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Review Article

A Review: Ependymomas Disease

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ABSTRACT

The ependymomas are relatively not a common tumor. Ependymomas are tumors of the brain and spinal cord that arise from ependymal cells lining the central fluid spaces (ventricles) of the brain and the central canal of the spinal cord. However, most clinicians agree that the radical removal of the is the most important prognostic factor. Tumor removal was not sufficient before the era of magnetic resonance imaging (MRI) and resulted in a considerable operative morbidity and mortality. As the micro neurosurgical techniques and microsurgical anatomy become popular and the MRI provide more detailed anatomical information preoperatively, radical removal of this complex and complicated tumor can be more feasible. In childhood ependymoma, the treatment related morbidity and motility can be the special issues, which can modify the policy of management safe tumor removal and minimal adjuvant treatment, which are extremely important

Prognostic factors: although many clinicians believe that the ependymomas are inheritably chemo resistant, the new targets for the treatment are under investigation or clinically tried. Also, the genetic alterations of ependymoma are developing and might be a promising target.

The surgical techniques and assistant modalities for tumor removal are still advancing. so, the outcome of ependymoma is still improving. Unfortunately newer treatment modalities, such as new chemotherapeutic agent and gene modification agent are still not promising, the history of ependymoma management is still in progress.

key words: morbidity, mortality, modalities, chemo resistance.

INTRODUCTION

Ependymomas are rare neuroepithelial tumors that arise from the ependymal cells of the cerebral ventricles, the central canal of the spinal cord and cortical rests. Ependymomas constitute 8– 10% of brain tumors in children and up to 4% of brain tumors in adults [1]. Ependymomas represent 15% of spinal cord tumors and up to 60% of spinal cord gliomas [1, 2]. Compared with intracranial ependymomas, spinal ependymomas are less prevalent and exhibit a better prognosis [3].

The WHO classification (2000, 2007) separates ependymomas into subependymomas (WHO grade 1), myxopapillary ependymomas (WHO grade 1), ependymomas (WHO grade 2), and anaplastic ependymomas (WHO grade 3).

Given the low incidence, the literature regarding ependymomas in adults is sparse [1, 4]. Most series combine pediatric and adult ependymomas, grade II and grade III tumors, are retrospective, include limited numbers of patients and span several decades in which diagnostic and therapeutic modalities have changed. As a consequence, the level of evidence regarding therapeutic strategies is low and universally accepted guidelines are lacking.

Recently, the genetic changes in ependymoma have undergone extensive analysis, but despite these efforts, ependymomas are not as well characterized as other primary brain tumors such as the malignant gliomas or medulloblastomas [5, 6]. The studies that have been performed do provide some potential insight into the pathogenesis of the disease, possibly helping to define the origin of the ependymoma stem cell, may generate prognostic markers and most importantly, may yield therapeutic targets, particularly focused on signal transduction modulators.

Tumor biology and outcome seem more closely related to tumor location. Patient age and WHO classification haveless bearing on genetic profile than tumor location with the distinction of brain versus spinal cord having the greatest impact on molecular characteristics and in adults prognosis. In this review we focus on state of art and relevant advances in the molecular biology and management of adult ependymomas of the adult.

They occur both in children and adults and constitute between five and ten percent of central nervous system tumors. More aggressively growing anaplastic ependymomas can be distinguished from more benign ependymomas by virtue of pathologic features such as irregular cellular shapes, greater cell density, and mitosis (cells in division). Ependymomas usually present with signs of increased intracranial pressure either from the size of the tumor itself or hydrocephalus (blockage of fluid flow) that result from the intraventricular location.

These are the epithelial cells (fig-2) that line the CSF-filled ventricles in the brain and the central canal of the spinal cord. The cells are ciliated simple cuboidal epithelium. Their apical surfaces are covered in a layer of cilia, which circulate CSF around the central nervous system. Their apical surfaces are also covered with microvilli, which absorb CSF. Ependymal cells are a type of Glial cell and are also CSF producing cells.

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Types of ependymal tumours : According to the World Health Organization (WHO) classification of tumors, there are four types of ependymal tumors:
1] Subependymomas,
2] Myxopapillary ependymomas,
3] Ependymomas, and
4] Anaplastic ependymomas,
and four variants: cellular, papillary, clear cell and tanycytic ependymomas belonging to third and fourth of ependymomas [7]

1) Subependymomas are well-circumscribed tumors that are usually located in or around the ventricles. Most are incidental tumors, but some may be large enough to cause symptoms. The long-term prognosis is generally excellent because these tumors rarely recur are also uncommon in children. [Fig 4 (a)]

2) Myxopapillary ependymomas are well-circumscribed tumors that occur primarily at the base of the spine in an area called the filum terminale. They are relatively uncommon in children. About 85% of ependymomas are benign myxopapillary ependymoma [Fig 4 (b)]

3) Ependymomas are fairly well delineated tumors. They can arise anywhere in the central nervous system, but commonly develop in the posterior fossa (the portion of the skull containing the cerebellum and brain stem), usually around the fourth ventricle, the spinal cord or the lateral ventricles (within the cerebral cortex). [Fig 4 (c)]

4) Anaplasticependymomas in general, exhibit a high growth rate and have been associated with a less favorable prognosis. [Fig 4 (d)]

i) Cellular ependymomas: Cellular ependymoma are highly cellular lesions presenting a monotonous appearance and devoid of anaplastic feature.

ii) Papillary ependymomas: Papillary ependymomas are characterised by a papillary architecture in which the central vascular core is surrounded by cylindrical cells.

iii) Clear cell ependymomas: Clear cell ependymoma is a variant observed predominantly in the supra-tentorial compartment and less frequently in the posterior fossa and spinal cord. It mostly affects youngers and young adults (Fig. 2c). Histologically, it resembles the classic 1p/19q-deleted oligodendroglioma with cells that are regularly distributed arranged back to back with clear cytoplasms. The similarity with oligodendrogliomas extends to the blood vessels, which show chicken-wire architecture. Perivascular rosettes may be inconspicuous and GFAP may be needed to highlight them. When areas of endothelial cell proliferation and mitosis are encountered in these tumours, they are graded as WHO grade III. When absent, the lesion is graded as II.

iv) Tanycytic ependymomas: Tanycytic ependymoma is a rare variant occurring more frequently in the spinal cord than in the brain. Tumour cells are typically elongated and arranged in fascicles requiring a differential diagnosis with schwannoma or pilocytic astrocytoma. Presence of perivascular rosettes (best observed at low magnification), absence of a rich reticulin network and scarcity of nuclei positively labelled with antibody against oligo direct the diagnosis towards ependymoma.

Epidermiology: Spinal tumors occur with an incidence of 1.1 case per 100,000 persons. Intramedullary spinal tumors comprise approximately 2-4% of all CNS neoplasms. The most common kinds of intramedullary tumors are ependymomas, astrocytomas, and hemangioblastomas. In adults, ependymomas are the most common tumor type, accounting for 40-60% of all intramedullary spinal tumors, with the mean age of presentation being 35-40 years.

In children, astrocytomas are the most common tumor type, accounting for around 60% of all intramedullary spinal tumors, and the mean age of presentation is 5-10 years. Intramedullary spinal tumors can arise anywhere in the spinal cord from the cervicomedullary junction to the filum terminale, but they are found most frequently in the cervical cord, presumably because it contains more neural tissue than the thoracic or lumbar segments.

Age: Presentation can take place at any age. Mù rk16 found in their series that there was a bipolar age distribution. At rest peak was situated between 0 and 10 years, and the second peak between 40 and 50 years. Others found that the mean age varies between 22 years 10,18 and 25 years.The prevailing opinion is that intracranial ependymomas mainly occur in young children and spinal ependymomas in older people. Figure 1 shows the age-distribution as we found it by reviewing the literature. Compared with adults, both better 11 and worse 12,18,19,21± 24 prognoses for children have been reported in the literature. However, Show *et al.*7 found that there was no difference in prognosis between these groups of patients. Amongst children, a worse prognosis has been reported for the very young (4 years). 12,16,25 One inference from these results could be that intracranial ependymomas and spinal ependymomas might be considered as two biologically different groups of tumours, each with their own etiology, age distribution, prognostic factors and treatment.

Sex: The distribution of ependymomas in female and male patients varies between 40± 57% and 43± 60%, respectively (mean 48.1%, 51.9%). Data concerning the sex-distribution among patients with an ependymoma are presented in Table I.

According to many authors the sex of the patient is probably not a significant prognostic factor.

Race: Goldwein *et al.*30 found in their series that Caucasian children fared significantly better than non-Caucasian (5-year survival 43 and 14%, respectively). Although they agree that this finding is a sensitive matter, they suggest that this racial variation has not been studied by others and that this might explain some of the differences in outcome that have been reported in the literature 30± 32.

Mortality/Morbidity: Depending on the patient population the reported 10-year overall survival rate for ependymoma can vary from 45-55%. The current 5-year survival rate for patients with intracranial ependymomas is approximately 50%, when rates from children and adults are combined[8]. Stratification based on age reveals 5-year survival rates of 76% in adults and 14% in children.

Etiology: To theorize the "cell of origin" of ependymomas and related tumors, one needs only to look back through the stages of normal ependymal cell development. The "stem cell" theory of tumorigenesis has it roots in the classic literature of neuropathology, dating back to early perspectives from Bailey and Cushing.[9] Radial glia, multipotent progenitor cells derived from the neuroepithelium of the primitive neural tube, give rise to multiple differing populations of elongated uni- and bipolar cells termed tanycytes; fetal ependymal tanycytes directly give rise to mature ependymocytes, whereas other tanycytic populations mature and remain as ependymal tanycytes within selective regions of the ventricular system, particularly the hypothalamic region of the third ventricle and within circumventricular organs. Specialized ependyma of the circumventricular organs and choroid plexus cells are additional highly specialized ependymal cells that ultimately derive from this developmental pathway.

Not only do choroid plexus tumors and ependymomas (including the various histologic subtypes) clearly recapitulate specific cell types found at various stages in this ontologic sequence, so too do a variety of other uncommon and/or recently recognized entities. These include astroblastoma, papillary tumor of the pineal region, chordoid glioma, angiocentric glioma, and pilomyxoid glioma[10]. In addition, recent gene expression profiling studies support the concept that radial glial cells from different neuroanatomic sites may be predisposed to acquiring particular genetic aberrations that result in ependymomas with site-specific genetic signatures and biologic potential[11]. This may well explain why phenotypically identical ependymomas from supratentorial, posterior fossa, and spinal locations may exhibit notably different clinical behaviors.

Location: Supratentorial ependymal tumors (including ependymomas and subependymomas) more frequently arise in the lateral ventricles compared with the third ventricle. In children, ependymal tumors occur most commonly within the fourth ventricle (posterior fossa), followed by supratentorial locations, the latter including both a mix of primarily intraventricular and intraparenchymal-centered tumors and a tendency toward anaplasia (WHO grade III).[12] That being said, an extraventricular localization does not nigate the possibility of an ependymoma, especially in the pediatric age group. Cortical ependymoma represents a rare type of supratentorial ependymoma that occurs in the superficial cortex of young adults, is often associated with seizures, tends to be low grade, and is curable by resection.[13]

Ependymomas are tumors of the brain and spinal cord that arise from ependymal cells lining the central fluid spaces (ventricles) of the brain and the central canal of the spinal cord.

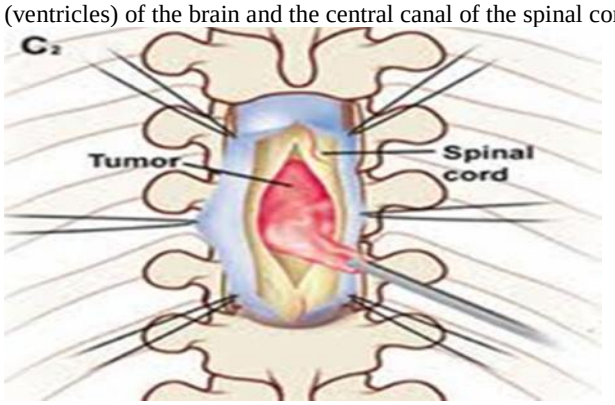


Fig 1 Ependymoma tumour

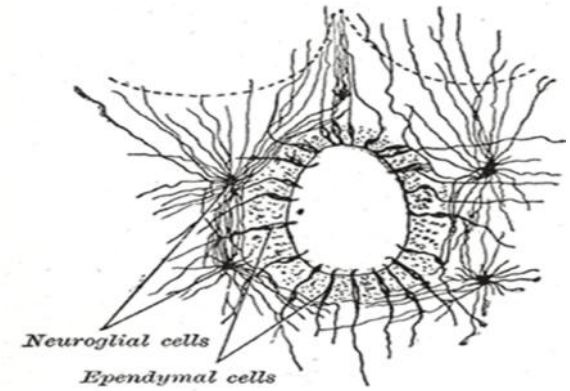


Fig 2 Ependymal cell

Ependymal tumors may arise at any level of the spinal cord, where they are much more common in the adult population, as noted earlier. Interestingly, certain histologic subtypes have preferred spinal locations. Conventional (WHO grade II) ependymomas, including the tanycytic variant, generally present as centrally situated intramedullary tumors within the thoracic/cervicothoracic cord,[14] whereas spinal subependymomas more often arise as encentric masses.[15, 16] Anaplastic (WHO grade III) spinal ependymomas are exceedingly rare.

The prototypical location of myxopapillary ependymoma is the region of the conus medullaris/cauda equina/filum terminale. Infrequently, these may arise at other cord levels, intracranial sites (both intraparenchymal and intraventricular), and subcutaneous sacrococcygeal areas.[17, 18, 19, 20, 21, 22] The ovaries and mediastinum are other rare sites of ependymal tumors.

Pathophysiology: The pathophysiology of intramedullary spinal cord tumors varies according to tumor type. Ependymomas are usually indolent, encapsulated tumors that are histologically benign. Pain and neurologic deficits arise as a result of a progressive stretching and distortion of nerve fibers. Usually a clear anatomical plan is present at surgery, and a gross visual anatomic resection results in a cure. Rare anaplastic subtypes can be invasive, however, and are more likely to recur or spread through CSF spaces. Even histologically benign–

appearing spinal ependymomas can metastasize in this way.

Causes

--The cause of ependymomas, like that of other brain tumors, is unknown.

--It is uncertain whether viruses (e.g. SV40) play a role in the development of ependymomas.

--Much more research is necessary to determine whether this is indeed a factor in humans, since these particular viruses do not normally affect humans.

Symptoms

Symptoms of an ependymoma are related to the location and size of the tumor.In neonates and infants, enlargement of the head may be one of the first symptoms.

- severe headache
- visual loss
- vomiting
- bilateral Babinski sign
- drowsiness
- Irritability, sleepiness.
- Increased pressure, which may develop if the tumor blocks the drainage of cerebrospinal fluid (the liquid that bathes the brain).
- Lethargy
- Double vision
- Facial numbness

The slow-growing nature of many of these tumors, symptoms precede diagnosis an average of 2 years. Patients with malignant or metastatic spinal cord tumors present in the range of several weeks to a few months after symptoms develop.

Pain and weakness are the most common presenting symptoms of spinal cord tumors. Pain is often the earliest symptom, classically occurring at night when the patient is supine. The pain is typically local over the level of the tumor but may radiate.

Progressive weakness may occur in the arms (cervical tumors) or legs (cervical, thoracic, conus tumors). Impaired bowel, bladder, or sexual function often occurs early. Patients may have poor balance. Rarely, symptoms of subarachnoid hemorrhage may be present.

Intratumoral hemorrhage can cause an abrupt deterioration, a presentation most often associated with ependymomas.

Ependymomas can grow in different parts of the brain, and symptoms may relate to the area of the brain that is affected:

- A tumour in the frontal lobe of the brain may cause gradual changes in mood and personality. There may also be paralysis (the loss of the ability to move) on one side of the body (hemiparesis).
- A tumour in the temporal lobe of the brain may cause problems with coordination, speech and may affect memory.
- If the parietal lobe of the brain is affected, writing and other such tasks may be difficult. Hemiparesis may also be present.
- An ependymoma in the cerebellum may lead to problems with coordination and balance.

The symptoms of an ependymoma in the spinal cord will depend on which part of the spine is affected. Symptoms include neck or back pain, and sometimes numbness or weakness in the limbs and loss of bladder control.

Differential diagnosis and investigations of ependymal tumours: The diagnosis of ependymomas, as a tumour entity, is generally quite easy. However, as other tumours share ependymal-like features such as perivascular rosettes, these have to be ruled out before establishing a final diagnosis of ependymoma. Among them, and in patients younger than 20 years.

It was first described in patients with epilepsy, frequently of long duration. This lesion presents a histological angiocentric pattern better observed at its periphery. As in ependymomas, tumour cells demonstrate EMA-positive intra-cytoplamicdots. Astroblastoma is a rare well-circumscribed glioma arising superficially in the cerebral hemispheres. It is a contrast-enhancing lesion constituted of cystic and solid areas presenting a “bubbly” aspect [23]. Short tumour cell processes are radially oriented towards vessels forming “astroblastic rosettes”. The latter feature may be observed albeit focally, in infiltrative gliomas. EMA-positive staining can be seen in astroblastomas. A lack of ependymal rosettes as well as perivascular fibrosis and hyalinisation help to distinguish astroblastomas from ependymomas.

Papillary glioneuronal tumour papillary glio neuronal tumour is an exclusively supra-ventorial contrast-enhancing lesion that may be cystic. It has a pseudo-papillary pattern. Core-like structures are centred on hyalinised vessels surrounded by a GFAP-positive fibrillary network. Synaptophysin-positive neurocytic cells fill intermediate zones.

Oligodendroglioma may have to be discriminate from a clear cell ependymoma. In such instances, EMA- and GFAP-positive staining will favour the latter diagnosis. Central neurocytoma formerly referred to as “ependymoma of the foramen of Monro”, a central neurocytomamay also evoke a differential diagnosis with clear cell ependymoma. This lesion presents in the ventricular system (mostly in the third) and consequently may induce intracranial hypertension. Histologically, nucleated areas alternate with fibrillary ones that are positively stained for synaptophysin but not GFAP.

Pilocytic astrocytoma may arise diagnostic problems, predominantly when it is located in the posterior fossa or in the spinal cord. When areas of loose-microcystic texture, Rosenthal fibres and granular bodies are not found, a nuclear immuno-positive staining for oligo favours an astrocytic neoplasm [14].

In addition, two tumours, classically observed in adults, have to be differentiated from ependymomas, and they are therefore briefly described. The papillary tumour of the pineal region, is an ependymoma-like tumour largely devoid of GFAP labelling, and showing intense staining for cytokeratins [16]. In adults, it is a major pitfall in diagnosis of ependymoma. Paraganglioma sometimes

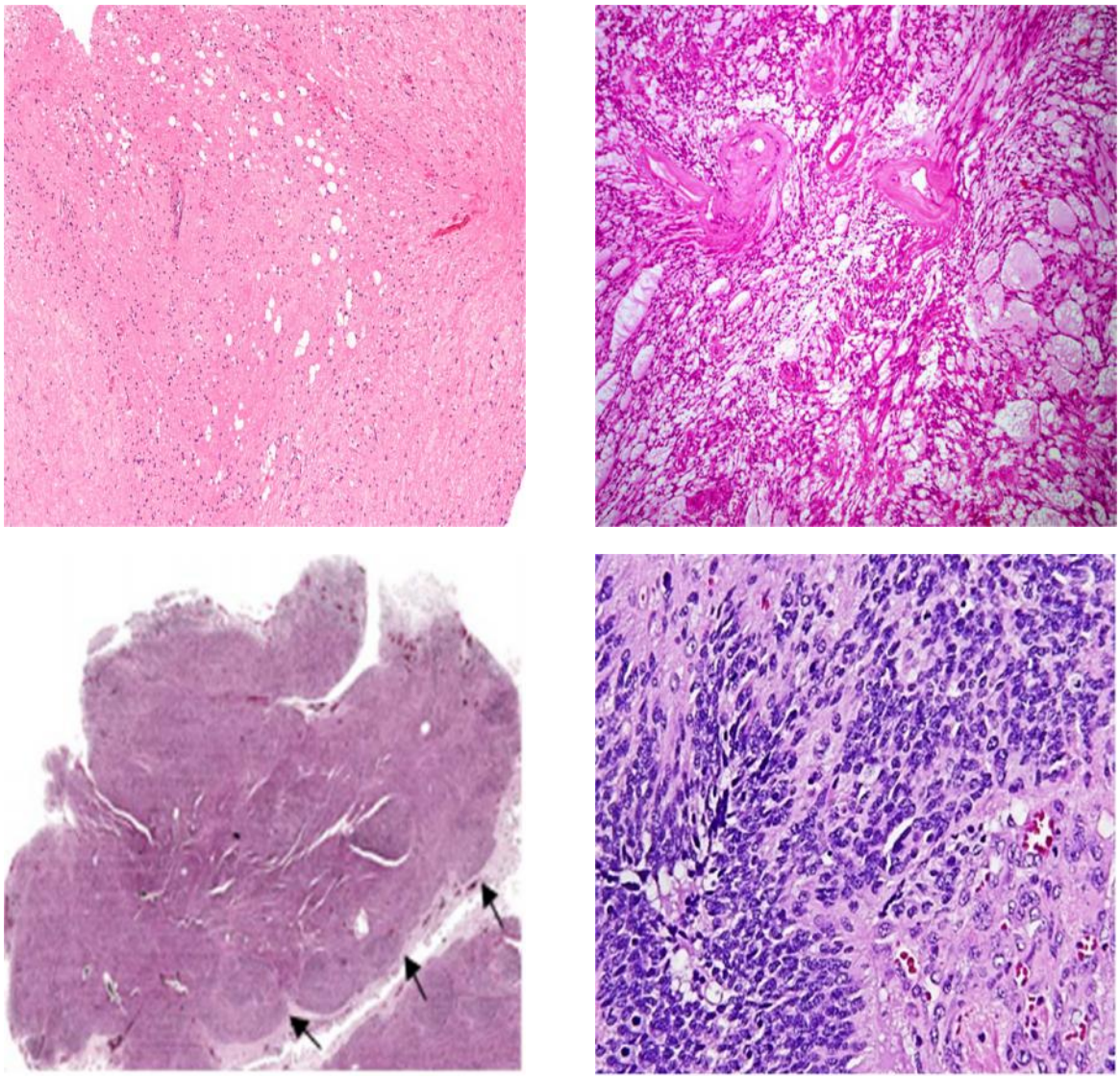


Fig-3 Ependymoma tumours*: a) Subependymoma b) Myxopapillary c) Ependymomas and d) Anaplastic*

requires differential diagnosis with ependymoma when located in the lower part of the spinal cord. Search for sustentacular cells by an antibody against PS100 will help to highlight lobules of chief cells which are synaptophysin and chromogranin-positive.

Position and size of the tumor can plan treatment. The doctor will examine thoroughly and test reflexes and the power and feeling in arms and legs. Doctor will look into the back of eyes using an ophthalmoscope to see if the nerve at the back of the eye is swollen. This can be caused by oedema (swelling of the tissues within the brain), which may occur due to an increase in the amount of fluid in the brain.

Will have a CT or MRI scan to find out the exact position and size of the tumor.

CT (computerized tomography) scan: A CT scan takes a series of x-rays that build up a three-dimensional picture of the inside of the body. The scan is painless but takes 10-30 minutes. CT scans use small amounts of radiation, which will be very unlikely to harmPatient. He will be asked not to eat or drink for at least four hours before the scan.

Doctor may be given to patient a drink or injection of a dye, which allows particular areas to be seen more clearly. For a few minutes, this may make feel hot all over. If

patient allergic to iodine or have asthma he could have a more serious reaction to the injection, so it is important to let his doctor know beforehand.

MRI (magnetic resonance imaging) scan: This test is similar to a CT scan but uses magnetism instead of x-rays to build up a detailed picture of areas of his body. Before the scan he may be asked to complete and sign a checklist. This is to make sure it's safe for patient to have an MRI scan.

Before having the scan, he'll be asked to remove any metal belongings including jewellery. Some people are given an injection of dye into a vein in the arm. This is called a contrast medium and can help the images from

the scan show up more clearly. During the test he will be asked to lie very still on a couch inside a long cylinder (tube) for about 30 minutes. It is painless but can be slightly uncomfortable, and some people feel a bit claustrophobic

during the scan. It's also noisy, but he'll be given earplugs or headphones.

Lumbar puncture: This test, which is known as a lumbar puncture, is carried out to see if there are any tumour cells present in the cerebrospinal fluid (CSF). The skin on his back is numbed with local anaesthetic, and a hollow needle is inserted between two of the spinal bones and into the spinal canal. A small amount of spinal fluid is withdrawn for tests. MRI scans can also show the presence of any tumour in the spinal cord.

Biopsy**:** To give an exact diagnosis, a sample of cells (biopsy) is sometimes taken from the tumour, which is then looked at under a microscope. The biopsy involves an operation. Patient doctor will discuss whether this is necessary in his case, and exactly what the operation involves. In some situations, the biopsy and surgery to remove the tumour may be done at the same time.

Medical Care: Medical management of patients with ependymomas includes adjuvant therapy (ie, conventional radiation therapy, radiosurgery, chemotherapy), steroids for treatment of peritumoral edema, and anticonvulsants in patients with supratentorial ependymoma.[27,28]

- Adjuvant treatment of histologically confirmed intracranial ependymoma remains an actively debated topic.
- The National Comprehensive Cancer Network (NCCN) suggests the following for adults: After a gross total resection (GTR) of an intracranial WHO grade II ependymoma, limited field fractionated external beam radiotherapy (LFFEBRT) can be considered versus mere observation. Postoperative LFFEBRT is recommended for WHO grade II ependymoma when subtotal resection is noted on postoperative MRI, and for grade III anaplastic ependymoma regardless of the extent of resection.[29]If postoperative spinal MRI or LP findings are positive, craniospinal radiation therapy is indicated regardless of grade or extent of resection. For recurrent ependymoma, the NCCN suggests that patients who have not received radiation therapy and if a patient has received radiation therapy, then chemotherapy, radiation therapy, or supportive care should be considered.[30]
- For children younger than 3 years, the use of chemotherapy has historically been fostered by the desire to avoid adverse radiation effects. Combination chemotherapy regimens comprising cisplatin, etoposide (VP-16), carboplatin, vincristine, and mechlorethamine, or ifosfamide, carboplatin, and etoposide (ICE), have been administered with variable success.
- In older children and adults, radiotherapy is the standard treatment following resection for most patients with WHO grade II ependymoma. While surgery alone has been piloted for a very select group of patients (those with supratentorial tumors who undergo gross total resection with a wide resection margin), most tumors of the posterior fossa cannot be fully resected and are likely to recur without postoperative radiation.[31,32]
- In 1990, Goldwein and colleagues reviewed 36 children (aged 0.8-16.8 y) with recurrent intracranial ependymoma who were treated for a total of 52 separate relapses from 1970-1989.[33]
  - In their study, initial therapy for relapse consisted of surgery in 33 cases and chemotherapy in 38 cases. Twelve patients received radiation at the time of first relapse, and 5 of these 12 who initially had been treated with surgery and chemotherapy alone were irradiated to full dose.
  - The 2-year actuarial survival and progression-free survival rates were 29% and 23%, respectively. The 2-year survival rate after treatment of first relapse was 39%. Of the 52, 44 subsequent relapses (and 1 septic death) occurred, 3 of which occurred in the 5 patients treated with definitive radiation. Twenty-seven relapses occurred exclusively with local disease. Eight patients had relapse outside of as well as in the primary site. Survival rate was better for patients who had histologically benign lesions at relapse (53% vs 9%, $P < 0.02$), and for patients in the first versus subsequent relapse ($P < 0.005$). Cisplatin and VP-16 appeared to be the most active chemotherapeutic agents.
- In 1992, Chiu and colleagues evaluated the clinical courses of 25 children aged 2 weeks to 15 years treated for intracranial ependymoma at M. D. Anderson Cancer Center.[34]
  - Nine patients had supratentorial primaries (5 high grade, 4 low grade), and 16 patients had infratentorial primaries (9 high grade, 7 low grade). Five patients underwent gross complete resection, and 20 patients had incomplete resection. Seven patients received craniospinal irradiation (25-36 Gy to the neuro-axis, 45-55 Gy to tumor bed), and 12 received local field irradiation (29-60 Gy, median 50 Gy). Five infants had adjuvant chemotherapy without radiotherapy, 6 children had postradiotherapy adjuvant chemotherapy, and 12 patients had salvage chemotherapy with various agents and number of courses.
  - Eight patients were alive, disease free, and without relapse from 1-12.5 years after diagnosis (median 42 mo). The primary failure pattern was local recurrence.
  - The data presented in this study suggested that the long-term cure rate of children with ependymoma is suboptimal; histologic grade may be of prognostic importance for supratentorial tumors; prognosis appears worse for girls and infants younger than 3 years; in well-staged patients, routine spinal irradiation could be omitted; and the role of adjuvant chemotherapy is unclear.
- In 1998, an extensive review and analysis of all published literature on the topic of intracranial ependymoma highlighted the difficulty associated with extrapolating data from single-institution studies.
  - Forty-five series were reviewed, including more than 1400 children. The largest series reported on 92

patients, and the accrual rate ranged from 0.32-12 patients per year. Notably, the extent of surgical resection was the only reported prognostic factor in these series that was consistently found to be a valid predictor of outcome.

- These findings were confirmed by a prospectively randomized trial published that same year evaluating Children's Cancer Group Protocol 921. Predictors of long-term survival included an estimate of the extent of resection made at surgery (total compared with less than total, P =0.0001) and the amount of residual tumor on postoperative imaging as verified by centralized radiologic review. Other factors, including centrally reviewed tumor histopathologic type, location, metastasis, and tumor (M and T) stages, patient age, race, sex, and chemotherapy treatment regimen were not found to be correlated significantly with long-term survival.

- More recently, in 2000, Stafford and colleagues evaluated the efficacy of stereotactic radiosurgery (SRS) for locally recurrent ependymoma and found that this technique may allow a high salvage rate in selected patients. In 12 patients (with a total of 17 tumors) treated with SRS, a medial survival of 3.4 years was achieved. In-field local control was achieved in 14 of the 17 tumor sites, and the estimated 3-year local control rate was 68%. Two patients developed treatment-related complications following therapy.[35]

Surgical Care: The extent of tumor resection is the most important prognostic factor associated with long-term survival for patients with nonmalignant forms of ependymoma, regardless of location. Thus, a gross total resection (GTR) is optimal.

- Children with posterior fossa lesions usually undergo surgery via a midline suboccipital approach. Despite the survival advantage of GTR, lesions of the posterior fossa are in close proximity to cranial nerves making GTR risky and fraught with the possibility of long-term neurologic dysfunction and disability. Posterior fossa syndrome, also referred to as cerebellar mutism, is a recognized complication of posterior fossa surgery and most common when brainstem invasion is observed.[42,43] Mutism can have a latency range of 1-7 days and duration of 6-365 days. Thus, consideration must be given to the balance between improved survival with GTR and potential postoperative morbidity.
- Hydrocephalus can be managed with a perioperative external ventricular drain, ventriculoperitoneal shunt, or, more rarely, third ventriculostomy.
- A reasonable algorithm of management affords the medical team the opportunity to assess the need for permanent CSF diversion after tumor resection. This can be accomplished by clamping the external ventricular drain postoperatively and monitoring intracranial pressure and/or clinical signs.

Table I: .Data concerning the sex-distribution among patients with an ependymoma.

WHO Grade	Histologic Characteristics
Grade I	Includes lesions with low proliferative potential, a frequently discrete nature, and the possibility of cure following surgical resection alone.
Grade II	Includes lesions that are generally infiltrating and low in mitotic activity but recur. Some tumour types tend to progress to higher grades of malignancy.
Grade III	Includes lesions with histologic evidence of malignancy, generally in the form of mitotic activity, clearly expressed infiltrative capabilities, and anaplasia.
Grade IV	Includes lesions that are mitotically active, necrosis-prone, and generally associated with a rapid preoperative and postoperative evolution of disease.

- Currently, no role exists for adjuvant therapy of spinal ependymoma after complete surgical resection. For patients who have postoperative residual tumor or early recurrence, radiation is considered on the basis of the individual patient's medical condition and neurological status.

- Conventional chemotherapy has yet to effect any improvement in outcome for ependymoma,[36,37] and radiotherapy to the developing brain is to be avoided due to its substantial neurocognitive effects. Therefore, recent emphasis has been placed on molecular subclassification of these tumors. hTERT negativity is associated with a 5-year survival rate of 84% compared to 41% for hTERT positive tumors.[38] Several genes have been identified as having associations with risk of relapse, age of onset, and location of tumor.[39,40] As more information regarding molecular signatures of ependymomas is gathered, more individualized therapies may be realized.[41]

- Although the approach to supratentorial lesions varies according to location, the goal of gross total resection should be the same as in infratentorial surgery.

- Intramedullary tumors are approached via standard laminectomy with the patient in the prone position.
- Although somatosensory evoked potentials and direct motor evoked potentials are employed routinely, only rarely do they influence surgical decisions or technique.
- Laminoplasty is performed in children but does not guarantee long-term stability.
- The strategies for intramedullary tumor removal depend upon the relationship of the tumor to the spinal cord. Most tumors are totally intramedullary and are not apparent upon inspection of the surface.
- Intraoperative ultrasound may be used to localize the tumor and to determine the rostrocaudal tumor borders.
- The extent of tumor resection is guided by the anatomy of the lesion, intraoperative monitoring, the surgeon's experience, and the preliminary frozen-section histologic diagnosis.

- The plane between an ependymoma and surrounding spinal cord is usually well defined and easily developed.
- Large tumors may require internal decompression with an ultrasonic aspirator or laser.
- A competent dural closure is essential to prevent CSF leaks.

- The role of surgery for filum terminale ependymoma depends on the size of the tumor and its relationship to the surrounding roots of the cauda equina.
- Gross total enblock resection should be attempted whenever possible. This usually can be accomplished for small and moderate-sized tumors, which remain well circumscribed within the fibrous coverings of the filum terminale and easily separable from the cauda equina nerve roots.
- A portion of uninvolved filum terminale is generally present between the tumor and spinal cord.
- Amputation of the afferent and efferent filum segments is required for tumor removal.
- Internal decompression is not used for small and moderate-sized tumors because this may increase the risk of CSF dissemination.
- Recurrences following successful enblock resection are rare.

Treatment: The standard of care for ependymoma is maximal surgical resection with an acceptable neurologic outcome followed by postoperative radiation therapy directed at the site of the primary tumor. Immediate postoperative irradiation is not a widely accepted practice in the treatment of children younger than age 3 multi agent chemotherapy has typically been administered in an effort to delay or avoid irradiation. However, an obvious role for chemotherapy has not been demonstrated for patients with ependymoma, especially those older than age 3. The poor outcome of children younger than age 3 has been attributed in part to the delay in administering radiation therapy. Therefore, the approach for this very young group of patients with ependymoma should be reevaluated in light of recent advances in radiation therapy.

Surgery: Ependymoma is a relatively slow-growing tumor with a propensity for local invasion. Subarachnoid dissemination is rare and considered incurable. Because the predominant pattern of failure for ependymoma is local, aggressive measures of local control are essential. Several institutional retrospective reviews [44,45.46,47.49,50,51] and two prospective phase III trials[52,53] have shown that the extent of surgical resection is the most consistent prognostic factor for patients with ependymoma. Sutton et al retrospectively evaluated 45 patients with ependymoma and found that the 5-year survival estimate after total or near total resection was 60%; the 5-year survival estimate after subtotal resection (defined as < 90%

tumor resection) was 21%. In a similar retrospective review of 40 patients, Pollack et al found that 5-year survival after gross total resection was 80%; after partial resection (ie, less than gross total resection), it was 22%.

Finally, Robertson et al prospectively treated 32 patients in the Children's Cancer Group (CCG) Protocol 921. They

found that the 5-year progression-free survival was 66% for patients with residual tumor measuring 1.5 cm^2, and 11% for those with residual tumors measuring more than 1.5 cm^2.

Resection Alone: Successful treatment of newly diagnosed or recurrent intracranial ependymoma by resection alone has been reported by two independent groups.[54,55] Hukin et al reported 10 pediatric cases in which gross total resection was the only initial therapy for intracranial ependymoma (eight supratentorial tumors and two posterior fossa tumors). At a median follow-up of 48 months, seven patients were free of disease without further intervention, and three patients experienced tumor recurrence at 9, 10, and 20 months after resection. Two patients with recurrence were effectively treated with an additional surgical procedure and postoperative radiation therapy. Palma et al reported on their success in treating supratentorial ependymoma with surgery alone. Of 12 surviving patients, 6 in their original series of 23 patients were treated with surgery alone, and only 1 experienced a recurrence after 10 years of follow-up. These findings indicate that some patients with intracranial ependymoma probably those with supratentorial tumors—require resection only. Thus, radiation therapy and its potential for late effects might be delayed until the time of recurrence for a very select group of patients. Although complete resection is instrumental in the long-term, event-free, and overall survival of patients with childhood ependymoma, it is performed in only 42% to 62% of patients.[56,57,58,59] Complete resection is more easily accomplished for tumors in supratentorial locations and those originating from the roof of the fourth ventricle. Aggressive attempts to resect tumors in other locations, including those involving the lower cranial nerves, are associated with increased morbidity.

Second Resection: Despite the high rate of incomplete initial resections, few studies have included a second surgical procedure for patients with residual disease.[60,61] The timing of a second resection is the subject of debate: Some oncologists favor the use of chemotherapy between the initial and second resections. The purpose of administering chemotherapy before a second resection is to make the tumor more amenable to resection and to prevent tumor progression during the interval between procedures. Foreman et al reported second resections in five patients with residual tumors located in the fourth ventricle. From April 1997 through April 2000, 40 pediatric patients were referred to St. Jude Children's Research Hospital for treatment of intracranial ependymoma[62]. 24 patients (60%) underwent complete resection, and 16 (40%) had residual tumor after their initial procedure and prior to referral. Of those 16, 12 were considered candidates for additional resection based on the location of the residual tumor and

neurologic status at the time of evaluation. A complete resection was performed in 10 patients and a near total resection in 2 patients with the second procedure. By

combining the number of patients with a complete resection after their initial procedure with the number of those with complete resection after a second procedure, we increased the group's rate of complete resection to 85%. The operative morbidity of these patients was also determined. Significant morbidity, defined as lower cranial neuropathy necessitating gastrostomy or tracheostomy, occurred in 4 of the 24 patients with initial complete resections and 4 of the 16 patients with initial incomplete resections. Significant morbidity occurred in only one patient who underwent a second resection. Of the 12 patients who underwent a second resection, 6 had tumors that progressed during the interval between surgical procedures, despite administration of chemotherapy. It is generally agreed that a complete resection—ie, one that results in a very low probability of leaving even microscopic residual tumor—is rarely achieved in ependymoma. Complete resection may be possible for patients with supratentorial tumors when a margin of normal tissue surrounding the tumor is also removed and biopsies of the operative cavity are negative. Biopsies of the operative cavity are seldom performed; however, such biopsies could be therapeutically beneficial and could contribute to the planning of radiation treatment.

Resection Classification: Current management of childhood ependymoma relies on three principal classifications of resection. A resection is classified as a gross total procedure when either no visible tumor or only microscopic tumor is identified with the operating microscope after resection, and no evidence of disease is identified in postoperative neuroimaging studies. Although the classification of near total resection has not been adequately defined, it generally includes patients with minimal residual tumor for whom a second resection would produce no benefit. For this reason, such patients are often treated in the same manner as those who have undergone gross total resection. In the current management of childhood ependymoma, a resection is classified as near total when minimal residual tumor is present. For purposes of future studies, this could be an area on a single image (< 1.5 cm^2), a single greatest dimension on a single image (< 5 mm), or a volume (to be determined). A resection is classified as subtotal, or incomplete, when macroscopically visible tumor is identified with the operating microscope after resection, and residual tumor larger than that used to define near total resection is present on postoperative neuroimaging studies.

Radiation Therapy: For nearly 20 years, the avoidance of radiation therapy has been the hallmark of trial designs for the treatment of brain tumors in young children. Strategies that either delay or avoid irradiation have been justified on the basis of concerns about the effects of irradiation on neurologic, endocrine, and cognitive functions. Although irradiation-induced deficits have not been well documented in cases of childhood ependymoma, this therapy has, in the past, paralleled that used for other more common childhood tumors such as medulloblastoma (the effects of which have been well documented). Since 1977, postoperative radiation therapy has been considered standard treatment for patients with ependymoma.

Supportive Studies: Mork et al were the first to demonstrate that postoperative radiation therapy improves outcome in ependymoma patients. These investigators reported a survival estimate of 17% for patients who underwent resection alone vs a 40% survival estimate for those who underwent resection and postoperative irradiation. Radiation therapy has been routinely administered to patients with ependymoma who are 3 years of age or older, but, as yet, no studies have critically challenged its role in the postoperative treatment of patients in this age group. On the other hand, the role of radiation therapy has been evaluated in several studies in infants and children younger than age 3, including the POG 8633 study.[63] This study showed that young children with completely resected ependymoma in whom radiation therapy was delayed for 2 years experienced a significantly worse outcome (5-year survival estimate: 38%) than those in whom therapy was delayed for 1 year (5-year survival estimate: 88%). Although a better event-free survival may be achieved in patients who have undergone complete resection, the volume of residual tumor in those undergoing incomplete resection may be smaller in this advanced neurosurgical era than it was in prior treatment eras. Indeed, more recent findings suggest that a contemporary incomplete resection differs considerably from one achieved with the technology available more than a decade ago.[64,65] Five-year progression-free survival estimates as low as 0% to 26% have been reported in patients with macroscopic residual tumor after surgery, despite the use of radiation therapy.[66,67,68,69,70] Of course, the neurosurgical era from which these findings were derived should be taken into account.

Optimal Radiation Dose and Volume: The optimal dose of radiation remains unclear. The evaluation of a dose-response relationship for a given type of tumor requires prospective evaluation. Retrospectively, an increase in the dose of radiation administered to the primary site appears to improve local control.[71,72] The recent POG 9132 study used hyperfractionated radiation therapy delivered to the primary site at a total dose of 6,960 CGy for the treatment of posterior fossa ependymoma. The investigators found that 19 patients who underwent subtotal resection had a better outcome (4-year event-free survival: 50%) than did a comparable group of patients who participated in the earlier POG 8532 study, which used a lower total dose of conventional radiation (4-year event-free survival: 24%),[73] Hyperfractionated radiation therapy did not improve survival estimates in patients with completely resected tumors. In addition, several retrospective studies have failed to demonstrate any benefits associated with the use of prophylactic craniospinal irradiation.[74,75,76,77] Conformal radiation therapy limits the highest doses to the primary site and decreases the dose received by normal tissues. Reducing the dose received by normal tissues is logical in children, but requires systematic definition of the treatment volume and prospective study

to determine that irradiation using more limited volumes does not increase the risk of marginal treatment failures. We recently reported the preliminary results of a St. Jude protocol (RT-1) in which 64 pediatric patients with localized
ependymoma received treatment between July 1997 and October 2000.

Evaluating Outcome: Reducing the volume of irradiation will only be beneficial if the rate of disease control remains the same and the incidence of side effects decreases. Several reports have compared outcomes in terms of disease control, but few investigations of functional outcome have been unbiased regarding radiation therapy. Pediatric patients have never been systematically evaluated for side effects before undergoing radiation therapy; thus, the side effects reported
for these studies include those caused by the tumor, resection, radiation therapy, and possibly other therapies including chemotherapy. A trial that compares conventional radiation therapy with conformal radiation therapy will never be performed because the dosimetric advantages of the newer treatment are obvious. Investigations that include careful evaluations performed before and after irradiation will be necessary to understand the effects of radiation dose and volume on functional outcome in pediatric patients. At St. Jude, patients with localized primary brain tumors such as ependymoma that require only focal irradiation are serially evaluated for evidence of CNS effects before and after radiation therapy. Before irradiation, morbidity in this group is high; nearly 50% of those with posterior fossa tumors show evidence of endocrinopathy, as determined by dynamic tests of endocrine function.[78] For example, the integral dose and volume for the temporal lobe may be correlated with neuropsychometric measures, whereas the integral dose and volume for the hypothalamus may be correlated with evidence of endocrinopathy. Assessing the effects of radiation dose and volume requires baseline and serial evaluation after irradiation, evidence of effect and observation for a period of time during which the effect is likely to be observed.[79] Using integrated three-dimensional dosimetry, we recently demonstrated the
effects of low and high-dose hypothalamic irradiation on the time course of growth hormone deficiency up to 12 months after irradiation.[80] Such information may be used a priori to optimize treatment planning and predict outcome. In assessing cognitive outcomes afterconformal radiation therapy, we have not observed a decline in IQ estimates during the first 30 months after treatment; this finding holds for the youngest children (age < 6 years) with infratentorial tumors treated to 59.4 Gy.

Chemotherapy: Several retrospective reviews have assessed the effectiveness of chemotherapy in the treatment of newly diagnosed ependymoma, and none have found that it improves overall survival.[81,82,83,84,85,86,87] The CCG 942 study is the only randomized trial that compared survival after irradiation alone with survival after irradiation and chemotherapy in pediatric patients (aged 2 to 16 years) with ependymoma. The investigators concluded that adjuvant chemotherapy with lomustine (CeeNu), vincristine, and prednisone did not improve outcome.[88] The CCG 921 study, a prospective randomized study of radiation therapy followed by either lomustine, vincristine, and prednisone or a combination of agents known as "8 in 1" (ie, eight drugs in 1 day), used survival analyses to demonstrate that the outcome of patients who received chemotherapy was no better than that of historical controls.[89]

Adjuvant Combination Chemotherapy: Ependymoma does respond to some chemotherapeutic regimens. However, the findings of single-agent phase II studies of recurrent ependymoma have been disappointing. Cisplatin has produced one of the highest response rates (30%) of all agents used to treat recurrent ependymoma.[90] Recent reports of adjuvant combination chemotherapy in pediatric patients with newly diagnosed ependymoma have demonstrated encouraging responses without improving survival, suggesting a limited role. For example, White et al reported an 86% response rate to four cycles of vincristine, etoposide, and cyclophosphamide (Cytoxan, Neosar) in seven children younger than age 4 who had been newly diagnosed. Duffner et al achieved a 48% response rate with two cycles of vincristine and cyclophosphamide administered to 25 infants and children younger than age 3. Mason et al reported a 16% response rate to four or five cycles of cisplatin, vincristine, etoposide, and cyclophosphamide in 10 children younger than age 6. A recent prospective study by Needle et al used irradiation followed by carboplatin and vincristine alternating with ifosfamide and etoposide in patients older than 36 months with newly diagnosed ependymoma. The 5-year progression-free survival estimates of the 10 patients with incompletely resected tumors was 80%. These excellent survival statistics for patients with incompletely resected ependymoma suggested that chemotherapy may be beneficial. However, it cannot be determined if their favorable outcome was related to the volume of residual tumor, radiation therapy, or histology. Unfortunately, radiation therapy was not standardized in this study; the fact that a portion of the patients received hyperfractionated radiation therapy confounds the analysis of the results.

Standard vs Dose-Intensive Chemotherapy: The POG 9233 study compared standard chemotherapy (six 12-week cycles of cisplatin, cyclophosphamide, etoposide, and vincristine) and dose-intensive chemotherapy (eight 9-week cycles of the same agents with differences in relative intensity) in a group of infants with brain tumors including ependymoma. Event-free survival estimates were significantly increased for patients with ependymoma treated with dose-intensive chemotherapy, yet there was no difference in overall survival estimates. The relative dose intensities (compared with standard doses) were 1.67 for cisplatin, 2.67 for cyclophosphamide, 1.54 for etoposide, and
1.33 for vincristine.[91] Grill et al recently reported the results of a French Society of Pediatric Oncology trial in

73 children treated with multiagent chemotherapy for 16 to 18 months after maximal resection. Irradiation was not included in the treatment regimen. Progression-free survival estimates at 2 and 4 years were 33% and 22%, respectively, with 50% of patients relapsing during the planned chemotherapy course. Salvage therapy included additional surgery, radiation therapy, and for some, high-dose chemotherapy. Overall survival for the entire group was approximately 52% at 5 years and for the patients who relapsed, 49% at 2 years after relapse. As expected, supratentorial tumors and children with complete resection fared better; 23% were alive at 4 years without irradiation.

Chemotherapy and Second Resection: Chemotherapy may make residual tumors more amenable to complete surgical resection. Foreman et al used chemotherapy between the initial and second resections in four patients with ependymoma. After chemotherapy, all the patients had viable tumor; complete resections were performed in three of the four, all of whom remained progression-free at 23 to 34 months after second-look surgery. The subjective impression of the investigators was that the tumors were better defined and easier to dissect after chemotherapy. Platinum-based therapy has produced the best results in studies with limited numbers of patients. Response rates as high as 67% were reported in a recent review by Gornet.[92] Carboplatin and etoposide are frequently used because they can penetrate the CNS. Results suggest that some neoplasms, particularly slower-growing tumors, respond better with prolonged exposure to chemotherapeutic agents. Needle et al demonstrated the effectiveness of treatment with oral etoposide in five patients with ependymoma; two patients responded, including one who achieved a complete response.

Future Role of Chemotherapy: Chemotherapy may serve four important functions in the future: Such treatment may be used (1) to bridge the interval necessary while planning a second resection; (2) to make the tumor more amenable to resection and improve the rate of complete resection at the time of the second procedure; (3) to reduce the morbidity of the second resection; and (4) bridge the interval required to prepare a child who has suffered neurologic complications from tumor or surgery for daily radiation therapy and often anesthesia. The selection of the best agents, the schedule of delivery, and the duration of chemotherapy necessary to achieve these goals are difficult to determine given the range of responses, the differences in toxicity profiles, and the lack of data from which to model such a study. Most investigators prefer to use combinations of drugs including carboplatin or cisplatin, etoposide, cyclophosphamide, and vincristine. Concerns about the use of carboplatin, which has a better toxicity profile, persist among investigators because this agent's equivalency to cisplatin has not been demonstrated. The findings of Gaynon et al support the use of carboplatin for patients with ependymoma. These researchers found a 40% overall response rate for patients with ependymoma who had not been previously treated with cisplatin. One of the principal reasons for using carboplatin is to avoid ototoxicity. Although one or two courses of cisplatin may be relatively less ototoxic than a longer or more conventional course of the agent, the risk of substantial and permanent hearing loss increases linearly with each dose.[93] In addition, substantial concerns about hearing loss arise for patients who receive cisplatin and radiation therapy.

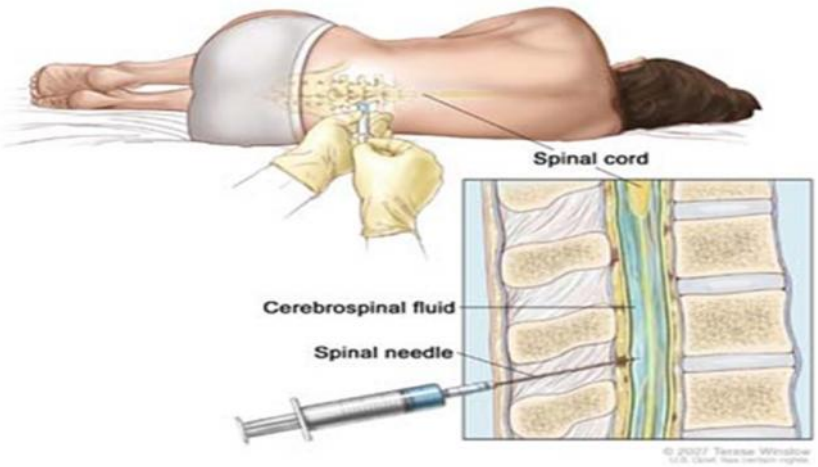
RATIONALE FOR FUTURE STUDIES

Ependymoma is a rare tumor and, with few exceptions, is rarely seen by pediatric oncologists.Therefore, onlymulti-institution studies conducted by a cooperative group such as the Children's Oncology Group can lead to improvements in outcome for children with ependymoma.Local control is the primary treatment objective because local recurrence is the predominant mode of failure. The local failure rate is highest among patients who have incomplete resection (despite postoperativeradiation therapy), and contemporary chemotherapy does not improve overall survival. However, marked advances have been made in neurosurgical technique and radiation These advances should significantly improve the outcome of patients with childhood ependymoma by increasing the rate of complete resection without added morbidity and by reducing or eliminating side effects attributable to radiation therapy. In addition, potentially important prognostic variables such as age, histologic characteristics, and location of primary tumor need to be evaluated in the context of a contemporary clinical trial.The availability of neurosurgeons and radiation oncologists with the expertise to treat pediatric ependymoma patients varies among institutions. Through the design and implementation of a multicenter treatment trial, we could increase the rate of complete resection and systematically deliver radiation therapy that is safe and effective. We couldalso develop a standard approach to assist care givers who are less familiar with the treatment of this rare disease.

The trial will also include conformal radiation therapy for all patients with ependymoma (maximal dose: 59.4 Gy; clinical target volume: 1.0 cm), and an observational study of pediatric patients who have undergone complete resection of supratentorial, differentiated ependymoma. Observation has not been suggested for supratentorial anaplastic tumors based on the St. Jude data.[94]

Current Recommendations: Immediate postoperative conformal radiation therapy is recommended for the treatment of childhood ependymomaon the basis of the following criteria. Maximal resection of the primary tumor, including second resection to achieve gross total resection diagnosis of ependymoma confirmed by an experienced neuropathologist. No evidence of tumor dissemination beyond the primary site as determined by neuroimaging studies of the brain and spine and by cytologic examination of cerebrospinal fluid (CSF) obtained from the lumbar CSF space Patient older than 12 months at the time of irradiation. Presence of an experienced radiation oncologist who specializes in the treatment of brain tumors in pediatric patients and a

Postoperative antibiotics are usually continued for 24 hours, and deep vein thrombosis prophylaxis is continued



radiation therapy department equipped to administer conformal radiation therapy to children who require general anesthesia.

Medication Summary: No specific medications exist to treat ependymomas; however, supratentorial ependymomas require medical treatment. For seizures, the patient is usually started on levetiracetam (Keppra), phenytoin (Dilantin), or carbamazepine (Tegretol). Levetiracetam is often used because it lacks the effects on the P450 system seen with phenytoin and carbamazepine, which can interfere with antineoplastic therapy. Vasogenic cerebral edema is treated with corticosteroids (eg, dexamethasone), generally in combination with an anti-ulcer agent. Corticosteroids also are effective to treat oedema associated with intramedullary tumors in the preoperative and postoperative settings. [95]

Anticonvulsants

These agents are used to treat and to prevent seizures.

- Levetiracetam (Keppra): Used as adjunct therapy for partial seizures and myoclonic seizures. Also indicated for primary generalized tonic-clonic seizures. Mechanism of action is unknown.
- Phenytoin (Dilantin): Blocks sodium channels and prevents repetative firing of action potentials. Effective anticonvulsant and first-line agent in treating partial and generalized tonic-clonic seizures.
- Carbamazepine (Tegretol): Like phenytoin, interacts with sodium channels and blocks repetitive neuronal firing. First-line agent to treat partial seizures and may be used for tonic-clonic seizures as well. Extended release form available, which is administered bid. Serum drug levels should be monitored (ideal range is 4-8 mcg/mL).
- Corticosteroids: These agents reduce peritumoral oedema, frequently leading to symptomatic and objective improvement.
- Dexamethasone (Decadron): Postulated mechanisms of action in brain tumors include reduction in vascular permeability, cytotoxic effects on tumors, inhibition of tumor formation, and decreased CSF production.

Further Inpatient Care: Patients with ependymomas who undergo surgical resection typically spend the night after surgery in an intensive care unit followed by an inpatient stay of 3-5 days. The final length of stay depends on each patient's neurological condition as well as tumor location and extent of resection.

until patients are ambulatory. Anticonvulsants are maintained at therapeutic levels throughout the inpatient stay for supratentorial ependymoma, while steroid dose is tailored to each patient's clinical status and gradually tapered pending improvement. Many patients benefit from occupational therapy and physical therapy/rehabilitation.

While patients are still in the hospital, they should undergo postoperative imaging to determine the extent of surgical resection. This is best evaluated within 3 days of surgery by a contrast-enhanced MRI of the brain because contrast enhancement during this period accurately reflects residual tumor. In addition, patients should have an MRI of the entire spine with and without gadolinium to rule out seeding. If not performed preoperatively, complete evaluations by consulting physicians, including a neurooncologist and radiation oncologist, should be considered.

Further Outpatient Care: Follow-up care with a rehabilitative medicine team is recommended for patients who sustain neurological deficits after spinal tumor resection.

Children with posterior fossa tumors must be monitored for signs of hydrocephalus, and all patients with supratentorial tumors should have serum levels of anticonvulsant drugs checked on a regular basis.

Inpatient & Outpatient Medications: For patients with supratentorial tumors, postoperative anticonvulsant medication is continued upon discharge. Steroids are usually tapered in accordance with the patient's clinical status and degree of oedema documented on postoperative imaging.

Transfer: At some institutions, transferring the patient to another facility may be necessary if the proper consultations cannot be obtained. In most cases, surgical resection can be performed on an urgent, but not emergent, basis.

Complications: In general, brain tumor resection has an overall mortality rate of 1-2%; 40% of patients remain healthy or have minimal deficits after surgery, 30% manifest no postoperative change relative to preoperative deficits, and 25% of patients sustain increased postoperative deficits that most often improve. Children who undergo resection of a posterior fossa lesion are at risk for postoperative cerebellar mutism. Nonspecific complications that can occur in any location of tumor include hemorrhage, infection, and worsening of neurological deficit.

Prognosis: Predictors of long-term survival include extent of resection made at surgery and amount of residual tumor on postoperative imaging.[96] Although lower WHO tumor grade, infratentorial location in children, absence of tumor invasion within the brainstem, absence of metastases,[97] improved performance status, and older age (for childhood ependymoma) have been associated with a survival advantage in isolated, retrospective series,[98] these factors are not significantly correlated with long-term survival.[99,100]

Medical Therapy: Treatment can be given for different reasons and the potential benefits will vary depending upon the individual situation. If patient have been offered treatment that aims to cure cancer, deciding whether to have the treatment may not be difficult. However, if a cure is not possible and the treatment is to control the cancer for a period of time, it may be more difficult to decide whether to go ahead.

If patient feel that he can't make a decision about the treatment when it is first explained to patient. Patient is free to choose not to have the treatment and the staff can explain what may happen if he do not have it. Although he don't have to give a reason for not wanting to have treatment, it can be helpful to let the staff know his concerns so that they can give him the best advice.

The treatment for an ependymoma depends on a number of things, including his general health, the size and position of the tumour, and whether it has spread to other parts of the brain or spinal cord. There are some risks associated with treatment to the brain and his doctor will discuss these with him.

His treatment will usually be planned by a team of specialists known as a multidisciplinary team (MDT). The team will usually include:

- a doctor who operates on the brain (neurosurgeon)
- a doctor who specialises in treating illnesses of the brain (neurologist)
- a doctor who specialises in treating brain tumours (an oncologist)
- a specialist nurse and possibly other healthcare professionals, such as a physiotherapist or a dietitian.

If the pressure in the skull is raised, it's important to reduce it before any treatment is given for brain tumours. Steroid drugs may be given to reduce swelling around the tumour. If raised intracranial pressure is because of a build-up of CSF, a tube (shunt) may have to be inserted to drain off the excess fluid.

Consent: Before patient have any treatment, his doctor will give him full information about its aims and what it involves. They will usually ask to sign a form saying that give his permission (consent) for the hospital staff to give him the treatment. No medical treatment can be given without patient consent.

Because most of these tumors are slow growing and locally contained, surgical extirpation, where possible, is the treatment of choice. In selected situations, watchful waiting can be considered. Steroids are used in the perioperative period or if a rapid decline in neurologic function occurs, but steroids are not considered tumoricidal.

Future and Controversies: Whereas the value of total excision of ependymomas is clear, the value of radical resection of astrocytomas is less certain. If an easily defined plane around the tumor can be followed and complete removal achieved, management is rather straight forward. However, if an ill-defined plane is present, the risk-to-benefit ratio for aggressive removal is unclear.

The role of radiotherapy in the management of slowly growing tumors is also controversial. In cases of residual or recurrent tumor, clear clinical indications have not been established. Reoperation, radiation, and watchful waiting with serial examinations and imaging are all viable options.[4, 5]

Intraoperative electrophysiologic monitoring is thought to be useful, but its efficacy is unproven. Although MRI greatly facilitates diagnosis of these lesions, pressure to control health care costs may delay diagnostic testing of mildly symptomatic patients.

Stereotaxic radiosurgery has found a place in the management of intracranial tumors. With anticipated future developments, spinal radiosurgery may have a role in management. Given the slow growth rates of these tumors, the role of radical surgery to remove all traces of the tumor is not advocated by most clinicians.

Development of neuroprotective agents for use during surgery warrants further study.Advances in imaging and surgical technique have led to removal of many tumors, with high success and low morbidity. However, the relative rarity of the tumor, along with its slow growth characteristics, makes the accumulation of large patient series difficult. Presently, in many situations, the clinician can only care for patients harboring intramedullary spinal cord tumors using an incomplete knowledge base regarding the optimal management.

CONCLUSIONS

It is obvious from these data concerning ependymomas, that there is no clear understanding of the epidemiology, biology and treatment of choice in these tumours. Many authors have stressed the importance of prospective studies with protocol based treatment strategies. Major drawbacks are the relatively small number of patients with ependymoma in each centre and the obvious lack of consensus among neurosurgeons, neuro-oncologists and neuropathologists.

We feel that it is justified to consider ependymomas of the spinal cord as a separate entity and we consider this as the only solid conclusion after our analysis of the available data for both intracranial and spinal tumours. On account of the heterogeneous data available in the reviewed literature neither positive nor negative judgement on the influence of localization and grade of the tumour, surgery, radiation and chemotherapy is possible at the moment.

Appropriate analysis of the results with the various therapeutic options can only be obtained by reliable data and on the basis of these data we strongly advocate a cooperative study of the effectiveness of treatments used. To allow reliable collection of data in the future, we wish to propose the multicentre use of a standardized format (standardized formats can be obtained by centres who wish to join this study at the authors' address) to stage and follow all patients with an ependymoma. The collected data should provide insight into the biological and clinical course of ependymomas. Hopefully, this insight will lead to more effective treatment.

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