Chapter

An Overview of Pediatric CNS Malignancies

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Abstract

Central nervous system tumours are the most common solid tumours and second most common malignancy in pediatric age group. They are the leading cause of cancer related morbidity and mortality. It accounts for 3.5% of all deaths in the 1–14 years age group. Childhood central nervous system (CNS) tumors differ significantly from adult brain tumors in reference to their sites of origin, clinical presentation, tendency to disseminate early, histological features and their biological behaviour. Supratentorial tumors are more common in infants and children up to 3 years of age and again after age 10, whereas between ages 4 and 10 infratentorial tumors are more common. The initial workup of patients with brain tumors must include a complete history, physical examination, imaging and biopsy confirmation of primary. The management of pediatric brain tumours is important due to their high incidence, challenging aspects of surgery and high mortality. Many CNS malignancies, which were once universally fatal are now curable with multimodality approaches that integrate surgery, chemotherapy and radiotherapy. In this chapter, we will discuss these issues in detail and summarize the ongoing efforts to reduce the morbidity and mortality in pediatric CNS tumours.

Keywords: CNS, pediatric, adjuvant, radiation therapy

1. Overview

Tumors of the central nervous system are the most common solid tumors in the pediatric age group and the second most common childhood malignancy. They are the leading cause of morbidity and mortality associated with cancer. Although it affects all ages, the incidence peaks among children between the ages of 3 and 7. In adults and older children, most tumours are supratentorial in location while in young children they are more commonly infratentorial in location [1].

2. Incidence

The incidence of childhood CNS tumor varies from 1.12 to 5.14 cases per 100,000 individuals [2]. Based upon data from the Central Brain Tumor Registry of the United States (CBTRUS), the estimated incidence of primary non-malignant and malignant CNS tumors for children and adolescents up to 19 years of age was 7.18 cases per 100,000 person-year in 2016 [3]. More than 100 different

Location	Tumor type	Relative frequency (%) in 0–17 years old
Supratentorial	Pilocytic astrocytoma	23.5
	Fibrillary astrocytoma	5
	Ganglioganglioma	2.5
	Dysembryoplastic neuroepithelial tumor	0.6
	Desmoplastic infantile ganglioglioma	0.6
	Choroid plexus papilloma	0.9
	Ependymoma	3.8
	Anaplastic ependymoma	3.8
	Anaplastic astrocytoma	7.2
	Glioblastoma	7.2
	Supratentorial PNET	1.9
	Choroid plexus carcinoma	0.6
Posterior fossa	Medulloblastoma	16.3
	ATRT	1.3
	Pilocytic astrocytoma	23.5
	Ependymoma	3.8
	Brainstem glioma	10–20
Pineal tumours	Germ cell tumour	2.5
	Pineal parenchymal tumour	1.9
Suprasellar	Craniopharyngioma	5.6
	Optic hypothalamic glioma	3–6

Table 1.
Common brain tumor types with location and frequency [5].

histological subtypes of CNS tumours are recognized but their incidence varies with age. Incidence in Africa is around 11 per 10,00,000 and in Japan and Europe it ranges from 20 to 30 per 1,000,000. The male to female ratio is 1.25:1, as slightly higher frequency of medulloblastoma and CNS germinoma is seen in boys [4]. The most common histological subtypes along with location are mentioned below (**Table 1**).

3. Etiology and pathogenesis

Development of brain tumours occurs as a consequence of cellular genetic alterations that allow them to evade normal regulatory mechanisms and destruction by the immune system. These changes may be caused by an inherited or acquired (chemical, physical or biological neuro-carcinogens) cause. Overall, only a very small percentage of brain tumors can be ascribed to the effect of inherited inclination (**Table 2**). The different environmental factors involved and alleged typically involve ionizing radiation, non-ionizing radiation, N-nitroso compounds, viral infections (JC virus, cytomegalovirus, HIV, SV-40, varicella-zoster, chicken pox) and head injury [6].

Syndrome	Gene locus	Gene	Type of CNS tumour
NF type 1	17q11	NF1	Neurofibroma, meningioma, optic nerve glioma
NF2	22q12	NF2	Meningioma, schwannoma
TS	9q34, 16p13	TSc1/TSC2	SEGA
VHL	3p35	VHL	Haemangioblastoma
Li-Fraumani	17q13	p53	Glioma
Gorlin's syndrome	9q31	PNET	

Table 2.
CNS tumour along with gene involved.

4. Pathology and classification

Astrocytic tumors

- subependymal giant cell astrocytoma
- pilocytic astrocytoma
- Pilomyxoid astrocytoma
- diffuse astrocytoma
- pleomorphic xanthoastrocytoma
- anaplastic astrocytoma
- glioblastoma
- giant cell glioblastoma
- gliosarcoma

Oligodendroglial tumors

- oligodendroglioma
- anaplastic oligodendroglioma

Oligoastrocytic tumors

- oligoastrocytoma
- anaplastic oligoastrocytoma

Ependymal tumors

- subependymoma

- myxopapillary ependymoma
- ependymoma
- anaplastic epedymoma

Choroid plexus tumors

- choroid plexus papilloma
- atypical choroid plexus papilloma
- choroid plexus carcinoma

Other neuroepithelial tumors

- astroblastoma
- angiocentric glioma
- chordoid glioma of the third ventricle

Neuronal and mixed neuronal-glial tumors

- gangliocytoma
- ganglioglioma
- Anplastic ganglioglioma
- desmoplastic infantile astrocytoma and ganglioglioma
- dysembryplastic neuroepithelial tumor
- central neurocytoma
- extraventricular neurocytoma
- cerebellar liponeurocytoma
- paraganglioma of the spinal cord
- papillary glioneuronal tumor
- Rosette-forming glioneuronal tumor of the fourth ventricle

Pineal tumors

- pineocytoma
- pineal parenchymal tumor of intermediate differentiation

- pineoblastoma
- papillary tumor of the pineal region

Embryonal tumors

- medulloblastoma
- CNS primitive neuroectodermal tumors
- atypical teratoid/rhabdoid tumor

Tumors of cranial and paraspinal nerves

- Schwannoma
- neurofibroma
- perineuroma
- malignant peripheral nerve sheath tumors

Meningeal tumors

- tumors of meningothelial cells
- mesenchymal tumors
- primary melanocytic lesions
- other neoplasms related to the meninges
- hemangioblastoma

Lymphoma and hematopoietic neoplasms

- malignant lymphoma
- plasmacytoma
- granulocytic sarcoma

Germ cell tumors

- germinoma
- embryonal carcinoma
- yolk-sac tumors
- choriocarcinoma

- teratoma
- mixed germ cell tumor

Tumors of the sellar region

- craniopharyngioma
- granular cell tumor of the neurohypophysis
- pituicytoma
- spindle cell oncocytoma of the adenohypophysis

Metastatic tumors
Modified from the WHO Classification of Tumors of the CNS, 2007 [7].

5. Clinical manifestations

The most common presenting symptoms of pediatric brain tumours are due to increased intracranial pressure. Headache and vomiting are two well-known symptoms associated with elevated intracranial pressure. Other signs, which reflect the increase in intracranial pressure, include drowsiness, confusion, nausea, sixth nerve palsy, papilledema, generalized seizures, and cognitive impairment. Focal signs and symptoms reflect the effect of the tumor on specific structures [8].

6. Radiological diagnosis

The features that play an important role in establishing the diagnosis are the age of the patient, location of the tumor and the imaging characteristics. Supratentorial tumors are more common in neonates and infants up to 2 years old, whereas infratentorial tumors are more common in children older than 2 years. Although some tumors may be found both supra- and infratentorially. Tumors that are considered mostly supratentorial and intraaxial include astrocytomas, such as diffuse astrocytoma, anaplastic astrocytoma, pleomorphic xanthoastrocytoma (PXA), subependymal giant cell astrocytoma (SEGA), and glioblastoma multi-forme (GBM); oligodendrocytoma; primitive neuroectodermal tumor (PNET); dysembryo-plastic neuroepithelial tumor (DNET); ganglioglioma; and desmoplastic infantile ganglioglioma. Some supratentorial extraaxial masses include arachnoid cysts, pineal region masses, and choroid plexus tumors.

Imaging is an important aspect in the management of patients with brain tumors. Imaging workup is largely based upon CT and MRI of the lesion. The technical development of CT and MRI methods has greatly enhanced brain tumor detection and sophisticated neuroimaging offers extra data by determining the metabolism and physiology of these lesions, which helps to diagnose and monitor brain neoplasms [9].

7. Computed tomography (CT)

CT scan plays an important role in establishing diagnosis of brain tumours. It can detect both blood and calcification. But some tumors, particularly tumors of

the brainstem, cerebellum, and suprasellar region as well as infiltrative tumors of the white matter, can be missed on CT neuroimaging [10].

7.1 MRI

It is the standard of care in children for imaging of suspected brain tumours.

The most useful imaging studies are T1-weighted sagittal images, gadolinium (Gd)-enhanced and unenhanced T1 axial images, T2-weighted axial images, and fluid-attenuated inversion recovery (FLAIR) sequences.

T1 images usually are better at demonstrating anatomy and areas of contrast enhancement. T2 and FLAIR images are more sensitive for detecting edema and infiltrative tumor.

7.2 Perfusion MRI

It plays an important role In differentiating low-grade tumors from high-grade tumors. It evaluates several hemodynamic parameters including cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT); however, CBV has been shown to be the most useful parameter for the evaluation of intracranial masses [11].

7.3 Functional MRI

It detects functional areas of the brain by identifying areas of brain activation which have increased blood flow and changes in cerebral metabolism. It is used to determine the extent of resection as it can prevent any functional compromise. It is essential for planning function-preserving surgery in patients with brain tumours [12].

7.4 Magnetic resonance spectroscopy

It is useful in the evaluation of brain tumors in pediatric patients by helping determine the diagnosis, grade, and extent of the tumor. MRS can also differentiate radiation necrosis from tumor recurrence because normal metabolite levels after treatment favor edema and postsurgical changes [13].

7.5 Positron emission tomography (PET)

PET has clearly defined roles in primary brain tumor imaging. The FDG uptake of high-grade gliomas is more as compared with low-grade or well-differentiated neoplasms, and FDG-PET can be useful in making a distinction between low- and high-grade gliomas [14].

A few limitations of FDG-PET as a cerebral imaging agent are that normal brain tissue has high physiologic glucose metabolic rate producing a high FDG uptake which may mask smaller lesions. Another issue is in the detection of tumors with only modest increases in glucose metabolism, such as low-grade tumors which may be difficult to interpret [15]. 18F-fluoroethyl-L-thyrosin (18F-FET) is a promising radiotracer in determining the grade of brain tumors.

7.6 Cerebral fluid analysis

Chemistry and cytology of the cerebral fluid are used to determine the spread of the tumor. Findings may be important in subsequent treatment approaches.

8. Histologic confirmation of diagnosis

Histopathologic diagnosis of brain tumours is necessary for decision making regarding appropriate management. Stereotactic biopsy has emerged as a comparatively safe method of histological diagnosis and has significantly reduced the risks associated with brain biopsy [16]. Tissue sampling can be obtained either with stereotactic, open, or endoscopic procedures and, overall, provides.

Greater than 90% diagnostic yield, while it may be significantly lower (60–70%) in small (<1 cm^3) and/or heterogeneous lesions [17].

8.1 Open biopsy

It is performed as an open technique by intraoperative neuronavigation. Typically, it is asserted for surface brain lesion, where hemostasis is critically vital or a surgical resection depending on frozen section histopathology is arranged. Although morbidity and mortality of open biopsy is more as compared to stereotactic biopsy but neoplastic tissue yield is better and it influences the likelihood of an accurate diagnosis.

8.2 Stereotactic biopsy

It can be frame based and frameless. The frame-based method is focused on the fixation of the stereotactic frame on the patient's head, whereupon the localizer is attached to the frame with many N-shaped posts. Under stereotactic circumstances, neuroimaging (CT, MRI, positron emission tomography [PET], etc.) is carried out and radiological information is transmitted to the specialized computer platform. The localizer posts are used as space coordinate references. For optimizing the target location and defining the ideal trajectory for biopsy, multiple pictures are combined.

The frameless biopsies are generally technically easier and require less preparatory efforts in comparison to frame-based ones [18].

8.3 Endoscopic biopsy

It is recommended for intra- and periventricular tumors and can be done with or without frameless stereotactic guidance. The advantages of this technique are

1. direct visualization of the lesion

2. vascular structures can be seen during tissue sampling

3. more pathological specimens can be taken.

4. cerebrospinal fluid (CSF) samples can be taken for tumor marker analysis

In case obstructive hydrocephalus, third ventriculostomy can be simultaneously done [10].

Exception may be produced in chosen patients such as patients with known active systemic cancer and numerous lesions radiographically associated with brain metastases, patients with classic clinical and MRI results of brain stem glioma or optic nerve meningioma, HIV-positive patients with CT or MRI results consistent with primary CNS lymphoma and positive Epstein-Barr virus polymerase chain reaction in the CSF, or patients with secretory germ-cell tumors [19].

9. Differential diagnosis

9.1 Infectious

Abscess-fever, acutely ill, ±systemic infection, ct findings show cyst cavity with smooth thin walls and restricted diffusion within cavity.

Cerebritis-fever, acutely ill, ±systemic infection, mri findings show diffuse T2 change, no mass meningitis-diffuse enhancement of meninges on T1-weighted imaging.

9.2 Vascular

Infarct—MRI findings show Gray and white matter involvement, wedge like vascular distribution associated with restricted diffusion and low signal.

Subdural hematoma: anemia, retinal hemorrhage.

Bleeding—homogenous, clears quickly, residual hemosiderin ring.

Treatment-related necrosis—central hypodensity, edema, >6 months after radiation therapy or chemotherapy, metabolic scan shows low activity.

9.3 Neoplasm

Primary-solitary, no prior cancer.

Metastatic-multiple, prior cancer, ++edema, located at gray/white junction hydrocephalus: headache, vomiting, subarachnoid hemorrhage, Guillain-Barré syndrome tuberculoma: exposure to tuberculosis.

Pseudotumor cerebri: after otitis media, hormonal abnormalities.

10. General management

A focused history and symptom-based neurological examination is required which may be sufficient to raise brain tumor suspicion. Mental status assessment, cranial nerves, motor skills, sensory examination, coordination, and gait are key components of the neurological examination.

Preoperative laboratory testing which includes a complete blood cell count, renal and hepaic profile. A baseline ophthalmologic evaluation, including visual field testing and fundoscopic evaluation, is important in preoperative evaluations because most patients do not complain of visual field deficits at presentation. Glucocorticoids are used to control neurologic signs and symptoms caused by cerebral edema.

Although there is little evidence to support the use of corticosteroids with regard to overall outcome, corticosteroids can relieve headache, nausea, and vomiting and remain a generally accepted treatment.

In assessing a child suspected of having a brain tumor, a thorough neurological examination is of critical importance. Most kids diagnosed with a brain tumor have abnormal results on the presentation of neurological examination [20].

11. Neurosurgical procedure

Surgery remains the main treatment modality for most pediatric brain tumors. Depending on tumor type, the goals of surgical intervention are:

- Tissue diagnosis
- Re-establishment of normal CSF pathways

- Diversion of CSF (shunting)
- Tumor debulking
- Complete tumor resection [5]

In the literature, overall surgical morbidity rates vary from 10 to 54%. The rates highly depend on the location of the tumour, grade and propensity to disseminate [21].

12. Radiotherapy

Radiotherapy plays an important role in the management of pediatric brain tumours. It can be used either as adjuvant treatment in case of resectable tumours or as a definitive management option in case of unresectable tumours [22].

The most common long term side effect of radiotherapy in pediatric age group is neurocognitive dysfunction and upto 20–60% patients suffer from neurocognitive deficit as a long term sequelae of radiotherapy [23]. Sophisticated radiotherapy techniques are warranted for to avoid future negative impacts of radiation on pediatric brain development.

Use of better immobilization and more suitable imaging techniques like high-resolution brain imaging with computed tomography (CT) and magnetic resonance imaging (MRI) to accurately define the tumour limits and precisely assess the normal brain structures has greatly improved the degree of efficacy achieved by radiotherapy without increasing the side effects [24].

Technological advancements like use of conformal radiotherapy allows high radiation dose distributions within targeted tissues while simultaneously attempting to reduce dose to surrounding normal tissues. Conformal radiotherapy can be accomplished through a variety of techniques, including intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy and proton beam therapy.

IMRT has shown promise in the treatment of a number of disease sites and is now being investigated in the use of pediatric tumors to reduce long-term toxicity. Stereotactic technique has the ability to reduce the treatment volume as it delivers highly conformal radiation to brain tumours and minimum dose to surrounding brain tissue. It can be delivered as stereotactic radiosurgery in which the entire dose is delivered as a single fraction or as fractionated stereotactic radiotherapy (FSRT) in which the treatment is delivered over weeks with multiple daily fractions. Only small margins of several millimeters are used for brain tumors, greatly reducing the volume of normal brain parenchyma receiving high doses of radiation.

13. Chemotherapy

High-dose chemotherapy with or without support by autologous stem cell transplantation, especially in children below the age of 3 years [25].

Palliative chemotherapy:

- May induce transient remission
- Increases the quality of life
- The benefits of chemotherapy or other treatments must be balanced by consideration of the toxicities

14. Special tumor types astrocytic tumor

Astrocytomas are the most common pediatric brain tumors, accounting for 7–8% of all childhood cancers [26]. Approximately 40% of all pediatric brain tumours are low grade astrocytoma, whereas most common primary CNS malignancy in adults being high grade astrocytoma [7]. Pediatric brain tumors are typically infratentorial, localized predominantly in the posterior fossa and brainstem [27].

Pediatric astrocytic tumours are further sub-classified by WHO grades (**Table 3**).

14.1 Genomic alterations low grade glioma

1. Most common genomic modification in cases of pilocytic astrocytoma involves activation of *BRAF* and the ERK/MAPK pathway [29]

2. Alternative *BRAF* gene fusions, *RAF1* rearrangements, *RAS* mutations, and *BRAF* V600E point mutations are less commonly observed in such cases [30].

3. Presence of the *BRAF-KIAA1549* fusion gene shows better progression-free survival (PFS) and overall survival (OS) [31].

4. Other pediatric low-grade gliomas (e.g., pilomyxoid astrocytoma) are also associated with *BRAF* activation through the *BRAF-KIAA1549* fusion [32].

5. In 53% pediatric grade II diffuse astrocytomas, the most common alterations reported are rearrangements in the MYB family of transcription factors [33].

Children having mutation in one of two tuberous sclerosis genes (*TSC1*/hamartin or *TSC2*/tuberin) are at a risk of developing Subependymal giant cell astrocytomas, cortical tubers, and subependymal nodules, as either of these mutations results in activation of the mammalian target of rapamycin (mTOR) complex 1 [34].

14.2 High grade glioma

The following pediatric high-grade glioma subgroups were identified on the basis of their DNA methylation patterns, and they show distinctive molecular and clinical characteristics:

1. Histone K27-mutation: **H3.3 (*H3F3A*) and H3.1 (*HIST1H3B* and, rarely, *HIST1H3C*) mutation at K27**. These cases occur predominantly in mid

Astrocytic tumour	Grade
Subependymal giant cell astrocytoma Pilocytic astrocytoma	I
Pilomyxoid astrocytoma Diffuse astrocytoma Pleomorphic xanthoastrocytoma	II
Anaplastic astocytoma	III
Glioblastoma giant glioblastoma gliosarcoma	IV

Table 3.
WHO grades of pediatric astrocytic tumours [28].

childhood (median age, approximately 10 years). They are almost exclusively midline, usually present in the thalamus, brain stem, and spinal cord, and carry a very poor prognosis.

H3.3K27M cases are usually present between ages 5 and 10 years, accounting for approximately 60% of cases in the midline and pons. The prognosis for H3.3K27M patients is extremely poor, with a median survival of <1 year [35].

H3.1K27M cases present at a younger age than H3.3K27M cases and are approximately 5 times less frequent. These cases have a slightly more favorable prognosis than do H3.3K27M cases (median survival, 15 vs. 11 months).

2. **H3.3 (*H3F3A*) mutation at G34**: The H3.3G34 subtype is associated with mutations in *TP53* and *ATRX* which show widespread hypomethylation across the whole genome. It is common in older children and young adults (median age, 14–18 years) and arises exclusively in the cerebral cortex [36].

About 5% pediatric high-grade gliomas have *IDH1*-mutation. They are almost exclusively common in older adolescents (median age in a pediatric population, 16 years).

Pleomorphic xanthoastrocytoma (PXA)-like: Approximately 10% of pediatric high-grade gliomas have DNA methylation patterns that are PXA-like [37].

15. Treatment

15.1 Low-grade astrocytomas

Low-grade astrocytomas (grade I [pilocytic] and grade II) spread by direct extension; dissemination to other CNS sites is uncommon. Complete excision is the treatment of choice and the outcome is favorable especially if the tumor is circumscribed [38].

Markers of poor prognosis for childhood low-grade astrocytomas are:

1. Young age.
2. Diffuse histology, especially IDH-mutant.
3. Inability to obtain a complete resection.
4. Diencephalic syndrome.
5. Intracranial hypertension at initial presentation [39].
6. Metastases.

15.2 High-grade astrocytomas

Gross total resection is recommended for anaplastic astrocytomas. Local invasion of adjacent brain tissue is relatively common. Prognosis is poor for younger patients.

Depending on the degree of resectability, other treatment options are:

- Radiotherapy usually causes short-term and partial remission.

- Multiagent chemotherapy improve survivability with variable long-term remission

- Effective drugs alone or in combination: cisplatin, carboplatin, cyclophosphamide, ifosfamide, etoposide, topotecan, procarbazine, temozolomide, lomustine (CCNU), carmustine (BCNU) [40].

15.3 Optic-hypothalamic glioma

Optic pathway-hypothalamic gliomas are rare astrocytic tumors that are more among young children. They comprise approximately 2% of all central nervous system tumors and account for 3–5% of pediatric intracranial tumors.

OPG was classified by Dodge et al. into the following three stages: (A) limited to the optic nerve; (B) involving optic chiasma (with or without extension to the optic nerve) and (C) involvement of hypothalamus and other structures [41].

The tumours do not produce symptoms at an early stage. The symptoms can be due to impingement on optic nerve or chiasma which leads to visual disturbances, involvement of hypothalamus causing endocrinopathies and hypothalamic dysfunction such as the diencephalic syndrome. It can also cause csf outflow block leading to hydrocephalus [42].

Surgery has a limited role in the treatment of these tumours as they lie close to critical structures. It is usually limited to establishing a histopathological diagnosis or debulking in case of large tumours. Although Gross total resection of low-grade glioma is strongly associated with improvement of both OS and PFS but Aggressive resection, often leads to blindness, hypothalamic damage and cognitive dysfunctions [43].

15.3.1. Chemotherapy

Carboplatin and Vincristine is the most frequently recommended first-line chemotherapy, and it is considered to be the standard treatment of OPG [44].

15.3.2. Radiation

Radiotherapy is considered as a treatment option for OPG but at a cost of long term complications of neurocognitive dysfunction and visual disturbances [45]. Radiation may therefore be useful for an adjuvant treatment in the case of chemotherapy refractory tumors. Prognosis depends upon the age of the patient and location of the tumour. Young age and tumour located in optic pathway and hypothalamus are considered as poor prognostic factors.

16. Brain stem tumors

Pediatric brainstem gliomas occur as two major types:

Focal brainstem gliomas, usually WHO grade I–II tumors.

Diffuse intrinsic pontine gliomas, range from WHO grade III–IV [46]. They usually arise in the medulla, pons, or midbrain.

Focal brainstem gliomas (FBSG): constitutes approximately 20% of pediatric brainstem gliomas and usually occur outside the pons. Most are either pilocytic astrocytomas (grade I) or fibrillary astrocytomas (grade II) [47].

FBSG is usually insidious in nature and the symptoms are related to site of tumour location. Most common symptoms include neck stiffness, cranial nerve deficit and contralateral hemiparesis.

Hydrocephalus is uncommon except in posterior exophytic tumours [48].

On MRI, FBSG can be seen with defined borders, lack of surrounding edema, iso- or hypointensity on T1, hyperintensity on T2, and homogeneous contrast enhancement [49].

Surgical resection has emerged as treatment of choice due to development of modern imaging and neurosurgical techniques. FBSG confined to cervicomedullary region and/ or exophytic are amenable to complete resection [50] even with incomplete resection, the long-term prognosis for this patient population is excellent.

Chemotherapy can be used as adjuvant after complete or incomplete tumour resection or in cases of tumour progression. Most commonly used chemotherapy regimen is vincristine and carboplatin, which achieves at least stable disease in 68–75% of patients, and a positive response in about 40% [51]. Other regimens comprise of 6-thioguanine, procarbazine, lomustine, and vincristine (TPCV), vinblastine [52], bevacizumab with or without irinotecan [53], everolimus [54], and a metronomic, oral, anti-angiogenic regimen consisting of celecoxib, thalidomide, fenofibrate, cyclosphosphamide, and etoposide [55].

Radiation therapy (RT), while often effective in inducing prolonged remission in FBSG, has severe associated toxicities, especially for young children.

Diffuse intrinsic pontine gliomas (DIPG) account for approximately 80% of pediatric brainstem tumors and with male to female ratio as 1:1. It is more common in younger age group. These tumors are almost always highly malignant and fatal [56].

The patients have DIPG have a more lethal and shorter duration course than FBSG as it is more aggressive disease. Patients usually present within 3 months of tumour development. The most common symptoms are cranial nerve palsies, most often of cranial nerves VI and VII but sometimes including III, IV, IX, and/or X, as well as long tract signs like hemiparesis.

On CT scan, DIPG appears isodense or hypodense, without calcifications. On MRI, DIPG is most often hypointense on T1 and hyperintense on T2. Contrast enhancement is variable in both modalities but is usually not diffusely uniform, as it often is in FBSG. Diffusion is most often increased [57].

Apart from medical management starting with dexamethsone, aimed to relieve neurological symptoms, not many treatment options are available. RT is the only therapy proven to prolong survival of patients, that too it is palliative in nearly every case.

Currently, RT is given at a dose of 54–59 Gy at 1.8 Gy daily fractions for 30–33 days locally, to the area of the tumor plus a 1–2 cm surrounding margin.

Chemotherapy has not shown any benefit in concurrent, adjuvant or palliative form.

The prognosis for DIPG patients remains devastatingly poor. Recent studies have shown median progression free survival of 7 months and an overall survival of 9–11 months. In one large series, 77% of patients responded to treatment, and it was for a transient period as the therapy is rarely curative [58]. Poor prognostic marker at diagnosis or post treatment is the presence of leptomeningeal disease and no studies confirm these patients will benefit from craniospinal irradiation [59].

17. Medulloblastoma

Medulloblastoma is the second most common central nervous system tumour of childhood, most commonly occurring between 4 and 7 years of age. It usually arises from the roof of the fourth ventricle or from the midline structures of the brain [60].

Etiology: for most patients the etiology is unknown but is associated with certain genetic disorders (i.e., Gorlin syndrome, Turcot syndrome, Li-Fraumeni syndrome, Rubinstein-Taybi syndrome, and ataxia telangiectasia) [61].

It has the propensity to disseminate along the cerebrospinal fluid (CSF) pathway, and metastatic disease at diagnosis is found in approximately 30% of patients. Spread outside the central nervous system (CNS) is very rare at diagnosis.

WHO classification 2007 categorises medulloblastoma as grade IV neoplasms under the group of embryonal neuroepithelial tumours. There are several histopathological subtypes of medulloblastoma. In addition to classic variant, other subtypes include desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity (MBEN), anaplastic medulloblastoma, and large cell medulloblastoma [25].

Molecular subgrouping of medulloblastoma divides it into four distinct subgroups which are identified on the basis of transcriptional profiling studies as wingless (Wnt), sonic hedgehog (Shh), Group 3, and Group 4 (**Table 4**). Each subgroup is defined by a unique set of demographic and clinical features, genetics, and gene expression [63].

Signs and symptoms: usually due to increased intracranial tension, hydrocephalus and cerebellar dysfunction, and comprise vomiting, macrocephalus, loss of developmental achievements in infants, and headache, vomiting, ataxia, and cranial nerve palsy in older patients.

Management: biopsy has no role in the diagnosis if it is radiographically supported. Medulloblastomas have distinct imaging characteristics on both computed tomography (CT) and magnetic resonance imaging (MRI). Since 75% of medulloblastomas arise from the cerebellar vermis, they tend to protrude into the fourth ventricle in pediatric age group. On CT scan, in case of young patients, effacement of the fourth ventricle is seen along with its dilatation which is secondary to obstructive hydrocephalus. In case of older patients, they are most commonly seen as a hyperdense mass arising from the vermis with cyst formation or necrosis.

On MRI, medulloblastomas are hypointense to grey matter on T1-weighted imaging with heterogeneous gadolinium enhancement on T2-weighted imaging

	WNT	**SHH**	**GROUP 3**	**GROUP 4**
Percentage	10%	30%	25%	35%
Age	Children and adults	Mainly infants and adults	Mainly infants and children	Mainly children and adults
Somatic nucleotide variant	*CTNNB1*, *DDX3*, *SMARCA4*, *CREBBP*, *TP53**	*PTCH1*, *SUFU*, *SMO*, *TERT*, *IDH1*, *TP53*, *KMT2D*	*SMARCA4*, *CTDNEP1*, *KMT2D*, *KBTBD4*	*KDM6A*, *KMT2C*
Somatic copy number alterations		*MYCN*, *GLI2*	*MYC*, *PVT1*, *OTX2*, *GFI1/1b*	*SNCAIP*, *MYCN*, *CDK6*, *GFI1/1b*
Cytogenetics	Monosomy 6	Gain of 3q, 9p, loss of 9q, 10q, 14q, 17p	i17q, loss of 8, 10q, 11, 16p, 17p, gain of 1q, 7, 17q, 18q	i17q, loss of 8p, 11p, X, gain of 7q, 18q
Prognosis	Very good	Intermediate	Poor	Intermediate
Incidence of metastasis	5–10%	10–15%	40–45%	35–40%
Pattern of relapse	Local and distal	Local	Distal	Distal

**It shows characterstics of each molecular subgroups of medulloblastoma.*

Table 4.
Molecular subgroups of medulloblastoma [62].

	Average risk	High risk
Residual postoperative tumour volume	<1.5 cm^2	≥1.5
CSF cytology/evidence of disease dissemination on MRI in brain and spine	Absent	Present

Table 5.
Risk stratification of medulloblastoma.

they appear iso- to hyperintense to grey matter and can seem heterogeneous due to cyst formation, calcification and necrosis. MR spectroscopy shows elevated choline peaks and decreased creatine and N-acetyl acetate peaks, with occasional elevation in lactic acid and lipid peaks [64].

Maximal safe resection is recommended in all medulloblastoma patients. Apart from surgical resection, the current standards of radiation therapy and medical management vary by extent of disease and age of the patient. Radiation therapy can be used to decrease the risk of recurrence but neurocognitive effects of radiation therapy have to be considered by weighing the risk benefit ratio.

Patients who are 3 years of age or older are stratified as either "average-risk" or "high-risk" depending upon postoperative residual tumor volume and the presence or absence of disseminated disease (**Table 5**).

Patients who are younger than 3 years of age, are treated without upfront radiation therapy due to the unacceptably high risk of severe neurocognitive impairment [65].

In the postoperative setting, average-risk patients >3 years old were previously treated with 36 Gy craniospinal irradiation (CSI) but now a boost to the posterior fossa is given for a total dose of 54 Gy due to the high rate of relapse within the posterior fossa. CSI dose of 23.4–24 Gy can be given with the addition of chemotherapy as supported by Studies conducted by the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group [66].

Current recommendations for post-radiation chemotherapy in average-risk patients include approximately 1 year of therapy consisting of 8 cycles at 6-week intervals of cisplatin, lomustine (CCNU), and vincristine. The St. Jude Medulloblastoma-96 trial has demonstrated a similar event-free survival of 83% when an alkylator-based, dose-intensive chemotherapy regimen consisting of four 4-week cycles of cyclophosphamide, cisplatin, and vincristine with autologous stem cell rescue was employed following each cycle [67].

For high risk medulloblastoma cases in children 3 years or older, the treatment is surgical resection followed by post-operative "standard dose" RT (36 Gy CSI with a boost to both the posterior fossa and focal sites of metastatic disease to 55.8 Gy) as well as adjuvant chemotherapy.

The most common adverse effect of craniospinal irradiation in children <3 years age is neurocognitive deficit. Therefore radiotherapy is either delayed or omitted in this subset of patients. There is evidence that regimens consisting of surgery and chemotherapy without RT can be successful in specific subsets of medulloblastoma patients. Outcomes in patients with relapsed disease are generally poor, with reported 5-year survival rates of approximately 25% [68]. Unfavorable prognostic factors include large tumor, csf dissemination, age <4 years, subtotal tumour resection (<90%), chromosome deletion 17p, c-*MYC* amplification.

18. Atypical teratoid rhabdoid tumors (ATRT)

Atypical teratoid rhabdoid tumours (ATRTs) are the most common malignant central nervous system tumours in children ≤1 year of age and represent

approximately 1–2% of all pediatric brain tumours [69]. ATRT is a primarily monogenic disease characterized by the bi-allelic loss of the *SMARCB1* gene, which encodes the hSNF5 subunit of the SWI/SNF chromatin remodeling complex [70]. The most common site of ATRT is posterior fossa, mainly cerebellar hemispheres (⅔ cases) [71]. It can also occupy fourth ventricle causing its displacement and compression by invading the adjacent cisternal space.

In patients <3 years of age, the most common treatment is high dose chemotherapy with autologous stem cell rescue, so that CSI can be avoided in young patients as poor outcomes are seen due radiotherapy induced neurocognitive impairment [72].

Despite using chemotherapy and radiotherapy as treatment options, ATRT has poor survival outcomes due to early dissemination and progression of the tumours [73].

19. Pineal tumors

Incidence of pineal tumours in children ranges from 2.7 to 11% [74]. Germ cell tumors (GCTs) account for nearly 50–75% of all pineal tumors [75], Pineal parenchymal tumors account for nearly 15–27% of pineal tumors and include pineocytoma, parenchymal tumor of intermediate differentiation, pineoblastoma and papillary tumor of the pineal region. Other described pineal tumors include glioma, ependymoma and atypical teratoid or rhabdoid tumors [76].

Preferred treatment strategy of different pineal region tumours [77] (**Table 6**).

Pineoblastoma <3 years	Radiotherapy is avoided Induction chemotherapy followed by consolidation myeloablative chemotherapy with stem cell rescue
Pineoblastoma 3–6 years	Induction chemotherapy followed by consolidation myeloablative chemotherapy with stem cell rescue
Pineoblastoma >6 years	Full-dose craniospinal irradiation (36 Gy) plus boost (total of 54 Gy) to the primary site along with concomitant daily carboplatin and weekly vincristine followed by 6 cycles of maintenance chemotherapy
Germinoma	Four cycles of chemotherapy with carboplatin and etoposide followed by whole ventricular irradiation to 23.4 Gy plus a boost to the primary site to a total dose of 30 Gy
Non-germinomatous germ cell tumour	Six cycles of chemotherapy with carboplatin, ifosfamide and etoposide followed by 30 Gy whole ventricular irradiation plus a boost to the primary site to a total dose of 50 Gy in patients with a radiographic and serologic complete response

Table 6.
Treatment strategies of different pineal tumours.

20. Ependymoma

Ependymoma accounts for 6–12% of all brain tumors in childhood. It represents the third most common brain tumor in this age group, following astrocytomas and medulloblastomas [78]. Ependymoma are classified according to the WHO pathological grading system (**Table 7**).

They are usually located in or adjacent to ventricles within the parenchyma. In pediatric age group majority of intracranial ependymoma are located at infratentorial region in posterior fossa, usually arising at the floor of fourth ventricle.

Prognostic factors include tumor location, size, surrounding anatomical structures, tumor appearance, genotype, comorbidities, clinical symptoms, and patient age [79].

Tumour type	Grade
Subependymoma (benign) myxopapillary ependymoma	I
Ependymoma	II
Anaplastic ependymoma	III

Table 7.
WHO pathological grades of ependymoma.

The current treatment of choice for pediatric patients with cranial ependymoma is resection, if possible, followed by radiation therapy alone [80].

21. Craniopharyngioma

They are low histological grade (WHO I) tumours which arise from epithelial remnants of rathke's pouch. They are usually located in sellar or parasellar location with an overall incidence of 0.5–2.0 new cases per million of the population per year, and constitute 1.2–4.0% of all childhood intracranial tumors.

Symptoms depend upon the location of the tumour:

Craniopharyngimas can present with nonspecific symptoms like headache and nausea due to increased intracranial pressure.

Intrasellar lesions can compress the pituitary gland and hypothalamus involving the hypothalamic-pituitary axes in 52–87% cases, leading to endocrine defects, particularly deficits in the secretion of growth hormone (75% of cases), gonadotropins (40%), adrenocorticotropic hormone (25%) and TSH (25%) [81].

Prechiasmal lesions may compress the optic pathway, leading to visual field cuts, decreased central visual acuity or vision impairment (62–84% of cases in children).

Retrochiasmal lesions may grow into the third ventricle and cause hydrocephalus or compress the optic tracts.

Craniopharyngiomas can cause direct impingement of brain parenchyma and produce neurological deficit.

In case of localized tumours the preferred choice of treatment is complete resection with preservation of visual, pituitary and hypothalamic function [82]. In case of incomplete resection, there are chances of residual tumour progression in 71–90% of patients, whereas the rate of progression after incomplete resection followed by radiotherapy is 21%. Therefore radiotherapy is recommended after surgical resection [83].

22. Conclusion

Since brain tumours are a leading cause of morbidity and mortality among children, the focus lies on how effectively they can be treated. Surgery plays a major role and can be curative in a number of tumours including pilocytic astrocytoma. Radiotherapy is curative in cases of PNET and ependymoma.

The survival and long-term outcome of patients with brain tumors will continue to enhance with future advances in nonsurgical methods, molecular and translational oncology research. For longer survival and reduced morbidity, new molecular diagnostics and new therapies such as immunotherapy, gene therapy and stem cell therapy may be promising.

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