NARRATIVE REVIEW

Consensus guidelines for the management of pineal region tumours for low- and middle-income countries

Saqib Kamran Bakhshi[1], Naureen Mushtaq[2], Rabeet Tariq[3], Moeez Tariq[4], Asim Hafiz[5], Ahmed Gilani[6], Hafiza Fatima Aziz[7], Muhammad Shahzad Shamim[8], Altaf Ali Laghari[9], Kaynat Siddiqui[10]

Pakistan Brain Tumour Consortium: (Authors list at the end of the supplement), Syed Ather Enam[11].

Abstract

Pineal region tumours are rare and mainly arise at a younger age. They can be categorized into various types: germ cell tumours (GCT), pineal parenchymal tumours (PPT), meningiomas, gliomas, pineoblastoma, pineal parenchymal tumours of intermediate differentiation, papillary tumours of the pineal region, and SMARCB1-mutant desmoplastic myxoid tumour. Within GCT, germinomas are the most prevalent, comprising the majority of tumours in this region, while non-germinomatous GCTs are also present. In rare instances, metastases from other sites may manifest. These tumours often lead to obstructive hydrocephalus and commonly exhibit symptoms related to mass effect, including headache, nausea, vomiting, and impaired gait stability. Different subtypes of pineal region tumours exhibit distinct radiological characteristics, thus imaging remains the primary diagnostic tool. Histologic diagnosis necessitates biopsy, unless in cases of germ cell tumours, particularly germinomas, which can be identified through elevated levels of tumour markers like alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) in both cerebrospinal fluid (CSF) and serum. While benign tumours might be effectively treated with radical resection alone, malignant tumours demand additional chemotherapy and radiotherapy following surgical removal.

Keywords: Pinealoma, alpha-fetoproteins, meningioma, germinoma, chorionic, gonadotropin, hydrocephalus, headache, vomiting, glioma, biopsy, nausea, gait, tumours.

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[1,7-11]Department of Neurosurgery, The Aga Khan University, [2]Department of Paediatric Oncology, The Aga Khan University, [3]Jumma Research Laboratories, The Aga Khan University, [4]Dow Medical College, [5]Department of Radiation Oncology, The Aga Khan University Hospital, Karachi, Pakistan. [6]Department of Pathology, University of Colorado, Children's Hospital Colorado, USA

Correspondence: Naureen Mushtaq **Email:** naureen.mushtaq@aku.edu

Introduction

The pineal region harbours various tissues, making it susceptible to a diverse group of tumours. Pineal neoplasms are rare, representing 3%-11% of childhood neurological malignancies, and less than 1% of adult brain tumours.[1] The tumours of the pineal parenchyma include pineocytoma, pineoblastoma, pineal parenchymal tumour of intermediate differentiation (PPTID), and papillary tumour of the pineal region (PTPR).[2] The WHO CNS5 recently incorporated the SMARCB1-mutant desmoplastic myxoid tumour of the pineal region.[2] Germ cell tumours (GCT) are the most frequent primary tumours of the region, with germinomas comprising 73%-86% of all tumours.[1] Other less common forms of GCT include benign lesions such as dermoid tumours, epidermoid tumours, and teratomas; and malignant tumours such as choriocarcinomas, embryonal carcinomas, and endodermal sinus tumours.[3,4] These can be classified into non-germinomatous GCT. Other lesions may include cysts[5,6,] meningiomas, ependymomas, astrocytomas, and metastases.

Methodology

The literature search of the high-quality data on pineal region tumours was done in March 2023 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. An expert panel was convened consisting of specialists and leading experts within the field of neuro-oncology to identify the gaps in the diagnosis and management of pineal region tumours within Pakistan. This group was tasked with identifying best-practice recommendations and their application within Pakistan as an LMIC. Recommendations were collated, reviewed, and debated regarding utility and evidence-based practices, in a process that has been previously detailed.[7]

Initial evaluation

Pineal tumours may present with mass-effect symptoms such as headache, nausea, vomiting, and gait instability which are often due to obstructive hydrocephalus causing a raised intracranial pressure.[3,8] As the pineal gland is close to the hypothalamus, compressive hypothalamic syndromes like diabetes insipidus can occur.[3] Hypopituitarism, extra-pyramidal signs, and hemi-syndromes can also be observed.[9] Up to 76% of patients present with Parinaud's syndrome due to mid-brain compression.

Intracranial choriocarcinoma, primarily in the pineal gland can present with precocious puberty. Apart from this, choriocarcinomas do not show distinct symptoms, other than those mentioned above.[3] Large pinealocytomas may induce Parinaud syndrome; which presents as an upward gaze palsy, convergence retraction nystagmus, and pupillary light-near dissociation.[3,8]

Neuroradiology

Neuroimaging serves as the primary method for diagnosing pineal tumours as this distinguishes not only the benign growths from malignant ones but also differentiates the tumours arising from adjacent areas.[10]

Konovalov and Pitskhelauri (2003) divided the tumours of the pineal region into five groups based on neuroimaging i.e., MRI and CT analysis; focusing on the size, expansion, and the tumours' interaction with neighbouring structures[11] as described in Table 1.

Table-1: Classification of Pineal region tumours based on size.

Tumour Group	Tumour extension	Tumour size
Small	Quadrigeminal cistern	< 2.5 cm
	Posterior third ventricle	< 2.5 cm
Medium	Posterior third ventricle and quadrigeminal cistern	< 4 cm
Large	The pineal region with expansion into lateral ventricles	> 4 cm
Giant	Whole third ventricle, fourth ventricle, and lateral ventricles	> 6 cm

Different classes of pineal region tumours give distinct radiological appearances. Table 2 describes the relevant CT, MRI, and MR spectroscopy (MRS) findings in all the primary pineal tumours.[9,12,13]

Tumour markers

Alpha-fetoprotein (AFP), human chorionic gonadotropin (β-hCG), placental alkaline phosphatase (PLAP), human placental lactogen (HPL), and lactate dehydrogenase (LDH) are considered tumour markers for GCTs, and are useful in for the diagnosis and the measuring the response to treatment. An increase in AFP (either serum or CSF) greater than 10 ng/ml and βhCG greater than 50 mIU/ml is considered marker-positive.[14] Germinomas are associated with elevated β-hCG, LDH, and PALP; however, elevated β-hCG levels in germinomas are not consistent and are associated with a poor prognosis. Elevations in CSF and serum AFP alone are found in pure endodermal sinus tumours, whereas increase of both hCG and AFP are found in embryonal carcinoma, and an increase in hCG alone is found in choriocarcinoma.[15,16] Table 3 summarizes the known serum markers of pineal GCTs.

Currently, no tumour markers are confirmatory for pineal parenchymal tumours; Melatonin, synaptophysin (Syn), and chromogranin are potential markers and are being investigated.[15,16] Other CSF and serum markers being investigated include human placental lactogen, octamer-binding transcription factor 4, cytokeratin, carcinoembryonic antigen, and c-kit (CD117).[16] Germ cell biomarkers may be more sensitive for diagnosis when compared to histopathology[17,] thus the need for a biopsy may be excluded in several cases.

Management

Treatment depends on histologic and molecular diagnosis. Benign tumours are cured by radical resection, whereas malignant tumours require adjuvant chemo- and radiotherapy.[11,14] Germinomas are an exception as they may be treated only with radiotherapy, which may or may not be combined with chemotherapy.[14,18,19]

Surgical intervention

The pineal gland is extra-axial and resides deep in the brain. Pineal region tumours may need surgical intervention for biopsy, or excision of lesion and CSF diversion (HCF). However, it is worth noting that bifocal tumours (pineal and suprasellar) with classical radiological features are pathognomonic for germinomas and may not require biopsy.

If CSF or serum markers are not positive for any malignant germ cell tumour, a biopsy is necessary for accurate histopathologic diagnosis to choose appropriate treatment modalities.[20] An open technique may allow maximal removal of the tumour, however, stereotactic biopsy is more feasible and less invasive, thus is the standard for biopsy of pineal region tumours.[20,21] Based on neuro-navigation, the surgical approach can vary, including orthogonal lateral, oblique anterolateral, or posterolateral approaches. However, the optimal trajectory is a low frontal approach that avoids the internal cerebral veins. For biopsies, the Nashold side-cutting biopsy needle is considered ideal. The procedure may be conducted under local or general anaesthesia

Table-2: Radiological Findings.

Tumor classification	CT findings	MRI findings	MRS findings
Germ cell tumours			
Germinoma	Hyper-attenuated circumscribed mass.	Solid mass, iso-high intensity to gray matter in T1WI and T2WI and homogenous post-contrast enhancement.A "butterfly" shaped structure on post-contrast axial cuts.	Consistent Tau is observation with increased Lip/Cr and Cho/NAA ratios.
Teratoma	Heterogenous mass with foci of low-fat attenuation. Strong heterogenous post-contrast enhancement.	High intensity foci on T1WI and T2WI depending on fat and protein components.	Increased Lip/Cr ratio on long-echo time and relatively lower total choline and creatine levels on single voxel short-echo.
Other GCTs	High densitymass of around 5 cm without calcification	Irregularly shaped, iso, low, or high intensity on T1WI, hyperintense on T2WI, homogeneous enhancement, and cystic components with perifocal oedema.Intra-tumoural haemorrhage is present in choriocarcinoma.	Insufficient data
Pineal parenchymal tumours			
Pineocytoma	Iso-hypoattenuating well-circumscribed lesions with mass effect.	Homogenous iso-signal T1WI and high signal T2WI lesions with robust contrast enhancement.	Insufficient data
Pineoblastoma	Large lobulated, slightly hypodense poorly demarcated homogenous mass.	Hypo-isointense heterogenous enhancing T1WI.	Increased Cho/NAA without lipid's peak and non-specific taurine peak.
PPTID	(Imaging features are same as in pineocytomas)	Total choline peak low as compared to creatine peak.	
PTPR	Cystic mass and mildly hyperdense soft tissue components without contrast enhancement.	Circumscribed lesions with T1WI, T2WI, and post-contrast enhancement. Protein inclusions can give hyperintense T1 signal.	Insufficient data
Desmoplastic myxoid tumour of Pineal region: SMARCB1 mutant	High-density lesion in the pineal area.	Slightly intense lesion on T1WI and mixed signal on T2WI.	Insufficient data

T1 weighted images: T1WI, T2 weighted images: T2WI, PPTID: pineal parenchymal tumour of intermediate differentiation, PTPR: pineoblastoma, and papillary tumour of the pineal region.

wherever indicated.[20] The endoscopic approach is commonly used for biopsies and may be performed via the transventricular route. It is considered a minimally invasive procedure; thus, it reduces the exposure of the functional region and minimizes the potential for complications, however, there is a significant risk of intraventricular bleeding and CSF dissemination of the tumour.[22]

Open microsurgical resection may be used for the resection of benign lesions, cytoreduction prior to adjuvant therapy, or in some cases a second-look surgery may be needed to remove residual tumours.[23] Although establishing a diagnosis with a biopsy followed by radiation and chemotherapy is a common practice, surgeons prefer direct radical open excision before establishing the diagnosis, for better outcomes regarding long-term recurrence-free survival in benign tumours [18,24–26], as well as provision of adequate samples for biopsy. The approach may be the infratentorial supracerebellar, occipital transtentorial, transcallosal interhemispheric, or transcortical transventricular.[27] The transient postoperative complications include impaired extraocular movements, pupillary dysfunction, and ataxia. Haemorrhage may occur in an incompletely resected tumour. Conservative management may be done for small haemorrhages; however, a large haemorrhage requires immediate evacuation. Venous infarct can also

Table 3: Serum markers.

Tumor	Serum marker
Germinoma	PLAP, CD117 (membrane labeling), Cytokeratin.Pure germinoma: OCT3/4 Germinoma with STGC: HPL, β-hCG.
Teratoma	AFP (if immature enteric type), Cytokeratin (low).
Choriocarcinoma	HPL, β-hCG, Cytokeratin.
Yolk Sac tumour	AFP, Cytokeratin
Embryonal cell carcinoma	PLAP, OCT ¾, CD30, Cytokeratin.

PLAP: Placental alkaline phosphatase, HCG: human chorionic gonadotropin, STGC: Syncytiotrophoblastic giant cells, AFP: Alpha fetoprotein, HPL: human placental lactogen hormone, OCT: Octamer-binding transcription factor .

occur and extend into the midbrain. Mortality is uncommon and may be due to brainstem manipulation, which can lead to cognitive impairments.[27] An endoscopic modification was introduced which allowed gross total resection (GTR) with decreased postoperative complications.[28]

Obstructive HCF is a common presentation of pineal tumours owing to the compression of the aqueduct of Sylvius. Endoscopic third ventriculostomy (accompanied by taking the biopsy samples) is the preferred strategy for management.[29-31] Ventriculoperitoneal shunting may be an alternative, however, it may harbour an approximate 5% risk of infection, metastasis, and malfunction.[23,32] Therefore, in the presence of HCP, endoscopic biopsy via the trans ventricular root should be considered, whereas, stereotactic biopsy may be used in its absence.

Pathological assessment

The normal pineal parenchyma is loosely lobular in appearance with 95% of cells being pinealocytes, the remaining are astrocytes, both being separated by fibrovascular stroma.[33,34]

Normal pinealocytes show robust positivity to Synaptophysin, Neurofilament (NF), and Rhodopsin (as pinealocytes are modified neurons related to rods and

Table-4: Morphologic patterns of the Pineal GCTs.

Germ cell tumours	Gross Morphology	Histo-pathology	Immuno-histo-chemistry
Germinoma	Well-circumscribed gray-pink tissue with complete obliteration of residual pineal gland	Two-cell populations present: Tumour cells (round to polygonal, central nucleus, clear cytoplasm, mitotic figures are seen but necrosis is rare, cells in sheets and large lobules with intervening stroma) and T-cells (forming granulomas mimicking intra-cranial sarcoidosis, STGCs may be present).	PLAP, β-hCG in tumour with STGC.
Teratoma	Large cystic mass	Mature teratoma presents with skin and adnexa from ectoderm, cartilage, muscle, bone, fat from mesoderm, and respiratory and enteric epithelium from endoderm. Mitotic activity is minimal or absent.Immature teratoma exhibits foetal tissue that has not fully differentiated.	AFP (immature teratoma)
Choriocarcinoma	Typically ovoid and well-defined mass with irregular infiltrating margins. and possible haemorrhage	Syncytiotrophoblast cells (vacuolated cytoplasm, multiple, pleomorphic, hyperchromatic nuclei with mitotic figures) and cytotrophoblastic cells (clear cytoplasm, round nucleus) are present.	β-hCG, HPL, cytokeratin 7.
Yolk Cell tumor	Large irregular mass	Small cells, prominent nucleus and mitotic figures.Schiller-Duval bodies present.	AFP
Embryonal Carcinoma	Gland-like aggregates with papillary projections	Polygonal or round cells with clear or eosinophilic cytoplasm.Mitotic figures and necrotic foci are present.	OCT4, PLAP, and CD30 positive and c-kit negative.

PLAP: Placental alkaline phosphatase, HCG: human chorionic gonadotropin, STGC: Syncytiotrophoblastic giant cells, AFP: Alpha feto-protein, HPL: human placental lactogen hormone, OCT4: Octamer-binding transcription factor 4.

Table-5: Morphology and histopathology.

Tumour classification	WHO Grade	Histopathology	Immunohis to chemistry
Pineocytoma	1	Two microscopic variants:Typical (displays well-differentiated cells with uniform cellularity, a diffuse or loosely lobular growth pattern, round or oval nuclei featuring 'salt and pepper' chromatin, the presence of pineocytomatous rosettes, and a scarcity of mitotic activity and necrosis)& Pleomorphic (hyperchromic bizarre nuclei and ganglionic elements, along with features of typical variant).	Syn, NF, Chromogranin A
Pineoblastoma	4	There is a presence of sheets composed of poorly differentiated cells. These cells have scanty cytoplasm, hyperchromatic nuclei with an elevated nuclear-to-cytoplasmic ratio. Additionally, there is the possibility of observing Homer-Wright rosettes (indicative of neuroblastic differentiation) or Flexner-Wintersteiner rosettes (indicative of retinoblastic differentiation).Mitotic bodies, foci of necrosis, and invasion of the adjacent tissue seen.	Syn, NF, Chromogranin A
PPTID	2 or 3	Features intermediate between pineocytoma and pineoblastoma. Sheet-like architecture, monomorphic round cells	Strong Syn staining, variable NF, negative for NeuN
PTPR	2 or 3	Similar to epithelial tissue, displaying varying degrees of papillary features alongside solid regions. Perivascular rosettes are also present. The cells have round to oval nuclei and eosinophilic cytoplasm. Mitotic activity and necrosis are observed within the tumour.	Cytokeratin (particularly CK-18), vimentin, S100
Desmoplastic myxoid tumour of Pineal region: SMARCB1 mutant	To be decided	Cord-like structures comprising small to medium-sized oval to spindled and epithelioid cells. These cells are surrounded by a matrix rich in collagen. Occasional calcifications might be observed, but instances of mitotic activity and necrosis are rare.	Loss of nuclear SMARCB1 (INI1) expression. Epithelial membrane antigen and CD34

PPTID: pineal parenchymal tumor of intermediate differentiation, PTPR: pineoblastoma, and papillary tumor of the pineal region, NF: Neurofilament, Syn: synaptophysin: SMARCB1: SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily B.

cones).[8, 34] The interstitial cells show the expression of Glial Fibrillary Acidic Protein (GFAP) and S100 protein (S-100P). [34]

Important differentials include differentiating pineocytoma from normal pineal or pineal cyst (normal pineal gland does not show pineocytomatous rosettes); differentiating pineoblastoma from medulloblastoma (pineal vs posterior fossa location) and atypical teratoid rhabdoid tumour (SMARCB1/ INI-1 loss should be ruled out in pineoblastoma). As mentioned above, germ cell neoplasms are frequent and should be considered by pathologists.

Younger populations are mainly affected by aggressive variants, whereas older individuals usually have benign tumours. [34] The morphologic patterns of the main pineal GCTs are described in Table 4.[33–36]

The morphologic, histopathologic, and immunologic details of pineal parenchymal tumours along with their respective WHO grades are shown in Table 5.[2]

Molecular markers and cytogenetics

Several genes are involved in molecular and cytogenetic techniques to diagnose pineal gland tumours. mRNAs for the enzymes required to synthesize melatonin including Tryptophan hydroxylase (TPH), serotonin N-acetyl transferase (SNAT), and Hydroxyindole O-methyl transferase (HOMT) are found in cells of pineocytomas.[33,37]

In pineoblastomas, seven specific genes expressed which have a role in cellular growth (HOXD13, Hist1H4E, POU4F2, PITX2, Hist1H3D), junctional modification (DSG1) and resisting cellular senescence (TERT).[38] Methylation analysis categorizes pineoblastomas into four distinct molecular subgroups: Pineoblastoma with disrupted miRNA processing (Type 1) in paediatric patients, Pineoblastoma with altered miRNA processing (Type 2) in older children (both marked by mutations in DROSHA, DICER1, or DGCR8), Pineoblastoma driven by MYC/FOXR2 activation in infants, and Pineoblastoma with RB1 alterations in infants.

Analysis of four specific genes using real-time reverse transcriptase PCR (PRAME, CD24, HOXD13, and POU4F2) in PPTID effectively distinguishes between low-grade and high-grade PPTIDs. The expression of these genes is notably higher in the latter category. 38 In the context of diagnosing PPTID, the presence of KBTBD4 in-frame insertions is a significant diagnostic criterion.[2]

A hypothesis suggests the origin of papillary tumours of the pineal region can be traced back to the sub-commissural organ.33 This theory is supported by a cDNA microarray study, which revealed elevated expression levels of specific genes (ZFH4, RFX3, TTR, and CGRP) known to be active in the sub-commissural organ. [38]

In all instances of desmoplastic myxoid tumours in the pineal region, there is a consistent loss of nuclear SMARCB1/INI1 protein expression.[35] Notably, the DNA methylation profiles observed in these reported cases show clustering patterns that are closely associated with AT/RTMYC and poorly differentiated chordomas.[39]

It is worth noting that all molecular and cytogenetic studies may not be feasible for LMICs as they do not significantly change the management plan.

Radiotherapy

Radiotherapy is an integral component in the management of pineal region tumours. The response to radiotherapy depends on the histological diagnosis e.g., germ cell origin or pineal parenchymal tumours.[40]

For pineal region germ cell tumours RT is essential for curative treatment. Because GCT is not as common in adults, therefore, the adjuvant therapy strategies are primarily informed by data derived from studies conducted on paediatric and adolescent populations. These approaches encompass various treatment volumes, including craniospinal irradiation (CSI), whole-brain irradiation (WBI), whole ventricular irradiation (WVI), or involved-field radiotherapy (IF-RT) targeting the tumour site. The determination of treatment volumes and dosage prescriptions is personalized based on factors such as histological subtypes, disease extent, the integration of chemotherapy, and the patient's response. An important goal of contemporary treatment technologies including volumetric-modulated arc therapy (VMAT) and intensity-modulated radiotherapy (IMRT) is to decrease the risk of long-term complications by reducing radiation doses to non-target brain areas.

Surgery is the main modality to deal most pineal parenchymal tumours. For low grade tumour like pineocytoma and grade 2 pineal parenchymal tumours radiotherapy is indicated if disease is unresectable or complete resection is not possible.[41] However, high grade tumour requires adjuvant radiation due to high risk of recurrence as studies have shown improved local control leading to better survival.[42, 43] Radiation treatment volumes depends upon MRI spine and CSF cytology finding and range from craniospinal irradiation in case of CSF dissemination to focal radiotherapy for localized disease. Owing to their low incidence in adult, the appropriate treatment for pineoblastomas is not established and usually derived from paediatric treatment protocol has shown a positive outcome.[44] The response of radiotherapy in pineoblastomas is better in older patients and those who undergo surgery.[45] Radiation doses of 24-36 Gy to the entire neural axis followed by tumour bed /tumour boost to 54-60 Gy in 1.8-2 Gy fraction have been described.[46]

Recently stereotactic radiation therapy/radiosurgery is increasingly being used due to high precision, desired dosimetry profile, and low morbidity for small residual or recurrent tumours.[47–49]

Chemotherapy

Chemotherapy has been shown to be highly effective in treating germinomas. In a phase-II trial evaluating neoadjuvant chemotherapy, the combination of carboplatin and radiotherapy exhibited significant activity in effectively treating newly diagnosed CNS germinomas, mainly in the pineal gland.[50] A chemotherapy regimen consisting of cisplatin and etoposide; or ifosfamide, cisplatin, and etoposide showed an excellent response.[51] The response to the same regime was also used to differentiate germinomas from germinoma-like and other tumours.[52] Shrinkage of non-germinomatous GCTs in children by chemotherapy with bleomycin, etoposide, and cisplatin before and after subtotal resection was reported.[53] with no deficits or recurrences.[54] Kellie SJ et al. assessed a regime including cyclophosphamide, etoposide, cisplatin, and bleomycin followed by two courses of etoposide, carboplatin, and bleomycin if patients had complete remission.[55]

Cisplatin, vinblastine, and/or bleomycin have been effective for pineal parenchymal tumours when combined with radiation.[56] Neoadjuvant chemotherapy with etoposide, cisplatin, and vincristine was effective in children with pineoblastoma aged 3-7 years, however, mild myelosuppression and mild to moderate high-frequency sensorineural hearing loss were the adverse effects.[57] Cyclophosphamide, vincristine, cisplatin, and etoposide were assessed and failed for the management of infant pineoblastomas.[58] There has been a case of PTPR being treated successfully with Temozolomide.[59]

Follow-up

Follow-ups include clinical evaluation, imaging, and biomarker monitoring for the assessment of treatment

Table-6: Summary of Recommendations for Pineal Tumours

Radiology	• Complete MRI brain and spine study is needed. • 'Minimum required' MRI brain 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, tumour size, and presence of haemorrhage/mineralisation. • Postoperative MRI is recommended within 72 hours of surgery. If delayed, then MRI should be performed after 6 weeks. o To identify the extent of resection. o To have a baseline to compare successive imaging. o Not required after biopsy.
Neurosurgery	• Surgical goals: Resection of tumor and opening of the CSF pathway, if needed. • Gross total resection should be attempted where possible. However, in case of tumour adherence to the surrounding critical structures, maximum safe resection should be performed. • Abstain from VP shunt as a temporising procedure unless there is a significant risk of deterioration due to hydrocephalus. Consider referring the patient to a facility where surgical resection can be done along with CSF diversion (EVD/VPS/ETV) if needed.
Neuropathology	• Haematoxylin and Eosin (H&E) slides for histological typing. • Immunohistochemical stains GFAP, Olig-2, EMA, p-53, SALL4, OCT3/4, pan-cytokeratin, Ki-67 (proliferative marker) and INI-1 for possible definite characterisation of these tumours.
Paediatric Oncology	• Germinomas: Carboplatin and etoposide. • Non-germinomatous: Cisplatin, etoposide, and Ifosphomide. • Pineoblastoma: Cisplatin, vincristine, and cyclophosphamide (treated as high-risk medulloblastoma).
Radiation oncology	• Advanced radiation treatment technologies such as volumetric-modulated arc therapy [VMAT], and intensity-modulated radiotherapy [IMRT] are recommended to reduce the risk of long-term toxicity. • Pineoblastoma: Treated on lines of High-Risk Medulloblastoma with Craniospinal Irradiation (36 Gy) and a tumour bed boost to 54 Gy. • Germinoma & NGGCT: Radiation treatment volume and dose depend upon the extent of residual disease at the time of radiation therapy and metastasis.

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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 every 3 months with pediatric oncologist.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, CSF: Cerebrospinal fluid, EVD: External ventricular drain, VPS: Ventriculoperitoneal shunts, ETV: Endoscopic third ventriculostomy, H&E: Hematoxylin and eosin, GFAP: Glial fibrillary acidic protein, EMA: dotlike epithelial membrane antigen, SALL4: Sal-like protein 4, OCT3/4: Octamer-binding transcription factor 3/4, VMAT: Volumetric modulated arc therapy, IMRT: Intensity-modulated radiation therapy, Gy: Gray, NGGCT: non-germinoma germ cell tumours, NOTB: Neuro-oncology tumour board.

outcomes. Radiologic assessment is necessary to assess the EOR and/or the response to chemo- or radiotherapy. A decrease in biomarkers corresponds to a positive response to the given treatment, whereas static or increasing levels of biomarkers show treatment failure.

Prognosis

Germinomas, although considered malignant, have the best prognosis and five-year survival of 90% due to a positive response to radiotherapy.[60, 61] Choriocarcinomas have the lowest survival rate in all GCTs due to frequent haemorrhages and progressive extra-neural and CSF metastasis, with elevated levels of hCG as a marker of poor prognosis.[62] Teratomas have a good prognosis with complete resection.[16] Highly malignant GCTs include choriocarcinoma, embryonal carcinoma, and yolk sac tumour which have a three-year survival of only 27.3%; mixed-tumours with a three-year survival of 9.3%.[36] Overall good prognostic group of germinomas includes germinomas and mature teratoma; the intermediate prognostic group includes immature teratoma; and the poor prognostic group consists of teratoma with malignant transformations, yolk sac tumours, choriocarcinoma, and mixed GCTs consisting of a component with malignant transformation. [36]

Pineocytomas[63] and pineoblastomas[64] are associated with extremely poor outcomes.[65,66] Smaller age and metastasis are the risk factors.[66,67] PTPRs have a 5-year survival rate of 73% and progression-free survival rate of 27% due to frequent local recurrences.[68]

Conclusion

Designed for doctors practicing in areas with limited resources, these guidelines offer a practical guide informed by valuable expertise (refer to Table 6 and Figure 1). Applying these guidelines could substantially enhance specific outcomes and promote a greater focus

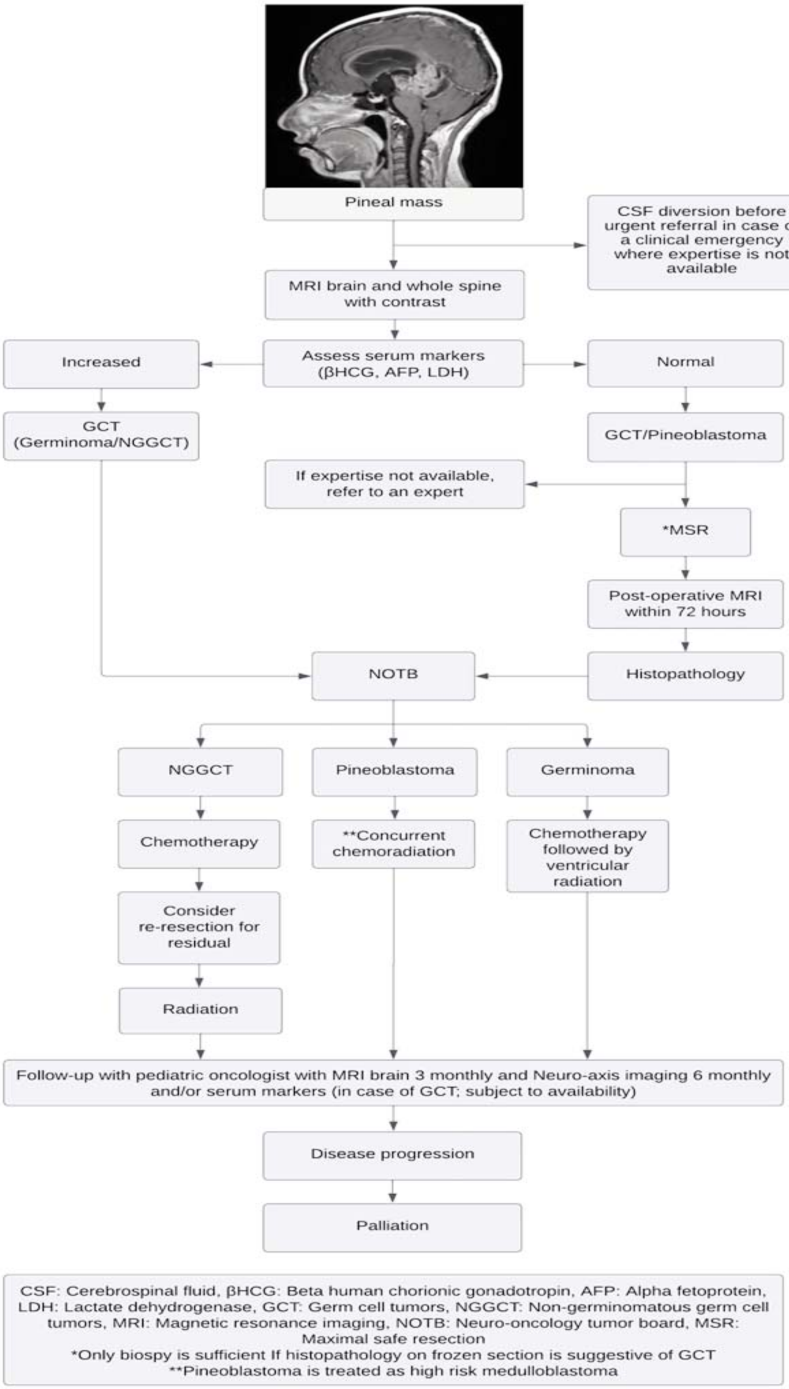

Figure-1: Management of Pineal region tumours algorithm.

on collaborative care in low- and middle-income countries (LMICs) like Pakistan.

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