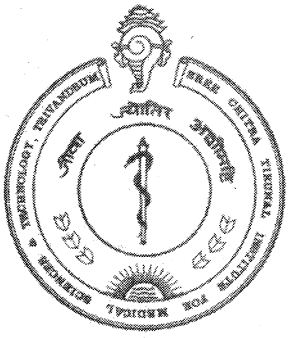
Childhood and adolescent meningiomas: A report of 38 cases and review of literature



Submitted for MCh Neurosurgery

By

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September 2009

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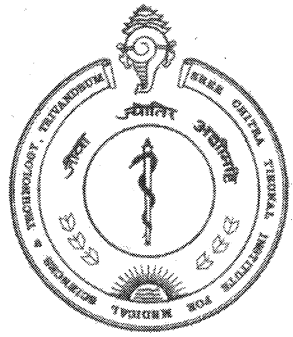

Submitted by	:	**Dr. B. Jayanand Sudhir**
Programme	:	**MCh Neurosurgery**
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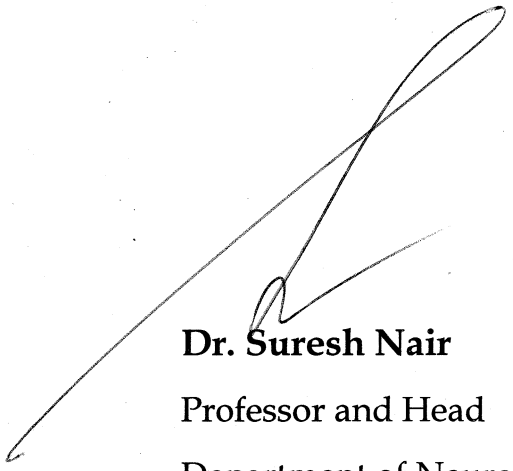
CERTIFICATE

This is to certify that the thesis entitled "**Childhood and adolescent meningiomas: a report of 38 cases and review of literature** " is a bonafide work of Dr. B. Jayanand Sudhir and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram under my guidance and supervision.



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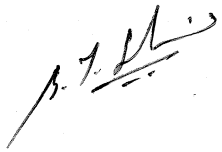
DECLARATION

This thesis titled "**Childhood and adolescent meningiomas: a report of 38 cases and review of literature**" is a consolidated report based on a bonafide study done by me during January 2005 to October 2008 under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of MCh Neurosurgery examination.



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Dr. B. Jayanand Sudhir

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INTRODUCTION

Meningiomas are uncommon childhood tumours. Every pediatric neurosurgeon has tried to resolve the problems relating to the clinical characteristics, biological behavior and outcome of this interesting and almost benign pathology, which rarely occurs in the first two decades of life. Cushing and Eisenhardt(13) encountered six (1.9%) children among 313 meningiomas documented in their classic 1938 monograph. Among 750 intra-cranial tumors reported by Matson 1969, only 3 (0.4%) were meningiomas (44). Since then, several series have been published (Table 16), yet the reported incidence remains unaltered making these tumours an interesting and distinct clinical entity. Paediatric meningiomas vary considerably in their histopathological, topographical and gender distribution throughout childhood and adolescence, reflecting different tumour dynamics as compared to adults.

Meningiomas are most commonly encountered after the second decade of life. However, they may occur at any age or even during foetal development. Amirjamshidi et al(5) in 2002 compiled in a list of 329 published cases of childhood meningiomas, to which they added 24 more patients. A recent report from the Central Brain Tumour Registry of the United States states that only 2.5% of all primary paediatric central nervous system tumours were meningeal in origin, whereas for all age groups combined, 22% of tumours were of meningeal origin(1). In general, paediatric meningiomas are commonly quoted as constituting 1.5–1.8% of all meningiomas and 0.4–4.1% of all childhood brain tumours(19, 20, 22, 26, 34, 40, 49, 52, 57, 59, 60, 65, 66, 71). Multifocal tumors, usually encountered in the context of NF2, are a recognized feature within the pediatric population, underscoring further

differences from their adult counterparts(24). Even though meningiomas are uncommon in the pediatric age group, they constitute a challenging issue for pediatric neurosurgeons, because of their different behavior as compared with adult meningiomas(14).

REVIEW OF LITERATURE

Epidemiology

Etiology

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Anatomic distribution

Pathology

Immunohistochemistry

Management

Recurrence

Prognosis

Epidemiology

The incidence of meningiomas among primary intracranial neoplasms in adults is approximately 20% and the reported incidence per 100,000 population varies from less than 1% to more than 6%. The incidence of intracranial meningiomas rises with increasing age and has been reported to be 3.5 times higher in patients older than 70years age than in younger patients, regardless of sex(42). Paediatric meningiomas are commonly quoted as constituting 1.5–1.8% of all meningiomas and 0.4–4.1% of all childhood brain tumours (19, 20, 22, 26, 34, 40, 49, 52, 57, 59, 60, 65, 66, 71). The incidence of pediatric meningiomas increases with age and more are reported in the second decade compared to the first. The male to female incidence ranges from 1:1.4 to 1:2.8. (21) In contrast to adult meningiomas, there is no female preponderance among paediatric meningiomas, and in certain series male subjects appear to outnumber their female counterparts(19, 25, 49) Ferrante and co-workers(25) reviewed 178 examples from literature and found a marginal male preponderance (M:F 1.3:1) The male predominance in childhood meningiomas is more marked in infants than in adolescents, and characteristically it seems to be absent in patients affected by neurofibromatosis(19). However, some authors like Glasier(28) and Darling(15) quote an equal incidence and others like Rochat(54) have found a female predominance as in adults. The sex hormone binding characteristics of paediatric meningiomas have not yet been well-characterised, and it is unclear to what extent the hormonal status affects the

sex predilection(1, 54). Meningiomas are multiple in 5-40% of patients especially when they are associated with neurofibromatosis type II(23).

Etiology

Trauma

Although numerous case-control studies have reported an increased association between a history of head trauma (vs. no head trauma) and the development of meningiomas, Annegers et al (1979) (6) found no significant increase in the number of any intracranial tumours in a prospective study of 2953 patients with head injuries over 29859 person-years. Similarly a population based cohort study conducted in Denmark with 228055 patients who were hospitalized with head injuries between 1977 and 1992 found no significant increase in the subsequent incidence of meningiomas(37).

Irradiation

Exposure to ionizing radiation is a known etiological factor in the development of meningiomas. An increased rate of meningioma formation has been seen in patients after irradiation for tinea capitis, in patients after treatment for primary head and neck malignancies, and in survivors of radiation exposure from the atomic bomb explosions in Hiroshima and Nagasaki. The causal relationship between radiation and paediatric meningioma is also well established. Current findings suggest a nearly ten-fold relative risk for children with radiation exposure over those without such exposure(29, 46). Radiation induced meningiomas typically present at an earlier age, arise within the prior

irradiation field, are more likely to be multifocal, have different cytogenetic characteristics, are more biologically aggressive with higher degrees of atypia and mitosis and are more likely to recur. There is also some suggestion of a dose effect, with higher levels of radiation exposure being associated with shorter latency periods for development of meningiomas(29). field and there was a sufficient time lag between the radiation and the development of the meningioma.

Genetics and Molecular biology

The association between NF-2 and meningioma is well known, and they may share common mechanisms of pathogenesis. Thirty to eighty percent of sporadic meningiomas and nearly all neurofibromatosis-related meningiomas have mutations in the NF-2 gene located in chromosome band 22q12, that result in mutations in the protein *merlin*. Chromosomal banding techniques have identified chromosome subband 22q12.3-qter, which is near the NF-2 gene but is believed to represent a separate and distinct locus in meningioma formation. The genetic factors involved in the tumorigenesis of meningiomas are currently a subject of investigation to inform screening and prediction of risk for tumor progression to atypical or anaplastic disease. The possibility of NF2 should be considered in any child with a meningioma and approximately 25–40% of children with meningiomas have NF2 (7, 49, 50). The more severe ("Wishart") variant of NF2 is more likely to present with paediatric meningioma(49). In Perry's series(49, 50), sporadic and NF2-associated paediatric meningiomas were histopathologically similar with the exception

that brain invasion was nearly exclusive to the sporadic tumours, a difference that reached statistical significance. Both NF2-associated and sporadic paediatric meningiomas frequently had demonstrable 1p and 14q deletions, alterations commonly associated with tumour progression in meningiomas. The large size of some paediatric meningiomas mentioned in several series and especially in those including NF pedigrees, implicates NF as a stigma suggestive of rapid tumour growth. Besides NF, Gorlin syndrome also known as multiple basal cell carcinomas is another familial tumour condition with autosomal dominant inheritance with an association with meningiomas(55).

Loss of expression of another tumour suppressor gene, DAL-1, which is located in 18p11.3, has been found in 30-70% of meningiomas and is thought to play a role in both early tumourigenesis and meningioma evolution. Other tumour suppressor genes implicated in the development or progression of meningiomas are SMARCB2 (22q11.2), p53 (17p), and CDKN2B (9p21). The fact that malignant and atypical meningiomas tend to have more chromosomal aberrations than benign tumours do, suggests progressive loss of tumour suppressors and potential activation of oncogenes. Some of the genes implicated in meningioma oncogenesis are c-*sis*, C-*myc*, Ha-*ras*, K-*ras*, c-*fos*, c-*erb*B and S6*k*. A variety of other chromosomal aberrations have been implicated in the formation and progression of meningiomas including losses on 1p, 2p, 6q, 10q and 14q and gains on 1q, 9q, 12q, 15q, 7q and 20. Alteration on chromosomes 1, 10, and 14 and reactivation of the telomerase subunit hTERT seem to be practically important in the progression of more biologically aggressive meningiomas. Radiation induced meningiomas have

been shown to express genetic alterations that are different than those of sporadic meningiomas. In particular, there are fewer losses of genetic material on chromosome 22 and more losses on chromosomes 1p, 6q, 9q, 18q and 19q.

Gonadal steroid hormones and receptors

Estrogen receptors have been reported in 0-94% of meningiomas and progesterone receptors in 40-100%. Recent studies using modern experimental and laboratory techniques have revealed minimal amounts of functional estrogen receptor. This finding is supported by the generally disappointing results of anti-estrogen agents (Tamoxifen and Mepitiostane) in treating meningiomas. Most investigators have identified high levels of progesterone receptors in meningiomas, and the presence of these receptors has correlated with less aggressive tumour biology, more favourable prognosis and a lower incidence of recurrence. Antiprogesterone agents used to treat meningiomas have yielded varied results; the most recent phase-III double-blind, randomized, placebo-controlled trial of mifepristone reported no significant benefit(32). Though one might not expect paediatric meningiomas to be hormonally driven, progesterone receptor (PR) is expressed with similar frequency, regardless of age at presentation. There is a roughly inverse association between PR expression and tumour grade in meningiomas of children and adults alike(18, 54).

Androgen receptors are found in meningiomas with about the same frequency as progesterone receptors and are expressed in 69% of males and 31% of

females(9). Testosterone stimulates in vitro meningioma cell growth, and it has been speculated that androgen receptors may help modulate progesterone receptor activity.

Other receptors and Growth Factors

Using polymerase chain reaction analysis. Carrol et al (1996) (10) detected D_1 receptor mRNA in meningiomas, particularly in females, as well as D_2 receptor mRNA and prolactin receptor mRNA, but the functional importance of these findings is unclear. Somatostatin receptors, particularly type 2a (hsst2a) receptors have also been reported at high levels in meningiomas. There have been a few reports of success using somatostatin analogues to treat meningiomas, but the role of somatostatin receptors in tumour progression or growth is still unclear. Growth hormone receptor mRNA is ubiquitiously expressed in meningiomas. Growth hormone receptor blockade by pegvisomant has been shown to result in decreased growth rates of primary meningioma cell cultures and reduced tumour growth and regression in an in vivo animal model.

Westphal and Hermann (1986)(68) discovered functionally intact epidermal growth factor (EGF) receptors, a product of the oncogene c-*erb,* and reported increased DNA synthesis after EGF treatment of meningioma cell cultures. Weisman et al (1986)(67) noted a modulatory effect on this receptor by platelet derived growth factor (PDGF) and revealed near maximal levels of DNA synthesis in meningioma cell cultures when PDGF and EGF were added together.

The finding of c-erb/EGF receptor expression in meningiomas prompted searches for other oncogene receptor- mitogen systems. Using Northern-blot analysis, Maxwell et al 1990(45) demonstrated that meningiomas express both the c-sys/ PDGF-2 proto-oncogene and the PDGF receptor (PDGFR) gene. Further studies revealed that PDGF-β is expressed in meningiomas, that PDGF-BB increases c-fos expression in meningioma cell cultures, and that over expression of PDGF- β and PDGF-BB is associated with higher grade and proliferative activity in meningiomas. These results support the concept of PDGFR activation by an autocrine-paracrine loop and the idea that PDGFR activation contributes to tumour cell proliferation or malignant transformation. Vascular endothelial growth factor (VEGF) levels are associated with increased angiogenesis, edema, and frequency of recurrence in meningiomas. Fibroblast growth factor and insulin-like growth factor 1 have also been identified in meningiomas and implicated in tumour progression. Many of the growth factor receptors (PDGFR, EGFR and VEGFR) are protein tyrosine-kinase receptors that activated ras and associated intracellular cascades, which mediate cellular proliferation, differentiation and transformation.

Clinical Features

There is no single symptom or sign that identifies patients who harbour intracranial or spinal meningiomas. A variety of presenting features depend primarily on the tumour's size and location; these features include headache, paresis, seizure, personality change or confusion and visual impairment. Headache and paresis are the most common symptom and sign respectively and each occurs in a third of patients. Meningiomas in particular locations may produce a consistent set of signs and symptoms. Tumours of the olfactory groove have been associated with the Foster-Kennedy syndrome (anosmia, ipsilateral optic atrophy and contralateral papilledema); tuberculum sellae meningiomas may cause significant and early visual loss (typically a chiasmal syndrome with optic atrophy and an incongruent bitemporal hemianopia). Cavernous sinus meningiomas may result in proptosis, diplopia or primary aberrant oculomotor degeneration and foramen magnum tumours often have associated nuchal and suboccipital pain with step-wise appendicular sensory and motor deficits. Childhood meningiomas are characteristically known to have non-specific symptoms and diagnosis is often difficult. The elasticity of skull and non-cooperation among children compounds the problem. Quite often a local swelling of the cranial vault may be the first sign. Common clinical manifestations of paediatric meningiomas include signs of increased intracranial tension, focal neurological deficits, seizures and other signs based on their location.

Radiologic diagnosis

Computed Tomography (CT) with contrast can detect most meningiomas. CT can optimally detect bone involvement involving both hyperostosis and bone erosion or remodeling. On enhanced CT scans, meningiomas are generally homogenously isodense or slightly hyperdense compared with normal brain. Because small meningiomas can be missed contrast enhanced studies are indicated.

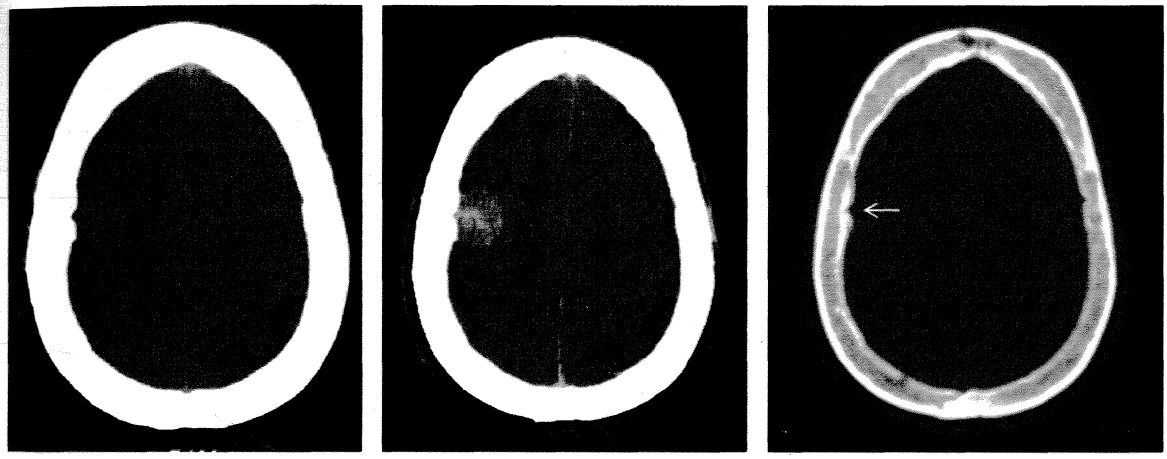


Fig 1: CT scan of a right frontal mid-convexity meningioma showing contrast enhancement and hyperostosis (white arrow)

Calcification may range from tiny punctuate areas to dense calcification of the entire lesion. With intravenous contrast, meningiomas typically enhance homogenously and often demonstrate morphologic features such as sharp demarcation and a broad base against bone or free fural margins. Approximately 15% of benign meningiomas have an unusual appearance on CT images. Areas of hyperdensity, hypodensity or non-uniform enhancement may be seen. These areas may represent haemorrhage, cystic degeneration, or necrosis respectively.

The Magnetic Resonance Imaging (MRI) characteristics of meningiomas are generally consistent. On T1 weighted images, 60-90% of meningiomas are isointense and the reminder are mildly hypointense compared to grey matter. On T2 weighted images, 30-45% of meningiomas have increased signal intensity and approximately 50% are isointense compared to grey matter. Their typical extraparenchymal location heightens the neuroradiologist's ability to diagnose these tumours.

There is increased interest in using MRI characteristics to subtype meningioma tissue before surgery. The results of these studies have been variable. Some have reported 75-96% accuracy whereas others have found no correlation. The MRI characteristics that allowed accurate preoperative identification of meningioma subtypes were confined to findings on T2 weighted images. Specifically, meningiothelial and angioblastic variants had higher signal intensity on T2 weighted sequences than fibroblastic and transitional meningiomas did. The amount of cerebral edema associated with meningiomas was also found to be greater in meningiothelial or angioblastic variants. Finally, a high signal intensity on T2 weighted images has been correlated with microscopic hypervascularity and soft tumour consistency.

Contrast enhanced MRI provides the most sensitive and specific means of detecting meningiomas. Most meningiomas enhance intensely and homogenously with intravenous contrast material, and in 10% cases, small additional meningiomas are encountered that are missed on un-enhanced MR images. Contrast enhancement of the dura mater extending away from the margins of the mass is typical of meningiomas, although this pattern can be

seen with other dural based lesions. This dural tail can represent either tumour extension or reactive change, and its resection is important to reduce the risk of recurrence. Post operative enhanced MRI has also been found to be sensitive and specific in detecting residual or recurrent meningiomas. Thick and nodular enhancement has a high correlation with recurrent or residual neoplasm.

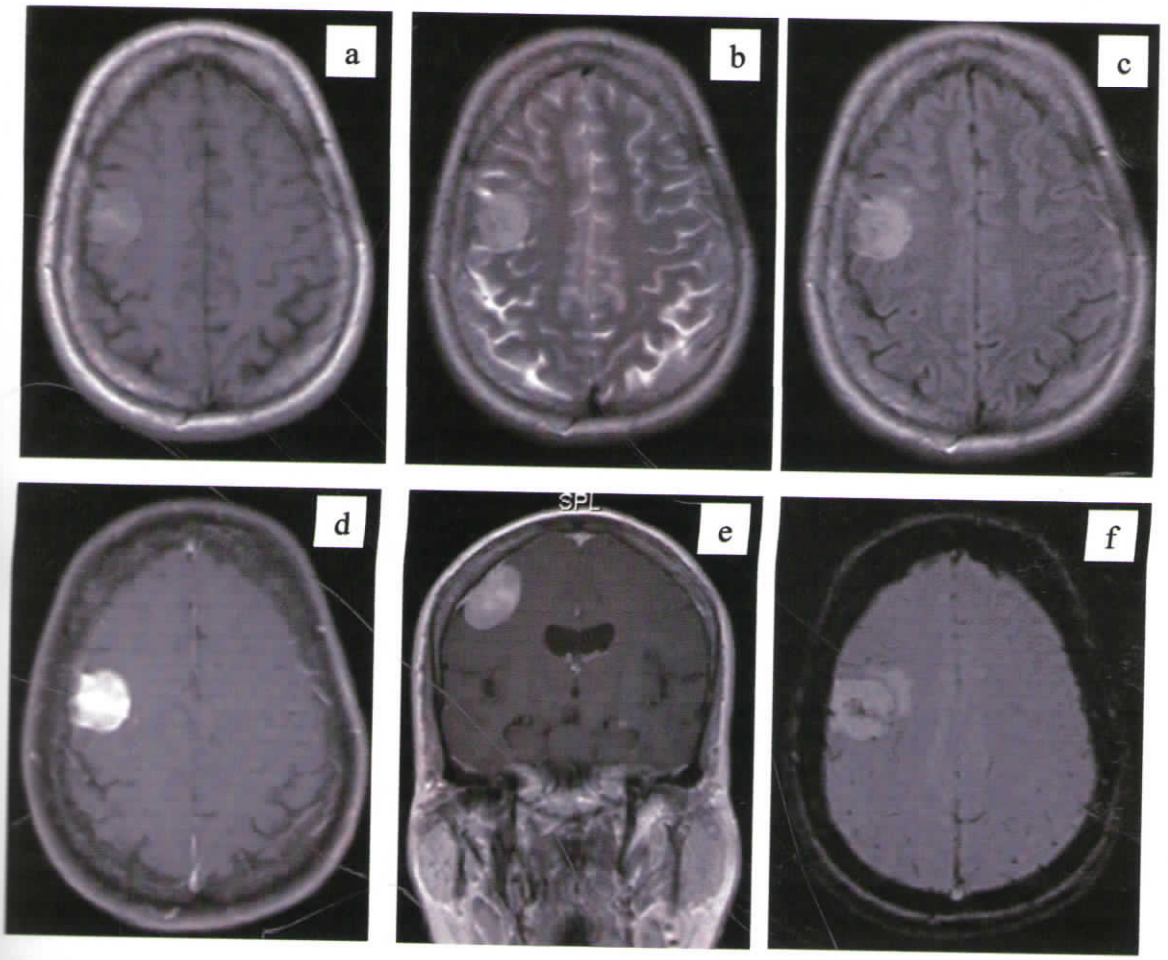


Fig 2: Right frontal mid-convexity meningioma: Isointense on T1 (a), hyperintense on T2 (b) and FLAIR (c), homogenously enhancing on contrast (d), coronal imaging (e) showing dural tail, susceptibility artifacts on SWI (f)

In vivo, MR spectroscopy is an evolving area of study. Compared with the MR spectra of normal brain, the typical MR spectra for meningiomas reveal a markedly increased choline peak and reduced N-acetyl aspartate and

phosphocreatine/ creatine peaks. An additional peak present in some meningiomas at 1.47ppm has been attributed to alanine.

Childhood and adolescence meningiomas have variable imaging characteristics. Cystic and calcified variants are known to occur frequently. Dural attachment is not as common as in adult meningiomas. The incidence of calcification and hyperostosis in CT scan is high especially in the paediatric meningiomas associated with NF. On CT scanning, hyperostosis of the overlying bone is seen in 50% of tumours and 50% have intra-tumoural calcification [25]. Magnetic resonance (MR) characteristics of paediatric meningiomas are similar to adult meningiomas. On MR imaging, the tumours are usually isointense to hypointense on T1, iso- to hypointense on T2 and exhibit good contrast enhancement [32]. T2 hyperintensities if seen, denote microcystic changes, dilated blood vessels, and high cellularity and usually suggest a syncitial or angiomatous variant. Presence of a dural tail sign on MR imaging is not obvious in all examples of paediatric meningiomas.

Although its role in diagnosing meningiomas has changed, angiography still remains an important pretreatment evaluation technique; it also demonstrates the tumor's vascularity and its feeders in preparation for preoperative embolization in cases of giant tumors(22).

Anatomical Distribution

Of all intracranial meningiomas, 85% are located supratentorially, one-third to one half of which are located along the base of the anterior and middle fossae.

Table 1 Common sites and relative incidence of intracranial meningiomas in adults

Site	*Relative incidence (%)*
Parasagittal or falcine	25
Convexity	19
Sphenoid ridge	17
Tuberculum sella	9
Posterior fossa	8
Olfactory groove	8
Middle fossa or Meckel's cave	4
Tentorial region	3
Peritorcular region	3
Lateral ventricle	1-2
Foramen magnum	1-2
Orbital or optic nerve sheath	1-2

Parasagittal and convexity meningiomas are the most frequent sites for meningiomas in both adults as well as in several series of paediatric meningiomas(25, 53, 66). However, paediatric meningiomas are known to favour uncommon sites like skull base and posterior fossa locations(19, 22, 25, 49, 53, 66). A second feature that seems to be typical of the paediatric

age is the higher incidence of meningiomas located within the ventricular system or lacking any apparent dural attachment like deep in the sylvian fissure. In their review, Herz et al(34). found that 28% of children with NF had intraventricular meningiomas. Incidence of multiplicity was significant in some series(66).

Other unique aspects reported for paediatric meningiomas are large tumour size, cyst formation and tendency to recur. Cystic changes are reported to occur in 13–50% of paediatric patients against 2–4.6% in adults meningiomas(11, 35, 48). Cyst formation was rare as noted in Amirjamshidi's(5) series of 24 patients with no case of cystic meningiomas being reported.

Spinal meningiomas typically arise from arachnoid cap cells in the dura mater near the region of the nerve root sleeve. They may also originate from meningiothelial cells making up the arachnoid villi near the dorsal root ganglia. This anatomic arrangement explains why these tumours frequently arise in a lateral location within the spinal canal. These tumours occur with approximately equal frequency as the nerve sheath tumours representing approximately 40% of intradural extramedullary tumours. Most spinal meningiomas occur after the fourth decade of life and have a significant predeliction for males (75-85% of cases). Meningiomas arise primarily in the thoracic region in approximately 80%. The cervical region is affected less often and lumbar and sacral tumours are relatively rare. These tumours typically grow in a globoid configuration with a region of dural attachment. Rarely they grow as a carpet like plaque (en plaque meningiomas).

Meningiomas tend not to invade the pia mater which improves the ability to resect them safely.

Pathology

Microscopically meningiomas have a varied but characteristic histopathologic appearance. This diversity forms the basis for their pathologic classification. The system based on the 2000 WHO classification which associates histopathology with information on recurrence and aggressiveness is used in this study. There are three grades of meningiomas. Grade I meningiomas are associated with a low risk of recurrence and aggressive growth, whereas Grade II and III meningiomas have a greater likelihood of one or both of these characteristics.

Grade I meningiomas:

Of the nine subtypes of Grade I meningiomas, the three most common are meningiothelial, fibrous and transitional. Although it is important that these and the other subtypes are recognized, the prognostic significance of each one is unclear. But they are currently considered equivalent.

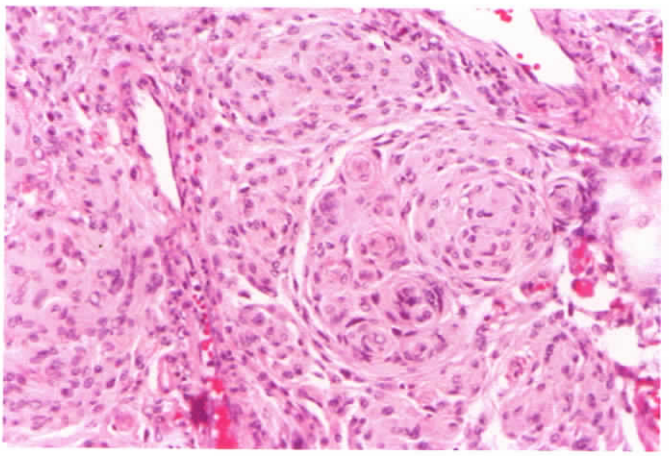


Fig 3: Meningiothelial meningioma with cells arranged in whorls.

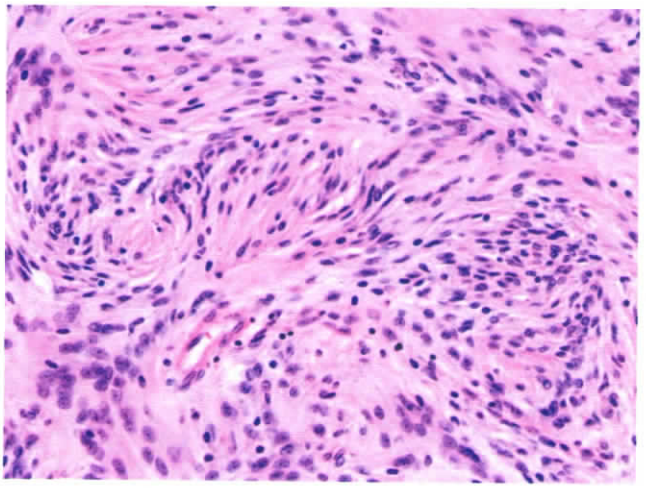
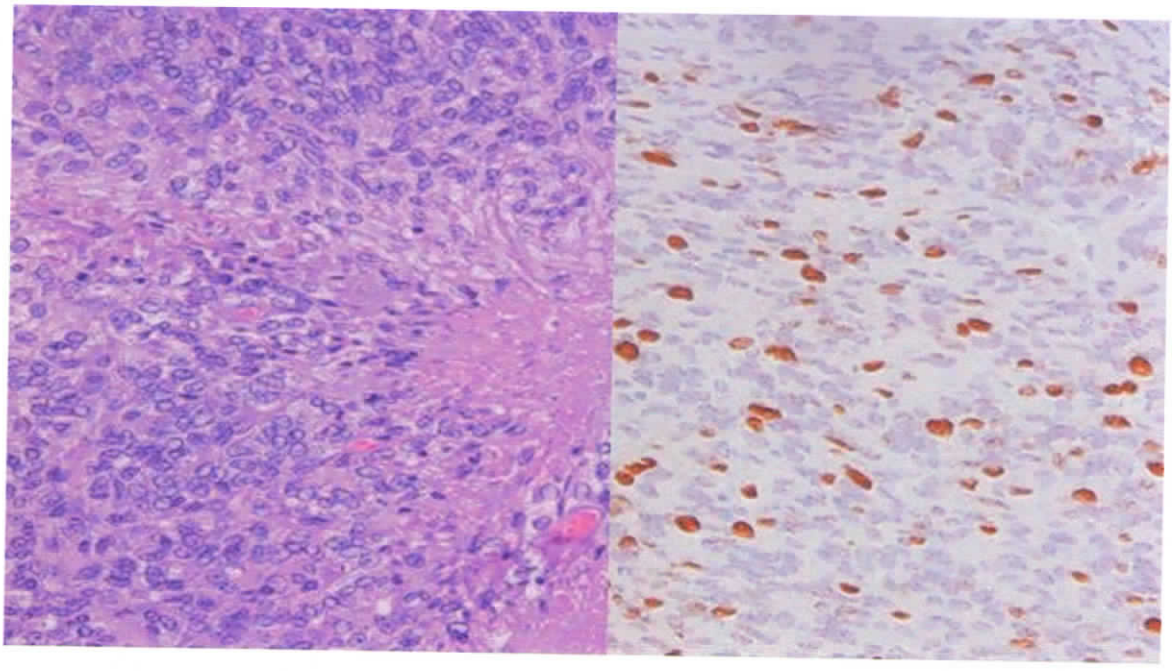


Fig. 4: Transitional variant of meningioma

Grade II meningiomas:

Apart from brain invasion and metastatic spread which define malignancy, certain features of Grade II meningiomas that may be seen by light microscopy suggest increased tumour aggressiveness and and increased recurrence rate. Among these atypical features, are loss of architectural pattern, high cellularity, increased number of mitotic figures (>4 mitoses per 20hpf), necrosis, prominent nucleoli and nuclear pleomorphism. The three subtypes of grade II meningiomas are atypical, chordoid and clear-cell type.



A B

Fig. 5: A. H&E stain showing high cellularity and sheets of meningothelial cells with a mitotic activity of 4 per 10 high power fields with foci of necrosis (center and lower right). (B) Ki-67 immunostaining with the MIB-1 antibody showing a labeling index of around 15%.

Grade III meningiomas:

The diagnosis of a grade III (malignant) meningioma traditionally requires histologic evidence of brain invasion or distant metastasis which in most cases is accompanied by further evidence of biologic aggressiveness such as cellular sheeting, nuclear pleomorphism, increased cellularity and mitoses (>20mitoses per 20 high power fields), and necrosis. When dissemination occurs, the most common location for metastasis are the lungs and pleura, abdominal viscera (especially the liver), lymphnodes and bones. Patients with meningiomas associated with frank malignancy are reported to have only a 2-

year median survival duration. The three subtypes of grade III meningiomas are anaplastic, papillary and rhabdoid.

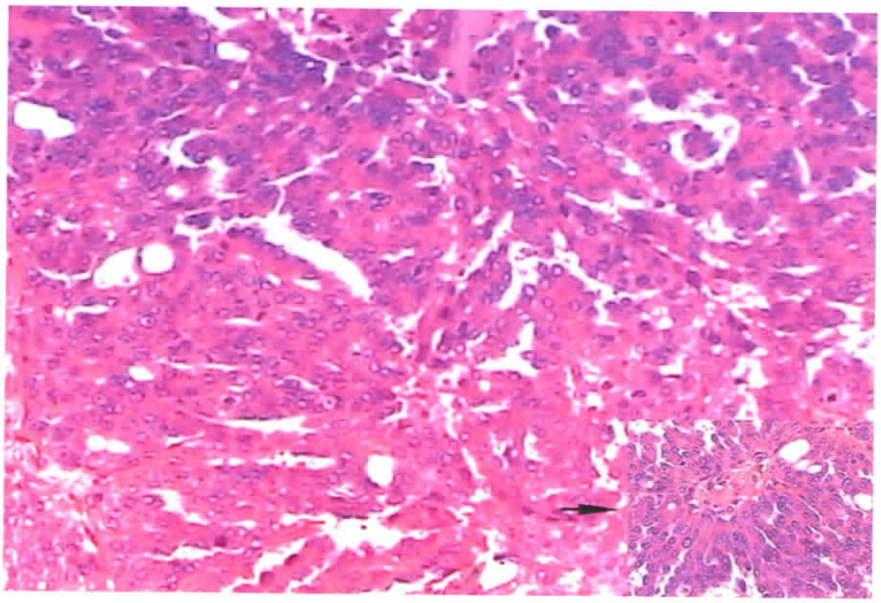


Fig. 6: Papillary meningioma: Photomicrograph of the tumor showing sheets of tumor cells arranged in papillary pattern and a papilla with fibrovascular core (inset) (H&E, ×200).

Childhood meningiomas are known to have a high incidence of atypical histopathology especially the clear cell variant and the papillary variants. Higher risk of malignancy (sarcomas 30%, papillary variant 40%) has been reported by some authors like Glasier(28) Current evidence does not support this higher risk and most authors(46, 55) accept an incidence of 2–5% (15, 36). Similarly, chordoid meningiomas, rhabdoid meningiomas and a unique histopathological pattern termed "sclerosing variant" are reported to be more common in children(17, 50, 55).

Immunohistochemistry

Epithelial membrane antigen (EMA) is useful in both age settings for confirming the meningothelial phenotype in anaplastic or sarcomatoid examples and glial fibrillary acidic protein (GFAP) highlights entrapped glial elements in those meningiomas with brain invasion(17, 50). MIB-1 (Ki-67) proliferative indices tend to correlate with tumour grade and to a lesser extent with the risk of recurrence in paediatric meningiomas, though the associations are weaker than in adult cohorts(18, 58). Immunohistochemical proliferative markers have been studied by Sandberg et al(58) in 14 meningiomas from children. They documented higher MIB-1 LI in atypical or malignant tumors (median 12.3%; range 7.0–31.6%) than those for tumors without atypia (median 7.0%; range 1.2–12.6%; p = 0.045). On the other hand, median MIB-1 LI for pediatric meningiomas without histological atypia did not differ significantly from that for adult meningiomas without atypia.

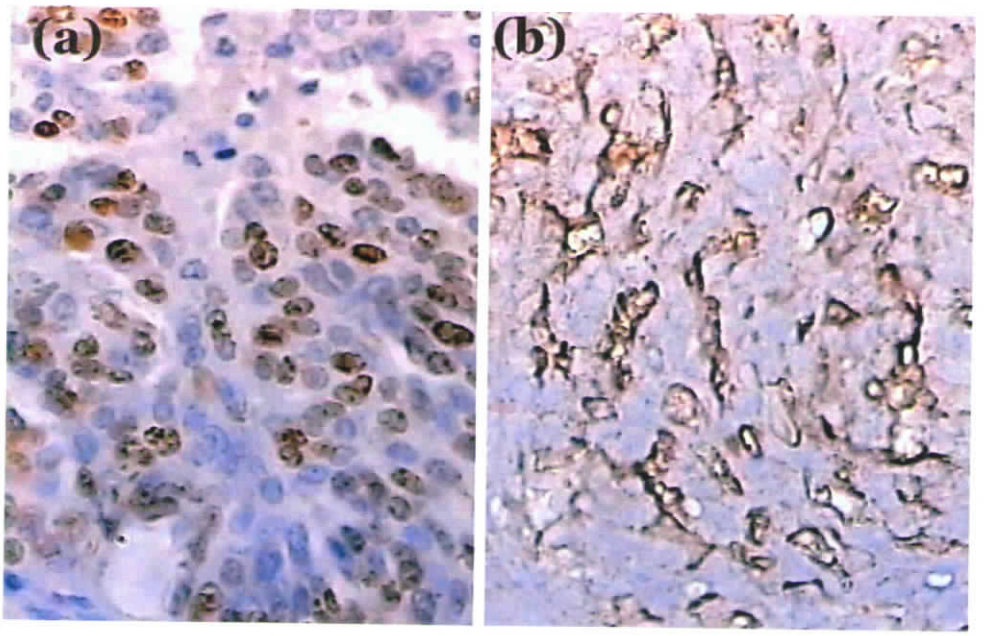


Fig. 7: Tumor cells showing immunoreactivity to (a) MIB-1 and (b) EMA (×400).

Management

The treatment of a meningioma depends primarily on the size and location of the tumour, the age of the patient, the associated symptoms and neurologic deficits. The mainstay of treatment is surgical resection, although small, asymptomatic, incidental meningiomas can typically be managed with observation and serial imaging. After surgery, re-imaging is typically performed at 6 month intervals initially, which may be extended to longer intervals if there are no radiographic signs of tumour growth and the patient remains asymptomatic. Treatment should be initiated when symptoms arise or tumour growth is documented. Critical parameters that affect the ease of surgical removal include the tumour's location, size and consistency, vascular and neural involvement and in case of recurrence, prior surgery or radiotherapy. New and innovative approaches have been devised to reach and widely expose meningiomas in any location. Furthermore, a greater appreciation of risk factors for and patterns of tumour recurrence has changed surgical planning and goals. The surgical goal now is to decrease the incidence of recurrence by resecting all of the neoplasm and all involved dura mater, soft tissue and bone. However, the tumour size and location and the involvement of adjacent structures may not allow all meningiomas to be completely resected in this manner.

Surgical approach:

In the operating room, the patient should be positioned to maximize the accessibility of the tumour, the chances of unimpeded venous drainage and the beneficial effects of gravity, the surgeon's comfort and above all, the patient's safety. In any position that places the patient's head above heart level, monitoring for air-embolism should be used, particularly because many meningiomas are located close to the venous sinuses and their large tributaries.

To the surgeon's advantage, a layer of arachnoid usually separates meningiomas from the brain, cranial nerves and blood vessels. By accessing and staying within this surgical plane, the surgeon can minimize the chances of neural or vascular injury. Early extensive tumour debulking allows the tumour capsule to collapse inward, thus facilitating the definition of the arachnoid plane. The method used to debulk the tumour which may be suction, coagulation, sharp excision, ultrasonic aspiration or laser vapourisation- depends on the tumour's consistency, vascularity and location. Once the tumour mass has been resected, careful attention must be given to the resection of the involved dura mater and bone. The involved dura mater is resected as widely as possible and then repaired with autologous pericranium, fascia lata or temporalis fascia or a dural graft. Vascularised pericranium, temporalis muscle or free tissue transfer is used to separate intracranial contents from the paranasal sinuses, aerodigestive tract and middle ear. Cranioplasty is performed as required to reconstruct calvarial defects.

The goal of surgical treatment of spinal meningiomas is gross total surgical excision with the intention of cure. Gross total excision can be achieved in most cases, largely because these tumours tend not to invade the spinal cord or the bone surrounding the dura mater. Even so, the recurrence rate may be as high as 10-15%. Simple posterior laminectomy provides adequate exposure in almost all cases. The addition of facetectomy, a lateral extracavitary approach, or an extreme lateral approach in the region of the foramen magnum may be required to gain access to ventral meningiomas. Sectioning of the dentate ligament and suture retraction to rotate the cord may also help. Even with these extended approaches, it may be difficult to visualize the entire margin of a ventrally situated tumour. Fortunately, there is ususlly a protective layer of arachnoid between these tumours and the ventral surface of the cord. While dorsal and dorsolaterally situated meningiomas may be removed en bloc (including the site of dural attachment), for ventrally situated tumours, the resection is generally piecemeal and resection of the dura mater may not be possible. When the tumour and the dura mater can be resected, a variety of dural patch materials (both natural and synthetic) are available for dural reconstruction.

Adjuvant radiotherapy

Although there have been no randomized, controlled or prospective studies with long-term followup conducted to evaluate the efficacy of radiotherapy in treating meningiomas, the use of external beam irradiation has become an important part of the management of these tumours, particularly as adjuvant

treatment for patients after subtotal tumour resection. In a prospective analysis of 140 patients with benign meningiomas treated by subtotal resection plus adjuvant radiotherapy over 23 years, Goldsmith et al 1994(30) reported 5 and 10-yr progression-free survival rates of 89 and 77 % respectively. In patients treated using CT planning (after 1980), the 5-yr progression-free survival rate was 98%. Recently, Soyuer et al (2004)(61) compared 92 patients with WHO grade I benign cerebral meningiomas who underwent gross total resection, subtotal resection plus adjuvant radiotherapy or subtotal resection plus delayed radiotherapy.

At a median followup of 7.7yrs, the 5-yr progression-free survival rates were 77%, 91% and 38% respectively. The overall 5 and 10-yr survival rates were not statistically different among the three groups or from the age-adjusted expected survival rate. Thus delaying radiotherapy until tumour recurrence without compromising overall patient survival is possible and may spare the patient from the potential toxicity of radiation. The data do not permit determination of which strategy is optimal. For meningiomas that are considered inoperable because of their location, poor patient health, patient refusal of surgery, external beam radiotherapy would seem beneficial for aggressive (atypical or anaplastic) tumours, but very little information exists to support this theory.

Stereotactic irradiation in the form of radiosurgery or conformal, fractionated or intensity modulated radiotherapy has increasingly been used to treat meningiomas with improved efficacy and diminishing untoward effects. Stereotactic irradiation uses various forms of energy, the most common of

which are photons from Cobalt-60 gamma-ray sources (gamma-knife) or linear accelerators (LINAC) and heavy particles (protons) from cyclotrons. Radiosurgery provides effective tumour control of small meningiomas. Kondziolka et al 1999(41) observed a 93% tumour control rate in patients whose meningiomas were treated by gamma-knife radiosurgery and a 61% incidence of tumour shrinkage in 99 patients who were followed for 5-10yrs. The incidence of new neurological deficits in this group of patients was 5%. In a recent retrospective study, Pollock et al 2003(51) reported that gamma-knife radiosurgery of small or medium sized beingn meningiomas, provided progression-free survival rates equivalent to that of complete surgical resection after a mean follow-up of 64months. Gamma-knife radiosurgery has also been shown to be an effective treatment for difficult to resect cavernous sinus meningiomas. Lee et al 2002(43), reported an actuarial tumour control rate of 93% at five years for benign cavernous sinus meningiomas; adverse effects of radiation were experienced by 6.7% of patients.

LINAC based radiosurgery also offers effective control of small meningiomas. A recent study of 43 patients who underwent LINAC based radiosurgery for skull-base meningiomas, reported a 7-year local control rate of 89.7%(12). This value correlated with the 5-yr control rate of 89% and a complication rate of 55 in a previous study of 127 patients(33). Spiegelmann et al 2002(62) reported that both the 3- and 7-yr actuarial tumour growth control rates were 97% for cavernous sinus meningiomas treated by LINAC based radiosurgery. They also reported a low incidence of long term cranial neuropathies.

Despite the promising results of stereotactic irradiation, there are some limitations and uncertainities with this modality. The targeted tumour is limited to 35-40mm because this is the size at which the tumour can receive a single dose of appropriate strength with a 1% risk of radiation necrosis. However, the increased availability and use of fractionated delivery of stereotactic irradiation have overcome this size limitation. Alheit et al 1999(4) reported a 1-yr progression-free survival rate of 100% in 24 patients who underwent fractionated stereotactically guided conformal radiotherapy for meningiomas. Seven of fifteen patients who had neurologic deficits before treatment improved, and two patients experienced early side-effects (one facial palsy and one Addisonian state). Other recent studies have reported benefit from stereotactic conformal radiotherapy for atypical and malignant meningiomas and for large cavernous sinus meningiomas.

Intensity modulated radiotherapy delivers fractionaled, conformal radiotherapy more effectively than traditional techniques to tumours with complex shapes. Initial reports have shown that this method is effective in treating meningiomas and controlling tumour growth and carries a low risk of side-effects.

Adjuvant radiotherapy appears to be beneficial after incomplete excision of meningiomas in adults, but it is rather risky to use radiotherapy for benign and partially excised cerebral lesions during childhood. Re-operation is thought to be better than adjuvant therapy(22). Tumour behaviour following resection was difficult to predict and paediatric patients with histologically benign meningiomas deserve careful and extended clinical follow-up(27, 34).

Atypical meningiomas are known to have long survival and benign ones are known to recur fast(54).

Adjuvant chemotherapy

Little information is available regarding the efficacy of traditional antineoplastic agents against benign or malignant meningiomas. Adjuvant chemotherapy (intravenous or intra-arterial cis-platinum, dacarbazine or doxorubicin) against malignant meningiomas and for recurrent benign or atypical meningiomas has been administered to a small number of paients but has generally been unsuccessful despite its effectiveness against other soft tissue tumours. Hydroxyurea has been shown to arrest meningioma cells in the S-phase of cell cycle and to induce apoptosis in vitro. Although a similar beneficial effect has been seen in a small subgroup of patients with recurrent and unresectable meningiomas, subsequent studies have shown little, if any, benefit. Interferon-α has been reported to be effective in prolonging the time to recurrence in a small group of patients with aggressive meningiomas and to have a lower toxicity than traditional chemotherapeutic agents. The South west Oncology group used Tamoxifen to treat 19 patients with unresectable or refractory meningiomas and observed tumour progression in 10 patients, temporary stabilization of the disease process in 6 patients, and a partial or minor response in 3 patients. (31). A recent phase III, double-blind, randomized study of Mifepristone did not show any benefit. (32).

Recurrence

The completeness of the tumour resection is the primary factor influencing the meningioma recurrence rate. Stafford et al(63) found a 25% recurrence rate at 10years in patients who had undergone a gross total tumour resection and a 61% recurrence rate in those who had undergone partial resection. Jääskeläinen (Nov 1986)(38) found an overall recurrence rate at 20years of 19%. Multivariate analysis showed that strong risk factors for recurrence included no coagulation of dural origin, invasion of bone and soft consistency of the tumour. The recurrence rate at 20years was 11% for patients with none of these risk factors, 15-24% for one risk factor and 34-56% for two risk factors. In a second study from the same group, the diagnosis of atypical and anaplastic meningioma carried an increased risk of recurrence of 38 and 78% at 5years respectively(39). The fact that cumulative relative survival rates (that is the observed to expected survival rates) at 1, 5, 10 and 15 years were 83%, 79%, 74% and 71% respectively, indicated increased mortality in patients with meningiomas. Using multivariate analysis, Stafford et al 1998(63) found that age younger than 40years, male sex, incomplete surgical resection, optic nerve involvement and four or more mitotic figures per ten high power fields were associated with a decreased progression-free survival rate. Other factors that have been implicated in the recurrence of meningiomas include mitosis, focal necrosis, brain invasion, syncitial tumours, hypervascularity, haemosiderin deposition, sheets of tumour cells, prominent nucleoli, nuclear pleomorphism and elevated proliferation index.

The use of Ki-67 labelling to develop a proliferation index is a common immunocytochemical technique for predicting a tumour's biologic aggressiveness and potential for recurrence. Labeling indicates averaging 1%, 5.5% and 12% have been identified for benign, atypical and anaplastic meningiomas respectively(2). The median MIB-1labelling index for pediatric meningiomas without histological atypia did not differ from that for adult meningiomas without atypia, in a study of 14 paediatric meningiomas by David Sandberg et al(58), suggesting that the more aggressive clinical features of meningiomas in children may be attributable to factors other than the rate of cellular proliferation.

Other markers of proliferation currently being investigated are progesterone receptors, topoisomerase II α, telomerase, transforming growth factors, mitosin, survivin, and other apoptosis related proteins. Positron emission tomography of glucose utilization have also been used to assess a tumour's biologic aggressiveness and potential for recurrence.

Prognosis

The clinical evolution of meningiomas in children is not reliably predictable and remains a problem. Consequently, childhood meningiomas are considered to carry a worse prognosis (35% 10 year survival rate) than meningiomas in the adult population(20, 59). Statistical analysis of outcome prognosticators is difficult due to the limited number of patients in most of the published series. Location and extent of excision appear to be more important than histology in predicting outcome. The role of proliferative indices and

biological markers are yet to be conclusively confirmed in paediatric meningiomas.

AIM OF THE STUDY

To report on a series of patients aged less than twenty years with cranial and/or spinal meningiomas treated in our institute, focusing on the clinical profile of the patients, tumour pathology, complications and to attempt to determine the factors influencing the outcome following surgical excision.

MATERIALS AND METHODS

Patient Population

Between January 1982 and December 2005, 49 meningiomas were diagnosed in 38 patients aged less than 20years. Forty-one of these tumours were surgically treated at Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram and had histologically proven meningiomas. Their hospital records including follow-up notes and imaging studies were retrospectively reviewed.

Preoperative Examination

The preoperative workup included a detailed neurological examination to establish baseline characteristics. Imaging studies included high-resolution CT and MR imaging depending on what was available at that time. If the internal carotid arteries or the vertebrobasilar system were involved by the tumor, a cerebral arteriogram was acquired and collateral blood flow was assessed through cross-compression studies.

Radical Excision

The patients underwent surgery in which modern techniques were used; the procedures were performed to accomplish total resection of the tumor. A variety of approaches were used depending on the location and size of the tumor. The adequacy of resection was noted based on the surgeon's observation and findings on the postoperative MR and/ or CT studies.

Outcome and followup

Post operative outcome of each patient was recorded using the Glasgow outcome score. The patients underwent regular follow-up and clinical examination at each visit. The follow-up period was defined as the period extending from surgery to the most recent clinical visit or patient contact. Patients with followup period less than six months were considered as lost to followup. Recurrent tumor was judged according to findings on imaging studies. All tumors were evaluated by a neuropathologist, and the diagnosis of meningioma was confirmed and classified in accordance with WHO classification of central nervous system tumours, 2000.

Data analysis

The outcome was analysed with respect to the following variables: age, gender, Neurofibromatosis association, extent of resection, tumour location, recurrence and the histopathological variant. Data was analyzed using SPSS software.

RESULTS AND ANALYSIS

A retrospective study was done in 38 patients aged below 20years, diagnosed with cranial and/or spinal meningiomas treated at SCTIMST over 23 years between January 1982 and December 2005. A total of 41 meningiomas were operated in 38 patients.

1) Age and gender distribution

The operated patients included 20 males and 18 females with a mean age of 15.53 years. The youngest child was 2.5 years of age. Six of the 38 patients were in the first decade and the rest were in the second decade.

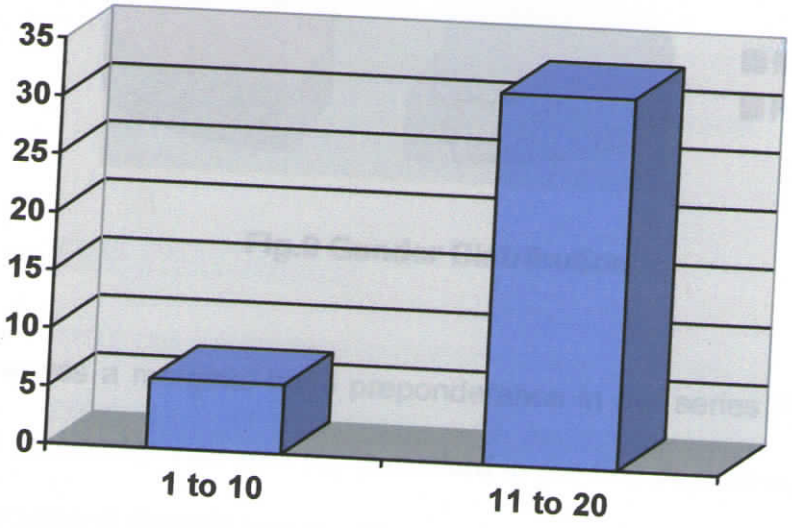


Fig. 8: Age distribution

Gender	*No. of patients*	*Percentage*
Male	20	52.7
Female	18	47.3
Total	38	100.0

Table 2: Gender distribution

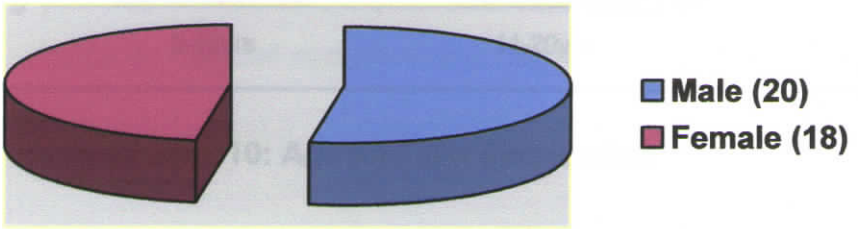


Fig.9 Gender Distribution

There was a marginal male preponderance in our series (M:F= 1.11:1). The male preponderance was more marked in the first decade while the incidence in the second decade was equal in each gender.

Age→ Gender↓	0-10yrs	11-20yrs
Male	4	15
Female	2	15

Table 3: Age and gender distribution

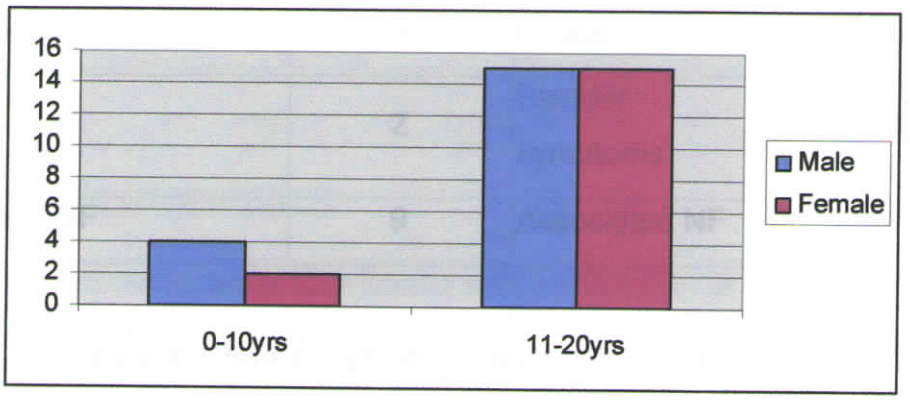


Fig. 10: Age and sex distribution

2) Clinical presentation

The commonest presenting symptoms were seizures (76.3%) followed by raised intracranial tension (71%) and focal neurological deficits (39.4%) (Table 4). None of the children gave any past history of trauma, but one child developed a right middle cranial fossa meningioma 2 years after undergoing radiotherapy for a right parietal anaplastic astrocytoma.

Signs and symptoms			
Cranial tumours	**No of patients**	**Spinal tumours**	**No of patients**
Raised intracranial pressure	14	Pain	4
Seizures	29	Limb weakness	5
Diplopia	3	Numbness	5
Visual blurring	13	Spasticity	4
Proptosis	9	Ataxia	4
Ptosis	2	Bladder symptoms	4
Associated NF	9	Associated NF	2

Table 4: Clinical symptoms at the time of surgery

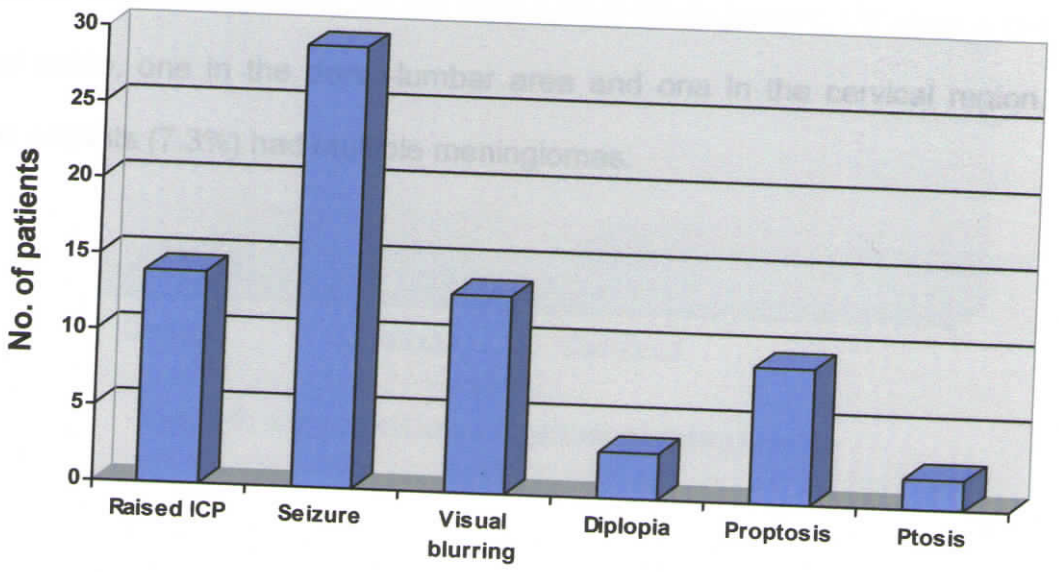


Fig. 11: Clinical presentation (cranial)

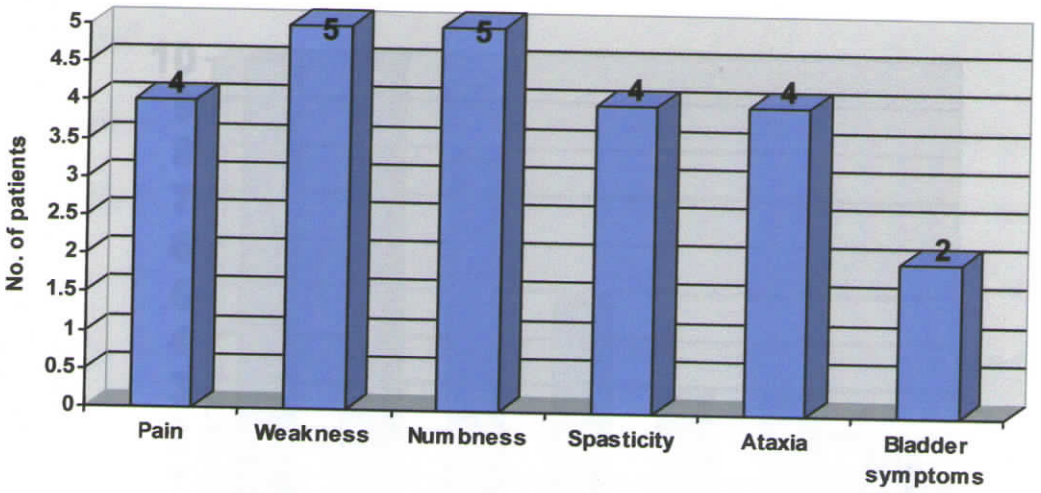


Fig. 12: Clinical presentation (spinal)

3) Anatomic Distribution

The location of the tumours was unique with ten (24.4%) at the skull base, ten (24.4%) parasagittal, eight (19.5%) spinal, five (12.2%) convexity, three posterior fossa (7.3%), three intraventricular (7.3%) and two optic nerve sheath (4.9%) meningiomas. Of the eight spinal meningiomas, six were in the dorsal spine, one in the dorso-lumbar area and one in the cervical region. Three patients (7.3%) had multiple meningiomas.

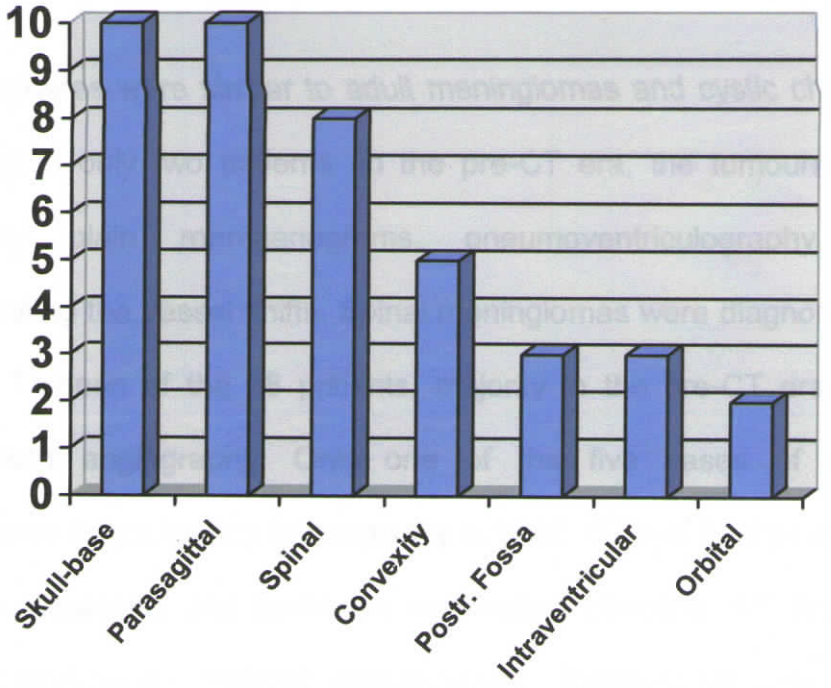


Fig. 13: Overall distribution

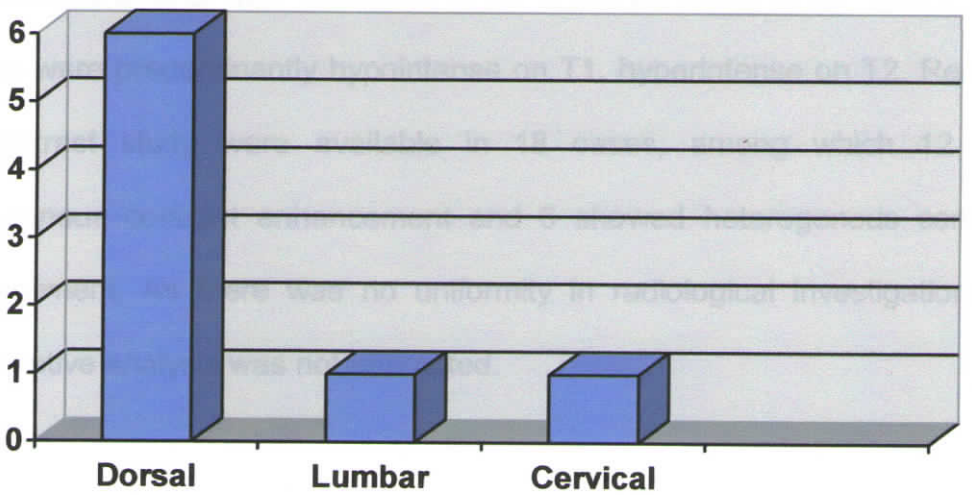


Fig. 14: Distribution of spinal meningiomas

4) Imaging

Radiological features were similar to adult meningiomas and cystic changes were observed in only two patients. In the pre-CT era, the tumours were diagnosed by plain roentgenograms, pneumoventriculography and angiography noting the vessel shifts. Spinal meningiomas were diagnosed by myelography. Thirteen of the 38 patients, majority in the pre-CT era were investigated with angiography. Only one of the five cases of spinal meningiomas was diagnosed by myelography in 1987. CT and MRI paved the way for better diagnosis and facilitated presurgical planning. CT features noted were calcification, contrast enhancement, hyperostosis and bone erosions. Calcification was observed in only two of our patients and hyperostosis in one. MRI was done in 21 of the 38 cases in our series. The lesions were predominantly hypointense on T1, hyperintense on T2. Reports on contrast study were available in 18 cases, among which 12 had homogenous contrast enhancement and 6 showed heterogenous contrast enhancement. As there was no uniformity in radiological investigations, a comparative analysis was not attempted.

5) Surgery and extent of resection

Standard surgical techniques were used and the extent of resection was graded as per Simpson's grading system. Grade I excision could be achieved only in 20 patients, grade II in nine, grade III in eight and grade IV in four. The major factor preventing total excision was the location.

Simpson's grade of excision	No. of tumours	Percentage
Grade I	20	48.7
Grade II	9	21.9
Grade III	8	19.5
Grade IV	4	9.7

Table 5: Extent of resection

6) Histopathology

Histopathological analysis revealed 30 (73.2%) grade I (six meningothelial, 12 transitional, seven psammomatous and five angiomatous), nine (21.9%) grade II (seven atypical, two chordoid) and two (4.9%) grade III (one rhabdoid, one anaplastic) meningiomas (Table 6). In two patients, the meningioma was seen as part of a collision tumour, with a glioma in one and with a schwannoma in the other.

Histopathology type	Our series	Literature
Meningothelial	6 (14.6%)	34%
Transitional	12 (29.3%)	23%
Psammomatous	7 (17.03%)	3%
Angiomatous	5 (12.2%)	5%
Atypical	7 (19.5%)	2–5%
Chordoid	2 (4.9%)	
Rhabdoid	1 (2.4%)	
Anaplastic	1 (2.4%)	

Table 6: Histopathology variants—our series compared to literature review

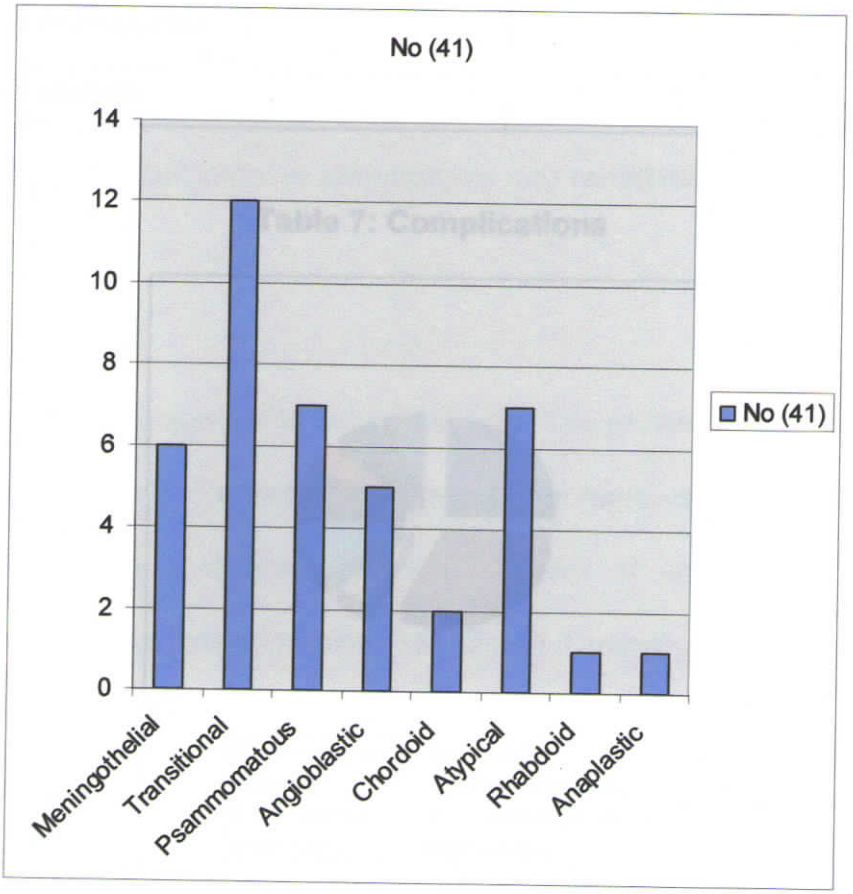


Fig. 15: Histopathology variants

7) ***Post operative complications***

Major post-operative complications included seizures, fresh deficits, pseudomeningocele and meningitis. Two patients in this study died in the postoperative period. We had one mortality due to post-operative sepsis.

Complication	Number of patients
Limb weakness	4
Visual deficits	5
CSF leak & meningitis	2
Hydrocephalus	1
Pseudomeningocoele	1
Hearing loss	1
Osteomyelits	1
Seizures	1

Table 7: Complications

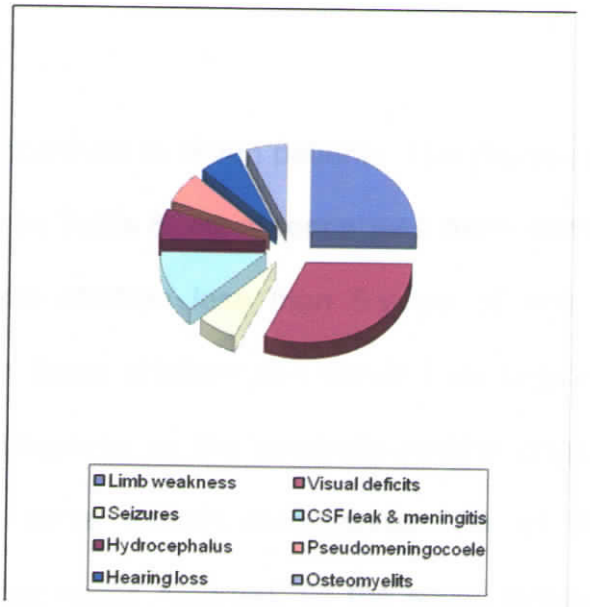


Fig. 16: Complications

8) Follow up

The follow up period ranged from 2 months to 26years with a mean of 4.74 years. Three patients with followup duration less than six months were considered lost to followup. However their neurological status at the last followup date was considered for comparison. Thirty patients had a minimum followup of one year. At the time of last follow up 32 patients had a good outcome, five had a poor outcome and we lost one patient due to post-operative sepsis. Of the five patients with poor outcome two were recurrent skull base lesions with post-operative motor and multiple cranial nerve deficits. One child with NF and multiple cranial and spinal meningiomas was incapacitated due to the multiple spinal lesions and was bed bound. Two children who presented late with blindness secondary to bilateral primary optic atrophy did not improve after surgery and remained dependent.

9) Recurrence

Recurrence was observed in seven patients. The profile of the tumours which recurred is given in Table 8. Recurrence was more common among males (5/7) and both the children less than 5 years of age in our series had recurrences. Both these children had Grade I meningiomas, one being an angiomatous meningioma in the cerebello-pontine angle and the other a transitional optic nerve sheath meningioma. Six of the ten skull base meningiomas in our series recurred. Of the seven tumours which recurred, one had undergone Grade I excision while the other three had undergone incomplete excision. The seven recurrences included five Grade I

meningiomas (three transitional and two angiomatous variant), one Grade II (atypical) and one Grade III (anaplastic) variant. While five of the thirty Grade I meningiomas recurred, one out of nine Grade II meningiomas and one out of the two Grade III meningiomas recurred. All the skull base meningiomas with recurrence were re-operated. The child with an orbital recurrence refused repeat surgery. Of the seven recurrent tumours, the Simpson's grade of excision was grade III in 4 cases, grade IV in 2 cases and grade I in one case. Hence these may be considered as tumour regrowth rather than recurrences.

No.	Age	Sex	Histopathology type	Location	Extent of resection (Simpson grade)	GOS
1	19	f	Transitional	Skull base (MCF)	III	4
2	17	f	Atypical	Skull base (MCF)	I	3
3	10	m	Angiomatous	Suprasellar	III	5
4	18	m	Anaplastic	Skull base	IV	3
5	6	m	Transitional	CP angle-foramen magnum	III	4
6	4	m	Angiomatous	CP angle	III	4
7	2.5	m	Transitional	Optic nerve sheath	IV	4

MCF middle cranial fossa, GOS Glasgow outcome score, CP cerebello-pontine

Table 8: Clinical features of the seven tumours with recurrence

10) Outcome

Outcome was assessed using the Glasgow Outcome Scale (GOS) at last followup. A GOS score of 4 and 5 was considered as good outcome while a score below 3 was considered as poor outcome. Overall a good outcome was noted in 32 patients, a poor outcome in 5 patients while one patient died. The outcome was analysed with respect to the following variables: age, gender, Neurofibromatosis association, extent of resection, tumour location, recurrence and the histopathological variant. The assessment of outcome was confounded by the patients with multiple meningiomas operated for more than one tumour. The outcome in such cases was decided considering the overall disability caused by the tumours.

a) Age

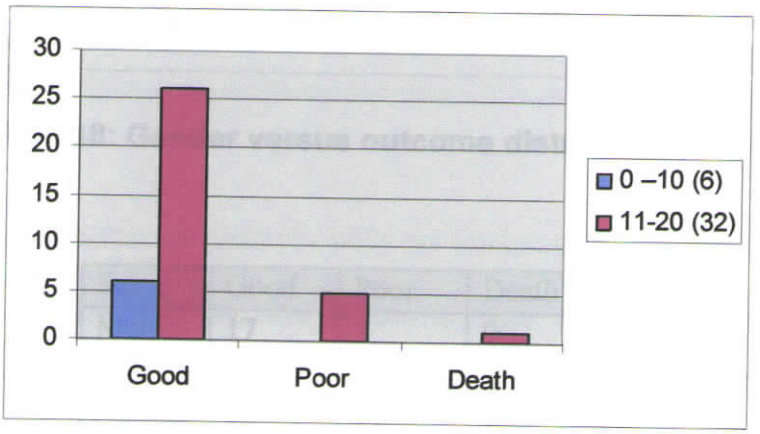


Fig. 17: Age versus outcome distribution

Age (yrs)	Good	Poor	Death
0–10 (6)	6	0	0
11-20 (32)	26	5	1

Table 9: Age versus outcome distribution

A good outcome was noted in all operated children aged less than ten years. Of the 32 patients in the second decade, a good outcome was seen in 26 (81.2%) cases, a poor outcome in 5 (15.6%). The patient who expired was in her second decade and was operated for an extensive skull-base meningioma.

b) Gender

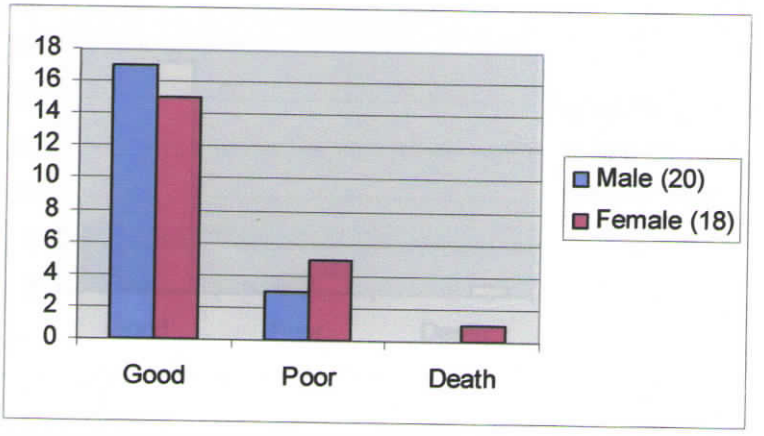


Fig. 18: Gender versus outcome distribution

Sex	Good	Poor	Death
Male (20)	17	3	0
Female (18)	15	5	1

Table 10: Gender versus outcome distribution

The outcomes in the genders were comparable: a good outcome in 85% of males and 83% of females.

c) **Neurofibromatosis association**

	Good	Poor	Death
NFI(8)	7	1	0
NFII (3)	1	2	0
No NF (27)	24	2	1

Table 11: Associated neurofibromatosis vs outcome distribution

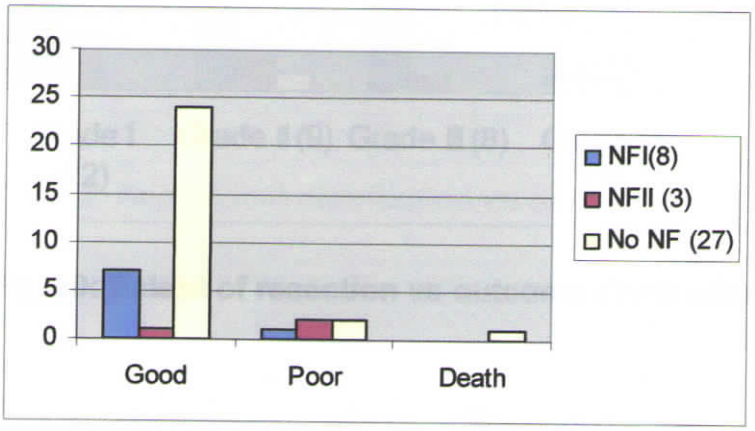


Fig. 19: Associated neurofibromatosis vs outcome distribution

The outcome was better in patients with no features on Neurofibromatosis. Among the neurofibromatosis, the outcome was better in patients with Neurofibromatosis type I compared to Neurofibromatosis type II. The worse prognosis in Neurofibromatosis type II could be attributed to highly vascular tumours encountered at surgery portending incomplete removal as well as vascular injury causing infarcts and neurological deficits.

d) Extent of resection

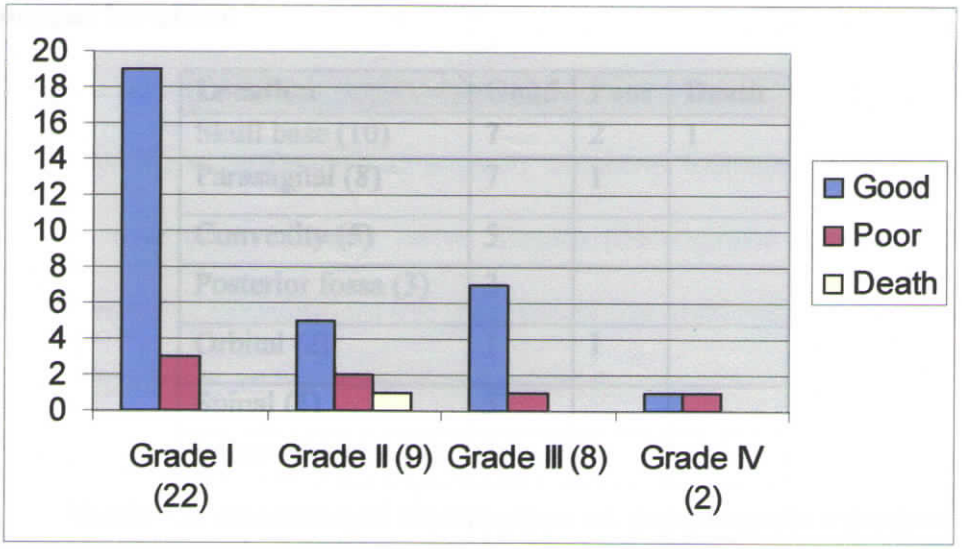


Fig. 20: Extent of resection vs outcome distribution

Extent of resection	Good	Poor	Death
Grade I (22)	19	3	0
Grade II (9)	5	2	1
Grade III (8)	7	1	0
Grade IV (2)	1	1	0

Table 12: Extent of resection vs outcome distribution

A Simpson's grade I excision reflected a better outcome. Higher grade of excision subjected the patient to surgery for re-growth or recurrences which

increased the chances of vascular injury and morbidity. Extensive skull-base meningiomas were excised with difficulty and deliberate subtotal excision to prevent anticipated morbidity had been advocated.

e) Tumour location

Location	Good	Poor	Death
Skull base (10)	7	2	1
Parasagital (8)	7	1	
Convexity (5)	5		
Posterior fossa (3)	3		
Orbital (2)	1	1	
Spinal (5)	5		
Intraventricular (3)	3		

Table 13: Anatomical distribution vs outcome distribution

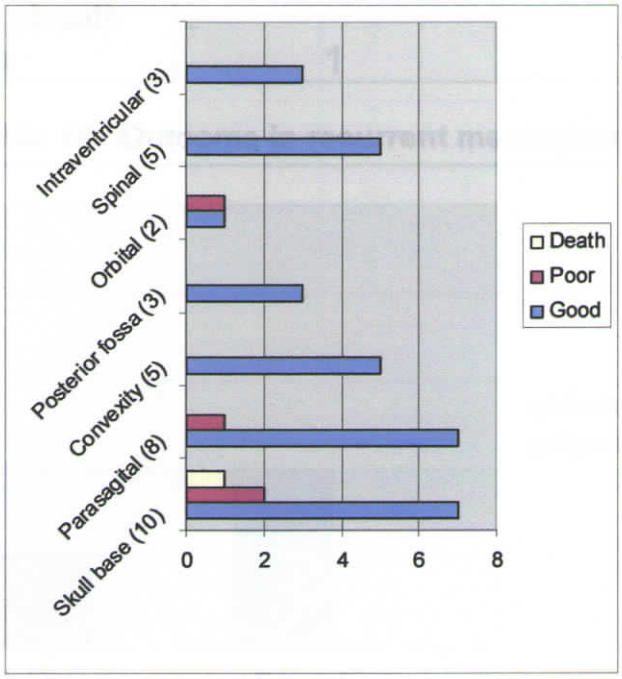


Fig. 21: Anatomical distribution vs outcome distribution

Analysis of outcome in relation to anatomic distribution of the tumour was confounded by patients with multiple meningiomas. In such cases, the overall outcome was assesses based on the functional disability caused by both the

tumours. A greater number of skullbase meningiomas had worse outcome. Only one of the eight parasagittal meningiomas had a poor outcome.

f) Recurrence

Six of the seven cases which developed recurrence were skull base meningiomas. Five of these had a good outcome following surgery for the recurrence. One case of optic nerve sheath meningioma which developed recurrence was not operated as the relatives of the child refused surgery. This child was dependent as his vision was impaired.

	Good outcome	Poor outcome
Skullbase meningioma	4	2
Optic nerve sheath meningioma	1	0

Table 14: Outcome in recurrent meningiomas

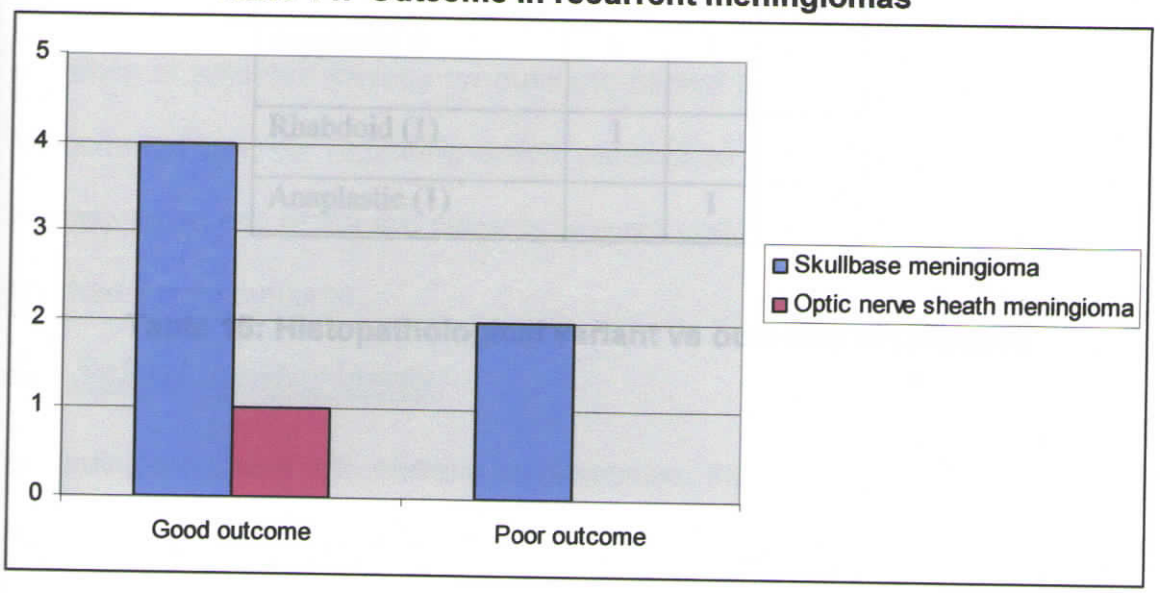


Fig. 22: Outcome in recurrent meningiomas

g) Histopathological variant

Histological grade of the tumour failed to have a bearing on the outcome as evidenced by atypical meningiomas having good outcome. One Rhabdoid meningioma operated from the middle cranial fossa floor had a good outcome. The commonest histological type was transitional variant; and majority of these had a good outcome

HPR	Good	Poor	Death
Meningothelial (6)	4	2	
Transitional (12)	10	2	
Psammomatous (7)	4	2	1
Angiomatous (5)	5		
Chordoid (2)	2		
Atypical (7)	6	1	
Rhabdoid (1)	1		
Anaplastic (1)		1	

Table 15: Histopathological variant vs outcome distribution

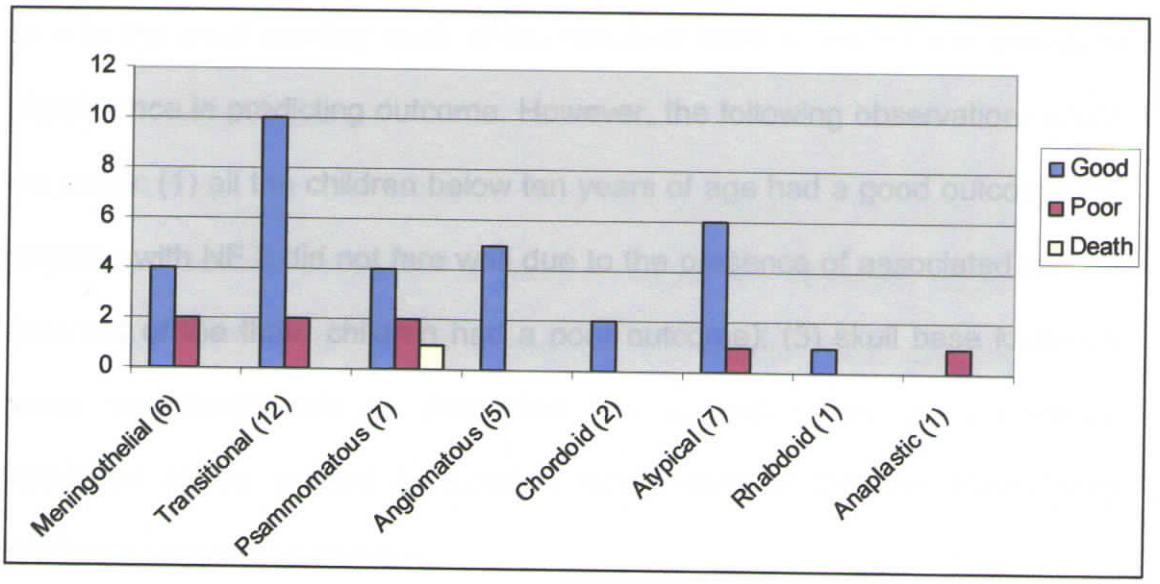


Fig. 23: Histopathological variant vs outcome distribution

11) Adjuvant therapy:

Three children operated for anaplastic, one each for rhabdoid and angiomatous variant were subjected to adjuvant therapy. The rhabdoid variant was given chemotherapy while the others underwent radiotherapy. The influence of adjuvant therapy on outcome cannot be assessed as there was no common agenda regarding which patients to be subjected to adjuvant therapy. However, of the five patients who did undergo adjuvant therapy, only one had a poor outcome.

12) Spinal meningiomas:

Excluding the cases with multiple meningiomas, there were 5 cases of spinal meningiomas. While three of these were located in the dorsal spine, two were located in the cervical spine. The outcome for all these cases was uniformly good. Three of the tumours turned out to be psammomatous variant while the other two were meningothelial and transitional.

Due to the small number none of the variables were found to be of statistical significance in predicting outcome. However, the following observations could be made: (1) all the children below ten years of age had a good outcome; (2) children with NF 2 did not fare well due to the presence of associated lesions (two out of the three children had a poor outcome); (3) skull base locations were associated with an increased risk of recurrence; (4) recurrence appeared to be related to location and extent of excision rather than histopathology in our series.

Illustrative cases

Skull base meningioma

A 12year old girl had presented in 1999 with proptosis of her right eye and headache. She was diagnosed to have an extensive skullbase meningioma extending from the right petrous apex to the orbital apex, spanning the paracavernous region. She underwent a right presigmoid petrous ridge approach and near total excision of the lesion. Postoperatively she developed total ophthalmoplegia of the right eye and lost her vision in the right eye.

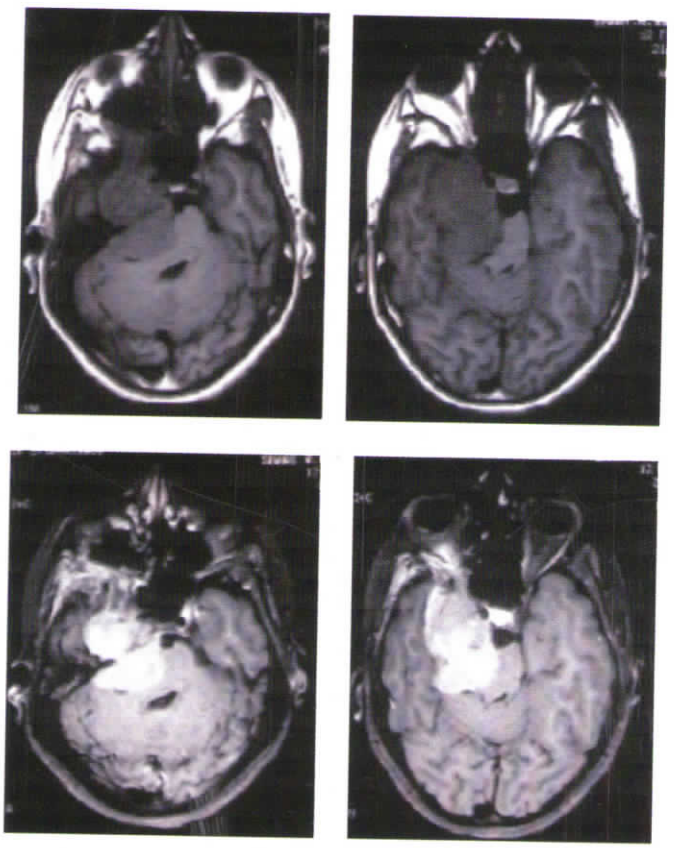


Fig 24: T1W imaging pre and post contrast showing the extent of the lesion spanning the skull base

In 2001 she was diagnosed to have a recurrence on imaging and was kept on followup.In 2006, at the age of 19years, she presented with worsening proptosis of the right eye. MRI revealed an extensive recurrence involving the orbital apex, infratemporal fossa, middle cranial fossa and petrous apex. She underwent re-exploration and subtotal decompression of the tumour. The histopathology of the tumour at both surgeries was Transitional variant of meningioma.In the followup period she developed CSF rhinnorhoea which was managed conservatively. Followup imaging showed a small residual tumour at the orbital apex. She also underwent enucleation of her right eye.

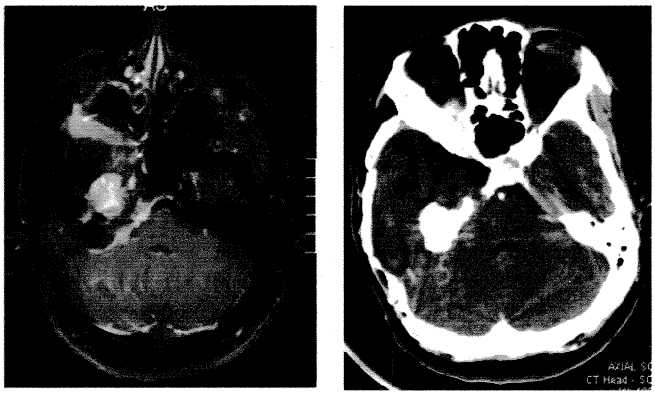


Fig 25: Followup imaging showing residual lesion in the middle cranial fossa base

Midthird parasagittal meningioma

A 17year old girl presented in 2004 with history of left focal seizures involving lowerlimb and associated with weakness of the limb. She was diagnosed to have a right mid-third parasagittal meningioma (Bonnal-Brotchi type 2). She underwent a pericoronal parasagittal craniotomy and Simpson's grade II excision of the lesion. The histopathology was reported as transitional variant of meningioma.

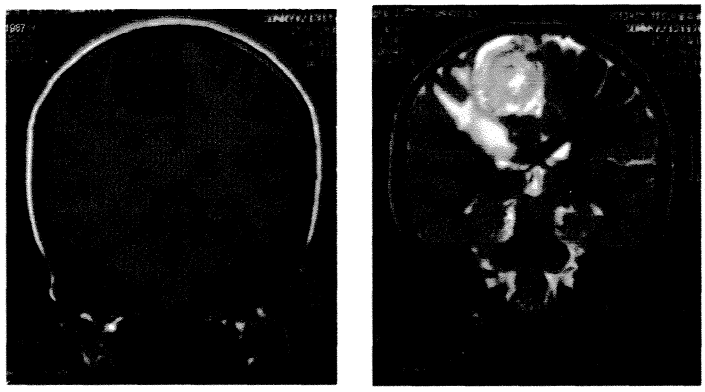


Fig 26: T1W and T2W coronal sequences showing the parasagittal meningioma

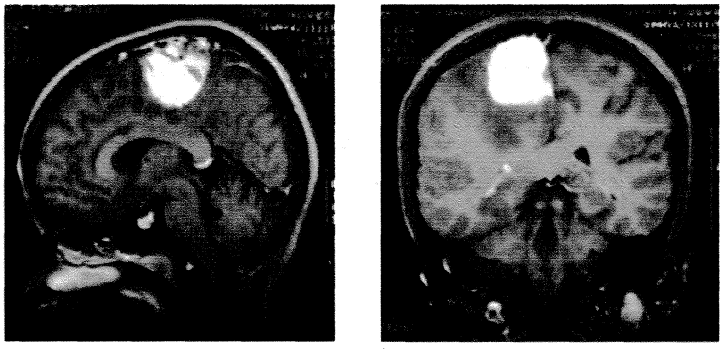


Fig 27: Post contrast imaging showing homogenous contrast enhancement

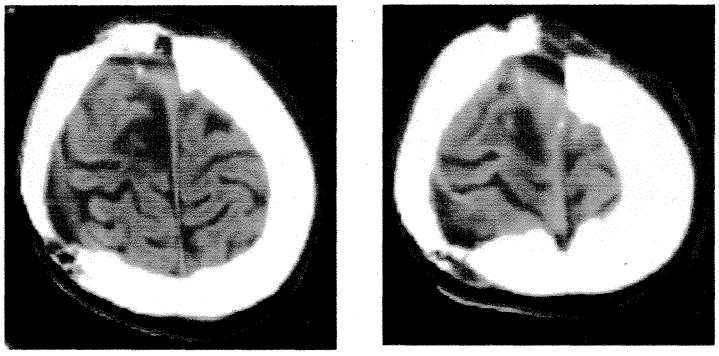


Fig 28: Postoperative CT scan showing extent of excision

During the followup period she had two episodes of left focal seizures of her left lower limb. Her lower limb weakness improved to normal power.

Discussion

Meningiomas are benign neoplasms that originate from the coverings of the brain. As they can be operated with low mortality and acceptable morbidity rates, allowing most patients to achieve a good outcome in the long term, they represent a special part of neurosurgical practice. Meningiomas are extra-axial, benign lesions that represent an area of significant interest owing to the fact that they are a common intracranial neoplasm and are also a disease process associated with a rich history dating back to the description of these growths by the pre- Columbian Incas. The classification of this condition then evolved from Paster's early illustration in 1614 of a "round, fleshy tumor, hard and full of holes, covered in its own membrane and entwined with veins" to Cushing's ultimate designation of this disease process as a "meningioma" in 1922(13). Meningiomas appear to arise from meningothelial cells in the arachnoid. As a result, common areas of presentation are the cerebral convexities and skull base, but can involve any area of the meninges within the calvarium and along the spine. Patients present with seizures, hemiparesis, visual field loss, speech deficit, and other focal symptoms depending on the location of tumor occurrence. Although a benign condition is frequently considered, high grade forms of meningioma exist and contribute to the morbidity and mortality associated with these tumors, with atypical and anaplastic forms constituting 5% to 15% of meningiomas. Currently, the WHO grading system is used to define benign, atypical, and anaplastic meningiomas. The histologic characterization of these tumors can further be defined as syncytial, meningothelial, fibrous, or transitional. This latter classification, however, is not associated with prognosis. Rare histopathologic

subtypes such as clear cell, chordoid, papillary, and rhabdoid reliably confer a worse prognosis, but are too infrequent to provide substantial data and prediction of survival risk. Environmental risk factors for meningioma are currently thought to be radiation and hormones. Tumors that develop postradiation therapy are more likely to be atypical, to recur, and to be multiple. Additionally, increased risk in premenopausal women on hormone replacement therapy, the presence of estrogen and progesterone receptors on tumor cells, and the increased overall incidence in women, suggest a role for endogenous and exogenous hormones in tumor pathogenesis. Head trauma and electromagnetic fields represent areas of controversy in the development of meningioma. Genetics are also known to play a significant role in the occurrence of these tumors, and the common association with neurofibromatosis type 2 (NF2) and non-NF2–related mutations is well known. Meningiomas can be single and sporadic, multiple and familial, or multiple nonfamilial. The existence of familial and multiple forms of this tumor suggest a genetic involvement in tumor pathogenesis. Although multiple tumors can occur independently, most commonly they are found in patients with NF2. Much study, therefore, surrounds the mutations common to both meningioma and NF2. Further definition of the genetic profile of meningiomas is bound to identify a method of determining prognosis owing to the poor association between current classification systems and patient survival and quality of life.

Meningiomas are most commonly encountered after the second decade of life. However, they may occur at any age and there have been published reports of meningiomas as early as infancy or even during fetal development. Review of the current literature indicates an overall adult incidence of 20-34%, with 90% of meningiomas occurring intracranially and 10% along the spine. The female/male ratio is 2:1, with a 20% incidence in men and a 38%incidence in women. This sex association is contrary to that of most brain tumors. Incidence increases with age, and is associated with a mean age of 58.7 years at diagnosis. Peak age of incidence is also later in women, occurring in the eighth decade as compared with the seventh decade for men. Racial background does not affect incidence. Reviewing the literature on large series of Pediatric meningiomas, Amirjamshidi et al(5) (2000) encountered 329 cases, to which they added 24 cases. A recent report from the Central Brain Tumor Registry of the United States, states that only 3% of all primary pediatric central nervous system (CNS) tumors were meningeal in origin, whereas for all age groups combined, 33.4% of tumors were of meningeal origin(1). In general pediatric meningiomas are commonly quoted as constituting 1.5 –1.8% (<2%) of all meningiomas and 0.4-4.1% of all childhood brain tumors(19, 20, 22, 25, 27, 34, 40, 49, 53, 57, 59, 60, 65, 66, 71)

Over a span of 23 years we encountered only 38 patients below the age of 20years harbouring intracranial and/or spinal meningiomas. As has been reported in literature we also observed that the incidence increases with age

and more in the second decade than the first. Only six children in our series were below the age of 10 yrs.

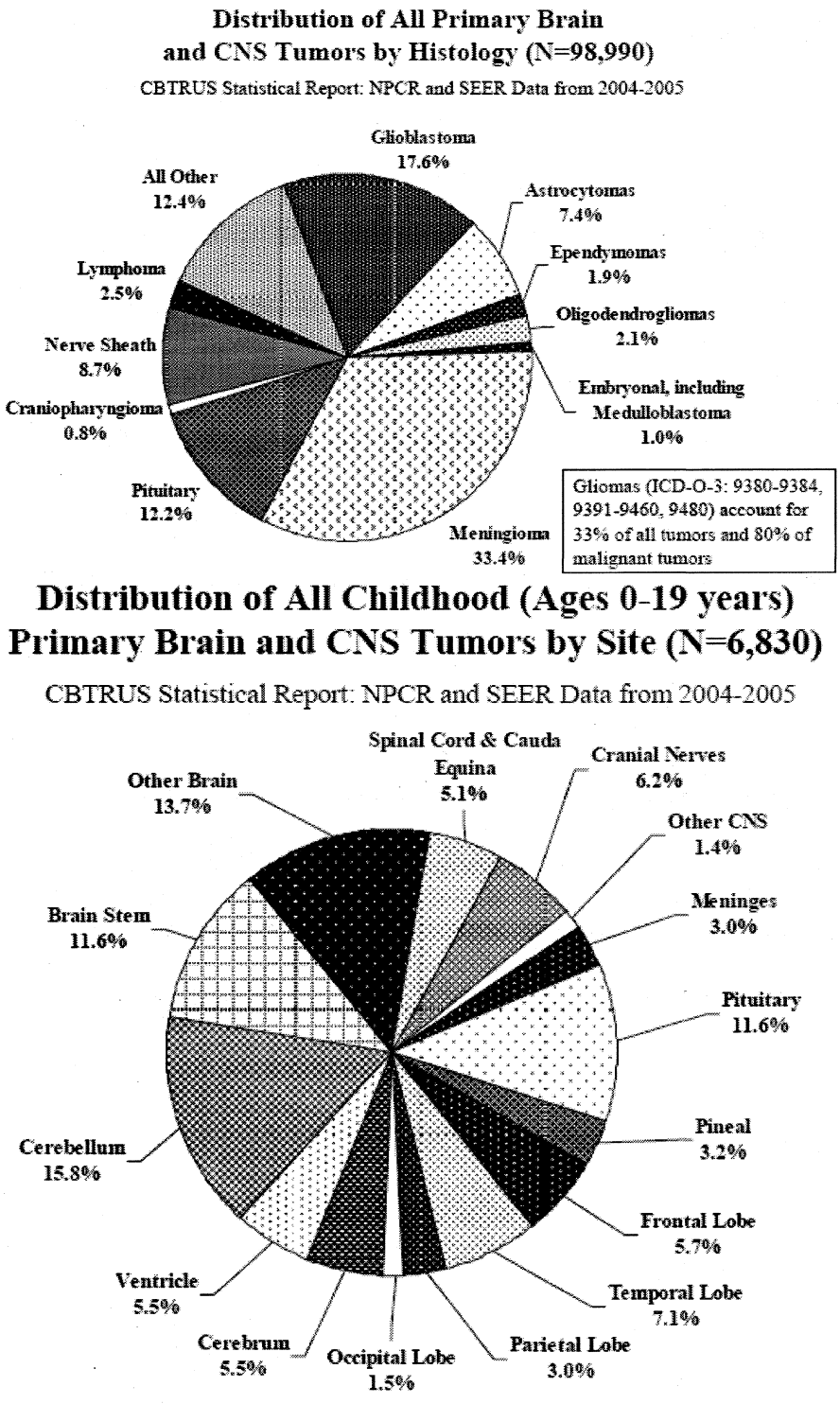


Fig. 29: CBTRUS statistical report

Unlike in adult meningiomas there is no female preponderance among pediatric meningiomas, and in certain series male subjects appear to outnumber their female counterparts(13, 15, 17). Ferrante and coworkers reviewed 178 cases from the literature and found a male/female ratio of 1.3:1(25). The male predominance in childhood meningiomas is more marked in infants than in adolescents, and characteristically it seems to be absent in patients affected by NF(19). Elizabeth Rushing(55) found a significant male predominance with the exception of spinal cord meningioma which were more common in females Our finding is similar with males showing a marginal preponderance (20 : 18). The male preponderance was marked in the first decade, while there was equal incidence between the genders in the second decade, probably indicating a tendency for increasing incidence in females as age advances to adulthood. However some authors like Glasier (28) and Darling(15) quote an equal incidence and others like Rochat(54) have however found a female predominance as well. The sex hormone binding characteristics of pediatric meningiomas have not yet been well-characterized, and it is unclear to what extent the hormonal status affects the sex ratio(20).

Reference	No of patients	Incidence (%)	Age range (years)	Sex (M:F)
Herz (1980)	9		4–18	4:5
Sano (1981)	18	3	6–26	10:8
Deen (1982)	51	2.5	7–20	25:26
Chan (1984)	04	1.1	3–16	2:2
Drake (1985)	13	1	3–16	10:3
Kolluri (1987)	18	4.2	5–15	9:9
Ferrante (1989	19	2.8	1.5–16	13:6
Germano (1994)	23	2.9	6–21	14:9
Turgut (1997)	13		0.1–14	7:6
Erdincler (1998)	29		1–10	18:11
Amirjamshidi (2000)	24	1.08	2–17	10:13
Rochat (2004)	22	1.4	1–14	8:14
Rushing (2005)	87		0.5–20	52:35
Tufan (2005)	11	2.7%	1.2–17	6:5
Our series (2008)	38	1.9	2.5–20	20:18

Table 16: Summary of data from series of paediatric meningiomas reported in the literature

The causal relationship between radiation and pediatric meningioma is well-established. Modan and coworkers(56) retrospectively studied nearly 11,000 patients who were irradiated for tinea capitis as children in Israel, finding a four-fold increased risk of meningioma in this group compared to a control group. Current findings suggest a nearly 10-fold relative risk for children with radiation exposure over those without such exposure. The average latency period has been reported as 11 to 43 years after irradiation and the average dose these patients received has been estimated to be less than 850 cGy. Radiations induced meningiomas typically present at an earlier age, arise within the prior irradiation field by definition, and are more likely to be multifocal. and exhibit higher degrees of atypia and mitosis. There is also

some suggestion of a dose effect, with higher levels of radiation exposure being associated with shorter latency periods. Zattara-Cannoni(70) recently described a characteristic derivative chromosome 1 in 6 radiation-induced meningiomas, suggesting that a region on 1p13 may be critical to the development of radiation-induced meningiomas(49). Al Mefty(3) reports that the age of patients with meningiomas at presentation and the latency period of radiation induced meningiomas are related to dose. Elizabeth also discovered that radiation induced tumours are more aggressive, certain to recur and more likely to be multiple and to have a higher histopathological grade and multiple clonal alterations especially on chormosomes 1p, 6q,and 22.

One patient in our series developed a right middle cranial fossa meningioma 2 years after undergoing surgery and radiotherapy for a right parietal anaplastic astrocytoma. The patient satisfied the Cahan's criteria for radiation induced tumours in that he did not suffer from any phakomatosis, the meningioma developed within the irradiated field and there was a sufficient time lag between the radiation and the development of the meningioma. The patient had a skullbase Rhabdoid variant of meningioma and a Simpson's grade I excision was achieved.

We could not establish the cause-effect relationship of trauma as an etiological factor for meningioma formation in our series.

The association between NF-2 and meningioma is well-known, and they may share common mechanisms of pathogenesis. The possibility of NF2 should be considered in any child with a meningioma and approximately 25-40% of

children with meningiomas have NF2(49). The more severe ("Wishart") variant of NF2 is more likely to present with pediatric meningioma. In Perry's series(49), sporadic and NF2-associated pediatric meningiomas were histologically similar, with the exception that brain invasion was nearly exclusive to the sporadic tumors, a difference which reached statistical significance. Biegel and associates(8) have demonstrated *NF2* gene mutations in pediatric meningiomas, strongly implicating this gene in their pathogenesis. Additionally, both NF2-associated and sporadic pediatric meningiomas frequently had demonstrable 1p and 14q deletions, alterations commonly associated with tumor progression in meningiomas. The large size of some pediatric meningiomas has been mentioned in several series and especially in those including NF pedigrees, implicates NF as a stigma suggestive of rapid tumor growth(5). Children with NF2 have a higher incidence of extracranial, intraocular, and multifocal meningiomas. Although Elizabeth Rushing(55) did not find a relation between NF2 and outcome they had two patients with Gorlin Syndrome in their series. Gorlin syndrome also known as multiple basal cell carcinoma is a familial tumour condition with autosomal dominant inheritance and an association with meningiomas. Eleven children in our series had evidence of associated NF1 and three children had NF2 with bilateral acoustic neurinomas but none had Gorlin syndrome. Unlike what has been described in the literature, the tumours in our series were not large or atypical.

Childhood meningiomas are characteristically known to have nonspecific symptomatology. The elasticity of skull and non cooperation

makes diagnosis difficult. Quite often a local swelling of cranial vault may be the first sign in many children. Common clinical manifestations of pediatric meningiomas include signs of increased ICP, focal neurological deficits, seizures and other rare symptoms and signs based on their location(5, 15). Seizures dominated the presenting symptoms followed by headache and raised intracranial pressure and focal deficits. A substantial proportion of our patients had visual symptoms.

In the case of spinal meningiomas, both sensory and motor symptoms dominated the presenting symptoms. Spasticity and ataxia were also common symptoms in those with spinal meningiomas.

Among the conventional methods, plain skull X-ray findings are nonspecific but valuable. The incidence of calcification and hyperostosis may be as high as 31–32% in some series of pediatric meningiomas including the cases of neurofibromatosis (NF). Presence of radiographically visible calcification nonetheless denotes the higher incidence of slow-growing, calcified/ psammomatous subtypes in this group of patients. On CT scanning, pediatric meningiomas hyperostosis overlying bone is seen with 50% of tumors and 50% have intratumoral calcification. Our findings were not similar though and calcification was observed in only two of our patients and hyperostosis in one. On MR imaging the tumours are usually isointense to hypointense on T1, iso to hypo (fibrous /transitional) on T2 with good contrast enhancement. T2 hyperintensities if seen are due to due to microcystic change, dilated blood vessels and high cellularity and usually denotes a meningothelial or angioblastic variant. Dural attachment and/or the so-called

dural tail sign on neuroimaging may not be obvious, making the distinction from intra-axial tumors more difficult (perry). MRI was done in 21 of the 38 cases in our series. The lesions were predominantly hypointense on T1, hyperintense on T2. Reports on contrast study were available in 18 cases, among which 12 had homogenous contrast enhancement and 6 showed heterogenous contrast enhancement. A correlation between T2 hyperintensity and meningiothelial or angioblastic variant was not obtained in this series. Among the 13 meningiomas which were T2-hyperintense, five were transitional, three each were atypical and meningiothelial and one each angioblastic and chordoid variants.

The convexity and parasagittal locations are the most frequent sites of meningiomas in adults (>50%) and in several series of pediatric meningiomas (55%)(66) However pediatric meningiomas are known to favour uncommon sites like pterional, peri- and suprasellar, petroclival, torcular, orbital, ethmoidal, subfrontal and subtemporal locations. We too had a similar observation with ten skull base meningiomas and three posterior fossa meningiomas. A second feature that seems to be typical of the pediatric age is the higher incidence of meningiomas localized within the ventricular system or lacking any apparent dural attachment like the deep sylvian fissure. In their review Herz et al(34) found that 28% of children with NF had intraventricular meningiomas. We had three cases of intraventricular meningiomas, none associated with neurofibromatosis. In Turgut's series(66) multiplicity was seen in 23%. We had two orbital meningiomas and five cases of spinal meningiomas but our incidence of multiplicity was low (5.2 %). Other unique

aspects within this youngest age group include large tumor size, cyst formation and tendency to recur. Cystic changes are reported to be occur in 13–50% of cases as against 2–4.6% in adults. In Amirjamshidi's series(5) of 24 cases no cyst formation was revealed and we too had only two cases of cystic meningiomas.

Childhood meningiomas are known to have high incidence of atypical histopathology especially the clear cell variant and the papillary variants. Table 6 shows that the meningotheliomatous subtype accounted for 14.6 % of our cases (34% in the literature,), transitional for 29.26% (23% in the literature), and angioblastic for 12.1 % (5% in the literature)(5). 21% of Amirjamshidi's series(5) of non-NF pediatric meningiomas were psammomatous in type which is quite different from any findings reported by other authors (about 3% psammomatous meningiomas). We too had a similar observation with 17.03% psammomatous meningiomas in our series. More risk of malignancy (3-14%) (sarcomas – 30% Glasier,(28) papillary tumours – 40% Mayoclinic(63)) has been reported among pediatric series but none in Turgut's series(66) of 13 had malignant changes. Darling et al(15) report that although in older literature incidence of malignant meningiomas was 10%, current evidence does not support this finding and a incidence of 2-5% is well accepted by many. The clear cell and papillary meningiomas, are specifically associated with a younger age of onset and are therefore, seen proportionately more often in childhood and even infancy. Although we did not have ant clear cell or papillary variant we had seven patients (18.4%) with atypical meningiomas. Similarly, chordoid meningiomas were first described

in a cohort of 7 children, whose systemic manifestations of Castleman disease (fever, anemia, weight loss and polyclonal hyperglobulinemia) disappeared following resection and reappeared with recurrences. Rhabdoid meningiomas have also been encountered in children. An interesting histologic pattern encountered in children is the "sclerosing variant" of meningioma which has been defined as a predominantly acellular, whorled mass of collagen with interspersed spindle cells. We had two children with Chordoid meningioma, but not fulfilling the criteria for Castlemans disease. Similarly we had one case of rhabdoid meningioma. Another pediatric entity, meningioangiomatosis is also typically characterized by extensive hyalinization and the cellular examples may be difficult to distinguish from either purely intracerebral or brain-invasive meningiomas.

Epithelial membrane antigen (EMA) is useful in both age settings for confirming the meningothelial phenotype in anaplastic or sarcomatoid examples and glial fibrillary acidic protein (GFAP) highlights entrapped glial elements in those meningiomas with brain invasion. MIB-1 (Ki-67) proliferative indices tend to correlate with tumor grade and to a lesser extent with the risk of recurrence in pediatric meningiomas, though the associations are weaker than in adult cohorts Though one might not expect pediatric meningiomas to be hormonally driven, progesterone receptor (PR) is expressed with similar frequency, regardless of age at presentation. There is a roughly inverse association between PR expression and tumor grade in meningiomas of children and adults alike.

The goal of treatment is total resection with wide dural clearance. Focal radiation therapy can forestall recurrence and may improve neurological deficits in patients with residual lesions. Adjuvant radiotherapy appears to be beneficial after incomplete excision of meningiomas in adults, but it is rather risky to use radiotherapy for benign and partially excised cerebral lesions during childhood and not really justifiable. Erdincler(22) feel that reoperation is better than adjuvant therapy. Seven subtotally excised tumours recurred in our series. Six of these were located in the skull base and one was an orbital meningioma. All the six skull base meningiomas which recurred were subjected to re-surgery. The outcome was good following the re-surgery in four of these cases.

The long term survival is not as good as expected. The overall survival rate was 35%, the mean survival duration for children who died during the observation was only 10yrs. (all surgery done in pre CT era). Although Sano(59), Drake(20) and Wakai have suggested poor outcome Turgut et al(66) observe that childhood and adolescent meningiomas have a good outcome if removed totally. Kadir Tufan et al(65) state that no data in existing literature about survival rates in pediatric meningiomas .

As in adults, poor outcome is more likely with skull base lesions, incomplete resections, and malignant histopathology. They also show a high tendency to recur. The association with NF appears particularly significant for the prognosis, in contrast to what occurs in the case of optic gliomas. Rochat(54) found a better prognosis for skull base and hemispheric lesions

compared to midline or infratentorial lesions although it was not statistically significant. Similarly boys fare slightly better.

.Tumor behavior following resection was difficult to predict and pediatric patients with histologically benign meningiomas deserve careful and extended clinical follow-up. It is well known and described earlier by Germano(27) and Herz(34) that pediatric meningiomas behave differently. Meningiomas branded as atypical and malignant are known to have long survival(54). Similarly low grade ones are known to recur fast.

The clinical evolution of meningiomas in children is not reliably predictable and remains a problem. Consequently, childhood meningiomas are considered to carry a worse prognosis (35% 10 year survival rate) than meningiomas in the adult population (20, 59). In contrast, our outcome was better and during the mean follow up period of 4.74 years the majority (32=84.2%) had a good outcome. One patient died due to post-operative sepsis and the rest (5=13.2%) had a poor outcome. Statistical analysis of outcome prognosticators was difficult due to the limited number of patients in most of the published series including ours. Location and extent of excision appear to be more important than histology in predicting outcome. The role of proliferative indices and biological markers are yet to be conclusively confirmed in paediatric meningiomas.

Current Philosophy

The current philosophy of management of meningiomas in children and adolescents is based on the guidelines set forth by Childrens' Cancer and Leukemia Group(CCLG) based in the UK(64).

Staging investigations

A MRI of the brain with contrast is the standard investigation in paediatric patients. MRI scan of the spine should also be performed in young children that require a general anaesthetic for the diagnostic imaging. In children, excessive blood loss is a possible complication and, particularly in the case of extremely large hemispheric tumours, preoperative angiography and possible embolization should be considered. Compared with adults blood loss during surgery has a relatively bigger effect on the smaller whole blood volume in children and should be minimized. Nevertheless, the complications and procedural difficulties of embolization need to be considered.

Histopathology

Although, in most cases, the diagnosis of meningioma can be made safely using the WHO guidelines, the use of the central pathology review process for brain tumours is encouraged. This will allow for consistency in the diagnosis, availability of tumour material for further research studies and, ultimately, an increase in the knowledge base regarding this rare tumour in childhood. Registration for tumour banking and constitutional DNA sampling as per National Protocol for Collecting and Banking of Childhood Cancer Tissue Samples for Research are advisable.

Treatment

A multidisciplinary approach including the neurosurgeon, clinical and paediatric oncologist, neuroradiologist, neuropathologist and, if indicated, ENT surgeon or ophthalmologist is advised to develop a treatment plan that will be tailored to the patient's age, tumour site and predicted clinical tumour behaviour. Access to adult surgical expertise is particularly important for specific tumour sites more commonly encountered in adult practice, i.e. skull base, cavernous sinus and petreous bone, and for this subgroup of patients referral to specialized neurosurgical services might be necessary.

Observation only approach

Serial imaging in incidental, asymptomatic meningiomas is not generally advisable. Nevertheless, patients suffering from NF-2 and multiple or surgically difficult to access meningiomas can be followed up in a specialist multidisciplinary team setting with an interest in NF-2(23).

Surgery

Complete resection of meningiomas remains the treatment of choice in most cases. Modern surgical techniques including image-guided surgery (frameless stereotaxy) will make the approach to tumours more precise, and may improve resectability and reduce surgical side-effects. The surgical approach will be influenced by the presentation, size and location of the tumour. In children, we are aware of their predilection for unusual anatomical locations compared with adults, in particular the intraventricular, parasellar, cavernous and infratentorial locations.

The majority of meningiomas in children (65%) will be dural based and supratentorial. The usual presentation is a hemispheric, superficial mass with wide dural base, although some tumours with no dural attachment in children are described. Resection of the dural origin/attachment is recommended as there is a higher reported incidence of recurrence if dural attachment is left behind. (38, 39, 69). In case of significant surgical defects of the dura one should consider repair of the dura. As always, a balance between safe surgical removal and risk of comorbidity needs to considered for each patient. A significant proportion of paediatric meningiomas have been reported in the intraventricular location, mainly in the lateral and third ventricles. Careful surgical planning and consideration to the chosen approach is advised. Image-guided neuronavigation is invaluable in planning an operative approach and strategy. This may include interhemispheric/transcallosal routes and transcortical/transventricular routes. As always, careful consideration to blood loss and comorbidity is important and if necessary, staged multiple procedures and partial resection in the case of giant tumours may be more appropriate if blood loss is a threat to life.

Meningiomas in any age group may be associated with the skull base and these locations include the parasellar/cavernous location, the infratentorial location including C– P angle and clivus. As skull-based tumour locations are relatively more common in adults very experienced surgical teams specializing in skull base approaches have developed(47). It is therefore recommended that a paediatric neurosurgeon and neurosurgeon specialized in skull base surgery perform these procedures jointly with or without their

other surgical colleagues, such as ENT and maxillofacial as appropriate. The use of intraoperative electrophysiological monitoring of the relevant cranial nerves is recommended when operating in the C– P angle and will invariably be routine practice for the facial nerve in C– P angle tumours. Irrespective of expertise, there may be some tumours that, because of their location or size, are too difficult or dangerous to remove. This may be because of involvement of vital neural structures, such as cranial nerves, or because the tumour is enveloping major vessels such as the carotid artery or venous sinuses. Examples include intracavernous meningiomas and, in such cases, multidisciplinary discussions regarding risks of surgical death or significant neurological deficits versus benefits of alternative therapies are particularly valuable.

Radiotherapy

Most paediatric patients will not require adjuvant radiotherapy following surgical resection. Focal radiotherapy may be considered in benign, grade I and atypical grade II meningiomas after multiple relapses not amenable to further surgical interventions or evidence of clinically relevant progression after incomplete resection particularly if the tumour threatens to compromise vital functions, e.g. vision. In anaplastic, grade III meningiomas, radiotherapy should be considered at the time of primary diagnosis regardless of surgical outcome. The NICE recommendation for adults suggested radiotherapy is considered for patients with a WHO grade II/III tumour, multiple relapses, invasion of the adjacent brain or extensive invasion of other tissues or contraindication to surgery.(1) Nevertheless, local treatment policies vary

regarding indications for radiotherapy in adults. Preference should be given to deliver conventionally fractionated, conformal radiotherapy. Only in exceptional circumstances will the tumour or tumour bed be small enough and appropriately located to be amenable for a radiosurgical approach (stereotactic radiosurgery, SRS). If in doubt patients should be discussed with an experienced clinical neurooncologist familiar with both treatment modalities.

Usually patients are immobilized in a supine position according to departmental policies. The use of three-dimensional planning is mandatory to define target volumes. If available locally CT/MRI fusion with the use of a stereotactic frame should be considered. It is recommended that the CT slice thickness of the planning scan should be equal or less than 0.5 cm. The gross tumour volume (GTV) is defined as the macroscopic visible disease at the time of progression including the previous tumour bed (based on pre and postoperative postcontrast T1-weighted MR sequences). In patients with anaplastic, partially resected tumours the GTV is defined as the macroscopic amount of residual disease, plus the postoperative tumour bed. In completely resected anaplastic meningiomas the GTV is defined as the primary tumour bed. Generally the radiotherapy will include the dural tail and any abnormal bone on radiology. Dose Volume Histograms (DVHs), if available should be constructed for the planning target volumes (PTVs). Treatment should be delivered by individually shaped, conformal fixed beams using the beams-eyeview facility of the planning system. Megavoltage photons with energies in the range of 4 – 6 MV of linear

accelerator megavoltage photons are to be used. Based on adult experiences margins of 0.5 – 1.0 cm between the gross tumour volume and planning target volume are recommended for benign and atypical meningiomas of childhood and 1.0 – 1.5 cm for anaplastic meningiomas. All doses will be specified according to ICRU 50/62. Regardless of underlying pathology a radiation doses of 50 – 55 Gy in conventional fractionation is recommended prescribed to the reference point. Dose increases to 60 Gy should only be considered in exceptional circumstances (e.g. WHO grade III meningiomas). All fields should be treated daily, 5 days per week. If stereotactic radiotherapy is indicated, given the rarity of the situation, consideration should be given to transfer the care for the radiotherapy phase to a centre experienced in Stereotactic Conformal Radiatherapy (SCRT) and to facilitate gathering of prospective data on outcome and morbidity. The indication for radiotherapy in childhood will be decided on an individual case basis by the multi-disciplinary team (MDT) considering age, number of tumour recurrences and accessibility to further surgical procedures, tumour grade associated risk of recurrence or aggressive behaviour.

Chemotherapy

Currently, there is no recommendation available to support the use of chemotherapy in children or adults(47)

Supportive care

All patients should be referred to the geneticists for screening investigations of genetic diseases that may remain asymptomatic at the tumour presentation in childhood(23). NF-2 for example is a disease that often

presents years after the diagnosis of a meningioma in childhood. Laboratory diagnosis of NF-2 relies on the detection of DNA mutations in the NF-2 gene on chromosome 22 leading to an abnormal merlin protein. Furthermore linkage studies from at least 2 affected family members are helpful(16). The presence of Gorlin syndrome should be excluded.

Long-term follow-up

Neuro-imaging follow-up is based on MRI surveillance and is recommended to be undertaken annually for at least 10 years since late recurrences are not uncommon. Continuing clinical support and review as per local standard practice for paediatric brain tumour patients is recommended.

Conclusions

- **Childhood meningiomas are uncommon but not rare lesions with a marginal male predominance.**
- **A higher incidence of skull base location and tumours with atypical histology was observed in this study, conforming with the observations made in other series.**
- **Favourable prognostic factors include younger age (<than 10 years), superficial location, total excision and absence of neurofibromatosis.**
- **Location and extent of excision appears to be more important than histopathology in predicting outcome.**
- **Absence of large series with long follow up precludes any definite conclusions on the clinical course and outcome.**
- **Studies are being conducted on the cytogenetic aspects of these tumours, and we hope that this leads to a suitable therapy for these challenging tumors.**

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