Treatment of oligodendrogliomas with or without postoperative irradiation

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The authors have reviewed the treatment results in 42 patients with intracranial oligodendroglioma treated from 1940 through 1983 at the University of California, San Francisco. Two patients who died postoperatively were excluded from analysis. Eleven patients had mixed tumors, with a minor astrocytic component. The overall survival rates for the 29 patients with pure oligodendroglioma were 61% and 33% at 5 and 10 years, respectively; these rates for the 11 patients with mixed tumors were 57% and 38% at 5 and 10 years, respectively. The 10-year survival rate for 14 patients with pure oligodendroglioma who received greater than 45 Gy irradiation was 56% versus 18% for 11 patients who did not receive postoperative irradiation (p = 0.09). Nine patients with mixed tumor who received more than 45 Gy postoperatively had survival rates similar to those for the 14 patients with pure tumors irradiated with more than 45 Gy (p = 0.89). All patients who died of their tumor had evidence of intracranial recurrence. One patient, who did not receive initial postoperative irradiation, also had clinical and myelographic evidence of spinal seeding. All five patients examined postmortem had tumor recurrence at the primary site; one patient also had intraventricular seeding. Six of the 10 patients with pure oligodendroglioma who had a repeat biopsy at the time of tumor recurrence or at postmortem examination showed histological progression to an anaplastic astrocytoma or glioblastoma multiforme. Based on this study, adult patients with pure or mixed oligodendroglioma currently are treated with partial-brain irradiation to a dose of about 60 Gy. In general, children are treated with partial-brain irradiation to about 50 Gy.

KEY WORDS • brain neoplasm • oligodendroglioma • astrocytoma • radiation therapy

Oligodendrogliomas are uncommon tumors, comprising 3% to 7% of primary intracranial neoplasms. Despite their reputation for having a long natural history, 10-year survival rates are approximately 10% to 30%. Primary treatment is surgical excision; the benefit of irradiation has been debated.

Part of the controversy regarding the role of irradiation for oligodendrogliomas may stem from the fact that the tumor pathology is not always clearly defined; many contain elements of other glial neoplasms. Some authors include “mixed” tumors with pure oligodendrogliomas, and it is possible that mixed tumors have a different prognosis than pure forms of oligodendroglioma.

We have reviewed all patients treated at the University of California, San Francisco (UCSF), for oligodendroglioma between 1940 and 1983 to investigate the role of radiotherapy in the treatment of these tumors and to evaluate the effect of other glial tumor elements on prognosis.

Clinical Material and Methods

Forty-two patients who received definitive treatment for oligodendroglioma at UCSF between 1940 and 1983 were identified through departmental records and the General Tumor Registry. Two patients who died from postoperative complications were omitted. The remaining 40 patients form the basis of this report. Some patients from this institution who were previously reported by Sheline, et al., are included.

Pathology specimens from 37 of the 40 patients were available for review and the diagnosis of oligodendroglioma was confirmed. The remaining three specimens could not be obtained; however, the original pathological diagnosis appeared unequivocal and those patients were included. Only tumors that were wholly or predominantly oligodendrogial were included. Eleven tumors had at least one focus of another histological type and were classified as “mixed” tumors. Each patient’s operative report was reviewed.

The decision whether or not to give postoperative...
Radiotherapy for oligodendrogliomas

**TABLE 1**

<table>
<thead>
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<th>Tumor pathology at diagnosis in 37 cases*</th>
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<tr>
<td>Pathological Diagnosis</td>
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<tr>
<td>pure tumors</td>
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<tr>
<td>oligo A</td>
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<td>oligo B</td>
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<td>mixed tumors</td>
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<td>oligo/MAA</td>
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<td>oligo/HAA</td>
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* Three patients whose pathology specimens were not available for review are excluded. Grading is according to the system of Smith, et al.13 Oligo = oligodendroglioma; MAA = moderately anaplastic astrocytoma; HAA = highly anaplastic astrocytoma.

irradiation varied with the opinion of the surgeon and the consulting radiotherapist. There was no set policy in effect during the study period regarding the use of radiotherapy. Twenty-eight patients were irradiated postoperatively. Two patients were treated with orthovoltage and the remainder with megavoltage irradiation. All doses are given in Gray (Gy, 1 Gy = 100 rads) and represent midplane, central axis, or minimum tumor dose. Four patients who received a tumor dose of less than 45 Gy were not included in the comparison of survival times for non-irradiated versus irradiated patients. Treatment was delivered at a daily dose of 1.50 to 1.80 Gy/day, 5 days/wk. Field sizes were designed to cover the primary tumor plus a generous (2- to 3-cm) margin. Only two patients received whole-brain irradiation. Six patients underwent postoperative irradiation at another hospital in accordance with our treatment recommendations, and were included in this series. Four recent patients (two with pure tumors and two with mixed tumors) received chemotherapy as part of their primary treatment.

The follow-up period ranged from 2 to 28 years. Duration of survival and relapse-free survival was calculated from the date of initial surgery. Two patients were lost to follow-up evaluation, 4.6 and 23 years following surgery and postoperative irradiation. They were censored in calculation of survival times. Twenty-three patients died as a direct result of their tumor and one patient died of causes unrelated to tumor (gastrointestinal bleeding).

Actuarial survival rates and freedom from relapse were calculated by the method of Kaplan and Meier.5 Differences between groups were calculated by the log-rank method.

**Results**

The study group included 18 males and 22 females, ranging in age from 11 months to 63 years (median 41 years). Eight patients were less than 18 years of age. Thirty-seven tumors (92%) were located in the cerebral hemispheres. Of the other three, one was located in the cerebellum, one in the sellar region, and one in the lateral ventricles. Calcifications were evident on skull radiographs or computerized tomography (CT) in 18 (45%) of the 40 tumors.

Thirty-one patients had a subtotal resection of their tumor. Three underwent biopsy only, one had no tissue diagnosis until the first recurrence, and four had gross total resection. In only one case did the surgeon state that all tumor tissue had been removed.

The tumors were graded using the classification system of Smith, et al.13 Of 26 pure oligodendrogliomas available for review, none were grade A, 10 were grade B, 14 were grade C, and only two were grade D (Table 1). Eight of 11 mixed tumors contained an astrocytic component considered highly anaplastic, and three contained an astrocytic component considered moderately anaplastic.

Survival rates at 5 and 10 years for all patients with pure oligodendroglioma were 61% and 33%, respectively (Fig. 1 left). Freedom from relapse was 33% and 25% at 5 and 10 years, respectively. Survival rates for all patients with mixed tumors were 57% and 38% at 5 and 10 years, rates similar to those for patients with pure tumors (p = 0.49, Fig. 1 right).

Fourteen patients with pure oligodendroglioma who
received postoperative irradiation with greater than 45 Gy had a 10-year survival rate of 56% compared to 18% for the 11 patients with pure oligodendroglioma who did not receive postoperative irradiation ($p = 0.092$, Fig. 2). The mean and median ages of the 11 patients who did not receive planned postoperative irradiation were 39 and 38 years, respectively; the mean and median ages of the 14 patients who did receive planned postoperative irradiation were 35 and 42 years, respectively. Four pediatric patients with pure tumors (aged 7, 10, 12, and 17 years) were given 45 to 54 Gy of partial-brain irradiation. Three of the four patients are currently alive at 2.5, 6.1, and 23 years following treatment.

Patients with mixed tumors who received postoperative irradiation (> 45 Gy) had a survival rate similar to that for the 14 patients with pure tumors who received postoperative irradiation ($p = 0.89$, Fig. 3). All but two patients with a mixed tumor received postoperative irradiation with greater than 45 Gy. One of the two received 18 Gy of a planned full course of irradiation, but refused further therapy and died 3.6 years following resection; the other patient, an 11-month-old child, was followed closely with serial CT scanning. Tumor growth was identified 3 months following surgery; he then received 45 Gy of irradiation and is without evidence of disease progression at 2.4 years.

One patient with a pure tumor lived more than 10 years following surgery alone. That patient was the only one for whom the surgeon stated in the operative report that all tumor had been removed.

Twenty-three patients have died from intracranial tumor recurrence. Only one (5%) demonstrated clinical evidence of spinal seeding. This patient had a subtotal resection of an oligodendroglioma of the left temporal lobe at 35 years of age. No postoperative irradiation was given. Local recurrence developed 5 years later. He was given 50 Gy of partial-brain irradiation over 47 days. Seven months after completing brain irradiation, he developed bilateral leg weakness. A myelogram showed a complete block at T-11. Laminectomy and biopsy demonstrated oligodendroglioma, presumably metastatic from the brain lesion. He received 39 Gy over 29 days to a limited spinal field but died 2 months later. Autopsy showed extensive local recurrence intracranially, without residual spinal tumor.

Autopsy reports were available for five patients. Of those, one showed recurrence at the primary site plus diffuse intraventricular seeding. Four of the five patients who were examined postmortem had only local infiltrative tumor recurrence.

In 10 patients who initially had pure oligodendroglioma, surgical resection or postmortem sampling of recurrent tumor was performed 1 to 11 years following initial therapy. Only four of the 10 patients had pure oligodendroglioma at the time of recurrence. Two had glioblastoma multiforme only, three had mixed oligodendroglioma and highly anaplastic astrocytoma, and one had a moderately anaplastic astrocytoma without evidence of oligodendroglioma.

Four patients received chemotherapy, consisting of some combination of procarbazine, vincristine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), or 6-thioguanine, as part of their definitive treatment and in addition to postoperative irradiation. Two received hydroxyurea with irradiation and one received bromodeoxyuridine with irradiation. All four patients are currently alive at 2.4, 2.5, 3.5, and 5.2 years following therapy.

One patient was believed to have had a complication of treatment, unrelated to her tumor. She had subtotal resection of a right frontal oligodendroglioma at 45 years of age. Postoperatively, she received 60 Gy to the whole brain with concomitant hydroxyurea as part of an ongoing protocol. Following irradiation, she received three cycles of combination chemotherapy with procarbazine, CCNU, and vincristine. Fourteen months after completing irradiation, she developed bilateral decreased visual acuity. Changes suggestive of radiation retinopathy were present in the right fundus. She also had bilateral optic nerve atrophy, consistent with radiation neuropathy. A CT scan at that time showed no evidence of tumor recurrence to account for the visual loss. The patient is alive 5 years after initial therapy.
Radiotherapy for oligodendrogliomas

Her visual acuity is 20/100 in the right eye and 20/400 in the left.

**Discussion**

Oligodendrogliomas, like low-grade astrocytomas, have an infiltrative growth pattern, and only rarely can complete excision be achieved. Following resection, most patients are left with gross residual tumor and, without effective adjuvant therapy, the long-term survival rate is low. Some investigators have shown increased survival after postoperative irradiation,\(^1\)\(^2\)\(^11\) while others have reported no benefit.\(^8\) All reported studies, however, have been retrospective and span long time intervals, so that changes in treatment technique over time could influence the results. Additionally, some investigators have included mixed tumors as well as pure oligodendrogliomas in their series or have not verified the original diagnosis of the cases included. Patients in the present series who received postoperative irradiation with greater than 45 Gy showed a tendency toward longer survival (\(p = 0.09\)). Furthermore, six patients treated with surgery alone as initial therapy received irradiation at the time of recurrence. Any survival benefit that accrued from irradiation at the time of recurrence would bias the results against immediate postoperative irradiation. The present series suggests that irradiation offers some prolongation of the time to recurrence and that it results in an increased number of long-term survivors.

Intracranial tumor recurrence was almost the sole mode of failure in our patients, whether or not they received irradiation. Only one (2.5%) of 40 patients exhibited clinical evidence of spinal seeding. All of the five patients on whom an autopsy was performed showed local recurrence; in one, there was also diffuse intraventricular seeding. Because local recurrence is the major reason for treatment failure, patients at UCSF are currently treated with partial-brain irradiation, using a generous (2- to 3-cm) margin around the tumor, as demonstrated by CT and magnetic resonance imaging. No dose-response analysis could be performed in this series of patients, as most were treated within a relatively narrow dose range of 45 to 60 Gy. A tumor dose of 55 to 60 Gy is currently used for adults, with a reduced dose of 45 to 50 Gy for children aged 3 years or younger.

Packer, *et al.*,\(^7\) recently proposed the use of prophylactic spinal irradiation for children with high-grade oligodendroglioma. There is no evidence in the present series to support such a policy, especially when one considers the possible long-term sequelae of such treatment. Other authors have also reported spinal seeding in less than 10% of patients.\(^3\)

Smith, *et al.*,\(^13\) devised a grading system for oligodendrogliomas, classifying the tumors from grades A through D. They demonstrated a worse prognosis for higher-grade tumors. By their criteria, 24 (92%) of the 26 pure oligodendrogliomas reviewed in the present series were grade B or C, the only two grades that were not associated with a difference in survival in the series of Smith, *et al.* There were only two grade D tumors in our series, and no grade A tumors. For the present series of patients, therefore, the classification system of Smith, *et al.*, was not prognostically useful. The clustering of tumors in grades B and C could have been due to differences in patient populations, but more likely reflects differences in interpretation of the grading criteria.

Oligodendrogliomas are often "mixed" tumors, containing areas of other glial differentiation. Rubinstein\(^10\) estimated that half of all oligodendrogliomas contain some component of a second tumor type. The significance of a second tumor type in what is predominantly an oligodendroglioma is unknown. Patients with oligodendrogliomas typically present with a long history of symptoms and a relatively protracted course following therapy. In contrast, moderate or high-grade astrocytomas are generally more aggressive tumors. It would seem, therefore, that oligodendrogliomas that contain an anaplastic astrocytic component might carry a worse prognosis than those that do not. Previous series have generally been limited to pure tumors, or have included all mixed tumors without analyzing survival of the patient groups separately. Smith, *et al.*,\(^13\) reported that the presence of astrocytic elements had no influence on prognosis, but they did not analyze their results by treatment or prognostic factors. In the present series there was no apparent tendency for mixed tumors with moderately or highly anaplastic elements to carry a worse prognosis, at least for patients who received postoperative irradiation. The only patient with a mixed tumor who did not receive immediate postoperative irradiation developed tumor recurrence 3 months following surgery.

Tissue from recurrent tumors removed from 10 patients who initially had a pure oligodendroglioma was available for pathological review. Six (60%) of the 10 tumors showed histological progression to anaplastic astrocytoma or glioblastoma multiforme. Histological progression of oligodendroglioma has been noted by previous investigators\(^4\) and has been reported for other central nervous system tumors. It may reflect overgrowth by more aggressive, astrocytic elements initially present in small numbers but unrecognized, or may result from neoplastic transformation of glial elements. Additionally, sampling error at the time of initial resection may lead to a failure to identify astrocytic elements that may already be present.

Four patients in the present series received chemotherapy as part of their definitive treatment. Although all are living without evidence of tumor recurrence or progression, the number of patients is too small and the follow-up time too short to permit conclusions about the efficacy of chemotherapy. Presently, there are no data in the literature regarding the efficacy of chemotherapy for these tumors. While chemotherapy is of some benefit in the treatment of anaplastic astrocytoma...
or glioblastoma multiforme, its benefit for slowly growing oligodendrogliomas remains speculative. Nevertheless, in light of the poor long-term prognosis with conventional surgery and irradiation, it is suggested that patients with oligodendrogliomas be considered for inclusion in chemotherapy trials.

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