Title Page

Effect of Treatment Modalities on Progression-Free Survival and Overall Survival, in Molecularly Subtyped WHO Grade II Diffuse Gliomas: A Systematic Review

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Abstract

Objective/Introduction
With the 2016 update of the WHO Classification of Tumors of the Central Nervous System incorporating molecular subtyping to histology, WHO grade II diffuse astrocytic and oligodendroglial tumors are now subcategorized by distinct molecular markers. Currently, there are no published systematic reviews quantifying differences in progression free survival (PFS) and overall survival (OS) on the basis of molecular subtypes of WHO grade II diffuse gliomas, against the background of administered treatments.

Methods
Utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Cochrane Handbook of Systemic Reviews of Interventions, we conducted a systematic review through MEDLINE, Embase, and CENTRAL.

Results
For OS, the first quartile (25%), median (50%), third quartile (75%), and 95% confidence interval were respectively identified (in months)—astrocytoma-wild type WHO II (A-wt II): 22.8, 32.2, 40.7, and 21.6-61.2; astrocytoma-mutant WHO II (A-mt II): 69.85, 115.2, 128.4, and 55.4-164.0; oligodendroglioma WHO II (OD II): 106.3, 163.7, 213.3, and 67.3-235.4 (p-value = 0.0001675). For PFS, the 25th, 50th, and 75th percentiles, and 95% confidence interval are as follows (in months), respectively—A-wt II: 6.90, 17.45, 19.57, and 3.00-23.69; A-mt II: 37.20, 43.20, 55.63, and 35.7-60.0; OD II: 47.42, 59.2, 88.28, and 46.3-91.2 (p-value = 0.01488).

Conclusion
This appears to be the first systematic review of OS and PFS in patients with WHO grade II LGGs, against treatment modalities, in molecularly stratified subsets introduced by the WHO 2016 classification of CNS tumors. Overall, A-wt II was confirmed to have a significantly shorter OS than A-mt II; meanwhile, there was no significant difference found between OS of OD II with A-wt II and A-mt II. Additionally, all three molecular subtypes were found to have statistically significant differences between PFS, with OD II having a statistically better PFS than A-mt II. These data can provide valuable prognostic insight to patients and clinicians. Additionally, assessing survival differences enhances understanding of treatment recommendations against molecular markers and may facilitate future clinical trial design.

1.1 Introduction

Aside generalizations, accurate epidemiological data on World Health Organization (WHO) grade II astrocytic and oligodendroglial tumours (low grade gliomas [LGGs]) remains elusive. Studies estimate annually about 2,000 to 3,000 LGGs are diagnosed in the United States [1, 2]. Affecting mostly fully functioning patients, usually in the second to fourth decades of life, combined with a natural history composed of clinical and radiological progression with an unpredictable malignant transformation, the actual burden of LGGs is considerable [3, 4]. In addition, due to lack of randomized controlled trials (RTCs) comparing multiple treatment modalities, their optimal management remains disputed, ranging from serial imaging to attempts of maximum safe resection, with combinations of neo-adjuvant or post-operative chemoradiotherapy [1].

More recently, compared to the 2007 predecessor, the 2016 update of the WHO classification of Central Nervous System (CNS) tumors, has incorporated molecular features with histology to create an integrated diagnosis [5]. Current diagnostic standards require determining status of isocitrate dehydrogenase (IDH) mutations and codeletion in chromosomal arms 1p and 19q [5]. Moreover, data supports the necessity to stratify survival outcomes by molecular subtypes—for one phase III trial demonstrated similar survival between initial treatment with chemotherapy (CT) versus radiation therapy (RT), until outcomes were analyzed with molecular diagnostics [6].

Since the 2016 WHO classification of LGGs, the current study appears to be the first comprehensive systematic review quantifying differences in progression free survival (PFS) and overall survival (OS) of molecularly stratified WHO grade II diffuse gliomas. By assessing differences in survival associated with surgery, radiation therapy, and chemotherapy, a better understanding can be developed on how molecular features influence treatment recommendations and can subsequently facilitate future clinical trial design.

2.1 Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Cochrane Handbook of Systematic Reviews of Interventions [7, 8, 9].

2.1.1 Eligibility Criteria

Study Types

Only clinical studies were included, with experimental and animal studies excluded.

Participants

Studies including data stratified for adult humans (18 years or older) with molecularly subtyped newly diagnosed WHO grade II diffuse gliomas (astrocytoma or oligodendroglioma) were included [5]. The genotypes were defined as follows: wild type astrocytomas, IDH-wild type;

mutant astrocytoma, IDH-mutant with non-1p/19q codeletion; oligodendroglioma, IDH-mutant with 1p/19q codeletion. Moreover, for studies that provided grade II gliomas with only positive codeletion (without IDH status), such tumors were assumed to be oligodendrogliomas, on the basis of most 1p/19q codeletion patients also having IDH-mt [10].

Interventions
Interventions targeting WHO grade II diffuse gliomas were not limited to any subcategory, and included surgery, chemotherapy, and radiotherapy.

Outcomes
The endpoints of overall survival and progression-free survival, in the unit of time (days, months, years) or rate, were collected. Our study defined OS as the time of intervention to death by any cause. PFS was defined as the time of intervention to tumor recurrence/progression, evidenced by radiological (magnetic resonance imaging [MRI]) or clinical deterioration. Clinical deterioration would include development of new or worsening of existing focal deficits or symptoms of elevated intracranial pressure. Radiologic deterioration would include increased or new tumor contrast enhancement, enlargement of volume, increasing mass effect, or increasing midline shift. Due to possibility of variation in outcome measure definitions, from each study the outcome measure definition was also collected.

Follow Up Time
Follow-up time was restricted to 48 months and collected.

Language
Only articles written in English were included.

Information Sources
Medical subheadings (MeSH) and text words related to low grade glioma (LGG), molecular subtypes, and treatment, were utilized for the search strategy. Medline (PubMed interface, 2008 onwards), Embase (Ovid interface, 2008 onwards), and Cochrane Central Register for Controlled Trials (Wiley interface, current issue), were all searched. 1 January 2008 was selected as the start date for the search, based the first paper subcategorizing gliomas on the IDH molecular marker [11]. No other electronic database searches were conducted. In relevant literature, references were manually searched for additional trials.

Search Strategy
No limits, other than dates were utilized in the database search limitations. An electronic search examined Embase (January 1, 2008 to December 11, 2018), MEDLINE (January 1, 2008 to December 11, 2018), and Cochrane Central Register of Controlled Trails (CENTRAL) (January 1, 2008 to December 11, 2018); the **Appendix** provides the search protocols, including keywords. Specific search strategies were developed under guidance of Queen Square Institute of Neurology (IoN) library and statistical services staff with expertise in systemic review searches. To assess the search sensitivity and quality, robust target references were utilized—all of which were identified [6, 12, 13, 14, 15].

2.1.2 Study Records

Data Management

Results of the literature search were imported to EndNote X9 (Clarivate Analytics, Philadelphia, Pennsylvania). Software utilization aimed to reduce data entry errors and reduce bias, such as by deduplicating references. All reports on studies were reviewed, in order to assess for inconsistencies amongst reports (e.g. design description, outcome presentation, total patients analyzed).

Selection Process

The authors screened all titles and abstracts on the basis of the inclusion criteria. Subsequently, literature meeting inclusion criteria (including uncertain results) had the full-text reviewed. For results that met inclusion criteria, the literature was included in the systematic review.

Data Items

In accordance with recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (chapter 7), the following data was collected into a Microsoft Excel spreadsheet: author, publication year, journal citation; setting; inclusion and exclusion criteria; study design; study population; tumor details at diagnosis (tumor size, location, and histology); risk of bias (including assessment of bias); length of follow-up; outcomes (OS, PFS) [16].

Data Synthesis

Data were placed into tables allowing for relative comparison of OS and PFS stratified on tumor type and treatment. A quantile-quantile plot was produced for the PFS and OS data, which indicated both datasets to be non-normally distributed. Due to non-normal distribution when the data was pooled (cases with n=1 were excluded), the summary measures included the 25-percentile, median, 75-percentile, and 95-percentile confidence interval of the median. Meanwhile, a nonparametric Kruskal-Wallis test was performed to determine if the survival outcomes stratified by genotype were significantly different; subsequently a pairwise analysis using the independent Wilcoxon rank sum test was utilized [17, 18]. All statistical analysis was conducted with R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria) [19].

3.1 Results

The search of Medline, Embase, and Central yielded a total of 8311 abstracts (**Figure 1**). Four additional papers were included after searching through systematic reviews identified in our search. After removing duplicates, 7542 abstracts were then screened by reading the title and full abstracts. From these, 7475 were excluded for not meeting the inclusion criteria of the study, and 67 were flagged for further review in the full-text assessment phase. Of the 67, 47 articles were removed for not providing raw data in the form of day/month/year for PFS or OS

(many abstracts met inclusion criteria, however provided data in the form of hazards ratios, p-values, or Kaplan-Meier graphs without the ability to extract raw PFS or OS), or being systematic reviews—19 were included for quantitative synthesis in the form of **Table 1** and **Table 2**. Of note, the systematic reviews that were excluded, did provide four additional articles that were also read in full, however none of these provided adequate data to be included in the quantitative synthesis.

3.1.1 Progression Free Survival Data

From the 19 studies, 11 provided PFS data (**Table 1**). Six studies were retrospective and five were prospective (with one randomized); all studies looked at patients 18 years and older, except the Morshed et al. paper examined patients over 60 years old [6, 14, 20, 21, 22, 23, 24, 25, 26, 27, 28].

Baumert et al., in a randomized open label phase 3 intergroup study, examined conformal radiotherapy versus dose-dense temozolomide, in high risk tumors (**Table 1**) [6]. The Houillier et. al. retrospective study examined temozolomide administered daily for 5-days at 200mg/m^2, repeated every 28 days for at least 12 cycles (or up to 30 cycles) [22]. OD-II, A-mt II, and A-wt II had the following PFS, respectively: 37.9, 32.9, and 18.7 months [22]. On a dose-dense temozolomide regimen, 1 week on/1 week off, for a median of 11 cycles (range, 2-18 cycles), the prospective single arm phase II study by Pellerino et. al., found a PFS of 46 months for OD-II [26]. For temozolomide daily for 5-days at 200mg/day, repeated every 28 days up to 12 cycles, the prospective trial by Wahl et. al., found OD-II, A-mt II, and A-wt II to have the following PFS, respectively: 58.8, 43.2, and 7.2 months [14]. Finally, in a prospective phase II open label study, examining low-dose temozolomide 50mg/mq/day 1 week on/1 week off until progression (or for a maximum of 24 months), for OD-II and A-wt II, had a PFS of 35 and 6 months, respectively [27].

The retrospective study by Franceschi et al., examined the impact of postsurgical therapy on PFS for OD-II [21]. Regardless of treatment, this cohort had a PFS of 59.6 months, but with treatment PFS increased to 79.5 months [21]. When treatment was stratified, to follow-up only, CT alone, RT alone, and combined RT with CT, PFS incrementally increased: 46.3 months, 50.8 months, 103.6 months, and 120.2 months, respectively [21].

Rather than looking at OD-II, Minichillo et al. examined A-mt II, and how postsurgical treatment influences PFS; however, the data for postsurgical treatment with CT was not provided [23]. Without postsurgical treatment PFS was 44.3 months, but with any treatment was 64.8 months [23]. When treatment was stratified to follow-up only and RT, PFS was found to be 35.7 months and 60.0 months respectively [23]. Opoku-Darko et al. also provided data, but in the form of eight individual cases (**Table 1**) [25].

One additional paper also examined postsurgical treatment, comparing RT alone to RT with CT. High risk OD-II with RT and CT had a 162 months PFS, but with RT alone had a 91.2 months PFS [28].

When examining the impact of surgery across molecular subtypes, one retrospective study demonstrated OD-II, A-mt II, and A-wt II had a PFS of 109.2, 38.4, and 21 months, respectively [20]. When examining surgical resection outcomes stratified to age, for those older than 60 years, the following was found: OD-II, A-mt II, and A-wt II had a respective PFS of 37.3, 55.9, and 16.2 months [24].

After pooling all the data together on the basis of genotype a Kruskal-Wallis test found all three tumor types had significantly different median PFS ($p = 0.01488$), while a Wilcoxon ranked sum test found a pairwise comparison between all PFS of genotypes to also be significantly different (**Table 3**). The 25th percentile, median (50th percentile), 75th percentile, and 95% confidence interval of the median for PFS of each genotype was found, respectively—A-wt II: 6.90, 17.45, 19.57, and 3.00-23.69 months; A-mt II: 37.20, 43.20, 55.63, and 35.7-60.00 months; OD-II: 47.42, 59.20, 88.28, and 46.3-91.2 months (**Table 3)**. A graphical representation stratified by treatment and genotype is displayed on **Figure 2**.

3.1.2 Overall Survival Data

From the 19 included studies, 13 provided OS data (**Table 2**). Four studies were prospective and nine were retrospective [12, 13, 14, 15, 20, 24, 26, 28, 29, 30, 31, 32, 33].

Most of these studies examined surgical outcome per genotype, however several did look at other treatment modalities. Gao et al. noted for high risk A-wt II, postoperative conformal RT versus postoperative dose-dense oral TMZ had the respective median OS of 55.4 and 36 months [29]. On the other hand, A-wt II patients receiving radiotherapy alone or radiotherapy with chemotherapy (PCV), had an OS of 61.2 months [12]. Youland et al. on the other hand, for high risk OD-II, found for post-operative patients, RT with CT compared to RT alone, produced an OS of 212.4 versus 235.4 months, respectively [28]. Pellerino et al., for OD-II treated with dose-dense temozolomide 1 week on/1 week off for a median of 11 cycles (range 2-18 cycles), found an OS of 76 months [26]. Lastly, Wahl et al. examined patients with gross residual disease after surgical resection who received postoperative monthly temozolomide daily for 5-days at 200mg/day repeated every 28 days (up to 12 cycles), looking at OD-II, A-mt II, and A-wt II, the respective OS were 116.4, 134.4, and 21.6 months [14].

All other studies looked at outcomes per extent of resection. For instance, Jakola et al., noted for A-mt II, OS for patients with watchful waiting was 67.2 months, while 122.4 months for early resection; for A-wt II, OS was 16.8 months for watchful waiting and 63.6 months for early resection; no data was provided for oligodendrogliomas, as the data had yet to fully mature [13]. Likewise, when Wijnenga et al. examined surgical outcomes, the data had not yet matured for the OD-II category, but for A-mt II and A-wt II, those who underwent surgery had an OS of 122.4 and 25.2 months respectively [15].

However, Etxaniz et al. did present data for OD-II undergoing surgery. When comparing OD-II, A-mt II, and A-wt II, median OS was found to be 138, 115.2, and 22.8 months, respectively [20]. Looking at similar variables, Franceschi et al. noted for OD-II, A-mt II, and A-wt II undergoing surgery, OS was 216.0, 164.0, and 32.2 months, respectively [31]. Examining similar treatments,

another retrospective study found for OD-II without MGMT methylation, A-mt II with MGMT methylation, A-mt II without MGMT methylation, and A-wt II had the following respective OS: 189.4, 202.7, 109.1, 87.9 months [30].

Again, only one paper examined patients over the age of 60 years. Morshed et al. found for OD-II, A-mt II, and A-wt II patients who underwent resection median OS was 67.3, 72.5, and 40.7 months, respectively [24].

After pooling all the data together on the basis of genotype a Kruskal-Wallis test found all three tumor types had significantly different median OS (p = 0.0001675), while a Wilcoxon ranked sum test found a pairwise comparison between OS for A-wt II versus A-mt II to be significantly different (**Table 3**). The 25th percentile, median (50th percentile), 75th percentile, and 95% confidence interval of the median for OS of each genotype was found, respectively—A-wt II: 22.8, 32.2, 40.7, and 21.6-61.2 months; A-mt II: 69.85, 115.2, 128.4, and 55.4-164.0; OD-II: 106.3, 163.7, 213.3, and 67.3-235.4 months (**Table 3)**. A graphical representation stratified by treatment and genotype is displayed on **Figure 3**.

4.1 Discussion

4.1.1 Overall Survival—General Considerations

Several key points can be extracted from this study. First, A-wt II tumors were found to have a significantly shorter OS compared to A-mt II (**Table 2***)*, confirming prior studies [20, 23, 34, 35]. Secondly, for OS, our data demonstrated no statistically significant difference between OD-II with A-mt II or A-wt II tumors (**Table 2**). Regarding PFS, all three tumor genotypes did have a statistically significant difference between them (**Table 2**). Finally, the PFS between A-mt II and OD-II was statistically significant (**Table 2**), with OD-II having a longer median PFS than A-mt II—such is potentially due to OD-II having earlier treatment with chemotherapy and radiotherapy than A-mt II tumors, and A-mt II tumors more likely to receive post-operative watch and scan treatment approach [36, 37]

4.2.1 PFS - WHO, grade II astrocytoma, Wild Type

Several trends are identified when examining the raw data for PFS (**Figure 2**). For A-wt II patients, treatment with post-operative dose dense temozolomide (75mg/m^2 daily for 21 days, repeated every 28 days for 12 cycles maximum) yielded the longest PFS, at 23.69 months [6]. The second longest PFS was with post-operative conformal RT, at 19.09 months [6]. Yet, there was no statistically significant treatment-dependent difference between the dose dense temozolomide and the conformal RT. Thus, to lengthen PFS, either dose dense temozolomide or conformal RT appear the best options.

The dosages of temozolomide—dose dense regimen, standard schedule (200mg/m^2 for 5 days, repeated every 28 days for 30 cycles maximum), and a low dose regimen (50mg/mq/day, 1

week on/1 week off)—were also compared. The dose dense regimen had the longest PFS at 23.69 months, followed by the standard schedule at 7.2 and 18.7 months, and finally the low dose regimen at 3 months [6, 14, 22, 25]. With the toxicity profile of dose dense and standard schedule relatively comparable, dose dense regimen appears more efficacious, yet due to the small number of studies, no safe conclusions can be made [38].

4.2.2 OS - WHO, grade II astrocytoma, Wild Type

However, for prolonging OS, a different treatment regimen was more beneficial—early resection with radiotherapy [12, 13]. When comparing watchful waiting to early resection, OS was 16.8 and 63.6 months, respectively [13]. Now when examining post-operative treatments, a radiotherapy-based regimen (RT alone or with PCV) resulted in the longest OS, at 61.2 months (post-operative temozolomide yielded in 21.6 months) [12, 14]. Therefore, regarding OS, a post-operative radiotherapy-based treatment regimen after early resection seems most beneficial for A-wt II tumors (**Figure 3**).

4.3.1 PFS - WHO, grade II astrocytoma, Mutant

Amongst A-mt II patients, radiotherapy had a better PFS than treatment with temozolomide or post-surgical follow-up only (**Figure 2)**. Two studies provided PFS for treatment with radiotherapy: 60 and 55.36 months [6, 23]. The three temozolomide data points did not demonstrate any observable trends with regards to dosage, rather the PFS were: 32.9, 36.1, and 43.2 months [6, 14, 22]. Post-surgical follow-up only had a value of 35.7 months, falling within the extremes of the temozolomide PFS values [23]. With the data currently available, to maximize PFS, radiotherapy appears to yield the best results for A-mt II. Overall, further studies with large sample sizes and directly comparing various treatment modalities are needed.

4.3.2 OS - WHO, grade II astrocytoma, Mutant

The dataset for A-mt II was composed of eleven values, with none of the studies providing conclusive insight into treatment (**Figure 3)**. For instance, one study indicated for high risk A-wt, RT (55.4 months) had a significantly longer OS than dose-dense TMZ (36 months) [29]. Meanwhile, comparing across two different studies, treatment with temozolomide (134.4 months) provided a longer OS than watchful waiting (67.2 months) [13, 14]. Thus, further studies examining the nuances of the treatment modalities are needed for A-mt II prior to making conclusions.

4.4.1 PFS - WHO, grade II oligodendroglioma

For OD-II, combination RT with CT produces the longest PFS, followed by RT alone, and finally temozolomide alone (**Figure 2**). A combination of radiotherapy and chemotherapy was found to have PFS at 120.2 and 162 months. Meanwhile, radiotherapy had the second longest PFS at 61.63, 91.2, and 103.6 months [6, 21, 28]. Finally, studies of temozolomide treatment alone produced the shortest PFS values: 35, 37.9, 46, 55.03, and 58.8 months [6, 14, 21, 22, 26, 27].

Therefore, on the basis of this data, for those with OD-II a combination of RT and CT should be considered, yet more robust comparative prospective clinical trials are needed.

4.4.2 OS - WHO, grade II oligodendroglioma

Amongst OD-II tumors, OS values stratified by treatment were inconclusive (**Figure 3**). One study examined radiotherapy, providing the longest OS value of all studies at 235.4 months [28]. Following the single RT value of 235.4, the second longest OS was with a combination of RT and CT (212.4 months) [28]. For temozolomide, OS values were 76 and 116.4 months, which was conclusively distinguishable from radiotherapy (235.4 months) [14, 26, 28]. Overall, RT with CT or RT alone maximizing OS for OD-II; however, better data will be needed before any conclusions can be drawn.

4.5.1 Stratification by Age

When stratifying based on age, those older than 60 years had different trends. For the general population without age-stratification, several of the datasets highlighted how OD-II have better survival outcomes than A-mt II, and A-mt II have better outcomes than A-wt II. Etxaniz et al. and Opoku-Darko et al. demonstrated this trend with surgery, Houillier et al. with postoperative initial TMZ treatment, and Wahl et al. with postoperative monthly TMZ cycles [14, 20, 22, 25]. However, these trends change when age is stratified. The data from Morshed et al. studied patients older than 60 years and found A-mt II tumors responded better to therapy than OD-II**,** and OD-II better than A-wt II [24]. Hence, future study designs should stratify results based on age—medicine well recognizes geriatric patients as having many physiologic differences compared to younger adults, such as liver metabolism amongst others [39].

4.6.1 Personalized treatments

Future optimal management strategies are likely to involve personalized paradigms. Even within molecular subtypes, each patient will likely have numerous confounding variables that influence outcomes. When looking at the case series of eight patients in the Opoku-Darko et al. study (**Table 1**), some of the earlier observed trends do not conform to this case series [25]. For instance, the OD-II tumor with the greatest EOR had a PFS less than the patient with biopsy, while one A-mt II tumor with 100% EOR had a PFS less than a biopsy patient, and another A-mt II tumor with chemoradiotherapy had a worse PFS outcome than a patient who did not receive RT or CT [25]. Therefore, the likely end result for LGG management will possibly be a complex algorithm that takes into consideration an abundant array of individualized patient variables, including possibly more genetic markers.

4.7.1 Study Limitations

There are a number of limitations to this systematic review and the included studies. For example, several datasets implied rather than providing explicit definitions for PFS and OS. Moreover, others did not detail the CT or RT regimen details, or simply combined CT and RT

together. Likewise, several of the methods sections minimally described the inclusion and exclusion criteria. Regarding statistics, certain datasets did not provide confidence intervals.

In addition, most studies included were retrospective, while some studies essentially compared patients who were suitable surgical candidates versus unsuitable (as surgical randomization is untenable due to lack of clinical equipoise). Another limitation is the inconsistent follow-up times amongst the studies, ranging from 20 to 216 months (18 years). Lastly, with this systematic review, most of the included studies involved small samples sizes, therefore limiting the conclusions. However, by presenting survival outcome data, this systematic review also highlights the problems with the ability to draw conclusions from current studies, thus by addressing these problems future clinical trial design may improve. However, by extension no treatment recommendations can be made from this review.

5.1 Conclusion

Overall, after stratifying WHO grade II gliomas based on molecular subtype and treatment modality, several findings were made regarding OS and PFS. Median OS for A-wt II (32.2 months), A-mt II (115.2 months), and OD-II (163.7 months) were found, as were median PFS for A-wt II (17.45 months), A-mt (43.20 months), and OD-II (59.20 months). Overall, A-wt II was confirmed to have a significantly shorter OS than A-mt II; meanwhile, there was no significant difference found between OS of OD II with A-mt II and A-wt II. Additionally, all three molecular subtypes were found to have statistically significant differences between PFS, with OD II having a statistically better PFS than A-mt II.

Future studies should also attempt to examine quality of life variables, accounting for treatment toxicity or post-operative neurologic function loss. However, knowing the raw PFS or OS data helps design better future clinical trials and provides patients with more tangible information when making critical and complex treatment decisions. Additionally, despite the limitations, this study makes sense of the best available data, helping better elucidate the progression and outcomes of WHO grade II gliomas.

Compliance with Ethical Standards

Declarations of Interest: None
Author Arash Ghaffari-Rafi declares he has no conflict of interest. Author George Samandouras declares he has no conflict of interest

Ethical Approval
This article does not contain any studies with human participants or animals performed by any of the authors.

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Appendix

Pubmed (MEDLINE) Search Strategy

(A)

1. **molecula***
2. **genetic*** or **genetics** or **genetic**
3. **mutation*** or **mutation**
4. **molecular genetic*** or **molecular genetic** or **molecular genetics**

Search **(((molecula*) OR (((genetic*) OR genetics) OR genetic)) OR ((mutation*) OR mutation)) OR (((molecular genetics) OR molecular genetic) OR molecular genetic*)**

(B)

1. **overall survival*** or **overall survival** or **overall survivals**
2. **survival*** or **survival** or **survivals**
3. **"os"**

Search **(((((((overall survival*) OR overall survival) OR overall survivals) OR survival*) OR survival) OR survivals) OR "os")**

(C)

1. **progression free survival*** or **progression free survival** or **progression free survivals**
2. **progression*** or **progression** or **progressions** or **PFS** or **PFSs**

Search **(((((((progression free survival*) OR progression free survival) OR progression free survivals) OR progression*) OR progression) OR progressions) OR PFS) OR PFSs)**

1. **low grade glioma** or **LGG** or **LGGs**
2. **grade 2 gliomas** or **grade ii gliomas**
3. **astrocytoma*** or **astrocytomas**
4. **oligodendroglioma*** or **oligodendrogliomas**

Search **((((((low grade glioma) OR LGG) OR LGGs)) OR ((grade 2 gliomas) OR grade ii gliomas)) OR ((astrocytoma*) OR astrocytomas)) OR ((oligodendroglioma*) OR oligodendrogliomas)**

(D)

1. **treatment*** or **treatments** or **treatment**
2. **treat*** or **treat** or **treats**

Search **(((((treatment*) OR treatments) OR treatment) OR treat*) OR treat) OR treats**

Sort by: **Best Match** Filters: **Publication date from 2008/01/01 to 2018/12/31**

Search **((((((((((((overall survival*) OR overall survival) OR overall survivals) OR survival*) OR survival) OR survivals) OR "os"))) OR (((((((((progression free survival*) OR progression free survival) OR progression free survivals) OR progression*) OR progression) OR progressions) OR PFS) OR PFSs)))) AND ((((molecula*) OR (((genetic*) OR genetics) OR genetic)) OR ((mutation*) OR mutation)) OR (((molecular genetics) OR molecular genetic) OR molecular genetic*))) AND (((((((low grade glioma) OR LGG) OR LGGs)) OR ((grade 2 gliomas) OR grade ii gliomas)) OR ((astrocytoma*) OR astrocytomas)) OR ((oligodendroglioma*) OR oligodendrogliomas))) AND ((((((treatment*) OR treatments) OR treatment) OR treat*) OR treat) OR treats)**

Embase Ovid Search Strategy

(1) exp glioma/
(2) glioma*.mp.
(3) LGG*.mp.
(4) astrocytoma*.mp.
(5) oligodendroglioma*.mp.
(6) (grade adj ii).mp.
(7) 1 or 2 or 3 or 4 or 5 or 6

(8) exp progression free survival/
(9) (progression adj free).mp.
(10) progression*.mp.
(11) PFS*.mp.
(12) 8 or 9 or 10 or 11

(13) exp overall survival
(14) (overall adj survival*).mp.
(15) OS*.mp.
(16) 13 or 14 or 15

(17) exp molecular genetics
(18) (molecular adj genetic*).mp.
(19) molecul*.mp.
(20) genetic*.mp.
(21) 17 or 18 or 19 or 20

(22) treatment*.mp.

(23) 12 or 16
(24) 7 and 21 and 22 and 23
(25) 24 and 2008:2018.(sa_year).

Key:
mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term wor

CENTRAL Search Strategy

(1) MeSH descriptor: [Glioma] explode all trees
(2) glioma*
(3) astrocytoma*
(4) oligodendroglioma*
(5) LGG*
(6) #2 or #3 or #4 or #5
(7) # 1 or #6

(8) MeSH descriptor: [Disease-Free Survival] explode all trees
(9) progression*
(10) survival*
(11) PFS*
(12) #9 or #10 or #11
(13) #8 or #12

(14) OS*
(15) overall*
(16) #14 or #15

(17) #13 or #16

(18) MeSH descriptor: [Molecular Biology] explode all trees
(19) genetic*
(20) molecul*
(21) #18 or #19 or #20

(22) MeSH descriptor: [Therapeutics] explode all trees
(23) treatment*
(24) #22 or #23

(25) #7 and #17 and #21 and #24