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SPECIAL ARTICLE

Management of Childhood Brain Tumors: Consensus Report by the Pediatric Hematology Oncology (PHO) Chapter of Indian Academy of Pediatrics (IAP)

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Abstract Brain tumors are the second most common childhood tumors and remain the leading cause of cancer related deaths in children. Appropriate diagnosis and management of these tumors are essential to improve survival. There are no clinical practical guidelines available for the management of brain tumors in India. This document is a consensus report prepared after a National Consultation on Pediatric Brain Tumors held in Delhi on 06 Nov 2008. The meeting was attended by eminent experts from all over the country, in the fields of Neurosurgery, Radiation Oncology, Pediatric Oncology, Neuropathology, Diagnostic Imaging, Pediatric Endocrinology and Allied Health Professionals. This article highlights that physicians looking after children with brain tumors should work as part of a multidisciplinary team to improve the survival, quality of life, neuro-cognitive outcomes and standards of care for children with brain tumors. Recommendations for when to suspect, diagnostic workup, initial management, long-term follow up and specific management of individual tumors are outlined.

Keywords Pediatric brain tumor · Diagnosis · Management

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Introduction

Central Nervous System (CNS) tumors are the second most common childhood tumors after leukemia [1], constituting approximately 20–25% of all childhood malignancies and remain the leading cause of cancer related deaths in children [2]. Pediatric brain tumors, though rare in practice, remain a common concern for patients and pediatricians.

An expert consensus meeting was held at Sir Ganga Ram Hospital, Delhi on 6th November 2008, under the aegis of PHO Chapter of IAP. The aim was to develop practice guidelines for diagnosis and management of childhood brain tumors in the Indian context. All the 32 experts had several years of experience in managing pediatric brain tumors.

Recommendations

Classification and Grading of Brain Tumors (According to WHO 2007 [3])

Histological grading helps the clinician in choice of therapies and determining the prognosis of the tumor. In

the recent WHO classification of brain tumors, few additional entities have been incorporated [3]. The group recommends usage of WHO classification in India to bring uniformity in diagnosis for treatment and prognosis.

General Signs and Symptoms of Intracranial Tumors

The group emphasized the warning signs (Table 1) that should warrant need for imaging to rule out brain tumors.

Diagnostic Studies

Imaging

CT scan is often the first imaging technique obtained because it is easily available [4]. However, MRI offers far superior tumor localization because of the superior image contrast, and its multiplanar capabilities; especially useful in posterior fossa and spinal tumors. Thus MRI is recommended as the first line imaging of choice in pediatric brain tumors. MRI specificity is enhanced with the contrast agent gadolinium diethylenetriaminepentaacetic acid dimeglumine (Gd-DTPA), which should be used in the evaluation of childhood CNS tumors. For the diagnosis of spinal cord tumors or determination of leptomeningeal dissemination of tumors, spinal MRI has supplanted all other techniques, including myelography or CT studies. PET is most helpful in the determination of transformation of a lower-grade tumor (primarily glial) to a higher-grade neoplasm and differentiation of post-therapy (especially post radiation) treatment effects from tumor progression [4].

Table 1 When to suspect brain tumor in children

- Headache

  In young children headache can present as irritability. Often worse in the morning, and improves throughout the day
- Vomiting (often early morning)
- Disturbances of gait and balance
- Cranial nerve abnormalities
- Impaired vision:

–Diplopia (6th nerve palsy). In young children diplopia may present as frequent blinking or intermittent strabismus

–Papilledema from increased ICP may present as intermittent blurred vision

–Parinaud syndrome (failure of upward gaze and setting-sun sign, large pupils and decreased constriction to light)

- Mental disturbances: Somnolence, irritability, personality or behavioral change, or change in school performance
- Seizures, usually focal
- Endocrine abnormalities: Midline supratentorial tumors may cause endocrine abnormalities due to effects on the hypothalamus or pituitary and visual field disturbances due to optic pathway involvement
- Cranial enlargement (characteristic of increased ICP in infants)
- Diencephalic syndrome can be seen in patients aged 6 months to 3 years with brain tumors who present with sudden failure to thrive and emaciation. The syndrome is caused by a hypothalamic tumor in the anterior portion of the hypothalamus or the anterior floor of the third ventricle

Immunohistochemistry

Immunohistochemical markers and molecular alterations may help in establishing diagnosis in ambiguous cases of pediatric brain tumors. In addition to routine immunohistochemical markers like GFAP, synaptophysin, NFP, NSE etc., many immunohistochemical tests (IHC), fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) based assays are available, which help in making a correct diagnosis. For example MIB-1 labeling index is used as an adjunct to histological grading [5]. These should be used for correct tumor characterization.

Cerebro Spinal Fluid (CSF) Studies

CSF should be sampled only when CT scan and/or neurosurgical opinion determines the study is safe to perform, because of the risk of coning in patients with untreated raised intracranial pressure. The following studies are recommended: cell count with cytocentrifuge for cytology of tumor cells, glucose and protein, α-fetoprotein (AFP), human Chorionic Gonadotropin (HCG). CSF is of value in the evaluation of tumors which are in proximity to the circulating CSF (medulloblastoma, ependymoma, brain stem glioma). Alfa-feto protein (AFP) and beta-human chorionic gonadotrophin (β-HCG) in the CSF may be elevated in non-germinomatous CNS germ cell tumors.

Bone Marrow and Other Diagnostic Studies

Bone marrow and bone scan studies are indicated in patients with medulloblastoma/embryonal tumors and supra-tentorial PNET, because of the risk of extra-neural dissemination.

Baseline Investigations Prior to Commencing Treatment

The following baseline studies must be done: ophthalmologic and endocrine assessment as indicated, audiogram and glomerular filtration rate, routine hematological and biochemical assessment pre chemotherapy, sperm cryopreservation should be considered for adolescent males undergoing intensive chemotherapy.

Management

Breaking the News of Diagnosis

News of the diagnosis and information about the prognosis should be imparted in an appropriate environment (a quiet, private place rather than a public setting; ideally no more than two health professionals should be present). Ensure that the parents have a clear enough idea of prognosis to be able to weigh up the merits and drawbacks of treatment.

Support and Follow up of Patients

Treatment/care should be planned in a coordinated fashion. A single pediatric oncologist and his team should ideally supervise care. Patients and relatives must know the main point of contact for advice/support at all stages of illness.

Neurosurgery

Resection of a tumor is justified to give rapid relief from distressing symptoms (for example, raised ICP) or when the tumor is in a non-eloquent area and the risks of resection are considered acceptable. When debulking is carried out, a complete macroscopic resection is preferable to partial removal. Where biopsy is considered in preference to more extensive resection, image directed biopsy should be used rather than freehand needle. Histological reporting should use one of the accepted grading systems (WHO). Early postoperative imaging (48–72 h) should determine the extent of tumor resection and must be performed.

Perioperative Surgical Considerations It is recommended to provide cortisol emergency cover during the perioperative period, if patient is not on high doses of corticosteroids, administer DDAVP, if the patients has diabetes insipidus (DI), prior to surgery, keep a close monitoring of fluid intake and urinary output during surgery and replace losses ml for ml, keep accurate 6–8 hourly fluid balance, insert a urinary catheter if necessary, check paired plasma and urine osmolality, plasma electrolytes and glucose immediately postoperatively and afterwards 8 hourly, check daily weight at 8.00 AM before breakfast, commence oral fluid intake and remove intravenous infusion as soon as feasible, continue to monitor fluid balance for at least 10 to 14 days as in inpatient post surgical setting; a classical triphasic response in anti diuretic hormone (ADH) secretion can occur. This can be associated to Cerebral Salt Wasting as well:

An initial phase of DI, due to edema, manifesting within 24 h post-operative and lasting up to 2 days. A second subsequent phase of either normal fluid regulation or of inappropriate ADH secretion (SIADH) lasting 1–14 days. The latter is presumed to be due to neurosurgical-induced vasopressin neuronal necrosis. A third phase of permanent DI can follow, especially after severe and prolonged SIADH. Each of the above three phases may also occur independently. Cerebral Salt Wasting, due to over secretion of atrial natriuretic peptide causing natriuresis and diuresis, can also develop as a primary (neuronal insult) or as a secondary response to SIADH.

Perioperative Seizure Medications Considering the lack of evidence supporting the use of prophylactic anticonvulsants, the authors recommend that prophylactic AEDs should not be administered routinely to patients who have newly diagnosed brain tumors and should be tapered and discontinued in the first postoperative week in patients who have not experienced a seizure [6]. Long-term treatment with AEDs is indicated once patients who have brain tumor suffer a seizure.

Radiation Oncology

Radiotherapy treatment Parents and relatives should take part in the decision about whether or not to have radiotherapy. The acceptable and effective total tumor dose for patients who are fit is variable for various tumors ranging from 21–60 Gy. Localized irradiation is preferable to whole brain irradiation except in primitive embryonal tumors where cranio-spinal irradiation is given. Appropriate customized immobilization should be made for each child. A detailed study of all preoperative and postoperative imaging, preferably with the help of a radiologist and operating neurosurgeon should be undertaken for determining accurate extent of disease for volume generation. Volumes should encompass the presenting enhancing radiological abnormality with appropriate margins as per the histologic subtype of the tumor. All efforts should be made to consider high precision conformal techniques in order to minimize doses of radiation to normal healthy tissues as much as possible. In very young children, radiation may have to be given under short anesthesia and necessitates some adjustments in the techniques [7]. The time from surgery to start of radiotherapy should be kept to a minimum, ideally 4 week. Children may experience mild nausea about 30 min to 1 h after treatment, especially in the first few fractions. Hair loss (localized/global, depending upon the volume and technique) starts about 2–3 wks into treatment. Children may feel tired and sleepy at the end of a course of radiation.

Chemotherapy

Routine adjuvant chemotherapy at primary diagnosis is recommended for primitive embryonal tumors, high grade glioma, intracranial germ cell tumors, low grade gliomas of

optic pathway affecting vision or other low grade gliomas presenting at a very young age and/or progressing despite radiotherapy. If the pediatric oncologist determines that chemotherapy should be administered, the appropriate treatment is varied for various brain tumors.

Long Term Follow up Care

Survivors of CNS tumors may experience many difficulties. Determinants of late effects in the survivors of brain tumors are:

Host Factors: Age, Genetics and Premorbid Conditions,
Tumor Factors: Site, Histology, Biology and Outcome,
Treatment Factors: Surgery, radiotherapy and chemotherapy [8].

The functional complexity of the CNS, and the susceptibility of the developing brain to injury results in special requirements for surveillance following treatment (Table 2).

Management of Common Pediatric CNS Tumors

For most tumors, the same modalities of treatment are used (i.e., surgery, radiation, and in an increasing number of patients chemotherapy), depending on the type of tumor present, its location and the age of the child.

Medulloblastoma

Medulloblastoma, arises in the posterior fossa, and is the most common malignant brain tumor of childhood representing approximately 20% of all childhood brain tumors. Staging studies should include MRI of the spine (with contrast, preferably preoperatively), lumbar CSF cytology, bone scan, liver function tests, and bone marrow examination. Histology and cytogenetics of the original tumor are essential to evaluate for large cell anaplastic subtype and for monosomy 22, which is characteristic of *atypical teratoid/rhabdoid tumor (AT/RT)*. Specific molecular genetic abnormalities like MYC-C, ERBB2 (markers of poor prognosis) and TRK-C (associated with good prognosis) should be tested if available.

The initial step in the treatment is surgical resection in most of the patients. Total or near-total resection of the primary tumor site is associated with better survival, predominantly in non-disseminated patients [9]. Significant postoperative complications may occur, including both septic and aseptic meningitis, postoperative cerebrospinal fluid leaks, and 25% of patients may develop cerebellar mutism syndrome following resection of midline cerebellar tumors [10]. Neurosurgery-related complications have not been related clearly to more aggressive surgery. Following surgery, patients usually are stratified into one of two risk groups, based on extent of surgical resection and disease extent at the time of diagnosis (Table 3) [11].

Patients greater than 3 years of age with average-risk disease are to be treated with cranio spinal (2,340 cGy) and local boost radiotherapy (5,580 cGy), supplemented with adjuvant chemotherapy [12]. Local tumor bed boost (with 1.5–2.0 cms margin, as opposed to whole posterior fossa boost) should be done with conformal RT techniques if available [13]. Different chemotherapeutic regimens have shown benefit in medulloblastoma. Probably, the best tested is the use of vincristine during radiotherapy and the combination of CCNU, cisplatin and vincristine, or cyclophosphamide, cisplatin, and vincristine following radiotherapy [12, 14]. The use of pre-radiotherapy chemotherapy has resulted in inferior survival [12, 14–17]. With such combination approaches, event free survival is about 80% in this group.

Children older than 3 years, who have high-risk medulloblastoma are treated with higher doses of cranio spinal radiation therapy (3,600 cGy) and similar doses of local radiotherapy, as used for children with average-risk disease, and chemotherapy during and after radiation therapy [15]. This group has approximately a 50% to 60% 5-year disease-free survival with this treatment modality. Recent trials have included the use of Carboplatin as a radiosensitizer during radiation therapy and the delivery of higher-dose chemotherapy, essentially an intensified cisplatin, cyclophosphamide, vincristine, and etoposide regimen, supported by peripheral stem cell rescue, following radiotherapy, with possibly better results [15, 18].

Treatment of patients younger than 3 years is problematic, because of the immaturity of the brain and the resultant deleterious effects of whole brain irradiation, increased likelihood of dissemination at the time of diagnosis in younger patients (40%). Infants who have desmoplastic/nodular tumors are quite responsive to chemotherapy, and 75% or greater of patients harboring this histologic variant may be cured by chemotherapy alone. Outcome is less favorable in infants who have classical, undifferentiated medulloblastoma, especially in those who have disseminated disease at the time of diagnosis. More intensive chemotherapeutic regimens using peripheral stem cell support or regimens that have been supplemented with high-dose, intravenous, and intrathecal methotrexate have shown possible increased efficacy [19, 20]. Survivors of medulloblastoma are at risk for significant long-term sequelae [21, 22].

Supratentorial Primitive Neuroectodermal Tumors

They are relatively uncommon, comprising 2.5% of all childhood brain tumors. Surgery forms the mainstay of the

Table 2 Sequelae, Risk Factors and Surveillance

Parameter	Sequelae	Risk factors	Surveillance
Physical health	Dental problems	Radiotherapy to field including jaw (base of skull, cervical spine)	Regular dental review
	Hearing loss	• Platinum chemotherapy • +/−Radiotherapy to field including middle ear (especially posterior fossa)	• Enquire speech and language development
	Neuro-endocrine and growth	• Tumors in area of hypothalamus or pituitary • Cranial radiotherapy	• Regular anthropometric monitoring • Regular endocrinology review • Pituitary function tests
	Secondary tumors	• Radiotherapy • Chemotherapy, particularly Epipodophyllotoxin and alkylating agents • Pre-disposition syndromes e.g. Neurofibromatosis type	• High index of suspicion for lesions (especially skin cancers, meningiomas, glial tumors) within radiotherapy fields • Patient education and regular examination of skin lesions (consider photographs of suspicious lesions)
	Shunts (blocked or infected)		• Inform patient of potential complications and symptoms
	Thyroid function	• Radiotherapy to field including thyroid (base of skull, cervical spine)	• Clinical screening • Annual thyroid function tests
	Alopecia	• Radiotherapy to field including scalp	• Clinical examination
Mental health	Neurocognitive	• Underlying tumor and location (e.g. temporal lobes)	Enquire:
	Behavioral	• Surgery, esp. around sellar area • Combination of cranial radiotherapy and chemotherapy • Prolonged school absence • Prolonged hospitalization • Physical disability: A. Short stature B. Obesity C. Alopecia D. Endocrinopathies	A. Schooling and education B. Behavior Consider referral to: A. Psychology B. Disability team C. Social Work team
Social and activities of daily living	Activities of daily living And self-care Education Employment	• Combination of cranial radiotherapy and chemotherapy • Neurocognitive or behavioral difficulties • Prolonged school absence • Prolonged hospitalization • Physical disability: A. Impaired mobility B. Short stature C. Obesity D. Seizures E. Visual impairment F.Auditory impairment	Enquire: A. Daily activities B. Self-care C. Education/employment Consider referral to: A. Psychology B. Social Work team C. Disability team

treatment, but the degree of surgical resection has been related variably to outcome. Radiotherapy and chemotherapy after surgery is similar to that employed for high-risk medulloblastoma patients.

Pineoblastomas

They are a sub variant of embryonal tumors and are managed in a similar manner to high-risk medulloblastomas.

Table 3 Risk stratification of Medulloblastoma [11]

Risk category	Average	High
Extent of disease	Negative CSF	Positive CSF cytology
	Normal MRI of spine	Positive MRI of spine with Gd-DTPA
	No leptomeningeal disease away from the primary site of tumor	Leptomeningeal disease present away from the primary site of tumor
Volume of residual tumor	≤ 1.5 cm^2	>1.5 cm^2
Histology	Undifferentiated	Large-cell anaplastic
Age at diagnosis	>3 years	<3 years

Atypical Teratoid/Rhabdoid Tumors

These tumors usually occur in children younger than 3 years. Immunohistochemical studies demonstrated that AT/RTs were different from medulloblastomas, they are positive for epithelial membrane antigen, vimentin, cytokeratin, glial fibrillary acidic protein, and, at times, smooth muscle actin and neurofilament protein. Dissemination has been reported in approximately 25% of patients at diagnosis. Management of AT/RTs has been extremely problematic. Outcome after treatment of infants on protocols used for children younger than 3 years with medulloblastoma, including high-dose chemotherapy protocols, has been disappointing, with prolonged survival occurring in less than 20% of patients who had nondisseminated tumors, primarily in those who had undergone a total or near-total resection. Survival seems more favorable in patients older than 3 years at diagnosis, treated with extensive resections, cranio spinal and local boost radiotherapy and chemotherapy.

Gliomas

Astrocytomas are the commonest pediatric CNS malignancy. The astrocytic tumors are further divided into diffusely infiltrating astrocytomas (WHO grade II–IV) and circumscribed gliomas, of which pilocytic astrocytomas are the commonest (WHO grade I).

Low-Grade Gliomas Most low-grade cortical gliomas in children are juvenile pilocytic astrocytoma (JPA) or diffuse fibrillary astrocytoma. Other forms, such as oligodendroglioma, oligoastrocytoma and mixed glioma are much less common [23]. On CT, diffuse astrocytomas appear as ill-defined, homogeneous masses of low density without contrast enhancement. MRI usually shows a mass that is hypodense on T1 weighted and hyperintense on T2 weighted images with little enhancement [24]. Complete surgical resection is curative for most, and even with incomplete excision, long-term progression-free survival is common [25]. If subsequent progression occurs, then re-resection generally is undertaken. For patients who have significant residual or progressive disease not amenable to resection, irradiation with focal conformal techniques to a dose of 5,000 to 5,500 cGy is warranted. Chemotherapy is reserved for very young children and infants and most commonly include Carboplatin and vincristine. Overall 5-year survival is 95%, while progression-free survival is 88%.

High-Grade Gliomas Frequently between 5 and 10 years of age, Anaplastic astrocytoma and glioblastoma are high-grade Gliomas (HGG) [26]. On CT and MRI, HGG typically appear as irregularly shaped lesions with partial contrast enhancement and peri tumoral edema with or without mass effect [27]. Radical (greater than 90%) surgical resection is the most powerful predictor of favorable outcome in HGG when followed by irradiation [28, 29]. Local or wide-field irradiation to 5,000 to 6,000 cGy is the mainstay of therapy. The addition of radiation therapy has improved 5-year survival rates (10% to 30%) compared with surgery alone (0%) [28]. More recently, temozolomide and concurrent radiation followed by maintenance temozolomide therapy is being increasingly utilized following significant survival advantage demonstrated in adult glioblastomas. High-dose chemotherapy for HGG has shown effective responses, and despite significant associated toxicity, may warrant further investigation [30].

Chiasmatic Gliomas Gliomas of the optic chiasm are usually low-grade. They are commonly associated with Neurofibromatosis type 1(NF-1) [31]. In children who have NF-1, tumor biopsy for histologic confirmation is not necessary because of the highly characteristic appearance on MRI. Radiation therapy with 5,000 to 5,500 cGy is generally reserved for older children who have progressive or symptomatic tumors. Therapy with Carboplatin and vincristine has demonstrated tumor shrinkage and/or stabilization in over 90% of children younger than 5 years of age [32, 33].

Brain Stem Gliomas Brain stem gliomas (BSGs) comprise 10% to 15% of all pediatric CNS tumors [23]. BSGs most commonly arise in the pons (diffuse intrinsic). They have

an almost uniformly dismal prognosis. In contrast, those arising from midbrain or medulla are likely to be low-grade lesions that have a more indolent course and better outcome. Diffuse pontine gliomas show CT and MRI characteristics similar to HGG within an enlarged pons. Low-grade BSGs are relatively discrete, often exophytic, and contrast enhancing with cyst formation. Surgical resection is not usually possible because of the proximity to vital structures. There is no apparent benefit from a surgical biopsy when the imaging and clinical picture are indicative of a diffuse infiltrating pontine glioma. For focal tumors (nontectal), complete resection may be safe and may not require any further therapy. Treatment is local irradiation with 5,400 cGy. Over 90% of patients who have diffuse intrinsic lesions transiently respond, but ultimately succumb to disease progression within 18 months of diagnosis. Neither hyper fractionated radiotherapy nor chemotherapy has been shown to add benefit [34]. Following the success of temozolomide in adult high-grade gliomas, similar schedule has been attempted in these patients but without any significant gain in outcome [35]. Low-grade lesions are treated with similar irradiation doses but overall respond less favorably than their counterparts in other locations [36, 37].

Ependymoma

Five percent to 10% of all childhood brain tumors are ependymomas [38, 39], most arise in the posterior fossa. Approximately 5% of ependymomas are disseminated at the time of diagnosis [40]. Mainstay of the treatment is surgery. The degree of surgical resection is a critical determinant of outcome. Those who have total or near-total resections have the highest likelihood of long-term disease control [41]. Second-look surgery after chemotherapy but before radiation may be considered if possible in view of crucial role of extensive surgery in patients with ependymomas. The need for radiotherapy in totally resected non-anaplastic ependymomas is somewhat controversial. Small series have suggested that totally resected supra-tentorial lesions can be treated with surgery alone. Most patients with completely resected infra tentorial tumors having received radiotherapy, have a resultant 5-year progression-free survival rates of 75% to 80% [41]. Local radiotherapy, using conformal treatment planning and doses ranging between 5,500 and 5,960 cGy, is as effective as cranio-spinal and local boost radiotherapy. Patients who have anaplastic tumors may fare less well. Patients, who have sub-totally resected ependymoma, after local radiotherapy, have 5-year progression-free survival rates of probably no higher than 50%. Combination therapy with radiation and chemotherapy has been reserved predominantly for children older than 3 years and those patients who have sub totally resected and/or anaplastic tumors [42, 43]. Ependymomas comprise 20% of infra tentorial tumors in infants. In children younger than 3 years chemotherapy usually is used in attempts to delay the need for radiotherapy, although there has been renewed interest in using local radiotherapy in children as young as 1 year who have infra tentorial tumors, especially for patients who have tumors not amenable to total surgical resection [44].

Craniopharyngiomas

Five percent to 10% of all childhood brain tumors are craniopharyngiomas. These tumors commonly present with failure of growth, delayed sexual maturation, weight gain, and in some cases, diabetes insipidus. Optimal management is still controversial. Complete tumor removal results in an 80% to 95% 10-year progression-free survival rate and cure, but this often are associated with significant behavioral and neuro-cognitive difficulties and permanent endocrine insufficiency. Most patients will need growth, thyroid, cortisol supplementation and chronic DDAVP replacement after total resection. Partial tumor resection and/or cyst aspiration followed by radiotherapy is alternative approach. It is as effective in controlling disease and results in less morbidity [45]. Conservative surgery and modern high precision radiotherapy employing conservative margins associated with excellent outcome, in terms of survival and preservation of function, is being increasingly adopted [46]. Intracavitary brachytherapy using p32 or y90, repeated cyst aspiration, or the use of intracyst bleomycin may be useful in selected situations [47, 48]. At present there is no established role for chemotherapy in craniopharyngioma.

Germ Cell Tumors

Approximately 2% to 5% of all childhood brain tumors are germ cell tumors. Origin is in the pineal and supra sellar region, but may occur throughout the brain. Majority are germinomas (~55%), teratomas, and mixed germ cell tumors (~33%), and the remaining 10% are malignant endodermal sinus tumors, embryonal cell carcinomas, choriocarcinomas, and teratocarcinomas. Histological confirmation is usually, but not always, required for the diagnosis of germinomas and distinction from other pineal region tumors such as pineoblastomas, pineocytomas, and teratomas [49]. Elevated CSF and, in selected cases, blood levels of AFP and β-HCG can be used to confirm a mixed germ cell tumor. Highly elevated levels of β-HCG alone are diagnostic of a choriocarcinoma. Surgery usually is preserved for those patients for whom CSF markers cannot make a diagnosis or when the tumor is very large and requires debulking. Ninety five percent or more of patients with pure germinomas can be cured, including those with disseminated disease at the time of diagnosis by cranio-

spinal plus local boost radiotherapy [50, 51]. Germinomas are also chemosensitive, and treatment with pre-radiation chemotherapy followed by more localized radiotherapy, usually whole ventricular therapy, may be as effective and result in somewhat less sequelae because of the avoidance of whole-brain radiation [52–54]. Mixed germ cell tumors, on the other hand, have only a 40% to 60% likelihood of long-term disease control after treatment with radiotherapy. In these patients, multidrug chemotherapeutic regimens, either given before or after radiotherapy, have resulted in better survival rates [55].

Choroid Plexus Tumors

The treatment of choice for choroid plexus papilloma is surgical removal. Risk of surgical mortality is high due to marked vascularity of the tumor, massive hydrocephalus and very young age. Choroid plexus carcinomas are locally invasive. For long-term disease control, gross total resection is recommended. Optimal treatment for sub totally resected choroid plexus carcinomas is unclear. Adjuvant chemotherapy and radiotherapy have been used and may result in tumor response [56–58].

Spinal Cord Tumors

Spinal cord tumors may be extremely difficult to diagnose in young children. They may present with delays in walking and gait disturbances. Tumors in the conus region result in bowel and bladder difficulties. In total, spinal cord tumors account for less than 10% of all CNS neoplasms. The most common primary CNS lesions are gliomas and ependymomas. Treatment of low-grade spinal astrocytomas is by extensive surgical resection or by partial resection followed by radiotherapy, or possibly, in very young children, chemotherapy [59, 60]. The outcome for children with ependymomas is variable. Long-term control after resection is possible and adjuvant radiotherapy is a useful adjunct. High-grade lesions are difficult to resect. Most patients relapse within 3 to 5 years of diagnosis despite adjuvant radiotherapy [59].

Annexure I

Chairperson: Anupam Sachdeva, President PHO Chapter, IAP

Conveners: S.P. Yadav, Sunil Bhat

Faculty/Experts who participated in National Consultative on Pediatric Brain Tumors: Dr Amita Mahajan, Pediatric Oncologist, Apollo Hospital, Delhi; Dr Sapna Nangia, Radiation Oncologist, Batra Hospital, Delhi; Prof. Raj Kumar, Neurosurgeon, SGPGI, Lucknow; Prof. Raj Warrier, Pediatric Oncologist, Manipal University, Manipal; Prof. Rakesh Jalali, Radiation Oncologist, Tata Memorial Cancer Hospital, Mumbai; Dr Amol Roy Choudhary, Radiation Oncologist, Rajiv Gandhi Cancer Hospital Delhi; Dr Samir Kalra, Neurosurgeon, Sir Ganga Ram Hospital, Delhi; Dr Rana Patir, Neurosurgeon, Sir Ganga Ram Hospital, Delhi; Dr Manish Vaish, Neurosurgeon, Sir Ganga Ram Hospital, Delhi; Dr Gauri Kapoor, Pediatric Oncologist, Rajiv Gandhi Cancer Hospital, Delhi; Dr Anupam Sachdeva, Pediatric Oncologist, Sir Ganga Ram Hospital, Delhi; Prof. Purna Kurkure, Pediatric Oncologist, Tata Memorial Cancer Hospital, Mumbai; Prof. Amita Trehan, Pediatric Oncologist, Post Graduate Institute, Chandigarh; Dr Sunil Bhat, Pediatric Oncologist, Sir Ganga Ram Hospital, Delhi; Prof. Subimal Roy, Neuropathologist, Sir Ganga Ram Hospital, Delhi; Prof. Chitra Sarkar, Neuropathologist, AIIMS, Delhi; Prof Ajay Sharma, Neurosurgeon, MAMC & GB Pant Hospital, Delhi; Dr A.N Jha, Neurosurgeon, Max Devki Devi Hospital, Delhi; Dr Deepak Aggarwal, Neurosurgeon, AIIMS, Delhi; Prof.Ashish Suri, Neurosurgeon, AIIMS, Delhi; Dr Harsh Mahajan, Neuroradiologist, Mahajan Imaging Centre, Delhi; Dr Archana Dayal Arya, Pediatric Endocronoligist, Sir Ganga Ram Hospital, Delhi; Prof. PK Julka, Radiation Oncologist, AIIMS, Delhi; Dr Himesh Gupta, Pediatric Onco-surgeon, Rajiv Gandhi Cancer Hospital, Delhi; Dr Rashmi Dalvi, Pediatric Oncologist, Bombay Hospital, Mumbai; Dr SP Yadav, Pediatric Oncologist, Sir Ganga Ram Hospital, Delhi; Dr Veronique Dinand, Pediatric Oncologist, Sir Ganga Ram Hospital, Delhi; Dr Manas Kalra, Pediatric Oncologist,Sir Ganga Ram Hospital, Delhi; Dr Nita Radhakrishnan, Pediatric Oncologist, Sir Ganga Ram Hospital, Delhi; Dr Satyendra Katewa, Pediatric Oncologist, Sir Ganga Ram Hospital, Delhi; Dr Major M Anjan, Pediatric Oncologist, Sir Ganga Ram Hospital, Delhi.

References

1. Rosemberg S, Fujiwara D. Epidemiology of pediatric tumors of the nervous system according to the WHO 2000 classification: a report of 1,195 cases from a single institution. Childs Nerv Syst. 2005;21:940–4.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006;56:106–30.
3. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization classification of tumors of the central nervous system. Lyon: IARC; 2007.
4. Vézina LG. Neuroradiology of childhood brain tumors: new challenges. J Neuro-Oncol. 2005;75:243–52.
5. Johannessen AL, Torp SH. The clinical value of Ki-67/MIB-1 labeling index in human astrocytomas. Pathol Oncol Res. 2006;12:143–7.
6. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;54:1886–93.

7. Munshi A, Jalali R. A simple technique of supine cranio spinal irradiation. Med Dosim. 2008;33:1–5.
8. Jalali R, Goswami S, Sarin R. Neuropsychological status in children and young adults with benign and low-grade brain tumors treated prospectively with focal stereo tactic conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66:S14–9.
9. Albright AL, Sposto R, Holmes E, et al. Correlation of neurosurgical sub specialization with outcomes in children with malignant brain tumors. Neurosurgery. 2000;47:879–87.
10. Robertson PL, Muraszko KM, Holmes EJ, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg. 2006;105(S6 Pediatrics):444–51.
11. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. J Clin Oncol. 1999;17:832–45.
12. Packer RJ, Gajjar A, Vézina G, et al. Phase III study of cranio spinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol. 2006;24:4202–8.
13. Murthy V, Jalali R, Sarin R, Nehru RM, Deshpande D, Dinshaw KA. Stereo tactic conformal radiotherapy for posterior fossa tumours: a modelling study for potential improvement in therapeutic ratio. Radiother Oncol. 2003;67:191–8.
14. Packer RJ, Sutton LN, Elterman R, et al. Outcome for children with Medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg. 1984;81:690–8.
15. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted cranio spinal radiotherapy followed by high-dose chemotherapy and stem cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicenter trial. Lancet. 2006;7:813–20.
16. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of pre radiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol. 2003;21:1582–91.
17. Kuhl J, Muller HL, Berthold F, et al. Pre radiation chemotherapy of children and young adults with malignant brain tumors: results of the German pilot trial HIT 088/089. Klin Pädiatr. 1998;210:227–33.
18. Kurkure P, Arora, Sarin R, et al. Concomitant chemo radiation in high-risk primitive CNS embryonal tumours prospective pilot study. Eur J Cancer. 2007;4:234.
19. Rutkowski S, Bode U, Deinlein F, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med. 2005;352:978–86.
20. Geyer JR, Sposto R, Jennings M, et al. Multi agent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. J Clin Oncol. 2005;23:7621–31.
21. Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. J Clin Oncol. 2001;19:3470–6.
22. Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE. Neuro Psychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose cranio spinal irradiation: a Pediatric Oncology Group study. J Clin Oncol. 1889;16:1723–8.
23. Gurney JG, Bunin GR. CNS and miscellaneous intracranial and intraspinal neoplasms. In: Ries LAG, Smith MA, Gurney JG, et al., editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995.NIH-PubNo99–4649. Bethesda: National Cancer Institute SEER Program; 1999. p. 51–63.
24. Finizio FS. CT and MRI aspects of supratentorial hemispheric tumors of childhood and adolescence. Childs Nerv Syst. 1995;11:559–67.
25. Pollack IF. The role of surgery in pediatric gliomas. J Neurooncol. 1999;42:271–88.
26. Ciurea AV, Vasilescu G, Nuteanu L, Silveanu-Vladu M, Teodorescu I, Lisievici M. Neurosurgical management of cerebral astrocytomas in children. Ann NY Acad Sci. 1997;824:237–40.
27. Marchese MJ, Chang CH. Malignant astrocytic gliomas in children. Cancer. 1990;65:2771–8.
28. Wolff JE, Gnekow AK, Kortmann RD, et al. Pre radiation chemotherapy for pediatric patients with high-grade glioma. Cancer. 2002;94:264–71.
29. Wisoff JH, Boyett JM, Berger MS, et al. Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. J Neurosurg. 1998;89:52–9.
30. MacDonald TJ, Arenson E, Sposto R, et al. Phase II study of high-dose chemotherapy before radiation in children with newly diagnosed high-grade astrocytoma: final analysis of Children's Cancer Group study 9933. Cancer. 2005;104:2862–71.
31. Burger PC, Cohen KJ, Rosenblum MK, Tihan T. Pathology of diencephalic astrocytomas. Pediatr Neurosurg. 2000;32:214–9.
32. Gropman AL, Packer RJ, Nicholson HS, et al. Treatment of diencephalic syndrome with chemotherapy: growth, tumor response, and long-term control. Cancer. 1998;83:166–72.
33. Packer RJ. Chemotherapy: low-grade gliomas of the hypothalamus and thalamus. Pediatr Neurosurg. 2000;32:259–63.
34. Mandell LR, Kadota R, Freeman C, et al. There is no role for hyper fractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a pediatric oncology group phase III trial comparing conventional vs. hyper fractionated radiotherapy. Int J Radiat Oncol Biol Phys. 1999;43:959–64.
35. Jalali R, Raut N, Arora B, et al. Prospective evaluation of radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. Int J Radiat Oncol Biol Phys. 2010;77:113–8.
36. Farmer JP, Montes JL, Freeman CR, Meagher-Villemure K, Bond MC, O'Gorman AM. Brainstem gliomas. A 10-year institutional review. Pediatr Neurosurg. 2001;34:206–14.
37. Rubin G, Michowitz S, Horev G, Herscovici Z, Cohen IJ, Shuper A, et al. Pediatric brain stem gliomas: an update. Childs Nerv Syst. 1998;14:167–73.
38. Robertson PL, Zeltzer PM, Boyett JM. Survival and prognostic factors following radiation therapy and chemotherapy for ependymoma in children: a report of the Children's Cancer Group. J Neurosurg. 1998;88:695–703.
39. Horn B, Heideman R, Geyer R. A multi-institutional retrospective study of intracranial ependymoma in children: identification of risk factors. J Pediatr Hematol Oncol. 1999;21:203–11.
40. Bouffet E, Perilongo G, Canete A, Massimino M. Intracranial ependymomas in children: a critical review of prognostic factors and a plea for cooperation. Med Pediatr Oncol. 1998;30:319–29.
41. Pollack IF, Gerszten PC, Martinez AJ, et al. Intracranial ependymomas of childhood: long-term outcome and prognostic factors. Neurosurgery. 1995;37:655–66.
42. Merchant TE, Mulhern RK, Krasin MJ, et al. Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. J Clin Oncol. 2004;22:3156–62.

43. Needle MN, Goldwein JW, Grass J, et al. Adjuvant chemotherapy for the treatment of intracranial ependymoma of childhood. Cancer. 1997;80:341–7.
44. Massimino M, Giangaspero F, Garrè ML, et al. Salvage treatment for childhood ependymoma after surgery only: pitfalls of omitting at once adjuvant treatment. Int J Radiat Oncol Biol Phys. 2006;65:1440–5.
45. Sands SA, Milner JS, Goldberg J, Mukhi V, Moliterno JA, Maxfield C, et al. Quality of life and behavioral follow-up study of pediatric survivors of craniopharyngioma. J Neurosurg. 2005;103:302–11.
46. Jalali R, Budrukkar A, Sarin R, Sharma DS. High precision conformal radiotherapy employing conservative margins in childhood benign and low-grade brain tumours. Radiother Oncol. 1995;74:37–44.
47. Merchant TE, Kiehna EN, Kun LE, et al. Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. J Neurosurg. 2006;104:94–102.
48. Kobayashi T, Kida Y, Mori Y, Hasegawa T. Long-term results of gamma knife surgery for the treatment of craniopharyngioma in 98 consecutive cases. J Neurosurg. 2005;102:428–88.
49. Balmaceda C, Modak S, Finlay J. Central nervous system germ cell tumors. Semin Oncol. 1998;25:243–50.
50. Packer RJ, Cohen BH, Cooney K. Intracranial germ cell tumors. Oncologist. 2000;5:312–20.
51. Legido A, Packer RJ, Sutton LN, et al. Supra sellar germinomas in childhood. A reappraisal. Cancer. 1989;63:340–4.
52. Bamberg M, Kortmann RD, Calaminus G, et al. Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89. J Clin Oncol. 1999;17:2585–92.
53. Bouffet E, Baranzelli MC, Patte C, et al. Combined treatment modality for intracranial germinomas: results of a multicentre SFOP experience. Société Française d'Oncologie Pédiatrique. Br J Cancer. 1999;79:1199–204.
54. Balmaceda C, Heller G, Rosenblum M, et al. Chemotherapy without irradiation a novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial. The First International Central Nervous System Germ Cell Tumor Study. J Clin Oncol. 1996;14:2908–15.
55. Yoshida J, Sugita K, Kobayashi T. Treatment of intracranial germ cell tumors: effectiveness of chemotherapy with cisplatin and etoposide (CDDP and VP16). Acta Neurochir Wien. 1993;120:111–7.
56. Berger C, Thiesse P, Lellouch-Tubiana A, Kalifa C, Pierre-Kahn A, Bouffet E. Choroid plexus carcinoma in childhood: clinical features and prognostic factors. Neurosurgery. 1998;42:470–5.
57. Pencalet P, Sainte-Rose C, Lellouch-Tubiana A, et al. Papillomas and carcinomas of the choroid plexus in children. J Neurosurg. 1998;88:521–8.
58. McEvoy AW, Harding BN, Phipps KP, et al. Management of choroid plexus tumours in children: 20 years experience at a single neurosurgical center. Pediatr Neurosurg. 2000;32:192–9.
59. Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ. Radical excision of intra medullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg. 2000;93:183–93.
60. Bouffet E, Pierre-Kahn A, Marchal JC, et al. Prognostic factors in pediatric spinal cord astrocytoma. Cancer. 1998;83:2391–9.