in 74 and 77%, respectively, preoperative cranial nerve deficits showed improvement in 27%. On the other hand, new cranial nerve deficits were noted in 23 patients (CN IX–XII) with difficulties with swallowing being the most common symptom. All of these cases were managed conservatively with prevention of aspiration being of utmost importance. After one month, swallowing improved sufficiently in 71% [50–52].

Conclusion

Surgical resection is the primary treatment modality for intracranial meningiomas with gross total resection being the goal of surgery in case of convexity meningiomas or parasagittal or falcine meningiomas. Meningiomas involving the SSS or the transverse or sigmoid sinus should be resected to the greatest extent possible but utmost care has to be taken not to compromise venous drainage.

In case of meningiomas arising at specific locations at the skull base surgical excision can be challenging and the best treatment strategies are the topic of ongoing development in skull base surgery. In certain skull base meningiomas, Simpson grade-I resection is hard to achieve with an acceptable morbidity due to close relations to major blood vessels and cranial nerves.

With the advent of radiosurgery, new treatment options have become available for those lesions in close relation to vital neurovascular structures. Figure 3 shows different treatment approaches in skull base meningiomas. Radiosurgery became the treatment of choice in cases of meningiomas arising within or invading the cavernous sinus due to high morbidity during surgical exposure. In case of petroclival meningiomas, there is an ongoing discussion whether radiosurgery is a viable option in small, asymptomatic meningiomas. Tumours arising in other locations of the skull base are usually amenable to surgical resection.

A major drawback of radiosurgery as a stand-alone therapy is the lack of histopathological diagnosis as well the lack of a precise grading.

At our institution, symptomatic tumours, meningiomas > 3 cm in diameter, as well as documented growth of a lesion are indications for surgical excision. Furthermore, the existence of a peritumoral brain oedema (PTBE) as an expression of the disruption of the arachnoid layer are indications for surgery.

Smaller, asymptomatic lesions without the occurrence of PTBE and highly calcified tumours may be followed conservatively.

Conflict of Interest

The authors declare there is no conflict of interest.

References:

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