In children, tumours of the central nervous system comprise 20% of all tumours and are second most common after leukaemia. Unlike adults, almost half of all the paediatric brain tumours are in the Infratentorial region as shown in table 1. In the infratentorial region, the common tumours are medulloblastoma, low grade cerebellar astrocytoma, brain stem glioma and ependymoma. In the supratentorial region, most of the paediatric tumours are in the supra or parasellar region (craniopharyngioma, optico-chiasmal or hypothalamic gliomas); hemispheric gliomas / PNETs or pineal region tumours.

Fortunately, with the exception of brain stem gliomas, high grade hemispheric gliomas and some undifferentiated malignant tumours, most paediatric brain tumours have a 50-90% chance of long term cure with appropriate management. The treatment in itself could however result in moderate to severe neuro cognitive, psychological and endocrine dysfunction. The radiation dose, volume of brain irradiated and the age at which radiotherapy is given all correlate with the incidence and severity of post radiation sequelae (Jannoun, IJROBP, 1990). The aim of treatment for childhood brain tumours is therefore not only to achieve long-term cures but also focus on treatment strategies with minimal treatment related toxicity. The goal is also to integrate available scientific evidence in routine practice respecting local issues in terms of patient population, logistics, financial support and continued monitoring during and after treatment.

Evaluation

Clinical evaluation: Nature, duration and course of symptoms to be recorded in detail.

- Seizure frequency, type and severity. Anti-epileptic medication and any known allergies
- Symptoms and signs of abnormal higher mental function, raised ICT, visual acuity and fields, papilloedema or optic atrophy, cerebellar dysfunction, focal sensory-motor deficit, cranial neuropathies, endocrinopathies.
- Assessment of developmental milestones, physical growth and sexual maturation, scholastic performance and social development.
- For all suprasellar chiasmal or hypothalamic gliomas evaluate for cutaneous stigmata of Neurofibromatosis type I; for Sub Ependymal giant cell astrocytomas- skin (adenoma sebaceum, ash leaf spots), renal angiomyolipoma or cardiac rhabdomyomas of tuberous sclerosis; and for Haemangioendothelomas- renal or pancreatic lesions of Von Hippel Lindau’s disease.

<table>
<thead>
<tr>
<th>LOCATION AND TYPE OF TUMOURS</th>
<th>% OF ALL BRAIN TUMOURS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infratentorial</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>20-25</td>
</tr>
<tr>
<td>Low-grade astrocytoma, cerebellar</td>
<td>12-18</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>4-8</td>
</tr>
</tbody>
</table>
Low-grade astrocytoma, brain stem 3-9
Malignant glioma, brain stem 3-6
Others 2-5
**Total** 45-60

**Supratentorial hemispheric**
Low-grade astrocytoma 8-20
Malignant glioma 6-12
Ependymoma 2-5
Mixed glioma 1-5
Ganglioglioma 1-5
Oligodendroglioma 1-5
Choroid-plexus tumour 1-5
Primitive neuroectodermal tumour 1-5
Meningioma 0.5-2
Other 1-3
**Total** 25-40

Supratentorial midline
Supracellular
Craniopharyngioma 6-9
Low-grade glioma, chiasmatic 4-8
hypothalamic
Germ-cell tumour 1-2
Pituitary adenoma 0.5-2.5
Pineal region
Low grade glioma 1-2
Germ-cell tumour 0.5-2
Pineal parenchymal tumour 0.5-2
**Total** 15-20

**Table 2** : The new WHO classification of brain tumours, Kleihues P, Burger PC, Scheithauer BW. Brain Pathology 3:255-68, 1993

**Neuroepithelial Tumors of the CNS**
1. Astrocytic tumors
   1. Pilocytic astrocytoma (WHO grade I)
   2. Astrocytoma (WHO grade II) - variants: protoplasmic, gemistocytic, fibrillary, mixed
3. Anaplastic (malignant) astrocytoma (WHO grade III)  
4. Glioblastoma multiforme (WHO grade IV) - variants: giant cell glioblastoma, gliosarcoma  
5. Subependymal giant cell astrocytoma (WHO grade I)  
6. Pleomorphic xanthoastrocytoma (WHO grade I)  
7. Oligodendroglioma (WHO grade II)  
8. Anaplastic (malignant) oligodendroglioma (WHO grade III)

2. Ependymal cell tumors  
1. Ependymoma (WHO grade II) - variants: cellular, papillary, epithelial, clear cell, mixed  
2. Anaplastic ependymoma (WHO grade III)  
3. Myxopapillary ependymoma  
4. Subependymoma (WHO grade I)  
5. Mixed gliomas  
6. Mixed oligoastrocytoma (WHO grade II)  
7. Anaplastic (malignant) oligoastrocytoma (WHO grade III)  
8. Others (e.g. ependymo-astrocytomas)

3. Neuroepithelial tumors of uncertain origin  
1. Polar spongioblastoma (WHO grade IV)  
2. Astroblastoma (WHO grade IV)  
3. Gliomatosis cerebri (WHO grade IV)

4. Tumors of the choroid plexus  
1. Choroid plexus papilloma  
2. Choroid plexus carcinoma (anaplastic choroid plexus papilloma)

5. Neuronal and mixed neuronal-glial tumors  
1. Gangliocytoma  
2. Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)  
3. Ganglioglioma  
4. Anaplastic (malignant) ganglioglioma  
5. Desmoplastic infantile ganglioglioma  
6. Central neurocytoma  
7. Dysembryoplastic neuroepithelial tumor  
8. Olfactory neuroblastoma (esthesioneuroblastoma)

6. Pineal Parenchyma Tumors  
1. Pineocytoma  
2. Pineoblastoma  
3. Mixed pineocytoma/pineoblastoma

7. Tumors with neuroblastic or glioblastic elements (embryonal tumors)  
1. Medulloepithelioma  
2. Primitive neuroectodermal tumors with multipotent differentiation  
   a) Medulloblastoma - variants: medullosomyoblastoma, melanocytic medulloblastoma, desmoplastic medulloblastoma  
   b) Cerebral primitive neuroectodermal tumor  
3. Neuroblastoma - variant: ganglioneuroblastoma  
4. Retinoblastoma  
5. Ependymoblastoma
Other CNS Neoplasms
1. Tumors of the Sellar Region
   1. Pituitary adenoma
   2. Pituitary carcinoma
   3. Craniopharyngioma

2. Hematopoietic tumors
   1. Primary malignant lymphomas
   2. Plasmacytoma
   3. Granulocytic sarcoma

3. Others
   1. Germ Cell Tumors
   2. Germinoma
   3. Embryonal carcinoma
   4. Yolk sac tumor (endodermal sinus tumor)
   5. Choriocarcinoma
   6. Teratoma
   7. Mixed germ cell tumors

4. Tumors of the Meninges
   1. Meningioma
   2. Atypical meningioma
   3. Anaplastic (malignant) meningioma
   4. Non-meningothezial tumors of the meninges

Laboratory Evaluation: In addition to routine laboratory investigations for preoperative anaesthesia work up, hormonal assays for tumours in the sellar/suprasellar region and electrolytes and urine/serum osmolality for suspected diabetes Insipidus. For patients on anti-epileptic drugs, serum levels should be monitored whenever appropriate.

Radiological Examination: Plain and Gadolinium enhanced MRI of the brain is preferable over CECT for almost all paediatric brain tumours, especially in suspected cases of brain stem gliomas, medulloblastoma, ependymoma, supra or parasellar tumours, Intra-ventricular and Pineal region lesions. Skull x rays do not provide any additional information. Specialized investigations such as MR spectroscopy or perfusion studies and PET scan, though considered investigational, can provide useful information in cases that pose major diagnostic difficulties. In addition to cranial imaging, if possible, spinal MRI should also be performed for tumours with high propensity for neuraxis dissemination such as medulloblastoma, intracranial germ cell tumour, undifferentiated round cell tumours such as ependymoblastoma and PNET and primary CNS lymphoma.

CSF studies:
1. Cytology for Malignant Cells: Indicated in Medulloblastoma, germ cell tumours, PNETs and Lymphomas. There should be at least 10-14 days interval between CSF examination and surgery.
2. Tumour markers: CSF (and serum) AFP and Beta HCG in all known or suspected cases of primary intracranial germ cell tumours. Considering the diagnostic difficulties and very different management and prognosis of various Pineal...
region tumours, tumour markers should be done for all pineal region tumours to rule out a germ cell tumour.

3. Biochemistry and culture: For suspected infections, demyelinating disorders and difficult diagnostic cases.

Post operative evaluation: Evaluate for any new post-operative deficit such as cranial neuropathy, motor, speech or visual deficit, diabetes Insipidus (for suprasellar region surgeries) or mutism (for cerebellar surgeries). Evaluate wound healing or any features of wound or meningeal infections, CSF leakage or rhinorrhea. Identify need for physiotherapy, speech therapy, counselling or rehabilitation.

Confirmation of diagnosis: For all brain tumours, it is imperative to correlate the clinical and radiological features with the histological diagnosis. In case of any discrepancy or diagnostic difficulty, joint discussion between clinicians, radiologists and pathologists is desirable. Immuno-histochemistry is especially useful in pineal region tumours, gliomas, hemangiblastoma, neuronal tumours and other tumours posing diagnostic difficulties.

Post operative Imaging: Ideally it should be done for all cases to judge the extent of resection or any post-operative complication. Immediate (within 24-48 ours) contrast enhanced MRI or CT scan is very important for tumours such as medulloblastoma, ependymoma, low grade or benign tumours, where the presence and volume of post operative tumour is a strong predictor of disease outcome or where the need for adjuvant treatment depends upon the presence or extent of residual disease.

Management of common paediatric brain tumours
The management of each child has to be individualised depending upon the clinical presentation, age, histology, tumour location, size and infiltration, diagnostic and therapeutic facilities / expertise available, patient’s affordability and likely compliance with the prescribed diagnostic or treatment protocol. Because of the diverse histological types and different locations of various paediatric brain tumours, a relatively small number of any specific paediatric brain tumours are treated even in the large cancer centres. Hence Level I evidence from multiple relatively large randomized trials is available only for medulloblastoma. There are a few small RCTs in brain stem gliomas and paediatric high grade gliomas. For most other paediatric brain tumours, evidence for the efficacy or toxicity of a particular treatment approach is generally from retrospective or prospective single institution studies as will be discussed.

Surgery is the mainstay of treatment in most paediatric brain tumours with the exception of diffuse pontine glioma, optic pathway gliomas, germ cell tumours, malignant gliomas and PNETs. Advances in neuro-imaging and microsurgical and stereotactically guided neurosurgical techniques have made it possible to achieve complete excision of the tumour with acceptable complication in a greater proportion of patients.

All patients with malignant brain tumours require post operative radiotherapy. Benign or low grade tumours may also require post operative radiotherapy if residual tumour is causing or likely to cause neurological dysfunction or there is documented progression or recurrence. While radiotherapy has been reasonably effective in a majority of these tumours, there have been concerns about treatment related
morbidity mainly due to the effect of ionising radiation to the growing brain. The morbidity includes neuropsychological impairment, endocrine dysfunction, growth retardation, risk of second malignancy and cerebrovascular events. Although the exact etiopathogenesis of these sequelae is not clearly established, it is likely a combination of the effects of tumour itself (particularly with respect to its location), surgery, radiotherapy, chemotherapy and other causes. It is also fair to assume that radiotherapy is at least partly responsible and therefore attempts should be made to minimise the doses and/or volumes of radiation to the surrounding normal brain while maintaining/improving cure rates. Radiotherapy is avoided in children (especially < 3 years) in low-grade tumours and efforts are underway to reduce the doses in other tumours such as medulloblastomas and germ cell tumours (based on phase II but without Level 1 randomised data). Also, a majority of the patients in whom the radiation is delayed eventually do require radiation therapy at later stage.

Dose of radiation per fraction in children should be kept below 2 Gy (generally 1.8 Gy for focal brain and 1.6-1.7 Gy for CSI). The total dose for benign or low grade tumours is 50-54Gy depending upon the age and volume and high grade tumours (e.g. malignant gliomas) 55-60Gy. One of the means in recent years to improve the therapeutic efficacy of radiation is the introduction of high-precision techniques of radiation planning and delivery. This has been largely possible with the major advances in imaging such as CT, MRI, which help in defining the tumour and its spread, technological revolution in radiotherapy planning with the emergence of dedicated computerized treatment planning workstations and high quality assurance programmes. Three dimensional conformal radiation therapy (CRT) and stereotactic conformal radiotherapy (SCRT), generally using multiple coplanar/non-coplanar beam arrangements are such techniques that have the potential to minimize doses to the normal brain and critical structures as compared to conventional radiotherapy. Maximal benefit of these techniques minimizing doses to normal brain is likely to be in children with tumours associated with good long-term survival. However, the evidence of the long-term effects from focal brain irradiation is so far from the retrospective trials. There is therefore need to evaluate this issue in prospective manner. We are at present conducting a randomized trial comparing stereotactic conformal radiotherapy with conventional radiotherapy in minimizing late sequelae in children and young adults.

Multiagent chemotherapy has a central role in primary intracranial germ cell tumours or lymphomas and results in improvement in disease free survival when used as an adjuvant in medulloblastoma, PNETs and malignant gliomas. In children with low grade gliomas below the age of 3 years in whom radiotherapy sequelae may be unacceptable, chemotherapy can result in objective responses in up to two thirds of patients, allowing radiotherapy to be instituted at a later age. In other paediatric brain tumour, role of chemotherapy is still considered investigational.

The details of surgery, radiotherapy and chemotherapy for specific tumours as practised at our centre are discussed in the following section.

**A. Medulloblastoma**

Patients with medulloblastoma require multimodal management with surgery, radiotherapy with or without chemotherapy. All patients should be assigned to appropriate risk stratification for the optimum management. A majority of evidence (in particular randomised data) has been generated based on these risk categories.

Average (standard) risk:
1. totally or near-totally (<1.5 Sq. cm. of residual disease) resected tumour
2. age > 3 years
3. No dissemination beyond posterior fossa

High risk:
1. age below 3 years
2. subtotal resection (>1.5 Sq.cm. of residual disease) on a post-operative CT/MRI scan
3. dissemination to non-posterior fossa location.

Surgery: is usually in the form of a posterior midline suboccipital craniectomy and attempted total excision. All attempts should be made to achieve total or near total excision of the tumour as it has a direct bearing on the probability of cure and the need for adjuvant chemotherapy, (Albright AL, Neurosurgery 1996). Facilities for paediatric neuro ICU and ventilatory support should be taken into account before embarking on a very aggressive neurosurgical approach. Due to the possibility of shunt related complications, CSF diversion shunt procedures are not recommended routinely if adequate tumour debulking has been achieved.

Radiotherapy: Craniospinal radiation is central to the management of these tumours. Depending upon the age and the use of chemotherapy, cranio-spinal irradiation (CSI) of 25 to 35 Gy and boost radiation to the posterior fossa to a total dose of 50-55 Gy over 6-7 weeks is the standard of care (Freeman, MPO 2002). Good immobilisation, customized shielding blocks with adequate safety margins around cribriform plate and temporal lobes and quality assurance is a major determinant in obtaining good cure rates in medulloblastomas (Mirallbell IJROBP 1997). Hence these children should receive radiotherapy preferably in tertiary centres where all modern radiotherapy facilities and expertise is available. Neuraxis irradiation can result in neuro-cognitive, psychological and endocrine dysfunction and the spinal radiation could affect vertebral growth, gonads and thyroid. These radiation sequelae depend on the CSI dose and age. While the standard of care is still a CSI dose of 35 Gy (for >3 years age) and posterior fossa boost of 20 Gy (SIOP ref), in North America and some European centres the most commonly used regimen is now reduced dose CSI (23.4-25 Gy) along with chemotherapy, while maintaining the posterior fossa dose of 50-55 Gy. However, this approach is based on non randomized excellent results seen in few specialized neuro-oncology units (Packer JCO 1999) and it is debatable whether they can be generalized specially since excess recurrences from reduced CSI dose (without chemotherapy) has been documented in previous studies (Bailey 1995).

Chemotherapy: The role of adjuvant chemotherapy has been evaluated in a number of randomized trials conducted from 1970 onwards by 3 SIOP trials, CCG and POG studies. All these RCTs show a significant improvement in the disease free survival, especially in the high risk patients (Tait, EJC 1990, Bailey, MPO 1995). However, in most trials, the improvement in the disease free survival has failed to translate in improved overall survival, possibly due to the relatively small number of patients (only few hundred patients) or late relapses (Tait, EJC 1990). The most recent SIOP / UKCCSG PNET-3 RCT of pre radiation chemotherapy versus RT alone in 217 patients (in non-disseminated tumours) again confirms improved DFS with chemotherapy but fails to show overall survival benefit in the entire group (Taylor, JCO 2003). In contrast to the findings from previous SIOP studies, significant
survival benefit was seen in patients with total excision but not in those with subtotal excision. The lack of benefit with chemotherapy in the presence of gross post operative tumour residue in this study may have been due to the delay in starting radiotherapy by giving pre-radiation chemotherapy or relative ineffectiveness of the chemotherapy regimen used (carboplatin instead of cisplatin). On multivariate analysis, in addition to the use of chemotherapy, the only other independent predictor of improved DFS was the completion of radiotherapy course within 50 days. Considering the central role of radiotherapy and the major adverse impact of prolongation in radiotherapy time, adjuvant chemotherapy whenever indicated should be given after radiotherapy to avoid prolongation of radiotherapy time, especially if growth factors cannot be used due to the cost and logistics.

**Average/standard risk**: The current standard therapy for children with average risk medulloblastoma is surgery followed by standard dose radiation to CSI (35Gy in 21 fractions over 4 weeks) followed by posterior fossa boost to a dose of 19.8Gy in 11 fractions.

**High risk**: For these patients, the post operative adjuvant treatment is CSI + posterior fossa dose as for average risk patients followed by 6 cycles of ICE chemotherapy. For patients with M3 beyond/unfit to receive radiotherapy upfront, patient are treated first with chemotherapy followed by radiation. For patients with localised leptomeningeal deposits, a boost (5-10Gy) of RT is given after standard CSI.

- **Inj Ifosphamide 1.5gm/sqm IV infusion D1-5**
- **Inj Cisplatin 20mg/sqm IV infusion D1-5**
- **Inj Etoposide 100 mg/sqm IV infusion D1-5**
- **Inj Mesna 20% of total dose of Ifosphamide in divided doses**
  - Repeated every 3 weeks
  - Hematological monitoring and growth factor support whenever necessary

**B. Brain stem gliomas**:

**Presentation**: Based on their location, imaging features and growth pattern, brain stem gliomas can be broadly classified as: Diffuse intrinsic tumours (80%); focal (well circumscribed, <2cm) tumours (5-10%), dorsal exophytic (10-20%) and cervicomedullary (5-10%) tumours. The clinical presentation depends upon the type of brain stem glioma. While the diffuse pontine gliomas typically have a short history of multiple cranial nerve palsies, long tract signs and ataxia, the dorsal exophytic tumours have a longer history and present with features of raised intra cranial pressure, cranial nerve palsies but long tract signs are very uncommon. The focal tumours that commonly arise from midbrain or medulla, have a long history of isolated cranial nerve palsy and contralateral hemiparesis.

**Treatment**: Traditionally all brain stem gliomas were almost exclusively treated with radiotherapy alone, sometimes after a biopsy. However, with better neuro-imaging, surgical techniques and post-operative care it is now possible to attempt surgical excision of selected dorsal exophytic, focal and some cervico-medullary tumours. In case of total excision and favourable histology, post operative radiotherapy is not indicated routinely in such tumours (Freeman IJROBP 1998). For diffuse pontine gliomas with characteristic clinical presentation and MRI appearance, biopsy is not necessary if it entails risk. These tumours are treated with conventionally fractionated radiotherapy to a dose of 54Gy in 30 fractions over 6
weeks which results in clinical improvement in 75% children, median survival of 6-9 months and 2 year survival of 20%. Various strategies to improve the cure rates with hyperfractionated dose escalated radiotherapy or chemotherapy were not found to be effective in randomized trials and therefore not practised in our centre (Mandell, IJROBP, 1999;). For histologically confirmed high grade gliomas, the radiation dose could be 60Gy in 30 fractions over 6 weeks.

C. Cerebellar Astrocytomas:
Vast majority of childhood cerebellar astrocytomas are low grade juvenile pilocytic astrocytomas and present with features of raised intra cranial pressure and cerebellar signs. These tumours often have characteristic imaging (cystic tumours with enhancing mural nodule). Maximal safe resection should be attempted for all cases. Post operative radiotherapy (localised fields to a dose of 54 Gy/30#) is required in selected cases with residual disease particularly in the brain stem. Chemotherapy is generally not indicated in these tumours. Low grade cerebellar astrocytomas have an excellent long term prognosis but they may have neurological or endocrine dysfunction even when radiotherapy has not been administered (Merchant TE, IJROBP 2002). For the rare paediatric high grade cerebellar astrocytomas, post operative radiotherapy (localised fields to a dose of 55-60Gy/30#) with or without adjuvant chemotherapy should be considered in all cases.

D. Ependymomas:
Ependymomas in children are twice as common in the 4th ventricular region as compared to the supratentorial hemispheric region. Fourth ventricular ependymomas typically present with features of raised intra cranial pressure or cranial nerve palsies while the supratentorial hemispheric ependymomas present with seizures, raised intracranial pressure of focal deficits. Histologically, most ependymomas are benign but they could be anaplastic. Ependymomas, especially high grade and infratentorial ones have a high propensity for spread along the cerebro-spinal fluid pathways.

Treatment:

Surgery: Most large retrospective studies have shown a strong correlation between the extent of surgery and survival. The 5 year survival rate of 40% with incomplete excision is significantly inferior to 75% with complete excision (Rousseau, IJROBP, 1994). Immediate post operative contrast enhanced MRI is useful in assessing volume of residual tumour and the need for re-excision.

Radiotherapy: Along with surgery, radiotherapy is the mainstay of treatment in ependymoma. While ependymomas have a higher propensity for CSF spread, routine use of cranio spinal irradiation (CSI) in the absence of documented CSF spread does not prolong survival or significantly alter the failure pattern as compared to focal brain irradiation. Considering the sequelae of CSI, and the relative lack of benefit with CSI (as compared to medulloblastoma), CSI is recommended only when CSF cytology or spinal MRI shows neauraxis spread of ependymoma (Pollack, NEJM, 1994; Rousseau, IJROBP, 1994, Vanuytsel IJROBP, 1992). For 4th ventricular ependymomas, the entire posterior fossa up to C2/3 junction or lower in case of spinal extension should be irradiated while in supratentorial tumours, focal irradiation of the tumour with 2-3 cms margins is recommended. Radiotherapy Dose recommended is 54Gy in 30 fractions over 6 weeks.

Chemotherapy: In various non randomised studies, no additional benefit was
observed with the use of adjuvant chemotherapy (Rousseau, IJROBP, 1994; Vanuytsel IJROBP, 1992, Grill J, Paediatr Drugs 2003).

E. Craniopharyngioma:

**Presentation**: These are one of the most common suprasellar tumours in children and young adults, often presenting with symptoms of optic pathway compression, raised intracranial pressure and endocrinopathies such as growth retardation. They have a characteristic radiological appearance of a solid cystic, rim enhancing calcified suprasellar mass and intraoperatively the pathognomonic machine oil fluid with shimmering cholesterol crystals is seen.

**Treatment**: Surgery is the mainstay of treatment but due to its adherence to the hypothalamus, optic apparatus and vessels, achieving complete excision safely could be a formidable surgical challenge. Hence complete microsurgical removal should be attempted in centres with adequate facilities and expertise. In subtotally resected tumours, post operative conformal radiotherapy to a dose of 54Gy in 30 fractions over 6 weeks results in good long term control rates comparable to completely excised tumours (Neurosurgery 2000) and acceptable toxicity. Rapid clinical worsening during radiotherapy from cystic enlargement, seen in about 15% patients if not promptly addressed by cyst aspiration is often fatal (Rajan, IJROBP, 1997). Intracavitary installation of beta emitting radioisotopes or bleomycin is being evaluated in predominantly cystic tumours. Following treatment these patients often require lifelong endocrine surveillance and hormone replacements.

F. Optic chiasmal / Hypothalamic Gliomas:

**Presentation**: Optic chiasmal / optic nerve and hypothalamic gliomas are common suprasellar tumours in children. For large tumours in this region, it may be difficult to distinguish between chiasmal and hypothalamic tumours on imaging and also intra-operatively. Tumours with significant extension along optic nerves and posterior optic tracts are likely to be chiasmatic in origin. Up to one third of patients with optic gliomas may have cutaneous stigmata of Neurofibromatosis type I (NF-I) such as Cafe-Au-Lait spots and neurofibromas. Vast majority of tumours in this region are low grade pilocytic astrocytoma with a long indolent course. Common presenting features are gradually worsening visual acuity and fields, precocious puberty or growth retardation, weight loss, diabetes Insipidus and sometimes raised intracranial pressure. Meningiomas of the optic nerve sheath are very rare.

**Management**: Very slowly growing or incidentally discovered NF-I associated chiasmal gliomas in children can be kept under close observation. For patients with NF-I and characteristic imaging features, histological confirmation may not be necessary. In other cases, open biopsy is preferable before instituting definitive treatment. In patients presenting with visual defects or other symptoms, radiotherapy is the mainstay of treatment. Conformal radiotherapy to a dose of 50-54Gy in 30 fractions over 6 weeks results in excellent long term survival and stabilization or improvement in vision in most patients (Saran, IJROBP 2003). In very young children with progressive symptoms, chemotherapy with baby brain protocol can arrest tumour growth for variable period of time and allow the delivery of radiotherapy (if required) at a later age (Packer, JCO 1993).

Baby brain Protocol : Inj Vincristine 1.5mg/sqm IV bolus
Inj Carboplatin 550mg/sqm IV infusion
Repeated 6 weekly

G. Supratentorial gliomas:

Gliomas are the most common hemispheric tumour. Low grade gliomas constitute more than half of the supra-tentorial hemispheric tumours in children. Others are high-grade gliomas and mixed tumours like oligodendrogliomas and gangliogliomas.

Common clinical presentations are seizure, raised intracranial pressure and focal neurological signs depending on the tumour location, any associated oedema or herniation. Management of cerebral hemispheric tumours depend upon the age, tumour location and histological type.

**Low-grade gliomas**: Surgery is the mainstay of treatment and in non eloquent areas total excision should be attempted. Post operative radiotherapy is indicated only in cases with gross residual tumours especially if there are residual focal deficits, mass effect or risk of progressive irreversible neurological worsening. Excellent long term cure (80-90%) is achieved after total excision or partial excision plus radiotherapy. Policy of post-operative observation with deferred radiotherapy until tumour progression is safe in cases with unequivocal histology, no unusual enhancement on CT or MRI and the patient is expected to comply with clinical and radiological follow up. Conformal radiotherapy to the residual tumour with 1-2 cm margins to a dose of 50-54Gy in 30 fractions over 6 weeks results in excellent long term results. For very large volume of brain irradiation or age below 3 years, the total radiation dose can be limited to 45Gy in 25–28 fractions. For very young children chemotherapy given to avoid or delay radiotherapy can result in objective responses and disease stabilization in up to two third of patients (Packer, JCO, 1993).

**Malignant gliomas**: Maximal safe resection followed by radiotherapy to the original tumour + 2-3 cm margins to a dose of 55-60 Gy/28-33# is the standard treatment for these patients. As compared to adults, the prognosis of paediatric malignant gliomas is slightly better. Only one small randomized trial has evaluated the benefit of adjuvant chemotherapy in paediatric malignant glioma. In this CCSG trial, the five year DFS improved from 18% after RT alone to 46% with the addition of CCNU, Vincristine and Prednisilone chemotherapy (Sposto, J Neuro oncol, 1989).

**Gangliogliomas**: Complete excision is possible in most of the cases with excellent long term results. Radiotherapy is usually not indicated in these tumours.

**Dysembryoplastic Neuro-Epithelial Tumour (DNET)**: Surgical excision is curative in almost all cases without any need for adjuvant treatment.

H. Ventricular tumours:

The common tumours in this location are either Central Neurocytoma, Sub Ependymal Giant Cell Astrocytoma (SEGA/SNGCA) or Choroid plexus papilloma. These are all slow growing tumours that present with obstructive hydrocephalus. Surgical excision is generally curative and focal radiotherapy is required occasionally for large residual or recurrent inoperable tumours.

For the rare choroid plexus carcinomas, adjuvant radiotherapy and chemotherapy is
indicated.

I. Pineal Region Tumours:

**Presentation**: They often present with features of raised intracranial pressure, compression of the surrounding structures and Parinaud’s syndrome, which manifests itself by upward gaze and pupillary abnormalities. The common pineal region tumours are the primary intracranial germ cell tumours, pineocytoma, astrocytomas and pinealoblastoma. The germ cell tumours can be further classified as Germinoma or Non Germinomatous germ cell tumour and these tumours can be located in the pineal or suprasellar region alone or bifocal tumours located at both sites. Pinealoblastoma and germ cell tumours have a propensity for CSF dissemination.

**Management**: The initial surgery could be an attempted total excision, open or stereotactic biopsy. Further management of pineal region tumours depend on the histology, tumour markers and CSF spread if any.

**Germinoma**: In patients with unequivocal histology, normal markers and CSF cytology excellent long term cure with minimal sequelae can be achieved with low dose Craniospinal Irradiation of 30 Gy + local tumour bed boost of 15Gy (MAKEI trial Bamberg M, JCO 1999). The sequelae of CSI on cognition, endocrine and gonads can be minimised by using chemotherapy followed by radiotherapy only to the tumour bed in this patient population. However, since the late toxicity of reduced dose CSI is only mild, it is a viable treatment option, especially considering the cost of chemotherapy and its potentially life threatening acute complications like severe dyselectrolytaemia for suprasellar germ cell tumours. In very young children, in order to avoid sequelae of CSI, chemotherapy followed by radiotherapy only to the tumour bed also achieves excellent results. In patients with malignant cells in the CSF or elevated CSF tumour markers, chemotherapy and CSI is required to obtain high cure rates.

**Non-germinomatous germ cell tumours**: In patients with normal CSF cytology and spinal imaging, chemotherapy with BEP along with focal radiotherapy to a dose of 45-55Gy using 3 fields. Patients in whom CSF cytology or MRI spine shows metastasis, chemotherapy and CSI (30 -35Gy) + local tumour bed boost of 15 Gy is recommended (Aoyama H, Radiother Oncol, 1998; Ogawa K, Cancer 2003).

**BEP regimen**
- Inj Bleomycin 18U/m2 IV or IM Day 1, 8 and 15
- Inj Etoposide 100 mg/m2 IV infusion Day 1-5
- Inj Cisplatin 20 mg/m2 IV infusion Day 1-5
- Total 4 cycles, repeated 3 weekly

**Pineoblastoma and other Supratentorial PNETs**

Poorly differentiated small round cell tumors of the cerebrum have been referred to as cerebral neuroblastoma and as primitive neuroectodermal tumors. These tumors in the pineal body have classically been called pineoblastomas. Histologically, these tumors may be similar to cerebellar medulloblastoma with varying proportions of features that suggest astrocytic or ependymal differentiation.
Management of these tumours is similar to that of medulloblastoma but the outcome in supratentorial PNETs is not as favourable as medulloblastoma. (Jakacki, JCO 1995)

**Follow-up**

All patients have a post-radiotherapy scan 6-12 weeks after RT completion, which acts as a baseline for future reference. Subsequent scans are done whenever indicated clinically. Patients should be continuously followed up and particular attention given to detect any late sequelae in the form of possible endocrine deficits with appropriate hormone replacement therapy. Children could also exhibit neurological and cognitive dysfunctions, which may need dedicated facilities such as occupational therapy, special schools for education and learning skills, teaching of blind patients and appropriate vocational rehabilitation. These may even need a life long policy of constant monitoring. Long term childhood brain tumour survivors at our centre are reviewed periodically in a special after completion of therapy (ACT) clinic, where many of these issues are dealt with. Our charity organisation (Brain Tumour Foundation of India, [www.brain tumourindia.com](http://www.brain tumourindia.com)) dedicated to the welfare of these patients also has been playing a critical part in the overall management and in particular, several of the issues addressed above.

**Paediatric Brain Tumours**

**Long-term psychological effects in children treated for intracranial tumors.**
Jannoun L, Bloom HJ.

The results are reported of the psychological assessment of 62 children who presented with primary intracranial tumors and who received radiotherapy at the Royal Marsden Hospital between 1963 and 1973. Evaluations were carried out 3-20 years after treatment. All patients were free from progressive tumor at testing. The average IQ of the total series was within the normal range (Full-Scale IQ 92) but 23% of the patients were functioning at an educationally subnormal level of intelligence (IQ less than 80). Sex, tumor type, tumor location and the radiotherapy volume and site of maximum dose were not found to have a significant effect on intellectual outcome. A significant correlation was found between intelligence and age at the time of treatment. Children who received treatment under the age of 5 years were more adversely affected (average IQ 72) than those who were aged 6-10 (average IQ 93) and those aged 11-15 years (average IQ 107). The incidence of neurological abnormalities and physical disability was significantly greater among patients with supratentorial tumors (72% of cases), compared with patients with infratentorial lesions (44% of cases). The results were discussed in terms of the management of young patients with intracranial tumors.

**Effects of medulloblastoma resections on outcome in children: a report from the Children’s Cancer Group.**
Albright AL, Wisoff JH, Zeltzer PM et al.

We reviewed the data of children with high-stage primitive neuroectodermal tumors (medulloblastomas) who were treated on Children’s Cancer Group-921 protocol to evaluate the correlation between tumor resection and prognosis. Patients enrolled in
the study had either tumors that were operatively categorized to be Chang tumor stage 3b or 4, postoperative residual tumors > 1.5 cm², or evidence of tumor dissemination (Chang metastasis Stages [M Stages] 1-4) at diagnosis. Resections were analyzed in two ways, as follows: 1) by the extent of resection (percent of the tumor that was removed), as estimated by the treating neurosurgeon; and 2) by the extent of residual tumor (how much of the tumor was left), as estimated from postoperative scans. Two hundred and three children were enrolled in the study with institutional diagnoses of primitive neuroectodermal tumors-medulloblastomas; diagnoses were confirmed by central neuropathological review in 188 patients. Progression-free survival (PFS) at 5 years was 54% (standard error, 5%). As in previous Children’s Cancer Group studies, age and M stage correlated with survival; PFS was significantly lower in children 1.5 to 3.0 years old at diagnosis and in those with any evidence of tumor dissemination (M Stage 1-4). On univariate analysis, neither extent of resection nor extent of residual tumor correlated with PFS. However, adjusting for other factors, extent of residual tumor was important; PFS was 20% (standard error, 14%) better at 5 years in children with no dissemination (M Stage 0) who had < 1.5 cm² of residual tumor (P=0.065) and was 24% (standard error, 14%) better at 5 years in children > 3 years old with no tumor dissemination (M Stage 0) and with < 1.5 cm² residual tumor (P=0.033). On the basis of our observations, we conclude that extent of tumor resection, as estimated by the neurosurgeon, does not correlate with outcome but that extent of residual tumor does correlate with prognosis in certain children (those who are > 3 years old, with no tumor dissemination). In contrast to age and M stage, the major factors associated with outcome, residual tumor is an important variable in outcome, one that neurosurgeons can control.

**Radiotherapy for medulloblastoma in children: a perspective on current international clinical research efforts.**
Freeman CR, Taylor RE, Kortmann RD et al.

BACKGROUND: The North America and four European pediatric cooperative groups have undertaken prospective studies for medulloblastoma continuously since the 1970s. In this article, we will review the results of these studies with respect specifically to the use of radiotherapy, and trace the developments that have led up to the present trials for patients with this tumor. PROCEDURE: Published and unpublished data from the North American CCG and POG and now COG studies, from the UKCCG and SIOP groups, as well as from the French and German groups were reviewed. Issues of especial interest included radiotherapy dose and dose fractionation schedules, scheduling of chemotherapy and radiotherapy, and technical aspects of treatment with radiotherapy that might impact on outcome. RESULTS AND CONCLUSIONS: Much progress has been made in the management of medulloblastoma in childhood as a consequence of the studies undertaken sequentially by these groups over the past two decades. It now seems clear that chemotherapy plays an important role for all patients. In patients with average risk disease, the use of chemotherapy has allowed a reduction in the dose of radiotherapy to the craniospinal axis and the combination of chemotherapy with radiotherapy appears to have brought about a significant improvement in disease-free and overall survival in this patient population. Patients with high-risk disease fare better now than in the past as a consequence of the routine use of aggressive chemotherapy and preliminary data suggest that the use of higher doses of radiation as in the POG studies is associated with a particularly favorable outcome. Accurate
delivery of radiotherapy is essential for optimal results. The availability of better tools at the treating centres and quality control as an integral part of cooperative studies are likely to bring about further improvements in outcome in the future.

**Pediatric medulloblastoma: radiation treatment technique and patterns of failure.**

PURPOSE: In this study factors are analyzed that may potentially influence the site of failure in pediatric medulloblastoma. Patient-related, disease-related, and treatment-related variables are analyzed with a special focus on radiotherapy time-dose and technical factors.

METHODS AND MATERIALS: Eighty-six children and adolescents with a diagnosis of medulloblastoma were treated in Switzerland during the period 1972-1991. Postoperative megavoltage radiotherapy was delivered to all patients. Simulation and portal films of the whole-brain irradiation (WBI) fields were retrospectively reviewed in 77 patients. The distance from the field margin to the cribiform plate and to the floor of the temporal fossa was carefully assessed and correlated with supratentorial failure-free survival. In 19 children the spine was treated with high-energy electron beams, the remainder with megavoltage photons. Simulation and port films of the posterior fossa fields were also reviewed in 72 patients. The field size and the field limits were evaluated and correlated with posterior fossa failure-free survival.

RESULTS: In 36 patients (47%) the WBI margins were judged to miss the inferior portion of the frontal and temporal lobes. Twelve patients failed in the supratentorial region and 9 of these patients belonged to the group of 36 children in whom the inferior portion of the brain had been underdosed. On multivariate analysis only field correctness was retained as being significantly correlated with supratentorial failure-free survival (p=0.049). Neither the total dose to the spinal theca nor the treatment technique (electron vs. photon beams) were significantly correlated with outcome. Posterior fossa failure-free survival was not influenced by total dose, overall treatment time, field size, or field margin correctness. Overall survival was not influenced by any of the radiotherapy-related technical factors.

CONCLUSION: A correlation between WBI field correctness and supratentorial failure-free survival was observed. Treatment protocols should be considered that limit supratentorial irradiation mainly to subsites at highest risk of relapse. Optimized conformal therapy or proton beam therapy may help to reach this goal. Treating the spine with electron beams was not deleterious. A significant correlation between local control and other technical factors was not observed, including those relating to posterior fossa treatment. The use of small conformal tumor bed boost fields may be preferred to the larger posterior fossa fields usually considered as the standard treatment approach.

**Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I).**
Tait DM, Thornton-Jones H, Bloom HJ et al.

Two hundred and eighty-six patients with medulloblastoma from 46 centres in 15 countries were treated in a prospective randomized trial designed to assess the value of adjuvant chemotherapy. All patients were treated by craniospinal irradiation. Those randomly allocated to receive adjuvant chemotherapy were given vincristine during irradiation and maintenance CCNU and vincristine, given in 6-weekly cycles,
for 1 year. The overall survival was 53% at 5 years and 45% at 10 years. At the close of the trial in 1979, the difference between the disease-free survival rate for the chemotherapy and control groups was statistically significant (P=0.005). Since then, late relapses have occurred in the chemotherapy arm and the statistically significant difference between the two groups has been lost. Although there is now no statistical difference between the two arms of the trial, a benefit for chemotherapy persists in a number of sub-groups; partial or sub-total surgery (P=0.007), brainstem involvement (P=0.001), and stage T3 and T4 disease (P=0.002). A number of prognostic factors for medulloblastoma have emerged; subtotal resection, extent of disease and being male sex carry a poor prognosis.

**Prospective randomised trial of chemotherapy given before radiotherapy in childhood medulloblastoma. International Society of Paediatric Oncology (SIOP) and the (German) Society of Paediatric Oncology (GPO): SIOP II.**

Bailey CC, Gnekow A, Wellek S et al.

In a multicentre randomised clinical trial 364 children with biopsy proven medulloblastoma were randomly assigned to receive or not pre-radiotherapy chemotherapy. Children with total or subtotal removal of the tumour, no evidence of invasive brain stem involvement, and no evidence of metastatic disease either within or without the cranium were designated “low risk”, those with gross residual tumour, evidence of invasive brain stem involvement or metastases in the central nervous system were designated “high risk”. All children were prescribed 55 Gy to the tumour bearing area. “Low risk” children could be randomised to “standard” radiotherapy 35 Gy to the craniospinal axis or “reduced” dose 25 Gy to the craniospinal axis. Chemotherapy consisted of vincristine, procarbazine, and methotrexate given in a 6-week module before radiotherapy, and for “high risk” children, vincristine and CCNU given after radiotherapy. No benefit for the receipt of pre-radiotherapy chemotherapy could be demonstrated for any group. In addition, a negative interaction was observed between the receipt of the chemotherapy and reduced dose radiotherapy with a particularly poor outcome being observed in this group of children.

**Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children’s Cancer Group Study.**

Packer RJ, Goldwein J, Nicholson HS et al.

PURPOSE : Medulloblastoma is the most common malignant brain tumor of childhood. After treatment with surgery and radiation therapy, approximately 60% of children with medulloblastoma are alive and free of progressive disease 5 years after diagnosis, but many have significant neurocognitive sequelae. This study was undertaken to determine the feasibility and efficacy of treating children with nondisseminated medulloblastoma with reduced-dose craniospinal radiotherapy plus adjuvant chemotherapy. PATIENTS AND METHODS : Over a 3-year period, 65 children between 3 and 10 years of age with nondisseminated medulloblastoma were treated with postoperative, reduced-dose craniospinal radiation therapy (23.4 Gy) and 55.8 Gy of local radiation therapy. Adjuvant vincristine chemotherapy was administered during radiotherapy, and lomustine, vincristine, and cisplatin chemotherapy was administered during and after radiation. RESULTS : Progression-free survival was 86% +/- 4% at 3 years and 79% +/- 7% at 5 years. Sites of
relapse for the 14 patients who developed progressive disease included the local tumor site alone in two patients, local tumor site and disseminated disease in nine, and nonprimary sites in three. Brainstem involvement did not adversely affect outcome. Therapy was relatively well tolerated; however, the dose of cisplatin had to be modified in more than 50% of patients before the completion of treatment. One child died of pneumonitis and sepsis during treatment. CONCLUSION: These overall survival rates compare favorably to those obtained in studies using full-dose radiation therapy alone or radiation therapy plus chemotherapy. The results suggest that reduced-dose craniospinal radiation therapy and adjuvant chemotherapy during and after radiation is a feasible approach for children with nondisseminated medulloblastoma.

Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children’s Cancer Study Group PNET-3 Study.
Taylor RE, Bailey CC, Robinson K et al.

PURPOSE: To determine whether preradiotherapy (RT) chemotherapy would improve outcome for Chang stage M0-1 medulloblastoma when compared with RT alone. Chemotherapy comprised vincristine 1.5 mg/m² weekly for 10 weeks and four cycles of etoposide 100 mg/m² daily for 3 days, and carboplatin 500 mg/m² daily for 2 days alternating with cyclophosphamide 1.5 g/m². PATIENTS AND METHODS: Patients aged 3 to 16 years inclusive were randomly assigned to receive 35 Gy craniospinal RT with a 20 Gy posterior fossa boost, or chemotherapy followed by RT. RESULTS: Of 217 patients randomly assigned to treatment, 179 were eligible for analysis (chemotherapy + RT, 90 patients; RT alone, 89 patients). Median age was 7.67 years, and median follow-up was 5.40 years. Overall survival (OS) at 3 and 5 years was 79.5% and 70.7%, respectively. Event-free survival (EFS) at 3 and 5 years was 71.6% and 67.0%, respectively. EFS was significantly better for chemotherapy and RT (P=.0366), with EFS of 78.5% at 3 years and 74.2% at 5 years compared with 64.8% at 3 years and 59.8% at 5 years for RT alone. There was no statistically significant difference in 3-year and 5-year OS between the two arms (P=.0928). Multivariate analysis identified use of chemotherapy (P=.0248) and time to complete RT (P=.0100) as having significant effect on EFS. CONCLUSION: This is the first large multicenter randomized study to demonstrate improved EFS for chemotherapy compared with RT alone. It is anticipated that this regimen could reduce ototoxicity and nephrotoxicity compared with cisplatin-containing schedules. The importance of avoiding interruptions to RT has been confirmed.

A detrimental effect of a combined chemotherapy-radiotherapy approach in children with diffuse intrinsic brain stem gliomas?
Freeman CR, Kepner J, Kun LE et al.

PURPOSE: To compare the proportion of patients that survive at least 1 year following treatment with hyper-fractionated radiotherapy (HRT) to a dose of 70.2 Gy on Pediatric Oncology Group (POG) study #8495 with that of patients treated with similar radiotherapy plus cisplatinum given by continuous infusion on weeks 1, 3, and 5 of radiotherapy on POG #9239. METHODS AND MATERIALS: The eligibility criteria for the two studies were identical and included age 3 to 21 years, previously
untreated tumor involving the brain stem of which two-thirds was in the pons, history less than 6 months, and clinical findings typical for diffuse intrinsic brain stem glioma, including cranial nerve deficits, long tract signs, and ataxia. The outcome of 57 patients who were treated at the 70.2 Gy dose level of POG #8495 between May 1986 and February 1988 was compared with that of 64 patients treated with identical radiotherapy plus cisplatinum on POG #9239 between June 1992 and March 1996. RESULTS: The number of patients accrued to POG #9239 was determined to guarantee that the probability was at least 0.80 of correctly detecting that the 1-year survival rate exceeded that of patients on POG #8495 by 0.2. However, the z value for this test was -1.564, giving a p value of 0.9411. That is, there is almost sufficient evidence to conclude that survival for patients receiving HRT plus cisplatinum on POG #9239 was worse than that for patients receiving the same radiotherapy alone on POG #8495. CONCLUSION: The finding that patients who received cisplatinum given as a radiosensitizing agent concurrent with HRT fared less well than those receiving the same dose of HRT alone was unexpected and is clearly a cause for concern as many current protocols for patients with diffuse intrinsic brain stem gliomas call for use of chemotherapeutic and/or biological agents given concurrent with radiotherapy.

There is no role for hyperfractionated 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. hyperfractionated radiotherapy.
Mandell LR, Kadota R, Freeman C et al.

PURPOSE: In June 1992, POG began accrual to a phase III study, POG-9239, designed to compare the time to disease progression, overall survival, and toxicities observed in children with newly diagnosed brainstem tumor treated with 100 mg/m² of infusional cisplatin and randomized to either conventional vs. hyperfractionated radiotherapy. METHODS AND MATERIALS: Patients eligible for study were those between 3 and 21 years of age with previously untreated tumors arising in the pons. Histologic confirmation of diagnosis was not mandatory, provided that the clinical and MRI scan findings were typical for a diffusely infiltrating pontine lesion. Treatment consisted of a six-week course of local field radiotherapy with either once a day treatment of 180 cGy per fraction to a total dose of 5400 cGy (arm 1) or a twice a day regimen of 117 cGy per fraction to a total dose of 7020 cGy (the second of the three hyperfractionated dose escalation levels of POG-8495) (arm 2). Because of previously reported poor results with conventional radiotherapy alone, cisplatin was included as a potential radiosensitizer in an attempt to improve progression-free and ultimate survival rates. Based on results of the phase I cisplatin dose escalation trial, POG-9139, 100 mg/m² was chosen for this trial and was delivered by continuous infusion over a 120-hour period, beginning on the first day of radiotherapy and repeated during weeks 3 and 5. One hundred thirty eligible patients were treated on protocol, 66 on arm 1 and 64 on arm 2. RESULTS: The results we report are from time of diagnosis through October 1997. For patients treated on arm 1, the median time to disease progression (defined as time to off study) was 6 months (range 2-15 months) and the median time to death 8.5 months (range 3-24 months); survival at 1 year was 30.9% and at 2 years, 7.1%. For patients treated on arm 2, the corresponding values were 5 months (range 1-12 months) and 8 months (range 1-23 months), with 1- and 2-year survival rates at 27.0% and 6.7%, respectively. Evaluation of response by MRI at 4 or 8 wks post
treatment was available in 108 patients and revealed a complete response in 1 patient of each Rx arm, a partial response (> 50% decrease in size) in 18 patients of arm 1 and 15 patients of arm 2, minimal to no response (stable) in 25 patients of arm 1 and 23 patients of arm 2, and progressive disease in 13 patients of arm 1 and 12 patients of arm 2. The pattern of failure was local in all patients. Morbidity of treatment was similar in both Rx arms, with no significant toxicity (including hearing loss) reported. Autopsy was performed in 6 patients, and confirmed the presence of extensive residual tumor in these cases. CONCLUSION: The major conclusion from this trial is that the hyperfractionated method of Rx 2 did not improve event-free survival (p=0.96) nor did it improve survival (p=0.65) over that of the conventional fractionation regimen of Rx 1, and that both treatments are associated with a poor disease-free and survival outcome.

**Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function.**

Merchant TE, Williams T, Smith JM et al.
Int J Radiat Oncol Biol Phys. 2002 Sep 1;54(1):45-50

PURPOSE: To prospectively evaluate pediatric patients with localized primary brain tumors for evidence of endocrinopathy before radiotherapy (RT). METHODS AND MATERIALS: Seventy-five pediatric patients were evaluated with the arginine tolerance test and L-dopa test for growth hormone secretory capacity and activity; thyroid-stimulating hormone surge and thyrotropin-releasing hormone stimulation test for the hypothalamic-thyroid axis; the 1-microg adrenocorticotropin hormone (ACTH) and metyrapone test for ACTH reserve; and, depending on age, a gonadotropin-releasing hormone stimulation test to determine gonadotropin response. The study included 38 male and 37 female patients, age 1-21 years with ependymoma (n=35), World Health Organization (WHO) Grade I-II astrocytoma (n=18), WHO Grade III-IV astrocytoma (n=10), craniopharyngioma (n=7), optic pathway tumor (n=4), and germinoma (n=1). Seven patients receiving dexamethasone at the time of the evaluation were excluded from the final analysis. RESULTS: Of 68 assessable patient, 45 (66%) had evidence of endocrinopathy before RT, including 15 of 32 patients (47%) with posterior fossa tumors. Of the 45 patients, 38% had growth hormone deficiency, 43% had thyroid-stimulating hormone secretion abnormality, 22% had an abnormality in ACTH reserve, and 13% had an abnormality in age-dependent gonadotropin secretion. CONCLUSION: The incidence of pre-RT endocrinopathy in pediatric brain tumor patients is high, including patients with tumors not adjacent to the hypothalamic-pituitary unit. These data suggest an overestimation in the incidence of radiation-induced endocrinopathy. Baseline endocrine function should be determined for brain tumor patients before therapy. The potential for radiation-induced endocrinopathy alone cannot be used as an argument for alternatives to RT for most patients. Pre-RT endocrinopathy may be an early indicator of central nervous system damage that will influence the functional outcome unrelated to RT.

**Intracranial ependymoma: long-term results of a policy of surgery and radiotherapy.**

Vanuytsel LJ, Bessell EM, Ashley SE et al.

Ninety-three patients with primary intracranial ependymoma were treated at the Royal Marsden Hospital, between 1952 and 1988, with postoperative radiotherapy.
The survival probability at 5, 10, and 15 years was 51%, 42% and 31%, respectively, and the corresponding progression free survival (PFS) probability, 41%, 38%, and 30%. Tumor grade was the single most important prognostic factor for survival and PFS with gender of lesser prognostic significance. Treatment parameters were stratified for grade. In patients with low grade tumors survival and PFS were better following complete macroscopic excision compared to incomplete surgery. The extent of resection had no significant influence on survival or PFS in patients with high grade tumors. Extent of irradiation did not influence PFS, irrespective of tumor grade, while patients with high grade tumors had marginally better survival following extensive irradiation compared to more limited radiotherapy. The main problem in the treatment of ependymoma remains local progression which was the cause of death in all but two patients. New treatment strategies should focus on improvement of local control, especially in incompletely resected low grade tumors and all high grade tumors. The use of spinal irradiation is unlikely to significantly improve treatment results.

**Treatment of intracranial ependymomas of children: review of a 15-year experience.**

**PURPOSE:** There are still major controversies in the optimal management of children with intracranial ependymomas. To assess the impact of tumor site, histology, and treatment, the outcome of children treated at the Institut Gustave Roussy was reviewed retrospectively. **METHODS AND MATERIALS:** Between 1975 and 1989, 80 children aged 4 months to 15.8 years were seen at the Institut Gustave Roussy for postoperative management of an intracranial ependymoma. Location of tumor was infratentorial in 63 cases and supratentorial in 17. Surgical treatment consisted of complete resection in 38, incomplete resection in 38 and biopsy only in 4. Postoperative irradiation was done in 65 patients and chemotherapy in 33. Surviving patients have been followed from 12-197 months with a median of 54 months. **RESULTS:** The 5-year actuarial survival and event-free survival are 56% and 38%, respectively. Thirty-four patients relapsed from 3-72 months after diagnosis (median 25 months). In 20 patients, the only site of failure was the original tumor site. Three patients failed locally and at distance, while 10 others failed only at distance. Survival at 5 years was significantly better for patients who had complete resection of the tumor (75% vs. 41%, p=0.001) and for those who received radiation therapy (63% vs. 23%, p=0.003). Event-free survival at 5 years was superior in patients with complete resection of the tumor (51% vs. 26%, p=0.002) and in patients who received radiation therapy (45% vs. 0%, p<0.001). Sex and tumor site had no impact on survival or event-free survival. There was no difference in survival, event-free survival, or pattern of failure between patients treated with local field, whole brain or craniospinal irradiation, while severe longterm sequelae were noted predominantly in the latter two groups. **CONCLUSION:** Considering that failures were predominantly local and that there was no apparent benefit from prophylactic irradiation, we recommend local field irradiation with doses above 50.0 Gy for all children with intracranial ependymomas, without meningeal dissemination at diagnosis. Special considerations are necessary for children < 3 years of age.

**Childhood ependymoma: a systematic review of treatment options and strategies.**
Grill J, Pascal C, Chantal K.

Childhood intracranial ependymoma have a dismal prognosis, especially in young children and when a gross total resection cannot be performed. Even in the absence of a radiologically proven residuum, around two-thirds of these young children will have a recurrence. Adjuvant therapy is therefore necessary for most, if not all, patients. Despite some indication that benign ependymoma (WHO grade II) could show a better outcome, histology cannot be used at present to stratify treatment protocols. Craniospinal irradiation combined with posterior fossa boost has deleterious adverse effects on cognition. Consequently, pediatric oncology teams have, firstly, tried to use chemotherapy to delay or avoid irradiation, and secondly, progressively reduced irradiation fields to the tumor bed without altering the prognosis. Cisplatin, at a dose of 120 mg/m$^2$ (cumulated response rate of 34% [95% CI 19-54%]) is the only single agent that has reproducibly shown some efficacy in ependymoma. Despite some combinations showing efficacy in the adjuvant setting, childhood intracranial ependymomas can, in general, be considered as chemoresistant. The overexpression of the multidrug resistance-1 gene and the 06-methylguanine-DNA methyltransferase have been implicated as possible mechanisms for this phenomenon. As the use of chemotherapy with current agents is questionable, phase II studies with new agents and combinations are necessary. Since the main problem of this disease is local relapse, it may not be necessary to irradiate the whole posterior fossa. However, local control of the disease by irradiation has to be improved. In this respect, hyperfractionation or radiosensitizers may be valuable therapeutic options. The treatment of children with ependymoma is a challenge for all caregivers. There is no doubt that any possible improvement in the management of this rare tumor will only be the result of well designed cooperative trials.

**Long-term outcomes for surgically resected craniopharyngiomas.**
[No authors listed]

OBJECTIVE: This retrospective study critically analyzed the long-term functional outcomes and tumor recurrence rates for surgically treated craniopharyngiomas. METHODS: This study used an outcome classification system that included functioning vision, independent versus dependent living, Karnofsky Performance Scale scores, academic levels, work status, and psychological status. Tumor recurrence rates were analyzed with respect to the extent of surgical resection and adjunctive radiotherapy. RESULTS: For 121 patients, with a mean follow-up period of 10 years, the overall “good outcome” rate was 60.3%. Factors associated with poor outcomes included lethargy at presentation, visual deterioration, papilledema, tumor calcification, hydrocephalus, and tumor adhesiveness at surgery. Gross total resection was associated with good outcomes ($P=0.017$) and decreased risk of recurrence ($P=0.024$). Subtotal resection was associated with increased risk of tumor recurrence ($P=0.0235$). The highest risk of recurrence was in the subtotal resection/no radiation group ($P=0.0001$). There were no differences in outcomes or recurrence rates between pediatric and adult patients. There were also no differences in outcomes or recurrence rates between papillary and adamantinous tumors. Approximately one-third of patients exhibited morbid obesity, and permanent diabetes insipidus was observed for 25 patients. CONCLUSION: A rigorous evaluation of outcomes for tumors such as craniopharyngiomas must consider not only the extent of resection, as judged by postoperative imaging, but also the long-term
physical, intellectual, and psychological functioning of the patients.

**Craniopharyngioma: improving outcome by early recognition and treatment of acute complications.**
Rajan B, Ashley S, Thomas DG et al.

PURPOSE: To assess the frequency, mode of presentation, treatment, and outcome of acute complications in patients with craniopharyngioma around the time of radiotherapy. METHODS AND MATERIALS: A review was made of 188 patients with craniopharyngioma treated with conservative surgery and external beam radiotherapy at the Royal Marsden Hospital between 1950 and 1992. RESULTS: Twenty-six (14%) (95% confidence interval: 9-19%) patients with craniopharyngioma developed acute deterioration immediately before, during and 2 months after radiotherapy with visual deterioration (19 patients), hydrocephalus (7 patients), and global deficit (7 patients). Cystic enlargement with or without hydrocephalus was the most common cause of deterioration. No patient or disease characteristics were predictive of deterioration on univariate or multivariate analysis. Eighteen patients had surgical intervention at the time of deterioration and survived the immediate period. Six of seven patients who did not have surgical intervention died. All patients who survived the postcomplication period completed the full course of external beam radiotherapy. The 10-year progression-free survival of 162 patients without deterioration was 86%, and of 18 patients with acute deterioration who recovered after surgery, 77%. CONCLUSION: Patients with craniopharyngioma develop acute deterioration around the time of radiotherapy owing to cystic enlargement and/or hydrocephalus which does not represent tumor progression. Early recognition and appropriate surgical treatment followed by conventional full-dose radiotherapy are associated with good long-term outcome.

**Stereotactically guided conformal radiotherapy for progressive low-grade gliomas of childhood.**
Saran FH, Baumert BG, Khoo VS et al.

PURPOSE: To describe the rationale, technique, and early results of stereotactically guided conformal radiotherapy (SCRT) in the treatment of progressive or inoperable low-grade gliomas (LGGs) of childhood. METHODS AND MATERIALS: Between September 1994 and May 1999, 14 children (median age 6 years, range 5-16) with LGG were treated with SCRT at the Royal Marsden NHS Trust. Tumors were located at the optic chiasm (n = 9), third ventricle (n = 2), hypothalamus, cranio cervical junction, and pineal region (each n = 1). Four patients received chemotherapy before SCRT. Immobilization was in a Gill-Thomas-Cosman frame (n=12) and subsequently in a specially designed pediatric version of the frame (n=2). Stereotactic coordinates and the tumor were defined by CT scanning with a fiducial system and MRI fusion. The median tumor volume was 19.5 cm³ (range 7.5-180). The planning target volume was defined as the area of enhancing tumor plus a 5-10-mm margin. The treatment technique consisted of 4 isocentric, noncoplanar, conformal, fixed fields. Treatment was delivered in 30-33 daily fractions to a total dose of 50-55 Gy. RESULTS: SCRT was well tolerated, with transient hair loss the only acute toxicity. The median follow-up was 33 months (range 2-53). At 6 months after SCRT, 4 of 12 children with neurologic deficits improved and 5 remained stable. Twelve children were available for MRI evaluation. Two had a complete response, 6 a
partial response, and 4 stable disease. One child with optic chiasm glioma had local progression at 25 months, and 1 developed diffuse leptomeningeal disease without local progression at 27 months. The 3-year local progression-free survival and overall survival rate after SCRT was 87% and 100%, respectively, compared with 89% and 98% for an historic control treated with conventional RT. New endocrine deficiencies were noted in 2 children after a follow-up of 20 and 23 months.

CONCLUSION: SCRT is a feasible, high-precision technique of RT for children with LGGs for whom RT is considered appropriate. The local control and acute toxicity of SCRT are comparable to a historic control of patients with conventionally delivered RT. The frequency of delayed hypothalamic-pituitary axis dysfunction reflects tumor location adjacent to the hypothalamus and pituitary. Additional follow-up is required to demonstrate that SCRT contributes to a reduction in treatment-related late toxicity, while maintaining the local control achieved with conventionally delivered RT in children with progressive LGGs.

Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood.
RJ Packer, B Lange, J Ater et al.

PURPOSE: This study investigates the response rate to and toxicity of carboplatin and vincristine in children with recurrent low-grade gliomas (LGGs) or patients younger than 60 months with newly diagnosed LGGs. PATIENTS AND METHODS: Twenty-three children with recurrent and 37 children with newly diagnosed LGGs were treated with a 10-week induction cycle of carboplatin and vincristine, followed by maintenance treatment with the same drugs. Patients were evaluated for response to treatment and toxicity. RESULTS: Twelve of 23 (52% +/- 10%; 95% confidence interval [CI], 0.32 to 0.72) assessable children with recurrent disease had an objective response to treatment, which included a greater than 50% reduction in tumor size in seven of 23 (30% +/- 10%; 95% CI, 0.10 to 0.50). Twenty-three of 37 (62% +/- 0.08; 95% CI, 0.46 to 0.78) of newly diagnosed patients had an objective response, 16 of 37 (43% +/- 0.08%; 95% CI, 0.27 to 0.59) with greater than 50% reduction in tumor size. The majority of those with an objective response had diencephalic tumors (n=29), but children with thalamic (n=2), cortical (n=1), and brain stem (n=2) LGGs also responded to treatment. Of the 35 patients with objective response to treatment, the maximum response was seen in 25 after completion of induction and in the remaining 10 after two to six cycles of maintenance treatment. Forty-nine of 53 (92% +/- .04%) patients who were stable or improved after induction remain without progressive disease (PD). Hematologic toxicity was common, but resulted in cessation of therapy in only one patient. Six children have been removed from the study because of allergic reactions, which were considered to be carboplatin-associated. CONCLUSION: Carboplatin and vincristine have activity in children with recurrent and newly diagnosed progressive LGGs. Objective responses to treatment after chemotherapy can be seen. This drug regimen is relatively well tolerated, and further studies are indicated to define the role of this combination of drugs in children with newly diagnosed LGGs.

Prospective clinical trials of intracranial low-grade glioma in adults and children.
Shaw EG, Wisoff JH.
Over the last decade, the results of 5 prospective clinical trials of intracranial low-grade glioma (LGG) have been published, 4 in adults with supratentorial LGG and 1 in children with infra- and supratentorial LGG. The data from the more than 1600 patients treated on these studies are summarized herein. European Organization for Research and Treatment of Cancer study 22845 randomized 311 adults to postoperative observation or radiation therapy (RT). There was no difference in the 5-year overall survival (OS) rate between the 2 arms. Irradiated patients had a significantly improved 5-year progression-free survival (PFS) rate. European Organization for Research and Treatment of Cancer study 22844 randomized 379 adults to low-dose (45 Gy) versus high-dose (59.4 Gy) RT. Similarly, an intergroup study conducted by the North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and Eastern Cooperative Group randomized 203 adults to low-dose (50.4 Gy) versus high-dose (64.8 Gy) RT. There was no difference in the 5-year OS or PFS rates between the 2 dose groups in either study. A Southwest Oncology Group study randomized 54 adults with incompletely resected LGG to RT alone or RT plus CCNU (lomustine) chemotherapy. There was no difference in outcome between the 2 treatment arms. Important prognostic factors for OS in these 4 adult trials included extent of surgical resection, histology, tumor size, and age. An intergroup study of the Children's Cancer Group and Pediatric Oncology Group enrolled 660 pediatric patients with management based on the extent of surgical resection: Children who underwent gross total tumor resection were observed postoperatively, whereas those who had subtotal resection or biopsy were either observed or administered RT at the discretion of their physician. Survival was most impacted by several prognostic factors, primarily extent of resection. Besides extent of resection, other prognostic factors that were consistent in predicting survival in these 5 clinical trials included patient age and tumor location, size, and histology. The data from these 5 studies indicate that for intracranial LGG in adults, postoperative RT is associated with improved 5-year PFS but not OS rates compared to postoperative observation. Radiation doses of 45 to 54 Gy result in 5-year OS and PFS rates that are similar to those for higher doses. The strategies of chemotherapy alone and RT plus chemotherapy are under investigation. For pediatric LGG, extent of surgical resection is the most important prognostic factor associated with favorable 5-year OS and PFS. Radiation therapy and chemotherapy are generally used in the settings of incomplete resection and recurrent disease, and these strategies are being investigated in prospective clinical trials. The schemata from recently completed and ongoing studies in both adult and pediatric intracranial LGG are reviewed.

The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study Group.
Spoto R, Ertel IJ, Jenkin RD et al.

Fifty-eight patients with high-grade astrocytoma were treated by members of the Childrens Cancer Study Group in a prospective randomized trial designed to study the effectiveness of chemotherapy as an adjuvant to standard surgical treatment and radiotherapy. Following surgical therapy, patients were assigned randomly to radiotherapy with or without chemotherapy consisting of chloroethyl-cyclohexyl nitrosourea, vincristine, and prednisone. Treatment with chemotherapy prolonged survival and event-free survival. Five-year event-free survival was 46% for patients in the radiotherapy and chemotherapy group, and 18% for patients in the radiotherapy-alone group. Five-year survival was similarly improved. The differences
in outcome due to treatment were statistically significant after correcting for imbalances in important prognostic factors (event-free survival, p=0.026; survival, p=0.067). The presence of mitoses or necrosis in the tumor specimen was associated with poorer outcome. Patients whose initial surgery was limited to biopsy, and patients with basal ganglia lesions, also had significantly worse outcome. Chemotherapy administered at the time of recurrence in a small number of patients did not produce any long-term survivors. This study is to our knowledge the only randomized trial to investigate effectiveness of chemotherapy in the treatment of high-grade astrocytoma in children.

**Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89.**
Bamberg M, Kortmann RD, Calaminus G et al.

**PURPOSE:** A multicenter prospective trial was conducted (Maligue Keimzell tumoren [MAKEI] 83/86/89) to assess outcome in intracranial germinoma after treatment with radiotherapy alone at reduced doses. **PATIENTS AND METHODS:** Between 1983 and 1993, 60 patients with histologically (n=58) or cytologically (n=2) confirmed germinoma were enrolled onto the study. Patients received radiotherapy alone (craniospinal axis/local boost). In the MAKEI 83/86 study (involving 11 patients), the dose to the craniospinal axis was 36 Gy and the dose to the tumor region was 14 Gy. In the MAKEI 89 study (involving 49 patients), doses were 30 and 15 Gy, respectively. **RESULTS:** Median patient age was 13 years (range, 6 to 31 years). Complete remission was achieved in all patients. The estimated (Kaplan-Meier) 5-year relapse-free survival rate was 91.0% +/- 3.9% at a mean follow-up of 59.5 months (range, 3 to 180 months); the estimated overall survival rate was 93.7% +/- 3.6%. Relapse occurred in five patients 10 to 33 months (mean, 18.4 months) after diagnosis (one patient developed a spinal canal metastasis and underwent salvage radiotherapy and chemotherapy; four patients had metastases outside the CNS and underwent salvage chemotherapy alone). Four patients died: one died from disease, two died from therapy-related complications, and one committed suicide. Acute complications with long-lasting sequelae were tumor or surgery related (three cases of blindness, six of reduced vision, two of hemiparesis). Psychosocial development was normal in the majority of patients. **CONCLUSION:** Radiotherapy directed toward the craniospinal axis or tumor site alone at decreased dose levels is effective. To reduce the risk of late side effects, further attempts to decrease total doses are justified. In cases of recurrent disease.

**Retrospective multi-institutional study of radiotherapy for intracranial non-germinomatous germ cell tumors.**
Aoyama H, Shirato H, Yoshida H et al.

The treatment outcome of 24 patients with pathologically-proven non-germinomatous germ cell tumor was retrospectively investigated to determine the effectiveness of radiotherapy. The patients were divided into three groups as follows: group 1, five patients with mature teratoma with or without germinoma; group 2, six patients with immature teratoma with or without germinoma; group 3, 13 patients with other highly malignant tumors. The overall actuarial survival and relapse-free rates at 5 years were 82% and 59%, respectively, with a median follow-up period of 62 months. The actuarial relapse-free rate at 5 years was 100% for group 1, 63%
for group 2 and 44% for group 3. There was no difference in the relapse-free rates between total resection and partial resection. Usage of chemotherapy was adversely related to survival probably due to selection bias. No local failure was observed with 10 Gy or more for group 1, 40 Gy or more for group 2 and 54 Gy or more for group 3. In groups 1 and 2, there was no spinal relapses without craniospinal irradiation. In group 3, three of eight patients who did not receive craniospinal irradiation and none of five patients who received craniospinal irradiation experienced spinal relapse. In conclusion, highly malignant GCTs show a high incidence of spinal metastasis and craniospinal irradiation may reduce the risk of spinal metastasis. Radiation dose and volume are to be determined according to the histopathological aggressiveness.

**Treatment and prognosis of patients with intracranial non-germinomatous malignant germ cell tumors: a multi-institutional retrospective analysis of 41 patients.**

Ogawa K, Toita T, Nakamura K et al.

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**BACKGROUND:** The relative roles of surgical resection, radiotherapy, and chemotherapy in the management of patients with intracranial non-germinomatous malignant germ cell tumors have been controversial. The authors retrospectively investigated the results of different treatment regimens in patients with these tumors. **METHODS:** The records of 41 patients who were treated between 1981 and 2001 were reviewed. They were grouped into patients with a good prognosis (n=3), an intermediate prognosis (n=24), and a poor prognosis (n=14) based on the histology of their tumors. Fifteen patients (37%) underwent surgical resection and received radiotherapy, and 26 patients (63%) also received chemotherapy. The median follow-up of 18 patients who remained alive was 61 months (range, 14-194 months). **RESULTS:** The 5-year actuarial overall survival rates for patients in the good prognosis, intermediate prognosis, and poor prognosis groups were 100%, 68%, and 8%, respectively. In the analysis, histology alone had a statistically significant impact on overall survival (P<0.0001). All 3 patients in the good prognosis group were treated successfully with surgical resection and radiotherapy. In the intermediate prognosis group, the 5-year actuarial overall survival rate was 44% for patients who underwent surgical resection and received radiotherapy (n=9) and 84% for patients who also received chemotherapy (n=15; P=0.01). Patients in the poor prognosis group who underwent surgical resection and received radiotherapy (n=3) or who underwent incomplete resection and received both radiotherapy and chemotherapy (n=8) all died of disease, whereas 2 of 3 patients who underwent macroscopic total resection and received both radiotherapy and chemotherapy survived free of disease. **CONCLUSIONS:** The treatment of patients with intracranial non-germinomatous malignant germ cell tumors should be based on tumor histology. For patients who had a good prognosis (mature teratoma with germinoma), surgical resection and radiotherapy were sufficient; however, for patients in the intermediate prognosis group, multimodal treatment, including surgical resection, radiotherapy, and chemotherapy, was effective. Conversely, for patients in the poor prognosis group, more intensive multimodal treatment, including macroscopic total resection, may improve the survival rate. Copyright 2003 American Cancer Society.

**Survival and prognostic factors following radiation and/or chemotherapy for primitive neuroectodermal tumors of the pineal region in infants and children: a report of the Childrens Cancer Group.**

Jakacki RI, Zeltzer PM, Boyett JM et al.
PURPOSE: To describe the biologic and clinical features of children with primitive neuroectodermal tumors (PNETs) arising in the pineal region (pineoblastomas) and evaluate prospectively the efficacy of radiation therapy (RT) and/or chemotherapy.

PATIENTS AND METHODS: Between 1986 and 1992, 25 children with PNETs of the pineal region were treated as part of a Childrens Cancer Group study. Eight infants less than 18 months of age were nonrandomly treated with eight-drugs-in-1-day chemotherapy without RT. The remaining 17 patients were treated with craniospinal RT and randomized to receive either vincristine, lomustine (CCNU), and prednisone or the eight-drugs-in-1-day regimen. RESULTS: Of 24 completely staged patients, 20 (83%) had localized disease at diagnosis. All infants developed progressive disease a median of 4 months from the start of treatment. Of the 17 older patients treated with RT and chemotherapy, the Kaplan-Meier estimate of progression-free survival (PFS) at 3 years is 61% +/- 13%. This is superior to the PFS of children with other supratentorial PNETs (P=.026). Following RT, 12 of 17 patients (70.6%) had a residual pineal region mass, which persisted for as long as 5 years before resolving; only four subsequently developed progressive disease. CONCLUSION: (1) Eight-in-1 chemotherapy without RT appears to be ineffective therapy for young children with PNETs of the pineal region. (2) For children more than 18 months of age at diagnosis treated with craniospinal RT and chemotherapy, the PFS is superior to that of children with other supratentorial PNETs. (3) A residual enhancing mass following RT is not predictive of treatment failure.