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Review article

The impact of surgery on survival after progression of glioblastoma: A retrospective cohort analysis of a contemporary patient population

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ABSTRACT

Despite updated management of glioblastoma (GB), progression is virtually inevitable. Previous data suggest a survival benefit from resection at progression; however, relatively few studies have evaluated the role of surgery in the context of contemporary GB treatment and widespread use of bevacizumab and chemotherapy. As such, the purpose of this study is to evaluate outcomes following surgical resection in patients with progressive GB since 2008. The records of all patients who underwent biopsy or resection of GB between January 1, 2008, and December 31, 2015, were retrospectively reviewed to identify 368 patients with progressive GB. Median survival and 95% confidence intervals were generated with the Kaplan-Meier method. Multivariate analysis, which controlled for age, Karnofsky Performance Status (KPS), extent of resection, adjuvant chemotherapy and radiation, tumor location, and tumor multifocality, of post-progression survival was carried out using a Cox proportional hazards model. Of 368 patients with progressive disease, 77 (20.9%) underwent resection at first documented progression. The median post-progression survivals for patients who did and did not undergo resection at this time were 12.8 and 7.0 months, respectively. In multivariate analysis, KPS $\geq$ 70 at progression (HR 0.438), receipt of bevacizumab at first progression (HR 0.756), and receipt of chemotherapy at first progression (HR 0.644) were associated with increased post-progression survival. Thus, surgery for progressive GB may not improve post-progression survival in the context of contemporary maximal non-surgical therapy. Further investigation is necessary to elucidate what role, if any, bevacizumab has in prolonging post-progression survival in patients with progressive GB.

1. Introduction

Glioblastoma (GB) is the most common primary malignancy of the central nervous system [20]. Standard therapy for newly diagnosed GB consists of surgical resection followed by concurrent involved field radiotherapy and temozolomide and subsequent adjuvant temozolomide [16,26]. The prognosis for patients with GB remains poor, with median overall survival of 14–17 months from time of diagnosis [9,25,26]. Options for nearly inevitable disease progression include resection, systemic chemotherapy, radiation therapy, or clinical trial enrollment. Among these options, two interventions are currently approved by the Food and Drug Administration (FDA) for progressive GB: bevacizumab, which is now commonly used in the United States in this population, and delivery of low energy alternating electric fields via the Tumor Treating Fields (Optune, Novocure Ltd, St. Helier, Jersey) device.

As quality of life for patients with newly diagnosed or progressive GB has improved over the last two decades, resection at progression has become an increasingly frequent choice and is performed on 20–30% of patients with progressive disease [15,33]. Surgery at progression may extend life, obtain tissue for diagnostic confirmation, allow entrance into a clinical trial, or improve symptoms by relieving mass effect. There is also a risk, however, of incurring new post-operative deficits, which may reduce quality of life, diminish survival, or delay subsequent treatment options. The majority of data suggest that there is a survival benefit associated with resection at progression [4,24,27], with increasing benefit associated with greater extent of resection (EOR) [2–4,18,21,22,35]. However, many of the patients included in these series were diagnosed and treated prior to the currently accepted standards of treatment and prior to the current widespread availability of bevacizumab and effective chemotherapy for progression [14]. In fact, recent studies have suggested that

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when the initial disease is managed according to current standards of treatment, resection at progression does not offer a survival benefit over non-surgical therapy [6,17,19]. To date, only three studies have evaluated resection at progression in the context of bevacizumab with or without chemotherapy at progression [18,19,34]. By reviewing a large contemporary series of GB patients treated at a single institution, we sought to update our understanding of which patients with progressive disease benefit from resection.

2. Materials and methods

2.1. Population

This study was approved by an Institutional Review Board, which granted access to an institutional brain tumor patient registry and waived the need to consent the subjects. We retrospectively identified all patients who received care at the neuro-oncology center of a large tertiary care institution and who underwent craniotomy for biopsy or resection of newly diagnosed GB between January 1, 2008 and December 31, 2015. GB pathology was confirmed in each case by neuropathologists in accordance with the 2007 World Health Organization (WHO) classification system. Patients with the pathologic diagnosis of gliosarcoma were included. Patients with both primary and secondary GBs were included in this study. Patients who underwent surgery or received treatment at other medical centers were included as long as adequate documentation (patient notes, pathologic specimens, peri-operative imaging) was available for review. In total, 563 patients met these criteria (Supplemental Fig. 1).

2.2. Data collection

All relevant data available in the health record system were reviewed in June 2016. Data collection included patient age at diagnosis, patient gender, date of initial pathologic diagnosis of GB, date of initial surgery, EOR at initial surgery, peri-operative KPS (recorded as $\geq$70 or <70) [7,26], adjuvant radio- and chemotherapy, and clinical trial enrollment. We also recorded the dates at which patient tumors were observed to progress, whether the tumor was multifocal or in an eloquent location at progression, date(s) and type of surgery at the time of observed progression, EOR for each craniotomy after initial progression, post-progression treatments, and date of death or last follow-up.

Date of initial diagnosis was defined as the first surgery at which the diagnosis of WHO Grade IV was established regardless of prior surgery for low-grade glioma. EOR was assessed via retrospective review of radiology, neuro-oncology, radiation oncology, and brain tumor board assessments of peri-operative imaging. Gross total resection (GTR) was defined as complete removal of contrast-enhancing disease on gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI). Any non-biopsy resection not considered to be a GTR was considered to be a subtotal resection (STR). Eloquent location at progression was defined by assessment of location of contrast-enhancing tumor in eloquent cortex (motor/supplementary motor cortex, primary somatosensory cortex, Broca's and Wernicke's area, and primary visual cortex) with intraoperative language-/motor-mapping or with pre-operative imaging and concurrent symptoms at presentation; in the brainstem; adjacent to or infiltrating the ventricles; or adherent to major blood vessels [5]. Multifocality was defined as multiple foci of contrast-enhancement on MRI. Peri-operative KPS was assessed by neuro-oncologists or radiation oncologists at peri-operative consultations. If KPS was not formally recorded, a score was retrospectively assessed based on chart review. Date of progression was retrospectively identified as the imaging date at which the patient's neuro-oncologist, neuro-radiologist, or the institutional brain tumor board felt the evidence supported progression. For cases in which radiographic diagnosis of progressive disease was equivocal, the date of diagnostic biopsy or surgery was recorded as the date of progression. An operation was only considered to be a resection at progression if the patient underwent a craniotomy for non-biopsy resection with confirmed post-operative pathologic diagnosis of progressive GB. As such, patients who underwent either stereotactic biopsy or craniotomy for debulking of subsequently confirmed pathologic diagnosis of pseudoprogression were considered to have not undergone resection for progression. In total, 368 patients had documented progression per these criteria and were included in all subsequent analyses (Supplementary Fig. 1). Resection, radiotherapy, cytotoxic chemotherapy, and bevacizumab for progression were recorded as binary variables after initial surgery and at first progression [11]. Deaths were recorded regardless of cause.

2.3. Statistical analysis

Statistical analysis was conducted with MATLAB (MathWorks, Natick, MA). Fisher's exact test (chosen over the Chi-square test given relatively small sample size) was used to compare binary variables, the Chi-square test was used to compare categorical variables, the Mann-Whitney *U* test was used to compare median values, the two-sample *t*-test was used to compare continuous variables, and the log-rank test was used to compare censored Kaplan-Meier survival curves. In order to accurately model the effects of post-progression treatment decisions and to address the inherent time bias that arises from prolonged pre-progression survival in patients who may also be better re-resection candidates [10], we used post-progression survival, instead of overall survival, as our primary outcome measure. Median survival and 95% confidence intervals were generated with the Kaplan-Meier method. Multivariate analysis was carried out using a Cox proportional hazards method for post-progression survival. Standard censoring was utilized for patients who were lost to follow up. Only variables that satisfied the proportional hazards assumption, as determined by examination of scaled Schoenfeld residuals, were included in the model; as such, clinical trial status and radiation at first progression were excluded [23]. Thirteen variables were included in the model: age at diagnosis, KPS at diagnosis, extent of resection at initial resection, post-operative radiation, post-operative temozolomide, time to first progression, eloquence at first progression, multifocal disease at first progression, KPS at first progression, number of resections at first progression, extent of resection at first progression, bevacizumab at first progression, and other chemotherapy at first progression. EOR at initial diagnosis (GTR, STR, biopsy), EOR at first progression (GTR, STR, no resection), and number of resections at progression (2+ re-resections, 1 re-resection, no re-resection) were treated as categorical variables with more than 2 levels. In order to avoid overestimation of significance and other sources of bias, variable selection methods were not used [13]. As there are more than 10 patients per included variable, the model is not at risk of being overfit [1,12,13]. Hazard ratios and 95% confidence intervals were generated for each variable in the model. All statistical tests used a significance level of $p \leq 0.05$. Results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [31].

3. Results

The characteristics of the overall patient population are summarized in Table 1. Two hundred and seventy-three patients

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