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

Rahul A. Sastry, Ganesh M. Shankar, Elizabeth R. Gerstner, William T. Curry

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 ≥ 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.

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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...
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 ≥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 perioperative 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 over-estimation 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

(74.2%) of patients died within the study period. The median follow-up period was 16.7 months. Of the 368 patients with documented progression, 118 (32.1%) underwent GTR at initial surgery, 182 (49.5%) underwent STR at initial surgery, and 68 (18.5%) underwent biopsy at initial surgery. Three hundred and fifty-two (95.7%) patients underwent subsequent treatment radiotherapy and temozolomide. One hundred and eighty-five (50.3%) of patients were enrolled in a clinical trial at some point during their disease course. The median overall survival for the entire patient cohort was 19.5 months (95% CI: 17.6–21.2 months, Fig. 1A). The median post-progression survival for the entire patient cohort was 8.1 months (95% CI: 7.16–8.74 months, Fig. 1B).

We collected demographic data to better understand the baseline differences between patients who underwent resection at first progression (n = 77 patients, 20.9%) and those who did not (n = 291, 79.1%) (Table 2). Patients who underwent resection for progression were significantly younger at initial presentation (56.4 years vs. 61.4 years, \( p = 0.002 \)) and underwent a greater proportion of GTRs (41.6% vs. 29.6%, \( p = 0.01 \)) at initial resection. Patients who underwent resection for progression experienced progression 2.7 months later than those who did not (13.7 months vs 11.0 months, \( p = 0.03 \)). Patients who underwent resection for progression presented with higher KPS at progression (94.8% KPS \( \geq 70 \) vs 79.7%, \( p = 0.001 \)) and were less likely to have either a multifocal (22.1% vs 51.6%, \( p < 0.001 \)) or eloquently situated tumor (66.2% vs 83.1%, \( p = 0.002 \)) at progression. A substantially smaller proportion of patients who underwent resection at first progression received bevacizumab at first progression (39.0% vs. 60.1%, \( p = 0.001 \)), although there was no difference in the proportion of patients who received bevacizumab at any time for first or subsequent progressions (71.4% vs. 77.3%, \( p = 0.30 \)). Rates of radiotherapy at first progression (9.1% vs. 6.2%, \( p = 0.44 \)) and chemotherapy at first progression (74.0% vs. 62.9%, \( p = 0.08 \)) did not differ significantly between these groups, however.

Among the 77 patients who underwent resection of progressive GB, 12 (13.6%) had further resections. At the time of resection for first progression, GTR was achieved in 26 (33.8%) and STR was achieved in 48 (61.4%) patients. Notably, 11 patients (3.8%) who did not undergo resection at first progression eventually underwent resection for a subsequent progression. None of these 11 patients underwent multiple reoperations for progression. Patients who underwent craniotomy for resection for first progression of GB had increased median post-progression survival (12.8 months vs 7.0 months) and median follow-up (21.6 vs. 16.0 months) when compared to patients who did not.

### 3.1. Multivariate analysis

We performed a multivariate analysis to identify the variables that were significantly associated with increased post-progression survival. Three variables were identified: KPS \( \geq 70 \) at progression (HR 0.438, 95% CI 0.307–0.624, \( p < 0.001 \)), bevacizumab at first progression (HR 0.756, 95% CI: 0.579–0.987, \( p = 0.04 \)), and cytotoxic chemotherapy at first progression (HR 0.644, 95% CI 0.485–0.855, \( p = 0.002 \)). Notably, in this multivariate analysis, extent of resection achieved at initial operation, whether a patient underwent resection at the time of progression, extent of resection at time of surgery for progression, and the number of post-progression resections were not significantly associated with increased post-progression survival, although extent of resection at time of initial recurrence did trend toward significance. Results from select variables of interest are briefly summarized in Table 3. Kaplan-Meier curves generated by univariate analysis of selected variables are presented in Fig. 2 and demonstrate relationships between these variables and post-progression survival without controlling for potential confounding factors.

### 4. Discussion

#### 4.1. Key results

We sought to reassess the survival benefit of resection for progressive GB in a patient population in which the use of adjuvant

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**Table 1**

Characteristics of 368 patients with documented progression of GB.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Documented Recurrence (n = 368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at Diagnosis (years)</td>
<td>60.3 years (Range: 18.5–90.1)</td>
</tr>
<tr>
<td>KPS at Diagnosis</td>
<td></td>
</tr>
<tr>
<td>( \geq 70 )</td>
<td>339 (92.1%)</td>
</tr>
<tr>
<td>(&lt; 70 )</td>
<td>29 (7.9%)</td>
</tr>
<tr>
<td>EOR</td>
<td></td>
</tr>
<tr>
<td>GTR</td>
<td>118 (32.1%)</td>
</tr>
<tr>
<td>STR</td>
<td>182 (49.5%)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>68 (18.5%)</td>
</tr>
<tr>
<td>Post-operative TMZ/Radiation</td>
<td>352 (95.7%)</td>
</tr>
<tr>
<td>Clinical Trial Enrollment</td>
<td>185 (50.3%)</td>
</tr>
<tr>
<td>Death Within Study Period</td>
<td>273 (74.2%)</td>
</tr>
<tr>
<td>Median Follow-Up (months)</td>
<td>16.7 (IQR: 12.0–25.2)</td>
</tr>
<tr>
<td>Median Overall Survival (months)</td>
<td>19.5 (95% CI: 17.6–21.2)</td>
</tr>
<tr>
<td>Median Post-Progression Survival</td>
<td>8.1 (95% CI: 7.16–8.74)</td>
</tr>
</tbody>
</table>

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Fig. 1. Overall and Post-Progression Survival for entire patient cohort. (A) Kaplan-Meier curve demonstrating overall survival for total cohort of 368 patients. The median overall survival for the entire patient cohort was 19.5 months (95% CI: 17.6–21.2 months). (B) Kaplan-Meier curve demonstrating post-progression survival for total cohort of 368 patients. The median post-progression survival for the entire patient cohort was 8.1 months (95% CI: 7.16–8.74 months).
chemoradiation following initial resection was high (95.7%) and in which the use of bevacizumab at progression was more widespread (76.1% of all identified) than has been reported in any previous study of this topic [18,19,34]. The results of this study suggest that, when controlling for several potentially confounding factors, resection of progressive GB is not significantly associated with prolonged post-progression survival even if a GTR is achieved. In addition, our analysis identified KPS ≥ 70 at first progression, use of bevacizumab at first progression, and use of chemotherapy at first progression as being significantly associated with improved post-progression survival.

4.2. Interpretation

Our conclusion that resection of progressive GB does not significantly prolong post-progression survival is at odds with some previous analyses. Notably, although Chaichana et al previously concluded that resection for progressive GB and the number of resections were both associated with improved overall survival in a case-control analysis [4], the low overall survival of single-resection patients (6.8 months) and low proportion of patients receiving both radiation (65%) and temozolomide (27%) following initial surgery limit the relevance of results to the current era of GB treatment. Similarly, Bloch et al noted extent of resection of recurrent GB correlated with overall survival [2]. Both of these studies have been critiqued as measuring overall survival rather than post-progression survival, as the former may overestimate survival in favor of patients who can undergo more intensive treatments, such as craniotomy, at the time of radiographic progression [10]. Our findings underscore the importance of accounting for these biases by performing post-progression survival analyses or treating variables as time-dependent covariates. For example, we find that repeat craniotomy is significantly correlated with post-progression survival when analyzed in a univariate analysis, likely reflecting the non-random assignment of healthier patients or those more focal resectable disease progression to surgical management. Furthermore, our multivariate analysis suggests that medical adjuvants may confer a post-progression survival benefit when used for salvage therapy, a finding that may have been underappreciated in studies that assessed the effect of surgery on overall survival. Our results are concordant with the conclusions reached by Ortega, et al. who determined that repeat resection was not significantly associated with increased overall survival in a contemporary patient population that was commonly treated with bevacizumab for progression [19]. Our findings expand on these data by including a larger and more heterogeneous population, considering more variables in our model, and examining post-progression survival instead of overall survival.

Taken together, these results suggest that resection for progression may have offered a clearer survival benefit before the widespread adoption of aggressive initial resection followed by concurrent chemoradiation. Despite the fact that resection for progressive GB may not be life-extending, there are still indications for progressing GB treatment. Similarly, Bloch et al noted extent of resection of recurrent GB correlated with overall survival [2]. Both of these studies have been critiqued as measuring overall survival rather than post-progression survival, as the former may overestimate survival in favor of patients who can undergo more intensive treatments, such as craniotomy, at the time of radiographic progression [10]. Our findings underscore the importance of accounting for these biases by performing post-progression survival analyses or treating variables as time-dependent covariates. For example, we find that repeat craniotomy is significantly correlated with post-progression survival when analyzed in a univariate analysis, likely reflecting the non-random assignment of healthier patients or those more focal resectable disease progression to surgical management. Furthermore, our multivariate analysis suggests that medical adjuvants may confer a post-progression survival benefit when used for salvage therapy, a finding that may have been underappreciated in studies that assessed the effect of surgery on overall survival. Our results are concordant with the conclusions reached by Ortega, et al. who determined that repeat resection was not significantly associated with increased overall survival in a contemporary patient population that was commonly treated with bevacizumab for progression [19]. Our findings expand on these data by including a larger and more heterogeneous population, considering more variables in our model, and examining post-progression survival instead of overall survival.

**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Confidence Interval (95%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.005</td>
<td>[0.994–1.016]</td>
<td>0.341</td>
</tr>
<tr>
<td>GTR at initial resection</td>
<td>1.028</td>
<td>[0.971–1.087]</td>
<td>0.889</td>
</tr>
<tr>
<td>STR at initial resection</td>
<td>1.042</td>
<td>[0.945–1.146]</td>
<td>0.481</td>
</tr>
<tr>
<td>KPS ≥ 70 at Diagnosis</td>
<td>1.372</td>
<td>[0.829–2.272]</td>
<td>0.219</td>
</tr>
<tr>
<td>Post-operative radiation</td>
<td>0.452</td>
<td>[0.192–1.062]</td>
<td>0.068</td>
</tr>
<tr>
<td>Post-operative temozolomide</td>
<td>1.087</td>
<td>[0.490–2.413]</td>
<td>0.837</td>
</tr>
<tr>
<td>Time to first documented progression</td>
<td>0.99</td>
<td>[0.978–1.003]</td>
<td>0.156</td>
</tr>
<tr>
<td>Eloquent at first progression</td>
<td>1.03</td>
<td>[0.742–1.429]</td>
<td>0.860</td>
</tr>
<tr>
<td>Multifocal disease at first progression</td>
<td>1.232</td>
<td>[0.957–1.585]</td>
<td>0.106</td>
</tr>
<tr>
<td>KPS &gt; 70 at first progression</td>
<td>0.438</td>
<td>[0.307–0.664]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rejection at first progression</td>
<td>0.975</td>
<td>[0.672–1.411]</td>
<td>0.805</td>
</tr>
<tr>
<td>Multiple resections at progression</td>
<td>0.707</td>
<td>[0.334–1.496]</td>
<td>0.364</td>
</tr>
<tr>
<td>GTR at resection at first progression</td>
<td>0.583</td>
<td>[0.317–1.070]</td>
<td>0.082</td>
</tr>
<tr>
<td>Bevacizumab at first progression</td>
<td>0.756</td>
<td>[0.579–0.987]</td>
<td>0.040</td>
</tr>
<tr>
<td>Chemotherapy for first progression</td>
<td>0.644</td>
<td>[0.485–0.853]</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Fig. 2. Kaplan-Meier curves demonstrating post-progression survival stratified by selected variables. (A) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by Karnofsky Performance Status (KPS) (KPS ≥ 70, KPS < 70) at first progression. Median survivals were 8.6 months (7.9–9.4 months) and 4.4 months (3.1–5.8 months) (log-rank \( p < 0.001 \)). (B) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by receipt of bevacizumab at first progression. Median survival was 8.15 months (6.94–9.10 months) for those who received bevacizumab and 7.86 months (6.76–8.91 months) for those who did not (log-rank \( p = 0.940 \)). (C) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by receipt of chemotherapy at first progression. Median survival was 8.64 months (7.95–9.37 months) for those who received chemotherapy and 5.85 months (4.89–7.36 months) for those who did not (log-rank \( p = 0.001 \)). (D) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by re-operation status. Median survival was 12.8 months (9.3–14.0 months) for those who underwent resection at first progression and 7.0 months (6.25–8.15 months) for those who did not (log-rank \( p = 0.002 \)). (E) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by maximum extent of resection achieved at resection at progression. Median survival was 14.4 months (12.8–26.3 months) for those who achieved Gross Total Resection, 9.4 months (7.16–12.2 months) for those who achieved Subtotal Resection, and 7.0 months (6.25–8.15 months) for those who did not undergo re-operation (log rank \( p = 0.007 \) when comparing Gross Total and Subtotal Resection).
4.3. Limitations and generalizability

We did not consider patients who underwent biopsy or resection of pseudoprogression as having undergone resection of progressive disease; however, these procedures undoubtedly carry their own benefits and risks of morbidity and mortality. Molecular characteristics of the tumor, notably including IDH1 mutation status and MGMT methylation status, were not included in our analysis as testing results were not routinely available for every patient throughout the study time period. While we have identified three variables as being independently associated with post-progression survival, it is possible that these are surrogate markers for other, as yet unidentified, features of these tumors or their hosts. Furthermore, the manner in which non-surgical treatments, such as chemotherapy, were classified failed to account for variation in dose and duration of treatment; as such, the results of this study cannot distinguish among specific therapeutic regimens. Additionally, because this is a single-institution study, a relatively large proportion of patients were lost to follow up and therefore limit the quality of available data. Finally, the generalizability of our results are limited by its retrospective nature and by variations in management of GB at other centers, and constantly evolving treatment options for GB. For example, the large number of our patients who are enrolled in clinical trials may not representative of the average GB patient.

5. Conclusions

Despite maximal treatment, progression of GB is a near inevitability. A variety of treatment options, including surgery, chemotherapy, radiation, and clinical trial enrollment, are available to patients at progression. In the context of contemporary treatment approaches, the frequent use of bevacizumab, and the recent suggestion of the efficacy of lomustine chemotherapy, we sought to reevaluate the role of resection for progressive GB. Our multivariate analysis suggests that undergoing resection of progressive GB is not associated with post-progression survival. Obtaining a gross total resection at first recurrence came close to significance, and if this is a reasonable goal of surgery, there may be benefit. Surgery may have other benefits, including tissue analysis in phase 0 clinical trials or reduction of mass effect, and we do not intend to rule out this option for glioblastoma patients. Our findings do support the concept that medical therapy is a reasonable choice in place of resection surgery for managing GB progression.

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Departmental.

Conflict of interest

None.

Presentations

E-poster, AANS Annual Meeting, April 22–26, 2017, Los Angeles, CA.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jocn.2018.04.004.

References


