

Recursive partitioning analysis of prognostic variables in newly diagnosed anaplastic oligodendroglial tumors

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Background. Anaplastic oligodendroglial tumors are rare, and median survival varies widely. Analysis of 1p19q deletion is performed commonly and is an important prognostic factor. However, age and other clinical variables also carry prognostic value, and it is unclear how to incorporate them into clinical decision making or to combine them for prognostication.

Methods. We compiled a retrospective database of 1013 patients with newly diagnosed anaplastic oligodendrogliomas or oligoastrocytomas and performed a recursive partitioning analysis to generate independent prognostic classes among 587 patients with informative 1p19q status. Variables included for survival classification were age (continuous), history of prior low-grade glioma, 1p19q deletion status, histology (presence or absence of an astrocytic component), tumor lobe, tumor hemisphere, gender, extent of resection, postresection treatment, and performance status at diagnosis.

Results. Recursive partitioning analysis identified 5 prognostic groups based on hazard similarity: class I (age <60 y, 1p19q codeleted), class II (age <43 y, not codeleted), class III (age 43–59 y, not codeleted, frontal lobe tumor or age ≥60 y, codeleted), class IV (age 43–59 y, not codeleted, not frontal lobe tumor or age 60–69 y, not codeleted), and class V (age ≥70 y, not codeleted). Survival differences were highly significant ($P < .0001$), with medians ranging from 9.3 years (95% CI: 8.4–16.0) for class I to 0.6 years (95% CI: 0.5–0.9) for class V.

Conclusions. These 5 distinct classification groups were defined using prognostic factors typically obtained during routine management of patients with anaplastic oligodendroglial tumors. Validation in a prospective clinical trial may better differentiate patients with respect to treatment outcome.

Keywords: 1p19q deletion, anaplastic, anaplastic oligoastrocytoma, oligodendroglioma, prognosis, recursive partitioning analysis.

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Anaplastic oligodendroglial tumors, anaplastic oligodendrogliomas (AOs), and anaplastic oligoastrocytomas (AOAs) are rare World Health Organization grade III primary brain tumors.¹ We previously compiled a retrospective dataset encompassing 1013 cases of AO/AOA diagnosed from 1981–2007 and published demographics, comparative outcomes, and changes in the initial postoperative treatment strategies over time.^{2,3} However, survival is highly variable, with some patients succumbing within months and others surviving for over 10 years from diagnosis.

Deletion of chromosomes 1p and 19q⁴ is a significant and favorable prognostic factor^{5–7} and is predictive of benefit from adding chemotherapy with procarbazine, lomustine, and vincristine (PCV) to radiotherapy.^{8,9} However, other clinical variables, such as age and performance status, also carry prognostic significance, as does extent of resection.⁷ It is unclear how to weigh molecular and clinical factors for relative importance and how to incorporate them into prognostication and treatment decisions.

Prognostic models have been generated for other brain tumors, such as glioblastoma,^{10–12} anaplastic astrocytoma,¹¹ low-grade glioma,¹³ and primary central nervous system lymphoma.¹⁴ However, to our knowledge, no such model exists for anaplastic oligodendroglial tumors. In the current report, we performed recursive partitioning analysis (RPA) on our retrospective dataset^{2,3} to generate independent prognostic classes using routinely available clinical variables.

Materials and Methods

We generated a decision tree using RPA, also termed Classification and Regression Trees, to stratify patients into distinct risk groups to predict overall survival,¹⁵ using our dataset collected retrospectively following institutional review board approval.² Classification and Regression Trees is a data-mining technique that searches among all the variables to partition the data into homogeneous subgroups. This algorithm first *partitions* (ie, divides) the data into 2 subgroups by searching through all possible prognostic variables to find the division that is most prognostic for survival. It is *recursive* in that it then repeats the search to identify additional partitions (subdivisions) within a previously identified subgroup. Each partition point is referred to as a node. The algorithm stops when the data have been divided into subgroups that are too small to divide further in a meaningful manner—for example, when <20 observations remain at any potential branch point or when <7 observations remain at a terminal node. The partitions and nodes form a “tree” that allows for a clinically intuitive visual display of the factors examined and any potential interactions.¹⁵ All analyses were conducted and completed at Memorial Sloan-Kettering Cancer Center by A.S.R. and K.S.P. using SAS version 9.2 and R version 2.3.1 software (the recursive PARTitioning package [RPART]).

As an internal validation, 10-fold cross-classification was performed within RPART by randomly dividing the full sample into 10 subsamples. In this way, the full model was “fitted” with 90% of the full sample, while the remaining 10% was used as a validation dataset. This procedure was repeated 10 times. The results from this 10-fold cross-validation were used to “prune” the full tree to a more parsimonious model.¹⁶

The tree in this analysis was built using the following collected variables of potential prognostic significance: age (as a continuous variable), gender, KPS at diagnosis (≥ 70 vs < 70), histology

(AO vs AOA), history of prior low-grade glioma (yes vs no), dominant lobe of tumor (frontal vs other), hemisphere of the tumor (right vs left vs bilateral), extent of resection (biopsy vs debulking), postoperative treatment (radiotherapy only vs chemotherapy only vs both), and 1p19q deletion status (codeleted vs not codeleted, ie, one or neither deleted). Among 1013 patients with newly diagnosed anaplastic oligodendroglial tumors treated with various strategies in the original dataset,² there were 587 with informative deletion results at both 1p and 19q treated at diagnosis with the commonly used strategies of radiotherapy, chemotherapy, or both (Table 1). Recursive partitioning analysis was performed on these 587 cases because analysis of 1p19q deletion status is now widely available, routinely performed, and incorporated into clinical decision making.¹⁷ Deletion status of 1p19q is also clearly prognostic for survival^{5–7} and is predictive of benefit from alkylator chemotherapy.^{8,9} Therefore, cases with unknown deletion status were excluded. Survival time was

Table 1. Patient characteristics

	n = 587	
Age, y		
Median		41
Range		18–83
Gender, n (%)		
Men	324	(55)
Women	263	(45)
Histology		
Anaplastic oligodendroglioma	337	(57)
Anaplastic oligoastrocytoma	250	(43)
Prior low-grade glioma		
Yes	81	(14)
No	498	(85)
Unknown	8	(1)
Extent of resection		
Resection	509	(87)
Biopsy	60	(10)
Unknown	18	(3)
KPS		
$\geq 70\%$	496	(84)
$< 70\%$	40	(7)
Unknown	51	(9)
1p19q deletion status		
Codeleted	280	(48)
Not codeleted	307	(52)
Lobe		
Frontal	335	(57)
Other	252	(43)
Hemisphere		
Right	259	(44)
Left	270	(46)
Bilateral	10	(2)
Unknown	48	(8)
Initial postoperative treatment		
Chemotherapy alone	128	(22)
Radiotherapy alone	121	(21)
Both	338	(58)

measured as the interval from histologic diagnosis of AO/AOA to death or last follow-up. Independent prognostic classes were generated with final nodes grouped by similar hazards. Kaplan–Meier curves present the final classification of prognostic groups and were tested for significance by log-rank.

Results

Clinical characteristics for the 587 cases are shown in Table 1. Only 3 variables contributed to the final tree (Fig. 1): age, deletion status, and tumor location. Among patients younger than 60 years, 1p19q codeletion was the strongest prognostic factor, and these patients survived longest. For patients younger than 60 but without codeleted tumors, the analysis identified another age band of 43–59 years. Tumor location was only prognostic among patients without codeleted tumors aged 43–59, in whom tumors with frontal lobe predominance were favorable. Among patients older than 60 years, codeletion was also favorable. For patients 60 and older without codeleted tumors, the analysis demonstrated another prognostic age band, with the very oldest (≥ 70) carrying the worst prognosis.

Therefore, RPA identified 5 distinct risk groups based on hazard similarity (Table 2): class I (age <60 y, 1p19q codeleted, tumor in any location); class II (age <43 y, not codeleted, tumor in any location); class III (age 43–59 y, not codeleted, frontal lobe tumor; or age ≥ 60 y and codeleted, tumor in any location); class IV (not codeleted and either age 43–59 y with tumor not in the frontal lobe or age 60–69 y with tumor in any location); and class V (age ≥ 70 y, not codeleted, tumor in any location). Kaplan–Meier survival analysis confirmed the existence of 5 distinct risk classification groups identified by RPA, with the best outcome for class I (median, 9.3 y; 95% CI: 8.4, 16 y), the worst for class V (median, 0.6 y; 95% CI: 0.5, 0.9 y), and with classes II, III, and IV intermediate (Table 2 and Fig. 2). The log-rank P -value for overall differences among the 5 curves was $<.0001$. Although the confidence intervals around the median for classes I and II

overlapped (Table 2), the hazards remained significantly different ($P = .02$; Fig. 2).

Discussion

We identified 5 independent prognostic classes using readily available clinical variables. Only 3 variables were identified in this classification schema: age, 1p19q codeletion status, and tumor location. The most powerful variable was age <60 or ≥ 60 years. Most prospective trials recognize the prognostic importance of age, and some use it as a stratification factor in randomization. However, seminal phase III studies used age cutoffs of 40^{6,9} or 50^{5,8} in randomization procedures or multivariate analyses.⁷ Our results (using age as a continuous variable) suggest instead that 60 years may be the most important cut point, and future trials may need to consider this in the statistical design. Additional age bands, <43 , 43–59, and ≥ 70 years, had prognostic value but were less significant than 1p19q status. Although the confidence intervals for classes I and II overlap, they are statistically and clinically distinct; separating them retains clinical value.

In addition, 1p19q deletion status, while important, was surprisingly not the most prognostic variable. Tumor location was important, but performance status, extent of resection, treatment, and histology did not contribute to the final model; however, these factors are interrelated. For example, extent of

Table 2. Independent prognostic classes

Class	<i>n</i>	Age, y	1p19q Codeletion	Dominant Lobe of Tumor	Median Overall Survival (95% CI)
I	256	<60	Yes	Any	9.3 (8.4–16.0)
II	174	<43	No	Any	8.9 (5.5–10.8)
III	40	43–59	No	Frontal	4.3 (2.9–6.0)
	24	≥ 60	Yes	Any	
IV	48	43–59	No	Not frontal	2.0 (1.6–2.3)
	27	60–69	No	Any	
V	18	≥ 70	No	Any	0.6 (0.5–0.9)

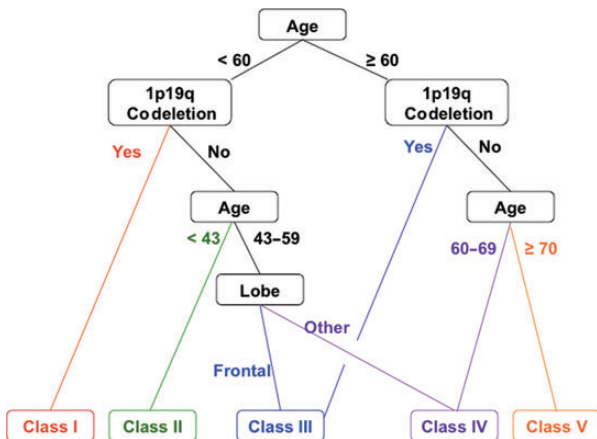


Fig. 1. RPA results for all patients ($n = 587$) with informative 1p19q deletion status showing the final decision tree with terminal nodes and consolidation into 5 distinct prognostic classes using commonly available clinical variables. Age is in years; lobe refers to predominant tumor location; colors indicate route to various classes (Fig. 2); black lines and text are associated with >1 class.

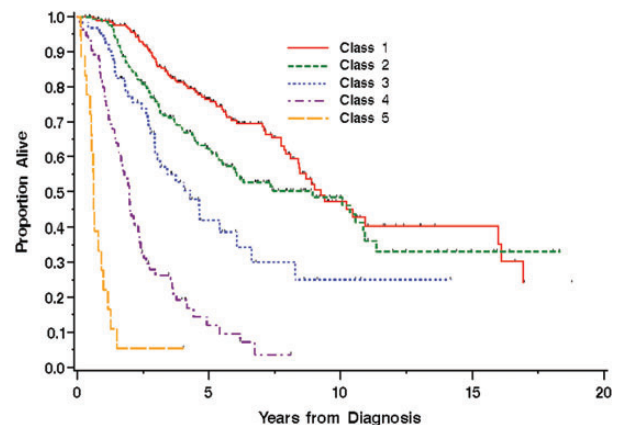


Fig. 2. Kaplan–Meier survival curves by prognostic class formed by groups of similar hazard (hazards for classes I–V: 0.59, 0.85, 1.2–1.7, 3.4–3.5, 8.2, respectively).

resection may have been partially addressed in the dataset because frontal tumors are more likely amenable to greater resection than tumors in other locations. Similarly, physician bias may have led to more aggressive treatment, including debulking resection rather than biopsy, in patients with higher KPS. Approximately 85% of patients had KPS ≥ 70 , and patients were not further subdivided into those with the very best performance groups (KPS 90–100). Others have suggested that tumors of mixed histology behave between those of pure oligodendroglial and pure astrocytic varieties. By contrast, our results indicate that 1p19q status exerts a more powerful influence on survival than traditional histology and are consistent with similar conclusions from a phase III study (NOA-04) of anaplastic gliomas conducted by the Neuro-oncology Working Group of the German Cancer Society.⁷

Our analysis was limited by the retrospective nature of the original dataset and the lack of central review of either pathology or imaging, as detailed elsewhere.² Accordingly, we did not attempt to differentiate gross total from subtotal resection, instead characterizing the extent of surgical excision as either biopsy or debulking. In addition, diagnostic criteria for gliomas have changed over time, especially for oligodendrogliomas.¹⁸ For example, the most recent World Health Organization criteria would now diagnose AOAs with necrosis as grade IV glioblastoma with an oligodendroglial component,^{1,19} and it is possible that such cases contributed to the poor prognosis in classes IV and V. However, histology (AO vs AOA) did not contribute to our final model, suggesting that the potential confounding effect was limited. As an alternative explanation, 1p19q codeletion is more common among AOs than AOAs, and codeletion may have been a surrogate for histology, especially in the absence of central pathology review. We also did not capture tumor size, which is prognostic in other brain tumors¹³ and may be important in AO/AOA. Finally, we did not perform testing for *IDH* mutation or *MGMT* promoter methylation, which are emerging as independent molecular prognostic factors.^{7,19,20} Recent results suggest that 1p19q codeleted tumors are a subset of those with *IDH* mutation; accordingly, lack of *IDH* mutation testing was likely most relevant for patients whose tumors did not have codeletion.²¹ However, *IDH* mutation may also have been partially addressed by age, as older patients almost never have *IDH* mutant tumors.²² Unfortunately, archival tissue was not available for either central pathology review or molecular interrogation, and the cost and logistical difficulties of locating, transporting, and analyzing tissue were insurmountable obstacles. However, *IDH* mutation and *MGMT* promoter methylation studies are not always widely available to community oncologists, and differences in laboratory method for both *IDH*^{23,24} and *MGMT*²⁵ testing can lead to discordant results. Moreover, other molecular abnormalities of potential prognostic significance have been recently discovered, and which of these can or should be routinely analyzed is an emerging area of investigation in neuro-oncology.²⁶ For example, we also did not test for mutations in *CIC*,^{27,28} *ATRX*^{29,30} (which appears mutually exclusive with 1p19q codeletion),³¹ *FUBP1*,^{28,30} or *NHE-1*³²; for Glioma-CpG island methylator phenotype (G-CIMP)^{33,34} (which appears to result from *IDH* mutation^{35–37} and may lead to and be more important than *MGMT* methylation³⁴); or for “intrinsic glioma subtype.”³⁸ Rather, our purpose was to generate a model using data routinely available in the clinic. At this time, we viewed 1p19q status as the most widely used molecular marker.¹⁷

As described in Materials and Methods, the current classification tree was subjected to robust internal validation. Ideally, an independent dataset for external validation is required. However, after carefully considering the other available studies, we concluded that the heterogeneity among existing datasets would likely preclude the validity of such analysis. For example, Radiation Therapy Oncology Group (RTOG) 9402 and European Organisation for Research and Treatment of Cancer (EORTC) 26951 were prospective randomized phase III studies, whereas ours was not. In addition, treatment in those studies always included radiotherapy (with or without PCV), whereas ours also included patients who did not receive radiotherapy as part of the initial treatment regimen, and also captured patients who received initial chemotherapy with temozolomide rather than PCV. RTOG 9402 excluded patients with KPS < 60 and then grouped them by KPS 60–70 or 80–100, and EORTC 26951 excluded patients with an Eastern Cooperative Oncology Group performance status > 2 and then grouped them by 0–1 or 2. By contrast, we had no limit on performance status and categorized KPS as < 70 or ≥ 70 . Finally, EORTC 26951 also excluded patients over age 70, which would have eliminated patients in our RPA class V.

In conclusion, the RPA prognostic model presented here is simple yet powerful. Although the model appears complex, we found that combining 3 routinely available variables (age, 1p19q codeletion status, and tumor location) powerfully predicted survival. Recursive partitioning analyses for other primary brain tumors are important. Our RPA may be a useful prognostic tool for patients with anaplastic oligodendroglial tumors.

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Conflict of interest statement. Relevant to this publication, A.B.L., T.F.C., N.A.P., J.G.C., H.I.R., P.Y.W., F.G.K., M.C.C., and W.P.M. consulted for and/or received honoraria from Schering Corp and/or Merck & Co; A.B.L. consulted for Bristol-Myers Squibb; A.B.L., J.G.C., D.S., P.Y.W., M.C.C., L.E.A., and N.A.P. consulted for Sigma-Tau Pharmaceuticals; N.A.P., M.C.C., and S.A.W. served on a Speaker's Bureau for Merck & Co (formerly Schering Corp). L.E.A. is now a full-time employee of and stockholder in F. Hoffmann–La Roche Ltd.

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