Chapter

# Clinical Profile, Patterns of Care and Outcomes of Childhood CNS Tumours in India

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## Abstract

Paediatric CNS tumours are the third most common childhood malignancy in India. They account for 14% of all cancers in the 1–14 years age group. There is dearth of adequate prospective or retrospective studies about patterns of care and outcomes. There is male preponderance. Primitive Neuro-ectodermal tumours (PNET) are the most common histology followed by astrocytoma and other gliomas among children from 0 to 19 years. Surgery, radiotherapy, and chemotherapy are the main modalities of treatment. Available data points to underutilisation of radiotherapy in clinical practice due to the fear of non-compliance. Paediatric CNS tumours outcomes are different from adult brain tumours due to their aggressive histology, variable clinical presentations, delay in diagnosis, etc. There is also shortage of adequate multidisciplinary paediatric neuro-oncology units in the country. Future directions include setting up more dedicated paediatric neuro-oncology units, implementation of new 2022 WHO classification by adopting molecular testing across different histology's, use of better radiation technology to prevent long term neurocognitive and other late effects and survivorship clinics to monitor for late effects and rehabilitate the childhood cancer survivors and, perhaps a registry. These issues are discussed in detail in this chapter.

**Keywords:** CNS, paediatric, brain tumours, clinical profile, multidisciplinary

## 1. Introduction

Paediatric CNS tumours are defined as tumours of brain, spinal cord, and meninges. Brain tumours form the largest group. Histology and clinical behaviour varies between different brain tumour types and they play a pivotal role in deciding specific treatment plan as per each tumour subtype [1]. Paediatric CNS tumours are among the most common paediatric cancers worldwide after leukaemia. As per GLOBOCAN estimates, there were 30,766 new cases of primary brain and other CNS tumours in children and adolescents aged 0–19 years in 2020, 24,388 of which were in children 0–14 years age.

Also, it was estimated that there were 15,337 deaths due to primary brain and other CNS tumours in children and adolescents age 0–19 years in 2020, 11,889 of which were in children 0–14 years old [2]. Recently, the revised 2021 WHO classification of Tumours of Central Nervous System has reinforced the adoption of molecular subtyping of medulloblastoma and newer paediatric diffuse gliomas have been added to the classification [3].

In India, as per the report of National Cancer Registry Programme (NCRP) 2012–2016 for age group 1–14 yrs., paediatric CNS tumours constitute 6.4% and 7.1% of childhood cancers in boys and girls respectively. Leukaemia and lymphomas constitute 60% of all childhood cancers. Paediatric CNS tumours are the second most common solid tumour in this age group after the bone tumours. Among all CNS childhood tumours 0–19 yrs., Primitive Neuroectodermal tumours (PNET) (37%) are most common followed by astrocytoma (20%) and other gliomas (20%) among both sexes [4].

A 55–120% increase in incidence of childhood brain tumours has been reported in both the sexes in India over the past 25 years from 1978 to 2002. This is most likely due to better neuroimaging facilities [5].

In this chapter, we discuss the clinical profile, patterns of care and clinical outcomes of paediatric CNS tumours in India based on the existing literature. Understanding these salient features will help us to know the current disease burden, treatment practices and in future, to plan prospective studies to improve the care of these childhood tumours.

## 2. Clinical profile

Multiple retrospective studies and few prospective studies are available regarding clinical profile of paediatric brain tumours. Institutions in the different zones of the country has reported their clinical profiles of paediatric brain tumours which are very much similar [6–10].

Most common symptoms reported are headache (55–90%) often associated with vomiting (35–50%), visual disturbances (35–60%), ataxia, etc., and other symptoms of raised intracranial pressure. Seizures have also been reported as presenting complaint [7, 11].

Increase in intracranial pressure can cause drowsiness, confusion, nausea, sixth nerve palsy, papilledema, generalised seizures, cognitive impairment, etc. There can be symptoms related to impairment of neurohormonal axis at the onset of disease; shortly after surgery or several months to years later following radiotherapy in children with brain tumours. The degree of neurohormonal axis involvement is related to the location of the tumour. The true prevalence of neuroendocrine dysfunction in patients is underestimated as a significant portion of the patient can be asymptomatic for a long time. Due to the radiosensitive nature of hypothalamus and pituitary, there is a higher risk of developing neuroendocrine disorders in patients undergoing RT. Involvement of the hypothalamus can cause hypothalamic syndrome characterised by thirst disorders, increase in appetite, sleep disturbances, impaired temperature regulations etc. Focal signs and symptoms when present reflect the involvement of specific structures directly by tumour or by compression [12]. The other common neuroendocrine disorders seen in children with CNS tumours are Growth hormone deficiency, precocious puberty and diabetes insipidus.

There is a slight male preponderance in all the studies reported as shown in **Table 1**.

**Tables 2** and **3** shows the age distribution and clinical presentation reported in various studies.

The most common tumours in paediatric brain tumours are supratentorial tumours in the age group (1–14 years) and among children up to 5 years, infratentorial tumours are the commonest. Though the NCRP data is suggestive of PNET as the most common histology, in different case series, astrocytoma is the most common single histology followed by medulloblastoma and there are variations in the different subsets based on the age groups like 1–5 years, 6–10 years and 11–14 years, etc.

**Tables 4** and **5** is a compilation of the location and different frequencies of various histological types of paediatric brain tumours as seen in the published studies respectively.

**Table 6** represents the most common types of astrocytoma.

| Characteristics | Divya Sree et al. [13] | Govindan et al. [14] | Trivedi et al. [7] | Dwivedi et al. [15] | Madhavan et al. [8] |
|---|---|---|---|---|---|
| No. of patients | 147 | 71 | 50 | 64 | 250 |
| Duration of study (In years) | 25 | 5 | 2 | 7 | 5 |
| Mean age (In years) | 11.06 | 8.3 | 8 | 13.2 | Not specified |
| M: F ratio | 1.1: 1 | 1: 0.9 | 1.2: 1 | 0.7: 1 | Not specified |

**Table 1.**
*Male: Female ratio of paediatric CNS tumours in various Indian studies.*

| Age distribution in years | Trivedi et al. [7] | Govindan et al. [14] | Divya Sree et al. [13] | Dwivedi et al. [15] | Madhavan et al. [8] | Total |
|---|---|---|---|---|---|---|
| 0–5 | 15 | 27 | 29 | 8 | 52 | 131 |
| 6–10 | 25 | 21 | 38 | 9 | 91 | 184 |
| 11–18 | 10 | 23 | 80 | 47 | 107 | 267 |

**Table 2.**
*Age distribution of paediatric CNS tumours in various Indian studies.*

| Clinical symptom | Madhavan et al. [8] | Dwivedi et al. [15] | Suresh et al. [16] |
|---|---|---|---|
| Headache | 61.2% | 92.3% | 37.5% |
| Vomiting | 53.1% | 23.1% | 62.5% |
| Hemiparesis | 51% | 28.8% | 20% |
| Impaired vision | 28.6% | 42.3% | 35% |
| Seizures | 20.4% | 11.5% | 2.5% |
| Incontinence | 8.2% | 3.8% | 5% |

**Table 3.**
*Clinical presentation of paediatric CNS tumours in various Indian studies.*

| Primary site of disease | Study author details | | | |
|---|---|---|---|---|
| **Location** | **Divya Sree et al. [13]** | **Trivedi et al. [7]** | **Dwivedi et al. [15]** | **Govindan et al. [14]** |
| | **No. of patients** | **No. of patients** | **No. of patients** | **No. of patients** |
| Brain | | | | |
| Supratentorial | | | | 40 |
| Cerebrum | 85 | 09 | 13 | |
| Ventricles | 02 | 15 | 02 | |
| Sellar region | 03 | 07 | 10 | |
| Cranial nerves | 0 | 0 | 04 | |
| Infratentorial | | 18 | | 31 |
| Cerebellum | 19 | | 14 | |
| Brain stem | 03 | | 04 | |
| Spinal Cord | | 01 | 10 | |
| Cervical | 29 | | | |
| Thoracic | 02 | | | |
| Lumbar | 02 | | | |
| Sacral | 02 | | | |

**Table 4.**
*Sites of paediatric CNS tumours in various Indian studies.*

| Study author | Three most common paediatric CNS tumours | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| Divya Sree et al. [13] | Juvenile pilocytic astrocytoma (37.5%) | Nerve sheath tumours (37.1%) | Embryonal tumours (21.4%) |
| Govindan et al. [14] | Medulloblastoma (22.5%) | Ependymoma (15.5%) | Pilocytic astrocytoma (14.1%) |
| Trivedi et al. [7] | Astrocytoma (28%) | Medulloblastoma (26%) | Ependymoma (16%) |
| Jain et al. [17] | Astrocytoma (34.7%) | Embryonal tumours (22.4%) | Craniopharyngioma (10.2%) |
| Shah et al. [18] | Astrocytoma (40.8%) | Embryonal tumours (29%) | Craniopharyngioma (11.8%) |

**Table 5.**
*Most common paediatric CNS tumours in various Indian studies.*

There is sparse date from India on the use of molecular studies for diagnosis of paediatric brain tumours as proposed in the 2016 WHO classification of CNS tumours and recently by 5th edition (WHOCNS5) [19]. A few studies reported the adoption of the molecular subtyping especially in medulloblastoma [20].

| Astrocytoma subtype | Jain et al. [17] | Divya Sree et al. [13] | Trivedi et al. [7] | Govindan et al. [14] |
|---|---|---|---|---|
| Pilocytic | 23% | 19.2% | 35% | 14.1% |
| Diffuse | 5.1% | 33.3% | 28.5% | Not specified |
| Anaplastic | 2.1% | 1.2% | 14.2% | Not specified |
| GBM | 4.4% | 19.2% | NS% | 5.6% |

**Table 6.**
*Types of astrocytoma in various Indian studies on paediatric CNS tumours.*

## 3. Patterns of care

Multidisciplinary team management in paediatric CNS tumours involves neurosurgery, radiation oncology, paediatric oncology, onco-pathology, neuroradiology, medical social workers, palliative care, and onco-nursing as depicted in the **Figure 1**.


**Figure 1.**
*Components of paediatric neuro-oncology multidisciplinary team.*

### 3.1 Surgery

The initial treatment modality is often surgery. This provides tissue for diagnosis and also is the main curative step in multimodality management. The aim is to achieve complete tumour resection if feasible.

In low grade gliomas, the commonly used surgical approaches depend on the location. A fronto-parietal or temporal craniotomies are done for respective locations. Though the aim is to have total resection of the tumours, preservation of function is also utmost important to have the quality of life preserved. A complete surgical excision is often feasible in non-diencephalic tumours like tumours in cerebral hemispheres and cerebellum.

Brain stem gliomas are another subset of gliomas which are not amenable for surgery because of their eloquent location and their prognosis is guarded. These tumours are observed or often treated with radiotherapy.

In high grade gliomas also, the anatomical location and the likely functional morbidity post-surgery plays an important role in the extent of surgical resection and in all cases, adjuvant radiation therapy preferably with highly precision radiation techniques is used.

PNETs are usually large lesions but can resected most of the times as the plane of cleavage from the surrounding normal structures is good. Blood loss during the resections becomes important and needs to be addressed concomitantly.

Medulloblastomas are located predominantly in the 4th ventricle and there are guidelines regarding the extent of resection. Midline suboccipital craniotomy, transvermian approach is the most common approach used. It is very well known that post-surgery macroscopic residual disease is a poor prognostic factor despite of adjuvant chemotherapy and radiation therapy. In patient presenting with raised intracranial pressure and marked hydrocephalus, CSF diversion procedure is preferred however preoperative ventriculo-peritoneal shunt is generally avoided to prevent seeding of peritoneal cavity and reverse herniation of superior vermis. Optimal maximally safe resection is the surgery of choice for medulloblastoma. Within 24–48 hrs of resection, a postoperative MRI is recommended to assess completeness of the surgery and residual tumour volume.

Newer techniques like endoscopy, stereotaxy have their specific roles in intraventricular lesions such as choroid plexus tumours and deep seated lesions.

**Table 7** has the details of surgical approach practiced in different case series from tbe country.

Tumour debulking and diversion of CSF depending on location of the tumour, grade, and risk of dissemination is also used often. Overall, surgical morbidity rates vary from 10 to 54% as per available literature [21]. The role for re-surgery is not well defined in case of recurrent brain tumours but often are considered when there is long disease free interval and there is less chances of morbidity post-surgery.

### 3.2 Radiation therapy

Radiotherapy is an important modality in paediatric brain tumours. It is used mostly as adjuvant to surgery. It influences the local recurrence and overall survival especially in medulloblastoma and other embryonal tumours. Highly conformal radiation techniques as stereotactic radiotherapy has shown to decrease the incidence of neurocognitive and neuroendocrine side effects.

| Indian study | Year of study publication | Total | Surgery | Radiation therapy | Chemotherapy |
|---|---|---|---|---|---|
| Dattatraya [31] | 2011 | 209-Medulloblastoma | 99.2% resection (53% total, 28,6% near total, 17.6% partial) | 67.3%-Craniospinal Irradiation (35 Gy to craniospinal axis and 20G to posterior fossa) | 32.7% (6.6% exclusively chemotherapy as below 3 yrs) |
| Madhavan [8] | 2017 | 250-mostly Astrocytoma | 92% resection (16% total, 46% partial, 20% biopsy) | 74% offered RT, only 42% received (32% defaulted) | 16% |
| Supriya [16] | 2017 | 52 | 69% (53%-total, 38%-subtotal) biopsy-6% | 54% | 50% |
| Nair [6] | 2018 | 375 | 76.5% Surgery (88%- total/ subtotal), 12%- Biopsy) | 58% | 26% |
| Chilkuri [25] | 2020 | 27 | 96% (total-57%, 40%-partial, 3%-biopsy) | 100% (proton) Median dose –54.8 cGy equivalent | 22%-adjuvant chemotherapy, 30% concurrent chemotherapy |

**Table 7.**
*Enumerates the patterns of care of paediatric brain tumours reported in Indian studies.*

Neurocognitive dysfunction is the most common long term side effect in paediatric age group and 20–70% patients suffer from neurocognitive deficit as a long term sequelae of radiotherapy [22]. Half of patients treated with conventional radiotherapy were found to have new neuroendocrine dysfunctions over 5 years follow up period. Newer radiation therapy like stereotactic conformal radiotherapy (SCRT) is useful in this context. Other late radiation-related adverse events include growth retardation, hearing impairment, vascular disorders, social and cognitive problems as well as secondary cancer incidence, which is described in various retrospective series as 9.3 to 19% at 30 years [23].

Proton therapy for paediatric cancers provide an innovative and conformal type of RT and is being increasingly used in treatment of childhood tumours as immature, growing tissue of children makes them particularly vulnerable to risk of secondary tumours and late radiation injury. This is possible due to superior dose conformity and lower normal tissue dose, offering better Quality of Life (QoL) for childhood cancer patients and survivors [24]. Chilkuri et al. demonstrated a low incidence of grade 3 acute toxicities despite a median dose of 54 CGE for CNS tumours with overall, 62%, 26%, and 0% of patients having grade 1, grade 2, and grade 3 fatigue, respectively [25].

Especially in craniospinal irradiation for medulloblastoma, multiple prospective and retrospective studies confirm this benefit though the patterns of failure and overall survival is similar between photon and proton therapy. Proton beam therapy conferred better dose sparing for the lens (Dmax < 10 Gy, thyroid (Dmean < 6 Gy and heart (Dmean <3.5G) and also significantly superior results for dose constraints of the hippocampus, normal brain, and brainstem when compared to photon therapy [26].

In non-medulloblastoma paediatric CNS tumours also, better use of intensity modulated radiotherapy and also proton therapy if feasible should be considered as there is evidence for lesser decline of neurocognitive functions in patients who received stereotactic radiation when compared to conventional radiation [27].

### 3.3 Chemotherapy

The role of chemotherapy in paediatric brain tumours is mainly as an adjuvant therapy to surgery and radiation therapy. Especially in embryonal tumours like medulloblastoma, chemotherapy given as concurrent with radiation therapy and as adjuvant results in better overall survival and disease control. In paediatric glioblastoma, the role of addition of temozolomide as concurrent and adjuvant therapy was studied by Mallick et al. and found to have superior overall survival rates with adjuvant temozolamide when compared to concurrent temozolamide alone.

In a retrospective analysis of 23 paediatric glioblastoma patients, the estimated median OS was 41.9 months at a median follow-up of 18 months (range: 2.1–126 months). For patients receiving concurrent and adjuvant TMZ, median OS was 41.9 months ($P = 0.081$) when compared to only concurrent TMZ which was 8 months. Estimated median OS for patients who did not complete six cycles of adjuvant TMZ was 9.5 months versus not reached for those who completed at least six cycles ($P = 0.0005$) [28].

### 3.4 Proton therapy

Since 2020, proton therapy is available in the Indian subcontinent. There are published literature from India on initial experience regarding the clinical profile and acute tolerance of proton therapy in childhood CNS tumours. Of total 39 patients in the 1–18 yrs. age group, 48% were CNS tumours. Majority of them received CSI (44%) followed by focal supratentorial or infratentorial radiation. Fatigue with radiation was seen as grade 1 (62%), grade 2 (26%), and none of patients had grade 3 fatigue. The various CNS tumours treated with proton therapy in this Indian study included medulloblastoma esp. craniospinal irradiation, glioma, ependymoma, craniopharyngioma, germ cell tumours, pinealoblastoma [25]. Globally, most of the paediatric oncologists prefer to use proton therapy in paediatric CNS tumours in view of the long term benefits previously discussed in this chapter.

### 3.5 Multidisciplinary treatment

Current practice of paediatric neuro-oncology depends precisely on the multidisciplinary team including neurosurgeon, radiation oncologist, paediatric oncologist, neuroradiologist etc. [29]. Detailed review of the various multimodality treatment protocols in paediatric neuro-oncology are out of the scope of this chapter [30].

Medulloblastoma is a classic example of multidisciplinary treatment. Post-surgery, for average risk the standard of care remains CSI to a dose equivalent to 23.4 Gy in 11 fractions followed by boost to the tumour bed up to a dose of 54–55 Gy along with vincristine used concomitantly on weekly basis. This is followed by adjuvant chemotherapy of 6 cycles using vincristine, cyclophosphamide, and cisplatin-based chemotherapy. High-risk patients are treated with standard dose CSI (35 Gy) delivered concurrently with carboplatin for first 15 fractions and the entire posterior fossa is boosted up to 54–55 Gy. Boost is also considered for areas with gross disease. This is followed by adjuvant chemotherapy follows same protocol as in standard-risk. A

large series on medulloblastoma by Mazumdar et al. has described the pattern of care in about 365 patients from 1985 to 2010 [31]. **Table 7** illustrates the role of multidisciplinary tumour boards as reported in various Indian studies.

## 4. Outcomes

There is lack of enough randomised controlled studies or prospective data on the outcomes from the lower- and middle-income countries (LMIC). Cure rates in children with brain tumours are seen to be lower in LMICs.

The improvement in survival for children with brain tumours noted in high income countries over last few decades are not seen in LMICs because of under-diagnosis, incorrect clinical assessment, and lack of availability of appropriate services like neurosurgical, radiotherapy and radiology [1].

Multidisciplinary team management in tertiary cancer centres is recommended to treat childhood CNS tumours because of the complexity and rarity of these cancers. Aggressive tumour subtypes with high histological grades, younger age, difficult localization with inoperability, and as often seen in LMICs, delays in diagnosis and treatment can contribute to dismal outcomes [28, 29].

Coordinated paediatric neuro-oncology units are available only in few centres in India. Comprehensive multidisciplinary treatment in a co-ordinated manner, study of the epidemiology of paediatric brain tumours, reduction of treatment abandonment, and improvement in the follow-up of paediatric brain tumour patients has been reported when such programs are started [6].

Prospective studies on neurocognitive function of young brain tumour patients who received SCRT revealed young age (<13 y) and left hippocampus dose predicted for clinically relevant decline in certain neurocognitive domains on multivariate analysis. A mean dose of ≤30 Gy to the left hippocampus as a dose constraint for preserving intelligence quotient was suggested by the authors [30].

Dattatraya et al. [31] reported 5-year PFS of 73% and 10 yr. PFS of 41% in their series of medulloblastoma patients for average risk. In case of high risk, the 5 yr. PFS was only 34%. They also reported a 10-year overall survival rate of 15% only in the patients who were treated from 1985 to 2000. The 5-year survival rate was found to be 33.2% (44 patients). 11.9% (29 patients) were recurrence-free at 5 years. Local recurrence was seen in 13.9% patients and all of which were re-explored. 5 were operated for spinal metastasis. Supratentorial metastasis was seen in 4.9% (10 cases) and 6.4% had spinal metastases.

A study on 200 young patients with low grade brain tumours (cerebral and cerebellar astrocytoma, optic pathway glioma, craniopharyngioma, ependymoma) from Tata memorial hospital by Jalali et al. [22] reported 5-year tumour control rate for the Stereotactic Conformal RT (SCRT) arm as 93% (95% CI, 84–98%) and 92% (95% CI, 83–96%) for the Conventional RT arm ($P$ = 0.49). At the time of progression, patients were managed with a range of attempted salvage therapies including re-excision, chemotherapy, and supportive care only; 6 of these patients in the SCRT arm and 5 in the Conventional RT arm experienced disease progression. There were 14 and 11 deaths in the SCRT and Conventional RT arms, respectively. For the entire cohort of 200 patients, as per intent-to-treat analysis, 5-year rate of overall survival in the SCRT arm was 86% (95% CI, 76–92%) and 91% (95% CI, 83–95%) for the Conventional RT arm ($P$ = 0.54).

Supriya et al. [16] reported outcomes in their series of 52 paediatric CNS tumours patients treated with multimodality treatment. Eight (15.3%) died due to the

progression of disease, but of more concern was that 44% abandoned treatment due to the progression/recurrence of disease. This happened mostly among the high-risk groups with poor prognosis such as medulloblastoma (high risk), pontine glioma and primitive neuroectodermal tumour.

In this same context, Nair et al. [6] published their experience on establishment of dedicated paediatric neuro-oncology unit and reported that patient follow-up rates improved from 37.2 to 82.6% and treatment abandonment decreased from 35.8% to 14.8% over the years of implementation of the paediatric neuro-oncology clinic.

In case of non medulloblastoma tumours like astrocytoma and ependymoma, there is no published literature regarding survival rates from the Indian subcontinent. This points to the need for developing a prospective national database for these cancers.

## 5. Future directions

Paediatric CNS tumours management depends precisely on multimodality approach starting from the diagnosis with latest neuroimaging tools, molecular pathology, neurosurgical interventions, higher radiation techniques including proton therapy wherever feasible, combination chemotherapy regimens and paediatric survivorship clinics for optimum rehabilitation of the children who get cured. This mandates dedicated paediatric neuro-oncology clinics in the institutions where they are being treated. There is substantial evidence to show that such integrated approaches can improve patient outcomes and decrease the treatment abandonment rates [6]. This is an important step in the future direction for paediatric CNS tumour management.

There is very scarce data on the patterns of care and clinical outcomes of paediatric CNS tumours treated in our country and other low- and middle-income countries [1]. There is improvement in overall survival in high income countries during the last few decades, but such information is lacking due to absence of a prospective national database on paediatric CNS tumours [32]. This data assumes importance for both the clinicians and administrative services to plan for improvement in tertiary oncology care for these patients and to establish adequate treatment support like financial and logistics to enable completion of planned treatment and to prevent abandonment of treatment. Also, as the cure rates improve, there is need for better rehabilitation of survivors into the mainstream. There are multiple studies on the paediatric brain tumour survivorship which recommend a multipronged approach to solve the issue [33].

The other challenge that current and future paediatric neuro-oncology management in LMICs face is the increasing incorporation of molecular classification into routine practice. There is more focus on the molecular subtyping in other paediatric CNS tumours apart from medulloblastoma where it has established as the standard practice.

In the current WHO classification of Gliomas, Glioneuronal Tumours, and Neuronal Tumours, 14 new types are added and nearly all of these newly recognised types can be diagnosed on the basis of standard histological, immunohistochemical, and molecular analyses [3]. The critical concern in this regard is the lack of adequate infrastructure to support these advancements and guidelines for classification in LMICs where the basic facilities for integrated paediatric neuro0oncology care itself is limited.

There is need for region specific consensus guidelines regarding the implementation of new WHO classification in India and other LMICs as developed in medulloblastoma [34]. Adequate networking between health care teams from each specialised centre would ensure exchange of advances in diagnosis, treatment nuances and promote pooled data for measuring outcomes.

## Conflict of interest

The authors report no conflict of interests.

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