Long-term outcome of hypothalamic/chiasmatic astrocytomas in children treated with conservative surgery

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The feasibility of radical surgery for astrocytomas of the optic chiasm/hypothalamus has been reported by several groups. Such surgery carries significant risks, however, including permanent damage to the pituitary gland, optic apparatus, hypothalamic structures, and carotid arteries. The benefits of radical surgery, both in terms of efficacy and toxicity, should, therefore, be evaluated against standard therapy, as is usually done for new chemotherapeutic protocols.

To this end, a retrospective review was performed of 33 patients treated at Children’s Hospital of Philadelphia between 1976 and 1991 who met criteria that would have made them eligible for radical surgery in many centers today, but were treated with either no surgery or conservative surgery (<50% resection) or biopsy followed by adjuvant therapy with local radiation therapy (29 patients) and/or chemotherapy with actinomycin-D and vincristine (18 patients). The review encompassed all children with a globular enhancing mass of at least 2 cm in the hypothalamic/chiasmatic region, no evidence of optic nerve involvement or involvement of the optic radiations by computerized tomography or magnetic resonance imaging, and follow up of at least 3 years. All but one patient had tissue confirmation of a low-grade or pilocytic astrocytoma. Thirteen of the patients were 2 years of age or younger at diagnosis.

Five individuals died: three of tumor progression, one of acute shunt malfunction, and one of intercurrent infection. The remaining 28 were alive at last follow up, a mean of 10.9 years from diagnosis. Twenty-three surviving patients have functional vision in at least one eye, 12 require no endocrine replacement, and 16 are in or have completed schooling with regular academic requirements.

If radical surgery is to become standard care for children with low-grade astrocytomas of the hypothalamic/chiasmatic region, long-term survival and functional outcome will have to equal or surpass those of historical controls who were treated conservatively.

KEY WORDS • astrocytoma • optic chiasm • hypothalamus • outcome
riptical surgery via a pterional or transcallosal approach. The goal of surgery was primarily to establish a histological diagnosis, and if a typical low-grade astrocytoma of the chiasm/hypothalamus was encountered, a biopsy and limited resection were performed. Large masses obstructing the foramen of Monro were debulked to relieve ventricular obstruction, but generally no attempt at gross total excision was made. Younger children were then usually treated with chemotherapy using actinomycin D and vincristine, and older children received conventional radiation therapy. If progression occurred, the modality that had not been previously used was offered. Radical surgical excision was offered if the tumor progressed despite both chemotherapy and radiation. Shunting was performed as clinically necessary.

This population provided the opportunity to review the long-term outcome of a subset of patients who, if they were treated today, would be candidates for radical surgery as primary treatment in many centers. The purpose of this review is to provide clinical data that could serve as a benchmark for comparison with series reporting results of radical surgery.

**Clinical Material and Methods**

**Patient Population**

Between 1975 and 1991 a total of 76 children less than 20 years of age were diagnosed and/or treated at the Children’s Hospital of Philadelphia for astrocytomas or presumed astrocytomas of the optic chiasm and hypothalamus. In some instances, patients were initially treated elsewhere and then referred for subsequent therapy. The records and imaging studies (computed tomography or magnetic resonance (MR) images) of these patients were reviewed to identify those who, in retrospect, fulfilled criteria that would make them candidates for radical resection, even though radical surgery was in fact not performed. These criteria included the following: 1) presence of a globular exophytic hypothalamic/chiasmatic mass greater than 2.5 cm without major extension into the optic radiations or optic nerves at initial diagnosis; 2) low-grade, or presumed low-grade, histology; 3) initial surgical resection of 50% or less of the tumor mass; 4) follow-up of at least 3 years. The presence of NF1 did not exclude a patient if the other criteria were met; however, unequivocal radiographic or clinical progression was required for children with NF1 to be treated.

Forty-three patients did not meet these criteria and were excluded from the study (Table 1). Six patients treated during the period of the study were excluded because they underwent a 50% or more resection of their tumors, reflecting a more aggressive surgical approach taken during the latter period of the study. Of these individuals, two have died, one because of surgical complications and one of progressive disease. Follow-up period for the survivors averaged 4 years. The small number of these patients and short follow up precluded a direct comparison with the more conservatively operated group. Four children were excluded because of malignant histology (anaplastic astrocytoma); one of these has died. Two were excluded because later imaging studies were consistent with a diagnosis of hamartoma, and neither has progressed. Thirty-one patients were believed not to be candidates for radical surgery because the tumors diffusely involved the optic pathways, with extensive involvement of the optic tracts, nerves, thalami, and radiations. Twenty-three (74%) carry a diagnosis of NF1; all are alive, although 21 have required radiation therapy or chemotherapy for progressive disease.

Thus, 33 children fulfilled criteria that would have made them candidates for radical surgery, and they form the basis of this report. They ranged in age from 2 months to 20 years at diagnosis (mean 4.3 years). Thirteen were diagnosed during early childhood (2 years of age or younger); clinical signs of NF1 were present in four patients. Thirty-two children had surgical biopsy; on the basis of follow-up imaging studies, 27 were estimated to have undergone less than a 20% resection of the tumor (biopsy), and five were estimated to have undergone resection of 20% to 50% of the tumor (subtotal resection).

Histological diagnosis was made by a single neuropathologist (L.B.R.); pilocytic astrocytoma was reported in 13 tumors, fibrillary in 11, ganglioglioma in one, and unspecified low-grade astrocytoma in seven. One patient without clinical signs of NF1 and a typical MR image appearance of a chiasmatic astrocytoma was treated with radiation therapy without biopsy; he is alive and free of progression 3 years from diagnosis and is presumed to have had low-grade histology.

Treatment varied according to age. Lesions diagnosed in early childhood were initially managed with chemotherapy in 10 cases with radiation therapy in three, at 1.4, 2, and 8 years of age, respectively. The youngest two of these patients had received radiation treatment at other institutions prior to referral to Children’s Hospital of Philadelphia. Of the 10 children initially treated with chemotherapy, seven eventually received radiation therapy for tumor progression at a dose of 5000 to 5500 cGy at 2 to 6 years of age. The tumor of one of the three patients initially treated with radiation eventually progressed, and chemotherapy was undertaken at 6 years of age. Tumors diagnosed in 16 children 3 years of age or older were treated initially with radiation therapy; three relapsed and went on to receive chemotherapy. Four were initially managed with chemotherapy, and three required subsequent radiation therapy. In summary, for the group as a whole, 29 received radiation treatment, 18 received chemothera-

**TABLE 1**

<p>| Clinical characteristics of hypothalamic/chiasmatic astrocytomas in 76 patients |
|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patients</th>
<th>Eligible</th>
<th>Ineligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age (yrs) at diagnosis</td>
<td>4.3</td>
<td>4.5</td>
</tr>
<tr>
<td>neurofibromatosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>radiographically diffuse</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>radical (&gt;50% resection)</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>malignant histology</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>presumed hamartoma</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>alive at last contact</td>
<td>28 (85%)</td>
<td>40 (93%)</td>
</tr>
<tr>
<td>total</td>
<td>33</td>
<td>43</td>
</tr>
</tbody>
</table>
Hypothalamic/chiasmatic astrocytoma

Five of the 33 patients have died at a mean of 6.9 years from diagnosis (range 2.6–19.1 years). Three died of tumor progression, after radiation, chemotherapy, and salvage radical resection failed; one died of acute hydrocephalus secondary to shunt obstruction 2.6 years from diagnosis with stable tumor, and one severely impaired patient died of intercurrent infection 19.1 years after diagnosis. The remaining 28 patients are alive at a mean of 10.9 years from diagnosis.

Age at diagnosis did not affect survival, as children diagnosed at 2 years of age or younger fared as well as older children (Fig. 1). In fact, only one of the five deaths occurred in the younger group. The effect of histology was unclear, because of the small number of deaths. Of the five patients who had died, three had fibrillary astrocytomas, one had pilocytic, and one was diagnosed with astrocytoma not otherwise specified. Histological appearance was not an independent variable, because the mean age of children with pilocytic astrocytomas was 3.7 years at diagnosis, compared with 10 years for children with fibrillary astrocytomas and 4.8 years for those with other types of low-grade astrocytomas.

Visual Acuity

No attempt was made to classify tumors as being either primarily located in the optic chiasm or hypothalamus, and thus patients presenting initially with visual loss were considered together with those with hypothalamic complaints. Visual acuity for the 28 surviving patients is shown in Fig. 2. Many of these patients have visual field deficits, but the visual acuity recorded reflects useful preserved fields of vision.

Five patients were classified as being functionally blind in both eyes; the remaining patients had useful vision in at least one eye, so that they were able to read. The patients who were functionally blind all presented as young children (2 years of age or younger) with severe visual impairment, and it is unclear if they have suffered any visual deterioration. The tumor of one patient responded dramatically to chemotherapy given at 2 years of age and he is essentially free of tumor at age 13 (Fig. 3) but remains blind. The other four children received radiation treatment at 3 to 6 years of age, but it is not clear if this affected their vision in any way. Histological type did not appear to correlate with blindness, as two of the blind patients had fibrillary astrocytomas and three had pilocytic astrocytomas.

Endocrine Replacement and Growth

Endocrine replacement for the 28 surviving patients is summarized in Fig. 4; data reflect both present and past requirements. The most frequently prescribed medication is thyroid replacement, which is required by nine patients, followed by growth hormone needed in eight. Some of the earlier patients in the series would probably have benefited from growth hormone replacement, but this was not available at the time or was refused. Five patients required treatment for diabetes insipidus and precocious puberty was treated in four. Twelve individuals did not need

Survival analysis was performed using the methods of Kaplan–Meier and Mantel–Haenzsel.

Results

Survival Rate

Five of the 33 patients have died at a mean of 6.9 years from diagnosis (range 2.6–19.1 years). Three died of tumor progression, after radiation, chemotherapy, and salvage radical resection failed; one died of acute hydrocephalus secondary to shunt obstruction 2.6 years from diagnosis with stable tumor, and one severely impaired patient died of intercurrent infection 19.1 years after diagnosis. The remaining 28 patients are alive at a mean of 10.9 years from diagnosis.

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endocrine replacement. The specific cause of this endocrinopathy cannot be determined from this series, because all but four received radiotherapy at some point. Two of the four patients who did not receive radiation treatment did require endocrine replacement.

Height and weight data were available for 27 surviving patients and are presented in Fig. 5. Patients tended to cluster into obese (> 90th percentile for weight, nine patients) and diencephalic (< 10th percentile for weight, eight patients). Height varied considerably within each group, but the low-weight (diencephalic) patients tended to be short, and the obese ones tended to be tall. Six of eight individuals who received growth hormone are within the normal range for height.

Education, Work Environment, and Behavior

All surviving patients were ambulatory at last follow-up review, although one had a significant hemiparesis related to radical surgery performed for tumor progression. One is deaf because of meningitis unrelated to her tumor; one receives a course of anticonvulsant medications.

All surviving children are school age or older. Current educational data were collected on 27 of the 28 patients. The one patient lost to follow up was in special education classes at the time of last contact and is assumed to still be in this setting.

Sixteen (57%) of 28 surviving patients are in, or have completed, regular school. Of these, five have attended at least some college, five are in, or have completed, high school, and the remainder are in elementary school or junior high. One of these is in a mainstream school for the visually impaired.

Twelve children (43%) required a special school, including resource room, learning-disabled classes, or special education. Seven are in, or have completed, high school, and the others are in lower grades.

Those patients in the regular school group were diagnosed at a mean age of 7.2 ± 6.5 years (standard deviation), compared with 4.5 ± 3.8 for the special education group. This difference was not significant (p = 0.2, unpaired t-test). Twelve patients in regular school underwent radiation therapy at a mean age of 11 ± 4.5 years; four did not receive radiation therapy at all. Special education children received radiation treatment at a mean age of 5.7 ± 3.8 years (Fig. 6). The effect of histology was unclear because numbers were small and it was not clear that histological subtype was an independent variable.

Nine patients were 18 years of age or older at the time of last follow up. One was in graduate school, two in college, two were married and working full time, two were unmarried and working full time, one was in special education, and one completed two semesters of college but was then unemployed and living at home.

Formal neuropsychological testing was not performed in the majority of patients, but telephone interviews with parents and the behavioral checklists revealed a number of problems. Of the 27 surviving patients for whom recent follow-up information was available, six were described as “having few or no friends,” three were receiving ritalin for attention deficit disorder, four were described as “passive,” and two as “very emotional.”

FIG. 3. Left: Computerized tomography scan in a 1-year-old boy presenting with marked visual impairment. Right: Scan obtained 10 years after treatment with vincristine and actinomycin D shows virtually no residual tumor; however, he remains blind.
Hypothalamic/chiasmatic astrocytoma

Discussion

The feasibility of radical surgery for some exophytic astrocytomas of the optic chiasm/hypothalamus has been reported by several groups. For the most part, only isolated case reports with limited follow up have been discussed.1,3,13,23 Wisoff, et al.,22 reported a series of 16 children who had surgery with the intent of performing radical resection. Eleven of these patients were thought to have had 60% to 95% of their tumors removed, one of whom was found to have a hypothalamic hamartoma. With a mean 27 months of follow up, six patients who underwent radical resection of their astrocytoma remained alive and clinically stable without need of further therapy. Infants 1 year of age or less fared poorly; the extent of resection was limited, and all three died. In this relatively small series, surgery was well tolerated, although one child suffered a carotid-distribution infarct. The authors concluded that surgical intervention appeared to be useful in selected exophytic tumors.

It is difficult to compare this group of patients with series in which children were treated with more limited surgery followed by adjuvant therapy. First of all, patients selected for radical surgery constitute only a small fraction of all those with presumed hypothalamic/chiasmatic low-grade astrocytomas. Patients with small tumors, nonprogressive or asymptomatic lesions, or diffuse infiltrating tumors with extensive involvement of the optic radiations or nerves as is common with NF1 are not candidates for radical surgery. Nonetheless, they are usually included in historical reviews that cannot, therefore, be used to compare outcomes with more recent surgical series.

Because it is unlikely that a randomized trial will ever be performed comparing aggressive surgical resection with limited surgery and adjuvant therapy, one must rely on historical controls of a comparable group of patients to determine the optimum therapy, which is often done in chemotherapy trials. In this report, we have attempted to provide such a control group. Certainly, it is difficult to select retrospectively a group of patients who would have undergone radical surgery today, but the criteria used were easily applied and are comparable to those used by Wisoff, et al.,22 in their selection process.

Survival Statistics

Survival with hypothalamic/chiasmatic astrocytoma is generally reported to be good in the short term regardless of treatment. Older series often report visual pathway astrocytomas as a single entity, which skews survival data because of the more favorable prognosis of anteriorly located (optic nerve) lesions.8 However, even reports that analyze hypothalamic/chiasmatic tumors separately report good survival in the short term. In otherwise unselected series, 5-year survival for posteriorly located visual pathway gliomas is reported to be 68% to 100% for patients treated with biopsy and radiation.2,5,11,17,19 With longer range follow-up data available, however, it can be seen that patients tend to relapse, so that 10-year survival ranges from 57% to 90%,2,5,11,19 and 13-year survival is 50%.20 Infants and young children represent a particularly poor risk group,9 in part because of biologically more aggressive tumors, and in part because of reluctance to use radiation therapy in this age group. Several researchers have reported the use of chemotherapy for this group of patients, and published results suggest that radiation treatment can be delayed by using this strategy.14,16

Survival in our selected series of “surgically amenable” hypothalamic/chiasmatic astrocytomas was also generally good. With a mean follow-up period of 10.9 years, 28 (85%) of 33 patients were alive. Children diagnosed at 2 years of age or younger fared as well as older children, perhaps because of the aggressive use of chemotherapy. In the surgical series by Wisoff, et al.,22 the three infants died despite attempts at radical debulking. Surgical morbidity appeared to be high in this group, and our results suggest-
ed that a more conservative surgical approach and adjuvant chemotherapy may be most appropriate for these younger children. Radiation therapy or surgical debulking might then be considered at progression. Occasionally, prolonged responses are seen and no further therapy may be required. For older children, no direct comparison with series treated with aggressive surgical resection is possible at this time. Because patients treated initially with radical surgery are followed for longer periods of time, such a comparison should be possible.

In trying to arrive at an optimum treatment strategy, it is essential to compare functional outcome as well as survival between different treatment groups. Survivors of hypothalamic/chiasmatic astrocytomas often have endocrinological, visual, and neurodevelopmental problems that are poorly documented in previous reports. These problems may arise from the tumor itself, from surgical complications, or as delayed effects of radiation or chemotherapy.

Visual Abnormalities

Visual abnormalities, including optic atrophy, visual field cuts, and diminished visual acuity are commonly present when tumors are initially diagnosed. Infants in particular may be nearly blind before a tumor is suspected. It may be impossible to determine in a survivor how much visual loss is attributable to the direct effects of the tumor and how much to therapy, especially because visual outcome does not correlate with tumor size or response to treatment. We could not determine the specific cause of visual dysfunction in many patients and can report only the outcome. Our series included five children who were functionally blind, but as they were already severely visually compromised when they were diagnosed during infancy it is unclear that they would have fared better with any treatment. The majority of our surviving patients (23 of 28 or 82%) have retained enough vision in at least one eye to read comfortably.

Most series do not report long-term status of vision but only responses to specific therapies. Radiation therapy is reported to result in short-term visual improvement in 10% to 40% of patients, stabilization in 48% to 77%, and worsening in 0% to 14%. Packer, et al., stated that chemotherapy resulted in stabilization of vision in the short term in 23 of 24 patients and Petronio and colleagues reported the same results in 16 of 19 subjects. The surgical series reported no worsening of vision as a direct result of surgical intervention, although Wisoff, et al., reported one child whose vision deteriorated when the tumor progressed after 70% resection.

It appears that tumors can often be stabilized with therapy and that visual outcome is largely determined by the status at the time of diagnosis.

Pituitary and Hypothalamic Function

Detailed endocrinological and growth data are lacking in the recent series advocating aggressive surgical resection as primary therapy. Panhypopituitarism, obesity, hyperphagia, and aggressive or passive behavior are known sequelae of radical surgery for craniopharyngioma, and it is to be anticipated that these problems will also occur in some patients undergoing radical surgery for hypothalamic/chiasmatic astrocytomas. These same problems are well known to be sequelae of radiation therapy in the suprasellar area and it is unclear at this time which strategy will result in the optimum outcome. With the exception of diabetes insipidus in infants or patients with a disordered thirst mechanism, panhypopituitarism is satisfactorily managed in the majority of patients without major impact on the quality of life.

Many of the surviving patients in our series have abnormal growth patterns, clustering into either diencephalic (low-weight) or obese groups. This is undoubtedly multifactorial in origin and is only partly amenable to hormonal replacement or dietary alteration.

Educational and Work Status

Patients with hypothalamic/chiasmatic astrocytomas often survive for decades. Because tumor progression, surgery, radiotherapy, and, to a lesser extent, chemotherapy may all affect cognitive function, it is essential that outcome analysis include detailed functional data such as type of school or, when age appropriate, capacity for self-sufficiency. Unfortunately, this type of data is rarely reported.

Our results confirm that many children treated with multimodality therapy suffer cognitive impairment and behavioral disturbances. Only 57% have attended or are presently enrolled in a regular academic school, whereas the remainder require some form of special help. On the other hand, eight of nine adult survivors are capable of functioning independently. Although there is a trend toward better educational functioning among children diagnosed at an older age, the factor most closely associated with need for special education was the administration of radiation treatment in early childhood. This supports the use of some other modality, either chemotherapy or radical surgery, as initial treatment for younger children. Children 10 years of age or older, however, appear to tolerate radiation therapy quite well. Although formal behavioral testing was not conducted on most of our patients, several surviving individuals were described as having few friends and suffering behavioral disturbances. Further work will be required to ascertain the specific causes of these problems.

Conclusions

It is unlikely that any single modality (surgery, radiation therapy, or chemotherapy) will be the optimum treatment for all children with hypothalamic/chiasmatic astrocytoma. The challenge for the future is to determine the most appropriate treatment for each patient, based on rate of tumor progression, age, radiographic demonstration of extension of the tumor, prior therapy, and visual/endocrine status. This will require comparison between groups of comparable patients treated according to different paradigms that report not only survival but functional outcome as well.

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