NARRATIVE REVIEW

Consensus guidelines for the management of primary supra-tentorial intraventricular tumour for low- and middle-income countries

Hafiza Fatima Aziz[1], Saqib Kamran Bakhshi[2], Rabeet Tariq[3], Muhammad Waqas Saeed Baqai[4], Mohammad Hamza Bajwa[5], Kaynat Siddiqui[6], Zanib Javed[7], Ahsan Ali Khan[8], Muhammad Shakir[9]
Pakistan Brain Tumour Consortium: (Authors list at the end of the supplement), Syed Ather Enam.

Abstract

Almost any primary or metastatic brain tumour can manifest in intraventricular (IV) locations. These tumours may either originate within the ventricular system or extend into the IV space through growth. Such neoplasms represent a broad spectrum, with supratentorial IV tumours forming a heterogeneous group. This group includes primary ependymal tumours, central neurocytomas, choroid plexus tumours, and notably, meningiomas, as well as a variety of non-neoplastic, benign, glial, and metastatic lesions that can secondarily invade the IV compartment. Often presenting with non-specific symptoms, these tumours can lead to delayed medical attention. The diversity in potential diagnoses, combined with their deep and complex locations, poses significant management challenges. This paper aims to delineate optimal management strategies, underscoring the importance of multidisciplinary care, especially in settings with limited resources, to effectively navigate the complexities associated with treating intraventricular brain tumours.

Keywords: Meningeal neoplasms, meningioma, neurocytoma, choroid plexus, neoplasms, intraventricular tumour, supratentorial tumours.

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Introduction

Primary Intraventricular (IV) Tumours of the supratentorial compartment are a histologically heterogeneous group of tumours. They include ependymal tumours arising from ependymal cells and subependymal glial plate, central neurocytomas from the septum pellucidum, and choroid plexus papilloma (CPP) and carcinoma (CPC) from the choroid plexus.[1] Ependymal tumours including ependymomas, subependymomas, and subependymal giant cell astrocytomas (SEGAs) account for about 1.6–1.8%, whereas choroid plexus tumours account for 0.2% of all primary tumours of the central nervous system (CNS).[2] Any intracranial tumour may have an intraventricular location. Some common IV lesions include colloid cysts, craniopharyngiomas, pituitary adenomas, and arachnoid cysts. Glial as well as metastatic tumours may secondarily involve ventricles. Intraventricular meningioma, although an uncommon form of intracranial meningiomas (0.5–3%), is one of the common IV tumours.[3]

The ventricular system is one of the most challenging territories for neurosurgery. Recent technical advancements and microsurgical expertise have revolutionised surgical corridors. However, dealing with intraventricular pathologies still poses substantial challenges, and surgical morbidity remains an added factor affecting patient outcomes.

In low- and middle-income countries (LMICs), where healthcare disparities are noticeable in managing brain tumours, the challenges of addressing intraventricular tumours are even more pronounced. Practicality and working dynamics in LMICs must be addressed separately to ensure a safe approach and standardized outcome. We proposed these guidelines by incorporating the most up-to-date evidence-based practices and reflecting the unique challenges faced by patients and healthcare providers in LMICs.

Methodology

The literature search of the high-quality data on intraventricular tumours was done on different databases including PubMed, Google Scholar, Scopus, and Embase in October 2023. The most relevant and high-quality studies were analyzed to develop the evidence-based recommendations. An expert panel was convened consisting of specialists and leading experts within the field of neuro-oncology to identify the gaps in diagnosis and management of intraventricular tumours within Pakistan. This group was tasked with identifying best-practice recommendations and their application within

[1-2,4-10]Department of Neurosurgery, The Aga Khan University, Karachi, Pakistan. [3]Jumma Research Laboratories, The Aga Khan University, Karachi, Pakistan.
Correspondence: Syed Ather Enam **Email:** ather.enam@aku.edu

the context of Pakistan as an LMIC. Recommendations were collated, reviewed and debated regarding utility and evidence-based practices, in a process that has been previously detailed.[4]

Initial evaluation

The clinical presentation of IV tumours is often nonspecific such as headache, gait abnormalities, and cognitive deficits; usually caused by hydrocephalus (HCP) and/or the tumour mass leading to increased intracranial pressure.

Ependymal tumours

All ependymal tumours appear iso- to hypointense to white matter on T1, whereas on T2 they appear hyperintense to surroundings. Gadolinium contrast shows heterogeneous enhancement in ependymomas, no to mild enhancement in subependymomas (larger lesions may be heterogeneous), and marked enhancement in SEGAs. Ependymomas are also more common in paediatric populations, subependymomas may be seen in adults and older children. SEGAs are seen only in young patients following tuberous sclerosis.[5-8]

Ependymomas commonly occur in the fourth ventricle. However, 30% arise from the surfaces of the lateral ventricles or the septum pellucidum.[9] Grade II tumours have a greater incidence of calcification than Grade III ependymomas, and cystic components may be present in both.[10]

Subependymomas commonly occur in the lateral ventricles (44.5%), followed by the fourth ventricle (43.1%) foramen of Monro (6.2%), and rarely the third ventricle.[11] They typically have a diameter of less than 1-2 cm. If large they may also contain cystic or calcific components.[11]

SEGAs are differentiated from subependymomas predominantly based on size. Subependymal nodules transform into SEGAs over some time and are usually seen as an IV mass near the foramen of Monroe. Calcification, haemorrhage, and/or accompanying HCP may be present. Contrast often shows marked enhancement7. Subependymal nodules and SEGAs are distinguished based on the potential for growth and mass effect.[5]

Ependymomas can manifest as either a cohesive mass or a combination of solid and cystic growth patterns. Magnetic resonance (MR) spectroscopy typically shows increased choline levels and diminished N-acetyl aspartate levels in ependymomas, while sub-ependymomas show a regular choline peak and reduced N-acetyl aspartate peak.[7, 9] Grade 3 ependymomas show restricted diffusion on DWI/ADC.[6, 9]

Central neurocytomas

Central neurocytomas are common around the foramen of Monro (50%), followed by lateral and 3rd ventricles (15% each), and 3rd ventricle (5%).[5] On CT scan they are hyperattenuating compared to white matter. Cystic region and /or calcification are frequently present. Contrast enhancement is usually mild to moderate.[5, 6]

On T1-weighted imaging, the lesion displays an uneven isointense lesion, while on T2/FLAIR sequences, it appears either similar or brighter in intensity. T2-weighted images may also reveal cystic regions, giving rise to a bubbly or Swiss cheese-like appearance, with some of these areas showing reduced intensity on FLAIR images. Diffusion-weighted imaging (DWI) indicates restricted diffusion in the solid portions of the lesion. Magnetic resonance spectroscopy (MR spectroscopy) could indicate a prominent choline peak. Angiography reveals a tumour blush supplied by choroidal vessels.[12, 13]

Choroid plexus tumours

Choroid Plexus tumours including Choroid Plexus Papilloma (CPP) and Choroid Plexus Carcinoma (CPC) are vividly enhancing IV masses. They are common in the fourth ventricle, and in the lateral ventricles in children: with a predilection for the trigone. HCP is more likely with CPP than CPCs. They appear iso to hyperdense on non-contrast CT. On MRI sequences they appear iso to hypointense on T1, and iso to hyperintense on T2 MRI sequences.

CPPs present as clearly defined, lobulated masses that exhibit uniform enhancement upon contrast administration. They often display an irregular frond-like pattern (cauliflower-like appearance). In contrast, CPCs are tumours characterized by heterogeneous enhancement, often featuring distinct regions of necrosis and cystic formation. Around 25% of CPP cases show speckled calcification. Angiography reveals a pronounced vascular blush, with the tumour supplied by enlarged choroidal arteries.[6, 14, 15]

Meningioma

IV meningioma originates from the stroma of the choroid plexus, a normal location for arachnoid cells that give rise to these tumours.[16] It arises from a region where arachnoid cells are found secondary to the embryonic origin of the choroid plexus. As with most intracranial meningiomas, those located in the ventricles are benign WHO-grade I tumours in 90% of cases.[17] They account for up to 5% of all IV tumours.[17-18] Their most common location is the atrium of the lateral ventricle, followed by

the trigone of the lateral ventricle.[17]

These are slow-growing lesions, typically found incidentally in radiology. The usual clinical presentations include headache or signs and symptoms of hydrocephalus or visual impairment. On MRI brain, they appear as well-circumscribed, mostly solid lesions, iso- or hypo-intense on T1 and T2 weighted images, and show homogenous contrast enhancement. CT angiogram or digital subtraction angiography (DSA) provides information about the blood supply, which can occasionally be embolised. IV meningiomas usually receive blood supply from the anterior choroidal artery, but larger lesions also receive supply from the posterior choroidal artery. The venous drainage is into deep ventricular veins.

Differentials and diagnostic challenges in LMICs

Other than primary IV tumours, other differential diagnoses of IV lesions may be IV meningiomas (most common), medulloblastoma, teratomas, gliomas (oligodendroglioma, pilocytic astrocytoma) cystic lesions, and IV metastases. IV meningioma appears as a well-circumscribed mass (isodense and isointense to grey matter) with homogeneous contrast enhancement, most commonly in the trigone of the lateral ventricles.[19] In children, almost one-fifth of all meningiomas occur within the ventricular system. In these patients, Neurofibromatosis should be always suspected.[19] Astrocytomas are frequently observed in the paediatric population but have also been identified in young adults. They predominantly affect the cerebellar hemispheres, although involvement of the foramen of Monro is possible. On CT scans, they present as either cystic or hypodense solid masses. When viewed on MRI, they can be challenging to differentiate from an intraventricular meningioma.[22] Medulloblastomas, the most prevalent malignant brain tumours among children, originate from the midline and are typically situated in the posterior fossa. These tumours often occupy the fourth ventricle and are commonly found within the cerebellar vermis, with an occurrence rate of approximately 67%-93%.[21] IV teratomas manifest as heterogeneous masses with areas of both low attenuation (attributable to fat content) and high attenuation reflecting calcifications. On MRI, they manifest as irregular, lobulated masses with a hypointense signal. Metastatic lesions from various primary cancers such as renal cell carcinoma, lung carcinoma, melanoma, gastric carcinoma, colon carcinoma, and lymphoma can also occur within the atrium of the lateral ventricle.[20]

There are multiple factors attributing to delayed diagnosis of such tumours in LMIC. Late presentation to a tertiary care center or good clinicians leading to delay in seeking neurosurgical care, limited resources to be able to get a good quality contrast MRI, and lack of neuro-radiologists to accurately describe such lesions and narrow down the differentials are among few challenges faced in LMIC.

Histopathology and molecular markers ependymal tumours

The WHO-CNS5 divides supratentorial ependymomas into ZFTA (RELA) fusion-positive and YAP1-MAMLD1 fusion. In 17-30% of cases, both these alterations are absent. In situations where different genetic mutations are identified, the term "NEC" (Not Elsewhere Classified) can be employed.[22, 23]

Subependymomas, classified as grade I tumours, arise from the subependymal glial layer with low cellularity and no mitoses, no necrosis, and are hypovascular. Loose perivascular pseudorosettes are occasionally seen.[5] Subependymoma cells express GFAP, whereas EMA is usually negative.[24]

SEGA cells that appear astrocytic, usually resemble with a lesser amount of ganglionic-appearing giant pyramidal-like cells. They are of a mixed neuronal and glial lineage arising from subependymal nodules in the ventricular wall of patients with tuberous sclerosis. SEGAs are S100 positive. GFAP, synaptophysin, class III beta-tubulin, NeuN, and SOX2 are variable. CD34 is negative.[24]

Central neurocytomas

Central neurocytomas, categorized as grade II tumours, exhibit a delicate grey hue and a friable texture. They may display instances of calcification and haemorrhage. On microscopy, the cells appear uniform and round, with a chromatin pattern resembling salt and pepper, finely speckled.[24] Immunohistochemically, central neurocytomas typically exhibit positivity for synaptophysin, NeuN, neuron-specific enolase, and MAP2, as well as class III beta-tubulin, whereas GFAP, IDH-1, and R132H are absent.

Choroid plexus tumours

CPPs, designated as WHO grade I lesions, are characterized by minimal mitotic activity (less than 2 mitoses per 10 high-power fields). Their appearance closely resembles normal choroid plexus tissue, taking on a cauliflower-like structure. Under a microscope, they showcase papillary formations with a delicate fibrovascular core. These papillae are lined by columnar or cuboidal epithelial cells featuring vesicular basal nuclei. In

terms of immunohistochemistry, cytokeratins (particularly CK7) and vimentin tend to be positive, while transthyretin is usually positive as well. The expression of S100 protein varies, and KIR7.1 is typically positive and specific.[24]

On the other hand, CPCs are categorized as grade III tumours that typically originate de novo, although there are rare instances where they can emerge as a malignant transformation of a CPP. CPCs appear as lobulated masses with areas of cyst formation and necrosis. Microscopically, the diagnosis of CPC is established when at least 4 out of 5 of the following features are present: an elevated mitotic rate (more than 5 per 10 high-power fields), heightened cellularity, nuclear pleomorphism, necrosis, and distorted papillary structure. The presence of microcalcifications and haemorrhage may also be noted. Distinguishing CPC from CPP involves identifying brain parenchymal invasion. The immunophenotype of carcinomas is akin to that of CPP, although S100 and transthyretin are more likely to be negative. The p53 protein is positive in individuals with a TP53 mutation.[24]

Most of the centers in LMIC are usually only equipped with basic neuro-pathological stains and lack molecular laboratories to assist in accurately diagnosing these tumours according to the recent WHO tumour classification[24] which is now largely dependent on molecular and genetic features of every CNS tumour.

Meningioma

Among a wide range of histological appearances, the most common subtypes are meningothelial, fibroblastic, and transitional meningiomas. All of these tumours are positive for Vimentin, a non-specific marker. Other important stains include those for somatostatin receptor 2a, S100, Ki-67 and progesterone receptors.

Management

Depending upon the clinical condition, the patient should be under the joint care of a neurologist and neurosurgeon at a tertiary care center with the availability of a neuro-intensivist along with respective medical and surgical suites. A lot of centers in LMIC lack such institutes.

Surgical resection

The extent of resection (EOR) is the single most important prognostic factor for IV tumours. The aim is to achieve gross total resection (GTR), however, for patients with sub-total resection (STR) adjuvant therapy including radio- or/and chemotherapy may be beneficial. The choice of adjuvant therapy depends on the histologic diagnosis.

Surgical resection of IV tumours is particularly challenging as they are deep-seated lesions within the ventricles. The approaches to the ventricles might involve important fiber tracts and essential cortical areas. The surgical approach to IV tumours requires good anatomical precision to preserve the eloquent areas and white matter tracts. Several adjuncts have been used such as navigation systems, tractography, ultrasonic surgical aspirators, high-magnification microscopes, and endoscopes. In LMICs, the cost of these adjuncts limits their use. With deep anatomical knowledge of cortical, subcortical, and IV regions and thorough surgical planning comparable outcomes can be achieved.

The presence of symptomatic HCP may require CSF diversion either with endoscopic/external ventriculostomy or permanent ventriculoperitoneal shunt, before the surgical excision.[25] However, permanent CSF diversion should be deferred. CSF pathways in most of the patients after surgical clearance will be open and do not require CSF diversion. This can potentially avoid the list of complications and the cost related to shunts. Dilated ventricular systems also provide a flexible corridor for an endoscopic approach, thus necessitating restraint in performing CSF diversion for asymptomatic/non-urgent cases.

The learning curve for IV tumours is steep, emphasizing the importance for surgeons practicing in LMICs to carefully consider it. When deciding on the surgical approach, several factors such as tumour size and location, vascular supply, and dominance of the involved hemisphere are necessary to take into account.[26, 27, 28]

A variety of surgical approaches exist for such tumours. It largely depends upon the exact location of individual tumours and their radiological characteristics. Common approaches include the subtemporal route that serves as the primary lateral corridor for accessing the third ventricle, interhemispheric approaches to the lateral and third ventricles, and the transcortical route in cases of significant unilateral lesions located in the frontal horn, anterior lateral ventricular body, or the anterior upper region of the third ventricle. It is important to de-vascularize IV meningioma during early part of resection. Thus, a high parietal or low temporal transcortical approach is most appropriate for most tumours in the lateral ventricles. Because of the solid and firm tissue of meningioma, ultrasonic aspirator (CUSA) is beneficial for debulking/resection. A supercerebellar infratentorial approach of the velum interpositum can reach the posterior part of the third ventricle, while a trans-sylvian approach is more suitable for anterior lesions. For lesions in the medial and posterior part of the temporal horn, and

for lesions extending into the surrounding cisterns, the transcortical and trans-sulcal approaches offer a shorter trajectory and less temporal lobe retraction.[26-29]

Both rigid and flexible endoscopes enhance the visualization and navigation of ventricular anatomy, thus, minimizing cortical and subcortical disruption. Ventricular dilation caused by HCP ample space for endoscopic maneuvering. Endoscopic-assisted microsurgical techniques contribute to smaller craniotomies, less brain retraction, and a lower risk of white matter damage.[30, 31]

The potential complications include haemorrhage (IV, intraparenchymal, or epidural), meningitis and/or ventriculitis, memory disturbances, CSF leak, cranial nerve deficit, and hormonal disturbances.[31] The rate of complications varies from 0 to 25%.[31-33] The extent of resection is the most significant for the long-term prognosis of most tumours[34, 35,] therefore multiple surgical resections or 'second-look surgery' may be necessary in certain patients with incomplete resections and/or recurrent tumours.[36,37] The severity of complications dictates the post-operative course but may generally require hospital stay in high dependency or intensive care units which again is a significant problem in resource-constrained settings.

Radiotherapy

The role of radiotherapy for primary IV tumours is still evolving. Each case needs to be reviewed on an individual basis in the neuro-oncology tumour board. Very few centers in LMIC specialize in craniospinal radiotherapy and the availability of appointment dates could be a significant issue in such patients. High-grade tumours with partial resection should get priority due to the aggressive course of the disease.

The role of adjuvant radiotherapy in primary IV tumours is established in ependymomas.[38,39] For subependymomas, routine postoperative irradiation is not recommended, however, it can be considered for cases with symptomatic residual or recurrent tumours.[40, 41] Incompletely resected SEGA tends to regrow, thus stereotactic laser interstitial thermal therapy can be offered to selected cases for optimal outcomes.[42, 43] Central Neurocytomas with greater than 2% residual tumour are at higher risk of local recurrence.[44-46] For central neurocytomas with STR, postoperative adjuvant has shown favorable outcomes for overall- and progression-free survival.[46-50]

While GTR can lead to a cure for the majority of patients with Choroid plexus tumours, it's important to note that outcomes can be adversely influenced by factors like young age, IV location, and high tumour vascularization, irrespective of the histological grading.[51-54] SRS has proven beneficial for individuals dealing with small, deeply situated residual, and recurrent CPPs.[55]

Adjuvant radiation in paediatric patients with CPCS has been shown to improve survival in patients following STR, however, it is important to weigh the advantages of potential tumour control against the risks of delayed neurological consequences, especially in patients below the age of 3 years.[56] For individuals aged over 3 years and adults, the addition of adjuvant radiotherapy proves advantageous, particularly when craniospinal irradiation is indicated for cases involving drop metastases, leptomeningeal dissemination, and parenchymal infiltration. In the context of patients with CPCs where only STR was achieved, craniospinal radiation can contribute to improved overall survival (OS).[56]

Chemotherapy

The definitive role of chemotherapy for ependymomas is under investigation and lack consensus guidelines for their use. Most of chemotherapeutic agents are very expensive and usually not easily available. Neuro-oncologists should undertake a detailed discussion with the patient or their caretakers regarding the possible duration, side effects, and cost before prescribing them.

mTOR pathways inhibitors (Everolimus) are effective in reducing SEGA volume and seizures, thus are offered especially for small and asymptomatic, or unresectable tumours.[57-68] In Central neurocytomas, few case studies have discussed chemotherapy as adjunctive therapy to surgery and radiation. Numerous chemotherapeutic agents, such as etoposide, cisplatin, cyclophosphamide, topotecan, carboplatin, and ifosfamide, have been explored for their efficacy. However, there is a lack of consensus on the most effective combination of these agents.[69, 70] In, choroid plexus tumours, adjuvant chemotherapy, while its application is restricted, has the potential to deter recurrence and extend overall survival in CPPs.[71, 72]

Follow-up and prognosis

EOR is the single most important predictor of prognosis and is confirmed by the postoperative MRI scan. Routine surveillance neuroimaging and close clinical follow-up are required in all cases, with shorter intervals between scans in cases of patients with STR undergoing radio- or chemotherapy. In LMICs after an initial post-operative MRI, the subsequent imaging may be with CT scans.

Supratentorial ependymomas have 5- and 10-year OS) rates of about 57.1% ± 8.7% and 41.8% ± 9.9%, respectively. The 5- and 10-year PFS rates are about 33.8%

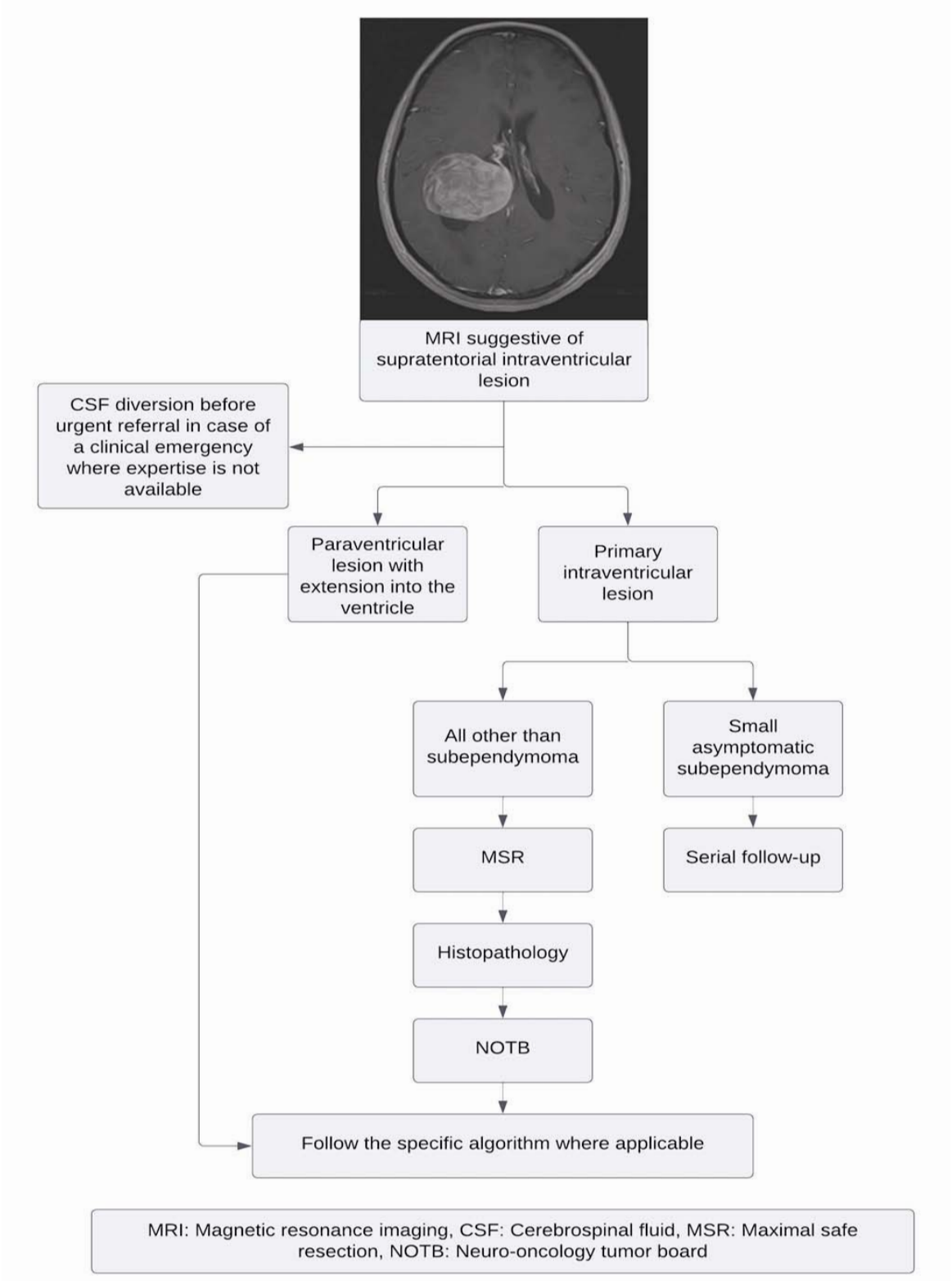

Figure-1: Management of Supratentorial Intraventricular Tumour algorithm.

Table-1: Summary of Recommendations for Supratentorial Intraventricular Neoplastic Lesion.

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, size, margins, enhancement pattern, presence of hydrocephalous, hemorrhage/mineralization. • Postoperative MRI is recommended and tailored to each pathology. For high it is recommended within 72 hours of surgery or after 6 weeks if delayed. For low-grade tumours, after 3 months. o To identify the extent of resection. o To have a baseline to compare successive imaging. o Not required after biopsy.
Neurosurgery	• CSF diversion before urgent referral in case of a clinical emergency where expertise is not available. • Maximal safe resection with preservation of critical neurovascular structures. • Intra-op EVD at the end of surgery is recommended.
Neuropathology	• Haematoxylin and eosin (H&E) preparation for histological typing. • Relevant immunohistochemical stains for definite characterization based on the histology of the tumour.
Medical and Radiation Oncology	• Tailored approach for each pathology after discussing in NOTB.
Follow-up	• First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology and NOTB recommendations. • Clinical follow-up with MRI tailored to histopathological diagnosis.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, CSF: Cerebrospinal fluid, EVD: Extraventricular drain, NOTB: Neuro-Oncology tumour board.

± 8.1% and 25.4 ± 8%, respectively. Ages younger than 55, greater EOR, and lower histologic grade are associated with improved OS and PFS.[73]

Subependymomas have an overall 5-year survival rate of about 89.2% and a recurrence rate of 1.3% (follow-up ranging from 15.3 to 120.0 months).[11] Age, tumour size, and postoperative radiation therapy are not predictors of prognosis.[11] Female gender, GTR, and location within ventricles or near the brainstem are associated with improved prognosis.[74]

Central Neurocytomas have a 2-year PFS of 75 %, tumour volume ≥30 cm3, STR, and a high mitotic count (≥3 per 10 high-power fields) are risk factors for recurrence.[75, 76]

CPPs have 1-, 5-, and 10-year OS rates of 92 ± 1.5%, 87 ± 1.9%, and 82 ± 2.7%, respectively.[77] The OS can increase to 100% in patients with complete resection.[78] Following STR, 50% of CPP patients may require a subsequent resection for recurrence.79 Increased mitotic activity is the sole atypical histological characteristic that is distinctly linked to recurrence. 79 CPC has OS of 51 ± 3%, 34 ± 4%, and 25 ± 4% after 1, 2, 5, and 10 years respectively. [78] GTR and adjuvant radiotherapy are associated with better prognosis in CPC, whereas chemotherapy can improve outcomes in both STR and non-irradiated tumours. [78]

Conclusion

Designed to aid healthcare professionals working in regions with constrained resources, these recommendations provide a pragmatic structure drawn from valuable observations (see Table 1 and Figure 1). Implementing these recommendations has the significant potential to improve particular results and promote increased emphasis on cooperative healthcare in low- and middle-income countries (LMICs), such as Pakistan.

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