

Efficacy of Treatment for Glioblastoma Multiforme in Elderly Patients (65+): A Retrospective Analysis

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ABSTRACT: **Background:** Glioblastoma multiforme (GBM) is an ultimately fatal disease that affects patients of all ages. Elderly patients (65 years and older) constitute a special subgroup of patients characterized by a worse prognosis and frequent comorbidities.

Objectives: To assess the efficacy of different treatment modalities in terms of survival in elderly patients with GBM.

Methods: Using retrospective analysis, we extracted, anonymized and analyzed the files of 74 deceased patients (aged 65 or older) treated for GBM in a single institution.

Results: Mean survival time was 8.97 months and median survival time 7.68 months. Patients who underwent tumor resection had a mean survival of 11.83 months, as compared to patients who underwent no surgical intervention or only biopsy and had a mean survival of 5.22 months ($P < 0.0001$). Patients who underwent full radiation treatment had a mean survival of 11.31 months, compared to patients who received only partial radiotherapy or none at all and had a mean survival of 4.09 months ($P < 0.0001$). Patients who underwent chemotherapy had a mean survival of 12.4 months, compared to patients who did not receive any chemotherapy and had a mean survival of 5.89 months ($P < 0.001$).

Conclusions: Age alone should not be a factor in the decision on which treatment should be given. Treatment should be individualized to match the patient's overall condition and his or her wishes, while taking into consideration the better overall prognosis expected with aggressive treatment.

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Glioblastoma multiforme is the most frequent primary brain tumor in adults [1,2]. The annual age standardized incidence rates per 100,000 for GBM in Israel is 3.26, similar to other countries [1,2]. In 2005, of the 327 patients diagnosed with malignant brain tumors in Israel, 148 were diagnosed

with GBM: 143 in Israeli Jews (96.6%) and 5 in Israeli Arabs (3.4%), while the total Israeli Arab population in 2005 constituted 19.6% of the total population of Israel [3,4]. This shows a higher relative risk for Israeli Jews.

GBM is a tumor comprising astrocytes and is defined as an astrocytoma grade 4. It is more frequent among the middle-aged and elderly. Two-thirds of patients are between 45 and 70 years old, mean 61–62 years. Patients older than 70 years constitute less than 10% of the total patient population with GBM [5,6].

Today, the common practice of treatment consists of resection of the tumor as much as possible, radiotherapy and chemotherapy. A study by Lacroix et al. [7] to determine whether the extent of tumor resection was associated with increased survival time in patients with GBM found that survival time was longer in patients who underwent resection of 98% or more of the tumor volume. This aggressive surgery has shown the greatest survival advantage in patients with favorable prognostic factors and less in patients with poor prognosis as measured by older age, performance status and the amount of tumor necrosis.

In recent years it became clear that radiotherapy has an important role in prolonging the survival time of elderly patients with GBM. In addition, the fear that this treatment modality may cause significant cognitive decline in this subpopulation of patients was disproved [8]. Nonetheless, there is still much controversy regarding the optimal radiotherapy protocol for the elderly population with GBM. The standard radiotherapy protocol today is 60 Gy in 30 fractions [1,9,10]. Because elderly patients with GBM have a relatively short survival time, attempts were made to shorten the duration of therapy without compromising its efficacy in order to improve their quality of life. Roa and colleagues [11] explored whether a radiotherapy protocol of 40 Gy in 15 fractions that takes 3 weeks has the same efficacy as the standard protocol that takes 6 weeks and concluded that there is no difference in survival between patients receiving standard radiotherapy and those receiving short-course radiotherapy. Short-course radiotherapy is not yet the standard of care and more studies are needed to prove its efficacy and clarify the exact optimal protocol. Despite the remarkable advances in radiotherapy

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GBM = glioblastoma multiforme

technology and accuracy in recent years, the prognosis has not improved although it may manifest in fewer treatment-related side effects [9].

Chemotherapy has become a major factor in recent years with the introduction of temozolomide [12]. O⁶-methylguanine DNA methyltransferase (MGMT) is a DNA repair enzyme that is ascribed a role in cancer cell resistance to alkylating agents, such as temozolomide. Loss of the MGMT protein as a consequence of *mgmt* gene promoter methylation predicts a good response to temozolomide [12]. Although the combined treatment modality has improved survival, the prognosis remains gloomy with a mean of 12.1 months for patients undergoing radiotherapy in addition to surgery and 14.6 months for patients who also undergo chemotherapy [1].

Many factors have been found to influence GBM prognosis. The younger the patient (< 65 years) and the higher the performance status (Karnofsky Performance Scale > 70), the better the outcome. Additional factors – such as more aggressive surgery, absence of loss of heterozygosity 10q, and possibly female gender and a histopathological profile that contains giant cells – are also predictive of better prognosis [13-15].

Older age at diagnosis is currently the most consistent negative predictor of survival. GBM tumors in elderly patients have some biological features that might be responsible for the poorer survival in this age group. For example, much higher mean cell proliferation indices (MIB-1) were found in patients older than 60 years as compared to younger patients. This suggests that faster tumor growth may be the major factor responsible for the poorer prognosis in elderly patients [16].

Treating elderly patients with GBM is a challenge, not only in terms of a poorer prognosis. Elderly patients are frequently treated with lower radiotherapy and/or chemotherapy doses, or are not treated at all. This can be attributed to the belief held by many physicians that this subgroup of patients has a poorer tolerance to treatment. This widely held belief is not easy to disprove and an optimal treatment protocol is not available for these patients because they are frequently excluded from clinical studies [8,17]. The role of adjuvant chemotherapy remains controversial in the elderly (≥ 65 years) owing to the claim that their glioma cells are less chemosensitive than those of younger patients, both in vitro and in vivo [10].

The purpose of this retrospective analysis was to address the questions of how effective maximal therapy is in the elderly population and whether there is sufficient indication for this difficult and expensive treatment, taking into account the side effects and the many comorbidities frequently found in this age group.

PATIENTS AND METHODS

We extracted the files of GBM patients aged 65 or older who received treatment or were followed in the Department of

Oncology, Rambam Health Care Campus, in Haifa, Israel between the years 1996 and 2007. All patients had deceased prior to data extraction. Data relating to demographics, comorbidities, time to diagnosis by imaging, time to histological diagnosis, type of treatment, and survival were collected and analyzed using SPSS 15. The data were analyzed without reference to the patients' identities (anonymized). Descriptive statistics of means, medians, standard deviations and percentages were calculated for each of the variables in the sample: dependent variables (time from radiological diagnosis to death) and independent variables (age and gender, location of tumor, background illnesses, chemotherapeutic treatment, surgical treatment, etc.). Time intervals were calculated from the onset of symptoms to radiological diagnosis, from radiological diagnosis to histological diagnosis, and from radiological diagnosis to death (the dependent variable).

Univariate analysis using the Mann-Whitney U test studied the relation between post-diagnosis survival and variables such as surgical treatment, radiotherapy and chemotherapy. The relations between different ordinal independent variables were analyzed using Fisher's exact test. A multivariate model was used to find variables that influenced post-diagnosis survival. Non-parametric tests were used to demonstrate the added value of each treatment (resection, resection + radiotherapy, resection + radiotherapy + chemotherapy) on survival time.

RESULTS

Seventy-four patients were found to match the criteria (≥ 65 years old with GBM). Mean and median ages were 71.89 and 72 years respectively (range 65–83 years). Forty-three (58%) patients were male. Sixty-eight patients (91.89%) were Israeli Jews and 6 (8.11%) were Israeli Arabs, while the total Israeli Arab population constituted about 20% of the total population of Israel.

COMORBIDITIES

We found that 59 patients had cardiovascular risk factors (high cholesterol level, hypertension, smoking), 36% had undergone surgery in the past, 30% suffered from cardiovascular disease, 22% suffered from diabetes mellitus, 14% had a previous malignancy, 4% had transient ischemic attack or cerebrovascular accident, and 42% had some other comorbidity.

TREATMENT

• RESECTION [Table 1]

Forty-two patients (56.8%) underwent resection, 26 (35.1%) had a biopsy only, and 6 (8.1%) had neither. Patients who underwent resection survived on average 11.83 months, compared to those who did not whose average overall survival time was 5.22 months ($P < 0.0001$). The mean age of patients who

Table 1. Number and survival time of patients who underwent different surgical procedures

Surgery	No. of patients	Survival time (mos)				
		Mean	SD	Median	Minimum	Maximum
None	6	3.73	2.91	2.65	0.73	7.83
Biopsy only	26	5.56	4.46	4.93	0.83	19.13
Resection	42	11.83	6.66	11.1	1.9	34.33
Total	74	8.97	6.59	7.68	0.73	34.33

Table 2. Number and survival time of patients who underwent different radiotherapy procedures

Radiation	No. of patients	Survival time (mos)				
		Mean	SD	Median	Minimum	Maximum
None	17	3.61	3.65	2.03	0.73	12.83
Partial (\leq 30 Gy)	7	5.26	4.15	3.8	2.2	13.97
Standard protocol	50	11.31	6.37	10.57	2.43	34.33
Total	74	8.97	6.59	7.68	0.73	34.33

Table 3. Number and survival time of patients who underwent chemotherapy

Chemotherapy	No. of patients	Survival time (mos)				
		Mean	SD	Median	Minimum	Maximum
No	39	5.89	4.71	5.37	0.73	20.13
Yes	35	12.4	6.73	11.37	2.9	34.33
Total	74	8.97	6.59	7.68	0.73	34.33

Table 4. Added value of each treatment modality (resection, radiotherapy, and chemotherapy) to the overall survival of the patient

Treatment modality	No. of patients	Survival time (mos)				
		Mean	SD	Median	Minimum	Maximum
Resection only	5	5.91	5.04	3.8	1.9	13.97
Other	69	9.19	6.66	7.77	0.73	34.33
Resection + standard radiotherapy only	8	10.94	5.1	9.47	6	20.13
Other	66	8.73	6.74	7.45	0.73	34.33
Resection + standard radiotherapy + chemotherapy	27	13.79	6.53	12.1	4.37	34.33
Other		6.2	4.81	5.9	0.73	20.13

underwent resection was 71.21 years, as compared to 72.78 years for patients who underwent biopsy only or neither. This small difference has no statistical significance ($P = 0.12$).

• RADIOTHERAPY [Table 2]

Seventeen patients (23%) did not receive any radiotherapy, 7 (9.5%) received only partial radiotherapy (30 Gy or less), and 50 (67.6%) received standard treatment (more than half the expected dose of 60 Gy in 30 fractions). Altogether, 57 patients received some degree of radiotherapy, with an aver-

age dose of 52.24 Gy. Patients who received standard radiotherapy survived 11.31 months on average, as compared to 4.09 months for patients who did not receive standard radiotherapy ($P < 0.0001$). Patients who received no radiotherapy or only partial radiotherapy had a mean age of 74.08 years, as compared to 70.84 years for patients who received standard radiotherapy ($P = 0.003$). Eighty-three percent of the patients who underwent tumor resection also received standard radiotherapy, whereas only 47% of the patients received standard radiotherapy when no resection was performed ($P = 0.001$).

• CHEMOTHERAPY [Table 3]

Thirty-five patients (47%) received chemotherapy, and most ($n=34$) received temozolomide. Of these, seven patients received carboplatin and etoposide (CARBO/VP16) as second-line treatment after temozolomide, one patient received procarbazine hydrochloride as second line after temozolomide, and a single patient received procarbazine hydrochloride without temozolomide. Patients who underwent chemotherapy had an average overall survival time of 12.4 months, as compared to 5.89 months for those who did not receive chemotherapy ($P < 0.001$). There was no significant difference ($P = 0.18$) between the mean age of patients who underwent chemotherapy (71.17 years) and patients who did not (72.54 years). Sixty-nine percent of patients who underwent tumor resection also received chemotherapy, as compared to 19% who did not undergo resection ($P < 0.0001$). Sixty-six percent of patients who underwent standard radiotherapy also received chemotherapy, as compared to 8% of those who received no radiotherapy or only partial radiotherapy ($P < 0.0001$).

To assess how much the addition of each treatment modality contributed to the overall survival of the patients, the data were reanalyzed and are shown in Table 4.

DISCUSSION

Our results demonstrate again the overall poor prognosis of elderly patients with GBM (mean survival 8.97 months, median survival 7.68 months). However, patients who received a more aggressive treatment had significantly improved survival. For each type of treatment (resection, radiotherapy, chemotherapy), patients who underwent treatment survived significantly longer than those who did not undergo treatment.

We also wished to assess how much the addition of each treatment modality contributed to overall survival [Table 4]. Although there were too few patients in this study to enable statistical significance, a clear trend can be seen. Patients who underwent resection alone had a median survival of 3.8 months. Those who underwent standard radiotherapy in addition to tumor resection had a median survival of 9.47 months. Finally, those who received the most aggressive

treatment, which included surgical resection of the tumor, standard radiotherapy and chemotherapy, had a median survival of 12.1 months. The survival time of patients who received aggressive treatment was significantly longer than that of patients who underwent symptomatic treatment. Even partial treatment had a significant effect in comparison to symptomatic treatment alone.

Because age is such an important prognostic factor in GBM, even small differences in the average age of a sample population may influence the prognosis. Therefore, it is difficult to compare the overall survival times in different studies. Mangiola and co-researchers [18] evaluated 34 GBM patients with a mean age of 70 years (range 65–78) and noted an overall median survival of 10.5 months. Those who received adjuvant radiotherapy had a median survival of 7 months, while those who received adjuvant treatment, which included radiotherapy and chemotherapy, had a median survival of 18 months. Brandes et al. [19] followed 23 patients who underwent surgery, radiotherapy and chemotherapy (temozolomide). The median age was 68 years (range 65–75 years). Their overall survival was 14.9 months. In comparison, 27 patients in our study were treated with tumor resection, standard radiotherapy and chemotherapy, and their mean and median overall survival was 13.79 months and 12.1 months respectively. Their mean and median ages were 70.81 and 70 years respectively (range 65–79 years).

Using a multivariate model, we observed the following:

- The survival time in a patient who did not undergo tumor resection decreased by 3.9 months when compared to a patient who did undergo tumor resection ($P = 0.006$).
- Survival in a patient who did not receive radiotherapy decreased by 4 months when compared to a patient who did receive radiotherapy ($P = 0.011$).
- Survival in a patient who received chemotherapy increased by 5 months when compared to a patient who did not receive chemotherapy ($P = 0.004$).

It is important to note that according to our results, age alone had little effect when considering treatment. There was no significant age difference between those who underwent tumor resection or those who received chemotherapy and those who did not. However, those who received radiotherapy had a tendency to be younger than those who received partial or no radiotherapy (mean age 70.84 years compared to 74.08 years).

No statistically significant difference in the prevalence of cardiovascular risk factors, diabetes mellitus, cardiovascular disease, history of surgery or history of malignancy was found between the patients who underwent tumor resection, radiotherapy or chemotherapy and those who did not. Three patients in our study suffered from transient ischemic attacks or cerebrovascular accidents before being diagnosed with GBM; all three received only supportive treatment.

Therefore, it seems that having a stroke or transient ischemic attack influenced the treatment choice. However, because of the small sample, a statistical difference was found concerning radiotherapy only ($P = 0.03$). The present study has shown that although elderly GBM patients suffer from a high percentage of comorbidities (as expected in this age group), this is not a sufficient justification to withhold treatment from all patients of this subgroup in general; rather, each case should be considered individually. In this retrospective work it was not possible to reassess the performance status of each patient; therefore, this important prognostic factor was not taken into account, at least not formally. There is a reasonable possibility that the patients were subjected to different treatment modalities based on the physician's own assessment of the patient's performance status and overall condition. This bias could not be refuted.

CONCLUSIONS

Elderly patients can gain significant benefit from aggressive treatment (resection, radiotherapy and chemotherapy). Aggressive treatment must not be withheld based on age alone and should be considered while taking into account the patient's overall condition, wishes and expectations. Even partial treatment can result in significant survival benefits when compared to symptomatic treatment alone.

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