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Impact of 1p/19q codeletion status on extent of resection in WHO grade II glioma: Insights from a national cancer registry

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ABSTRACT

Objective: Traditionally, extent of resection (EOR) has been seen as a surgical parameter that can predict survival outcomes of surgically managed WHO grade II gliomas. The aim of this study was to evaluate if such an influence was potentially affected by 1p/19q codeletion status based on a national cancer registry.

Patient and methods: All adults diagnosed with grade II gliomas between the years 2004 to 2014 were queried from the National Cancer Database (NCDB). The population was then divided based on 1p/19q codeletion status, and then Kaplan-Meier, univariate and multivariate Cox regression analyses were utilized to evaluate the prognostic effect of EOR.

Results: In total, 1,498 grade II gliomas satisfied inclusion for analysis, with the 1p/19q non-codeleted in 705 (47%) cases, and codeletion in 793 (53%) cases. When the cohort was divided based on codeletion status, Kaplan-Meier modelling and univariate regression analyses indicated that gross total resection (GTR) was significantly associated with greater 5-overall survival (OS) in both 1p/19q non-codeleted and codeletion groups. Upon multivariate analysis which incorporated adjuvant therapy status, the significance of GTR was only retained in the 1p/19q non-codeletion group after post-hoc adjustment.

Conclusion: Our findings indicate that the survival impact of GTR in grade II gliomas may be affected by 1p/19q codeletion status within the first five years after surgery based on overall survival. Therefore, molecular diagnostics have potential clinical application in surgery outcomes, and validation of the reported findings will assist in surgical planning if such an association can be thoroughly established.

1. Introduction

Low grade gliomas (LGG), which includes World Health Organization (WHO) grade II gliomas, present a clinical dilemma in management for although benign, they possess an appreciable tendency to progress to malignancy years later. [1] As such, the optimal treatment for these tumors, including surgical resection, is controversial [2,3]. Studies [4,5] have observed improved overall survival (OS) with greater extent of resection (EOR) in grade II glioma, however due to their lack of prospective and randomized natures, distinct causality has yet to be firmly established.

The 1p/19q codeletion occurs when there is complete deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), determining the codeletion status. [6] In 2015, the most comprehensive genomic analysis of LGG was published by the Cancer Genome Atlas Research Network, which identified the 1p/19q codeletion as a significant prognostic factor for longer OS [7]. One year later, the WHO Classification for Tumors of the Central Nervous System effectively validated the long-held belief that this marker was pathognomonic for oligodendroglioma, a common LGG [8]. In the context of grade II glioma management however, there remains today great uncertainty as to how the 1p/19q codeletion status in LGG can affect and be used to prognosticate these tumors beyond histopathology.

There is an emerging belief that biomarkers such as 1p/19q codeletion status may influence the overall success of glioma resection, in particular affecting the survival benefit of EOR. [9,10] This has yet to be directly demonstrated in grade II glioma. Therefore, the aim of this study was to investigate the five-year overall survival significance of

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EOR in grade II glioma groups delineated by 1p/19q codeletion status using a national cancer registry to report any potential merit in outcome influence by this molecular status.

2. Patient and methods

All data used for this study were extracted from the National Cancer Database (NCDB), a database maintained by the Commission on Cancer and the American Cancer Society which describes over 70% of new cancer diagnoses from 1500 hospitals in the United States. [11] The database was queried for all WHO LGG diagnosed between 2004–2014 that satisfied the following criteria: 1) histological diagnosis of WHO grade II, 2) glioma histopathology, primarily astrocytoma, oligodendroglioma and mixed astro-oligodendroglioma, 3) evidence of surgical intervention with EOR as either biopsy, subtotal resection (STR) or gross total resection (GTR), 4) confirmed 1p/19q status of either absent or present, 5) confirmed mortality status and last time of contact, and 6) patients ≥18 years old. Additionally, an exclusion criterion was 1) if either chemotherapy and radiation therapy status was not reported.

All patient and tumor characteristics were pooled collectively, and then separated into two groups based on 1p/19q codeletion status being absent or present. Comparison of characteristics between the two groups were performed utilizing the Wilcoxon rank sum tests for continuous variables and Chi-squared test for categorical data. These characteristics were age, Karnofsky Performance Score (KPS), sex, histology, frontal lobe location, chemotherapy use, radiation therapy use and EOR. EOR was delineated as either biopsy, STR or GTR. Preliminary survival analyses were conducted using the Kaplan-Meier technique and interaction with survival indicated by log-rank P-values, and follow-up time was limited to the first 60 months to ensure adequate cohort size. Life tables were constructed to provide estimates of 1-, 2- and 5-year OS.

Univariate Cox regression analysis was then performed to identify specific prognostic factors in both groups. Categorical variables with ≥90% occurring in one category were excluded to avoid statistical imbalance. The variables which appeared to potentially influence OS ($P < 0.15$) were then included in a multivariate Cox regression analysis using proportional hazard ratio (HR) modelling. All P-values were 2-sided with significance defined as $P < 0.05$. We then conducted a Bonferroni correction post-hoc analysis for multivariate regression results to determine the significance of our findings accounting for the multiple potential interactions between parameters. All statistical analyses were conducted with STATA 14.1 (StataCorp, College Station, Texas).

3. Results

3.1. Characteristics

A total of 1498 WHO grade II glioma cases were identified to satisfy all criteria, with the 1p/19q non-codeleted in 705 (47%) cases, and codeletions in 793 (53%) cases (Table 1). There were 60 cases of singly deleted 1p or 19q, however, they were excluded on the basis of insufficient statistical power. Overall, there were 651 (43%) female and 847 (57%) male patients, with median age of 40 years and median Karnofsky Performance Score (KPS) of 90. In terms of histology, 233 (16%) cases of astrocytoma, 840 (56%) cases of oligodendroglioma, and 416 (28%) of mixed astro-oligodendroglioma were identified. There were 857 (57%) glioma localized to the frontal lobe. In terms of therapy regimens, 568 (38%) received chemotherapy and 431 (29%) received radiation therapy, which were not mutually exclusive. For surgical outcomes, biopsy was performed in 349 (23%) cases, subtotal resection (STR) in 553 (37%), cases, and gross total resection (GTR) in the remaining 596 (40%) cases. Median follow-up was 56 months (range, 0.3–75).

Comparing the 1p/19q non-codeleted versus codeletion groups, the incidence of histology, frontal lobe location, chemotherapy and radiation therapy were significantly different (**all $P < 0.01$**) (Table 1). It is worth noting that EOR was not statistically different between the two groups (**$P = 0.60$**).

3.2. Overall survival

Overall, Kaplan-Meier estimates for 1-, 2- and 5- year OS were 98%, 95% and 83% respectively. Kaplan-Meier analysis indicated that OS was statistically significantly influenced by 1p/19q codeletion status, histology, frontal lobe location, chemotherapy, radiation therapy and EOR separately (**all log-rank $P < 0.01$**) (Table 1).

In the 1p/19q non-codeletion group, Kaplan-Meier estimates for 1-, 2- and 5- year OS were 97%, 94% and 76% respectively (Fig. 1, A). When separated in terms of EOR, estimates for 1-, 2- and 5- year OS were 94%, 90% and 73% in the biopsy group, 96%, 93% and 73% in the STR group, and 99%, 97% and 80% in the GTR group (**log-rank $P = 0.04$**). Pairwise comparisons showed no statistical difference between biopsy and STR groups ($P = 0.61$)

In the 1p/19q codeletion group, estimates for 1-, 2- and 5- year OS were 99%, 96% and 89% respectively (Fig. 1B). When separated in terms of EOR, estimates for 1-, 2- and 5- year OS were 97%, 95% and 87% in the biopsy group, 99%, 95% and 87% in the STR group, and 99%, 99% and 91% in the GTR group (**log-rank $P < 0.01$**). Pairwise comparisons showed no statistical difference between biopsy and STR groups ($P = 0.70$)

3.3. Univariate analysis

Univariate Cox regression analysis for OS identified the following as significantly favorable in both 1p/19q non-codeleted and codeletion groups: younger age, frontal lobe location, no use of chemotherapy or radiation therapy, and GTR (**all $P < 0.02$**) (**Supplementary Table 1**). In addition, oligodendroglioma histology was shown to be significantly favorable in the 1p/19q non-codeleted group only (**$P = 0.02$**).

3.4. Multivariate analysis

When parameters of interest identified by the univariate analysis were incorporated into the multivariate Cox regression analysis, higher KPS (HR, 0.97; **$P < 0.01$**) in the 1p/19q non-codeleted group, and oligodendroglioma histology (HR, 0.02; **$P = 0.04$**) in the 1p/19q codeletion group, were shown to be significantly favorable (Table 2). Furthermore, in the 1p/19q non-codeleted group, GTR retained statistical significance for longer OS (HR, 0.05; **$P = 0.02$**), as shown in the univariate analysis. However, in the 1p/19q codeletion group, GTR was no significantly prognostic for longer OS (HR, 1.02; $P = 0.99$). After Bonferroni adjustment in the 1p/19q non-codeleted group, both higher KPS (**$P < 0.01$**) and GTR ($P = 0.04$) remained significantly prognostic.

4. Discussion

The purpose of this study was to investigate if the effect of EOR upon five-year overall survival was affected 1p/19q codeletion status in grade II glioma. We observed that when accounting for other prognostic factors, GTR was a significant factor in the 1p/19q non-codeleted cohort. However, when the codeletion was present, the significance of GTR was not retained. The exact consequence of this observation is unclear, however, it does suggest that molecular diagnostics remain relevant to the surgical management of grade II glioma and that outcomes should be considered in light of 1p/19q codeletion status. [12,13]

To the best of our knowledge, this is the first report to show separate 1p/19q codeletion groups with differing prognostic significance of GTR in grade II glioma. Snyder et al. [14] incorporated 1p/19q codeletion

Table 1
Patient and presentation characteristics. KPS, Karnofsky Performance Score; STR, subtotal resection; GTR, gross total resection.

	Overall			1p/19q codeletion status				
				Absent		Present		P-value
Factor	No.	%	Log-rank P	No.	%	No.	%	
Total	1,498	100%	.	705	100%	793	100%	
1p/19q co-deletion			< **0.01**					
Absent	705	47%		.	.	.	.	.
Present	793	53%		.	.	.	.	.
Continuous data								
Median age (yrs)	40.0	.	.	37.0	.	43.0	.	1.00
Median KPS	90.0	.	.	90.0	.	90.0	.	0.72
Categorical data								
Sex			0.34					
Female	651	43%		303	43%	348	44%	0.38
Male	847	57%		402	57%	445	56%	
Histology			< **0.01**					< **0.01**
Astrocytoma	233	16%		214	30%	19	2%	
Oligodendroglioma	840	56%		193	27%	647	82%	
Mixed	416	28%		293	42%	123	16%	
Frontal lobe location			< **0.01**					< **0.01**
No	641	43%		364	52%	277	35%	
Yes	857	57%		341	48%	516	65%	
Chemotherapy			< **0.01**					< **0.01**
No	930	62%		466	66%	464	59%	
Yes	568	38%		239	34%	329	41%	
Radiation therapy			< **0.01**					< **0.01**
No	1,067	71%		459	65%	608	57%	
Yes	431	29%		246	35%	185	43%	
Extent of resection			< **0.01**					0.60
Biopsy	349	23%		166	24%	183	23%	
STR	553	37%		251	36%	302	38%	
GTR	596	40%		288	41%	308	39%	

status into their multivariate analyses of 92 grade II glioma, and reported that EOR was significantly predictive of OS, similar to our overall analysis. It is worth noting that they did not separate their cohorts based on codeletion status as we then proceeded to do. Additionally, as our study demonstrated that the oligodendroglial histology is a significant predictor of OS itself if the 1p/19q codeletion is present, this confounding factor is not accounted for in an oligodendroglioma-only cohort as was in their study.

Although in WHO grade III glioma, Kawaguchi et al. [10] reported in their cohort of 124 patients a similar implication to our results, where GTR resulted in significantly longer OS than non-GTR in glioma without the 1p/19q codeletion. However, they did not delineate between biopsy and STR, nor were they able to perform a multivariate analysis, meaning that there were still potential for confounding within the EOR parameter itself. Nonetheless, these findings support the notion that the 1p/19q codeletion indeed may delineate the prognosticative ability of EOR in more than just one grade of glioma. [9]

How the 1p/19q codeletion may better influence the survival effect of EOR in LGG is currently unclear. Given the relatively high 5-year OS of LGGs compared to other brain tumors, the observation that 1p/19q codeletion confers superior survival outcomes compared to 1p/19q intact tumors may dilute the statistical power to detect other prognostic factors when survival is relatively higher. [15–17] Anatomically, it has been suggested that those with the codeletion have a predilection for more eloquent areas and diffuse presentation, factors less amenable to GTR and its often assumed benefits [18,19]. From a biological aspect, glioma with the 1p/19q codeletion appear to be respond better to adjuvant therapy [20] and are less likely to progress to malignancy [21], which could contribute to superior survival irrespective of EOR. These features are particularly important to consider, given the recent advances in imaging analyses which can now predict in vivo IDH status with acceptable accuracy in glioma patients without having to biopsy and perform sequence analysis. [22]

There are a number of considerations that need to be recognized that limit the validity of the current results. The retrospective nature of the NCDB prevents clarification of the data, possible misdiagnoses, longer follow-up and patients that did not satisfy all selection criteria due to insufficient data. The inability to confirm how EOR of STR and GTR were determined prevents the formation of more robust conclusions. Additionally, volumetric data may be better suited in determining the true effect of 1p/19q codeletion on surgical EOR, but such data is beyond the scope of the NCDB. [9] Collectively, these aspects will be best validated by prospective clinical studies.

There are other clinical parameters worth considering in this analysis that were not available in the database. For example, IDH1/2 status would assist in not only confirming the histopathological diagnoses of these studies, but also validating our findings as another potential confounder to the prognostic significance of EOR. [7] In its truest form, the 2016 WHO Classification of Tumors of the Central Nervous System would not require IDH1/2 status to separate grade II astrocytomas from oligodendrogliomas, however, we appreciate 1p/19q codeleted astrocytoma LGG have been reported making interpretation of the 1p/19q codeletion astrocytoma cohort difficult [8,23]. In addition, it is not clear in the database if the reported surgery was when the 1p/19q diagnosis was made – in other words, if biopsy was first performed, and then the patient returned to surgery for resection after diagnosis, or if the patient underwent resection with no biopsy. Better understanding of sequence will enable us to understand how best to incorporate this molecular diagnosis into surgical practice in the future.

Further to that, the optimal analysis approach to handling such large, and potentially practice-changing big data requires more careful consideration in the future. There remains the concern for interactions between both reported and non-reported parameters using a regression analysis approach. Although we attempted to account for this by using a post-hoc comparison, we cannot with full confidence claim that there is no internal confounding that affected these results, indicating the need for more robust analyses. While regression remains the most popular

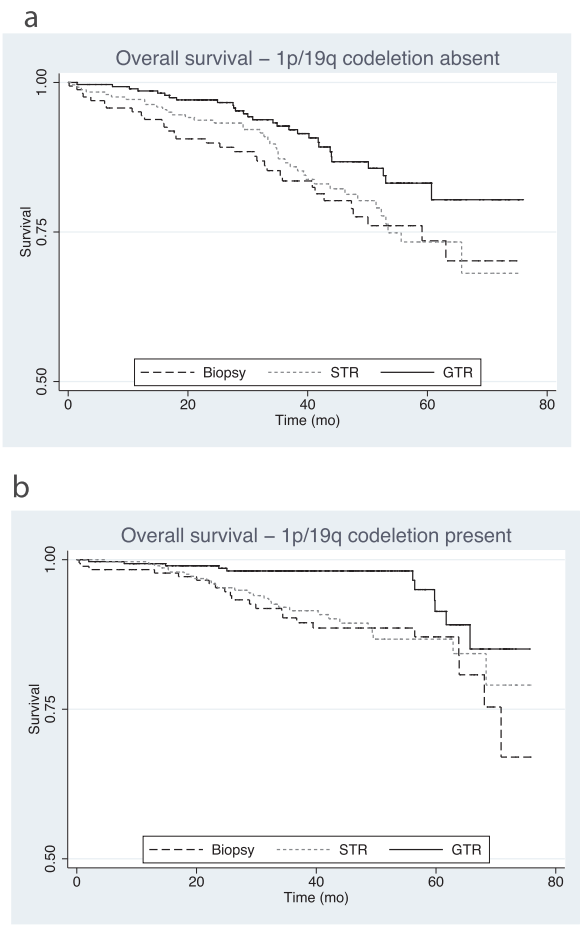

Fig. 1. Kaplan-Meier plot of overall survival by **A.** 1p/19 codeletion: absent vs present (Log-rank P < 0.01) and **B.** EOR: Biopsy vs GTR vs STR (Log-rank P < 0.01).

Table 2
Multivariate Cox regression models analysing overall survival based on 1p/19q codeletion status. HR, hazard ratio; CI, confidence interval, REF, reference variable; KPS, Karnofsky Performance Score; STR, subtotal resection; GTR, gross total resection.

	1p/19q codeletion status					
	Absent (n = 705)			Present (n = 793)		
Factor	HR	95% CI	P	HR	95% CI	P
Continuous data						
Median age	0.99	0.96-1.04	0.96	0.96	0.87-1.05	0.32
KPS	0.97	0.94-0.99	< **0.01**	1.00	0.94-1.06	0.99
Categorical data						
Histology						
Astrocytoma (REF)	.	.	.	.	.	.
Oligodendroglioma	0.36	0.09-1.47	0.16	0.02	0.01-0.86	**0.04**
Mixed	0.62	0.21-1.83	0.39	0.11	0.01-3.86	0.23
Frontal lobe location						
No (REF)	.	.	.	.	.	.
Yes	1.04	0.36-3.06	0.94	3.01	0.29-31.8	0.36
Chemotherapy						
No (REF)	.	.	.	.	.	.
Yes	1.44	0.45-4.61	0.54	0.46	0.06-3.59	0.46
Radiation therapy						
No (REF)	.	.	.	.	.	.
Yes	1.08	0.38-3.13	0.88	2.89	0.41-20.0	0.28
Extent of resection						
Biopsy (REF)	.	.	.	.	.	.
STR	0.45	0.14-1.44	0.18	3.73	0.23-54.2	0.34
GTR	0.05	0.01-0.59	**0.02**	1.02	0.04-28.7	0.99

analysis technique currently in use in neurosurgical analyses, the emergence of more sophisticated machine learning techniques has signaled the potential to shift analytic efforts to ones that better handle datasets of the NCDB size, such those that do not assume orthogonality or independence of parameters, e.g. clustering and deep learning models. Exploration of such techniques under experienced supervision has the potential to reshape the impact of analyses like this, and we welcome their anticipated uptake moving forward.

5. Conclusions

Our study evaluated whether or not the prognostic significance of EOR in grade II glioma was affected by 1p/19q codeletion status. We observed that those tumors in the 1p/19q non-codeletion group could benefit more from GTR compared to those with the codeletion present. However, the inherent limitations of a database study prevent more robust conclusions being drawn currently as maximal resection is likely important in all grade II glioma to achieve optimal outcomes, irrespective of codeletion status. Our findings add to the small, but growing, literature highlighting the clinical significance of molecular diagnostics in managing grade II glioma with surgery. Larger, prospective studies in the future will clarify how valid the reported observations are, and determine how exactly it would be best incorporated into optimizing the postoperative management of grade II glioma.

Disclosures

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Conflicts of interest

The authors report no conflicts of interest.

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