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Original Research Article

Differences in patterns of care and outcomes between grade II and grade III molecularly defined 1p19q co-deleted gliomas

Debra Nana Yeboa [a,b,*], James B. Yu [c,d], Eric Liao [b], Jason Huse [e], Marta Penas-Prado [f], Benjamin H. Kann [c], Erik Sulman [g], David Grosshans [a], Joseph Contessa [c]

[a] MD Anderson Cancer Center, Division of Radiation Oncology, Houston, TX, United States
[b] MD Anderson Cancer Center, Health Services Department, Houston, TX, United States
[c] Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT, United States
[d] Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center, Yale University, New Haven, CT, United States
[e] MD Anderson Cancer Center, Department of Pathology, Houston, TX, United States
[f] National Institute of Health, Neuro-Oncology Branch, Bethesda, MD, United States
[g] New York University, Radiation Oncology Department, New York, NY, United States

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ABSTRACT

Molecular markers are redefining classification of lower grade gliomas and ushering in a paradigm shift in their management. Our objective was to evaluate the differences in pattern of care and outcome by comparing grade II and grade III molecularly defined 1p19q co-deleted gliomas. We evaluated 1618 patients in the National Cancer Database diagnosed with 1p19q co-deleted gliomas from 2010 through 2014 and treated with surgery followed by radiation therapy (RT), chemotherapy (CT), or combined-modality therapy. Differences in patterns of care included that fifty-one percent of grade II tumors received surgery alone, whereas most patients with grade III tumors (86%) received surgery or biopsy followed by a form of post-operative therapy ($p < 0.001$). In a propensity score matched cohort, the Cox multivariable proportional hazards model with frailty testing identified significant covariates were age, comorbidity, histology and grade. Outcomes were different in overall survival even after adjusting for treatment received. The hazard for death for grade III 1p19q co-deleted gliomas was about 3.6 times higher ([HR] 3.69, 95% confidence interval [CI] 2.03–6.68, $p < 0.001$) than grade II 1p19q gliomas. Oligodendroglioma histology was associated with a lower likelihood of death (HR 0.40, 95% CI 0.23–0.70, $p < 0.001$). Our study is among the largest series to report on 1p19q co-deleted gliomas, which would otherwise require decades to acquire outside of large databases.

1. Introduction

Historically, patterns of care for 1p19q co-deleted gliomas have been driven largely based on tumor grade. Information on prior treatment patterns is pertinent in view of the shift toward management and outcomes becoming dependent on molecular classification. Studies reported that a molecularly based classification system had improved prognostic value over traditional histology and grade [1–4]. The system divides lower grade gliomas into three groups: type I (co-deletion of 1p and 19q and mutations in the gene for isocitrate dehydrogenase [IDH]), type II (IDH mutation alone), and type III (IDH wild-type) [3–5]. In an analysis of Japanese patients and The Cancer Genome Atlas (TCGA) Consortium, patients with type I 1p19q co-deleted grade II versus grade III gliomas had similar overall survival (OS) in the long term, with Kaplan Meier curves crossing after approximately 6–8 years [4]. A second TCGA analysis found that age, grade (II versus III), and molecular subtype were significantly predictive of mortality and survival after adjusting for other clinical factors such as histology [3]. Thus, as molecular classifications evolve to define management outcomes, differences in treatment patterns and outcomes according to tumor grade provide secondary complementary information.

Given the natural history of the disease with prolonged median survival, it may take 10 years to enroll the number of patients needed to report long term outcomes. To address the gap in knowledge of how treatment patterns, grade, and histology influence outcomes in the current molecular classification of 1p19q co-deleted gliomas, we analyzed patterns of care (extent of resection,

* Corresponding author at: 1515 Holcombe Blvd, Unit 97, Houston, TX 77030, United States.
E-mail address: dnyeboa@mdanderson.org (D.N. Yeboa).

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use of radiation and/or chemotherapy) and outcomes for patients with grade II and grade III 1p19q co-deleted gliomas in a large observational cohort study.

2. Methods

2.1. Study cohort and treatment definitions

Patients with 1p19q co-deleted brain tumors were identified from the National Cancer Database (NCDB) (Fig. 1), a database jointly sponsored by the American Cancer Society and the American College of Surgeons representing approximately 70% of new cancer diagnoses nationwide and more than 1500 Commission on Cancer–accredited facilities [6].

We first identified 1982 patients in the NCDB with a diagnosis of both 1p and 19q deletion (i.e., 1p19q co-deleted) from 2010 to 2014. We excluded 246 patients with infratentorial gliomas and patients <19 years old; then an additional 97 patients with grade I, grade IV, or unknown grade gliomas; and finally, 21 patients with incomplete treatment information or income, leaving 1618 patients with 1p19q co-deletion grade II or grade III oligodendroglioma, mixed glioma, or astrocytoma histology (Fig. 1).

A treatment variable was then created based on different permutations of biopsy, surgery, RT, or chemotherapy. The 1618 patients were identified as having undergone biopsy only; surgery only; biopsy or surgery followed by RT; biopsy or surgery followed by chemotherapy; or biopsy or surgery followed by postoperative combined chemotherapy and RT.

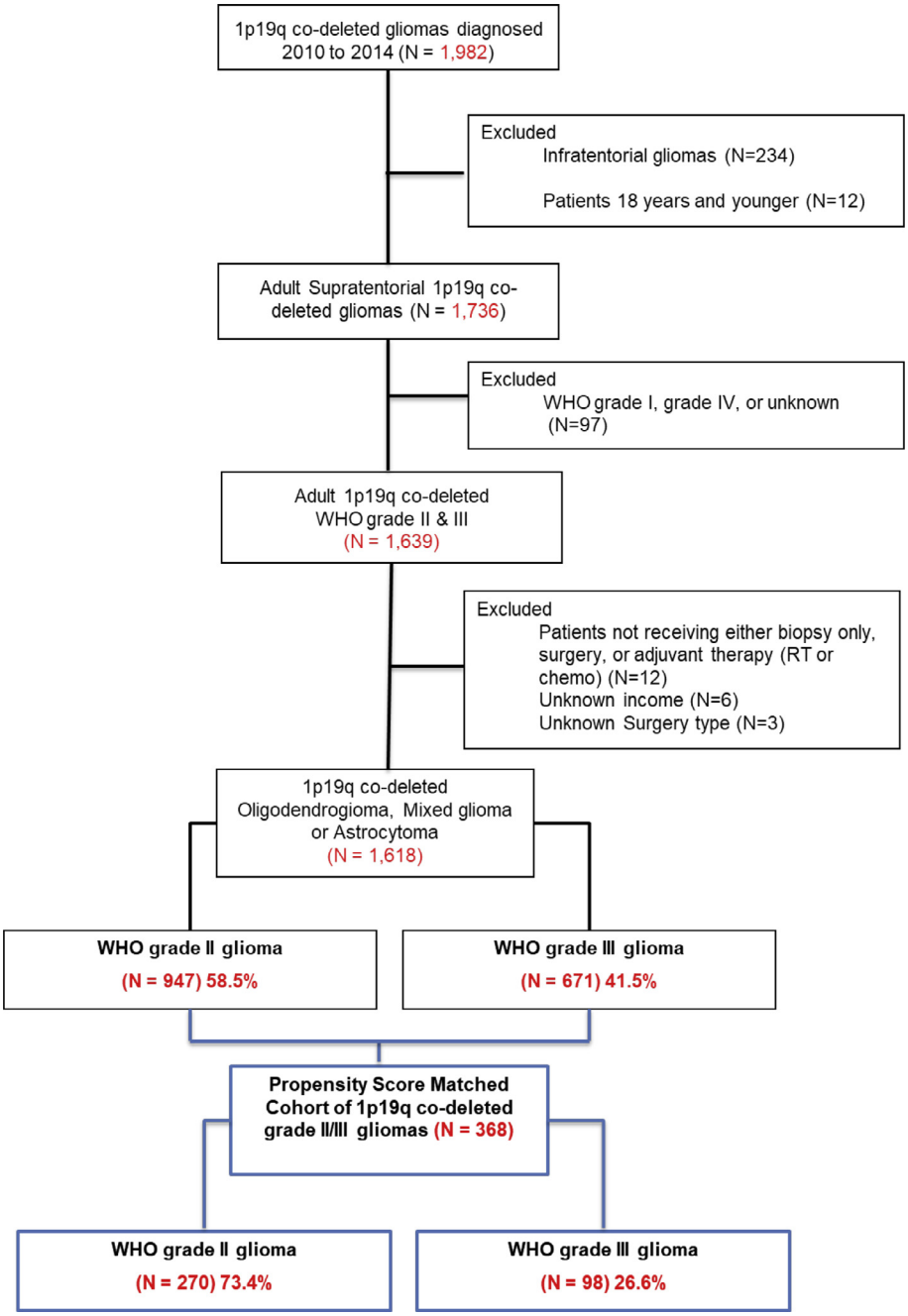

Fig. 1. Study cohort consort diagram.

2.2. Statistical analysis

Patient demographic and clinical covariates assessed included age at diagnosis, sex, race, Charlson-Deyo comorbidity score (CDCS), facility where patient was diagnosed, geographic location, median income quartile, tumor grade and histology. The Charlson-Deyo comorbidity score is a comorbidity metric available in NCDB and is among the most common comorbidity metrics for health services data [7]. The original Charlson index measured 19 weighted comorbid conditions influencing all-cause mortality and was adapted by Deyo et al. for large administrative databases [8]. The chi-square test and Wilcoxon signed-rank test were used to evaluate covariate differences between patients with grade II vs. grade III 1p19q co-deleted glioma. Summary statistics were used to compare the percentages of patients with grade II or III glioma receiving different forms of treatment. Kaplan-Meier analysis and log-rank tests were used to assess OS over time. Cox proportional hazards regression modeling was used to assess associations between the World Health Organization (WHO) glioma grade and the outcome of death when adjusting for significant clinical covariates, with a p value <0.05 defining significance. Validation of the Cox proportional hazards assumption was done before the analysis by using log-log survival plots.

Additionally, propensity score matching was done in an attempt to further balance patients by known covariates. Propensity score matching was done with scores estimated from a logistic regression model predicting the likelihood of receiving surgery, adjusted by age, gender, race, income, comorbidity, disease grade, histology, and diagnosis year. Matching was done 1:1 nearest-neighbor matching without replacement. Survival analysis including Kaplan-Meier and log-rank tests were repeated on the propensity score matched cohort. Additionally, a sensitivity analysis of all patients receiving definitive treatment was included with Kaplan-Meier and log-rank tests to further attempt to minimize confounders associated with receipt of treatment. Multivariable adjusted Cox proportional hazards regression modeling was used to assess associations with overall survival among the propensity score matched cohort. A frailty model was also used for the propensity score matched cohort analysis. Statistical analyses were done with Statistical Analysis Software (SAS) v9.4.

3. Results

3.1. Patient characteristics

Though all patients shared the same molecular subtype of 1p19q co-deletion, there were statistically significant differences in age. The median age at diagnosis for grade II 1p19q co-deleted gliomas was 43.2 years in comparison to 47.6 years for grade III gliomas ($p < 0.001$). Almost 42% of grade II patients were age 19–39 years old in comparison to 28.3% of grade III, and 20.7% of grade III patients were over 60 years old in contrast to only 10.7% of grade II patients ($p < 0.001$). No significant differences were found in sex, race, or comorbidity between tumor grade groups (Table 1). The majority of patients were white (90.9%) and without significant comorbidity (CDCS = 0 in 83.7%). More grade III patients were diagnosed at an academic/research program or cancer center/comprehensive cancer center than grade II patients. Seventy-six percent were oligodendrogliomas, while 23.8% were classified as mixed gliomas or astrocytomas. Significantly more grade II patients did not undergo a resection (14.8%) in comparison to grade III (6.7%) ($p < 0.001$). Patterns of initial treatment varied significantly by tumor grade. Fifty one percent of patients with grade II tumors underwent resection alone, whereas most patients with grade III tumors (86%) received resection or biopsy followed by a form of post-operative therapy ($p < 0.001$) (Table 1).

In the propensity score matched cohort, significant covariates were consistent with the primary original cohort in several aspects. We identified that age was still significantly different among the 1p19q co-deleted subtype. While 41.0% of grade II patients were age 19–39, only 19.4% of grade III patients were age 19–39 years old. Similarly, 35.7% of grade III patients were over 60 years old, while only 14.4% were grade II ($p < 0.001$). More grade III patients were diagnosed at an academic program than a cancer center (51% vs 29.6%) ($p < 0.001$). Oligodendrogliomas made up 77.4% of grade II patients in comparison to 55.1% of grade III patients ($p < 0.001$). In the propensity matched cohort, significantly more grade II patients underwent surgery followed by chemotherapy alone (25.9%) in comparison to grade III patients (11%). In contrast 64.3% of grade III patients underwent adjuvant chemotherapy and radiation in comparison to 15.9% of grade II patients ($p < 0.001$). (Table 1).

4. Outcomes by clinical characteristics and treatment

In a Cox multivariable proportional hazards model for the entire cohort adjusting for multiple clinical and patient factors, covariates that conferred differences in likelihood for mortality were age, race, comorbidity, tumor histology, and tumor grade. Age $\geq$60 years was associated with worse OS (hazard ratio [HR] 5.98, 95% confidence interval [CI] 3.86–9.26, $p < 0.001$) as was age $\geq$40–59 years in comparison to patients $\leq$39 years (HR 2.03, 95% CI 1.34–3.07, $p = 0.001$). Having at least 1 comorbidity was associated with a hazard of death twice that of those without (HR 2.04, 95% CI 1.49–2.79, $p < 0.001$). In the entire cohort, oligodendroglioma histology was associated with lower hazard ratio of death in comparison to mixed glioma/astrocytoma (HR 0.41, 95% CI 0.30–0.56, $p < 0.001$). Grade III histology was associated with a higher risk of death (HR 2.17, 95% CI 1.53–3.07, $p < 0.001$).

Within the propensity score matched cohort, the Cox multivariable proportional hazards model with frailty testing identified significant covariates were age, comorbidity, histology and grade similar to the primary overall cohort. Patients $\geq$60 years had a higher likelihood of death (HR 4.65, 95% CI 2.09–10.32, $p < 0.001$) as did those with at least one comorbidity (HR 3.76, 95% CE 2.12–6.69, $p < 0.001$). Patients with oligodendroglioma histology had a 60% lower hazard of death (HR 0.40, 95% CI 0.23–0.70, $p = 0.001$). In contrast, the hazard for death for grade III was about 3.7 times higher ([HR] 3.69, 95% confidence interval [CI] 2.03–6.68, $p < 0.001$). On both adjusted Cox proportional hazard analysis for the entire cohort and in the propensity score match, treatment modality was not yet significantly associated with differences in hazard of mortality (Table 2).

The overall survival estimates at 60 months (5 years) were different for grade II and grade III gliomas. Sixty-month survival was 90% (grade II) vs 74% (grade III) in the entire cohort and 86.7% (grade II) vs 57.4% (grade III) in the propensity matched cohort ($p < 0.001$) (Fig. 2). Additional sensitivity analysis was done among the cohort of patients that received a form of definitive treatment after biopsy or surgery. It revealed that for those receiving adjuvant radiation the 60-month survival was 75.2% vs 79.8% (grade II vs grade III) in the entire cohort and 71.9% vs 75.0% (grade II vs grade III) in the propensity score matched cohort (Supplement Fig. A). For patients receiving adjuvant chemotherapy, the 60-month survival estimates for grade II vs grade III patients in the overall cohort were 92.4% vs 82.4% in the entire cohort, and in the propensity score matched cohort were 89.1% vs 80.0% (Supplement Fig. B). For patients receiving adjuvant chemotherapy and radiation therapy, the 60-month overall survival were 82.5% vs 72.6% (grade II vs grade III) in the overall cohort patients and were 95.4% vs 54.5% in the

Table 1
Patient clinical and sociodemographic characteristics of the study and propensity score matched cohort.

	Entire cohort							PS matched cohort						
	All		WHO Grade					All		WHO Grade				
			Grade II		Grade III		p-value			Grade II		Grade III		p-value
	N	Col%	N	Col%	N	Col%		N	Col%	N	Col%	N	Col%	
All cases	1618	100	947	100	671	100	–	368	100	270	100	98	100	–
Age (years)							<0.0001							<0.0001
19–39	586	36.2	396	41.8	190	28.3		132	35.9	113	41.9	19	19.4	
40–59	794	49.1	452	47.7	342	51.0		162	44	118	43.7	44	44.9	
≥60	238	14.7	99	10.5	139	20.7		74	20.1	39	14.4	35	35.7	
Sex							0.582							0.278
Male	898	55.5	531	56.1	367	54.7		216	58.7	163	60.4	53	54.1	
Female	720	44.5	416	43.9	304	45.3		152	41.3	107	39.6	45	45.9	
Race							0.346							0.669
White	1470	90.9	855	90.3	615	91.7		346	94	253	93.7	93	94.9	
Other	148	9.1	92	9.7	56	8.35		22	5.98	17	6.3	*	5.1	
Comorbidity							0.537							0.953
No comorbidity	1354	83.7	797	84.2	557	83.0		311	84.5	228	84.4	83	84.7	
Comorbidity ≥1	264	16.3	150	15.8	114	17.0		57	15.5	42	15.6	15	15.3	
Facility Type							<0.0001							<0.0001
Cancer Center/Other	400	24.7	211	22.3	189	28.2		93	25.3	64	23.7	29	29.6	
Academic/Research Program	632	39.1	340	35.9	292	43.5		143	38.9	93	34.4	50	51.0	
Unknown	586	36.2	396	41.8	190	28.3		132	35.9	113	41.9	19	19.4	
Facility Location							<0.0001							<0.0001
North East	209	12.9	104	11.0	105	15.7		47	12.8	28	10.4	19	19.4	
South	150	9.27	78	8.2	72	10.7		38	10.3	24	8.8	14	14.3	
Central	421	26.0	237	25.1	184	27.4		101	27.5	73	27.0	28	28.6	
West Coast	252	15.6	132	13.9	120	17.9		50	13.6	32	11.9	18	18.4	
Unknown	586	36.2	396	41.8	190	28.3		132	35.9	113	41.9	19	19.4	
Income ($)							0.249							0.642
<48,000	560	34.6	335	35.4	225	33.5		129	35.1	98	36.3	31	31.6	
48,000–62,999	449	27.8	248	26.2	201	30.0		123	33.4	87	32.2	36	36.7	
≥63,000	609	37.6	364	38.4	245	36.5		116	31.5	85	31.5	31	31.6	
Histology							<0.0001							<0.0001
Oligodendroglioma	1233	76.2	778	82.2	455	67.8		263	71.5	209	77.4	54	55.1	
Mixed glioma/Astrocytoma	385	23.8	169	17.9	216	32.2		105	28.5	61	22.6	44	44.9	
Treatment							<0.0001							<0.0001
No treatment/Biopsy only	61	3.8	50	5.3	11	1.6		61	16.6	50	18.5	11	11.2	
Biopsy/Surgery + RT	135	8.3	95	10.0	40	5.9		33	8.97	28	10.4	*	5.1	
Biopsy/Surgery + chemo	322	19.9	202	21.3	120	17.9		81	22	70	25.9	11	11.2	
Biopsy/Surgery + CRT	534	33.0	117	12.4	417	62.2		106	28.8	43	15.9	63	64.3	
Surgery only	566	35.0	483	51.0	83	12.4		87	23.6	79	29.3	*	8.2	
Year of Diagnosis							0.767							0.975
2010	279	17.2	172	18.2	107	16.0		84	22.8	63	23.3	21	21.4	
2011	287	17.7	168	17.7	119	17.7		70	19	51	18.9	19	19.4	
2012	311	19.2	182	19.2	129	19.2		68	18.5	48	17.8	20	20.4	
2013	334	20.6	188	19.9	146	21.8		64	17.4	48	17.8	16	16.3	
2014	407	25.2	237	25.0	170	25.3		82	22.3	60	22.2	22	22.5	
Surgical resection							<0.0001							0.014
Total gross resection	717	44.3	399	42.1	318	47.4		86	23.4	53	19.6	33	33.7	
Subtotal resection	716	44.3	408	43.1	308	45.9		98	26.6	78	28.9	20	20.4	
No surgery	185	11.4	140	14.8	45	6.7		184	50	139	51.5	45	45.9	

* N suppressed for patients <10 per NCDB data use agreement.

propensity score matched cohort (Supplement Fig. C). For patients undergoing surgery alone, grade II patients had higher overall survival of 93.4% compared to 65.9% for grade III gliomas. In the propensity score matched cohort, OS was 80.1% for grade II while all grade III patients receiving only surgery alone passed or were censured by 60 months (Supplement Fig. D).

5. Discussion

Our study revealed variations in treatment patterns by grade among 1p19q co-deleted glioma and showed outcomes differed within the cohort. After adjustments for differences in treatment received, patients with grade III gliomas had a higher likelihood of death than that for their grade II glioma counterparts, as did older patients with comorbidities or non-oligodendroglioma histology. Our study was robust with both a cohort of over 1600 patients and with a propensity score analysis to adjust for known covariates.

Recent landmark studies detailing molecular characteristics in lower-grade glioma have redefined prognostic tumor subtypes that can be used to personalize and optimize therapy [1–4]. Molecular analysis of the heterogeneous cohort of IDH mutant diffuse gliomas have found overall survival between grade II and grade III to be similar [9,10]. An analysis of mitotic index and grade in 475 IDH mutated gliomas found OS to be similar between 10 and

Table 2
Multivariable cox proportional hazard model of overall survival in the study and propensity score matched cohort.

	Cox PH Reg.				Frailty model			
	Entire cohort N = 1618				PS matched cohort N = 368			
	HR	95% CI		p-value	HR	95% CI		p-value
Age (years)				<0.001				<0.001
19–39	1.000				1.00			
40–59	2.03	1.34	3.07	0.001	1.75	0.81	3.75	0.148
60+	5.98	3.86	9.26	<0.0001	4.65	2.09	10.32	<0.001
Sex				0.246				0.078
Female	1.00				1.00			
Male	1.18	0.89	1.57	0.246	1.66	0.94	2.92	0.078
Race				0.162				0.078
White	1.00				1.00			
Other	1.40	0.87	2.27	0.162	1.53	0.58	4.03	0.078
Comorbidity (Charlson-Deyo)				<0.001				<0.001
No comorbidity	1.00				1.00			
Comorbidity ≥1	2.04	1.49	2.79	<0.001	3.76	2.11	6.69	<0.001
Income ($)				0.001				0.189
<48,000	1.00				1.00			
48,000–62,999	0.69	0.49	0.98	0.038	0.64	0.35	1.18	0.158
≥63,000	0.51	0.37	0.72	<0.001	0.57	0.29	1.13	0.110
Histology				<0.001				<0.001
Mixed glioma/Astrocytoma	1.00				1.00			
Oligodendroglioma	0.41	0.30	0.56	<0.001	0.40	0.23	0.70	0.001
WHO Grade				<0.0001				<0.0001
Grade II	1.00				1.00			
Grade III	2.17	1.53	3.07	<0.001	3.69	2.03	6.68	<0.001
Treatment				0.322				0.273
No treatment/Biopsy only	1.00				1.00			
Biopsy/Surgery + RT	0.92	0.39	2.19	0.866	0.95	0.30	2.97	0.942
Biopsy/Surgery + chemo	0.58	0.25	1.34	0.203	0.58	0.20	1.66	0.312
Biopsy/Surgery + CRT	0.81	0.36	1.82	0.616	1.03	0.41	2.59	0.943
Surgery only	0.70	0.31	1.58	0.399	1.97	0.77	5.06	0.156
Year of Diagnosis (continuous)	1.07	0.95	1.20	0.247	1.05	0.85	1.30	0.627

15 years, though outcomes by grade of the 211 1p19q co-deleted gliomas included are unknown [9]. The relative rarity of 1p19q co-deleted gliomas, contributing about one-fourth of lower-grade gliomas [3], makes analyzing prognostic factors more challenging. Our study benefits from a notably large sample size of 1618 co-deleted gliomas and additionally accounts for the treatment differences in management of grade III vs II 1p19q co-deleted glioma which was not included in the overall survival analysis of prior studies. Thus, findings from our study are complementary to the molecular studies that support the use of personalized post-operative therapy addressing both molecular and clinical factors for 1p19q co-deleted gliomas.

First, our findings reflect national patterns of care for post-operative treatment selection and supports that post-operative therapy improves survival outcomes in patients with grade III 1p19q co-deleted glioma. Consistent with prior guideline treatment recommendations, patients with grade II or grade III gliomas received therapy according to grade [11]. Patients with grade II tumors were more likely to receive resection alone because a subgroup of these patients with favorable disease may reserve post-operative therapy for salvage. For instance, the European Organisation for Research and Treatment of Cancer (EORTC) trial 22,845 found no difference in median OS rates at about 7 years for early versus delayed RT in low grade gliomas [12]. In our study patients with grade III gliomas were more likely to receive post-operative therapy consistent with prior randomized control trials supporting the use of adjuvant RT and chemotherapy [13–15]. In an institutional review of anaplastic oligodendrogliomas which included 301 1p19q co-deleted gliomas, 93 patients received chemotherapy alone, 133 received chemotherapy and radiation, 54 received radiation alone, and 21 received other or no therapy [16]. Thus, while practice patterns of post-operative therapy may still be based on either molecular characteristics or grade, there are variations in institutional practice preferences that must be taken into account.

The prognostic value of tumor grade in 1p19q co-deleted gliomas is evolving and requires further clarification as molecular classification is increasingly being incorporated into treatment decision-making algorithms. Clinical trials such as CODEL [17] have already been amended to include patients with both grade II and III gliomas. The CODEL trial is examining RT followed by procarbazine, lomustine (CCNU), and vincristine (PCV), versus RT and concurrent TMZ and adjuvant TMZ. Because the trial was recently amended to include both grade III as well as high-risk grade II 1p19q co-deleted gliomas, it will provide valuable insight for future management, and eventually the results from this study may further clarify if there will be a role for grade in future treatment decision-making. NRG BN005 [18] is enrolling both grade II or grade III IDH mutant gliomas and randomizing patients to protons versus intensity modulated therapy with photons to assess for improvement in neuro-cognitive toxicity profiles. Both cohorts would be treated to 54 Gy, a dose typically used previously for only grade II. The rationale is grade II and grade III IDH mutant gliomas may have similar prognosis and thus be managed similarly. We await the final results of these important trials to address the influence of both combined-modality therapy and tumor grade [19].

Lastly, histology and grade were found to influence overall survival in our study cohort. Approximately 23% of 1p19q co-deleted gliomas were non-oligodendroglioma in the prior conventional neuropathology assessment, similar in range to the 18% reported in The Cancer Genome Atlas Network [2] publication identifying a subset of 2% astrocytomas and 16% mixed gliomas. Grade, rather than histologic group, was significantly associated with survival in

	Entire Cohort		PS matched cohort	
	WHO Grade II N=947	WHO Grade III N=671	WHO Grade II N=270	WHO Grade III N=98
Survival rate est.				
12 M	0.989	0.948	0.978	0.865
24 M	0.968	0.891	0.962	0.764
36 M	0.961	0.880	0.948	0.751
48 M	0.933	0.772	0.901	0.596
60 M	0.900	0.740	0.867	0.574

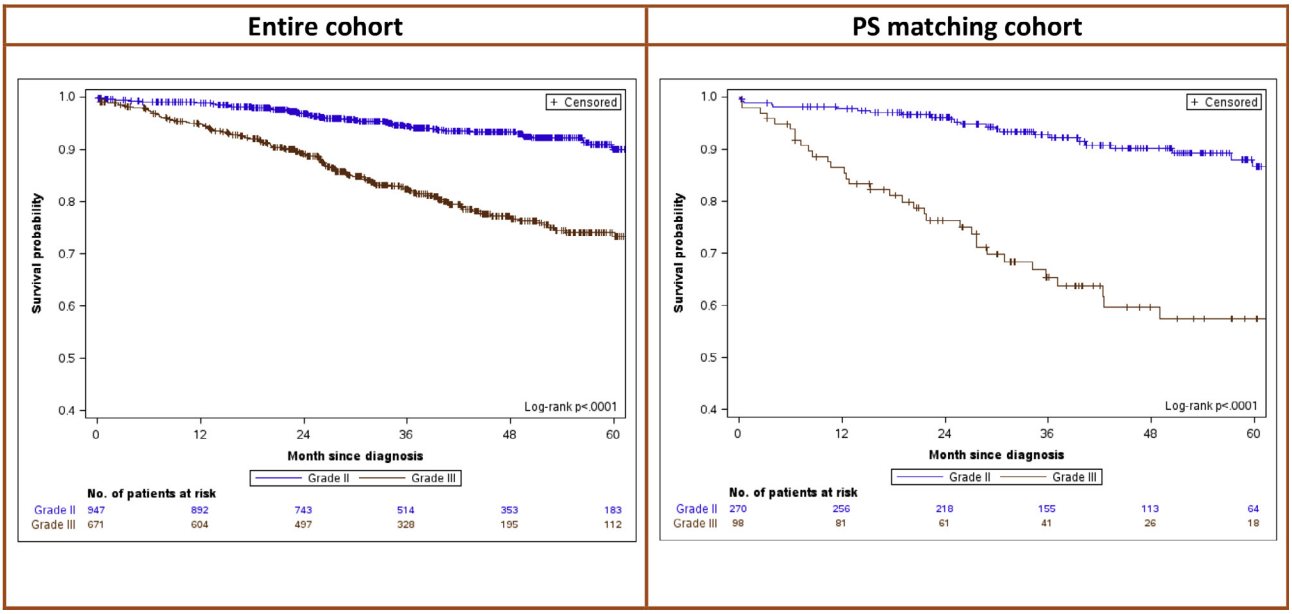

Fig. 2. Overall survival (OS) of patients with 1p19q co-deleted gliomas by tumor grade with Kaplan Meier OS estimates for the study and propensity score matched cohort.

the Cancer Genome Atlas Network analysis. Survival graphs from the supplemental appendix (S22) show worse overall survival for astrocytomas during the initial years despite similar molecular profile. Outcomes overlapped only after at least 10 years [2]. These are likely consistent with our study's early data. Secondly, from the Eckel-Passow et al. [3] study the multivariable overall survival analysis in the cox proportional hazard model of Grade II–IV gliomas showed the hazard ratio for grade to be significant (1.49 [1.03–2.15]). When examined by histology though, the confidence intervals crossed the reference value of one. For instance, the HR for astrocytoma or mixed gliomas histology compared to oligodendrogliomas were 1.42 [0.84–2.39] and 1.21 [0.74–1.99] [3]. These variations may be related to length of follow up. Histology may in the initial years show possible differences in outcomes and provide early prognostic information. Further investigation is needed into the molecular drivers that contribute to long term survivors and similar outcomes after 10 years among the different histological groups.

Our analysis is complementary to molecular based analysis yet has limitations inherent to observational databases. The study primarily addresses planned initial post-operative therapy outcomes for treatment with recorded surgery alone, post-operative RT, post-operative chemotherapy, and combined modality, and does not address sequential therapy, which in randomized trials has shown benefit over modalities such as post-operative RT alone [13,20]. Next, although significant survival differences were identified, follow-up time was limited and some subgroups has small sample size. Longer follow-up time may clarify the role of tumor grade in the emerging molecular era. Our findings, however, are consistent with the separation in OS during the initial follow-up years of the cohort of Japanese patients and TCGA Consortium [4] as well as the second TCGA analysis that identified age and grade as significant to OS on adjusted analysis [3]. Our analysis is consistent with the early differences in survival curves from TCGA analysis and can provide hypothesis generating information for future analysis on patient outcomes by grade. Patient performance status and biases for treatment selection are also potential confounders. Nevertheless, OS outcomes were significantly different for patients with grade II versus grade III glioma on Kaplan-Meier analysis at up to 5 years on propensity score matched analysis to account for known covariates, although we could not adjust for the unknown. Our findings are also consistent with outcomes for low grade and anaplastic gliomas when examined separately [21,22] as well as the TCGA analysis identifying age and grade to be predictors [3]. NCDB data lacked IDH status. There are reports of a series of 8 glioblastomas that harbored 1p19q co-deletion [23]. However, the vast majority of 1p19q co-deletions harbor IDH mutations and would be type I gliomas consistent with reported molecular classifications [24]. Our study was limited to grade II and grade III gliomas to minimize the likelihood of these exceptions in the data. Lastly, the specific chemotherapy agent (PCV vs. temozolomide) was not available for analysis. However over 90% of patients were treated with single-agent chemotherapy suggesting use of temozolomide [data not shown]. For IDH mutant, 1p19q co-deleted

grade III gliomas, the time to treatment failure was different between PCV vs TMZ in a prospective randomized trial of sequential chemoradiation, although no difference in OS was found [25].

In conclusion, our study with one of the largest cohorts of specifically grade II versus grade III 1p19q co-deleted gliomas, provides relevant information on real-world outcomes in a national cohort. While we await the results of clinical trials such as CODEL and BN005, our study offers context regarding historical treatment patterns and outcomes in the community for 1p19q co-deleted gliomas. Further data are needed with longer follow-up to determine the clinical effectiveness of various post-operative therapies for all 1p19q co-deleted gliomas related to treatment, grade and histology.

Compliance with ethical standards

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2018.12.003.

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