Role of chromosomal 1p/19q co-deletion on the prognosis of oligodendrogliomas: A systematic review and meta-analysis

Nan Hu, Rachel Richards, Randy Jensen

Abstract

Background: The impact of chromosomal 1p/19q co-deletion on the prognosis of oligodendrogliomas has been measured in many studies previously. However most studies used 1p/19q co-deletion as a covariate to be adjusted for in a multivariable model that aimed to assess treatment effects, thus not directly measuring the effect of the 1p/19q co-deletion on prognosis. We conducted a systematic review and meta-analysis to synthesize the results and provide insight on how 1p/19q co-deletion affects prognoses of WHO grade II/III oligodendrogliomas.

Methods: Weighted mean difference (WMD), standardized mean difference (SMD), and hazard ratios (HRs) were used to report pooled effect of 1p/19q co-deletion on prognosis of oligodendrogliomas. The Meta-ANOVA model was used to obtain the pooled HRs.

Results: The difference in median overall survival (OS) time is 0.24 (95% CI: 0.15 to 0.33) and the WMD for 5-year OS rate is 6.87% (95% CI: 6.66% to 7.07%), favoring patients with co-deletion. The pooled hazard ratio (HR) for mortality is 0.28 (95% CI: 0.13 to 0.62), favoring 1p/19q co-deletion. For progression free survival (PFS), the SMD of median PFS time is 0.13 (95% CI: 0.04 to 0.21), in favor of 1p/19q co-deletion. When comparing therapies among patients with 1p/19q co-deletion, we found that those receiving radiation therapy (RT) and chemotherapy (CT) had a significantly better prognosis than those who received RT only, with pooled HR of 0.64 (95% CI: 0.51 to 0.80).

Conclusions: Our pooled results show that chromosomal 1p/19q co-deletion has a significant protective effect on prognosis of grade II/III oligodendrogliomas. © 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Oligodendrogliomas are a rare primary brain tumor [1]. The world health organization (WHO) rates these tumors as low grade (grade II) or high grade/anaplastic (grade III). Grade II tumors may evolve into grade III tumors over time [2]. The incidence of oligodendrogliomas, including anaplastic oligodendrogliomas, is approximately 0.3 per 100,000 people in the United States [3]. Deletion and co-deletion of chromosome 1p/19q occurs in 50% to 70% of WHO grade II and III oligodendrogliomas found in the United States [3]. The chromosomal 1p/19q co-deletion has been shown to be an important control factor of overall survival (OS) and progression free survival (PFS) in previous clinical studies that examined therapy effects on survival using multivariable models [4,5]. Patients with 1p/19q co-deletions have also been shown to have longer OS and PFS regardless of the treatment they receive [4,5].

Oligodendrogliomas are rare diseases, the need for a meta-analysis exists in order to better estimate the effect of chromosomal 1p/19q co-deletion on their prognosis such as OS and PFS. We sought to investigate the effect of 1p/19q co-deletion, as a predictor, on OS and PFS. Most previous studies used the molecular structure of 1p/19q co-deletion as a covariate to be adjusted for in multivariable analyses when assessing the effect of treatment. Consequently, the effect of 1p/19q co-deletion as an exposure on the prognosis of oligodendrogliomas is not explicit. In this meta-analysis, we use the Meta-ANOVA method [6] to evaluate the effect of 1p/19q co-deletion on OS and PFS by synthesizing the results in multivariable analyses in previous studies.

Oligodendrogliomas are known to be chemosensitive and respond positively to treatment although the best treatment for these types of...
tumors is controversial [7]. The most studied treatments are radiation therapy (RT) alone and RT in combination with chemotherapy (CT). In this systematic review and meta-analysis, we also provide the pooled results that compare the survival between RT alone and RT combined with CT among oligodendroglioma patients with 1p/19q co-deletion.

Our study selects literature for patients diagnosed with both WHO grade II and III oligodendrogliomas.

2. Material and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [8].

2.1. Literature search

The electronic databases PubMed, Medline, and Embase were searched to find prospective articles to be included in our meta-analysis. Key words and phrases used to find potential articles were “oligodendrogliomas”, “1p/19q” (or “1p19q”), “radiation therapy” and “chemotherapy”. In addition, a search of abstracts presented at the American Society of Clinical Oncology (ASCO) was also conducted using the same search terms. Included studies were published in English from October 2005 to April 2014.

2.2. Inclusion criteria

Studies to be included in our meta-analysis met the following inclusion criteria: (1) patients were clinically diagnosed with WHO grade II or III oligodendrogliomas; (2) studies reported 1p/19q chromosome co-deletion status; (3) studies reported the following information: OS, PFS, use of surgery or adjuvant therapies (i.e., using both radiation therapy and chemotherapy, or using only the radiation therapy). In cases where studies published were updates of previous studies conducted involving the same study patient population, only the most recent publication was included in the analysis.

2.3. Data collection

Data was collected from each article by an abstractor (RR) and reviewed by a second evaluator (NH) when needed. Data extraction was done using a data abstraction sheet developed in Microsoft Excel. The specific items we recorded in the Excel spreadsheet can be found in the Supplemental Methods Section in the Supplementary Materials.

2.4. Statistical methods

The hazard ratios (HRs) and their confidence intervals (CIs) from each multivariable Cox regression model were collected as reported in each article during the data extraction phase. One of the main issues when combining effect sizes from separate Cox models is the concern of how comparable they are. Each separate study might adjust for a different set of covariates in the Cox model so the coefficients could have altered interpretations across studies [6]. To account for this, we conducted a pooled analyses via Meta-ANOVA to evaluate the effect of 1p/19q chromosomal co-deletion on OS and PFS. The pooled HRs obtained from the Meta-ANOVA model was used to measure the effect. The details for using Meta-ANOVA method in our analysis can be found from the Supplemental Methods section in Supplementary Materials.

The standardized mean difference (SMD) and weighted mean difference (WMD) were used to compare the OS/PFS rate at given time point as well as the median OS/PFS time between patients with and without 1p/19q co-deletion [35]. The details for calculating SMDs and WMDs in our analyses can be found from the Supplemental Methods section in Supplementary Materials.

All statistical tests were two-sided, and a p-value lower than 0.05 was considered as statistically significant. Data analyses were carried out using Review Manager (Copenhagen, Denmark) [9], or RevMan.
Table 1
Characteristics of all studies meeting study inclusion criteria.

<table>
<thead>
<tr>
<th>Article</th>
<th>Total sample size</th>
<th>% of Males</th>
<th>Source</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahluwalia et al. [4]</td>
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<td>52%</td>
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<td>USA</td>
</tr>
<tr>
<td>Cairncross et al. [30]</td>
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<td>Journal</td>
<td>Canada</td>
</tr>
<tr>
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<td>84</td>
<td>56%</td>
<td>Journal</td>
<td>Italy</td>
</tr>
<tr>
<td>van den Bent et al. [16]</td>
<td>368</td>
<td>58%</td>
<td>Journal</td>
<td>Europe</td>
</tr>
<tr>
<td>Anderson et al. [17]</td>
<td>291</td>
<td>60%</td>
<td>Journal</td>
<td>North America</td>
</tr>
<tr>
<td>Gorilla et al. [31]</td>
<td>368</td>
<td>58%</td>
<td>Journal</td>
<td>Germany</td>
</tr>
<tr>
<td>Taal et al. [23]</td>
<td>53</td>
<td>72%</td>
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<td>USA</td>
</tr>
<tr>
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</tr>
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<td>Kim et al. [25]</td>
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<td>USA</td>
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<tr>
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<tr>
<td>Kuo et al. [27]</td>
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<td>Journal</td>
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<td>Mikkelsen [13]</td>
<td>48</td>
<td>60%</td>
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<td>USA</td>
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<tr>
<td>van den Bent et al. [33]</td>
<td>165</td>
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<td>Germany</td>
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<tr>
<td>Vogelbaum et al. [5]</td>
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<td>Wick et al. [28]</td>
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<tr>
<td>Gianmini et al. [34]</td>
<td>247</td>
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<td>Brangés et al. [15]</td>
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<td>46</td>
<td>–</td>
<td>Journal</td>
<td>USA</td>
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</tbody>
</table>

version 5.3, SAS (SAS Institute Inc., Cary, NC, USA) version 9.4 and Stata (Stata Inc., College Station, TX, USA) version 14.

2.5. Assessment of heterogeneity

To check for heterogeneity, for each analysis we calculated the pooled HR and SMD estimate using a random effects model. The I² statistic tests the null hypothesis that each study is evaluating the same effect.

2.6. Assessment of publication bias

Each pooled analysis outcome was qualitatively and quantitatively assessed for publication bias using funnel plots and Egger’s test, respectively.

3. Results

3.1. Study characteristics

Our electronic database searches in PubMed, Medline, and Embase resulted in a total of 276 articles initially. After removing duplicates there were 209 articles remaining for screening. The screening process further narrowed our results and removed 187 additional articles due to not meeting inclusion criteria (3), reported in a language other than English (19), single case report (11), having irrelevant data (35), literature review (98), or having outcomes reported in a way that was not usable to our analysis (21). This left is with 22 studies that contributed to our analysis (Fig. 1). The median and mean sample size of the 22 studies was 58 and 167 respectively, and the average male to female ratio was 58% to 42%. A total of 7 studies (32%) were conducted in the United States. All included articles were published in peer-reviewed journals. Table 1 lists each study and its characteristics in detail.

3.2. Overall survival

One study and 543 patients were found to compare the median OS time between patients with chromosomal 1p/19q co-deletion and patients without co-deletion. The difference in median OS time and 95% CI to be 0.24 year and (0.15 to 0.33) year, in favor of the chromosomal 1p/19q co-deletion.

Two studies and 91 patients were included in our pooled analysis of the five year OS. We calculated the WMD to be 6.87% with a 95% CI (6.65% to 7.08%), in favor of the co-deleted group. The obtained WMD is statistically significant at the 0.05 test level.

Nine studies and 2079 patients were included in our pooled analysis of chromosomal 1p/19q co-deletion versus no deletion. Our pooled analysis used multivariable and univariable time-to-event models to estimate HRs and their 95% CI. We used both Meta-ANOVA [6] and the DerSimonian and Laird (D&L) random effect estimator [10] that omits covariates in the Cox models. Statistically, the estimated pooled effect (in terms of logarithm of HR in Cox models) using D&L method is to be biased towards zero if important covariates are omitted from the model. Equivalently, the pooled HR ratios will be biased towards one. The pooled effect estimated using Meta-ANOVA will significantly reduce the bias. However, since the indicator variables for inclusion of covariates were included in the model, the variance estimates of the pooled effect will be larger than that estimated using the D&L estimator. Table 2 presents the pooled effects (95% CIs) on OS of 1p/19q co-deletion and 1p/19q co-deletion together with another prognostic factor (IDH-1 mutation, total resection and older age) by two methods (Meta-ANOVA and D&L). The Meta-ANOVA analysis resulted in a pooled HR of 0.28 (95% CI: 0.13 to 0.63), favoring patients with 1p/19q co-deletion, adjusting for the covariates in the multivariable analyses, including age, extent of resection, IDH-1 mutation and type of therapy (radiation and chemotherapy versus chemotherapy only). This indicates that 1p/19q co-deletion has a significant protective effect on prognosis of grade II and III oligodendrogliomas. Patients having 1p/19q co-deletion and without IDH-1 mutation have a 91% reduction in the hazard of death compared to patients without co-deletion and with IDH-1 mutation, after adjusting for age, extent of resection, and adjuvant therapy, (HR = 0.09, 95% CI: 0.03 to 0.23). Similarly, the Meta-ANOVA results give a pooled HR of 0.19 (95% CI: 0.06 to 0.55) for 1p/19q co-deletion and total resection. This is to say, patients with 1p/19q co-deletion and a total resection have an 81% reduction in hazard of mortality compared to patients without both co-deletion and total resection. Finally, the estimated Meta-ANOVA pooled effect on OS of 1p/19q co-deletion and older age (40+) is 0.29 (95% CI: 0.13 to 0.63). That is, patients with 1p/19q co-deletion and younger age (less than or equal to 40) have a 71% reduction in the hazard of death compared to patients with no 1p/19q co-deletion and older than 40 years.

Two studies and 592 patients were included in our pooled analysis of chromosomal 1p/19q co-deletion and 1p/19q co-deletion with another prognostic factor (IDH-1 mutation, total resection and older age) by two methods (Meta-ANOVA and DerSimonian & Laird methods).

Table 2
Pooled effects (HRs and 95% CIs) on OS of chromosomal 1p/19q co-deletion and 1p/19q co-deletion with another prognostic factor (IDH-1 mutation, total resection and older age) by two methods (Meta-ANOVA and DerSimonian & Laird methods).

<table>
<thead>
<tr>
<th>Pooled HR</th>
<th>95% CI</th>
<th>Pooled HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.28</td>
<td>0.13–0.62</td>
<td>0.45</td>
<td>0.32–0.63</td>
</tr>
<tr>
<td>0.09</td>
<td>0.03–0.23</td>
<td>0.10</td>
<td>0.05–0.21</td>
</tr>
<tr>
<td>0.19</td>
<td>0.06–0.55</td>
<td>0.20</td>
<td>0.07–0.38</td>
</tr>
<tr>
<td>0.28</td>
<td>0.13–0.63</td>
<td>0.30</td>
<td>0.11–0.84</td>
</tr>
</tbody>
</table>

* By assuming the pooled Meta-ANOVA effect (log of HR) approximates to a Normal distribution.
0.64 (95% CI: 0.31 to 1.32), favoring 1p/19q co-deletion although the results were not significant. The corresponding $I^2 = 50\%$ with a $p$-value of 0.16 indicating there could be heterogeneity. These results are most likely due to the small number of studies included in this analysis, see Fig. 2.

### 3.3. Progression free survival

Two studies and 591 patients were included in our pooled analysis of the median PFS time. We calculated the SMD and 95% CI to be 0.13, and (0.04 to 0.21) respectively, in favor of 1p/19q chromosome co-deletion. There was no indication of heterogeneity as the estimated $I^2 = 0\%$ ($p$-value = 0.68), see Fig. 3.

Two studies and 77 patients were included in our pooled analysis of the six-month and one year PFS rate. We calculated the WMD in PFS rate at 6 months and 1 year to be 21.2% (95% CI: 20.9% to 21.3%) and 12.2% (95% CI: 12.0% to 12.4%) respectively, both statistically significant and in favor of chromosomal 1p/19q co-deletion.

### 3.4. Adjuvant therapies

Three studies and 1248 patients were included in our pooled analysis comparing adjuvant therapies. We calculated the pooled HR to be 0.64 (95% CI: 0.51 to 0.80) respectively, in favor of radiation therapy and chemotherapy compared to radiation therapy alone. There was no indication of serious heterogeneity across studies, $I^2 = 46\%$, $p$-value = 0.16, see Fig. 4.

### 4. Discussion

We conducted a pooled analysis to measure the effect of the chromosomal 1p/19q co-deletion on prognostic outcomes, OS and PFS. In previous literature, the 1p/19q co-deletion was considered as a covariate in the multivariable models that assessed effect of treatment, biomarkers and prognostic factors on survival outcomes of oligodendroglioma [11–15]. To our best knowledge, systematic reviews and meta-analysis of the effect of 1p/19q co-deletion on OS and PFS times [1].

The type of studies in this meta-analysis is a mixture of randomized studies and observational studies. Therefore, we conducted sensitivity analyses for the Meta-ANOVA and the pooled hazard ratio for mortality comparing 1p/19q co-deleted anaplastic oligodendroglioma patients treated by RT and CT versus RT only, since both of the meta-analyses included randomized and observational studies. For the meta-analysis of therapies for 1p/19q co-deleted patients, we found the conclusion drawn did not change across type of studies. The sub-analysis of non-randomized studies gave a pooled hazard ratio of 0.58 (95% CI: 0.44–0.76), indicating a benefit of 1p/19q co-deletion, as an exposure, on OS and PFS, suggesting that additional studies in the future are warranted.
favoring patients treated by both RT and CT. The randomized study provided hazard ratio of 0.75 (95% CI: 0.59–0.95), in favor of patient treated by both RT and CT. Although the randomized studies gave a relative smaller effect, both type of studies were provide statistically significant result, favoring patients treated by both therapies. For the Meta-ANOVA model comparing the effect of 1p/19q co-deletion on overall survival, we also found that the conclusion drawn did not change across type of studies. Using all of the non-randomized studies, the pooled HR of survival comparing 1p/19q co-deleted patients versus non co-deletion patients from the Meta-ANOVA is 0.15 (95% CI: 0.05–0.49). On the other hand, using all of the randomized studies, the pooled HR is 0.42 (95% CI: 0.29–0.62).

In the non-randomized study conducted by Anderson and Mark [17], patients were all diagnosed with anaplastic oligodendroglioma (AO) with chromosomal 1p/19q co-deletion. The chemotherapy being administered in the study was PCV. In another non-randomized study by Lassman and colleagues [1], patients were diagnosed with anaplastic oligodendrogliomas or anaplastic oligoastrocytomas and were chromosomal 1p/19q co-deleted. The chemotherapy that was used in this study contained included PCV and TMZ. In the recent randomized study by van den Bent and colleagues [16], all patients were diagnosed with anaplastic oligodendrogliomas, and the chemotherapy given to the patients was PCV only. To the best of our knowledge, there has been no report comparing efficacy between the use of PCV and TMZ as chemotherapeutic agents for anaplastic oligodendroglioma patient. These two chemotherapies appear to be similar for anaplastic oligodendroglioma patient with 1p/19q co-deletion, in terms of efficacy. Thus, we believe that our meta-analysis comparing the survival of oligodendroglioma patients with 1p/19q co-deletion between RT + CT and RT only would be informative and provide useful clinical evidence on this issue.

One concern when comparing different studies is the accuracy of the histological diagnosis [18]. Given that this meta-analysis is focused on the effects of 1p/19q loss, we have the advantage of being quite certain that the tumors being examined here are oligodendrogliomas. 1p19q loss is found at a much higher rate in oligodendrogliomas compared to astrocytomas or even mixed oligoastrocytomas [19–21]. Furthermore, when comparing multiple studies, there are concerns of accurately distinguishing between grade II oligodendrogliomas and grade III anaplastic oligodendrogliomas because of the subjective nature of the WHO grading system for oligodendrogliomas. Histological differences between grade II and III tumors relies on the finding of “significant” hypercellularity and pleomorphism in the higher grade tumors [22] that could introduce inter-observer variability between different pathologists. This a limitation of this study but probably not a major issue given that the inter-observer variability rate is most likely low and randomly distributed across each study.

Our systematic review and meta-analysis has another two limitations except for those mentioned above. First of all, in some of our pooled analyses, the number of included studies is small, which may lead to biased results although publication bias was not present in our meta-analyses. In addition, all of our analyses were conducted using aggregated patient data (APA) since individual level data was not available.

5. Conclusions

In conclusion, our results show the significant protective effect chromosomal 1p/19q co-deletion has on survival of patients with grade II and III oligodendrogliomas. Patients with this co-deletion have significantly longer OS/PFS times compared to those without the co-deletion. Patients with the co-deletion also are shown to have significantly longer OS times when treated with radiation therapy as well as chemotherapy in comparison to radiation therapy alone. Results from our pooled analysis using the Meta-ANOVA technique indicates that the chromosomal 1p/19q co-deletion has a significant protective effect on OS and PFS among patients with grade II and III oligodendrogliomas when important covariates are adjusted for.

Acknowledgement

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Appendix A. Supplementary methods

Supplementary methods to this article can be found online at http://dx.doi.org/10.1016/j.inat.2016.06.008.

References


