NARRATIVE REVIEW

Consensus guidelines for the management of intracranial meningioma for low- and middle-income countries

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Abstract

Intra-cranial meningiomas represent the most common type of extra-axial brain tumour in adults. Characteristically slow-growing and often asymptomatic, these tumours may only require observation in some cases. However, lesions that cause a significant mass effect necessitate intervention, primarily through surgical means. Additionally, in cases of significant unresectable low-grade residual meningioma or high-grade tumours, radiation therapy becomes essential. Notably, current management guidelines predominantly reflect data derived from high-income countries, failing to address constraints prevalent in the developing world, such as limited financial resources and restricted access to advanced surgical facilities. This manuscript introduces guidelines specifically tailored for the management of meningioma in patients from low- and middle-income countries, considering their unique healthcare challenges and resources.

Keywords: Meningioma, brain neoplasms, health care, neurooncology.

DOI: https://doi.org/10.47391/JPMA.S3.GNO-18

Introduction

Meningiomas, arise from meningeal cells of the central nervous system, and are the most frequent extra-axial primary brain tumour in adults. Age-related increase in meningioma incidence has been found and overall accounts for 37.6% of all primary brain tumours. Of these, 54.3% are reported as benign.[1] They are uncommon in children and are frequently found in women between 40 and 60 years of life. Most of them occur spontaneously, but some are familial (found in relation to neurofibromatosis, von Hippel-Lindau syndrome and some other syndromes) or occur after radiotherapy.

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Meningiomas are most commonly found on the surface of the brain such as cerebral convexity and parasagittal regions, followed by the medial and lateral base of the skull regions. Compared to medial skull base meningioma, non-skull base and lateral skull base meningioma have a higher frequency of atypia and malignancy, as well as higher recurrence rate.[2] The World Health Organization (WHO) categorizes meningioma in 3 histologic grading: Grade 1 is the most common and has a benign course, while Grades 2 and 3 are not very common but have more aggressive course and higher recurrence rate.[3] The 5-year survival rate for non-malignant meningioma is approximately 88% which reduces to 66.5% in cases of malignant meningioma.[4]

Due to resource constraints in low- and middle-income countries (LMIC), many patients with meningioma do not seek timely treatment. Current guidelines on meningioma management are based on data from developed countries, and do not take into account the limitations of LMICs. These guidelines provide comprehensive framework for effective management of patients diagnosed with meningioma in resource limited settings.

Methodology

A systematic database search was done in July 2023 to identify gaps in the diagnosis and management of intracranial meningioma in the low- and middle income countries. The literature search of the high-quality data on meningiomas was done on different databases including PubMed, Google Scholar, Scopus, and Embase. The most relevant and high-quality studies were analysed to develop the evidence-based recommendations. A panel of experts comprising neurosurgeons, oncologists, neuro-radiologists, radiation oncologists and neuropathologists collected and analysed published evidence within their respective fields regarding the diagnosis and management of intracranial meningioma. These evidences were collected to identify the best-practice recommendations for the management of intracranial meningioma in LMIC settings. After extracting the data of local and regional published articles, the data was reviewed and discussed with senior faculty of each

working group. Expert opinions were used to decide the quality of evidence. Recommendations were made for the practical application of best-practice guidelines to LMIC settings, such as in Pakistan.

Initial evaluation (Screening and diagnosis)

Clinical presentation and evaluation

As with other intracranial tumours, the clinical presentation of intracranial meningioma varies based on its location and size. However, the majority of these meningiomas are asymptomatic and often diagnosed incidentally. They can be seen originating from any dural surface and if symptomatic, the clinical presentation results from the mass effect produced by compression of surrounding brain parenchyma or vascular structures and includes localised neurological impairments, seizures (generalized or focal), and signs and symptoms of elevated intracranial pressure such as headache and vomiting. Meningiomas typically have slow growth with a low incidence of metastasis and the common sites for meningioma metastasis include the lung, liver and bone. The 5-year survival rate of patients with meningioma also reduces with metastasis.[5]

Diagnostic workup

MRI with contrast is the preferred diagnostic modality when there is clinical suspicion of a brain tumour. They typically appear as solitary round dural based tumours with homogenous and prominent contrast enhancement and adjacent dural enhancement (dural-tail sign). They are iso-intense with brain parenchyma on T1-weighted imaging and iso-intense or hyper-intense on FLAIR imaging. However, approximately 10-15% of meningiomas resemble metastases or malignant glioma on MRI with atypical features.[6]

However, when MRI is contraindicated (e.g. if the patient has a pacemaker) then CT scan with contrast can be used instead. On CT scan, meningioma usually appears iso-dense with brain parenchyma. Also, CT scan is more sensitive in defining bone remodelling features such as hyperostosis of skull as a result of slow growing meningioma, intraosseous tumour growth or in detection of psammomatous calcifications within meningioma which is seen in approximately 25% of cases. The neuroimaging features such as the presence of a dural-tail sign, calcification, uniform enhancement, and regular border suggest the presence of a more benign meningioma while the presence of peritumoural oedema, intratumoural necrosis, intratumoural cystic change, cortex invasion, bone destruction, and hyperostosis of the adjacent skull suggests the presence of a high grade meningioma.

As meningiomas are highly vascular tumours, cerebral angiography can also be performed in selected cases which can be followed by preoperative embolisation. During angiography, meningioma is found to have a dual arterial supply with pial arteries supplying the tumour's outermost area and dural arteries supplying the tumour's inner core. MR spectroscopy can also be used to differentiate between meningioma and other intracranial neoplasms particularly in patients who are unable to undergo surgery and observation is being considered.

Management of meningioma

For asymptomatic, non-growing, incidentally diagnosed meningioma, only active monitoring can be done using annual clinical assessment and repeat imaging at regular intervals. However, the definitive diagnosis of a growing or symptomatic meningioma requires a surgical procedure to obtain tumour tissue for histological classification, grading and molecular genetics as this will guide all subsequent decision-making. Generally, the standard recommended treatment for growing or symptomatic meningioma is gross complete (total) resection including the removal of any involved dura. However, different radiation strategies are frequently used when surgical resection alone appears to be insufficient.

Observation

Incidentally diagnosed meningioma that are asymptomatic and small (≤3 cm in diameter) can be observed. These tumours can remain undiagnosed because of their slow growth and once diagnosed, close active monitoring with clinical and neuroimaging follow ups can be sufficient. This will avoid post-surgical complication risks associated with the surgical approach. However, before opting for observation in such cases, a careful evaluation of factors that can predict these tumours' growth is required. The two most significant radiographic findings are the presence of tumour calcification and the T2-weighted MRI signal intensity. Studies have shown gradual growth in tumours with calcification and hypointense signals on T2 weighted MRI, while there is rapid growth in tumours with hyperintense signals on T2 weighted MRI.[7] Therefore, a follow-up observation strategy can be explored in patients with radiological signs of slow-growing, asymptomatic meningioma. This strategy involves repeating imaging three or six months after diagnosis, then every year for five years, followed by once every two years.[8] This follow up strategy is complied until the tumour becomes symptomatic or large enough to consider surgical intervention. However, in elderly patients with shorter life expectancy and having benign radiological features there

is no need for follow up imaging.

Surgical technique

The approach needed to resect intra-cranial meningioma or any other intra-cranial tumour depends on its size, location, proximity to intra-cranial neurovascular networks and the degree of dural attachment. The goal of resection is gross-complete removal of the tumour, which also includes removal of any associated dura. The extent of resection can be determined by the surgeon's own judgement and by a postoperative MRI that can be performed within 48 hours after surgery or can be delayed until three months postoperatively. The degree of surgical resection is also one of the most significant predictors for recurrence, as with sub-total resection, the likelihood of disease recurrence/ progression is high. Generally, subtotal resection is considered for tumours with difficult localization, such as skull base meningioma, even in cases of benign histologic grading of tumours with healthy brain invasion.

Pathologic assessment

Histopathology

The classification used by the World Health Organization (WHO) for meningiomas is based on the histological features. Under the WHO 2021 classification method, meningiomas are classified as a single tumour type with 15 sub-categories. Grades range between WHO grade 1 (meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory and lymphoplasmacytic-rich meningioma), WHO grade 2 (atypical meningioma including brain infiltrative meningioma, choroid and clear cell meningioma), and WHO grade 3 (anaplastic/malignant meningioma).[9]

Grade 1 accounts for more than 80% of meningioma cases. Histologically, these tumours have benign features lacking anaplastic features found in the other two grades. The characteristics 'psammoma bodies' which are the result of calcification of meningeal cells can be seen in histopathology.

Grade 2 accounts for approximately 17% of meningiomas. The presence of necrosis, conspicuous nuclei, hyper cellularity, high nuclear-cytoplasmic ratio, or raised mitotic figures are some of the atypical characteristics seen in grade 2 meningioma. Furthermore, the likelihood of recurrence is higher with atypical meningiomas compared to benign meningioma.

Approximately 3% of meningiomas are WHO grade 3 and are known as anaplastic or malignant meningiomas. They have a high level of mitotic figures (at-least 20 mitoses per 10 high-power fields) and are associated with higher risk for distant metastasis.

Adjuvant treatment

Radiotherapy

Meningioma outcomes and management strategies are mostly determined by the degree of surgical excision and the WHO histopathologic classification. Postoperative radiation therapy is recommended for WHO grade 3 meningioma, WHO grade 2 meningioma after sub-total excision or in some patients after gross complete resection because patients are frequently lost to follow-up, and WHO grade 1 meningioma with growing-residual tumour. However, radiation therapy is considered the preferred first line treatment in patients with inoperable meningioma such as those encasing neurovascular structures. Approximately 30-35% reduction in size of meningioma following radiation therapy have been observed in multiple studies with most occurring in the first 3 years after radiation.[10]

Dowook Kim et al. in their study, on patients treated with adjuvant radiotherapy for atypical meningioma, found that greater tumour size, higher mitotic figures and brain invasion affect the treatment outcomes while the degree of surgical excision was not found to affect the outcome after radiation therapy. Additionally, they also found a dose-response relationship between radiation exposure and the effectiveness of the treatment, with greater doses producing better survival results.[11]

The dose and volume of radiotherapy, therefore, may affect overall survival. According to recent studies, depending on the tumour's extent, stereotactic and fractionated radiotherapy can be used in patients with WHO grade 1 meningioma after sub-total resection. Stereotactic radiation (12–16 Gy in a single dose) is preferred over fractionated radiotherapy (54 Gy administered at 1.8 Gy per fraction) for small tumours. For WHO grade 2, the role of adjuvant radiotherapy after gross total resection is unclear, however, after subtotal resection adjuvant fractionated radiation (54-60 Gy administered at 1.8-2.0 Gy per fraction) is advised.[12] Regardless of the degree of surgical resection, all patients with WHO grade 3 meningioma, including those who have a TERT promoter mutation and/or CDKN2A/B deletion, need postoperative radiation therapy. Due to the aggressive clinical history of these meningiomas, recent studies have recommended radiation dosages of 60 Gy administered at 2.0 Gy per fractions. NRG-Oncology Radiation Therapy Oncology Group (RTOG) conducted a Phase II clinical trial in which meningioma patients were categorized in three prognostic groups based on the WHO grade of tumour, presence of recurrence and the

Table-1: Summary of Radiation Therapy recommendation based on prognostic group.

RISK GROUP	DESCRIPTION	RADIATION DOSE	VOLUME
LOW RISK	WHO grade 1 meningioma s/p GTR or STR	Observation	————--
INTERMEDIATE RISK	WHO grade 2 meningioma S/P GTR Recurrent WHO grade I meningioma	54 Gy/30 fractions	Margin of 1cm
HIGH RISK	WHO grade 3 meningioma (any resection) WHO grade 2 meningioma S/P STR Recurrent WHO grade 2 meningioma	60 Gy/30 fractions	Margin of 2 cm

S/P: surgical procedure, GTR: Gross total resection, STR: Subtotal resection, Gy: Gray.

degree of tumour resection.[13] Table-1 summarizes the recommendation for radiation therapy according to prognostic group of patients as per this trial. RTOG trial also shows improved outcomes with Intensity Modulated Radiation Therapy (IMRT) for high grade meningioma.

Chemotherapy

There is currently insufficient data to determine the significance of chemotherapy in the management of meningioma. For patients with recurrent meningioma, surgically not accessible and not responding to radiotherapy, National Comprehensive Cancer Network (NCCN) guidelines recommend alpha-interferon analogue, somatostatin (growth hormone-inhibiting hormone) receptor agonist and vascular endothelial growth factor (VEGF); however, there are no conclusive studies determining the efficacy levels of these medications.[14] Palbociclib, a CDK4/6 inhibitor, was found to enhance radiation activity against meningioma especially when meningioma cells were p-16 deficient and Rb intact, diminishing cell growth in vivo using mouse models with aggressive meningioma.[15] A phase II clinical trial was conducted using Nivolumab, a programmed cell death protein 1 blocker, in patients with recurrent/ anaplastic meningioma and results showed no significant side effects with this drug; however, there was also no significant improvement in progression-free survival.[16] More research and clinical studies are needed to transform the effectiveness of chemotherapy in the treatment of meningioma.

Management/ follow-up after surgery

The standard recommended treatment options are surgery and radiation therapy. Postoperatively, frequent neuroimaging at regular intervals along with clinical assessment is recommended according to WHO grade of tumours. For any grade, the first follow up should be after 3 months and thereafter, it depends on the WHO grade of tumour. For WHO grade 1 patients, follow-up is recommended every year for the first five years, then every two years. For WHO grade 2 patients, every six months for the first five years, then yearly. For WHO grade 3 patients, further follow ups should be every 3-6 months.[8] For any grade, if 5-year scans do not show any increase in size of residual disease or any recurrence then follow-up can be discontinued; but if there is recurrence/ increase in size of residual disease then continue follow-up as recommended.

Miscellaneous/ prognosis/ outcomes/ quality of life

The prognosis for meningioma is generally favorable. Patients with WHO grade 1 tumour often have a five-year progression-free survival rate of about 90%, WHO grade 2 patients typically have a five-year progression-free survival rate of 60-90% and WHO grade 3 patients have a rate of 28% after gross complete resection. However, for a 10-year overall survival rate, this decreases to 53% for patients with grade 2 and 0% for patients with grade 3 even after receiving the best possible treatment.[17] Prognosis depends on factors such as age, symptoms burden, histological tumour grade and extent of resection. Meningioma grade is also correlated with the degree of prognosis with grade 3 having higher risk of recurrence and worse prognosis. The health related quality of life is also affected and the known risk factors for worse quality of life includes tumour size, location, histological grade, seizure burden and recurrent tumour. Identifying at-risk patients, such as those with high grade meningioma, frontal or skull base location or larger size tumours, can help in counselling the patients regarding their expected quality of life.

Gaps in knowledge

There is still a need for further research in meningioma with the recent emerging large scale molecular studies, in particular genomic and epigenomic, to improve current management strategies for patients in LMIC. New

Table-2: Summary of Recommendations for Meningioma.

Radiology	• MRI brain with and without contrast. • 'Minimum required' MRI protocol: o Imaging on at least 0.5T. o Sequences: Axial T2 and coronal or axial FLAIR sequence; pre-contrast T1 and contrast enhanced T1. • Tumour location, tumour margins, enhancement pattern, size, vascular supply, venous sinus and bone involvement, and presence of haemorrhage/mineralization. • CTA can aid surgical planning in selected cases. • First postoperative MRI is recommended after 6 months for grade 1 and 3 months for grade 2/3. o To identify the extent of resection. o To have a baseline to compare successive imaging.
Neurosurgery	**Surveillance** • Asymptomatic, small, non-growing, incidentally diagnosed meningioma, only active monitoring is recommended. • Repeat clinical evaluation and MRI after 3 months then 6 months then annually for 5 years, followed by every 2 years until the tumour becomes symptomatic or large enough to consider surgical intervention. Surgery • Extent of resection depends on tumour size, location, proximity to neurovascular structures and the extent of dural involvement. • GTR including the resection of involved dura and overlying bone is recommended. • STR can be considered for tumours located near critical neurovascular structures.
Neuropathology	• Haematoxylin and eosin (H&E) preparation for histological typing. • Histopathological assessment should assess mitotic activity, atypical/ anaplastic features like necrosis, cellularity, and glial invasion to classify according to the WHO classification system. • Immunohistochemical stains EMA, S-100, CD34, STAT-6 and GFAP to differentiate from non-meningeal tumours.
Medical & Radiation Oncology	• Radiation therapy can be considered as the first line in patients with unresectable meningioma. • Postoperative radiation is advised in WHO grade 3 (regardless of EOR), WHO grade 2 after STR, and in cases of recurrence irrespective of the grade. • Radiation can be considered in patients with LMIC limitations in WHO grade 2 with GTR and grade 1 with STR. • Conformal radiation with advanced techniques such as 3DCRT/IMRT/VMAT with a conventional fractionation schedule is recommended. However, for grade 1 meningioma stereotactic radiation can be considered in selected patients. • The common radiation dose for grade 1 is 54 Gy given at 1.8 Gy per fraction, for grade 2 is 54–60 Gy given at 1.8–2.0 Gy per fraction, and for grade 3 is 60 Gy given at 2.0 Gy per fraction for five days a week for 6-7 weeks. • Stereotactic radiation treatment can be considered as the preferred radiation approach in re-irradiation settings in centres having site-specific expertise and practice after discussion in radiation oncology peer review meetings. • Chemotherapy has not yet proven to be effective in the treatment of meningioma.
Follow-up	• First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology and NOTB recommendations. • For WHO grade 1, annually for five years and then every two years. • For WHO grade 2, every 6 months for five years and then annually. • For WHO grade 3, further follow-ups should be every 3-6 months. • For all grades, if the 10-year scan is satisfactory, follow-up can be discontinued but if recurrence is detected, then an annual scan is recommended.

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MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, CSF: Cerebrospinal fluid, VPS: Ventriculoperitoneal shunt, ETV: endoscopic third ventriculostomy, NOTB: Neuro-oncology tumour board, EPN: Ependymoma, MIB1: Mindbomb Homolog-1, ZFTA: Zinc Finger Translocation Associated, STR: Subtotal resection, Gy: Gray.

research including molecular studies can aid in the investigation of molecular pathology diagnostics, predictive algorithms and treatment modalities for meningioma.

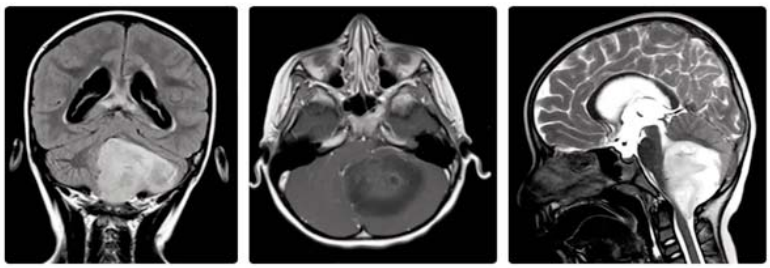
Conclusion

These guidelines are formulated based on valuable experience (refer to Table 2 and Figure 1) and are designed for physicians working in low-resource setups. Their application has significant potential to improve outcomes and aims for a strong emphasis on multidisciplinary care within LMICs, such as Pakistan.

Disclaimer: None.

Conflict of Interest: None.

Funding Disclosure: None.



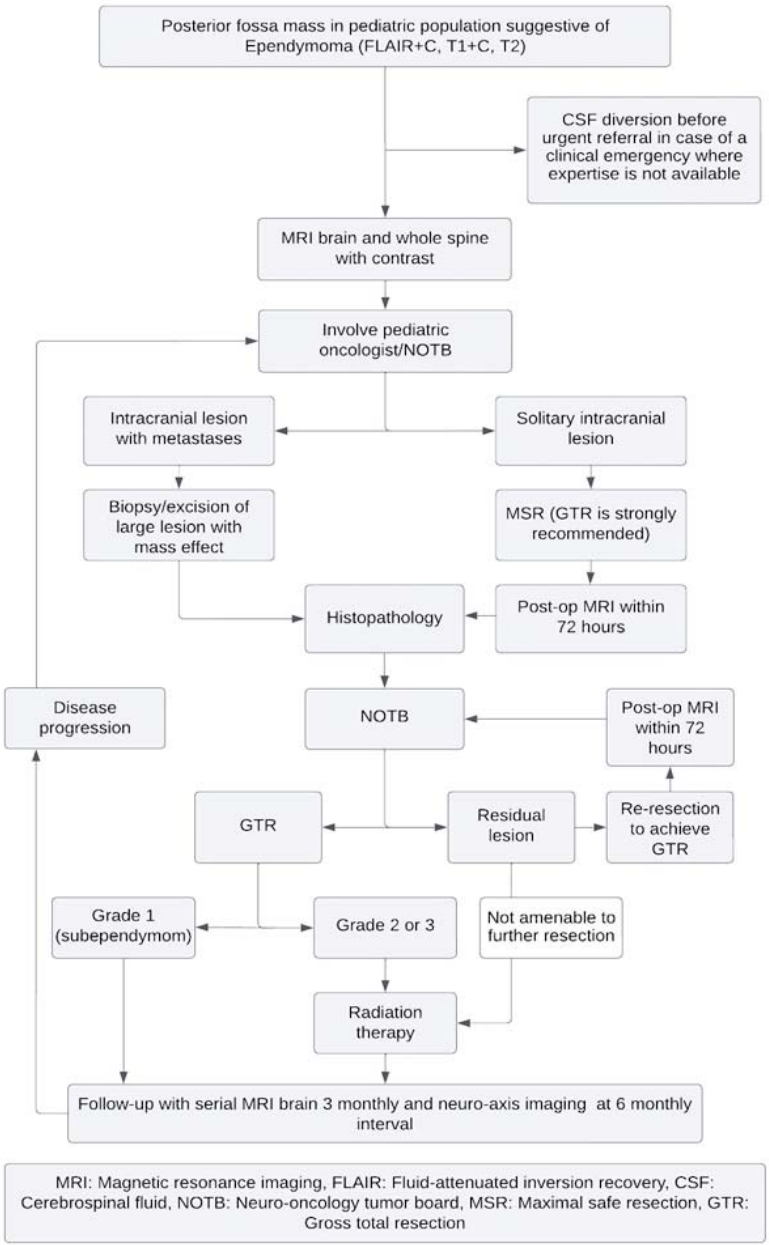


Figure-1: Management of intracranial meningioma algorithm.

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