Seizure Outcomes and Survival in Adult Low-Grade Glioma over 11 years: Living Longer and Better

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Improved Survival in Low-Grade Glioma over 11 years

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Abbreviations: Low-Grade Glioma (LGG)

Conflict of Interest:

None declared.

Abstract

Background: There has been a trend towards earlier and more aggressive resection for Low-Grade Gliomas (LGG). This study set out to compare seizure control and survival of adults with LGG seen in the same neuro-oncology clinic over 11 years and to determine if a change in surgical philosophy has led to a corresponding improvement in outcomes.

Methods: Retrospective analysis using case-note review of 153 adults with histologically verified or radiologically suspected LGG, collecting data on patient, tumor and seizure characteristics between 2006 and 2017.

Results: We studied 79 patients in 2006 and 74 patients in 2017. There was no significant difference between the two groups in age at presentation, tumor location or integrated pathological diagnosis. The numbers of complete or partial resections increased from 21.5 % in 2006 to 60.8% in 2017 ($p<0.05$). Five and Ten-year Overall Survival increased from 81.8% and 51.7% in 2006 to 100% and 95.8% in 2017 ($p<0.001$); similarly Five and Ten - year Progression-Free Survival increased from 47.0% and 30.7% in 2006 to 93.1% and 68.7% in 2017. The proportion of patients with intractable epilepsy reduced from 72.2% in 2006 to 43.2% in 2017 ($p<0.05$). The neurosurgical morbidity rate was identical in both groups (11.8% in 2006 vs 11.1% in 2017)

Conclusion: Management of LGG over the last eleven years has led to substantial improvements in survival and seizure control. This is most likely to be due to a change in surgical philosophy with early resection now favored over watchful waiting where possible.

Key Words

Key words: Low-Grade Glioma, Survival, Epilepsy, Early Resection, Prognosis

Introduction

Low-Grade Gliomas (LGG) are a heterogeneous group of slow-growing primary brain tumors and account for 15-20% of all gliomas. The most common LGGs in adults are IDH-mutant astrocytomas and IDH mutant, 1p/19q codeleted oligodendrogliomas (WHO Grade II) , Oligoastrocytomas are no longer recognized as a distinct histological entity since the advent of integrated molecular diagnosis and publication of the new WHO 2016 classification[1]. WHO Grade II gliomas have an inherent tendency to transform to higher grades over time. Median survival varies from 5-–15 years depending on the age of the patient, the histological type, the presence of *Isocitrate Dehydrogenase* gene (IDH) mutations, Loss of Heterozygosity at chromosomes 1p and 19q and tumor location.

Seizures are the most common presenting symptom of adult LGG [2], and epilepsy may be the only clinical manifestation for many years. Seizure control is an important part of the clinical management of these patients, due to their significant impact on Quality of Life [3]. Around 50% of patients with LGG have intractable epilepsy[4,5], defined by the International League Against Epilepsy as "a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules to achieve sustained seizure freedom".

The management of adult WHO Grade II IDH Mutant LGG has been one of the most controversial areas in neuro-oncology due to the highly variable natural history of the disease and the dearth of high-quality evidence to support a policy of early intervention.

Historically, management of LGG patients consisted of watchful waiting, with biopsy or resection and oncology treatments withheld until progression. This was supported by several older studies that demonstrated no improvement in outcomes of LGG with early resection or early radiotherapy. A prospective randomized trial of early vs delayed radiotherapy did not show any survival advantage for early radiotherapy[6] and surgery was regarded as of little benefit[7] due to a high recurrence rate, and risk of permanent neurological deficit in previously intact individuals with a potentially long survival. Thus, the majority of patients with LGG were not actively treated but monitored with regular imaging until progression.

Over the last 10-15 years, there has been increasing enthusiasm and evidence for earlier and more extensive surgical resections[8], due to advances in our understanding of the morbidity and mortality of untreated LGG, improved preoperative functional and anatomical imaging, widespread acceptance of

awake craniotomies and increased access to postoperative rehabilitation. Although there are no prospective randomized trials of surgery for LGG, observational studies of patients with Gross Total Resections have shown a five year overall survival of over 90%[9]. A recent study from Norway comparing two neurosurgical centers with opposing philosophies (Early Resection versus Watch and Wait) has shown a significant survival benefit in patients treated at the center advocating Early Resection without an increase in neurosurgical morbidity[10].

In light of this, we conducted a retrospective case note review of two patient cohorts treated in our neuro-oncology service, separated by eleven years, with data from the first cohort collected in 2006 and data from the second collected in 2017. Up to 2006, the prevailing philosophy was watchful waiting with early resection reserved for low risk tumors e.g. non-dominant frontal and temporal lobe – whereas in the last ten years, there has been an incremental uptake of early surgery when technically feasible so that the majority of patients with solitary discrete gliomas are now offered early resection within the anatomical limits of the visible tumor.

Within each cohort, patients were followed up every six months until death. We compared patient and tumor characteristics, as well as treatments and clinical outcomes, to see whether this evolution in surgical philosophy favoring earlier resection has had an impact on survival and seizure control.

Methods

Adult patients with LGG treated at the National Hospital for Neurology and Neurosurgery under the care of JHR were selected if they had a diagnosis of histologically verified or radiologically suspected WHO Grade II LGG. Two patients were subsequently excluded from the survival analysis of the 2006 cohort as their histology on review was of a Grade I glial tumor rather than a Grade II glioma.

All patients were seen in the neuro-oncology clinic by JHR and data on age, gender, presenting symptoms, seizure history, tumor location and histology, surgery, oncological treatment and time to malignant transformation or death (if either event occurred) were collected after anonymization. Interventions were deemed "early" if they occurred within a year of tumor diagnosis. Tumors were classified histologically as astrocytoma, oligodendroglioma or oligoastrocytoma, as the 2006 patient group lacked the information on molecular genetics required by the 2016 classification. We were able to reclassify 51 of the 79 patients of the 2006 cohort after analyzing histological samples with molecular tests. 24 patients had no available material and analysis was inconclusive on a further 5 patients. Both histological and molecular data were recorded for both cohorts where possible. Patients were molecularly re-classified using the WHO 2016 guidelines(1) into IDH-mutant, 1p/19q co-deleted oligodendrogliomas, IDH-mutant astrocytomas, or IDH wildtype astrocytomas using the methodology outlined by Jaunmuktane *et al*[11].

Patients were followed up at 6 monthly or yearly intervals by JHR. Patients with aggressive tumors that progressed within 6 months to one year of original diagnosis, were referred onto oncology and thus our cohort reflect longer survivors. This practice remained consistent across both time points.

Details of anti-epileptic drugs and seizure type and frequency were extracted from the clinical notes. Seizure outcome was classified by Engel's groups[12] – usually describing seizure outcomes after surgery but adapted for the purposes of this study. We defined Class 1 as complete seizure freedom, Class 2 as yearly seizures, Class 3 as monthly seizures and Class 4 as more than weekly seizures.

The data were compared with a similar unpublished retrospective study on a comparable patient group in 2006 by RW[13]. Four patients from the 2017 cohort had survived from the 2006 cohort, and thus were excluded from the 2017 cohort. Six patients in the 2017 cohort presented before 2006 but weren't included in the original 2006 audit as they were referred to the clinic after 2006.   The only new data collected by this study for the 2006 cohort was Overall Survival, as too few patients had

died by 2006 to allow for meaningful comparison, and the molecular pathology tumor as this wasn't routinely done at the time.

Data were analyzed using Microsoft Excel 365 and IBM SPSS 24. Gaussian distribution was determined with the Shapiro-Wilk Test. Differences between groups were assessed using independent T-tests or the Kolmogorov-Smirnov test for normally and non-normally distributed data respectively. The Chi-squared test was used for comparison of categorical variables, with the Fisher-exact test employed if a category had a frequency <5. Five - and Ten - year Progression-Free and Overall Survival were calculated using Kaplan-Meier analysis, and were used as median survival hadn't been reached by the 2017 cohort. Significance between Kaplan-Meier curves was determined using the Log-Rank (Mantel-Cox) test.

Ethics

This study was an updated analysis of a prospective imaging study of LGG approved by the Local Research Ethics Committee of the National Hospital for Neurology and Neurosurgery (99/N092).

Results

Similar patient demographics and tumor characteristics allow for comparison between the groups

There were 79 patients in the 2006 and 74 patients in the 2017 cohort, and no significant overlap in their dates of presentation ($p<0.001$). Median follow up for both cohorts was 5.5 years (*Supplementary Figure 1*). There were no significant differences in mean age ($p=0.3$) at diagnosis. There were more females in 2006 than 2017 ($p=0.02$) (*Table 1*). Patients were more likely to have a bifrontal tumor in 2017 (6 in 2017 vs 0 in 2006, $p=0.01$), though there were no other significant differences in tumor laterality (*Table 2*). Patients were more likely to have a temporal lobe tumor in 2006 ($p=0.03$) and a multifocal tumor in the 2017 cohort ($p=0.025$), but there were no other differences in tumor location (*Table 2*). There were no differences in tumor histology between the two groups (*Table 3*). Molecularly confirmed oligodendrogliomas were more common in the 2017 cohort ($p=0.03$) and there were more tumors for which a genetic diagnosis was unavailable (27 in 2006 vs 14 in 2017, $p=0.048$). Allowing for these differences, the two cohorts were broadly similar in terms of demographics, tumor location and histology.

Progression-Free and Overall Survival has improved significantly between 2006 and 2017

Five-year Progression-Free Survival (PFS) increased from 47.0% in 2006 to 93.1% in 2017, and 10-year PFS increased from 30.7% in 2006 to 68.7% in 2017 ($p<0.001$). The Five-year Overall Survival (OS) rates similarly increased from 81.8% in 2006 to 100% in 2017 and ten-year survival from 51.7% in 2006 to 95.8% in 2017 ($p<0.001$). *(Figure 1)*.

When separating patient groups by histological and molecular diagnosis, a similar survival benefit was seen in the 2017 cohort with each subtype. On average, both PFS and OS was better in patients with oligodendrogliomas compared to those with IDH-mutant astrocytomas, and this difference is more pronounced at the 10-year time point. *(Supplementary Figures 2 & 3)*.

Seizure outcomes have improved between 2006 and 2017

27% patients were seizure free for one year or more (Engel class 1) in 2006 compared with 57% in 2017 ($p<0.001$). These patients would therefore be eligible to drive again. All the other classes showed improvements from 2006 to 2017 - 30% had yearly seizures in 2006 compared with 20% in

2017, 17% had monthly seizures in 2006 compared with 12% in 2017 and 25% had weekly seizures in 2006 compared with 11% in 2017 (*Table 4*).

Patients in the 2017 group underwent a significantly higher number of resections

Patients in the 2017 cohort underwent a significantly higher (*p*<0.001) number of early resections compared with the 2006 cohort (21.5% vs 60.8%). In the later cohort, there was no significant difference increase in the proportion of partial resections (52.6% in 2006 vs 60% in 2017, p=0.392) or total resections (47.4% in 2006 vs 40% in 2017, p=0.392). None of the patients in the 2006 cohort underwent early chemotherapy or early radiotherapy whereas 5 and 9 patients respectively had early chemotherapy or early radiotherapy in the 2017 cohort. There were significantly fewer patients on a watchful waiting protocol in the 2017 cohort (78.4% in 2006 vs 35.1% in 2017 (*p*<0.001)) *(Table 5)*.

There was no difference in surgical morbidity and mortality between the two groups

Complications from surgery were rare across both cohorts, and no patient died after surgery. In 2006, 2 out of the 17 (11.8%) patients who underwent early resection were left with significant complications – one with mild dysphagia and right sided weakness, and the other with an infected bone flap which had to be removed in a later surgery. In 2017, 5 out of the 45 patients (11.1%) who had early surgery were left with significant complications. One patient developed a left superior quadrantanopia, one had mild dysphagia, another developed a profound Supplementary Motor Area syndrome which eventually recovered with intensive therapy, one patient had a right foot drop and another patient developed an infected bone flap requiring a cranioplasty.

AEDs and seizure outcomes

The most commonly used Anti-Epileptic Drug (AED) in 2006 was carbamazepine (29%), followed by phenytoin (25%). In 2017, the most commonly taken AED was levetiracetam (66%) followed by lamotrigine (36%). In the 2017 patient group, 62 (94.4%) took a new AED, with only 2 exclusively on an older AED. In the 2006 cohort, 32 (40.5%) took a new AED.

There was no difference in the mean number of AEDs taken by patients in 2006 compared to 2017 (1.6 (95% CI 1.4-1.8) vs 1.7 (95% CI 1.5-1.9)). 3 patients in the 2006 cohort took no AED compared with 8 in 2017 (p=0.228) (*Supplementary Table 1*).

Discussion

This study set out to investigate the differences in survival and seizure outcomes between two patient groups with low-grade gliomas (LGG) over 11 years, and to investigate the effect of earlier surgical intervention. Having established that the two patient groups were broadly similar in age, gender, tumor location and histology, we have shown that there was a significant increase in both Progression-Free and Overall Survival and seizure outcomes in 2017 compared with 2006, but not at the expense of surgical morbidity impairing Quality of Life. The chances of surviving 5 years increased from 81.5% in 2006 to 100% in 2017 and of surviving 10 years from 51.7% to 95.8%. Patients with histological or molecularly diagnosed oligodendrogliomas tended to have better survival, with this difference more pronounced at the 10-year timepoint, consistent with the literature. A proportion of IDH-wildtype astrocytomas are associated with worse prognosis than IDH-mutant astrocytomas, specifically when they represent early stages of IDH-wildtype glioblastoma[14], however only one patient in the 2006 cohort and none in the 2017 cohort had an IDH-wildtype glioblastoma. The unusually low number of IDH-wildtype gliomas is likely due to the early referral to oncology that occurred in patients with gliomas that progressed within 6 months to one year,. However, as this practice remained consistent across both cohorts, it allows for meaningful comparison. This practice also explains the higher than expected survival for these patients. Although molecular analysis of archival material from the 2006 cohort showed a significantly fewer number of oligodendrogliomas than the 2017 cohort, the survival advantage remained between the different histological and molecular groups. Furthermore, when comparing survival between tumors in the 2006 cohort that had been biopsied and those that had not been biopsied, no significant difference was seen (supplementary figure 4). This eliminates the potential bias that could have occurred if the non-biopsied tumors were predominantly IDH- wildtype1p 19q non-codeleted gliomas.

The only other significant difference in tumor characteristics was the increased number of tumors located in the temporal lobe in the 2006 cohort. While there is no evidence that this impacts on survival, there is some evidence that temporal lobe tumors are more likely to result in intractable epilepsy. However, patients in the 2006 cohort with temporal lobe gliomas had almost double the rate of seizure freedom compared to the cohort average, so it is unlikely this biased our results.

Crucially, the proportion of patients who were seizure free for over a year rose from 27.8% in 2006 to 56.8% in 2017. Complete seizure-freedom is of vital importance to patients, as it is a requirement for the Drivers Vehicle Licensing Authority to return patients their driving licenses[15] thus preserving their independence. There were improvements across the other Engel classes, with significantly fewer patients in the 2017 cohort (10.8% vs 24.1% in 2006) having frequent seizures more than once a week.

The change in surgical approach to glioma treatment that has happened over the last decade, where early intervention is being favored over watchful waiting, is confirmed by the significant increase (p<0.001) in surgical resections, both partial and complete, in the 2017 cohort compared with the 2006 cohort (21.5% in 2006 vs 60.8% in 2017). We believe that early resection is the factor most responsible for the improvement in both survival and epilepsy outcomes, as the groups are similar in almost every other regard.

This is in line with a growing body of evidence that suggests early resection is associated with improved outcomes in LGG It is well known that surgery improves seizure control in a significant proportion of patients with LGG, including pharmacoresistant epilepsy. The Extent of Resection was not formally assessed, as this was not routinely measured, but the proportion of patients who underwent a macroscopic complete resection, as evidenced by the absence of FLAIR signal on the postoperative MRI scan, was broadly similar across both cohorts (47.4% in 2006, 40% in 2017). Furthermore, despite riskier and more frequent surgery being undertaken more frequently in the 2017 cohort, there were no surgical deaths and a similar morbidity rate.

Similarly, there was a significant increase in referrals for early radiotherapy and early chemotherapy, in the 2017 cohort, although the numbers are much smaller. Early radiotherapy has not been a standard of care in our institution based on the data from the EORTC 22045 trial showing no Overall Survival advantage from early radiotherapy[6].Tthe data on the survival advantage of chemotherapy after radiotherapy which emerged from the RTOG9802 trial were only published in 2016[16], hence only 2 patients in the 2017 cohort had both early radiotherapy and chemotherapy which is unlikely to have affected the overall results. There was also no significant difference in seizure control between patients who received either early radiotherapy or early chemotherapy in the 2017 cohort (supplementary tables 2 and 3). Therefore, the most likely explanation for the improvements in

seizure control and survival between the two cohorts remains the earlier and more aggressive resection of gliomas in the 2017 cohort.

Further work has recently been completed looking at the impact of 1p19q codeletion status on survival following surgical resection. In a retrospective review of patients, Lu et al. reported that gross total resection only conferred a survival benefit in 1p19q non-codeleted gliomas after multivariate analysis incorporating the use of adjuvant therapy[17]. This follows a similar study demonstrating poorer outcomes in IDH-mutant astrocytoma where even very small postoperative volumes negatively affected Overall Survial[18], highlighting the importance of as large as possible Extent of Resection in this molecular subgroup. Our data demonstrate that resection vs watchful waiting confers a survival benefit in both 1p19q codeleted and non-codeleted gliomas, which is in line with Jakola et al. who also demonstrated a survival benefit to 1p19q non-codeleted glioma[10], and it would be interesting to see in future studies to what degree extent of resection impacts survival within different integrated groups.

There was no change in the number of AEDs used, rather there was a switch from carbamazepine to levetiracetam as a first line agent. As expected, more patients were on newer AEDs in the 2017 cohort than in the 2006 one. Levetiracetam and carbamazepine have similar efficacy[19], and indeed no newer AEDs have proven efficacy for the treatment of epilepsy greater than that of carbamazepine[20]. Although this study didn't examine side-effect profiles, newer AEDs are reported to have fewer adverse effects and they are not enzyme inducing, which is a relevant consideration for women and patients being prescribed chemotherapy later in the course of the disease. We were not able to compare Quality of Life between the two cohorts as these data were not routinely collected.

There were several limitations to this study. Firstly, the data were collected retrospectively from clinical notes and so were sometimes incomplete. The retrospective nature of the study also meant there was no randomization and, due to the rarity of the condition, sample sizes at both timepoints were small. The lack of tumor material from a proportion of the 2006 cohort also reduced the number of patients with molecularly reclassified tumors.

Nevertheless, the similarity in demographics and tumor characteristics between the two cohorts treated at the institution has allowed for a rare opportunity to compare the management and outcomes over a decade and to demonstrate a significant increase in survival and seizure freedom.

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Figure Captions

Figure 1 – Progression-Free Survival (PFS) and Overall Survival (OS) for whole group in 2006 and 2017

Dashes represent censoring

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