PRIMARY Glioblastoma Multiforme in Younger Patients: A Single-Institution Experience

Cüneyt Ulutin¹, Merdan Fayda¹, Gorkem Aksu¹, Oguz Cetinayak¹, Okan Kuzhan², Fatih Ors³, and Murat Beyzadeoglu¹

¹Department of Radiation Oncology, ²Division of Medical Oncology, ³Department of Radiology, GATA Hospital, Ankara, Turkey

Aims and background: To report our experience of patients with primary glioblastoma multiforme of young age by evaluating the characteristics, prognostic factors, and treatment outcomes.

Patients and methods: Seventy patients with primary glioblastoma multiforme (GBM) treated at our department between 1996 and 2004 were studied. The male-female ratio was 2.6:1. The median age was 53 (16-74). Sixty-eight patients (97%) were operated on before radiotherapy and 2 patients (3%) underwent only stereotactic biopsy. All patients received radiotherapy. Postoperative chemotherapy as an adjuvant to radiotherapy was given to 9 patients (12%). The patients were divided into 2 groups according to their age (group A ≤35 years, n = 21 vs group B >35 years, n = 49). Survival was determined using the log-rank test. Cox regression analysis was performed to identify the independent prognostic factors. Karnofsky performance status (KPS) was determined to identify the independent prognostic factors. Karnofsky performance status (KPS) was 70% or higher in 36 patients (52%). Preoperative midline shift was present in 45 patients (64%). The patients were divided into 2 groups (total cranium vs partial), total radiotherapy dose (60 vs 66 Gy), and adjuvant chemotherapy (present vs absent) were evaluated in univariate analysis.

Key words: brain tumor, prognosis, radiotherapy.

Introduction

Glioblastoma multiforme (GBM) is one of the most common primary brain tumors in adults and carries a dismal prognosis. Despite the improvement of microneurosurgical techniques, molecularly targeted therapies and new systemic agents combined with radiotherapy, improvements of survival have been minimal and the median survival for GBM patients is about 9-12 months. Most patients die due to disease progression within 2 years and cure was only reported in a few cases.¹⁻⁶ Primary (de novo) GBM constitutes about 80% of all glioblastomas. Primary GBM is characterized by a short patient history of usually less than 3 months and absence of pre-existing less malignant astrocytoma as described by Scherer.⁷

The incidence of GBM increases with age, especially after the third decade. GBM generally occurs in the sixth or seventh decade of life. Between the ages of 75 and 84 the incidence reaches 20 cases per 100,000 population. Younger patients constitute a relatively small proportion of the reported GBM series.⁸⁻¹⁰ For this reason, we evaluated the outcomes of GBM patients by comparing the treatment results of younger and older patients. Although the number of patients included in this study is limited, we would like to present our experience with younger patients.

Patients and methods

Patients

Seventy patients with primary glioblastoma multiforme (GBM) were treated at our institution between 1996 and 2004. Twenty-one (30%) were 35 years or younger. The male-female ratio was 2.6:1. Median age was 53 years (range, 16 to 74 years). A preoperative history of seizures was present in 24 patients (34%). Karnofsky performance status (KPS) was 70% or higher in 36 patients (51%). The tumor was larger than 4 cm in 36 patients (52%). Four (6%) patients had multicentric tumor. The preoperative waiting period was more than 1 month from the initial symptoms in 41 patients (58%). Preoperative midline shift was present in 45 patients (64%). The patients were divided into 2 groups according to age (group A ≤35 years, n = 21 vs group B >35 years, n = 49). The characteristics of all patients are presented in Table 1. Twenty-one of the 70 patients

Correspondence to: Dr Cüneyt Ulutin, Kızılcık sok. 10/10 Anıttepe, Ankara, Turkey. Tel +90-312-3044684; fax +90-312-3044150; e-mail culutin@yahoo.com

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were in the younger age group; 17 of these patients were male. Tumor localization in this group was the temporal lobe in 7 (22%), frontal lobe in 5 (16%), parietal lobe in 9 (29%), and occipital lobe in 5 (16%) patients. Multilobar involvement was present in 5 (16%) patients. The Karnofsky performance status was more than 70% in 80% of the younger age group. A preoperative history of seizures was present in 8 patients (38%). Midline shift was observed in 12 patients (58%) in this group. In 12 patients (58%) the preoperative waiting period was more than 1 month. Microscopic total resection was achieved in 7 (33%) patients. Thirteen patients (62%) underwent subtotal resection, and 1 underwent biopsy only. Adjuvant chemotherapy was given to 5 patients (16%) in group A.

Surgery

Sixty-eight patients (97%) underwent surgery before radiotherapy. Microscopic gross total resection was performed in 28 (40%) patients, 40 patients had subtotal resections (57%), and the remaining 2 patients (3%) had only biopsy before initiation of radiotherapy. In 17 patients (24%) the tumor was located in the temporal lobe, in 15 patients (21%) in the frontal lobe, in 19 patients (27%) in the parietal lobe, in 11 patients (15%) in the occipital lobe, in 7 patients (10%) in more than one lobe, and in 1 patient (1%) in the cerebellum.

Radiotherapy

All patients received external-beam radiotherapy. Radiotherapy was given 5 days a week with 2 Gy per fraction. A Co-60 machine was used with the isocentric technique. The total radiation dose was 60 Gy in 61 patients (87%). The remaining 9 patients (13%) received 66 Gy. In 59 patients (84%) 46-Gy total cranium irradiation was used, followed by a local boost of 14-20 Gy. Eleven patients (16%) received radiotherapy with large partial fields. In patients treated with total cranial fields, the clinical target volume (CTV) was the whole brain at 46 Gy followed by a 14-20 Gy local boost to the contrast-enhancing lesion on MRI. In patients treated with partial fields, the CTV was the contrast-enhancing lesion plus a 3-cm margin at 46 Gy followed by a 14-20 Gy boost like in patients treated with whole-brain irradiation.

Chemotherapy

Postoperative chemotherapy adjuvant to radiotherapy was given to 9 patients (12%). Six cycles of a procarbazine (60 mg/m²), vincristine (1.4 mg/m²) and BCNU (80 mg/m²) regimen were applied.

Statistics

All statistical analyses were done with the SPSS package, version 7.5. Survival was determined with the Kaplan-Meier method and differences were compared using the log-rank test. Cox regression analysis with the forward logistic regression method was performed to identify independent prognostic factors.

Follow-up

After radiotherapy, patients underwent follow-up visits every 3 months. They were evaluated with radiological imaging and physical examination. Most of the patients were evaluated by magnetic resonance imaging.

Results

Multicentric tumors were more commonly seen in group A than in the older group (16% vs 6%). The frontal lobe was more frequently involved in the older group (25% vs 16%; Table 1). During follow-up, re-craniotomy was performed in 2 patients (3%). One patient (1%) in group A developed spinal seeding metastases and was given spinal radiotherapy. One patient (1%) received chemotherapy for local disease progression. Forty-eight patients (68%) were treated symptomatically with dexamethasone (3-4 x 8 mg/day) after disease progression was detected.

Analyses were performed after the death of the patients (n = 52) due to disease progression. The median survival of the whole group was 10.3 months. In univariate analysis the following survival differences were found: younger age versus older age: median 19.5 months vs 5.27 months (P = 0.0012); Karnofsky perfor-
Performance status ≥70 vs <70: median 15.3 months vs 2.67 months (P <0.0001); external radiotherapy dose 60 Gy vs 66 Gy: median 11.6 months vs 3 months (P = 0.02); total cranium vs partial radiotherapy fields: median 8 months vs 21.9 months (P = 0.08); male vs female: median 8 months vs 13.7 months (P = 0.52); midline shift present vs absent: median 7.2 months vs 12.8 months (P = 0.21); tumor size ≤4 cm vs >4 cm: median 6 months vs 13.9 months (P = 0.12); preoperative waiting time longer vs shorter than 1 month: median 11.8 months vs 12.6 months (P = 0.59); total vs subtotal resection: median 14.4 months vs 3.8 months (P = 0.37); adjuvant chemotherapy received vs not received: median 11.1 months vs 10.3 months (P = 0.6); unilobar vs multilobar invasion: median 10.03 months vs 2.47 months (P = 0.40); preoperative seizure history present vs absent: median 14.43 months vs 7.9 months (P = 0.12). Regression analyses were done for factors identified as significant in univariate analysis. A worse performance status (KPS <70) was found to be the only independent poor prognostic factor (P = 0.014, 95% CI HR = 0.0043 [0.0001-0.15]) (Table 2, Figure 1). As shown in Figure 2, there was no significant survival difference in younger (n = 17) and older (n = 19) patients with a better performance status (≥70; P = 0.11).

Discussion

The incidence of GBM usually peaks at the sixth or seventh decade of life 8. In our study younger patients (aged ≤35 years) make up 30% of the cases, while in many trials they were not represented at this rate 9. Younger age is one of the most important prognosticators in the reviewed literature. Simpson et al. 11 in the evaluation of data from 3 RTOG (Radiation Therapy Oncology Group) randomized trials reported that patients younger than 40 years had the best survival rates. Another important factor for survival in patients with GBM is performance status. In many trials, the Karnofsky performance status was identified as a major prognostic factor 4,6,8. In our study, KPS was found to be the

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<th>Table 2 - Prognostic factors in 70 glioblastoma patients</th>
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<tr>
<td><strong>Age</strong></td>
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<td><strong>Radiation field</strong></td>
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<td>Total cranium + local boost</td>
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<td><strong>Radiotherapy dose</strong></td>
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KPS, Karnofsky performance status.
only factor that independently affected survival \((P = 0.004, \text{Figure 1})\). We also investigated the age effect on survival in 36 patients with better KPS \((\geq 70)\). Although the difference was statistically insignificant, the median survival was 23.4 and 14.4 months respectively, in favor of younger patients \((P = 0.11, \text{Figure 2})\). In some studies, tumor location was suggested to have an impact on survival. Gehan and Walker showed that patients with parietal tumors had a worse survival\(^\text{12}\). In another study, patients with frontal lobe tumors had a better survival than patients with temporal and parietal lobe lesions\(^\text{11}\). In our study we found no statistically significant difference between tumor locations. The median survival for the different locations was: temporoparietal 13.9 months, frontoparietal 21.9 months, occipital 2.70 months, parietal 7.9 months, temporal 10.3 months, and frontal 13.7 months (Table 1).

The effect of the extent of surgery is controversial. The effect of total versus subtotal resections on survival is still a matter of debate; however, there is consensus that the tumor should be removed as much as possible without causing any significant neurological deficit\(^\text{11}\). In our study, although the median survival was 14.4 months versus 3.8 months in favor of cases with total tumor removal, the difference was not statistically significant \((P = 0.37, \text{Table 1})\).

Radiotherapy (RT) has an important role in the treatment of GBM, both in the adjuvant and primary treatment setting (i.e., in inoperable cases)\(^\text{14}\). It remains the most effective postoperative treatment\(^\text{2}\). The use of whole-brain radiotherapy after surgery increased the median survival in a few randomized trials\(^\text{4,15}\). Partial brain irradiation appears to be a reasonable approach because most of the local recurrences occur in a margin of 1-2 cm around the initial tumor volume\(^\text{16}\). The optimal irradiation dose is another point of interest. In an RTOG randomized trial, total doses of 60 and 70 Gy (1.8-2 Gy/fraction) were compared, and no significant difference was found\(^\text{17}\). In our study, the radiotherapy fields had no significant impact on survival (total cranial vs partial radiotherapy fields: median survival of 8 months versus 21.9 months \([P = 0.08]\)). Five of the 11 (45%) patients treated with local fields were in the younger age group. Only 16 (27%) of the patients who had total cranial irradiation were in the younger age group. Four of them (6%) had multilobar tumors. However, 3 of the 11 patients (27%) treated with local fields had multilobar tumor invasion. Eight of the 11 patients (72%) who were treated with partial fields also had a better performance status. This is the likely cause of their relatively long survival. Radiotherapy doses of 60 to 66 Gy were applied, and the median survival was 11.6 months versus 3 months in favor of 60 Gy \((P = 0.02, \text{Table 2})\). However, the number of cases treated with 66 Gy was 9. Although the importance of this significance cannot be evaluated in multivariate analysis due to the limited number of patients, 7 of these 9 patients (77%) had a poorer performance status. This was the possible explanation of the worse outcome. Preoperative midline cranial shift is not an uncommon initial sign in GBM. Approximately 74% of patients present with midline shift\(^\text{18}\). Kreth \textit{et al.}\(^\text{19}\) found an adverse effect of the presence of midline shift in a subset analysis. In contrast, we did not observe the same effect, which was probably related to the poor performance status of our patients with midline shift. Furthermore, extent of surgery seems to be more important than midline shift\(^\text{19}\).

The presence of seizures is one of the other controversial prognostic factors. Some studies reported a favorable effect on survival\(^\text{20,21}\) whereas others found no effect\(^\text{22,23}\). We also did not find any significance. However, seizures may be an alerting symptom resulting in an early diagnosis, which probably leads to total removal of the tumor.

**Conclusions**

GBM is a rapidly fatal disease with rapid progression, even in young patients. The current standard of care is resection to a feasible extent followed by radiotherapy. With these conventional therapies the median survival was 19.5 months in our younger patients. The relatively long survival and relatively high survival rate of these patients was particularly due to their better performance status. In younger patients with a good performance status the median survival reached a duration of 23.4 months. Tailored therapy approaches with novel methods should be proposed for this subset of patients.

**References**