

International retrospective study of over 1000 adults with anaplastic oligodendroglial tumors

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Treatment for newly diagnosed anaplastic oligodendroglial tumors is controversial. Radiotherapy (RT) alone and in combination with chemotherapy (CT) are the most well studied strategies. However, CT alone is

often advocated, especially in cases with 1p19q codeletion. We retrospectively identified 1013 adults diagnosed from 1981–2007 treated initially with RT alone ($n = 200$), CT + RT ($n = 528$), CT alone ($n = 201$), or other strategies ($n = 84$). Median overall survival (OS) was 6.3 years and time to progression (TTP) was 3.1 years. 1p19q codeletion correlated with longer OS and TTP than no 1p or 19q deletion. In codeleted cases, median TTP was longer following CT + RT (7.2 y) than following CT (3.9 y, $P = .003$) or RT (2.5 y, $P < .001$) alone but without improved OS; median TTP was longer following treatment with PCV alone than temozolomide alone (7.6 vs. 3.3 y, $P = .019$). In cases with no deletion, median TTP was longer

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following CT + RT (3.1 y) than CT (0.9 y, $P = .0124$) or RT (1.1 y, $P < .0001$) alone; OS also favored CT + RT (median 5.0 y) over CT (2.2 y, $P = .02$) or RT (1.9 y, $P < .0001$) alone. In codeleted cases, CT alone did not appear to shorten OS in comparison with CT + RT, and PCV appeared to offer longer disease control than temozolomide but without a clear survival advantage. Combined CT + RT led to longer disease control and survival than did CT or RT alone in cases with no 1p19q deletion. Ongoing trials will address these issues prospectively.

Keywords: oligodendroglioma, oligo-astrocytoma, PCV, temozolomide, 1p19q.

Anaplastic oligodendroglial tumors are rare primary brain neoplasms.¹ Often indolent, they are typically incurable despite maximal therapeutics. The role of extensive surgical resection is controversial, but extrapolation from glioblastoma suggests it would be beneficial. The optimal timing and sequence of radiotherapy (RT) and chemotherapy (CT) alone or in combination is undefined as established in 3 randomized phase III trials.²⁻⁴ We previously conducted a survey of recommendations for treatment of newly diagnosed disease and found no consensus.⁵ RT is effective, but patients with 1p19q codeleted tumors can survive decades⁶ and are at risk for delayed radiation toxicity. Up to 42% of surveyed neuro-oncologists recommend CT alone in 1p19q codeleted cases, deferring RT until after disease progression.⁵ Among CT regimens, temozolomide (TMZ) has largely replaced the combination of procarbazine /1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea (CCNU, lomustine)/vincristine (PCV),⁵ at least in part because it is viewed as better tolerated and easier to administer. However, controversy remains whether TMZ efficacy is equivalent to that of PCV.⁷

Two international phase III trials recently opened for patients with anaplastic gliomas stratified by 1p19q deletion status. The “Concurrent and/or Adjuvant TMZ for 1p19q Nondeleted Tumors” (CATNON) study will randomize patients to 1 of 4 treatment arms involving combinations of RT with or without TMZ at different time points. By contrast, the “Codeleted Tumors” (CODEL) trial randomizes patients with 1p19q codeleted tumors to RT alone, RT with concurrent and adjuvant TMZ, or TMZ alone. The existence of 5 treatment regimens between these 2 trials demonstrates the absence of a current standard.

As CODEL and CATNON will take years to accrue and mature, we conducted an international retrospective study to compare outcomes following various initial treatment strategies. We sought to address efficacy of CT alone versus CT + RT as our primary analysis, stratified by 1p19q deletion status when available. If data permitted, we also planned to compare CT regimens, particularly PCV and TMZ.

Methods

Patients

In this institutional review board–approved study, we identified patients from departmental and physician databases with newly diagnosed histologically confirmed (locally) anaplastic oligodendrogliomas (AOs) or anaplastic oligoastrocytomas (AOAs). We retrospectively collected demographic, treatment, and survival data. Included patients were at least 18 years old at diagnosis, which occurred from 1981 to 2007. Patients with a prior diagnosis of low-grade glioma were included provided histologic confirmation of anaplastic transformation to AO or AOA was obtained before RT and/or CT. As some patients could have sought care from more than one participating physician during their disease course, an algorithm cross-referencing gender and dates of birth, diagnosis, and death screened for potential duplicate entries. Patients enrolled in international phase III studies (i.e., RTOG 9402² and EORTC 26951³) or bone marrow transplant trials⁸ were excluded because the goal was to generate a unique data set capturing outcome following routinely used treatment strategies in an observational study.

Treatment

Extent of resection (EOR) was recorded as biopsy or resection. The initial postoperative treatment strategy was classified as RT alone, CT + RT (sequential and/or concurrent), CT alone, other, or no therapy within 6 months of histologic diagnosis. CT regimen was defined as PCV alone, TMZ alone, or other. PCV was defined as at least 1 cycle of procarbazine, lomustine (or carmustine), and vincristine alone or in combination. RT or CT “alone” referred to the initial treatment strategy, notwithstanding further therapy administered after disease progression(s).

Key data collected included gender, age, and KPS (recorded from the medical record if available, otherwise estimated as <70 or ≥ 70) at diagnosis, history of a low-grade glioma, histology (AO vs. AOA), EOR, dominant tumor hemisphere and lobe, 1p19q deletion status, and initial postoperative treatment. Results of 1p19q analysis were obtained from patient records if available, otherwise from testing of retrieved archival tissue by fluorescence in-situ hybridization. Tumor size, treatment related toxicities, and efficacy of salvage therapies were not captured.

Statistical Analyses

Overall survival (OS) was defined as the interval from histologic diagnosis of AO/AOA to death or last follow-up. Time to progression (TTP) was defined as the interval to first progression (determined by the contributing investigator based on examination of available records and films) or last documented disease control. Progression and survival data were updated as of

January 12, 2009. OS and TTP were estimated using Kaplan–Meier methodology. Univariate analyses were performed using the log-rank test and multivariate analyses using the Cox proportional hazards model. All analyses were performed with SAS (version 9.2).

Results

Patient Characteristics

There were 1030 patients, but 17 received care at more than one participating center. Among 1013 unique patients included in the analysis, 573 (57%) were men and 440 (43%) were women, with a median age of 42 years (Table 1). Histology was AO in 587 (58%) and AOA in 426 (42%). KPS at diagnosis was ≥ 70 in 837 (83%) and < 70 in 101 (10%). The predominant tumor location was in the frontal lobe (569, 56%) followed by the temporal (171, 17%) and parietal (121, 12%) lobes. Occipital disease was rare (30, 3%). There was no predilection for hemispheric lateralization (approximately 47% each) and only 19 (2%) were bilateral. Data for KPS, tumor location, and laterality were unavailable in the remaining cases. A prior low-grade glioma was diagnosed in 152 (15%) cases.

Deletion of 1p was detected in 368 (52%) of 703 informative cases, partial deletion in 13 (2%), and no deletion in 322 (46%). Deletion of 19q was detected in 351 (56%) of 631 informative cases, partial deletion in 10 (2%), and no deletion in 270 (43%). Fewer cases were tested for 19q than for 1p, in part because 19q testing did not become routine until approximately the year 2000. However, all 631 cases tested for 19q deletion were also tested for 1p. Codeletion (excluding partial loss) of 1p and 19q was observed in 301 (48%) and no deletion (neither 1p nor 19q) in 242 (38%) of these 631 cases with complete 1p19q information. Discordant deletions (1p deletion with no 19q deletion, no 1p deletion with 19q deletion) or partial deletions were observed in the remaining 88 (14%). Codeletion was more frequent among AOs than among AOAs (68% vs. 20%, $P < .0001$).

Treatment

All patients underwent surgery, with resection in 856 (85%), biopsy in 116 (11%), and unknown in 41 (4%). Following surgery, the initial treatment strategy was RT alone in 200 (20%) patients, CT followed by RT in 135 (13%), RT + concurrent CT in 112 (11%), RT followed by CT in 281 (28%), CT alone in 201 (20%), and another regimen in 20 (2%); 64 (6%) patients received no postoperative CT or RT (Table 1).

There was substantial crossover of modalities following disease progression, and the majority of patients who progressed received both CT and RT during their disease course. For example, 73% (93/127) of patients who progressed after CT alone then received RT, including 74% (46/62) of those treated initially with TMZ and 70% (40/57) of those treated initially with PCV.

Similar crossover from RT alone to CT was observed. Efficacy was not recorded for salvage treatments.

Survival and Progression

Median OS was 6.3 years (95% confidence interval [CI]: 5.7, 7.4) for the entire cohort ($n = 1013$) with median follow-up of 5.2 years among 502 (50%) surviving patients. Median TTP was 3.1 years (95% CI: 2.8, 3.5), with median follow-up of 4 years among 380 (38%) patients censored for progression (Table 2).

Median OS (Table 2, Fig. 1) of all patients treated with CT alone was 7.0 years (95% CI: 5.4, not reached); for those treated with CT + RT (sequential and/or concurrent), median OS was 7.3 years (95% CI: 5.9, 8.4, $n = 528$). This difference was not significant ($P = .84$). However, median OS of patients treated with RT alone was 4.4 years (95% CI: 2.8, 6.0), and this was significantly shorter than median OS for those treated with CT alone ($P = .0008$) or CT + RT ($P < .0001$).

Median TTP (Table 2, Fig. 1) following CT alone was 2.8 years (95% CI: 2.1, 3.7), which was significantly shorter ($P = .0005$) than 4.1 years (95% CI: 3.5, 5.4) for patients treated with CT and RT. Median TTP following RT alone was 1.8 years (95% CI: 1.5, 2.3), and this was significantly shorter than that for CT alone ($P = .0099$) or CT + RT ($P < .0001$).

Effect of Chromosomal Analyses

Median OS was longer ($P < .0001$) in 1p19q codeleted cases (8.5 y, 95% CI: 7.7, 10.0) than in those with no deletion (3.7 y, 95% CI: 3.0, 4.6). Median TTP was also longer (4.5 y, 95% CI: 3.9, 5.9 vs. 2.2 y, 95% CI: 1.6, 3.0; $P = .0001$) (Table 3, Fig. 2).

Among patients with 1p19q codeleted tumors treated initially with CT + RT ($n = 133$), median TTP was 7.2 years (95% CI: 5.2, 8.1), significantly longer ($P = .003$) than the 3.9 years (95% CI: 3.2, 4.7) for those receiving CT alone ($n = 93$) and longer ($P < .001$) than the 2.5 years (95% CI: 1.7, 3.7) for those receiving RT alone ($n = 54$). However, differences in OS did not approach significance (8.4 y following CT + RT, 10.5 y following CT alone, 8.7 y following RT alone) (Table 3, Fig. 3). To compare the efficacy of PCV versus TMZ, we determined survival in patients with 1p19q codeleted tumors treated with either regimen alone. Median TTP was longer ($P = .0186$) following PCV alone ($n = 21$, 7.6 y, 95% CI: 4.2, 9.3) than TMZ alone ($n = 68$, 3.3 y, 95% CI: 2.6, 4.2) (Table 4, Fig. 4). This remained significant when accounting for potential confounders on multivariate analysis, including extent of resection, KPS, age, and histology. Median OS also trended toward favoring PCV (10.5 vs. 7.2 y, $P = .16$; Table 4, Fig. 4). Duration of follow-up was shorter for those treated with TMZ: median follow-up for survivors was 7 years among patients receiving PCV and 3.6 years for TMZ. Comparing PCV versus TMZ in patients who received CT + RT, the TTP and OS did not significantly differ between chemotherapy regimens ($P = .26$ for

Table 1. Clinical and molecular characteristics

	All (n = 1013)		Treatment None (n = 64)		CT alone (n = 201)		CT + RT (n = 528)		RT alone (n = 200)		Other (n = 20)	
Age (years)												
Median	42		38		43		41		44		41	
Range	18–89		18–82		20–83		19–85		19–89		29–61	
Gender (n, %)												
Men	573	57%	38	59%	110	55%	298	56%	116	58%	11	55%
Women	440	43%	26	41%	91	45%	230	44%	84	42%	9	45%
Histology												
AO	587	58%	43	67%	155	77%	262	50%	114	57%	13	65%
AOA	426	42%	21	33%	46	23%	266	50%	86	43%	7	35%
Prior LGG												
Yes	152	15%	14	22%	45	22%	64	12%	26	13%	3	15%
No	848	84%	48	75%	155	77%	456	86%	172	86%	17	85%
Unknown	13	1%	2	3%	1	1%	8	2%	2	1%	0	0%
Extent of resection												
Resection	856	85%	54	84%	165	82%	466	88%	153	77%	18	90%
Biopsy	116	11%	7	11%	29	14%	49	9%	29	14%	2	10%
Unknown	41	4%	3	5%	7	4%	13	3%	18	9%	0	0%
Diagnosis date												
1980s	34	3%	2	3%	1	1%	12	2%	19	10%	0	0%
1990s	395	39%	39	61%	53	26%	195	37%	95	48%	13	65%
2000s	584	58%	23	36%	147	73%	321	61%	86	43%	7	35%
KPS												
≥70%	837	83%	46	72%	175	87%	453	86%	147	74%	16	80%
<70%	101	10%	11	17%	20	10%	41	8%	26	13%	3	15%
Unknown	75	7%	7	11%	6	3%	34	6%	27	13%	1	5%
1p19q status												
Known ^a	631											
1p19q co-del	301	48%	20	53%	93	73%	133	40%	54	45%	1	17%
No 1p or 19q del	242	38%	12	32%	20	16%	155	46%	50	41%	5	83%
1p del no 19q del	26	4%	3	8%	4	3%	14	4%	5	4%	0	0%
No 1p del, 19q del	48	8%	1	3%	5	4%	32	10%	9	7%	0	0%
Missing 1p or 19q data	382		26		73		190		79		14	
Lobe												
Frontal	569	56%	35	55%	123	61%	303	57%	98	49%	10	50%
Temporal	171	17%	13	20%	28	14%	90	17%	32	16%	8	40%
Parietal	121	12%	7	11%	23	11%	60	11%	30	15%	1	5%
Occipital	30	3%	0	0%	8	4%	14	3%	8	4%	0	0%
Other	69	7%	3	5%	17	9%	37	7%	11	6%	1	5%
Unknown	53	5%	6	9%	2	1%	24	5%	21	10%	0	0%
Hemisphere												
Right	466	46%	33	52%	96	48%	243	46%	87	44%	7	35%
Left	473	47%	24	37%	99	49%	249	47%	88	44%	13	65%
Bilateral	19	2%	1	2%	4	2%	11	2%	3	1%	0	0%
Unknown	55	5%	6	9%	2	1%	25	5%	22	11%	0	0%

Abbreviations: AO, anaplastic oligodendroglioma; AOA, anaplastic oligo-astrocytoma; LGG, low grade glioma; KPS, Karnofsky performance status; del, deletion; NA, not applicable; Obs, observation; CT, chemotherapy; RT, radiotherapy; TMZ, temozolomide; PCV, procarbazine, lomustine (CCNU), vincristine; CT + RT indicates sequentially and/or concurrently; 95% CI, 95% confidence interval. RT or CT "alone" refers to the initial treatment strategy, notwithstanding further therapy administered after disease progression(s).

^a14 patients had partial deletions of 1p or 19q.

Table 2. Outcome by treatment

Survival	All (<i>n</i> = 1013)		Treatment					
			CT alone (<i>n</i> = 201)		CT + RT (<i>n</i> = 528)		RT alone (<i>n</i> = 200)	
	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Overall survival time (y)	6.3	5.7–7.4	7.0	5.4–NR	7.1	5.9–8.4	4.4	2.8–6.0
Overall survival rate (%)								
1 year	93	91–94	94	90–97	95	93–97	84	78–88
2 years	80	77–82	81	75–86	83	80–86	67	60–73
5 years	57	53–60	59	51–66	58	53–63	48	40–55
10 years	39	35–43	43	33–53	41	35–46	29	22–36
Time to progression (y)	3.1	2.8–3.5	2.8	2.1–3.7	4.1	3.5–5.4	1.8	1.5–2.3
Time to progression rate (%)								
1 year	76	73–79	75	68–80	83	79–86	63	56–69
2 years	60	57–63	59	51–65	67	63–71	47	39–54
5 years	39	35–42	31	23–39	47	42–52	26	20–33
10 years	21	18–25	16	8–26	31	25–37	10	5–17

NR, not reached.

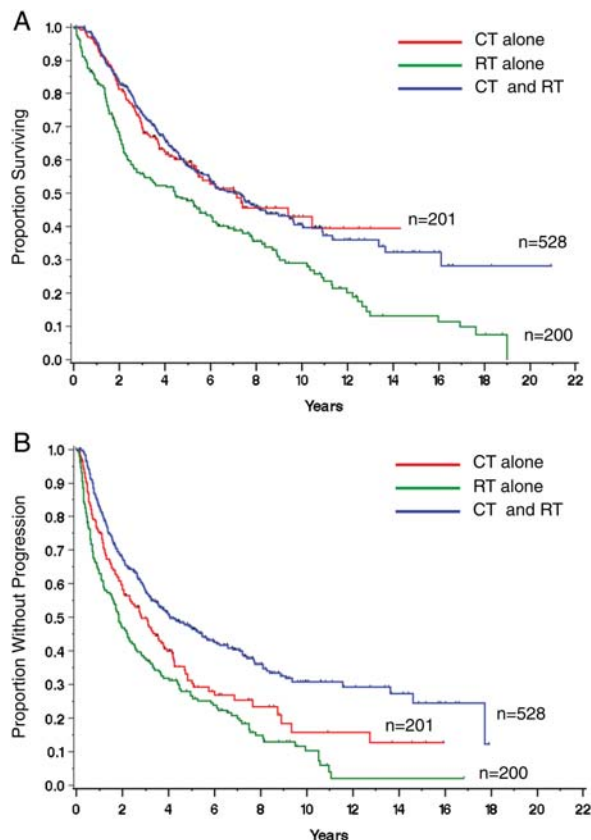


Fig. 1. Kaplan–Meier estimates of overall survival (A) and time to progression (B) by initial treatment with chemotherapy (CT) alone, radiotherapy (RT) alone, or CT + RT combined (concurrently and/or sequentially).

TTP, $P = .62$ for OS; Supplemental Table S1, Supplemental Fig.). There were too few patients treated with various iterations of PCV (e.g., “intensive” dosing,⁹ standard dosing,¹⁰ CCNU alone) to compare outcome.

The median TTP in cases with no deletion of 1p or 19q treated with CT + RT ($n = 155$) was 3.1 years (95% CI: 2.5, 4.3) and this was significantly longer ($P = .0124$) than 0.9 years (95% CI: 0.4, 3.8) following CT alone ($n = 20$) and significantly longer ($P < .0001$) than 1.1 years (95% CI: 0.6, 1.7) following RT alone ($n = 50$). Survival also significantly favored CT + RT (5.0 y, 95% CI: 3.8, 6.7) over CT alone (2.2 y, 95% CI: 1.4, 5.5; $P = .02$) and RT alone (1.9 y, 95% CI: 1.4, 2.8; $P < .0001$) (Table 3, Fig. 3).

The small number of cases with no deletion of 1p or 19q treated with either PCV alone ($n = 8$) or TMZ ($n = 9$) alone precluded meaningful comparison between these CT regimens in this cohort. Among patients who received CT + RT, median TTP and OS did not significantly differ between chemotherapeutic regimens ($P = .17$ for TTP, $P = .37$ for OS). However, long-term disease control was greater following PCV and RT than TMZ and RT, as reflected in the tails of the curves (Supplemental Table 1, Supplemental Fig.).

Multivariate Analyses

Univariate analysis demonstrated that KPS (<70 vs. ≥ 70), age (as both a continuous variable and across various thresholds, including 40, 50, and 60 y, not shown), extent of resection (biopsy vs. resection), and deletion status (codeletion vs. no deletion) were the strongest predictors of survival (Table 5). Other significant factors included treatment (CT vs. RT and CT + RT vs. RT alone), location (frontal vs. other, unilateral vs. bilateral), and histology (AO vs. AOA). Neither laterality (left vs. right for unilateral tumors) nor diagnosis date affected survival. Survival was longer in patients with de novo anaplastic tumors, rather than those with a prior history of low-grade glioma, but neither this nor histology was significant on multivariate analysis. Prognostic factors for TTP were similar to those for

Table 3. Outcome by treatment and 1p19q deletion

Survival	All		Treatment					
			CT alone		CT + RT		RT alone	
	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
1p19q codeletion								
N	301		93		133		54	
Overall survival time (y)	8.5	7.7–10.0	10.5	9.4–NR	8.4	7.1–16.1	8.7	7.0–15.9
Overall survival rate (%)								
1 year %	98	95–99	99	93–100	99	95–100	936	81–97
2 years %	94	91–96	98	91–99	96	92–99	83	70–91
5 years %	73	67–78	79	67–86	73	64–81	68	53–79
10 years %	43	34–51	57	33–75	46	34–59	37	21–53
Time to progression (y)	4.5	3.9–5.9	3.9	3.2–4.7	7.2	5.2–8.1	2.5	1.7–3.7
Time to progression rate (%)								
1 year %	87	82–90	88.1	79–93	95	89–97	72	57–82
2 years %	74	68–78	73	63–81	83	75–88	58	43–70
5 years %	48	42–54	37	24–50	62	52–71	33	20–46
10 years %	19	12–28	12	1–35	31	18–46	5	0–18
No 1p19q deletion								
N	242		20		155		50	
Overall survival time (y)	3.7	3.0–4.6	2.2	1.4–5.5	5.0	3.8–6.7	1.9	1.4–2.8
Overall survival rate (%)								
1 year %	87	82–90	85	60–95	93	88–96	70	55–81
2 years %	66	59–71	55	31–73	74	66–80	47	32–60
5 years %	42	35–48	34	15–55	49	41–57	24	13–37
10 years %	31	24–38	13	1–39	41	32–49	11	4–24
Time to progression (y)	2.2	1.6–3.0	0.9	0.4–3.8	3.1	2.5–4.3	1.1	0.6–1.7
Time to progression rate (%)								
1 year %	66	60–72	46	23–67	75	67–81	50	35–64
2 years %	51	44–57	35	14–56	61	52–68	28	16–42
5 years %	34	28–41	28	10–50	39	31–48	23	12–37
10 years %	17	11–25	14	1–41	26	17–36	4	0–15

OS, with deletion status, treatment, age, KPS, extent of resection, and history of low-grade glioma as significant on multivariate analysis (Supplemental Table S2).

Discussion

Controversies among treatment options are best tested and answered in prospective randomized studies, and we encourage enrollment in ongoing trials. Results from the CODEL and CATNON phase III trials will be critically important to help make definitive treatment recommendations for AO and AOA. However, anaplastic oligodendroglial tumors are sufficiently rare (5%–10% of all gliomas)¹ that it is difficult to study them prospectively. Two large international phase III trials required over 12 years from activation to initial publication,^{2,3} with some analyses remaining immature.¹¹ CATNON and CODEL are larger studies and could take at least that long. In the interim, we sought to address several therapeutic issues concerning the initial

treatment of AO/AOA with a unique, large, international retrospective data set.

We confirmed the critical role of age, 1p19q deletion status, extent of resection, and KPS on survival in patients with AO/AOA. We also demonstrated the prognostic importance of tumor location. We suggest that PCV chemotherapy may be more effective than TMZ. These findings became evident because of the size of our study and raise important questions about how to treat such patients.

Treatment with CT + RT (sequentially and/or concurrently) at diagnosis lengthened TTP but not OS vs. CT alone for the overall cohort, likely because the majority of patients who received CT alone were treated with RT after progression. Unexpectedly, RT alone was associated with inferior TTP and OS.

In codeleted cases, TTP was shorter following CT than CT + RT, but differences in OS did not approach significance. We also observed shorter TTP following RT alone than CT alone. Deferring RT would avoid the risk of late RT-induced neurocognitive decline resulting from early RT^{12–14} that, part, led up to 42%

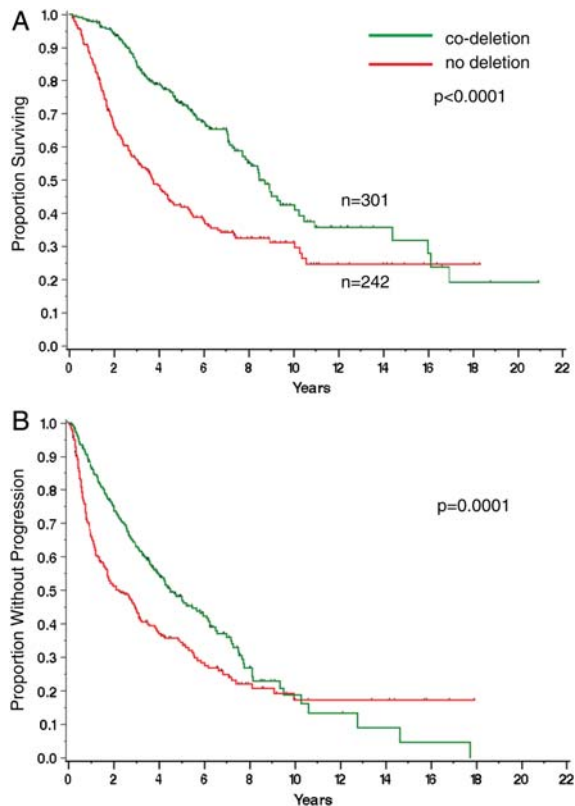


Fig. 2. Kaplan–Meier estimates of overall survival (A) and time to progression (B) for patients with tumors harboring 1p and 19q deletion (codeletion) or neither 1p nor 19q deletion (no deletion).

of neuro-oncologists to advise deferred RT in codeleted cases.⁵ CODEL will address this issue and compare quality of life and neurologic function following various initial treatment regimens. Among cases with no 1p or 19q deletion, both TTP and OS were shorter following CT or RT alone than CT + RT. This contrasts with subset analyses from RTOG 9402² and EORTC 26951³ and may reflect potential biases inherent in observational data. However, extrapolating from glioblastoma, in which 1p19q codeletion is rare, combined modality therapy (RT + TMZ) is now the accepted standard of care over either RT¹⁵ or CT alone¹⁶ and is paradoxical,³ as glioblastoma is considered less chemosensitive than codeleted tumors. CATNON will address this issue prospectively.

TMZ has largely replaced PCV in the treatment of gliomas. Surprisingly, our data demonstrated that PCV alone afforded better disease control than TMZ alone in 1p19q codeleted cases, with median TTP longer by more than 4 years, a medically and statistically significant difference despite the small sample size for each group. Recent results also suggest that responses of low-grade oligodendrogliomas to PCV are more durable than with TMZ,¹⁷ and complete responses of AO/AOA to PCV are more frequent (>50%)⁹ than to TMZ (6%).¹⁸ It is plausible that our finding is explained in part by a diagnostic shift in the definition of AO and AOA, with less stringent histologic criteria applied

over time,¹⁹ resulting in use of PCV in cases with more classic oligodendroglial histology that may be more responsive to treatment because TMZ was not available at the start of the study period. However, all patients in this sub-analysis had 1p19q codeleted tumors, which partially addressed this concern. No preplanned, powered formal prospective comparison of PCV versus TMZ has been conducted for patients with newly diagnosed AO or AOA, and none is likely to emerge. Randomized trials either were designed for patients with recurrent astrocytic tumors²⁰ or were not powered for this comparison. For example, NOA-04, a phase III trial by the Neuro-oncology Working Group of the German Cancer Society, randomized patients with newly diagnosed anaplastic gliomas (including anaplastic astrocytomas, AOs, and AOAs), but the size of each treatment cohort was underpowered for direct comparison of PCV versus TMZ alone in codeleted AO/AOA.^{4,7,21} PCV is well established as a more toxic regimen than TMZ,^{3,4,22} and patients with codeleted tumors may become long-term survivors at risk for late toxicities such as myelodysplasia. The risk for late hematologic toxicities may be higher with PCV, as the treatment intensity may be greater than with commonly used TMZ regimens. We did not collect toxicity information or address whether any potential improvement in disease control justifies greater potential toxicity. The observation that PCV led to longer TTP (and possibly OS) than did TMZ merits further study, but the limitations involved in this comparison herein caution against a definitive treatment recommendation.

Our study had several limitations, particularly its retrospective nature. We attempted to control for potential confounders through multivariate analyses. However, the observational nature of the study did not account for other or intangible clinical factors, as could a randomized design. Although tumor location was collected, tumor size was not captured, which could have affected resectability. Extent of resection and disease progression were also not confirmed by central imaging review or by using standardized response criteria.^{23,24} Treatment duration was not captured, and the potential impact of longer therapy on outcome was not examined. Similarly, detailed information on postprogression therapy (including resection, RT, or CT) was not collected, and we did not assess the potential influence of subsequent treatment(s) on OS. We also did not capture other clinical factors of potential prognostic importance reported in prior studies of anaplastic gliomas, such as symptom type or duration,²⁵ or histologic factors such as necrosis,³ endothelial abnormalities,³ and degree of anaplasia.²

Molecular information was also incomplete. For example, tumors exhibiting 1p deletion but without 19q testing may have harbored codeletion. However, lack of available archival tissue precluded 19q testing in such cases. Therefore, we analyzed the importance of codeletion against no deletion but did not examine the consequences of 1p or 19q deletion alone. The number of patients with partial deletion of either 1p or 19q was also low (<2%), and we did not assess clinical relevance.

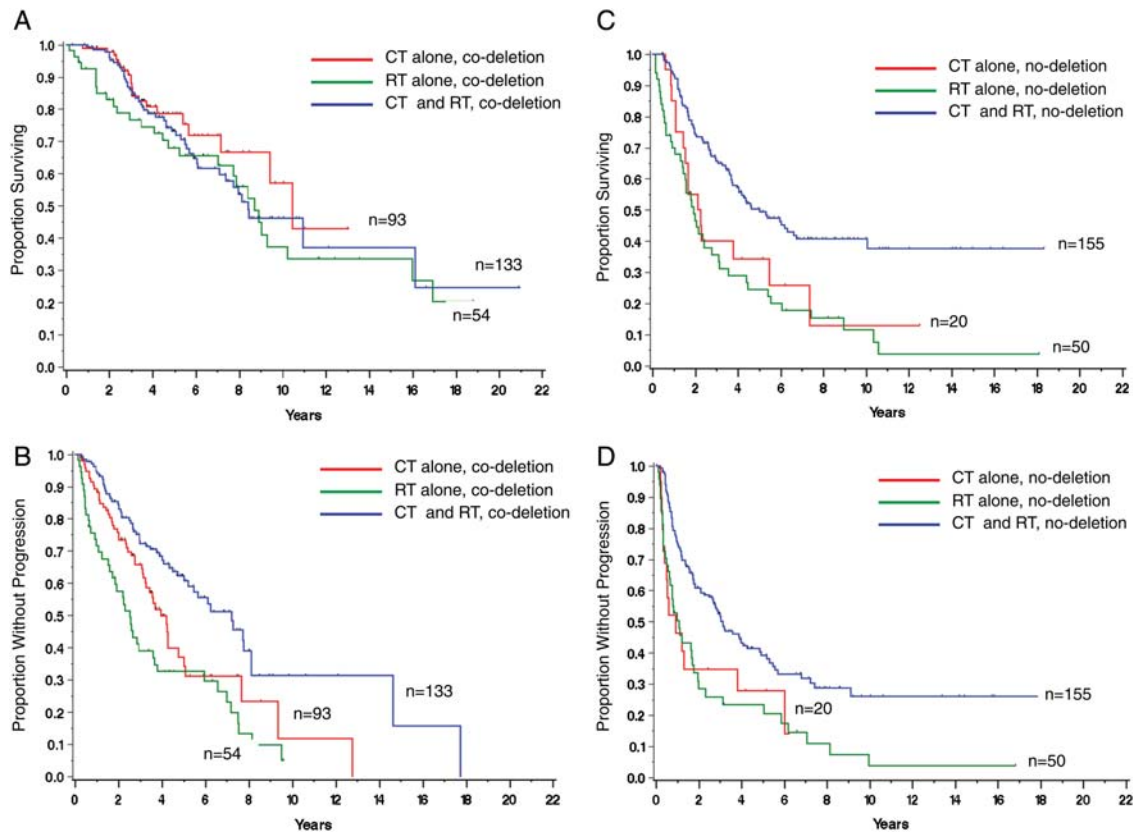


Fig. 3. Kaplan–Meier estimates of overall survival (A and C) and time to progression (B and D) by initial treatment (CT alone, RT alone, or CT + RT) and deletion status.

Table 4. Outcome following TMZ vs. PCV alone in 1p19q codeleted cases

Survival, 1p19q codeletion	TMZ alone (n = 68)		PCV alone (n = 21)	
	Median	95% CI	Median	95% CI
Overall survival time (y)	7.2	7.2–NR	10.5	5.6–NR
Overall survival rate (%)				
1 year %	100	Not estimable	95	71–99
2 years %	98.4	89–100	95	71–99
5 years %	72	55–83	90	66–97
10 years %	48	11–78	62	25–85
Time to progression (y)	3.3	2.6–4.2	7.6	4.2–9.3
Time to progression rate (%)				
1 year %	88	78–94	86	62–95
2 years %	68	55–78	86	62–95
5 years %	24	10–42	64	38–81
10 years %	24	10–42	17	1–50

Central pathology review was not performed because most archival tissue was not available, and the logistics of collecting, shipping, and reviewing material were both impractical and prohibitively expensive. Accordingly, shifting histologic criteria over time¹⁹ could have led to inclusion of cases as AO or AOA

that might be more appropriately classified as anaplastic astrocytomas¹⁹ or glioblastoma (if necrosis were evident),²⁶ an important consideration also noted by others.²⁷ However, despite the lack of central review, 48% of tested tumors harbored 1p19q codeletion. This is within the range of 25%–65% reported for codeletion in prospective studies that did require central review,^{2–4} lending further confidence that our data set reasonably encompassed AO and AOA. In addition, 68% of AOs in this study harbored codeletion, as did 20% of AOAs, which was similar to the codeletion rates reported in trials requiring central review that reported results by histology.^{2,4}

We also observed patients with tumors harboring 1p19q codeletion who died rapidly and those with no deletion who were long-term survivors (Fig. 2). There was no obvious clinically important prognostic factor that distinguished these groups. Possible explanations include erroneous chromosomal analyses or histology, or the impact of other molecular features not analyzed, such as *MGMT* promoter methylation and isocitrate dehydrogenase (*IDH*) mutations.^{4,27,28} However, 1p19q deletion status typically cosegregates with both *MGMT* promoter methylation and *IDH* mutation.^{28,29} For example, one study reported all 1p19q codeleted tumors also harbored *IDH* mutations.³⁰ 1p19q testing is also widely available, whereas assays for *MGMT* promoter methylation and *IDH* mutation are emerging.

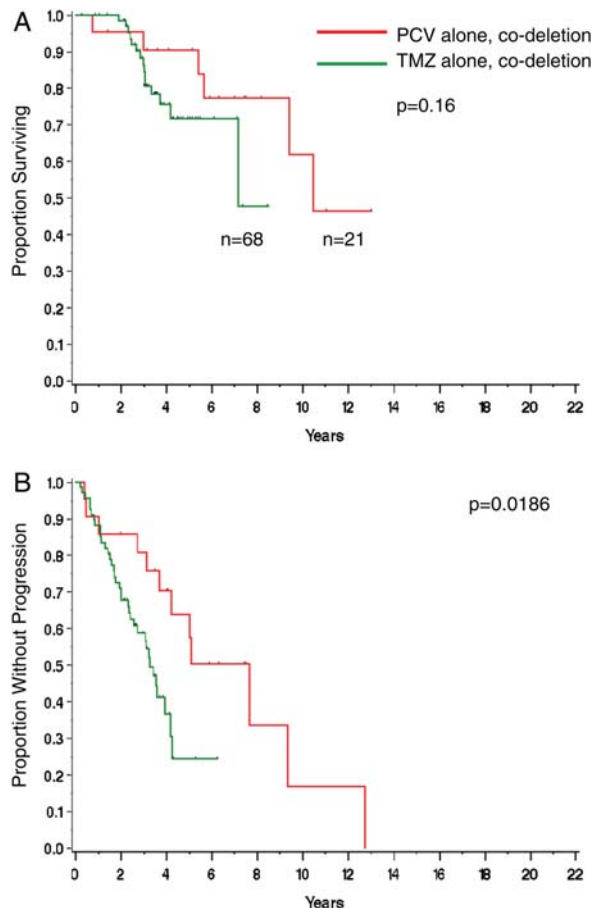


Fig. 4. Kaplan–Meier estimates of overall survival (A) and time to progression (B) in codeleted cases treated initially with either PCV or TMZ alone.

Subject to the limitations of study design, our data suggest that initial treatment with CT alone may be a reasonable option for patients with 1p19q codeleted tumors, and PCV appears to offer longer disease control than TMZ but with greater known toxicity and without a clear prolongation of survival. In cases with no 1p19q deletion, most neuro-oncologists advocate incorporating RT into the up-front treatment strategy,⁵ typically combined with CT as in glioblastoma.¹⁵ The only prospective randomized study to address outcome following CT alone, NOA-04, suggested non-inferiority of primary CT versus RT in anaplastic gliomas generally (rather than AO/AOA specifically),⁴ but did not report results by 1p19q deletion status or assess combined CT + RT.^{4,7} Our results suggest that combined CT + RT leads to longer disease control and survival than does CT or RT alone in AO/AOA with no 1p19q deletion. We did not address anaplastic astrocytomas, as did NOA-04.⁴

Successful completion of the CODEL and CATNON trials is essential to understand the optimal treatment

approach for newly diagnosed anaplastic gliomas, and we encourage accrual. While awaiting results from prospective studies, treatment of newly diagnosed AO/AOA is an area with many controversies and little consensus. Despite its limitations, our data set is mature, with medians well defined for all endpoints; is larger than completed phase III trials (RTOG 9402,² EORTC 26951,³ and NOA-04⁴); and provides practical data using routinely available information, such as histology and 1p19q status, that may help to guide treatment discussions.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

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Table 5. Predictors of overall survival

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
1p19q status				
Codeletion	0.50 (0.4, 0.7)	<.0001	0.47 (0.3,0.7)	<.0001
No deletion	1		1	
Initial treatment				
CT alone	0.69 (0.5,0.9)	<.001	0.58 (0.4, 0.9)	<.001
CT + RT	0.63 (0.5,0.8)		0.55 (0.4, 0.8)	
RT alone	1		1	
Histology				
AO	0.77 (.6, .9)	<.001	0.83 (0.6, 1.2)	.31
AOA	1		1	
Diagnosis date				
1980s	0.72 (0.4, 1.2)	.46	0.42 (0.2, 1.1)	.22
1990s	0.97 (0.8, 1.2)		0.88 (0.6, 1.3)	
2000s	1		1	
Age				
≥50	2.67 (2.2, 3.3)	<.0001	2.99 (2.1, 4.2)	<.0001
<50	1		1	
KPS				
<70	3.07 (2.4, 4.0)	<.0001	2.80 (1.7, 4.5)	<.0001
≥70	1		1	
Extent of resection				
Biopsy	2.25 (1.8, 2.9)	<.0001	1.79 (1.2, 2.7)	<.001
Resection	1		1	
Lobe				
Frontal	0.63 (.5, .8)	<.0001	0.72 (0.5, 0.98)	.04
Other	1		1	
Hemisphere				
Bilateral	1.77 (1.0, 3.1)	.04	2.61 (1.1, 6.0)	.03
Unilateral	1		1	
Prior LGG				
Yes	0.73 (0.5, 0.99)	.04	0.78 (0.5, 1.3)	.32
No	1		1	

HR, hazard ratio; LGG, low-grade glioma.

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