Neoplasm

Evaluating the prognostic factors effective on the outcome of patients with glioblastoma multiformis: does maximal resection of the tumor lengthen the median survival?

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Abstract

Background: The ETR that should be undertaken in patients with GBM remains controversial. This study aims to reiterate some independent predicting factors and to underscore the role and the ETR in increasing the survival of patients in the situation of developing countries, that is, without preoperative MRI or tractography. The authors submit additional information to be added to the list of CTRs in the management of malignant brain tumors.

Methods: The authors prospectively analyzed a cohort of 35 consecutive patients with histologically proven GBM who underwent tumor resection in surgically amenable areas for the first time at Sina Hospital, Tehran, between 2003 and 2005. Demographic data, volumetric measurements, and other characteristics identified on preoperative and immediate postoperative MR imaging as well as intraoperative and postoperative clinical data were collectively analyzed by SPSS for Windows, version 11.5 (SPSS, Chicago, Ill).

Results: Cox proportional hazards model multivariate analysis identified the following independent predictors of survival: Karnofsky performance scale \( \geq 80 \) (\( P = .01 \)), ETR (\( P = .01 \)), tumor location in functionally silent prefrontal area (\( P = .002 \)) vs tumor location in corpus callosum (\( P = .001 \)), postoperative RT (\( P = .004 \)), and postoperative chemotherapy (\( P = .001 \))

Conclusion: Maximal resection of the tumor volume is an independent variable associated with longer survival times in patient with GBM. Gross total resection should be performed whenever possible, although not at the expense of increased morbidity.

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Keywords: Controlled trials; Developing country; Glioblastoma multiformis; Prognosis; Resection; Survival

1. Introduction

Glioblastoma multiforme is the most common primary CNS tumor. Glioblastoma multiforme comprises almost 25% of primary CNS tumors and 50% to 55% of adult gliomas [30].

The optimal treatment for patients with GBM still remains a controversy. Continued refinements in microsurgical techniques and the use of adjunctive technologies have reduced major neurologic morbidity to 8.5% and mortality to 1.7% for patients undergoing craniotomy, respectively [30]. Extensive resection of the primary tumor may lead in a better short-term outcome, but there has been little scientific evidence so far to give maximal tumor resection a credit to prolong survival of the cases. Despite recent advances in surgical techniques and adjunctive therapies, the prognosis for GBM still remains poor with a median survival of approximately 1 year [23]. The results of a critical and comprehensive review of the literature
performed by Sanai and Berger [23] proved the lack of class 1 evidence confirming the unbiased effect of ETR on the outcome of patients undergoing surgery for GBM.

Radical resection of malignant gliomas carries the risk of injuring the adjacent vital structures in the brain due to the infiltrative nature of the neoplasm, especially when it is located within the eloquent areas. The major role of surgery is to extirpate the tumor along its macroscopic boundaries and debulk it as completely as possible [12,22,33]. Studies have shown that tumor cells may invade far beyond the main tumor mass into the brain due to the infiltrating nature of the malignant gliomas. Although many authors stress the consistent finding of a variable zone of microscopic tumor infiltration of the brain outside of the enhancing area, extending at least as far as the abnormal T2 signal intensity, a great deal of evidence confirms the presence of the tumor cells centimeters beyond the presumed tumor margin [7,10,22]. As volumetric data were collected to determine the amount of residual tumor mass as accurately as possible based on pre- and postoperative imaging techniques, maximal resection emerged as a strong predictor of survival [3,8,9], whereas high-quality imaging is necessary and should include MRI [1,27,29]. Early studies have shown that even hemispherectomy is inadequate for the control of malignant gliomas [12]. In the situation in developing countries wherein several high-technology instruments are used in a restricted way, this requires the operating physician having a grasp of knowledge in the anatomy of the region and paying meticulous attention to changes in color and consistency of the tissue while working in the vicinity of the tumor. With significant reduction in the mass effect of the tumor, the patient may tolerate RT better and experience fewer side effects [9].

Several factors can affect the survival of patients with GBM, the more prominent of which are age, preoperative performance status according to the KPS, tumor location, preoperative imaging characteristics, the extent of tumor excision, and finally, postoperative RT [17]. Performing a prospective multivariate analysis in a cohort of patients operated by a single group of surgeons (FA and AA), we may reliably identify the independent significant predictors of survival of such patients. In this study, we tried to create a multivariate analysis and to overcome the possible selection biases affecting the outcome demonstrated by other authors [28].

Hereby, it is not intended to illustrate a new event but only to present a correctly designed and managed prospective surgical cohort performed by a group of young investigators (FA, MRZ, MA) so that their findings may be added to the literature for possible meta-analysis in the future.

2. Clinical material and method

Thirty-five consecutive patients with GBM who underwent craniotomy by a single group of surgeons (FA and AA) at Sina Hospital, TUMS, between 2003 and 2005 were enrolled in this study. All cases were classified from the histopathology point of view to GBM or grade 4 astrocytoma, according to the classification of the WHO. The demographic data, clinical manifestations, KPS score on admission, and history of previous head and neck RT were all prospectively recorded.

Volumetric assessments were performed in all patients based on preoperative and postoperative MR images obtained within 72 hours after operation. If there was any contraindication in performing MRI, patients would then be followed with CT scan.

Tumor mass was measured on the globoid scale (ie, $A \times B \times C/2$) [1,3,18]. We were not furnished with any computer software program.

Deep lesions were defined as those involving the insula, thalamus, basal ganglia, or third ventricle. In our institute, the rationale for treatment of deep-seated gliomas has been to obtain biopsy samples to confirm the pathology, followed by appropriate adjuvant therapy; therefore, we had to discard them and focus on the superficial lesions.

Tumor proximity to the eloquent brain cortex was graded according to Table 1, suggested by Sawaya et al [25]; and to clarify the analysis of the correlation between different variants, each case had a specific functional grading number regarding this classification. Patients were followed from the time of the surgery until the final event (ie, death) occurred.

3. Statistical techniques

$\chi^2$ test was used to identify the significance of a given variable ($P < .05$). Cumulative survival duration was measured by the Kaplan-Meier curve. Cox proportional hazards model was used to perform univariate and multivariate analysis and identify independent predictors of

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### Table 1

Grading of the intraparenchymal tumors according to the functional location of the lesion according to Sawaya et al [25]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Functional location</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: noneloquent brain = 5 cases</td>
<td></td>
</tr>
<tr>
<td>II: near eloquent brain = 16 cases</td>
<td></td>
</tr>
<tr>
<td>III: eloquent brain = 14 cases</td>
<td></td>
</tr>
</tbody>
</table>

- Frontal or temporal pole
- Right parieto-occipital lobe
- Cerebellar hemisphere
- Near sensory or motor cortex = 13 cases
- Near calcarine fissure
- Near speech center
- Corpus callosum = 3 cases
- Near dentate nucleus
- Near brain stem
- Motor or sensory cortex
- Visual center
- Speech center
- Internal capsule
- Basal ganglia
- Hypothalamus and thalamus
- Brain stem
- Dentate nucleus
survival. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows—ver.11.5; SPSS, Chicago, Ill).

4. Results

4.1. Clinical findings

The demographic and clinical characteristics of the 35 patients with GBM are summarized in Table 2. There were 24 men (69%) and 11 women (31%) with a mean age of 49.3 years (SD, 17 years). The most common chief complaint on admission was headache and limb paresis (each 34.3%). The most prevalent sign on examination was papilledema (62.9%) followed by hemiparesis (36.7%). Five patients had minor changes in the level of consciousness.

The preoperative KPS score was higher than 80 in 28 cases (80%). Four patients had history of low-grade glioma treated with craniotomy and RT and 2 other cases had history of head and neck RT for other pathologies.

Thirty-three patients (94.3%) could be followed with serial MR imaging studies, and in 2 patients, MRI was contraindicated. One case had a metallic prosthetic heart valve and another became ventilator dependent in the ICU in the postoperative period.

The preoperative MRI characteristics can be summarized as tumor location within sensory/motor strip in 13 cases (38.2%), involving the corpus callosum in 3, located within the eloquent brain cortex (functional grade III) in 14 cases (41.2%) (Table 1), MRI showing necrosis within the tumor in 20 patients (58.8%), evident peritumoral brain edema in 19 cases, and no surrounding edema in 1 case. The mean preoperative tumor volume was 51 mL.

4.2. Complications and postoperative managements

The postoperative complications are summarized in Table 3, and the most common of them was hemiparesis, which occurred in 12 cases. Four patients (11.8%) died within 30 days after operation. One died because of progressive cerebral edema despite aggressive temporal lobectomy performed as a reoperation. Three others died because of myocardial infarction in the postoperative period. The mean duration for postoperative ICU care was 3.1 days (range, 1-18 days) and the mean duration of postoperative hospital stay was 7.6 (±3.8) days. Twenty-two cases (66.7%) underwent conventional postoperative RT and 13 cases (40.2%) received chemotherapy. Twenty-five patients died during the follow-up period, 6 were still alive at the time of preparation of this material, and 4 were lost from the study. Reoperation was performed in 10 cases in different periods; in 2 cases aiming for control of progressive brain edema, in 1 case to evacuate a delayed intracerebral hematoma associated with coagulopathy, in 1 case to drain a persistent subdural hygroma, and in 6 other cases to decompress late tumor recurrences.

4.3. Length of survival

The median length of survival for all patients was 38 (±20) weeks (Table 4).

4.4. Univariate and multivariate analysis of survival

It was decided to analyze the results of the follow-up in 27 patients who lived longer than 1 month and were not lost during the period of the study:

1. Preoperative KPS score less than 80 was a significant negative predictor of survival (P < .07). Patients with KPS scores of 80 or higher (n = 14) lived an average of 52 weeks, which was considerably longer than their controls (mean survival, 32 weeks).

<p>| Table 3 | Postoperative complications in patients with GBM |</p>
<table>
<thead>
<tr>
<th>Complication</th>
<th>Number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent hemiparesis</td>
<td>12 (41.3)</td>
</tr>
<tr>
<td>Focal hematoma (diameter ≥ 1 cm)</td>
<td>6 (20.6)</td>
</tr>
<tr>
<td>Persistent dysphasia</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Persistent personality change</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (6.8)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Total</td>
<td>29 (100)</td>
</tr>
</tbody>
</table>

<p>| Table 4 | Life table in the respective 35 patients |</p>
<table>
<thead>
<tr>
<th>Weeks (no. of patients)</th>
<th>Survival (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>85</td>
</tr>
<tr>
<td>16</td>
<td>85</td>
</tr>
<tr>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>36</td>
<td>51</td>
</tr>
<tr>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>66</td>
<td>22</td>
</tr>
<tr>
<td>≥80</td>
<td>16</td>
</tr>
</tbody>
</table>
2. The ETR was significantly greater in functional tumor grade 1 than in grades 2 or 3, that is, 97% vs 75% (P < .004). However, patients with functional grade 1 tumors did not demonstrate considerably longer survival than their controls (P = .3).

3. Tumors located in the premotor frontal lobe had the longest survival (63 weeks), whereas those in corpus callosum had the shortest (13 weeks), respectively (P < .037) (Table 4).

4. We classified our patients into 3 subgroups according to the objective measurements gained through the pre-and postoperative imaging studies showing the ETR (Table 5): class A (n = 11) had their tumors resected more than 95%, class B (n = 5) had resection rates between 80% and 95%, and class C (n = 13) had less than 80% resection rate. The extent of resection was a major predictor of survival (P < .07). Owing to the relatively small sample size, we were unable to provide a more sophisticated categorization system.

5. Patients with greater extents of resection experienced better short-term and long-term course on the KPS score than their controls. Class A patients harbored the highest postoperative KPS score, which persisted later in the follow-up period (Table 6).

6. Among these 27 patients, 6 cases refused to undergo RT. Considering those 6 cases as the control group, patients with adjuvant RT (n = 21) lived significantly longer than their controls (P < .004). However, patients with functional grade 1 than in grades 2 or 3, that is, 97% vs 75% (P < .004).

7. The radio-oncology department had his plan for suggesting chemotherapy for the patients. Chemotherapy was advised for all the patients after terminating the course of RT. Twelve patients accepted and underwent treatment but 15 others (control group) refused, mostly because of financial problems and disappointment about the efficiency of treatment. Postoperative chemotherapy could have a relatively significant impact on the median length of survival of our cases. Those who received adjuvant chemotherapy experienced a median survival of 53 weeks, whereas the median survival was 34 weeks in the control group (difference of means, 19 weeks).

8. Six patients who underwent reoperation for the recurrent GBM had a median survival of 65 weeks. This finding could not be compared with those unsuitable for reoperation either due to low KPS or deep tumor recurrence.

9. Evidence of necrosis on imaging implicated grave prognosis. Patients who showed this finding (n = 15) had a mean survival of 31 weeks, which was considerably shorter than their control group without MR-visible tumor necrosis, which was 57 weeks (P < .01).

10. Sex and treatment status (ie, elective vs urgent craniotomy) did not appear to have significant impact on survival.

11. Patient’s age (≥ 60 vs < 60 years) appears as a significant predictor of survival when 4 independent variables of age, preoperative KPS score, ETR, and tumor functional grade were simultaneously put in the regression model (P < .05); however, it lost its power in the final analysis.

12. At the end of analysis, we entered all the probable independent variables in the model. Table 7 summarizes the final independent predictors of survival. Interestingly, age, tumor functional grade, necrosis on imaging, history of previous low-grade glioma, and seizure presentation on examination lost their significance in the ranking scale. In this table, the significant P values can be interpreted as the meaning of the predictors upon the outcome of the patients.

5. Discussion

A long-standing controversy in the neurosurgical literature involves the efficacy of “maximal resection of malignant gliomas” [23]. The optimal extent of resection in any patient depends on the tumor location and size, the patient’s general status, and the experience of the individual surgeon [1,20,24,30]. In a comprehensive retrospective
analysis on 416 patients with GBM, Lacronix et al [20] illustrated the role of aggressive surgical resection as an independent variable in the patients’ overall survival. They stratified their cases on an outcome scale; age, KPS score on admission, and presence of necrosis on imaging constituted the ranking scale. They concluded that maximal tumor resection still showed significant advantage when it was measured separately in each subpopulation of patients.

In our study, age group lost its significance as an independent variable when it entered the final step in the multivariate analysis. Although Lacronix et al [20] illustrated age group as a strong predictor of survival, Albert et al [1] achieved the same results as the present analysis.

The present analysis confirmed that patients who had KPS scores of 80 or more on admission showed survival advantage in both the univariate and multivariate analyses. Hentschel and Sawaya et al also emphasized the same trend in their own patients [14,20,25].

The present study also proved the assertion that aggressive surgical resection would prolong the median survival (P < .01); gross total resection (≥95%) and subtotal resection (resection rate between 80% and 95%) both resulted in longer survival, whereas maximal tumor resection still remained significant in the multivariate analysis (Table 7). The present analysis reconfirms the results of some other authors who stressed this factor as a strong predictor of survival [1,20].

Tumors in eloquent cortex (ie, grade 3), as well as those in deep-seated areas, may traditionally be approached by open biopsy; or the diagnosis may be confirmed less invasively by stereotactic procedures. The rationale for this last attempt is to obviate any deterioration in the neurologic status due to surgical manipulation. On the contrary, tumors in noneloquent cortex (grade 1) may be more conveniently resected. Jackson et al [16] illustrated that the discrepancy rate between the biopsy and the resected specimens is 38%, even with expert neuropathologist’s review. He found that the resulting discrepancy would have affected therapeutic regimens in 26% of cases and had prognostic implications in 38% of cases. It is emphasized by some authors that in cases where a surgical resection of the lesion is possible, little can be gained by performing a stereotactic biopsy before the open craniotomy unless an abscess, lymphoma, a metastasis, or other nonneoplastic lesion was the suspicious preoperative diagnoses [10,19,28].

In the present study, tumors located in the noneloquent cortex (grade 1) were more radically resected and those in the premotor frontal area had also a fair survival advantage. Although one may suggest that tumors in grades 2 and 3 had less extensive resections (with a mean rate of 80%, Table 7), this multivariate analysis cannot provide a particularly independent role for tumor functional grade as a predictor of survival. Sawaya et al [24] were convinced that patients with grade 3 tumors had worse prognosis [20,25].

Tumors that incorporated corpus callosum had a gleam outcome with a median survival of 13 weeks. Sawaya classified butterfly gliomas as grade 2, whereas Albert et al [1] disregarded them from the analysis as surgically unamenable tumors. Ammirati and colleagues [3] found that KPS improved by a mean of 6.8 compared to the preoperative scores in the completely resected group, whereas there was no improvement in the scores in the subtotally resected group. Fadul et al [11] showed that patients undergoing radical resections were at no greater risk of being neurologically impaired at 1 week after surgery and had fewer neurologic complications than those undergoing lesser amount of resection. The patients in the present study did not succumb into increased morbidity and mortality with more radical resection. On the contrary, they enjoyed better KPS scores in the short- and long-term follow-up period. Paradoxically, those patients with lesser degree of tumor removal had more complications (Tables 3, 5, and 6).

Patients who lodged more voluminous tumor masses conferred worse prognosis in this study (P < .007). This impact faded out when the multivariate analysis was performed (Tables 2 and 6). Other investigators have alleged contradictory comments about the role of primary tumor volume on survival [1,20]. It can also be perceived from this study that the evidence of necrosis in preoperative imaging could aggravate survival. Although it was a significant factor in the univariate analysis, it could not emanate still significant in the multivariate phase. Necrosis was seen in 58% of the present cases, which was less prevalent than that in other studies [1,20,25]. Lacronix et al [20] and Sawaya et al [25] alleged that the more infiltrative GBMs had more extensive peritumoral edema and if the amount of edema exceeded the tumor mass itself, it would confer worse prognosis. The present could not arrive at the same conclusion.

The interesting observation in this study was that the surgeon was regrettably much inaccurate when he figured out the extent of resection at the operating table. If the surgeon (FA and AA) assumed that he had removed the tumor totally or subtotally, he had overestimated 42% to 50% of the time! Albert et al [1] also demonstrated that the opinion of the surgeon at the time of surgery is remarkably unreliable, with only a 30% correlation with MRI. He stressed that postoperative imaging was the key in determining the extent of resection. Ideally, aggressive tumor removal of 99% would perform 2 log kill and leave 10^7 cells still alive. This virtually mandates adjuvant therapy in patients with GBM. If no adjuvant therapy is administered, the patient usually dies within 3 months despite maximal surgical resection [31]. Barker et al [4] found that patients with high-grade glioma who showed favorable imaging response to RT could lead a longer survival. From the oncologic point of view, a decrease of 50% or more in the cross-sectional area of the tumor after RT is considered a favorable response [6]. In this study, those cases who received postoperative RT could lead a longer life (P < .001) and the role of RT still remained significant in the multivariate analysis (Table 7).

Stewart [27], in a meta-analysis of 12 studies, compared the effect of “combined RT and chemotherapy” with “RT
alone” in patients with high-grade glioma. He concluded that chemotherapy could prolong survival duration. Keles et al [18] found survival advantages in patients with recurrent GBM who were given the oral chemotherapeutic agent temozolomide. The present study was not intended to compare different chemotherapeutic regimens; however, it illustrated that patients who underwent combined RT and chemotherapy conferred longer survival. The chemotherapist colleagues participating in the present research prescribed drugs only if the patient underwent a full course of RT and obtained KPS score of 70 or higher. This rationale may have introduced some kind of bias in the present study. A review of the literature shows a modest effect for chemotherapy on the outcome of similar patients [18,24,27,30,32]. Hochberg and Pruitt [15] observed that more than 90% of recurrent GBMs would regrow in an area within the 2-cm margin of the original resected cavity. Liang et al [21] who incorporated serial MRI to follow their patients reached the same confirming results. The present study also confirmed similar assertion.

Reoperation for the recurrent GBM is considered in restricted circumstances [2,12,13,24]. A patient with recurrent GBM may be considered for reoperation if (1) he is younger than 60 years, (2) he has KPS score of 60 or higher, (3) he has a life expectancy of 3 months or longer, (4) the latent period between the surgery and the time of recurrence is longer than 6 months, and (5) the recurrent tumor is surgically accessible [2,13]. In carefully selected cases, reoperation can lengthen the survival period for about 16 weeks [30]. In the univariate analysis of the data in the present study, this factor was a significant predictor of better survival (P = .05). “Secondary GBMs” usually originate from dedifferentiation of the low-grade gliomas and are estimated to comprise 20% of the GBM cases [5]. These so-called “secondary GBMs” are seen in relatively younger age groups (ie, 45 years of age) with a long history of seizure activity. The older the patient is at the time of diagnosis of a low-grade glioma, the higher will be the probability of subsequent dedifferentiation [26]. Secondary GBMs are said to demonstrate different cellular and molecular mechanism of action in contrast with the de novo GBMs and harbor a more favorable prognosis [24,30]. In the present study, 4 cases of GBM were met who had their original low-grade glioma resected previously and had undergone RT. Unfortunately, they manifested a median survival of 31 weeks, which was considerably shorter than their controls (ie, 47 weeks). Delivering a course of booster RT in similar cases is controversial; therefore, it was not recommended for every case in this series.

6. Conclusion

With the advances in surgical techniques and preoperative imaging technologies, it is possible to maximally resect malignant gliomas, even within functionally critical areas without increased morbidity. Gaining enough experience may substitute instruments with sophisticated technology, at least partially, by which the surgeons may deliver acceptable service to their patients in rather difficult situations of the underdeveloped countries. This CTR has not been designed to evaluate the efficacy and efficiency of different high-tech preoperatively used instruments on the outcome of patients with different functional gradings of GBM or to suggest the inevitability of performing an effective surgery by an experienced group of surgeons without using sophisticated technology. It has been attempted to confirm statistically and in an evidence-based manner that gross total resection of the tumor is an independent favorable predictor of survival of the patients and makes the patient lead a better postoperative course [18].

References


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