Oligodendrogliomas: the Mayo Clinic experience

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Eighty-one patients with pure supratentorial oligodendrogliomas underwent surgery alone (19 patients) or surgery plus postoperative radiation therapy (63 patients) between the years 1960 and 1982. The median survival time and the 5-, 10-, and 15-year survival rates for these 82 patients were 7.1 years, 54%, 34%, and 24%, respectively; these values were significantly different from those for an age- and sex-matched normal reference population. Univariate and multivariate survival analyses were performed on 13 possible prognostic factors including: patient age and sex; presence of seizures; site, size, side, computerized tomography (CT) enhancement, grade, and calcification of the tumor; and treatment (extent of surgical resection, lobectomy, radiation dose, and radiation field). Of these factors, tumor grade as classified by the Kernohan and St. Anne-Mayo methods was most strongly associated with survival. Patients with Grade 1 or 2 tumors by either grading method had a median survival time and 5- and 10-year survival rates of approximately 9.8 years, 75%, and 46%, respectively, compared to 3.9 years, 41%, and 20% for those with Grade 3 or 4 tumors. The extent of surgical resection was also associated with survival. The 19 patients who underwent gross total resection of their tumors had a median survival time and 5- and 10-year survival rates of 12.6 years, 74%, and 59%, compared to 4.9 years, 46%, and 23%, respectively, for the 63 who had subtotal resection. When comparing the 19 patients who underwent surgery alone with the 63 who had surgery plus postoperative radiation therapy, there did not appear to be a survival benefit to be gained from the addition of postoperative radiation therapy. However, the patients who had surgery alone tended to have gross total resections and lower tumor grades. Analysis of the subset of 63 patients who underwent subtotal resection alone or with radiation therapy showed that the median survival time and 5- and 10-year survival rates were: 2 years, 25%, and 25% for the eight patients with subtotal resection alone; 4.5 years, 39%, and 20% for the 26 patients with surgery and low-dose (< 5000 cGy) radiation therapy; and 7.9 years, 62%, and 31% for the 29 patients receiving surgery and high-dose radiation therapy (≥ 5000 cGy), respectively.

Key Words · oligodendroglioma · radiation therapy · grading system · outcome

Pure oligodendrogliomas are uncommon gliomas constituting only 4% of primary intracranial tumors. Typically, they occur in middle-aged adults who present with a several-year history of seizures, and are shown by computerized tomography (CT) scan or magnetic resonance (MR) image to be supratentorial, frequently calcified mass lesions. Treatment options for these as well as other ostensibly favorable slow-growing gliomas have included observation, with or without biopsy, and resection, with or without postoperative radiation therapy. In addition to controversies regarding appropriate therapy, questions have been raised about the impact of tumor grade on patient survival and hence on treatment decisions.

The following analysis is a retrospective review of our experience with patients having pure oligodendrogliomas who received either surgery alone or surgery and postoperative radiation therapy between the years 1960 and 1982, the “megavoltage era” of radiation therapy at the Mayo Clinic. The clinical and pathological issues previously alluded to will be examined with respect to our data. We will limit our literature review to modern series of pure oligodendroglioma, permitting comparison to our own series and drawing appropriate conclusions.

Clinical Material and Methods

All patients with supratentorial oligodendrogliomas and mixed oligoastrocytomas operated on during a 23-year period (1960 through 1982) were identified from the files of the Mayo Clinic Tissue Registry. Histological sections as well as clinical charts were then reviewed. Patients with either inadequate pathological material or...
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<table>
<thead>
<tr>
<th>Grade</th>
<th>Kernohan\textsuperscript{7,8}</th>
<th>St. Anne-Mayo\textsuperscript{9,10}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no cell anaplasia; mild cellularity; no mitoses; minimal endothelial or adventitial proliferation of vessels; broad transition zone to normal brain</td>
<td>none of the following criteria: nuclear abnormalities mites endothelial abnormalities necrosis</td>
</tr>
<tr>
<td>2</td>
<td>most cells normal; small numbers with anaplasia; mild cellularity; no mitoses; minimal endothelial or adventitial proliferation of vessels; less-broad transition zone</td>
<td>one of the above criteria</td>
</tr>
<tr>
<td>3</td>
<td>anaplasia in 5 of cells; increased cellularity; mitoses present; more frequent endothelial and adventitial proliferation of vessels; frequent regional necrosis; narrowed transition zone</td>
<td>two of the above criteria</td>
</tr>
<tr>
<td>4</td>
<td>extensive anaplasia, few &quot;normal&quot; appearing cells; marked cellularity; numerous mitoses; marked vessel proliferation; extensive necrosis; transition zone may be sharply demarcated</td>
<td>three or four of the above criteria</td>
</tr>
</tbody>
</table>

mixed oligoastrocytomas, those who did not survive at least 1 month postoperatively, and those lost to clinical follow-up study were excluded, leaving 82 patients who were deemed eligible for inclusion in the study.

Pathology

Based on a review of hematoxylin and eosin-stained material, patients were classified according to two grading systems, the classification of Kernohan, et al,\textsuperscript{7,8} and the St. Anne-Mayo method\textsuperscript{9,10} (Table 1). A separate and more detailed analysis of the pathological considerations for this study is in preparation. Tumors classified as Grades 1 or 2 by either system were considered to be "low-grade" tumors, and those of Grade 3 or 4 were designated as "high-grade." The Kernohan grade distribution of the 82 tumors was as follows: Grade 1, 17 patients (21%); Grade 2, 21 patients (26%); Grade 3, 22 patients (27%); and Grade 4, 22 patients (27%). Utilizing the St. Anne-Mayo grading system, the following distribution was obtained: Grade 1, eight patients (10%); Grade 2, 19 patients (23%); Grade 3, 39 patients (48%); and Grade 4, 16 patients (20%).

Patient Population

Characteristics of patients were obtained from their Mayo Clinic charts. The 82 patients consisted of 55 males (67%) and 27 females (33%) ranging in age from 4 to 88 years (median 44 years). Five patients (6%) were 18 years of age or younger. Seizures were present in 72 patients (88%). The median interval between the onset of symptom(s) and the tissue diagnosis was 2.9 years (range 3 days to 29.9 years).

Tumor Characteristics

Tumor characteristics including site, side, and size were identified from operative reports and imaging data, including plain skull x-ray films, ventriculograms, pneumoencephalograms, radionuclide brain scans, angiograms, and CT scans. Estimates of tumor size were made based on preoperative imaging data, the neurosurgeon's intraoperative assessment, or measurement of the gross pathological specimen. Computerized tomography scans were available for patients treated beginning in the mid-1970's. The presence or absence of calcification was variably assessed on plain skull x-ray films, CT scans, or histological sections.

The distribution of sites involved was as follows: frontal lobe only, 14 patients (17%); temporal lobe only, 18 patients (22%); parietal lobe only, nine patients (11%); and multiple lobes or other sites, 41 patients (50%). The overall sites of involvement were as follows: frontal lobe, 41 patients (50%); temporal lobe, 34 patients (42%); and parietal lobe, 26 patients (32%). The right side was involved in 44 patients (54%) and the left in 38 patients (46%). There were 17 "large" tumors (\geq 5 cm) (21%), 15 "small" tumors (< 5 cm) (22%), and 50 tumors in which the size was unknown or could not be accurately assessed. Of the 28 patients with CT, in 18 instances (64%) the tumor showed contrast enhancement and in 10 (36%) no enhancement was seen. Calcifications were present in 35 tumors (43%).

Treatment

The extent of surgical resection was determined solely from information in the operative report. No consideration was given to postoperative imaging studies. The surgical treatment of the 82 patients included gross total removal in 19 patients (23%) and subtotal removal (including one patient who had only a biopsy) in 63 patients (77%). A lobectomy was performed in 28 patients (34%), nine of whom underwent gross total removal of their tumor.

Information regarding postoperative radiation therapy was available for all patients. In several instances, patients were referred and irradiated elsewhere. As a result, some components of the complete postoperative radiation therapy information, including total dose, dose per fraction, overall treatment time, energy, or field utilized, were unavailable. Of 82 patients, 63 (77%) received postoperative radiation therapy, whereas 19 (23%) did not for the following reasons: irradiation was not indicated in view of gross total resection in 11 patients; the physician did not consider irradiation would be beneficial in four; patient refusal in two; and poor medical condition in two. Three patients received postoperative chemotherapy as part of Mayo Clinic brain-tumor clinical research protocols for patients with
high-grade gliomas: BCNU (carmustine), MCCNU (methyl lomustine), and vincristine were administered to one patient each.

The total radiation dose, calculated at the midplane for opposed fields and at the intersection of field centers for nonopposed fields, ranged from 1800 to 6480 cGy (median 5000 cGy). For the purposes of this analysis, the “low-dose group” will be defined as the 30 patients receiving less than 5000 cGy, and the “high-dose group” will be defined as the 33 patients receiving 5000 cGy or more. The median number of treatments, dose per fraction, and treatment days were 25 treatments, 200 cGy, and 25 days, respectively. Eight patients were treated with split-course radiation therapy, defined as a planned or unplanned treatment interruption of greater than 1 week. The extent of the radiation field in the 58 patients for whom this information was known is as follows: whole brain, 20 patients (34%), whole brain plus localized boost, nine patients (16%), and partial brain, 29 patients (50%).

Statistical Analysis

The endpoint used for this study was survival. Survival distributions were estimated with Kaplan-Meier curves. The expected survival curve for the group was calculated from the average survival data obtained from a large Midwestern population for a group of 82 people of the same age and sex distribution as the patients in this study. The log-rank test was used to assess the strength of association between survival time and single variables corresponding to factors thought to be prognostic for survival. To assess the association of survival with multiple patient, tumor, and treatment characteristics, forward and backward stepwise procedures for generating proportional-hazards general linear models were used, as proposed by Cox.

Results

Survival

At the time of the analysis, 54 patients (66%) had died, 50 from their disease and four of unrelated causes. The median follow-up time for the 28 patients who remain alive, including 23 without clinical or radiographic evidence of disease progression and five with recurrence, was 8.5 years (range 3.0 to 22.3 years). The median survival time and the 5-, 10-, and 15-year survival rates, calculated from the date of surgery, for the entire group of 82 patients were: 7.1 years, 54%, 34%, and 24%, respectively (Fig. 1 left). In contrast, when measured from the date of first symptoms, the median survival time and the 5-, 10-, and 15-year survival rates were 11.6 years, 83%, 61%, and 41%, respectively (Fig. 1 right). The observed survival distributions in Fig. 1 were significantly different from the corresponding age- and sex-matched expected survival curves of a normal reference population (p < 0.0001).

Univariate and Multivariate Survival Analyses

There were 13 possible prognostic factors for which adequate data were available to perform univariate and multivariate analyses of survival. Three of these were patient factors: age (< 20 years vs. 20 to 59 years vs. ≥ 60 years); sex (male vs. female); and seizures (present vs. absent). Five factors were related to the tumor: site (frontal vs. temporal vs. parietal), size (< 5 cm vs. ≥ 5 cm), side (right vs. left), calcification (present vs. absent), and CT enhancement (present vs. absent). The single pathological factor was tumor grade (Kernohan and St. Anne-Mayo low- vs. high-grade). Four treatment factors were: extent of surgical resection (gross total vs. subtotal), lobectomy (performed vs. not performed), radiation dose (none vs. < 5000 cGy vs. ≥ 5000 cGy), and radiation field (whole brain irradiation with or without localized boost vs. partial-brain irradiation).

Factors associated with improved survival were: age less than 20 years, a frontal or parietal tumor location, presence of calcification, no CT enhancement, Kernohan and St. Anne-Mayo low-grade tumor, gross total resection, and a radiation dose of 5000 cGy or more. Factors associated with inferior survival were: age 60 years or more and lobectomy performed. The other factors, including sex, seizures, temporal location, tumor size and side, surgery alone, or partial-brain irra-
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![Graphs showing survival data for patients by Kernohan grade (left) or St. Anne-Mayo grade (right). Tumors graded 1 or 2 on either side are classified as "low grade." Grade 3 or 4 tumors are considered "high grade." P values indicate significant differences between low- and high-grade tumors.]

Figure 2. Graphs showing survival data for patients by Kernohan grade (left) or St. Anne-Mayo grade (right). Tumors graded 1 or 2 on either side are classified as "low grade." Grade 3 or 4 tumors are considered "high grade." P values indicate significant differences between low- and high-grade tumors.

Of all the prognostic factors, tumor grade showed the most consistent and strongest association with survival in both univariate and multivariate analyses.

Figure 2 shows the association of Kernohan and St. Anne-Mayo grades with survival. The median time of survival and the 5- and 10-year survival rates of the 38 patients with Kernohan Grade 1 or 2 tumors were: 9.7 years, 76%, and 43% compared to 3.2 years, 36%, and 26% for the 44 patients with Kernohan Grade 3 or 4 tumors. The median survival time and the 5- and 10-year survival rates for the 27 patients with St. Anne-Mayo Grade 1 or 2 tumors were: 9.8 years, 73%, and 49%; those for patients with St. Anne-Mayo Grade 3 or 4 tumors were: 4.6 years, 45%, and 13%, respectively. Figure 3 shows the survival curves for the three patient subsets defined by age. For the six patients under 20 years of age, the survival rate at 5 years and beyond was 83%. The median survival time and the 5- and 10-year survival rates of the 69 patients between the ages of 20 and 59 were 7.3 years, 56%, and 32%, compared to 1.8 years, 14%, and 0% for the seven patients aged 60 years or older, respectively. Figure 4 shows the survival curves for the patients with and without gross total tumor resection. The 19 patients who underwent gross total resection had a median survival time and 5- and 10-year survival rates of 12.6 years, 74%, and 59% compared to 4.9 years, 46%, and 23% for the 63 patients who had subtotal resection.

In an attempt to assess the extent to which apparent treatment benefits might be subtly influenced by differences in the distributions of the prognostic factors (selection biases), the distributions of the various patient, tumor, and pathological prognostic factors among the treatment groups (surgery alone vs. surgery plus postoperative radiation therapy) were compared. Gross total resections were performed in 58% of the 19 patients who had surgery alone but in only 13% of those who received postoperative radiation therapy as well. Furthermore, the 19 patients who had gross total resections tended to be younger (21% < 20 years old) and have lower-grade tumors (37% low-grade) than the 63 who underwent subtotal resection (3% < 20 years old and 14% low-grade). These imbalances must be considered when interpreting Fig. 5, which shows the survival of all 82 patients compared with that of those treated with surgery alone and those treated with surgery plus postoperative radiation therapy. The median survival time and the 5- and 10-year survival rates of the 19 patients who underwent surgery only were 12.6 years, 74%,

![Survival curves for the 82 patients with oligodendrogliomas by age. Percentages denote 5- and 10-year survival rates in subpopulations younger than 20 years, between 20 and 59 years, and over 60 years.]

Figure 3. Survival curves for the 82 patients with oligodendrogliomas by age. Percentages denote 5- and 10-year survival rates in subpopulations younger than 20 years, between 20 and 59 years, and over 60 years.

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Survival curves for the 82 patients with oligodendrogliomas by treatment, including surgery alone or surgery plus postoperative low-dose (< 5000 cGy) or high-dose (≥ 5000 cGy) radiation therapy. Percentages are 5- and 10-year survival rates.

63%, and 55%, compared to 4.6 years, 46%, and 23% for the 30 patients receiving low-dose radiation therapy, and 9.0 years, 61%, and 36% for the 35 patients receiving high-dose radiation therapy. The association of postoperative radiation therapy with survival in the 63 patients who underwent subtotal resection is shown in Fig. 6. The median survival period of the eight patients who had subtotal resection alone was only 2 years, with 5- and 10-year survival rates of 25%, compared to 4.5 years, 39%, and 20% for the 26 patients receiving subtotal resection with low-dose irradiation, and 7.9 years, 62%, and 31% for the 29 patients undergoing subtotal resection and high-dose irradiation, respectively.

**Tumor Progression and Treatment Toxicity**

Tumor progression was documented clinically, radiographically (by CT or MR imaging), pathologically, or by some combination of these methods. The median time to tumor progression was 5.8 years. Survival rates, judging from the date of documented tumor progression, were 40% at 1 year and 24% at 2 years, with a median survival period of 7.2 months. The tumor recurred intracranially in all 50 patients whose disease progressed; one patient with a Grade 3 tumor was noted to have diffuse seeding of the cranial meninges at the time of reoperation. No patient developed spinal axis dissemination or distant metastases.

Twenty of the 50 patients who had tumor progression received further treatment. Four patients initially treated with surgery alone received radiation therapy at the time of tumor progression. Three of these patients died of further progression at 3 months, 2.5 years, and 6.5 years following radiation therapy; one patient remains alive 4.5 years after treatment. Five patients initially treated with surgery and postoperative radiation therapy underwent additional treatment with moderate-dose radiation therapy. All but one of these patients died within 5 months of retreatment; the sole survivor lived for 2.5 years. Five patients initially treated with surgery and postoperative radiation therapy underwent subsequent surgical resection; all five died within 15 months following reoperation. Six patients initially treated with surgery and postoperative radiation therapy were given additional treatment with chemotherapy alone. Five of these died, one of radiation necrosis of the brain stem at 3 months, and the others at 1 year, 16 months, 3.25 years, and 6.5 years from the date of recurrence; one patient remains alive nearly 10 years following treatment with 6 months of BCNU chemotherapy. The latter patient had presumed recurrence based on progressive neurological symptoms and signs, as well as an increasing mass of CT scan, but did not have pathological verification of tumor recurrence.

Major radiation sequelae occurred in three patients (5% of the 63 receiving radiation therapy), all of whom received whole-brain irradiation plus a localized boost to total doses of 5000, 5500, and 5580 cGy. All three also had histologically proven tumor progression. One patient died of brain-stem radiation necrosis verified at autopsy; this patient was treated at another institution and received 5500 cGy with conventional fractionation. The other two patients had typical radiation-induced dementias with progressively worsening memory, gait disturbance, and white matter changes seen on CT scans or MR images of the head.

**Discussion**

**Survival Data**

The survival data of patients with supratentorial oligodendrogliomas in this series are within the range observed in other series in the modern literature. The median survival time of 7.1 years, the 15-year survival rate of only 24%, as well as the observation that the survival of patients with oligodendrogliomas is significantly less than that of an age- and sex-matched reference population, do not support the notion that these tumors are "benign."

**Grading Methods**

Utilizing two established methods of grading gliomas, we identified tumor grade as the single
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most important prognostic variable in both univariate and multivariate analyses. The median survival time and the 5- and 10-year survival rates for patients with Kernohan or St. Anne-Mayo Grade 1 or 2 tumors were approximately 9.8 years, 75%, and 46%, compared to 3.9 years, 41%, and 20% for patients with Grade 3 or 4 tumors. Although several modern series have identified individual pathological factors as being prognostically significant, notably necrosis and hypervascularity, only one previously reported series found an association between tumor grade and survival times.

**Surgical Resection**

In our series, patients who underwent gross total resection had better survival times than those whose tumors were subtotally resected. The patients undergoing gross total resection also tended to be younger and have lower-grade tumors. The median survival time and the 5- and 10-year survival rates of patients who underwent gross total resection were 12.6 years, 74%, and 59%, respectively, compared to 4.9 years, 48%, and 26% for those having subtotal resection. In the series of Mark, et al., patients undergoing gross total resection had a median survival period of 3.8 years compared to 2.7 years in patients with less than gross total resection. Similarly, in Whitton and Bloom's series, patients who underwent total or subtotal resection had a 5-year survival rate of 84% compared to 41% for those who underwent either partial resection or biopsy. In the analysis of Lindegaard, et al., patients with only gross total resection had median survival times and 5- and 10-year survival rates of 7.0 years, 54%, and 38%; no improvement in survival with the addition of postoperative radiation therapy was noted. These data suggest that selected patients who undergo gross total resection may not need adjuvant radiation therapy.

**Postoperative Radiation Therapy**

When examining the results of those series comparing patients undergoing surgery alone and those with surgery plus postoperative radiation therapy, two opposing conclusions can be drawn: that there is no benefit to be gained from postoperative radiation therapy or, alternatively, that postoperative radiation therapy offers some benefit. In our series, when the favorable surgical subset of 19 patients undergoing gross total resection was excluded, there was a suggestion that patients receiving high-dose radiation therapy survived longer than those who had low-dose radiation therapy or surgery alone (Fig. 6). The median survival time and the 5- and 10-year survival rates of those patients undergoing high-dose radiation therapy were 7.9 years, 62%, and 31%, compared to 4.5 years, 39%, and 20% in the patients treated with low-dose radiation therapy, and 2.0 years, 25%, and 25% in those patients undergoing subtotal resection alone, respectively. Although Lindegaard, et al., also observed that radiation therapy appeared to be most beneficial in patients who had undergone less than gross total resection, they did not observe evidence of a dose response over a range of 20 to 60 Gy. Similarly, Bullard, et al., found no significant association of radiation dose with survival time.

The extent of the radiation field, whole-brain with or without a boost versus partial-brain, did not appear to have any prognostic value in our irradiated patients. In that all three radiation complications were observed in patients who received whole-brain irradiation, our recommendation is to treat only partial-brain fields encompassing the tumor, defined on CT scan or MR image, with a 2-cm margin. Until further information becomes available, doses of 5000 cGy or more are reasonable. Currently, our institution in cooperation with the North Central Cancer Treatment Group is involved in a prospective randomized study in which patients receive either 5040 or 6480 cGy in 180 cGy fractions to partial-brain fields. This study includes patients with all histological subtypes of infiltrative low-grade gliomas, including oligodendrogliomas, mixed oligoastrocytomas, and ordinary astrocytomas.

**Conclusions**

The survival periods of patients with supratentorial oligodendrogliomas, like those with other infiltrative gliomas, are significantly shorter than expected and are associated primarily with tumor grade. Selected patients who undergo gross total resection, particularly younger patients with low-grade tumors, may not require postoperative radiation therapy. All other patients appear to benefit from postoperative radiation therapy. At this time, candidates for radiation therapy should receive treatment to partial-brain fields with total doses of 5000 cGy or more.

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**References**


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