The Ki-67 labeling index as a prognostic factor in Grade II oligoastrocytomas

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Object. This study was conducted to determine whether proliferative tumor activity, as assessed using the Ki-67 immunohistochemical labeling index (LI), has prognostic utility for patients with Grade II oligoastrocytomas.

Methods. The study period spans the years 1988 to 2000. In a retrospective analysis, the authors selected cases with biopsy-proven diagnoses of Grade II oligoastrocytomas on initial presentation. The authors added new patients to this group and followed all patients prospectively at the University of Virginia Neuro-Oncology Center.

Twenty-three adult patients were followed for at least 1 year (median 40.3 months). Eleven patients with Grade II tumors and initial Ki-67 LIs less than 10% had a significantly longer median time to tumor progression (TTP, 51.8 months compared with 9.9 months) and a longer median survival (93.1 months compared with 16.1 months) than 12 patients with initial Ki-67 LIs of 10% or greater. Twelve patients with Grade III oligoastrocytomas had a mean TTP that was similar to the TTP of patients with Grade II tumors and high Ki-67 LIs (mean 4 months compared with 9.9 months) and duration of survival (13.3 months compared with 16.1 months).

Conclusions. Patients with a Grade II oligoastrocytoma and a Ki-67 LI of 10% or greater have a much shorter TTP and potentially a poorer disease prognosis than expected—more similar to patients with a Grade III oligoastrocytoma. These results indicate that in the future a measure of proliferative activity should be taken into consideration along with the World Health Organization grading criteria for oligoastrocytomas.

Key Words • mixed glioma • oligoastrocytoma • Ki-67 • outcome analysis • survival • disease progression

Oligoastrocytomas (mixed gliomas) consist of varying proportions of neoplastic astrocytic and oligodendroglial cells that can be diffusely intermingled or separated into distinct areas. Traditionally, oligoastrocytomas were grouped with oligodendrogliomas, but the recent revision of the WHO classification for tumors of the central nervous system creates a subgroup for oligoastrocytomas. Despite the fact that as an individual tumor type oligoastrocytomas have been raised in the consciousness of clinicians and pathologists, there are still many unsolved problems in the diagnosis, classification, and determination of malignancy, biological behavior, and treatment of these tumors. Currently, there are no definitive histopathological criteria for a diagnosis of oligoastrocytoma. Some investigators have defined an oligoastrocytoma as a tumor in which a second minor glial component, either astrocytic or oligodendroglial, exceeds 30% of the cells. Interpretation of the admixed cellular elements in these gliomas may be problematic, however, because of the great variability in the composition of the two cell populations within the tumor and the lack of a specific marker for oligodendroglial cells.

The two neoplastic cell populations may be focally or diffusely distributed. Oligoastrocytomas have been subdivided into a compact type and a diffuse type, according to the distribution of the two cellular elements. Distinct areas of each cytological component characterize the compact type, whereas the diffuse type has intermingled astrocytic and oligodendroglial cells (Fig. 1).

Criteria for grading low-grade and anaplastic oligoastrocytomas are as ambiguous as the histological definitions of these tumors. The WHO classification offers less precise guidelines for grading these tumors than for grading diffuse astrocytomas. Accordingly, a tumor is considered a Grade II oligoastrocytoma when it is “composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling the tumor cells in oligodendroglioma and diffuse astrocytoma,” there is “mild to moderate cellularity … with no or low mitotic activity,” and “necrosis and microvascular proliferation are absent.” On the other hand, Grade III oligoastrocytomas, that is, anaplastic oligoastrocytomas, are tumors with the “histological features of anaplasia, including nuclear atypia, cellular pleomorphism, and high mitotic activity. In addition, microvascular proliferation and necrosis may be present.”

Some histologically defined Grade II oligoastrocytomas do not fulfill the WHO criteria for Grade III oligoastrocytomas but display some histological features that are worri-

Abbreviations used in this paper: KPS = Karnofsky Performance Scale; LI = labeling index; PCV = procarbazine, lomustine, and vincristine; TTP = time to progression; WHO = World Health Organization.

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some and seem more “atypical” than the ones seen in low
grade tumors. Oligoastrocytomas with intermediate grading
features present a challenging issue for the neuropathologist
and neurooncologist because of uncertainty in their natural
history and biological activity.
Quantification of cellular proliferation has been shown to
relate to the length of survival in patients with “pure” oligo-
dendrogliomas and astrocytomas. Although proliferation
does not correlate with tumor invasion, the Ki-67 antibody
LI does correlate with tumor grade. The Ki-67 LI has been
found to be an independent predictor of TTP and length
of survival in patients with astrocytomas and those
with oligodendrogliomas. Another assessment of prolif-
eration, bromodeoxyuridine labeling, has also been corre-
lated with survival time in astrocytic tumors. The ex-
ception is a study in which it was shown that the Ki-67 LI
does not confer additional prognostic information for pa-
tients with recurrent gliomas, perhaps due to the influence
of treatment on tumor growth.
Outcomes for patients with oligoastrocytomas are sparse-
ly reported due to the relative rarity of this type of tumor.
Compared with other low-grade tumors, the prognosis for
oligoastrocytomas is extremely variable. In a study by Coons, et al., in which the authors did not distinguish
between oligodendrogliomas and oligoastrocytomas, the
Ki-67 LI varied most widely within Grade II tumors, de-
spite the fact that their histopathological findings were es-
tentially identical. In the 16 cases that deviated from the
expected pattern of patient survival, the Ki-67 LI helped
predict outcome more accurately. The median survival of
patients in the “low-grade, high Ki-67” group was the same
as patients with Grade III tumors (612 days compared with
576 days). In a similar study of 80 patients with astrocy-
tomas, a Ki-67 LI cutoff of 1.5% discriminated Grades II
and III tumors.
Given the relationship of Ki-67 to outcomes in Grade
II oligodendrogliomas and astrocytomas, we reasoned that
the Ki-67 LI may confer additional information in patients
with oligoastrocytomas. The aim of the current study was to
evaluate whether measuring proliferative tumor activity by
applying the Ki-67 LI to patients with histological Grade II
oligoastrocytomas would be a useful prognostic parameter
for these patients.

**TABLE 1**

*Summary of patients with Grades II and III oligoastrocytomas undergoing each treatment*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All Grade II</th>
<th>Grade II w/ Ki-67 LI &lt; 10%</th>
<th>Grade II w/ Ki-67 LI ≥ 10%</th>
<th>Grade III</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no. of patients</td>
<td>23</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>0.81</td>
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<tr>
<td>surgical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>biopsy only</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1 resection</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>&gt;1 resection</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01†</td>
</tr>
<tr>
<td>at diagnosis</td>
<td>14</td>
<td>5</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>at progression</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>at diagnosis</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>at progression</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>refused</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square test.
† Patients with Grade III tumors were more likely to undergo radiotherapy up front than patients with Grade II tumors.

**Clinical Material and Methods**

**Patient Population**

Twenty-three adult patients who initially presented with
Grade II oligoastrocytomas between 1988 and 2000 were
diagnosed (diagnosis confirmed by biopsy) and followed at
the University of Virginia Neuro-Oncology Center. Some of
these patients were initially selected by reviewing records
retrospectively; the others were added at admission. All pa-
tients were then followed prospectively. Data from 12 con-
secutive patients who initially presented with Grade III oligoastrocytomas during the same period were collected for a comparison (none of these Grade III tumors had progressed from Grade II lesions). Eight additional patients with Grade II oligoastrocytomas were excluded because sufficient tissue was no longer available from the initial sample for the Ki-67 analysis.

The remaining 23 patients were followed up for at least 1 year after the initial diagnosis (median follow up 40 months [range 12–175 months]). No patient was lost to follow up. This study was performed with the approval of the University of Virginia Human Investigations Committee.

Charts were reviewed for characteristics of clinical treatment and patient outcomes by raters (M.E.S. and E.F.) blinded to the Ki-67 LIs of the patients. Dates of death were verified by cross-listing with the Virginia State Death Registry, which is accessed through the University of Virginia Clinical Data Repository.

Twelve men and 11 women had Grade II oligoastrocytomas. The median age of these patients at presentation was 37.6 years (range 22–59 years). All patients had a KPS score of 90 or greater at presentation. Each patient presented with one or more of the following symptoms: seizures (22 patients), headaches (10 patients), neurocognitive problems (six patients), lateralized motor changes (four patients), balance problems (four patients), and vision changes (two patients). Treatment is summarized in Table 1.

Neuropathological Methods

All cases were reviewed by a single neuropathologist (M.B.S.L.) who was blinded to the clinical outcomes of the patients. Diagnoses were evaluated according to the guidelines set forth in the WHO classification of tumors of the nervous system.31

The baseline initial Ki-67 LI was obtained by performing an immunohistochemical analysis with the monoclonal antibody MIB-1 (dilution 1:200; Immunotech, Marseilles, France), which “recognizes” the antigen Ki-67. The antigen retrieval technique was performed. Briefly, sections of tumors and control specimens were incubated in a 0.01 mmol/L sodium citrate buffer (pH 6) and then microwaved for three 5-minute intervals at 100% maximum power in a 700-W microwave oven. All slides were stained using the automated Ventana Nexes IHC stainer (Ventana Medical Systems, Tucson, AZ). In all cases, 1000 to 2000 nuclei were counted and the percentage of positive Ki-67 nuclei was assessed (Fig. 2).

Statistical Analysis and Epidemiological Methodology

The endpoints used for the study were time from initial surgery to TTP and time from the initial surgery to the death of the patient (survival time). In the univariate survival analysis we used Kaplan–Meier curves to estimate the distributions and log-rank tests to assess differences between levels of potential prognostic variables. Multivariate survival analyses (for example, Cox proportional hazards models) were not performed because the total number of patients was not sufficiently large to allow an analysis of more than one predictor at a time.17 The possible explanatory variables that were analyzed included the baseline Ki-67 LI and established predictors of poor outcomes including higher tumor grade,31 older patient age at diagnosis36,41,17,49 (comparison of < 40 and ≥ 40 years based on the median age and using age as a continuous variable), and extent of resection.36,45 Patients who are independent in their activities of daily living at a baseline KPS score of 70 or higher face a better prognosis than patients needing physical assistance.36 Because there were no baseline differences in the patients’ levels of independence (all patients had a baseline KPS Score ≥ 90), this variable was not analyzed further. The effect of treatment (surgery, radiotherapy, and chemotherapy) was analyzed. Data were stratified by tumor grade when noted.

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**Fig. 2.** Photomicrographs demonstrating Ki-67 immunohistochemical staining in two oligoastrocytoma specimens, one with a relatively low Ki-67 LI (left) and the other with a higher Ki-67 LI (right). Original magnification × 20.
Nevertheless, a more conservative division of the Ki-67 LI, separating 10% or less from 10% or greater was thus chosen to separate the groups maximally. Thus, a cutoff of the Ki-67 LI at less than 10% and 10% or greater was used to separate the high and low Ki-67 LI groups. Therefore, in the current analysis, initial Ki-67 LIs of 5, 10, 15, and 20% were correlated with the TTP and survival variables.

Table 2 shows outcomes for patients with Grade II oligoastrocytomas combined, Grade II tumors split by low and high Ki-67 LIs, and Grade III tumors. Patients with Grade II oligoastrocytomas in whom the initial Ki-67 LIs were low had a statistically significantly longer median TTP (51.8 months) than those in whom the Ki-67 LI was high (9.9 months; p = 0.0007; Fig. 3). The median duration of survival was also shorter in patients with high Ki-67 LIs (16.1 months) than in patients with low Ki-67 LIs (93.1 months), although this difference is not statistically significant (Fig. 4). The lack of a significant difference between these groups likely relates to the relatively few patients with high Ki-67 LIs who have died thus far (three of 12 patients; Table 3); extreme caution should therefore be taken in interpreting the survival data.

### Table 2: Relationships among tumor grade, patient age, Ki-67 LI, TTP, and survival time

<table>
<thead>
<tr>
<th>Factor</th>
<th>All Grade II</th>
<th>Grade II w/ Ki-67 LI &lt; 10%</th>
<th>Grade II w/ Ki-67 LI ≥ 10%</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>23</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>med age (yrs)</td>
<td>37.6</td>
<td>33.3</td>
<td>35.2</td>
<td>60.1</td>
</tr>
<tr>
<td>mean Ki-67 LI (%)</td>
<td>11.0</td>
<td>6.4</td>
<td>16.0</td>
<td>25.3</td>
</tr>
<tr>
<td>med follow up in mos (range)</td>
<td>(12–175)</td>
<td>(40–175)</td>
<td>(12–54)</td>
<td>(2–66)</td>
</tr>
<tr>
<td>med TTP in mos (range)</td>
<td>25.1</td>
<td>51.8</td>
<td>9.9</td>
<td>4.0</td>
</tr>
<tr>
<td>med survival in mos (range)</td>
<td>39.1</td>
<td>93.1</td>
<td>16.1</td>
<td>13.3</td>
</tr>
<tr>
<td>med time from progression to death in mos (range)</td>
<td>13.0</td>
<td>29.0</td>
<td>2.4</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*med = median.

### Results

In previous studies investigators have used various percentages of Ki-67 LI to differentiate groups prognostically. In one series of patients with Grades I through IV oligodendrogliomas (Kernohan grading system) a Ki-67 LI of less than or greater than 5% significantly discriminated the patients’ survival. Nevertheless, a more conservative division of the Ki-67 LI, separating 10% or less from 10% or greater has been shown to be an independent prognostic factor in predicting TTP in Grades II, III, and IV astrocytomas. Therefore, in the current analysis, initial Ki-67 LIs of 5, 10, 15, and 20% were correlated with the TTP and survival variables to determine the cutoff that best discriminated the two groups. The 10% cutoff showed a moderately high correlation with TTP and duration of survival (Spearman r = 0.59 and 0.62, respectively), whereas other correlations between the groups likely relates to the relatively few patients with high Ki-67 LIs who have died thus far (three of 12 patients; Table 3); extreme caution should therefore be taken in interpreting the survival data.

### Time to Progression and Duration of Survival

Table 2 shows outcomes for patients with Grade II oligoastrocytomas combined, Grade II tumors split by low and high Ki-67 LIs, and Grade III tumors. Patients with Grade II oligoastrocytomas in whom the initial Ki-67 LIs were low had a statistically significantly longer median TTP (51.8 months) than those in whom the Ki-67 LI was high (9.9 months; p = 0.0007; Fig. 3). The median duration of survival was also shorter in patients with high Ki-67 LIs (16.1 months) than in patients with low Ki-67 LIs (93.1 months), although this difference is not statistically significant (Fig. 4). The lack of a significant difference between these groups likely relates to the relatively few patients with high Ki-67 LIs who have died thus far (three of 12 patients; Table 3); extreme caution should therefore be taken in interpreting the survival data.

### Effect of Treatment

As shown in Table 1, patients did not receive uniform treatment in this series, due to changes in practice over time. A chi-square frequency analysis, however, demonstrated that the only significant difference in treatment given to patients was that patients with Grade III tumors were more likely to undergo radiation treatment up front at diagnosis than patients with Grade II tumors (p = 0.01). Qualitatively, it was noted that patients recently found to have a Grade II oligoastrocytoma and a high Ki-67 LI received more aggressive, up-front radiotherapy and chemotherapy; however, a chi-square analysis did not show significant differences between the groups for the likelihood of receiving either radiotherapy (p = 0.295) or chemotherapy (p = 0.219) at diagnosis rather than at progression. Therefore, it is unlikely in this sample that the differences in TTP in the Grade II Ki-67 groups were due to differences in treatment. If there is a benefit of earlier treatment, this would become apparent in a longer-term analysis.

### Relationship of Tumor Grade and Patient Age

In a univariate survival analysis focusing on patients younger than 40 years of age and those 40 years and older, there was no significant difference in TTP or survival in patients with Grade II tumors. Patients with Grade III tumors were significantly older than those with Grade II tumors, and age 40 years and older was a significant factor when all patients (Grades II and III) were combined (p = 0.011). An analysis of tumor grade demonstrated all Grade II tumors with high Ki-67 LIs (p = 0.001 compared with Grade III tumors). Cum = cumulative; F/up = follow up.

### FIG. 3. Graph depicting the analysis of TTP. Log-rank tests indicate no difference between Grade III oligoastrocytomas and Grade II oligoastrocytomas with high Ki-67 LIs. The TTPs in both types of tumor are significantly different from that in Grade II oligoastrocytomas with low Ki-67 LIs (p = 0.0003 compared with Grade II tumors with high Ki-67 LIs; p = 0.001 compared with Grade III tumors). Cum = cumulative; F/up = follow up.

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![Graph showing the analysis of duration of survival.](image)

**Fig. 4.** Graph showing the analysis of duration of survival. Logrank tests indicate no difference between Grade III oligoastrocytomas and Grade II oligoastrocytomas with high Ki-67 LIs (p = 0.08). There is also no significant difference between Grade II oligoastrocytomas with low Ki-67 LIs and those with high Ki-67 LIs (p = 0.11), although Grade II tumors with low Ki-67 LIs are significantly different from Grade III tumors (p < 0.002). The Ki-67 LI is a prognostic factor in Grade II oligoastrocytomas.

formed. In the combined sample of Grades II and III patients, the initial Ki-67 LI was significantly correlated \((r = 0.53, p < 0.001)\) with presenting age. Within Grade II tumors, however, the initial Ki-67 LI was not correlated with the patients’ presenting age \((r = 0.06, p = 0.771)\).

**Discussion**

According to the most recent updates from the Central Brain Tumor Registry of the United States, composed of 11 collaborating state cancer registries that reported incidence data from 1990 to 1994, oligoastrocytomas account for 1% of all reported brain tumors. Patients with these tumors have a mean age of 40 years at diagnosis, a younger average age than patients in whom astrocytomas are initially diagnosed. According to Surveillance, Epidemiology, and End Results data covering the period 1973 to 1996, patients with oligoastrocytomas have a relative survival rate of 73.7% at 2 years, 57.7% at 5 years, and 40.5% at 10 years (adjusted for expected survival in the US population for age, sex, and calendar year). Nevertheless, this report includes 20 years of data collected before 1993 and, thus, the actual make-up of the oligoastrocytoma patient population according to current WHO criteria is unknown.

Predictors of poor survival in patients with oligoastrocytomas have included the following: older patient age, \(^{11,12,26}\) subtotal rather than gross-total resection, \(^{11,12,14}\) larger tumor volume, \(^{26}\) poor performance status, \(^{26,41}\) and both female \(^{11,26}\) and male sexes. \(^{2} \) Survival is extremely variable in patients with low-grade oligoastrocytomas. One study of 43 Grades I and II oligoastrocytomas (Kernohan grading system) found that tumor grade did not predict the duration of survival. \(^{30}\) Another study provided evidence indicating that tumor grading and survival were not correlated in 20 patients with low-grade oligoastrocytomas; four of 20 patients died within 5 years, whereas one of 10 patients with Grade III oligoastrocytomas died within 5 years. A literature review did not uncover data on survival or TTP in patients with mixed oligoastrocytomas regardless of whether the tumors were Grade II or III. Our study provides survival and TTP data for these tumors. For patients with Grade II mixed oligoastrocytomas the TTP was 25.1 months and the mean survival time was 39.1 months; for patients with Grade III lesions the TTP was 4 months and the mean survival time was 13.3 months (Table 2).

In our series, the initial Ki-67 LI for Grade II oligoastrocytomas was investigated as a potential prognostic parameter and was found to be unexpectedly high in patients with Grade II tumors. In comparison with previously reported Ki-67 LIs for oligodendrogliomas, the mean Ki-67 LI for Grade II oligoastrocytomas in our series was more consistent with high-grade oligodendrogliomas than Grade II oligodendrogliomas. The Ki-67 LI for our Grade II oligoastrocytomas was also comparable to previously reported values for anaplastic astrocytomas and glioblastomas multiforme, unlike the Ki-67 LIs for Grade II astrocytomas, which have been reported to range from 0.88 \(^{11}\) to 2.2% \(^{14}\). Thus, in our series, the Ki-67 LI, TTP, and potential duration of survival in patients with Grade II oligoastrocytomas with high Ki-67 LIs are more consistent with those associated with Grade III tumors. \(^{1,10,12}\) This result could not be explained by the effects of patient age \(^{34}\) in our study population. Therefore, the Ki-67 LI appears to be a prognostic parameter for patients with oligoastrocytomas.

Optimal treatment of oligoastrocytomas is difficult to evaluate because of their low incidence and the small numbers of tumors in reported series. Most studies have combined patients into groups that included both oligodendrogliomas and oligoastrocytomas, which was a bias of classification prior to 1993. Low-grade mixed gliomas have been historically treated with surgery, radiotherapy, or observation. A recent retrospective report of 106 patients with low-grade oligodendrogliomas (77 patients) and oligoastrocytomas (29 patients) concluded that there were no apparent survival differences between immediate and deferred treatment or among choices of initial therapy. Because of the toxicities associated with chemotherapy and radiotherapy, the authors recommended deferring treatment until “clinically necessary.” Recently a report on 290 patients with low-grade gliomas from the European Organization for Research and Treatment of Cancer and the Medical Research Council study on patients given radiotherapy immediately postoperatively and those given it at progression was pub-
lished.\textsuperscript{21} At a median of 5 years, patients treated with upfront radiotherapy had a significantly shorter TTP than patients treated at progression (44% compared with 37% of patients treated at progression) albeit with a relatively small effect size. There was no difference in overall survival at 5 years (63% of patients compared with 66%),\textsuperscript{2} again suggesting that waiting until progression before undergoing radiotherapy may be a reasonable option.

Reported median survival times for anaplastic oligoastrocytoma after surgery and radiation range from 30 to 65 months.\textsuperscript{3} There is increasing evidence that oligoastrocytomas are chemosensitive.\textsuperscript{16} Patients with a “pure” oligodendrogloma demonstrate a greater response to chemotherapy than patients with oligoastrocytomas.\textsuperscript{21} Among patients with Grade III oligoastrocytomas treated with temozolomide at recurrence, the objective response rate was 22.2% compared with a response rate of 48.7% in patients with anaplastic oligodendrogliomas.\textsuperscript{3} Kim and colleagues\textsuperscript{22} reported that 89% of patients with Grade III or IV oligoastrocytomas had at least a partial response to PCV, although tumor shrinkage was less frequent and clearly less durable than that found in patients with Grade III oligodendrogliomas. Boiardi, et al.,\textsuperscript{3} reported an improvement in TTP and survival time (compared with previous studies in the literature) for 32 patients with anaplastic oligoastrocytomas treated with surgery, radiotherapy, and neoadjuvant cisplatin and camptothecin chemotherapy, although only the extent of resection significantly predicted longer survival. A recent randomized, controlled clinical trial (Radiation Therapy Oncology Group, RTOG 94-02) for pure and mixed anaplastic oligodendrogliomas has shown that PCV plus radiation treatment significantly improved progression-free survival when compared with radiation treatment alone, but median survival was not improved.\textsuperscript{4}

Future prognostic studies of oligoastrocytomas will need to incorporate the results of molecular cytogenetic studies. Approximately one third of oligoastrocytomas demonstrate chromosome 1p deletions.\textsuperscript{19,\textsuperscript{24}} This deletion confers a favorable prognosis both when the initial treatment is radiotherapy and when PCV chemotherapy is used at the time of recurrence.\textsuperscript{15} The other very powerful finding of the RTOG 94-02 study was that patients with chromosome 1p/19q deletions lived much longer (median survival not yet reached) than patients without this chromosomal deletion (median survival 2.8 years).\textsuperscript{3}

Conclusions

Prognosis and treatment are particularly difficult to discuss with patients with Grade II oligoastrocytomas whose tumors have some signs of anaplasia but do not meet the WHO criteria for Grade III oligoastrocytomas. There is significant uncertainty as to whether such tumors will behave in an indolent or aggressive fashion, making accurate discussions of prognosis and treatment difficult. Our results indicate that measurement of proliferative activity may be worthwhile in the differentiation between a low-grade and a high-grade oligoastrocytic tumor. Based on our preliminary data we suggest that patients with a histological WHO Grade II oligoastrocytoma and a high Ki-67 LI have a much poorer prognosis, at least in terms of TTP, than would be expected from a Grade II tumor. Indeed, in one recent report of patients with WHO Grade II astrocytomas, tumor samples that displayed increased cellularity, nuclear atypia, and a marked proliferative potential (Ki-67 LI > 10%) were classified as WHO Grade III.\textsuperscript{12} At our institution, the pathologists readily alert clinicians that a high Ki-67 LI predicts more aggressive behavior. Clearly, our results require confirmation in a larger sample with a longer follow-up review. Given these data, however, we feel justified to recommend more aggressive surgical treatment when possible and consideration of radiotherapy and chemotherapy early in the postsurgical course.

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