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Current treatment of thalamic gliomas in children

Mark M. Souweidane,[1] and Harold J. Hoffman,[2]
[1] *Chief Clinical Fellow in Pediatric Neurosurgery, The Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8;* [2] *Chief, Division of Neurosurgery, The Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8*

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Abstract

Historically, the outcome of children with thalamic gliomas has been poor. Because of the potential for severe perioperative mortality, conservative approaches toward these lesions have been commonly instituted. However, recent improvements in therapeutic approaches have been numerous. These refinements have most importantly centered on improving the neurosurgical technique of tumor resection by integrating computer-assisted, stereotactic approaches. In so doing, perioperative mortality has dropped from as high as 40% to as low as 0–1%. Gross total resection confirmed with postoperative imaging is becoming an expectation. However, because of anatomical limitations or malignant histology, incomplete resections will undoubtedly occur in an effort to preserve neurological function. At the same time, not all residual disease implies a poor outcome. Indolent, low-grade gliomas of childhood are not limited to the cerebellum or optic/hypothalamic regions, and histologically similar lesions in the region of the thalamus occur with some frequency. In this case scenario, incompletely resected low-grade lesions should be followed sequentially with routine imaging; further therapy, be it surgical or adjuvant, is instituted only if disease progression is documented. Children found to have malignant gliomas of the thalamus should undergo surgical resection in an effort to relieve them of any existing mass effect. Subsequently, adjuvant therapy is utilized depending on the exact histopathology and the child's age. Thus, what evolves from recent data and current surgical techniques is an aggressively directed therapy based upon anatomical considerations and tumor type.

Introduction

Thalamic glioma is a disease primarily of children and young adults. The majority of these lesions in the pediatric age group are of astrocytic derivation and more precisely, of the low-grade variety. Because of their location within the compact diencephalon, the duration of symptoms is relatively short. The symptoms that result reflect the effects of pressure upon the corticofugal fibers, the ventricular system, the optic radiations and the thalamic nuclei. Due to the central location of these lesions, the surgical challenge has previously been viewed as insurmountable. However, an improved understanding of growth patterns, primarily achieved through refined imaging, a great reduction in operative mortality, and increased efficacy of adjuvant therapeutic strategies have all led to a more aggressive approach to these lesions. Current therapeutic intervention, involving radical surgical resection, can result in long-term survival and cure in some situations. The outcome following treatment is dependent upon several factors, most notably, the patient's age and the glioma subtype.

General characteristics

After the first two years of life, pediatric brain tumors of the supratentorial hemispheres account for approximately one third of all brain tumors [1–3]. Some of these tumors are lobar in location, while a significant number have a predilection for deep midline locations such as the thalamus and hypothalamus, the pineal region, and the optic apparatus. Within the general population, thalamic tumors account for roughly 1% of brain tumors [4–7]. Series of thalamic tumors in children have been reported, but not as a subset of pediatric brain tumors. In Hoffman's series of 88 patients with low-grade astrocytomas of the midline, the thalamic location accounted for 15% of this total, second to the optic/hypothalamic region [8].

The thalamic gliomas, although by no means exclusive to the pediatric age group, do cluster toward the pediatric and young adult ages. Due to referral patterns, most series of thalamic gliomas tend to favor either the adult or pediatric group and, less commonly, encompass both groups. Tovi's series of 49 patients with thalamic gliomas revealed that roughly one third of their patients were less than 20 years of age [7], while McKissock and Paine reported 71% of their 24 patients were less than 25 years of age [6]. The seventy-two patients in Kelly's series had a mean age of 35.4 years with more than one third being twenty years of age or less [9]. Within the pediatric age group, there exists no sex predilection, no preference for lateralization, and a mean age at the time of presentation of approximately 8 years [10, 11].

Clinical characteristics

The clinical presentation of the child with a thalamic tumor can be varied, but several common characteristics are found. The duration of symptoms is fairly short, a trait not unexpected, given the compact nature of the diencephalon and the proximity of the ventricular and capsular systems. In the pediatric series of Bernstein *et al.* 93% of the 60 patients presented with less than one year of symptoms, with 80% of these patients having symptoms for less than four months [11]. Although studies reviewing patients of all ages with thalamic tumors have similarly recognized a fairly short duration of symptoms, the average duration of symptoms is slightly more protracted in adults, with one third of patients having symptoms lasting more than twelve months [4, 6]. This difference may be somewhat misleading, due to the fact that CT imaging was partially utilized as a diagnostic aid in Bernstein's series, while the studies of Arseni, and McKissock and Paine were conducted in the pre CT era.

As with most pediatric brain tumors, signs and symptoms referable to raised intracranial pressure are common in the child with a thalamic tumor. This may result from the mass effect, exerted by the tumor, from obstructive hydrocephalus of one or both lateral ventricles at the level of the foramen of Monro, or from a combination thereof. The classical symptoms of elevated intracranial pressure, namely frontal headache, decreased spontaneity, and vomiting, account for the majority of these symptoms. Raised intracranial pressure will be apparent on fundoscopic examination revealing papilledema. In the infant, a large head circumference with a tense fontanelle and split sutures confirms elevated pressures.

The signs referable to motor as well as sensory modalities are dependent upon the site of origin and the direction of tumor growth. The classical thalamic syndrome of Dejerine and Roussy, although occasionally present, is the exception rather than the rule [4, 7, 12]. More typically, however, motor or sensory deficits in varying degrees will accompany the signs of raised intracranial pressure. Previous authors have found it convenient to categorize patients into two broad clinical groups that correspond to an anatomical division of the thalamus [4, 12]. The internal medullary lamina subdivides the thalamus into two broad groups of nuclear masses, the dorsomedial group and the ventrolateral group. This latter group of thalamic nuclei represents the primary relay site for many fundamental sensory modalities. Further, this nuclear complex is in close proximity laterally to capsular fibers of the corticospinal tracts. Thus, it follows that lesions arising in the region of the ventrolateral thalamus will result in early deficits in sensation and impair-

ment of motor strengh. In contrast, those lesions arising in the dorsomedial thalamus will more likely produce early obstructive hydrocephalus. Continued lateral extension of the tumor with impingement on the internal capsule results in motor deficits at later stages in the disease.

Interestingly, epilepsy has been found as a presenting complaint or as part of a symptom complex in patients with thalamic tumors. This manifestation is reported as frequently as 30–40% of cases [4, 5, 7], although others have found seizures to be less frequent [6, 10, 11]. The types of seizures vary from simple partial sensory seizures to complex partial fits with secondary generalization.

Ocular and ophthalmologic findings are also frequently detected. Hemianopias resulting from optic tract compression are quite common. Ocular signs most often found include a poorly reactive, miotic pupil ipsilateral to the lesion, and divergent extraocular motions. An ipsilateral third nerve palsy can also occur. These findings result from tumor infiltration or compression of the optic radiations, the retrolenticular segment of the internal capsule, or the rostral mesencephalic tegmentum.

Although these lesions are in close association with the basal ganglia, involuntary movements are infrequent, being present in approximately 12% of cases [13]. These movement disorders most commonly take the form of tremor, and less frequently dystonia. Under very rare circumstances, chorea, ballismus or athetoid movements are found.

Speech disturbances, seldom a presenting complaint, can sometimes be found on close examination. The deficits, most commonly reported as aphasias, have been more accurately described as anomia and perseveration [14]. These deficits are limited to lesions involving the dominant thalamus.

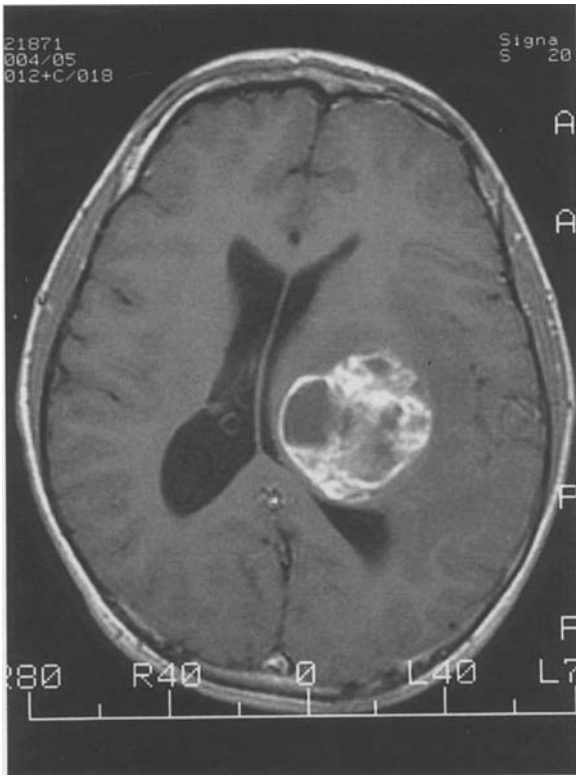
Other less common symptoms can be predicted based on the anatomical structure involved. Inferior extension of the tumor can result in various signs and symptoms depending on the structure of involvement. Extension into the mammillothalamic fibers or the fornices can lead to alterations in cognition and memory. Involvement of the hypothalamus will lead to endocrinopathies, which should be suspected in all children. Occasionally, sensorimotor deficits can be the result of tumor infiltration into the midbrain by way of descending white matter tracts.

Radiological characteristics

The radiographic assessment of these tumors is limited to computed tomography (CT) and magnetic resonance imaging (MRI). These imaging modalities will clearly reveal a thalamic lesion and its resultant mass effect on adjoining structures, such as anterior displacement of the caudate nucleus and anterolateral displacement of the lenticular nuclei and internal capsule. Frequently found is an obstruction of the ventricular system, usually at the level of the third ventricle. Occasionally, this obstruction can occur at the ipsilateral foramen of Monro thus causing an isolated expansion of the ipsilateral lateral ventricle.

Tumor characteristics obtained from imaging that can aid in predicting tumor type and hence prognosis can also be determined. Most notable among these features is cyst formation. The presence of large cystic changes with an enhancing nodular component is usually diagnostic of the juvenile pilocytic astrocytoma, an entity with an excellent post-treatment prognosis. The typical solid, low-grade astrocytoma will appear hypointense on CT and with decreased signal intensity on T1-weighted MR images. The longer relaxation times with MR will have increased signal strength in the area of the tumor, as well as in areas of peritumoral edema. The T2-weighted sequences are also ideal for investigating multifocal disease. The presence of tumor enhancement on contrast scans is felt by some to predict tumor histology and a poorer prognosis [15–17]. This phenomenon has been reported to be true even when controlled for age [15]. Although the typical appearance of a glioblastoma in adults is well known, namely a ring-enhancing mass with a central area of necrosis surrounded by generous white matter edema, tumor enhancement in low grade tumors has failed to predict a more aggressive biological behavior [11, 18], and tumor subtyping based on radiographs should never be used to determine therapy.

The confines of tumor growth can be determined



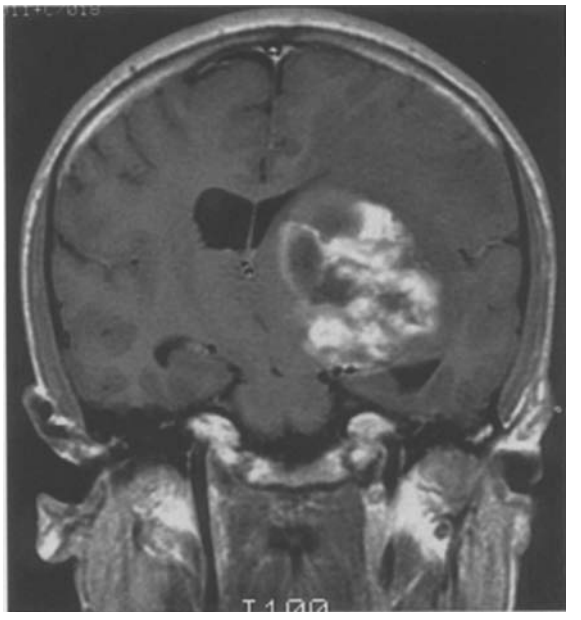


Fig. 1. Preoperative MRI scan of a 15 year old boy presenting with signs and symptoms of increased intracranial pressure. A) Axial and B) coronal T1 weighted images with gadolinium enhancement revealing a left posterior thalamic lesion with resultant distortion of surrounding structures.

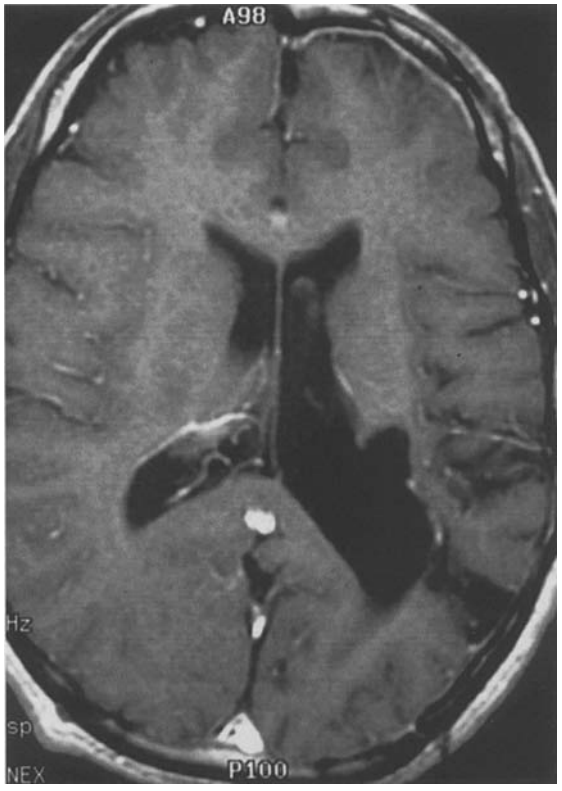
best with triplanar MRI, keeping in mind that with higher grade astrocytomas, tumor extension is well beyond the area of signal change [19]. Direct extension should be looked for in the area of the massa intermedia, the ependymal surface of the ventricular system, and within the septum and corpus callosum. The presence of tumor extension into any of these anatomical regions is a poor prognostic sign and eliminates the possibility of a complete surgical resection.

The role of cerebral angiography in thalamic tumors as a diagnostic aid is less useful since the advent of MRI. The exception to this is when suspicion exists as to a possible vascular lesion or as a tool in surgical planning for determining leptomingeal and perforator vessel anatomy.

Pathology

Astrocytomas account for approximately 88% of primary thalamic tumors [4–7, 20]. The exact origin of neoplastic cells has been ascribed to a rich population of subependymal glial cells and the glial elements of the white matter tracts that subdivide the diencephalic nuclei [12, 21–23]. This glial matrix is composed primarily of astrocytes with relatively rare oligodendrocytes. The presence of neuronal elements within the thalamic nuclear masses account for the rare gangliogliomas, and the juxtaposition of the third ventricular ependymal surface for the infrequent ependymoma involving this region. Accounting for approximately 10% of all intracranial germ cell tumors, rare reports of germ cell tumors of the thalamus also exist [24, 25].

The subtyping of thalamic gliomas, based on the WHO classification schema [26], reveals different proportions of tumor grades dependent upon the age of the cohort. From several series encompassing patients of all ages, glioblastoma multiforme was responsible for roughly 45% of all thalamic tumors with confirmed pathology. This figure is comparable to the frequency of glioblastoma among astrocytomas of the cerebral hemispheres in adults. However, higher grade astrocytomas make up a much smaller percentage of gliomas in the pediatric



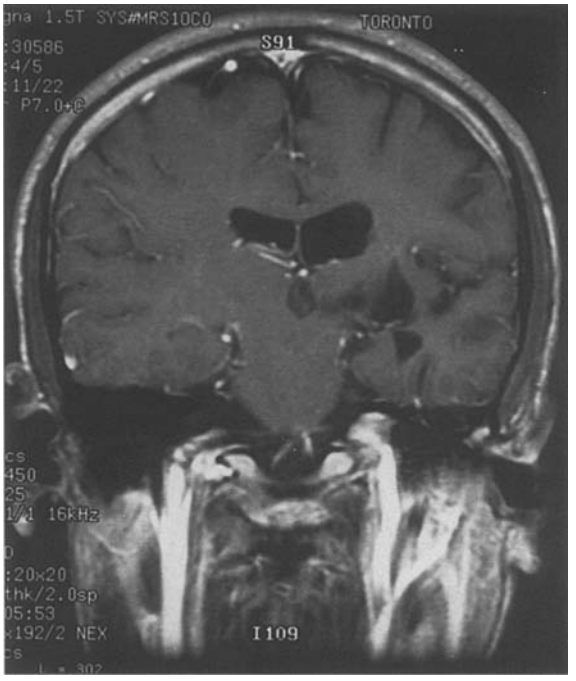


Fig. 2. Postoperative MRI scan three years following a posterior parietal approach and gross total excision using frameless stereotactic guidance. Gadolinium enhanced A) axial and B) coronal images without any evidence of tumor recurrence.

age group. Glioblastoma multiforme has been shown to be responsible for only 5 to 9% of pediatric brain tumors [27–29] and this histological group accounts for a similar percentage of thalamic tumors. Of 60 thalamic tumors in children reported by Bernstein *et al.*, 41 were histologically identified with only 5% of these being glioblastoma [11].

Further evidence pointing toward the fact that the pediatric thalamic gliomas tend to be of a more favorable histology than their adult counterparts can be found by examining histology as a function of age. In Kelly's series on thalamic astrocytomas, histological diagnosis was made in all 72 patients [19]. Of thirty-four patients with grade 4 astrocytoma, the average age was 51 years and only two patients (6%) were 20 years of age or less. In contrast of 27 patients with pilocytic astrocytoma, the average age was 16 years and seventeen patients (63%) were less than or equal to 20 years of age. Further, Wald *et al.* reviewed eight cases of cystic astrocytomas of the thalamus [30], a well known entity for its indolent behavior and excellent response to surgical therapy. In that series, the average age was 6 years and no patient was older than 15 years at the time of diagnosis. The uniqueness of the pediatric age group with reference to thalamic gliomas, or more generally, hemispheric gliomas is readily evident; less aggressive astrocytic tumors are more frequent in the pediatric population.

Treatment

The treatment of pediatric astrocytomas is focused upon achieving three main goals. These objectives are 1) to relieve the patient of his or her symptoms, 2) to obtain a tissue diagnosis, and 3) to treat the primary disease. All patients are begun on corticosteroid therapy in an effort to reduce the mass effect from secondary cerebral edema and also to prepare the patient for surgical intervention. Anticonvulsants as well as gastric protective agents are also administered preoperatively. The need for CSF diversion must be evaluated since the incidence of ob-

structive hydrocephalus is high. The role of shunting or placing a ventricular drain should be limited to those patients exhibiting signs of severely raised intracranial pressure. Even though most patients will be relieved of their obstructive hydrocephalus with tumor debulking, shunting has proven effective if time is needed for the appropriate preoperative planning.

Obtaining tissue for histological diagnosis is a necessity if the appropriate therapy is to be instituted. Because of the location of thalamic tumors deep beneath the cortical surface and in the vicinity of important surrounding structures, surgical accessibility is limited. Historically, attempts at resection of thalamic lesions have led to disastrous rates of surgical morbidity and mortality [4, 6, 31, 32]. Due to these results, a more conservative therapeutic approach evolved. Torkildsen recommended a palliative lateral ventriculocisternotomy in an effort to alleviate the symptoms of obstructive hydrocephalus from tumors in the region of the third ventricle [32]. Patients were then left to succumb to their neoplastic process at a rate dependent upon tumor type. For similarly placed tumors, Ward and Spurling offered patients a subtemporal decompression followed by radiotherapy [33]. Nonresponders would then undergo exploratory craniotomy, with the expectation of discovering either a benign, radioresistant lesion, which would be resected, or a highly malignant glioma, which would be debulked. The difficulty with this rationale was that the former group of patients received no benefit and, more likely, suffered deleterious effects from whole brain irradiation, and the latter group seldom survived surgery.

With improved neuroanesthetic technique, perioperative steroid use, intraoperative illumination and magnification, and a better understanding of surgical neuroanatomy, the risks associated with craniotomy have been substantially reduced. The more recent improvement dealing with the resection of thalamic tumors has not only relied upon the aforementioned modalities, but more importantly, utilized intraoperative computer-assisted resection. The ability to image these lesions in triplanar format, reconstruct a volumetric representation of the tumor, and finally, to reference this reconstruction to either a stereotactic frame or the patients skin surface anatomy, offers the neurosurgeon the ability to precisely direct the resection from a safely determined trajectory without injury to critical neural structures. Using variations of this theme, the operative morbidity with biopsy [34–36] or radical resection [9, 37–40] has approached zero for tumors situated in and around the thalamus.

The role of a preoperative tissue biopsy in children with thalamic tumors is debatable. Due to the predominance of low grade lesions in children, the majority of patients will ultimately require surgical intervention as a component of their therapy. Further, the symptoms attributed to mass effect from tumor burden or obstructive hydrocephalus are commonly responsive to tumor resection and unaffected by biopsy. The claim has also been made that with stereotactic biopsy, an erroneous diagnosis can be made due to an inherent sampling error, although this argument has been countered. Because of the above mentioned reasons, it is the belief of the current authors that in children with thalamic tumors, a single operative procedure utilizing computer reformatting and stereotactic applications be performed, using an intraoperative open biopsy to define the ultimate goal of surgery. The exceptions to this methodology are the cases in which multifocal or diffuse disease exists, thus making a gross total resection impossible, or in cases where mass effect is minimal and the radiographic analysis suggests an aggressive tumor. In either scenario, stereotactic biopsy would be an appropriate initial step in therapy. Therefore, with highly refined surgical techniques that are currently available, radical resection of thalamic tumors is usually possible with acceptable morbidity.

The use of adjuvant therapy for thalamic astrocytomas in children parallels the indications followed for lobar astrocytomas. The primary determinants used in this assessment are the histology of the tumor, the extent of tumor removal, and the age of the patient. In general, for localized lesions of low-grade histology, either completely or subtotally excised, no adjuvant therapy is administered. These patients are then followed with sequential imaging, using primarily surgical intervention for recurrent disease; in the case of unresectable lesions, adju-

vant therapy is instituted. For malignant tumors, adjuvant therapy is always instituted, regardless of extent of resection. The selection of adjuvant therapy is based primarily upon the age of the patient. Children less than the age of 5 years are treated initially with chemotherapy; those older than this are given radiation therapy. In view of the adverse effects of external beam radiation therapy on the developing brain of children, and the promising reports of effective chemotherapy regimens [41, 42], the use of radiation is being substituted more commonly with chemotherapy. However, the long-term efficacy of using chemotherapy preferentially as a first-line agent has yet to be determined.

In summary, the current mode of therapy for pediatric thalamic gliomas has evolved from a number of convergent trends in neuro-oncology. These premises are as follows: 1) low grade tumors account for the majority of pediatric thalamic gliomas; 2) for a given tumor pathology, the pediatric patient has a better prognosis than the adult patient; 3) resection of pediatric low-grade gliomas improves outcome; and, 4) surgical resection is possible in the region of the thalamus.

Outcome

The outcome of the child treated for a thalamic glioma depends on several factors. Noteworthy among these determinants are the histological diagnosis, the age of the patient, and the degree of resection. Even though pediatric astrocytomas have an overwhelming chance of being low-grade tumors, valid concern is whether or not a given lesion will behave in an indolent fashion. Evidence exists in the adult population that even with aggressive therapy, low-grade astrocytomas will ultimately progress to a malignant subtype and that cures are rare [43, 44]. Such is not the case with low-grade pediatric astrocytomas. Repeated investigations have shown that a younger age is a reliable indicator of a better prognosis following treatment for low-grade astrocytomas [15, 17, 45–47]. In a review of 461 cases of low-grade astrocytomas of the brain, Laws *et al.* showed survival to be strongly dependent upon the patient's age [45]. In that study, the 5-year survival rate for patients less than 19 years of age was 83% compared to 12% for patients greater than 50 years. Similarly, when Piepmeier compared patients over 40 years of age with those less than 40 years, the survival rate was nearly doubled for the younger patients. Comparisons between pediatric and adult patients with low-grade astrocytomas of the hemispheres have suggested that children not only have a better prognosis after treatment, but that the biology of the pediatric low-grade astrocytoma may be distinct [46, 48, 49].

In addition to the patient's age, another factor that has been found to affect outcome after treatment of hemispheric low-grade astrocytomas has been the extent of resection. Although significant disagreement exists with regard to the benefits of cytoreductive surgery for glioblastoma, good evidence currently points to the positive role of radical resection for low-grade astrocytomas [10, 17, 45]. Such a beneficial response has also been reported for pediatric patients with astrocytic tumors [8, 48, 49]. With regard to thalamic astrocytomas, it has been argued that no relationship exists between outcome and extent of resection [10]. However, the recommendation for a nonaggressive surgical approach has evolved not from objective criteria based on patient outcome as a function of resection, but rather from the high perioperative morbidity associated with attempted resection.

With current surgical techniques, the efficacy of radical resection of thalamic astrocytomas has been re-evaluated [8, 9, 39, 40, 50]. In Hoffman's review of 88 low-grade astrocytomas affecting midline structures, 13 of which were thalamic lesions, recurrence rates were dependent upon the extent of resection [8]. Specifically, with a resection estimated to be 50% or greater of the original tumor mass, recurrence rates were 24%, versus 43% when there was less than 50% resection of tumor. Although an earlier study from the same institution failed to indicate any benefit from the extent of surgical resection for low-grade thalamic lesions, caution must be used in interpreting this information, since this former cohort of patients extended as far back as 1951 [11], a period preceding current surgical abilities and postoperative imaging techniques. In 1975, Hirose *et al.* reported on 18 pediatric patients with

thalamic tumors and their outcome [10]. In that series, eight of nine patients who underwent partial resection of their tumor succumbed to death from recurrent disease; however, there was no pathological correlate in these cases. In addition, the role of aggressive surgical resection for thalamic astrocytomas of certain histological subtypes, namely pilocytic low-grade and cystic astrocytomas has become established [20, 30, 39]. This is not to say, however, that the ultimate goal is complete resection in every case. Discretion must be exercised in each individual case so as to balance the benefits of achieving a radical resection with the necessity of preserving neurological function, a task that must be based on computer-generated representations of spatial relationships between tumor and normal brain.

For patients in whom a subtotal resection is performed to avoid the risk of incurring neurological deficit, long-term disease-free survival can occur with certain low-grade astrocytomas. Pathologically, such indolent tumors are recognized by their histological mixture of dense astroglial tissue with loose, reticulated, microcystic areas. These tumors, more commonly cystic, have been termed juvenile pilocytic astrocytomas (JPA), polar spongioblastomas and Bergstrand tumors [51, 52]. Although this peculiar growth behavior has been recognized in some thalamic tumors [8, 9], this phenomenon is best represented in series pertaining to hemispheric low-grade astrocytomas in children as well as adults [22, 49, 53–55]. The similarity between supratentorial and cerebellar astrocytic tumors has been pointed out for some time [49, 52, 54]. The exact reason for the indolent behavior recognized with these tumors is not known, but certainly these lesions do not represent predecessors to more malignant phenotypes. At the same time, agreement exists that these lesions are truly neoplastic and not of a hamartomatous nature [56]. Recognizing the shortcomings of histopathology, attempts to predict biological behavior based on other parameters, such as labeling indices and genetic markers, have not become universally accepted at this point in time [57].

There are few reports that document long-term outcome for thalamic tumors in children utilizing the therapy schema outlined above, since the routine use of aggressive surgical intervention is a relatively recent concept. Bernstein's 1984 review of 60 thalamic tumors in children revealed only 20 survivors at a mean follow-up of just over 9 years [11]. Of these 20 survivors, there were no patients harboring malignant tumors, 8 with low-grade histology, and the remaining 12 had no pathological diagnosis. Even though this report was presented as late as 1984, this predated the current philosophical and technical standards. Using an aggressive surgical approach assisted by computer-generated volumetric analysis and stereotactic resection, Kelly reported on 23 patients with pilocytic astrocytomas of the thalamus [9]. Of 19 patients undergoing complete radiographic resection, 18 were alive and well, without evidence of recurrence at a mean follow-up period of 22 months. Confirming the impact that histology has on outcome, that same report showed that of 7 patients with grade 4 astrocytomas of the thalamus undergoing resection, 6 have died within the period of follow-up. The only survivor in that group was reported after only 5 months of follow-up. In 1994, Villarejo reported on 8 patients, seven with low-grade and one with a malignant tumor of the thalamus, all less than the age of 9 years at the time of diagnosis [40]. Although no mention is made as to whether computer-assisted resection was used, all patients were alive at a mean follow-up period of 5.8 years.

The application of modern postoperative adjuvant therapy for thalamic gliomas has not been adequately assessed. Most regimens have evolved from the experience gained with hemispheric astrocytomas. There have been suggestions that the use of radiation therapy has not had an impact on the outcome of children with low-grade astrocytomas [8]. However, postoperative radiotherapy has characteristically been reserved for patients with higher grade tumors and in patients with subtotal excisions. In other words, the patients destined to do poorly because of other factors are also the patients most likely to receive radiation therapy. Currently, we institute radiotherapy in all patients more than five years of age with malignant gliomas, irrespective of the extent of resection. Radiation is also utilized in those rare cases of low-grade lesions that have documented disease progression that is not amenable to further surgical intervention. Well

known are the potential risks inherent in radiation therapy, including intellectual impairment, endocrine deficiencies, induced neoplasms and vascular abnormalities. Because of the deleterious effects of radiation, the use of empiric radiotherapy without knowledge of tumor histology or without an attempt at surgical cure [58] is unjustified and dangerous.

Chemotherapeutic regimens have shown some promise in the treatment of low-grade astrocytomas of children. These beneficial effects have clearly been established for the typical low-grade lesions of the optic apparatus and hypothalamus in children [41, 42]. Extending this treatment approach to include children afflicted with low-grade lesions of the thalamus and mesencephalon, Hoffman *et al.* have shown some suggestions as to the beneficial use of chemotherapy [8]. However, chemotherapeutic regimens are used as a first line of adjuvant therapy only and never as a primary mode of treatment. Chemotherapy is also used in children less than four years of age with histologically proven malignant tumors. Depending on the outcome of the patient, the extent of disease, and the patient's age at the completion of chemotherapy, consideration can then be given to proceding with radiation therapy at that point.

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Address for offprints: H.J. Hoffman, Chief, Division of Neurosurgery, The Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8