Postprogression survival in patients with glioblastoma treated with concurrent chemoradiotherapy: a routine care cohort study

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Glioblastoma is the commonest malignant brain tumor in adults. Most patients develop progressive disease before they die. However, survival after developing progressive disease is infrequently reported. We identified patients with histologically proven disease who were treated with concurrent chemoradiotherapy during 2006–2013. We analyzed overall survival (OS), progression-free survival and postprogression survival (PPS) in relation to age, O6-methylguanine-DNA methyltransferase promoter methylation and extent of surgical resection. We identified 166 patients. Median survival was 13.5 months; 2-year OS was 21.7%. Median progression-free survival and PPS were 7.03 and 4.53 months, respectively. Age and extent of surgical resection were correlated with OS. Only the extent of surgical resection was associated with PPS. Our work suggests that the established prognostic factors for glioblastoma do not appear to help predict PPS.

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Keywords: glioblastoma • overall survival • postprogression survival • prognostic factors • progression-free survival • treatment

Practice points

- Postprogression survival (PPS) is rarely reported in studies of first-line treatment.
- The prognostic factors that predict PPS are poorly understood.
- In this paper, we report a cohort of patients treated as part of routine practice, and report PPS.
- Median survival of the investigated cohort was 13.5 months.
- Age and extent of surgical resection were correlated with overall survival. Only the extent of surgical resection was associated with PPS.
- Our work suggests that the established prognostic factors for glioblastoma do not appear to help predict PPS.

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults and has the highest average years of life lost of all cancers [1]. There has only been one trial which has shown improved survival in the last 10 years [2], and current optimal treatment for GBM is maximal surgical resection followed by radiotherapy with concomitant and adjuvant chemotherapy with temozolomide, which is associated with a median survival of 15 months and 5-year survival of 9% [3]. The results from randomized trials have been confirmed by data from routine practice.

Multiple studies have identified prognostic factors in newly diagnosed patients with GBM. These include age, performance status, extent of surgical resection and MGMT status [4,5]. However, prognostic factors in patients with relapsed GBM are less clear.

Future
Medicine

Although it is possible to estimate prognosis at diagnosis, such estimates are necessarily uncertain. For patients with GBM, most patients will develop disease progression before they die [6], and in randomized trials, progression-free survival (PFS) correlates well with overall survival (OS) [7]. Disease progression is an event that both patients and clinicians understand, and is a key decision point for patients considering further treatment. Predictions of survival have been shown to be important for patient decision-making [8], and clinicians are often poor at predicting survival [9], but there is very little literature on survival after progression (postprogression survival, PPS) in patients with GBM. As well as the value to patients, the ability to predict PPS might provide a basis for stratification of patients enrolled in clinical trials. Existing trial data do not provide this information: reports of first-line treatment typically report PFS and OS. Despite the fact that for any one patient, OS equals the sum of PFS and PPS, for any group, the sum of median PFS and median PPS does not equal median OS. The authors believe this study is an important addition to the current available work, as there is almost no other literature available in this specific area. Many trials of patients with relapsed disease enroll cohorts who are substantially unrepresentative of those who received first-line treatment. The question remains, therefore, whether we can offer a guide to prognosis for patients with GBM who have received first-line chemoradiotherapy and who have developed progressive disease, based on the whole patient group rather than those well enough to enter Phase I or II clinical trials, and whether we can identify prognostic factors to refine that estimate of PPS.

This study reports the OS, PFS and survival after progression (PPS) of a single center cohort of patients with histologically confirmed GBM treated with concurrent chemoradiotherapy and examines the impact of potential prognostic factors on PPS.

Methods

We identified all adult patients (≥ 18 years of age) with a histological diagnosis of GBM who were treated with concurrent chemoradiotherapy (60 Gy in 30# over 6 weeks; Temozolomide 75 mg/m² daily) at single tertiary oncology center between July 2006 and February 2013 and for whom we had either a date of last follow-up or a date of death.

We collected demographic, pathology, imaging, treatment and outcome data from electronic hospital records. Dates of last follow-up and dates of death were collected from electronic records (completed on 10 July 2014). The date of diagnosis was taken as the date of histological diagnosis. Where this was not available, we estimated the date of diagnosis by backdating from the date of starting radiotherapy. The date of first disease progression was defined as the date of the first MRI that demonstrated radiological progression. To account for pseudoprogression, an initial MRI suggestive of disease progression was only taken as being positive if supported by a second scan at least 4 weeks later, or if there was clear clinical decline. The extent of surgical resection was based on prospectively collected surgical estimate and postoperative MRI. MGMT promoter methylation was assessed using pyrosequencing assays, with methylation greater than 15% defined as being positive. Patients were excluded if they did not demonstrate evidence of progression at the time of analysis, or if this information was unavailable due to loss to follow-up.

OS was defined as the interval from the date of diagnosis until death, PFS as date of diagnosis until first disease progression or death and PPS as the interval from date of first disease progression until death, respectively. Survival was estimated using the Kaplan–Meier method, and we analyzed the impact of age, MGMT status and surgical resection on OS and PPS. We assessed the impact of age on survival by dichotomizing the sample at near the median age, and the impact of surgery by considering gross total resection versus other surgery.

Statistical analysis was performed using RStudio Version 0.98.501. We used the log-rank test to assess the statistical significance of differences in survival. There were no corrections for multiple hypothesis testing. Due to the retrospective use of anonymized data, no ethical approval was sought for this work.

Results

We identified 168 patients. In 166 patients, we were able to determine both the date of diagnosis (backdating from the start of radiotherapy in nine patients) and either death or last follow-up, and were available for analysis of OS. In 144 patients, we were able to obtain both a date of progression and date of death, and these were used for analysis of PFS and PPS (Figure 1). Data on patients' performance status and steroid use were not available. Median age was 57 months; 63% were male; 60% had an MGMT promoter status recorded, of whom 15% were MGMT-methylated. 12% had a gross total resection, 13% a subtotal resection and 75% of patients had a biopsy only. Median time between surgery and starting chemoradiotherapy was 35 days. Median survival was 13.5 (95% CI: 10.9–16.6) months; 2-year OS was 21.7%. Median PFS was 7.03 months and median PPS was 4.53 months.

Figure 1. Consort diagram.

OS: Overall survival; PFS: Progression-free survival; PPS: Postprogression survival.

Age at diagnosis and extent of resection were both associated with improved OS. Younger age (<55-year old) at diagnosis and gross total resection were associated with longer OS (<55 vs >55; 18.0 vs 11.5 months; $p = 0.0103$ and gross total resection vs nongross total resection; 58.5 vs 13.2; $p = 0.0000426$). MGMT methylation (methylated vs unmethylated; 11.0 vs 16.6; $p = 0.471$) and female sex (female vs male; 20.4 vs 12.2; $p = 0.0535$) were associated with improved OS, but did not reach statistical significance (Figure 2).

Age at diagnosis and extent of resection were both associated with improved PFS. Younger age (<55-year old) at diagnosis and gross total resection were associated with longer PFS (<55 vs >55; 8.54 vs 5.47; $p = 0.0134$ and gross total resection vs nongross total resection; 42.12 vs 6.11; $p = 0.0000541$). MGMT methylation (methylated vs unmethylated; 4.36 vs 9.79; $p = 0.119$) was associated with improved PFS, although did not reach statistical significance. Sex was not associated with PFS (female vs male; 6.7 vs 7.53; $p = 0.901$; Figure 2).

Gross total resection was associated with improved PPS (gross total resection vs nongross total resection; 20.17 vs 4.34; $p = 0.0101$). Neither age (<55 vs >55; 4.3 vs 4.53; $p = 0.156$), MGMT methylation (methylated vs unmethylated; 6.11 vs 6.67; $p = 0.636$) or sex (female vs male; 61.6 vs 46.4; $p = 0.0604$) was associated with PPS (Figure 2).

PFS was not correlated with PPS ($p = 0.1$; Figure 3). A very extended PFS (>18 months) was associated with a longer PPS, but this was not statistically significant (13 vs 4.3 months; $p = 0.226$).

A total of 37 patients received further treatment on disease progression. Three patients received temozolomide alone, one received Avastin alone, six patients received PCV only, nine patients received PCV in combination with temozolomide, 15 patients received Avastin in combination with temozolomide and three patients received Irinotecan in combination with temozolomide and Avastin.

Patients who received chemotherapy for treatment of disease progression had a longer PPS, in comparison to those that did not receive treatment. Median PPS in those treated after progression was 8.18 months compared with 3.61 months in those who were not ($p = 0.0147$).

A total of 20 patients received bevacizumab, either upfront or for progression. Those that received bevacizumab did not have longer OS, PFS or PPS ($p = 0.0681$; 0.475 and 0.088, respectively).

Figure 2. OS, PFS and PPS by sex (A), age (B), MGMT status (C) and extent of surgical resection (D).

F: Female; GTR: Gross total resection; M: Male; N: Negative; Non-GTR: Non-gross total resection; OS: Overall survival; P: Positive; PFS: Progression-free survival; PPS: Postprogression survival.

Figure 3. Correlation between Progression-free survival and Post-progression survival.

Discussion

We have reported the OS of a group of 166 patients with a histological diagnosis of GBM treated with concurrent chemoradiotherapy at a single center over a 7-year period. The OS and PFS in our cohort is consistent with that reported in trials and in other series [3,10], and our results are consistent with existing evidence on the importance of age and extent of surgical resection as prognostic factors. Surgical resection and treatment rates at progression were low, and a recent audit of our practice has shown significant increases in rates for both measures.

There are several weaknesses to our study – it is based on patients from a single center, and due to the retrospective nature, performance status and steroid use was not available. However, many of the data were either collected prospectively (extent of surgical resection) or are unlikely to be affected by bias (age at diagnosis, MGMT status, date of progression on MRI).

Furthermore, multivariate analysis was not used in our study because given that most factors were not prognostic, the value of a multivariate analysis would be very limited. For those reasons, we omitted it from our manuscript.

It could be argued that progressive disease in GBM is not as objective outcome measure as we would hope it to be, given that pseudoprogression or radionecrosis may confound the outcome. However, we attempted to reduce the impact of this by requiring either two serial MRI scans reported as showing progression, or one scan with subsequent clear clinical deterioration. In addition, those patients who progressed early did not have increased OS, as has been reported for patients with pseudoprogression [11], and more recent work has suggested that pseudoprogression is less common than previously thought [12]. Furthermore, if pseudoprogression was a significant factor, one would expect PFS and PPS to be inversely correlated, which they are not. Radionecrosis is another potential confounder. However, with a median PFS of 7 months, and a literature-based estimate of 2–5% radionecrosis risk at 12 months, this is unlikely to have been a common problem in our cohort. Remarkable survival of patients with gross total resection is closely linked to the very small number who had a total resection, explaining both the distribution of treatment and the survival. Our finding that MGMT methylation status was not prognostic is probably a statistical artifact – only 99 patients had MGMT assayed, as it was not standard practice at the beginning of the time period. We cannot comment on the value of IDH1 or IDH2 mutations, or steroid use, as these were not available in a sufficient number of patients. Upfront use of bevacizumab has been shown to improve PFS but not OS (and hence presumably shorten PPS), but we had too few patients to be able to assess this. Postprogression treatment rates were low, mainly due to poor performance status.

With the exception of the extent of surgical resection, the factors that are known to be prognostic at diagnosis do not predict survival after relapse, and PFS did not predict PPS (i.e., the time from progression to death). This is in contrast to other tumor sites, where the disease-free interval is of prognostic value [13,14].

We reported the survival of patients who received salvage treatment. However, since it is clearly subject to indication bias, it would be wrong to regard receipt of salvage treatment as a prognostic factor in the same way as other factors, which are available at baseline.

Very few patients in the cohort had a re-resection. It is clear that the PPS is better in patients who have an initial total resection. On a very simple level, this may be because those who have had a total resection and develop

progressive disease have longer to live until the disease reaches the initial volume. Therefore, the authors believe that salvage treatment, particularly when not widely used, needs to be treated with caution as a prognostic factor.

Previous work on prognosis after disease-progression in patients with GBM is limited, and comes mainly from three studies based on the pooled results of patient enrolled in Phase I or II clinical trials [15–17]. These have suggested a range of potential prognostic indicators, including performance status, number of lesions, size of lesion, tumor location, age, male sex, time since diagnosis and steroid treatment. However, different studies have found conflicting subsets of factors to be of value, few of the included patients were treated with initial chemoradiotherapy, the studies included patients at both first and second relapse, and most patients relapsed much later than is usual for GBM patients (10, 10 and 21 months), given that 50% of patients treated with radical chemoradiotherapy progress within 4–6 months [2,18].

There is little other work assessing PPS in patients with GBM who have received concurrent chemoradiotherapy. One study reported that patients who develop progressive disease greater than 18 months from diagnosis have greater 2- and 5-year PPS and OS [19], but given that 18-month survival is longer than the median survival, being free of progressive disease at that time point is clearly likely to be associated with an improved survival. Most first-line studies tend to report PFS and OS, rather than PPS specifically, and one cannot use these figures to calculate PPS (e.g., our cohort has a median PFS of 7 months, PPS of 4 months and OS of 13.5, where $7 + 4$ does not equal 13.5). The role of reoperation in GBM is unclear, but may improve functional outcomes [20], and cognitive function and exercise capacity have both been shown to be prognostic in patients with recurrent disease [21,22].

Patients with GBM are often aware of the poor prognosis at diagnosis, but the available figures are statistical averages. As patients proceed through treatment, it is possible to identify time points at which the prognosis may be refined ('conditional survival'). Early response assessment has been shown to be prognostic [23], but may be confounded by pseudoprogression. However, disease progression is an event that carers and patients understand, and which often marks the start of functional decline. We have worked with patient and charity representatives to help define the potential value of estimating PPS. Once patients develop progressive disease, most patients and carers understand that the disease is not curable. Better, and personalized, estimates of PPS might allow them to make choices about whether to opt for active treatment (either as part of standard care or within a clinical trial) or to focus on quality of life, allow them to organize their financial and end of life plans, and allow health services to understand the economic implications of progressive disease. Such data might influence patients' willingness to enroll in clinical trials, given the potential survival outside of a clinical trial, and might allow the design of pragmatic clinical trials that focus on reducing the burden of care and unnecessary hospital admissions as patients approach the end of their lives. However, our study shows a clear need for further work to understand PPS, particularly in those treated as part of routine care, rather than the small proportion of patients enrolled into Phase I/II trials.

Conclusion & future perspective

In our study, age and extent of surgical resection were correlated with OS. However, only the extent of surgical resection was associated with PPS. Our work suggests that the established prognostic factors for glioblastoma do not appear to help predict PPS. Therefore, further work to understand PPS is required. In the revised WHO 2016 Classification of CNS tumors, the former entity of 'Glioblastoma' is classified as 'Glioblastoma IDH-wildtype,' 'Glioblastoma IDH-mutant' or 'Glioblastoma NOS.' Given that the time period of this study significantly predated the current understanding of IDH1/2 mutations, these were not assessed at the time of treatment diagnosis. Further studies of a similar kind can be improved by incorporating IDH1/2 mutation status in the OS, PFS and PPS analysis.

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Ethical conduct of research

The authors state that 'no ethical approval needed (anonymized data from retrospective review of patients treated as part of routine care)'; however, they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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