Treatment results of juvenile pilocytic astrocytoma

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Treatment results for 36 patients with juvenile pilocytic astrocytoma treated from 1942 through 1985 at the University of California, San Francisco, were reviewed. Twenty-two tumors were located in the posterior fossa, 10 were in the hypothalamic region, and four were in the cerebral hemispheres. Twenty-eight patients were less than 18 years of age. The overall survival rate was 83% and 70% at 10 and 20 years, respectively. All 12 patients who had total tumor resection remain disease-free; only two of the 12 received postoperative irradiation. The 10- and 20-year freedom-from-progression for the 19 patients who had incomplete resection and received at least 40 Gy of postoperative irradiation was 74% and 41%, respectively. All patients who failed treatment had local recurrence. One patient developed diffuse meningeal seeding, after four local recurrences in the posterior fossa over a 23-year period. Six patients failed treatment and had a repeat biopsy at the time of recurrence or at postmortem examination, and three showed histological progression of the tumor to an anaplastic astrocytoma. Based on this study and others in the literature, a protocol has been adopted whereby patients who have total tumor resection are not treated with postoperative irradiation. Patients who have incomplete tumor resection and are older than 3 years of age are currently treated with postoperative partial-brain irradiation, to a dose of 45 to 60 Gy. In general, young children with incomplete resection are followed closely with computerized tomography or magnetic resonance imaging and are treated with chemotherapy or irradiation if tumor progression is documented.

KEY WORDS: brain neoplasm • juvenile pilocytic astrocytoma • glioma • radiation therapy • childhood

There is no universally accepted grading or classification system for astrocytomas. In general, tumors have been divided into aggressive "high-grade" lesions (highly anaplastic astrocytoma and glioblastoma multiforme) versus less aggressive "low-grade" lesions. Some low-grade astrocytomas can be subclassified histologically as fibrillary and juvenile pilocytic types. According to Rubinstein, the diagnosis of juvenile pilocytic astrocytoma (JPA) is made when piloid fibrocytic astrocytes are intermixed with loosely arranged areas of protoplasmic astrocytes (Fig. 1). Other features, including Rosenthal fibers, vascular proliferation, and calcification are often present but not required for the diagnosis. Necrosis or mitoses are rarely, if ever, present. Usually, JPA's contain microscopic cysts, and commonly they contain one or more macroscopic cysts. Some tumors develop as a single large cyst with a wall composed of compressed normal brain tissue or degenerated tumor, and a single mural nodule of viable tumor.

The role of radiotherapy in treatment of high-grade gliomas is well established. It has been shown in prospective randomized trials that irradiation prolongs survival time in patients with glioblastoma multiforme and anaplastic astrocytoma. The role of radiotherapy for low-grade astrocytomas is less certain. Previous investigators have reported long-term survival rates of 25% to 100% following complete surgical excision without postoperative irradiation. Patients who have had only subtotal resection, however, are at higher risk of recurrence and would benefit from an effective adjuvant therapy. Whether or not irradiation is effective for low-grade astrocytoma has been debated. Some uncontrolled retrospective studies suggest that postoperative irradiation is of benefit. Generally, JPA's have been reported to carry a better prognosis than other low-grade astrocytomas, and some authors have not advocated the use of radiotherapy, even after incomplete resection. This study presents the results of treatment of JPA's
FIG. 1. Typical histology of juvenile pilocytic astrocytoma showing bundles of highly fibrillated astrocytes admixed with loosely aggregated stellate astrocytes. H & E, × 40.

at the University of California, San Francisco (UCSF) from 1942 through 1985, and evaluates the prognosis of patients with or without irradiation. Tissue sections for all patients were reviewed prior to their inclusion in the study.

Clinical Material and Methods

Thirty-eight patients who received definitive treatment for JPA at the UCSF from 1942 to 1985 were identified through departmental records and the General Tumor Registry. Two patients who died from postoperative complications were excluded from the analysis. The remaining 36 patients form the basis of this report. Some patients previously reported from this institution by Leibel, et al., are included. Tumor sections from all patients were reviewed and the diagnosis of JPA was confirmed based on the criteria of Rubinstein. No patient with mixed tumor, with an oligodendroglioma or other astrocytic component, was included in the study. Each patient's operative report was reviewed.

There was no set policy in effect regarding the use of radiotherapy during the study period. However, the treatment policy actually utilized was in fact almost uniform, as the surgeons and radiotherapists believed that incompletely excised tumors required treatment and that completely excised tumors did not. Only two patients who were believed to have had a complete surgical resection received postoperative irradiation, and all but one patient who had incomplete resection received postoperative irradiation. Six patients were treated with orthovoltage irradiation and the remainder with megavoltage irradiation. All doses are given in Gray (Gy; 1 Gy = 100 rads) and represent the midplane, central-axis, or minimum tumor dose. Treatment was delivered at a dose rate of 1.60 to 1.80 Gy/day, 5 days/wk. Field sizes were designed to cover the primary tumor plus a generous margin (2 to 3 cm). One patient received whole-brain irradiation. Two patients received their postoperative irradiation at another hospital in accordance with our treatment recommendations, and are included in the series. One patient received 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) as part of his primary treatment.

The follow-up period ranged from 2 to 33 years. Survival and relapse-free survival times were calculated from the date of initial surgery. Patients were considered to have disease progression if there was progression of symptoms (eight patients) or evidence of tumor enlargement on computerized tomography (CT) scans.
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(one patient). Since patients treated early in the study period did not have serial CT scans, the numbers for tumor progression may not include some patients who had tumor progression, but were without progressive symptoms. One patient was lost to follow-up review 13 years following surgery. He was censored in calculation of survival data. Six patients died as a direct result of their tumor and one patient with neurofibromatosis died from a neurofibrosarcoma of the mandible, which arose outside the irradiated volume. He was also censored in calculation of survival data.

Actuarial survival and freedom-from-progression were calculated by the method of Kaplan and Meier. Differences between groups were calculated by the log-rank method.

Results

There were 17 males and 19 females in this series. The patients ranged in age from 1 to 29 years (median 8 years). Eight patients were 18 years of age or older. Two patients had neurofibromatosis. Twenty-two tumors were located in the posterior fossa, 10 were in the hypothalamic region, and four were in the cerebral hemispheres. Of the 22 tumors in the posterior fossa, 16 were thought to have arisen in the cerebellum and the other six in the brain stem. Of the 10 tumors in the hypothalamic region, six were believed to have arisen from the optic nerves or chiasm. Twenty-three tumors were noted to have a macroscopic cystic component; six of these were composed of a large cystic cavity with a single mural tumor nodule (four in the cerebellum and two in the cerebral hemispheres). Twenty-three tumors were noted to have a macroscopic cystic component; six of these were composed of a large cystic cavity with a single mural tumor nodule (four in the cerebellum and two in the cerebral hemispheres). Sixteen patients were treated prior to 1975, when CT scanning first became available.

Twelve patients were believed to have had a total excision of their tumor; these included nine of 16 tumors of the cerebellum but none of the six tumors that arose in the brain stem. Two of the four tumors in the cerebral hemispheres and one of the 10 tumors in the hypothalamic region were thought to be totally excised (Table 1).

For all 36 patients, 10- and 20-year freedom-from-progression rates were 77% and 56%, respectively. Survival at 10 and 20 years for all patients was 83% and 70%, respectively (Fig. 2). Of the 12 patients who had a total resection, only two received postoperative irradiation. No patient who was thought to have had a total resection has had tumor recurrence. Twenty-four patients had less than a total resection: six had biopsy only and 18 had subtotal resection. Of the six tumors that involved the brain stem, three were biopsied only and three were subtotally resected. Only one patient, with a right optic nerve tumor, was not treated with postoperative irradiation. She had what was described as a debulking operation, which included removal of a portion of the right optic nerve. She is currently being followed with CT and magnetic resonance (MR) imaging and is without evidence of progression 6.5 years after surgery. The remaining 23 patients with less than total excision received postoperative irradiation. One was moribund at initiation of irradiation, and treatment was stopped after 24 Gy when it seemed that further therapy was futile; the patient died 2 months after surgery. A second patient's therapy was interrupted for 5 months due to infection and hydrocephalus. Twenty-one patients, excluding the one who received only 24 Gy and the one whose therapy was interrupted, received irradiation with curative intent, with 26 to 59 Gy. Of these, only two patients received less than 40 Gy: one had a local recurrence after 26 Gy; and the other, who had neurofibromatosis, died of a mandibular neurofibrosarcoma 14.3 years after surgery and irradiation for his JPA. The 10- and 20-year freedom-from-progression for the 19 patients who had an incomplete resection and who received at least 40 Gy was 74% and 41%, respectively (Fig. 3). Survival at 10 and 20 years was 81% and 54%, respectively (Fig. 4).

In all, nine patients have failed treatment. Of those nine tumors, four were in the brain stem, three were hypothalamic, one was in the left cerebellar hemisphere, and one was in the parietal lobe. Autopsy was performed on four patients who died of tumor recurrence; all four had only local failure, without evidence of intraventricular or spinal seeding. Two additional patients had CT scans at the time of recurrence, showing only local failure.
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One patient developed evidence of cerebrospinal fluid seeding. She was brought for evaluation at 5 years of age with a cerebellar tumor and was treated with subtotal resection, a ventriculoatrial shunt, and 45 Gy partial-brain irradiation which was interrupted for 5 months (after 25 Gy) due to infection and hydrocephalus. She had four subsequent local recurrences, underwent several attempts at resection, and received a second course of posterior fossa irradiation. Multiple shunt revisions were performed. At 26 years of age, her tumor progressed histologically to an anaplastic astrocytoma. At the age of 28 years, she developed clinical evidence of diffuse meningeal seeding and died.

Tissue sections of recurrent tumor from six patients were available for review. Three specimens showed only JPA, without progression to a more anaplastic histology. Three of the recurrent tumors had foci of anaplastic astrocytoma at the time of recurrence, with nuclear and cytoplasmic pleomorphism, mitoses, and areas of necrosis, in addition to areas still recognizable as JPA.

Tumor control in relation to radiation dose is shown in Fig. 5. Only those patients who had incomplete resection followed by definitive irradiation are included. All four patients treated with a planned dose of 46 Gy or less were 3 years of age or younger at the time of therapy; of these, three had tumor progression. Of the 17 who received greater than 46 Gy, only four had tumor progression.

Following completion of therapy, a new endocrine deficiency or neurological impairment was diagnosed in six patients. None of these patients had evidence of tumor recurrence or progression to account for the new impairment. The first patient had subtotal tumor resection followed by 59 Gy partial-brain irradiation for an extensive hypothalamic lesion at age 10 years. He developed a seizure disorder immediately postoperatively. At 43 years of age he has moderate mental retardation and works in a sheltered workshop. The second patient had a subtotal resection and 50 Gy partial-brain irradiation for a posterior fossa lesion at the age of 2 years. He presented originally with left extraocular muscle abnormalities, requiring numerous corrective operations. At 14 years of age, he is reading at the fifth grade level. The third patient had a biopsy and 51 Gy partial-brain irradiation for a suprasellar tumor at the age of 9 years. Three years after treatment, he developed a seizure disorder which was controlled with medication. He also developed a low testosterone level, probably related to irradiation of the hypothalamic-pituitary axis. The fourth patient with a new impairment unexplained by treatment failure had a biopsy and 50 Gy partial-brain irradiation for a suprasellar tumor at the age of 9 years. At 10½ years old, growth hormone deficiency was diagnosed. Earlier evaluation was not performed, so that the date of onset of the deficiency is unknown. She is currently receiving growth hormone replacement and is growing normally. The fifth patient had a biopsy and 50 Gy partial-brain irradiation for a chiasmal tumor at the age of 18 years. Several years later, she developed panhypopituitarism, believed to be secondary to irradiation; this condition was controlled by hormone supplementation. The last patient in this group had a gross total resection of a posterior fossa tumor at the age of 8 years. At 33 years of age, he was diagnosed as having minimal brain dysfunction with an attention deficit. Although some of these problems probably were related directly to irradiation (endocrine dysfunction in two patients), in general it was not possible to be certain of their etiology. In most cases, the relative roles of the primary tumor, hydrocephalus, surgery, and irradiation could not be ascertained.

Discussion

Juvenile pilocytic astrocytoma most commonly occurs in children, although approximately 25% of these tumors are found in patients 18 years of age or older.12
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There is no evidence that the prognosis differs with the patient’s age. The tumors occur, in decreasing frequency, in the posterior fossa, hypothalamic region, and cerebral hemispheres. The microscopic features are identical, regardless of the tumor site. While most previous authors have limited their series to one location, there is no evidence that tumor location per se influences prognosis, except that it may affect the likelihood of total resection.

The literature on the results of treatment of JPA’s is sparse. The tumors have commonly been grouped together with other low-grade astrocytomas of the cerebellum, brain stem, or cerebral hemispheres, and have not been reported as a separate entity. Furthermore, when irradiation has been used, most authors have not reported sufficient details to enable the adequacy of the irradiation to be judged. Other authors have not reviewed the pathology of their cases, and the tumors have been misclassified. This may be a particular problem in older series, when JPA’s were not always regarded as a distinct subgroup of tumors and may have been classified simply as astrocytoma, or by the older term “polar spongiosblomastoma.” Nevertheless, a consideration of the present data together with previously published findings permits some conclusions regarding the results of treatment of JPA’s.

It is generally agreed that complete resection of a JPA is usually curative, the recurrence-free survival rate without adjuvant therapy being nearly 100%. Tumors comprised of a large cystic cavity with a single mural nodule are apparently curable with excision of the nodule only, as the cyst wall usually does not contain viable tumor. In the present series, six patients had large cystic tumors with a single mural nodule. Three of the six patients underwent complete excision of the mural nodule, without postoperative irradiation. Two had incomplete and one had complete excision of the nodule, followed by postoperative irradiation. In no case was excision of the cyst wall attempted. Biopsies of the cyst wall in one patient showed gliosis without malignancy. None of the six patients had recurrence of their tumor.

The management of patients with incomplete resection is a subject of considerable debate. Some investigators believe that JPA’s are relatively benign tumors, and that close observation following incomplete resection is appropriate therapy, reserving adjuvant therapy for those who show disease progression. From the data presented here, it is evident that incompletely resected tumors have a substantial risk of progressing, despite the addition of irradiation. Table 2 summarizes published recurrence rates following irradiation with a minimum of 40 Gy. Overall, 10 (34%) of 29 patients have failed despite postoperative irradiation with at least 40 Gy. Since there was only one patient in the present series who did not receive irradiation following incomplete resection, the role of radiation in preventing or delaying tumor progression could not be assessed from these data. Similarly, other reports fail to provide sufficient information to resolve this issue. Until more adequate data are available, it is the policy at UCSF that for older children (≥ 3 years) and adults, postoperative irradiation is given to those who have undergone an incomplete JPA resection. The rationale for this policy is based on the concept that irradiation is most likely to be successful when the residual tumor volume is smallest. Depending upon the age of the patient, a dose of 50 to 60 Gy at 1.8 Gy/day is given to a target volume that includes the tumor demonstrated by CT and MR imaging plus a 2- to 3-cm margin.

Because of the higher susceptibility of the younger child’s brain to damage from irradiation, postoperative irradiation is withheld from children less than 3 years of age. These patients are followed clinically and with CT and MR imaging. If and when progression is documented, irradiation is given. Since JPA’s usually grow slowly, this policy permits delay of irradiation until the child is older and the brain less susceptible to radiation injury. Obviously, this is a trade-off between irradiation of the smallest tumor volume and the risk of radiation injury.

![Fig. 5. Tumor dose and total days over which irradiation was given for 21 patients who had incomplete resection, followed by definitive irradiation. Solid symbols represent patients who demonstrated disease progression and open symbols those without recurrence. Triangles represent patients who only underwent biopsy of their tumor and circles represent those who had subtotal resection.](image)

### TABLE 2

**Progression or recurrence of juvenile pilocytic astrocytoma**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Total Cases</th>
<th>Failures</th>
<th>Follow-Up Period (yrs)</th>
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<tbody>
<tr>
<td>Marsa, et al., 1973</td>
<td>7</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>Garcia, et al., 1985</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wallner, et al., 1988</td>
<td>19</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>total</td>
<td>29</td>
<td>10</td>
<td>34</td>
</tr>
</tbody>
</table>

* Data for patients with incomplete resection and postoperative irradiation (≥ 40 Gy).
injury. Another possibility in treating young children is to administer chemotherapy in the hope of delaying tumor progression, assuming that chemotherapy would be effective and that it is less toxic than irradiation to the developing brain. Irradiation could then be administered after the child has matured further. A third possible approach would be to wait for the first indication of tumor regrowth and then give chemotherapy in the hope of gaining further delay before instituting radiotherapy or additional surgery. Because of the limited number of patients with JPA, identification of an effective chemotherapeutic agent would require a multiinstitutional study. It is still too early to say which of these policies presents the best balance between controlling tumor progression and minimizing the deleterious effects of treatment.

References