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Chapter

Surgery for Recurrent Glioblastoma

Vamsi Krishna Yerramneni, Ramanadha Reddy Kanala, Vasundhara S. Rangan and Thirumal Yerragunta

Abstract

Recurrence of glioblastoma (GB) is inevitable. As the optimal management for recurrent glioblastoma continues to evolve, clear treatment guidelines for are lacking. Existing literature does not clarify the role that second surgery plays in the treatment of these patients. Although few studies report that second surgery is beneficial in select patients and leads to longer overall survival (OS), other studies have demonstrated the limited impact that repeat surgery has on the eventual patient outcome. Maximal safe resection (high extent of resection—EOR) has been proven to improve the OS at reoperation, even when undertaken for cases where the first surgery achieved only a limited EOR. Karnofsky Performance Score (KPS) and age at presentation are valuable prognostic factors that predict better OS and aid in better patient selection for surgical management. The true value of reoperation versus systemic treatment, their effects the patient's QoL and the added increase in overall survival is better judged after detailed investigation by means of a prospective, randomized trial.

Keywords: EOR—extent of resection, KPS—Karnofsky Performance Score, rGB—recurrent glioblastoma

1. Introduction

Glioblastoma (GB) is not only the most common primary intrinsic brain tumor of adulthood, but also the most frequently encountered malignant subtype. The standard treatment for newly diagnosed GB remains maximal surgical resection followed by concomitant or adjuvant chemotherapy [1]. The culmination of all the developments in diagnostics, imaging, surgical refinements and adjuvant therapies has not translated into any significant boost to the median overall survival (OS) of these patients. Prognosis continues to be dismal and OS has risen by just about 3.3 months (from 11.3 to 14.6 months) [2]. In select cohorts (consisting of a very favorable subset of patients), a median OS of 20.5 months has been observed. Recurrence is inevitable in GB despite every kind of known therapy. The standard care of the recurrent GB (rGB) is incompletely defined. Considering the ineffectiveness of therapy for first time disease, patients with recurrent disease are left with even more limited truly useful treatment options. With no clear standard of care, available options include reexcision of the lesion, angiogenesis inhibitor agents, and other targeted therapies, some of which have been the subject of clinical trials. In current practice, second surgery is performed in less than one half of the patients

who present with rGB. This might be either due to a seemingly inoperability of the lesion or poor surgical fitness of the patient [3, 4]. Several studies and reviews are published, but undertaking extensive surgery in the recurrence of a disease defined by poor prognosis continues to remain controversial.

2. Criteria for diagnosis of recurrent GB

Criteria for diagnosis have undergone many modifications over past decade. Magnetic resonance imaging every 2–3 months remains the gold standard for assessment of response and progression of the GB. The Macdonald criteria have served as the standard tool in follow up and evaluation of this disease until 2010 and their widespread use has led to the observation of several shortcomings [5, 6]. These include the problem of measuring tumor deposits shaped irregularly (including tumor forming the lining of cystic or excision cavities), observer to observer variability, lack of guidance for the evaluation of multifocal tumors as well as non-enhancing portion(s) of the tumor [5, 6]. Wen et al. published updated criteria in 2010 with restricted parameters for diagnosis of progressive disease within 3 months after completion of adjuvant therapy and integration of the evaluation of T2/FLAIR sequences as well of corticosteroid use [6].

According to the Macdonald et al. [5] criteria, progression of the tumor is defined as development of one or more of the following features:

"25% increase in sum of the products of perpendicular diameters of enhancing lesions, development of any new lesion on imaging and/or clinical deterioration."

The lack of specificity of enhancement in GB patients treated with surgery, radiation or chemotherapy as well as other difficulties in standardization of assessment by the above criteria led to the need for updated Response Assessment in Neurooncology group (RANO) criteria. These criteria define progression as presence of any one of the following:

"≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease."

Figure 1 is an example of recurrent GBM managed by surgery followed by Bevacizumab chemotherapy.

3. Indications of surgery

Surgery is indicated in patients who show both:

1. Progression of disease according to MacDonald or RANO radiological criteria.

2. Deterioration in clinical status (as manifested by development of new deficits, change in neurological status due to mass effect of the lesion, seizures, or, features of raised intracranial pressure).

The decision to undertake repeat surgery is especially valid in young patients, patients with good functional status and a conveniently resectable tumor.

In rGB, surgery is undertaken with the main aim of cytoreduction. The reduced tumor burden is thought to cause an improvement in OS [7, 8]. Lu et al. in their meta-analysis concluded that repeat surgery has an overall positive role in managing recurrent GBM. It was observed that surgery resulted in a prognostic benefit that was observed to be independent of demographic as well as clinical parameters [8]. Various factors which are found to affect prognosis are age, extent of resection at repeat surgery, adjuvant chemoradiation, tumor location, methylation status, in addition to

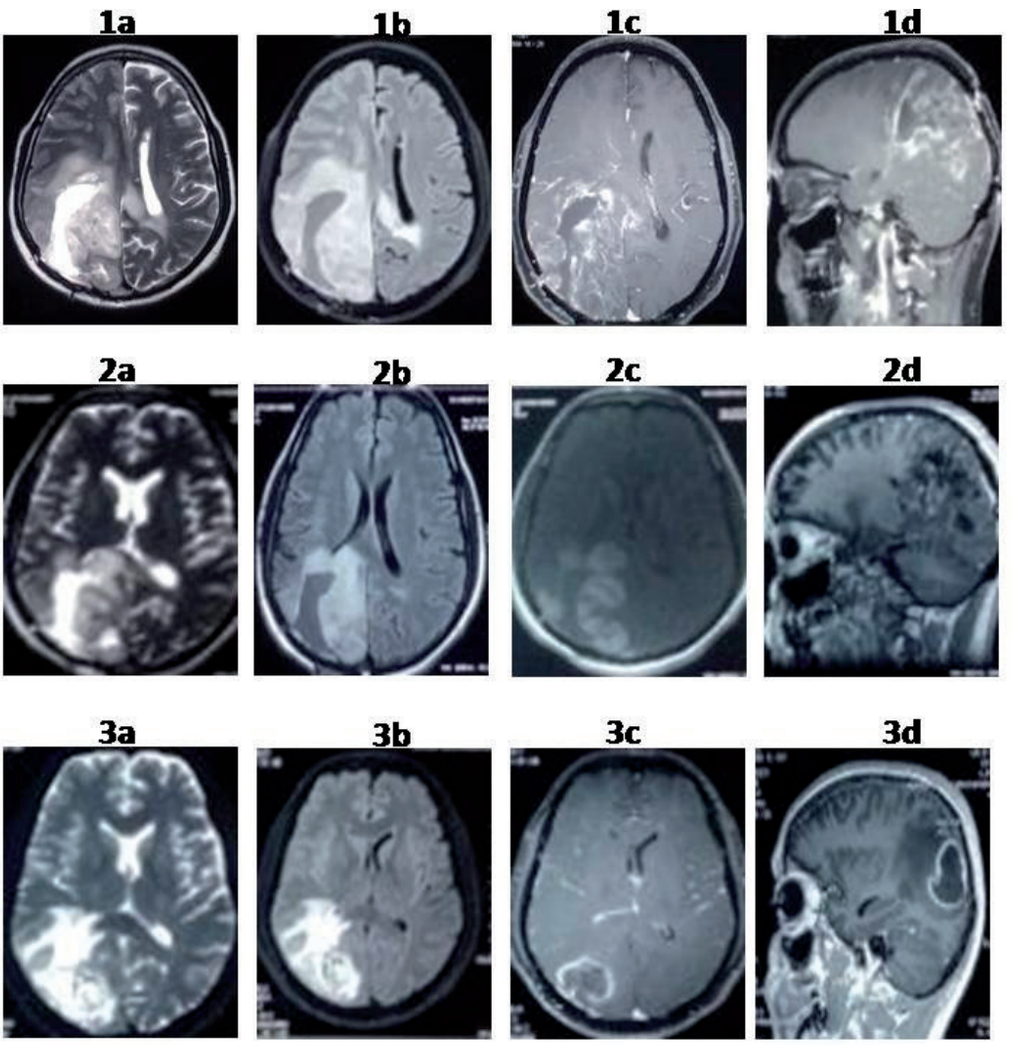

Figure 1.
(1a–1d) MRI brain T2 Axial, Axial FLAIR, Axial contrast and sagittal contrast images showing Right ParietoOcciptial mass with surrounding edema with corresponding enhancement on the contrast. Surgical excision of the tumor was done with around 60% excision followed by chemoradiotherapy as per Stupp Protocol. (2a–2d) One year after the initial treatment patient follow up MRI (2a–d) shows Tumor regrowth. Patient was taken up for Redo surgical excision and around 70% of the tumor excision was achieved. After second surgery patient was treated in another center with bevacizumab and he came back to us in 3 months with regrowth of the tumor. (3a–3d) Patient had low platelet count as a result of the bevacizumab therapy and was in poor general condition. Surgery excision was not considered as the outcome in patients with poor performance score in recurrent tumor is bad though the MRI does not show an extensive tumor. Poor performance scores with a not so extensive gross tumor on MRI indicate microscopic infiltration.

functional assessment of the patient using scores like Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group (ECOG) score. Nonetheless, studies conducted that have analyzed patient groups after matching for many of these factors have still observed the prognostic advantage conferred by surgery undertaken for recurrent disease. The potential benefit is not limited to the first recurrence only. Superior OS in patients with GB experiencing more repeat surgeries for continuously recurring GB independent of other features has been previously shown [9, 10].

Various factors have been analyzed with respect to surgery in recurrent GB:

3.1 Age

Recent literature proves that age is an important prognostic factor with OS being longer in patients who are younger at the time of diagnosis, in contradiction to older studies which failed to show any meaningful correlation between age and prognosis [9, 11–14]. Although gender has not been commonly thought to be a factor affecting prognosis, a study by Tugcu et al. has interestingly noted that male gender was a factor according better prognosis.

3.2 Timing of second surgery

Studies have shown that survival is not affected by the time interval between initial diagnosis/surgery and repeat surgery [15, 16].

3.3 Performance score

Studies have reported that better performance score at the time of presentation (KPS $\geq$ 70) correlates strongly with a longer OS [14, 16–18]. Chang et al. [16, 18, 19] documented that the most important factor affecting OS is KPS at the time of recurrence. Quick et al., on the same lines, have demonstrated that good statistical parallel exists between KPS score and OS in their series [20]. Moreover, Michaelsen et al. have reported that the ECOG Performance Status significantly affects the OS following therapy [13].

3.4 Molecular markers

The role of molecular markers in predicting/affecting survival in recurrent GB has been controversial. Studies have shown an association between loss of MGMT expression and survival in patients with GB. Although this correlation was confirmed to have a prognostic significance at the time of first surgery, Brandes et al. reported that MGMT methylation status has no particular place in the prediction of outcome following repeat surgery. Similarly, multiple authors have noted that MGMT status at the time of redo surgery in GB patients has no effect on OS or on SFR [21, 22]. Mutations of IDH1 and IDH2 are known to be suggestive of secondary GB and to confer favorable prognosis [23, 24]. This was confirmed by Hartmann et al. who reported longer OS in patients with IDH mutant tumors as compared to the IDH wild-type ones. On the contrary, Amelot et al. have reported comparable long term survival in patients with and without IDH1/2 mutation [25, 26].

3.5 Extent of resection

That a greater extent of resection (EOR) confers an obvious advantage in patients being treated for GB has been demonstrated by multiple studies. This has been more widely evaluated and concluded at the time of first surgery [27–32].

It suffices to say that surgical resection of the tumor is still the most effective therapy in GB, leading to instant decompression and improvement in the efficacy of adjuvant radiation by reducing tumor bulk. An increase in survival by an average of 5.5 months was noted by Quick et al. in patients in whom atleast 95% of tumor was excised. This benefit was noted irrespective of tumor size. However, it is not as clear if such an advantage is conferred again during operation for recurrence [20]. On inquiry into whether this same benefit holds true in cases of recurrent GB, Robin et al., in their review article found 16 studies reinforcing the role of EOR in patient survival.

According to Stupp et al. surgery (5ALA fluorescence guided complete tumor resection) [35] done at the time of noting disease progression, along with additional chemotherapy (Temozolamide) and radiotherapy improved the average patient survival to more than 14 months. It was thereby suggested that, in patients where surgery for tumor recurrence is deemed prudent, Maximal Safe Resection of the GB should be aimed for [33].

The next logical question that arises would be the role of such ambitious surgery in further recurrences after the second operation. In a series of 578 primary GB patients were studied with reference to the number of repeat surgeries undertaken, Chaichana et al. concluded that patients who underwent multiple resections had better median survival than those who had single time surgery. The 15 patients in this study who underwent resection four times had a median survival of 26.6 months compared to those who were operated once (354 patients), twice (168 patients) and thrice (41 cases). These patients were found to have a median survival of 6.8, 15.5, 22.4 respectively [9].

Bloch et al. also conducted a valuable study on results of multiple resections in 107 patients by four-way subgroup analysis after noting EORs during both first and second surgery. Whether the initial as well as subsequent surgery achieved Gross Total Resection (GTR) or Sub Total Resection (STR) of the tumor was made note of. Patients were then categorized into four resection groups: GTR/GTR, GTR/STR, STR/GTR, and, STR/STR. On follow up, the study established that a survival advantage was conferred by performing complete tumor resection during both initial surgery as well as second surgery for recurrence of GB [31].

A series by Oppenlander and colleagues also confirms the advantage conferred by increased EOR in patients operated for rGB. A survival advantage was observed with even 80% resection of tumor volume. The OS for the entire cohort studied was 19.0 months while median survival on Kaplan-Meier curves showed survival upto 20 months and even 30 months when EOR was greater than 81 and 97%, respectively. Multivariate analysis identified EOR, age, and KPS as independent predictors of survival [30].

Of particular interest is a study by Sanai et al. where in cases when a more complete resection was deemed imprudent due to the tumor being located in eloquent brain, more limited resection (78% EOR) of the contrast enhancing lesion did correspond to a survival benefit that was of significance statistically [4]. Despite being largely based on class II to III evidence, surgically reducing the amount of residual tumor does translate to longer PFS and better OS.

4. Survival following reoperation for recurrent or progressive glioblastoma

With the advancement of refinement in surgical techniques and in nonsurgical adjunctive therapies, our understanding of the impact of surgery on survival in both newly diagnosed and recurrent GB increases. As elaborated so far, varied

studies have come to the common conclusion that a survival benefit is accorded by surgery, especially by the maximization of EOR, not only in newly diagnosed GB, but also in recurrent cases [9, 11, 16, 20, 34].

A detailed review of relevant literature by Ryken et al. suggests that reoperation adds about 8 or 9 months to the OS in select patients, without the added burden of significant morbidity. This positive outcome is especially observed in patients with age less than or equal to 50, KPS scores equal to or greater than 60 or 70 as well as favorable tumor location [36].

It can now be safely said that the most effective therapy in recurrent GB is surgical resection as it improves the efficacy of radiotherapy. Patient selection should take into consideration the so far observed positive prognostic factors and maximal safe tumor volume resection should be the surgical goal [33] in those patients who are candidates to second surgery.

5. Complications

Although surgery logically aims at maximal cytoreduction, the safety of this goal is compromised by factors such as highly infiltrative nature of tumor, eloquent, deep seated/periventricular location, advanced age and/or coexistence of comorbidities. A multicenter retrospective study documented a 2–4% increase in the rate of neurological and non-neurological complications in repeat surgery when compared with initial surgery [37].

Following surgery for rGB, mortality rate has been shown to lie in the range of 0–11% with morbidity rate varying from 13 to 69%, leaving a significant number of rGB patients in a condition that precludes administration of adjuvant therapy [19]. This risk, therefore, appeared to nullify the survival benefit of reoperation at recurrence when compared with patients of recurrence who received no treatment at all. Hence, the importance of safer surgery avoiding morbidity as well as judiciousness in decision making cannot be overstated.

6. Conclusions

The available literature suggests a higher OS in selected patients who were managed with repeat excision of tumor at the time of recurrence of Glioblastoma. Although a debate remains open regarding the benefit of such excision, a clear trend in its favor has become more evident. The decision of undertaking surgery for rGB should be individualized and should surely be considered in patients with a favorable functional score at the time of presentation with recurrent disease as well as favorable preoperative neurological and radiological characteristics. The goal of such repeat surgery should be the resolution of symptoms, stabilization or improvement in QoL, increase in the time to further progression and reduction in requirement of steroid therapy. There is also the additional advantage of the possibility to offer intracavitary adjunctive therapy as well as an improved response to other adjunctive therapies [36]. As is customary to state, the actual value of such repeat surgery in comparison with systemic treatments and the effect of each on patient QoL and survical remains a topic for further prospective, randomized trials.

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