Molecular Subtypes of Anaplastic Oligodendroglioma: Implications for Patient Management at Diagnosis

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ABSTRACT

Purpose: In a prior study of anaplastic oligodendrogliomas treated with chemotherapy at diagnosis or at recurrence after radiotherapy, allelic loss of chromosome 1p correlated with better chemotherapeutic response and overall survival. However, in this group of patients in whom therapeutic management was not uniform, loss of 1p did not identify all chemosensitive tumors, nor did all patients whose tumors harbor a 1p loss have long survival.

Experimental Design: To clarify the clinical relevance of molecular genetic testing at the time of diagnosis for patients with anaplastic oligodendrogliomas, we studied a larger, more homogeneous group of 50 patients with histologically defined anaplastic oligodendrogliomas treated with a chemotherapeutic regimen as the principal initial therapy.

Results: We demonstrate that these tumors can be divided genetically into four therapeutically and prognostically relevant subgroups. Patients whose tumors have combined but isolated losses of 1p and 19q have marked and durable responses to chemotherapy associated with long survival, with or without postoperative radiation therapy. Other tumors with chromosome 1p alterations also respond to chemotherapy, but with shorter duration of response and patient survival. Tumors lacking 1p loss can also be divided into two subgroups: those with TP53 mutations, which may also respond to chemotherapy but recur quickly, and those without TP53 mutations, which are poorly responsive, aggressive tumors that are clinically and genotypically similar to glioblastomas.

Conclusions: These data raise the possibility, for the first time, that therapeutic decisions at the time of diagnosis might be tailored to particular genetic subtypes of anaplastic oligodendroglioma.

INTRODUCTION

Malignant gliomas are the most common type of primary brain tumor, with ~12,000 new cases diagnosed each year in the United States (1). For nearly a century, malignant gliomas have been classified on the basis of their histological appearance as astrocytomas (including glioblastomas), oligodendrogliomas, ependymomas, or mixed gliomas. For each type, surgical resection and radiation therapy have been the mainstays of treatment. Cytotoxic drugs have had a relatively minor therapeutic role because responses to chemotherapy generally have been infrequent, brief, and unpredictable. The only notable exception has been tumors with oligodendrogliomatous histology, which have a greater likelihood of radiographic response to chemotherapy. Unfortunately, the microscopic distinction between high-grade oligodendrogliomas, which often are chemosensitive, and glioblastomas, which are notoriously recalcitrant to the chemotherapies used at present, is problematic because these two types of malignant glioma may share histological features such as small cells, vascular proliferation, and necrosis. Such problems raise the question of whether histological diagnosis can be refined in a clinically useful way. Clearly, more precise identification of chemosensitive tumors and potential long-term survivors at diagnosis would afford greater flexibility in initial treatment decisions for such patients, and improved identification of resistant tumors might justify prescribing novel treatments at diagnosis for patients with a poor prognosis (2). With a rational basis for delivering or withholding chemotherapy, effective treatments will be appropriately prescribed, and ineffective, toxic, and costly treatments specifically avoided.

Allelic loss of chromosomal arm 1p is emerging as a marker of chemotherapeutic response (3) and long survival (3, 4) in patients with histologically defined anaplastic oligodendrogliomas. Furthermore, 1p loss may also identify other treatment-sensitive malignant gliomas, including rare glioblastomas (5). However, 1p loss does not identify all chemosensitive anaplastic oligodendrogliomas, nor do all patients whose tumors harbor 1p loss have long survival, although those with chromosome 1p and 19q loss may have particularly favorable outcomes (4). In addition, prior studies included patients treated with a variety of chemotherapeutic and radiotherapeutic regimens (3, 4). For example, in our previous study, some patients were treated with chemotherapy at diagnosis, whereas others were treated with radiation therapy at diagnosis and only received chemotherapy at recurrence (3). The practical utility of assess-
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neuropathologists, blinded to the genetic results, as anaplastic neously managed group than studied previously. Therefore represents a substantially larger and more homoge-

tional clinical and genetic parameters on these cases, together previous study (3), the present series reports analysis of addi-

follow-up time from diagnosis was 107 months (minimum, 7 months). All nonresponding tumors had been treated with PCV. Median response to chemotherapy, with 10 complete responses. 11 were not irradiated. At the start of chemotherapy, 38 tumors with 10q amplification, 7/50 (14%). Ring enhancement at diagnosis 29/50 (58%). 10q loss, using similar single-strand conformation polymorphism analysis and sequencing approaches (9). Homozygous deletion of the CDKN2A gene and PTEN gene were evaluated by comparative multiplex PCR (10, 11) and EGFR gene amplification by differential PCR (12).

viability categories or from formalin-fixed, paraffin-embedded sections of therapy trials for oligodendroglioma.

sional DNA/tumor DNA pairs using microsatellite markers on 1p36.3 (D19S219, D19S112, D19S412, and D19S596), 10q23-24 (D10S185 and D10S2491, near PTEN), and 10q25-26 (D10S587; Refs. 3, 7). Exons 5–8 of the TP53 gene were screened for mutation by single-strand conformation polymorphism analysis and direct sequencing (8). Exons 1–9 of the PTEN gene were screened for mutations in tumors with 10q loss, using similar single-strand conformation polymorphism analysis and sequencing approaches (9). Homozygous deletion of the CDKN2A gene and PTEN gene were evaluated by differential PCR (12).

**Materials and Methods**

Clinical Parameters. The study included 50 patients treated at the London Regional Cancer Center with histologically confirmed anaplastic oligodendrogliomas in whom chemotherapy was used as an integral part of an overall patient management strategy from diagnosis. The cases are detailed in Table 1. Forty-eight patients received combination chemotherapy with PCV.1 1 received carmustine (BCNU), and 1 received temozolomide. Thirty-four of these patients received radiation therapy after chemotherapy (as consolidation or at recurrence), 5 received radiation therapy concurrent with chemotherapy, and 11 were not irradiated. At the start of chemotherapy, 38 tumors were assessable for radiographic response to chemotherapy: 25 (66%) responded to chemotherapy, with 10 complete responses. All nonresponding tumors had been treated with PCV. Median follow-up time from diagnosis was 107 months (minimum, 7 months). Although half of these patients were included in a previous study (3), the present series reports analysis of additional clinical and genetic parameters on these cases, together with longer follow-up times, and excludes patients treated with chemotherapy only at recurrence after radiation therapy. This therefore represents a substantially larger and more homogeneously managed group than studied previously.

All 50 tumors were classified and graded by at least two neuropathologists, blinded to the genetic results, as anaplastic oligodendrogliomas, WHO grade III (Fig. 1; Ref. 6). Cases with definite astrocytic tumor components were considered oligoastrocytomas and excluded. Thirty-four tumors showed radiographic contrast enhancement, with 9 displaying ring enhancement. These investigations have been approved by the Massachusetts General Hospital Subcommittee on Human Studies and the Review Board for Health Science Research Involving Human Subjects at the University of Western Ontario. None of the patients in this analysis are included in ongoing chemotherapy trials for oligodendroglioma.

**Molecular Genetic Analysis.** Tumor DNA was extracted from microdissected formalin-fixed, paraffin-embedded sections; constitutional DNA was extracted from blood lymphocytes or from formalin-fixed, paraffin-embedded sections of adjacent, uninvolved brain or other tissues (7). Allelic chromosomal loss was assessed by loss of heterozygosity assays in constitutional DNA/tumor DNA pairs using microsatellite markers on 1p36.3 (D18S2734, D18S199, and D18S508), 19q13.3 (D19S219, D19S112, D19S412, and D19S596), 10q23-24 (D10S185 and D10S2491, near PTEN), and 10q25-26 (D10S587; Refs. 3, 7). Exons 5–8 of the TP53 gene were screened for mutation by single-strand conformation polymorphism analysis and direct sequencing (8). Exons 1–9 of the PTEN gene were screened for mutations in tumors with 10q loss, using similar single-strand conformation polymorphism analysis and sequencing approaches (9). Homozygous deletion of the CDKN2A gene and PTEN gene were evaluated by differential PCR (12).

**Statistical Analysis.** The primary goal of the analysis was to test the a priori hypothesis that a particular grouping of the patients according to molecular genetic events is associated with chemotherapeutic response, duration of response to chemotheraphy, and overall survival. Secondary analyses were undertaken to investigate the effects of all of the observed genetic alterations, without regard for the a priori hypothesis. Associations among all of the observed genetic alterations were examined, and the effects of the genetic alterations on therapeutic response, duration of response, and survival were investigated. The added effects of nongenetic features were also examined.

Odds ratios and tetrachoric correlations were used to measure the pair-wise associations among genetic alterations (13). Fisher’s exact test was used to compare response rates, logistic regression was used to model response, and Cox proportional hazard regression was used to model duration of response and survival. Duration of response and survival were both censored at the time of last follow-up. Classification trees were constructed using CART (14) to best group the genetic alterations with respect to response. All reported P values are two-sided.

Response to chemotherapy was defined radiographically as a decrease in tumor size of ≥50% (15). Care was taken to control for steroid effects and other false-positive responses (16, 17). For comparison, the absence of disease progression 6 months after the start of chemotherapy was considered as an alternative definition of response (18).

Duration of response was measured from the start of chemotheraphy to the first sign of radiological or clinical progression. Duration of response was also analyzed using the alternative definition of response, but with measurement from 6 months...
after the start of chemotherapy. Survival was measured from diagnosis. The analyses were refined further by stratifying for the starting time of radiation therapy. This was done through the use of time-dependent strata (19), defined by whether the patient had started radiation therapy.

RESULTS

Molecular Genetic Findings and Groups. The molecular genetic results are listed in Table 1 and demonstrate that this series of anaplastic oligodendrogliomas is genotypically similar to those of other published series (3, 6, 9, 20–23). Allelic losses of 1p and 19q were positively associated with one another \((P < 0.001)\), whereas loss of 10q, \(PTEN\) alteration, \(TP53\) mutation, \(EGFR\) amplification, and \(CDKN2A\) deletion were negatively associated with 1p and 19q loss and positively associated with each other. These associations suggested the presence of at least two groups of tumors: those with 1p and 19q loss, and those with the other genetic alterations. However, because not all patients whose tumors display 1p loss have long survival and not all chemosensitive oligodendrogliomas harbor 1p loss (2–5), we postulated that these cases could be further subdivided. For example, it has been suggested that patients whose tumors have combined 1p and 19q loss have longer survivals (4); we therefore sought to determine whether combined 1p and 19q loss also predicted response to chemotherapy and duration of chemotherapeutic response. In addition, a number of studies have suggested that \(TP53\) status may be related to clinical course in patients with gliomas (24, 25), directing interest toward \(TP53\) status as a predictor in our cases. On the basis of such \(a priori\) possibilities, we postulated that cases with 1p loss could be separated into those with combined 1p and 19q loss only (combined, isolated 1p/19q loss; genetic group 1) and those with 1p loss that either lacked 19q loss or had one of the other genetic alterations (“other” 1p loss; group 2) and that those cases lacking 1p loss could also be separated into those with \(TP53\) mutations (group 3) and those lacking \(TP53\) mutations, which were tumors that often had alterations of the other genes (group 4; Fig. 2). When we used these definitions, only 1 of the 50 patients could not be classified because chromosome 10q loss was not evaluable.

Analyses of Chemotherapeutic Response by Molecular Genetic Parameters. Rates of neuroradiological response to chemotherapy were significantly different among the four groups \((P < 0.0001)\), with those of groups 1 and 2 significantly higher than those of groups 3 and 4 \((P < 0.0001; \text{Fig. } 2)\). All 21 neuroradiologically evaluable tumors with 1p loss in groups 1 and 2 had visible responses to chemotherapy, whereas radiographic responses were observed in 33\% of tumors in group 3 and only 18\% in group 4. Similar differences in rates of response to chemotherapy were also noted when the alternative definition of response was used; all responders in groups 1 and 2, except for one, remained progression free 6 months after starting chemotherapy, compared with 75\% in group 3 and only 15\% in group 4. Although group 3 had a higher response rate than group 4, the difference was not statistically significant, most likely because of the small number of patients; the approximate power for this comparison using Fisher’s exact test was <2\%.

Classification trees were constructed to find the best data-derived groupings of the genetic alterations with respect to
response. When we used radiographic response, patients were not subdivided beyond their 1p loss status (misclassification error rate, 3 of 37). However, when we used the alternative definition of response, patients were divided into three genetic groups: those with 1p loss, those without 1p loss and with TP53 mutation, and those without 1p loss and without TP53 mutation (misclassification error rate, 4 of 47). These groups correspond to the hypothesized groups 1 and 2 combined, group 3, and group 4, respectively.

The predictive power of each of the genetic alterations for response was further assessed via logistic regression (Table 2). In addition to 1p loss, which was a perfect predictor of response, response was negatively associated with 10q loss, PTEN mutation, CDKN2A deletion, and EGFR amplification, and positively associated with 19q loss. These relationships were also demonstrated using the alternative definition of response. Multivariate models were not fit because of the dominance of 1p loss in predicting response and the small number of patients without 1p loss.

**Analyses of Duration of Response by Molecular Genetic Parameters.** Patients whose tumors had combined, isolated losses of 1p and 19q (group 1) had a significantly longer duration of radiographic response to chemotherapy than patients in genetic group 2 (P = 0.004). They also had a significantly longer duration of response than patients in genetic groups 3 and 4 (P = 0.004). A significantly different duration of response was not detected between patients in group 2 and patients in groups 3 and 4 (P = 0.757). These results were also seen when we stratified additionally for the starting time of radiation therapy and when we used the alternative definition of response. The median duration of response for group 1 was >31 months, compared with 10.6 months for group 2, 6.7 months for the 2 (of 6) responders in group 3, and 5.0 months for the 2 (of 11) responders in group 4 (Fig. 2).

In Cox models of the influence of individual genetic alterations on duration of response to chemotherapy, the hazard of progression was significantly decreased for patients with 1p and 19q loss and was significantly increased for patients with 10q loss, PTEN alteration, and CDKN2A deletion (Table 2). Similar results were obtained when time-dependent strata were introduced to adjust for variable start of radiation therapy. Likewise, similar results were obtained for the alternative definition of response. Multivariate models are not reported because of the small numbers in this analysis.

**Analyses of Overall Survival by Molecular Genetic Parameters.** For patients in group 1, the median survival time from diagnosis was >123 months. In contrast, patients in groups 2 and 3 had median survivals of ~70 months, and patients in group 4 had a median survival of only 16 months (Figs. 2 and 3). Each of the pairwise comparisons of survival among the four hypothesized groups was statistically significant, with the exception of the comparison between groups 2 and 3. Identical results were obtained when time-dependent strata were used to adjust for the variable starting time of radiation therapy.

In Cox models of survival, the hazard of death was significantly decreased for patients with 1p and 19q loss, and it was significantly increased for patients with 10q loss, PTEN alteration, CDKN2A deletion, and EGFR amplification (Table 2). In a multivariate model, selected using backward elimination, only 1p loss and CDKN2A deletion remained significant predictors at the 0.05 level. Loss of 1p predicted increased survival (hazard ratio, 0.13; P = 0.0002), and CDKN2A deletion predicted decreased survival (hazard ratio, 5.71; P = 0.001).

**Addition of Nongenetic Parameters in Predicting Response and Survival.** Nongenetic parameters (patient age, KPS, neuroradiological enhancement, and ring enhancement) were included in additional analyses of response, duration of response, and overall survival. For both definitions of response, ring enhancement was a strong univariate predictor of lack of response [odds ratio, 0.036 (P = 0.004) for neuroradiological response; odds ratio, 0.059 (P = 0.002) for 6-month progression-free response]. In this model, therefore, ring enhancement segregated with 10q loss, PTEN alteration, CDKN2A deletion, and EGFR amplification as predictors of poor response to chemotherapy. With regard to duration of response, radiological enhancement was highly associated with an increased hazard of progression after response to chemotherapy (odds ratio, 4.37; P = 0.007). Because of the small numbers of patients, the effect of ring enhancement was not estimable in these models.

In univariate models of overall survival, enhancement and

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**Table 2** Predictors of neuroradiological response, duration of response, and overall survival

<table>
<thead>
<tr>
<th>Feature</th>
<th>Odds ratio</th>
<th>P</th>
<th>Hazard ratio</th>
<th>P</th>
<th>Hazard ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age at diagnosis ≤45 years</td>
<td>1.264</td>
<td>0.733</td>
<td>0.869</td>
<td>0.825</td>
<td>0.519</td>
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<td>KPS ≥80</td>
<td>0.917</td>
<td>0.899</td>
<td>1.419</td>
<td>0.581</td>
<td>0.584</td>
<td>0.218</td>
</tr>
<tr>
<td>Enhancement at diagnosis</td>
<td>0.0667</td>
<td>0.577</td>
<td>8.662</td>
<td>0.041</td>
<td>3.867</td>
<td>0.015</td>
</tr>
<tr>
<td>Ring enhancement at diagnosis</td>
<td>0.036</td>
<td>0.004</td>
<td>7.576</td>
<td>0.080</td>
<td>18.024</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1p LOH*</td>
<td>*</td>
<td>*</td>
<td>0.180</td>
<td>0.017</td>
<td>0.115</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>19q LOH</td>
<td>3.694</td>
<td>0.072</td>
<td>0.101</td>
<td>0.001</td>
<td>0.177</td>
<td>0.0002</td>
</tr>
<tr>
<td>10q LOH</td>
<td>0.057</td>
<td>0.002</td>
<td>*</td>
<td>*</td>
<td>9.064</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PTEN alteration</td>
<td>0.067</td>
<td>0.021</td>
<td>23.495</td>
<td>0.026</td>
<td>18.782</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDKN2A deletion</td>
<td>0.139</td>
<td>0.034</td>
<td>3.489</td>
<td>0.026</td>
<td>7.969</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EGFRA amplification</td>
<td>0.139</td>
<td>0.034</td>
<td>*</td>
<td>*</td>
<td>11.965</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>0.307</td>
<td>0.170</td>
<td>2.518</td>
<td>0.253</td>
<td>1.717</td>
<td>0.300</td>
</tr>
</tbody>
</table>

*LOH, loss of heterozygosity.
*+, not estimable in this model (e.g., all patients with 1p loss of heterozygosity responded).
ring enhancement joined 10q loss, PTEN alteration, CDKN2A deletion, EGFR amplification, and TP53 mutation as predictors of poorer overall survival. None of the clinical variables, including age <45 years, was associated with differences in overall survival. In a multivariate model, KPS, ring enhancement, and diffuse (nonring) enhancement joined 1p as significant predictors of survival. Ring enhancement and diffuse (nonring) enhancement predicted decreased survival (hazard ratios, 64.1 and 11.7; P < 0.0001 and P = 0.001, respectively), whereas high KPS and 1p loss predicted increased survival (hazard ratios, 0.15 and 0.04; P = 0.0004 and P < 0.0001, respectively).

DISCUSSION

We previously reported that specific chromosomal losses predicted chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas (3). The clinical utility of this earlier, smaller study was compromised, however, by the inclusion of many patients who had received chemotherapy only at the time of recurrence, limiting its ability to address the issue of therapeutic management at the time of initial diagnosis. In addition, the previous work analyzed a smaller number of clinical and genetic parameters; for example, the important variable “duration of response to chemotherapy” (as distinct from “time to tumor progression”) was not adequately addressed. The present results extend those prior observations by demonstrating that, at the time of diagnosis, histologically defined anaplastic oligodendrogliomas can be divided into four prognostically and therapeutically relevant genetic groups (Fig. 2). Patients whose anaplastic oligodendrogliomas had isolated, combined allelic losses of 1p and 19q (group 1) had a uniformly excellent prognosis; patients with anaplastic oligodendrogliomas harboring other 1p losses (group 2) or TP53 mutations (group 3) had an intermediate prognosis, and patients whose anaplastic oligodendrogliomas had neither 1p loss nor TP53 mutation (group 4) had a poor prognosis (Fig. 3). Moreover, patients in group 1 had durable responses to chemotherapy; those in group 2 also responded to chemotherapy, but these responses were brief. Those in group 3 may have responded to chemotherapy, but briefly, and those in group 4 seldom responded to chemotherapies in use at present.

These findings suggest that molecular diagnosis may soon influence the clinical management of patients with anaplastic oligodendrogliomas, particularly those in groups 1 and 4. For example, group 1 patients might be treated initially with chemotherapy because durable responses can be anticipated, at the same time deferring radiation therapy, which is the customary postoperative treatment for malignant glioma. Indeed, in this series, 14 patients whose tumors had the genetic signature of isolated 1p and 19q loss were alive >7.4 years after diagnosis, including 6 patients who never received radiation therapy. Despite a Kaplan-Meier curve that is remarkably flat for a cohort of malignant gliomas, 9 of the 23 group 1 patients have not yet received radiation therapy. Given the neurotoxicities of radiation therapy, which become evident only in long-term survivors, an argument could thus be made to delay irradiation in patients whose anaplastic oligodendrogliomas have combined, isolated 1p/19q loss, especially if the location and size of the tumor are such that large volumes of normal brain tissue will be included in the irradiated field. At the least, the results provide a strong rationale for incorporating molecular analyses into prospective trials that would evaluate whether radiation therapy can be delayed in patients with particular biological subtypes of anaplastic oligodendroglioma.

Patients in genetic groups 2 and 3 remain good candidates for chemotherapy at diagnosis and someday may have durable responses to new cytotoxic agents. At present, however, these patients must be monitored closely for recurrence and should be treated with radiation therapy postoperatively. Patients in genetic group 4, on the other hand, lack meaningful responses to chemotherapy and have a particularly ominous prognosis. Group 4 patients are highly likely to have ring enhancement on neuroradiological examination, which was the only clinical or radiographic feature highly predictive of aggressive behavior.
and which was never observed in cases with isolated, combined 1p/19q allelic loss. The present results argue against the use of initial PCV chemotherapy in this group of patients; because there is little expected therapeutic gain, avoidance of PCV could both spare bone marrow reserves and provide additional time for other therapeutic approaches. Although patients in group 4 should be offered radiation therapy at diagnosis, one could argue that these patients are the very group who are logical candidates for experimental therapies at diagnosis, as standard treatment yields such poor outcomes.

The genetic features noted in groups 3 and 4 are also characteristic of high-grade astrocytomas, such as glioblastoma (26, 27). Approximately one-third of glioblastomas have TP53 mutations, most often in young adults, and a distinct one-third have EGFR gene amplification, often with chromosome 10, PTEN, and CDKN2Alp16 alterations, and typically occur in older adults (26, 28). Notably, in the present series, EGFR, PTEN, chromosome 10, and CDKN2A abnormalities clustered in anaplastic oligodendrogliomas in generally older adults, and TP53 mutations were more common in tumors of younger adults (Fig. 2). These observations suggest parallels between the two groups of non-1p-losing anaplastic oligodendrogliomas and the two well-defined molecular subtypes of glioblastoma. To exclude the possibility that group 3 and 4 tumors were misdiagnosed glioblastomas, these cases were reviewed by a third neuropathologist, also blinded to the genetic results, and found to be in accord with current criteria for anaplastic oligodendroglioma (6). Indeed, some cases were histologically classic for oligodendroglioma, showing no features even suggestive of glioblastoma (Fig. 1, right-hand panel). Thus, histologically defined anaplastic oligodendrogliomas that are genotypically similar to glioblastomas (group 4) appear clinically more akin to glioblastomas. For purposes of treatment planning and prognostication, therefore, genotyping may someday override the gold standard of histopathology, a prospect alluded to in the most recent iteration of the WHO classification for brain tumors (29).

The above genetic markers clearly and objectively distinguish between different biological types of malignant glioma. In the setting of a lesion histologically consistent with an oligodendroglioma, therefore, combined but isolated 1p and 19q loss constitutes an effective marker for a malignant glioma that is potentially curable with available therapies, allowing emphasis to be placed on a management strategy that maximizes tumor control while minimizing neurotoxicity. The molecular genetic tests used in this analysis, although not yet widely available, should be relatively easy to establish in most pathology laboratories; many of the alterations can be detected by either PCR or fluorescent in situ hybridization assays, with good concordance between these techniques (22). In a recent editorial, we suggested that molecular typing of malignant gliomas could in the future prove a viable means for identifying therapeutically responsive tumors, as well as providing a basis for placing a priori nonresponsive tumors into alternative therapeutic arms (2). The rapid progress in this field over the past few years suggests that this time has come.

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REFERENCES


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