Effectiveness of Maximal Safe Resection for Glioblastoma Including Elderly and Low Karnofsky Performance Status Patients: Retrospective Review at a Single Institute

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Abstract

Elderly and low Karnofsky performance status (KPS) patients have been excluded from most prospective trials. This retrospective study investigated glioblastoma treatment outcomes, including those of elderly and low KPS patients, and analyzed the prognostic factors using the medical records of 107 consecutive patients, 59 men and 48 women aged from 21 to 85 years (median 65 years), with newly diagnosed glioblastoma treated at our institute. There were 71 high-risk patients with age ≥70 years and/or KPS ≤70%. Based on the extent of resection, the patients were classified into 3 groups: more than subtotal resection (subtotal, n = 44), partial resection (partial, n = 29), and biopsy only (biopsy, n = 34).

Median overall survival (OS) of all 107 patients was 13.5 months. Median OS was 13.2 months in the high-risk group. Median OSs were 15.8, 12.8, and 12.1 months in the subtotal, partial, and biopsy groups, respectively. Multivariate analysis of 73 patients in the subtotal and partial groups found age < 65 years (p = 0.047), 60 Gy irradiation (p = 0.009), O6-methylguanine-deoxyribonucleic acid methyltransferase-negative (p = 0.027), and more than subtotal removal (p = 0.003) were significant prognostic factors. The median postoperative KPS score tended to be better than the preoperative score, even in the high-risk group. We recommend maximal safe resection for glioblastoma patients, even those with advanced age and/or with low KPS scores.

Key words: glioblastoma, temozolomide, resection, O6-methylguanine-deoxyribonucleic acid methyltransferase, prognostic factor

Introduction

Extensive resection of glioblastoma multiforme (GBM) is widely reported to improve outcomes,5,9,16,18) and 95% or more tumor resection improves survival.14) Therefore, the maximum possible resection that can be achieved without reducing performance status is regarded as the standard for surgical treatment of GBM. A combination of standard radiotherapy (60 Gy/30 fractions) plus concurrent and adjuvant administration of temozolomide (TMZ), an alkylating agent with excellent oral bioavailability, has been introduced based on the randomized phase III trial by the European Organisation for Research and Treatment of Cancer and National Cancer Institute of Canada Clinical Trials Group in 2005. Since then, TMZ has become the standard treatment for newly diagnosed GBM patients.20) Patients with GBM are often elderly and/or have low Karnofsky performance status (KPS) scores, and high-risk patients have been excluded from most prospective trials. Therefore, the treatment effects of TMZ plus maximal safe resection for all GBM patients remain unclear.

The present study reviews the outcomes of all patients with GBM treated at our institute, which manages most GBM cases in our city and surrounding suburbs, using the same treatment strategy for GBM consisting of surgical resection and/or irradiation, and discusses surgical resection, prognostic factors, and subgroups of elderly and low KPS patients.

Subjects and Methods

We retrospectively analyzed the medical and surgical records of 107 patients, 59 men and 48 women
Table 1  Patient demographics (n = 107)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Biopsy group</th>
<th>Partial group</th>
<th>Subtotal group</th>
<th>p Value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>107 (100%)</td>
<td>34 (31.8%)</td>
<td>29 (27.1%)</td>
<td>44 (41.1%)</td>
<td></td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>59/48</td>
<td>13/21</td>
<td>19/10</td>
<td>27/17</td>
<td>0.807</td>
</tr>
<tr>
<td>Median age (range), yrs</td>
<td>65 (21–85)</td>
<td>69.5 (28–85)</td>
<td>63 (31–74)</td>
<td>64 (21–81)</td>
<td>0.664</td>
</tr>
<tr>
<td>Age &gt;70 yrs</td>
<td>33 (30.8%)</td>
<td>15 (44.1%)</td>
<td>5 (17.2%)</td>
<td>13 (29.5%)</td>
<td></td>
</tr>
<tr>
<td>Median KPS (range), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preoperative</td>
<td>60 (30–100)</td>
<td>70 (30–100)</td>
<td>60 (50–100)</td>
<td>60 (50–100)</td>
<td>0.949</td>
</tr>
<tr>
<td>postoperative</td>
<td>60 (0–100)</td>
<td>55 (0–100)</td>
<td>50 (0–90)</td>
<td>70 (40–100)</td>
<td>0.007</td>
</tr>
<tr>
<td>KPS &lt;70%</td>
<td>54 (50.5%)</td>
<td>16 (47.1%)</td>
<td>16 (55.2%)</td>
<td>22 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Median follow up (range), mos</td>
<td>12.1 (1.2–115)</td>
<td>11.0 (1.2–23.9)</td>
<td>10.8 (3.8–27.0)</td>
<td>14.6 (3.5–115.2)</td>
<td>0.505</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>86 (80.4%)</td>
<td>31 (91.2%)</td>
<td>21 (72.4%)</td>
<td>34 (77.3%)</td>
<td></td>
</tr>
<tr>
<td>Treated with ACNU/MCNU</td>
<td>33 (30.8%)</td>
<td>10 (29.4%)</td>
<td>5 (17.2%)</td>
<td>17 (38.6%)</td>
<td>0.069</td>
</tr>
<tr>
<td>Treated with TMZ</td>
<td>36 (33.6%)</td>
<td>6 (17.6%)</td>
<td>15 (51.7%)</td>
<td>15 (34.1%)</td>
<td>0.152</td>
</tr>
<tr>
<td>Irradiation 60 Gy</td>
<td>83 (77.6%)</td>
<td>20 (58.8%)</td>
<td>24 (82.8%)</td>
<td>39 (88.6%)</td>
<td>0.505</td>
</tr>
<tr>
<td>MGMT negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Univariate p values were derived from comparisons between the subtotal and partial groups. ACNU: nimustine, KPS: Karnofsky performance status, MCNU: ranimustine, MGMT: O6-methylguanine-deoxyribonucleic acid methyltransferase, TMZ: temozolomide.

Aged from 21 to 85 years (median 65 years), with newly diagnosed GBM, confirmed histologically, who were treated at our department between January 2000 and September 2010 (Table 1). The pathological diagnosis was made by an experienced neuropathologist at our institute according to the World Health Organization guidelines. Preoperative KPS scores ranged from 30% to 100% (median 60%). The median follow-up period was 12.1 months. During the follow-up period, 86 patients (80.4%) died.

In our institute, sodium fluorescein is injected intravenously just prior to surgical resection, with the intention of resecting enhanced lesions. We select open surgery if tumor resection exceeding 80% can be expected without damaging eloquent functions. Biopsy is generally performed in extremely elderly patients (age >80 years) and patients with very low KPS scores (<50%).

The extent of resection was assessed based on residual tumor volume, as shown by lesion enhancement on postoperative computed tomography (CT) or magnetic resonance imaging performed within 3 days after surgery. Tumor volume was estimated by measuring the major (A) and perpendicular minor axes (B) and height (C), and then calculated employing the following formula: $A \times B \times C \times \frac{1}{2}$. Based on the extent of resection, the patients were classified into 3 groups: more than subtotal (>90%) resection (subtotal group, n = 44), partial (<90%) resection (partial group, n = 29), and biopsy only (biopsy group, n = 34) (Table 1).

There were 33 patients aged over 70 years of age and 54 patients with preoperative KPS scores below 70%. Seventy-one patients (age >70 years and/or KPS <70%) were classified as the high-risk group, because such patients had been excluded from some randomized phase III trials. These patients were also subclassified according to extent of resection: subtotal (n = 29), partial (n = 20), and biopsy (n = 22).

Postoperative conventional focal irradiation was delivered at a dose of 60 Gy in 30 fractions for patients aged <75 years and at a dose of 30–39 Gy in 10–13 fractions for patients aged ≥75 years. Eighty-three patients received irradiation with 60 Gy, 24 with <60 Gy (Table 1).

Prior to approval of TMZ in Japan, postoperative radiotherapy was given in combination with nimustine (ACNU) or ranimustine (MCNU) chemotherapy to 33 patients (ACNU/MCNU-treated group), most of whom were younger than 65 years. After 2006, TMZ was given in 36 patients (33.6%), with no age and KPS restriction. Patients treated with TMZ in combination with radiation and/or one or more courses of adjuvant TMZ therapy formed the TMZ-treated group. Of the 36 patients treated with TMZ, 7 received ACNU/MCNU concomitant with radiation therapy followed by adjuvant TMZ administration. Thirty patients received 1 to 24 courses (median 6) of adjuvant TMZ therapy. Twenty-five patients did not receive any chemotherapy.

Expression of O6-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) was assessed by immunohistochemical staining with clone MT3.1 (Chemicon International, Inc., Temecula, California, USA) in 70 patients. Expression was rated as positive or negative based on a cut-off level of 30% of...
nuclei stained for MGMT.

To evaluate the resection rates as prognostic factors, statistical analyses were performed for the partial and subtotal groups. Among the 73 patients in the subtotal and partial groups combined, age (≤65 years versus >65 years), preoperative KPS (>60% versus ≤60%), MGMT (positive versus negative), with or without TMZ, 60 Gy versus <60 Gy irradiation, and extent of resection (subtotal or partial) were evaluated as prognostic factors. In addition, postoperative KPS scores at the end of irradiation were compared between the partial and subtotal groups.

The chi-square test or the Mann-Whitney U test was used to assess the statistical significance. Overall survival times, determined as the period from the date of operation until the time of death or the date of the last available follow up, and rates were calculated according to the Kaplan-Meier method. The relationships of survival times and rates to prognostic factors were evaluated with the log-rank test. The Cox proportional hazard model was used for multivariate analysis. Statistical significance was defined as a p value less than 0.05. All analyses were performed using IBM SPSS statistics 19.0 (IBM Corp., Armonk, New York, USA).

Results

Median overall survival (OS) for the 107 patients was 13.5 months, with a 2-year survival rate of 15.2% (Fig. 1A). Survival was significantly better in the subtotal group (median OS 15.8 months) compared to the partial group (median OS 12.8 months) (p = 0.003, Fig. 1B). Comparison between the partial group and biopsy group (median OS 12.1 months) revealed no statistically significant difference in Kaplan-Meyer survival curves.

There were no statistically significant differences in male/female ratio, age, preoperative KPS, MGMT positive rate, ACNU/MCNU-treated, or TMZ-treated proportion between the subtotal and partial groups (Table 1).

Younger patients (≤65 years, n = 40, median OS 16.2 months) had significantly longer survival than older patients (>65 years, n = 33, median OS 13.2 months) (p = 0.037, Fig. 2A). No significant difference in survival rates was found between the 38 patients with preoperative KPS of ≤60% (median OS 13.2 months) and the 35 with preoperative KPS of >60% (median OS 16.9 months), although higher KPS tended to favor longer survival (p = 0.223, Fig. 2B). MGMT was positive in 49 cases (70.0%) and negative in 21 cases (30.0%). The MGMT-negative group (median OS 21.4 months) had significantly longer survival than the MGMT-positive group (median OS 14.1 months) (p = 0.008, Fig. 2C). Eight long-term survival patients, i.e., 3 years or more,
were all included in the total group, of whom 6 (75.0%) were MGMT-negative. Patients receiving 60 Gy irradiation (median OS 15.6 months, n = 63) had significantly better outcomes than those given <60 Gy (median OS 9.7 months, n = 10) (p = 0.001, Fig. 2D).

Among the TMZ-treated patients (n = 30), median OS was 20.4 months, and median OS was significantly higher in the subtotal (24.6 months, n = 15) than in the partial (14.1 months, n = 15) group (p = 0.006, Fig. 3). Postoperative KPS scores ranged from 0% to 100% (median 60%). The subtotal group had significantly higher KPS scores (median 70%) than the partial group (median 50%) (p = 0.007, Table 1).

To determine independent prognostic indicators in these patients, a Cox regression model was used with variables of age, TMZ, 60 Gy irradiation, MGMT, and removal rate. Consequently, younger age (p = 0.047), TMZ (p < 0.001), 60 Gy irradiation (p = 0.009), MGMT-negative (p = 0.027) and removal rate (p = 0.003) were found to be significant prognostic factors (Table 2).

Median OS for the 71 high-risk patients was 13.2 months. Median OSs for the high-risk patients in the subtotal, partial, and biopsy groups were 14.8, 13.1, and 11.8 months, respectively (Fig. 4A). Among the TMZ-treated high-risk patients (n = 25), the median OS was 20.4 months, and median OSs in the subtotal, partial, and biopsy groups were 67.9 (n = 9), 14.1 (n = 11), and 13.3 (n = 5) months, respectively (Fig. 4B). Pre- and postoperative KPS scores in the high-risk group are shown in Fig. 5. The median postoperative KPS score tended to be higher than the preoperative score only in the subtotal group.

**Discussion**

The present study investigated the outcomes of GBM patients treated in one district of Japan, including elderly and low KPS score patients. Approximately half of the patients had KPS scores of ≤60%...
and nearly 30% were >70 years of age in this study. Despite these rather fragile patient characteristics, therapeutic outcomes were relatively favorable: the median OS was 13.5 months and the 2-year survival rate was 15.2%. The median OS was 11.8 months among 267 GBM patients (median age 61 years, median preoperative KPS 70%) treated at a single institute, but TMZ was used only in 20 patients.\textsuperscript{17} The median OS was 12.2 months among 500 GBM patients (median age 60 years, median preoperative KPS 80%) in another institute.\textsuperscript{16} The following variables were found to be significant prognostic factors favoring longer survival by multivariate analysis in the subtotal and partial groups: younger age, TMZ therapy, 60 Gy irradiation, MGMT-negative, and more than subtotal resection (Table 2). Some were previously reported to be prognostic factors for GBM.\textsuperscript{1,8,10}

Reducing tumor volume surgically is generally associated with longer survival of GBM patients. Three randomized phase III trials supported the effectiveness of cytoreductive surgery for GBM, and concluded that complete resection appears to improve survival and may increase the efficacy of adjuvant therapies.\textsuperscript{18} However, elderly (age >65 or 70 years) patients and patients with low KPS (KPS score <60% or 70%) were excluded from all 3 trials.

Recently, the extent of the resection threshold was investigated for 500 consecutive newly diagnosed GBMs.\textsuperscript{10} The results indicated that resection exceeding 78% can impact patient survival, and that this trend continues even at the highest levels of resection. The study included elderly (range 20–90 years, median 60 years) and low KPS (range 20–100%, median 80%) patients. Although the objectives were to examine younger patients with better KPS scores than those in our study, these results suggest that maximal safe resection can be beneficial for GBM patients including the elderly and those with low KPS scores.

Maximal safe resection only contributes to prognostic improvement and may also enhance the therapeutic response to TMZ. Analysis of the survival of patients analyzed based on the extent of resection, as described by the surgeons,\textsuperscript{19} showed that patients receiving only radiotherapy after surgery had better outcomes if resection was total (median OS 14.2 months) rather than partial (median OS 11.7 months). In addition, survival in the total resection group was further prolonged if TMZ was combined with irradiation after surgery (median OS 18.8 months) versus only irradiation after surgery (median OS 13.5 months). Assessment of the relationship between GBM volume and the response to chemotherapy concluded that, in patients with recurrent supratentorial GBM, smaller residual tumor volume (<10 cm\textsuperscript{3}) was associated with better response to chemotherapy.\textsuperscript{7}

In the present study, survival outcomes were significantly better in the subtotal than in the partial group. Median OS in the high-risk groups were consistent with this result, especially in the TMZ-treated patients. One of the major benefits of TMZ is that it can be used for elderly and low KPS patients without severe adverse events. Based on this study, maximal safe resection and radiochemotherapy using TMZ appears to be one of the best treatment options for such high-risk patients. To improve the resection rate, surgical assistance systems such as intraopera-
tive electromagnetic monitoring, neuronavigation, and intraoperative image diagnosis are essential. In our institute, a neuronavigation system was introduced in 2006 and intraoperative CT has been performed since 2010. These surgical assistance systems are not discussed in this study but the therapeutic results may have been biased by their use.

MGMT expression is an important factor in the survival of GBM patients. MGMT expression is negatively associated with survival due to its involvement in resistance to TMZ chemotherapy.[^6^] MGMT expression is also a factor predicting the response to irradiation, and an independent prognostic factor for survival.[^4^][^15^][^20^][^22^] In our department, immunohistochemical staining has been used to detect MGMT expression. This method is advantageous because paraffin-embedded specimens can be used.[^12^] However, high rates of intra- and interobserver variability have been reported.[^13^] Reported cut-off levels for MGMT-positive nuclei range from less than 5% to as much as 35%,[^3^][^13^] partly attributable to the various antibodies and methods of antigen retrieval employed.[^13^] In the present study, we used a cut-off level of 30% to distinctly divide glioblastoma cases into two subgroups with different survivals (unpublished data), and multivariate analysis revealed MGMT expression to be an independent prognostic factor. However, further investigations concerning the cut-off level of MGMT-positive nuclei and adoption of a standardized staining method is essential to obtain consistent results from immunohistochemical staining.

Postoperative KPS scores were significantly higher in the subtotal than in the partial group. Interestingly, not only did KPS scores not decrease postoperatively, but scores actually improved in patients in whom “maximal safe resection” could be performed. Among the high-risk patients as well, median postoperative KPS scores tended to be more favorable than preoperative scores in the subtotal group. In addition, among the TMZ-treated high-risk patients, the survival time of the subtotal group tended to be better than those of the other two groups.

This study has various limitations. First, this was a retrospective analysis of clinical outcomes of GBM patients based on clinical records. Second, the present study did not address the problem of progression-free survival. In the treatment of GBM with TMZ, particularly in patients with a favorable response, temporary enlargement of GBM, so-called pseudo-progression, is often seen on imaging studies.[^2^] The strict differentiation of true progression from pseudo-progression is difficult at present, so progression-free survival was not analyzed in the present study. Finally, we did not investigate additional therapies such as re-operation and stereotactic radiotherapy after recurrence. Since our treatment policy has remained consistent for the past 11 years, nearly all of our patients were followed up employing essentially the same protocol.

The present study suggests that maximal safe resection followed by radiochemotherapy using TMZ is one of the optimal treatments, regardless of age and KPS, for patients with GBM. Future prospective studies focusing on elderly and low KPS patients with GBM are essential. We also anticipate that surgical assistant systems will be developed and that surgical techniques will be further improved, ultimately prolonging the survival of patients with GBM.

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