Glioblastoma Multiforme: an Advanced Analysis of 153 Patients and Review of the Literature

Glioblastoma Multiforme: uma análise avançada de 153 pacientes e revisão da literatura

Mohammad Sadegh Nikdad[1,2] Farshid Farhan[3] Milad Shafizadeh[1,2] Atefeh Sadat Mirmohseni[1,2] Mohsen Afarideh[1,2] Shabnam Asadi Komeleh[1,2] Marzieh Lashkari[3] Morsaleh Ganji[1,2] Alireza Ghajar[1,2] Saeed Shafiei[1,2] Yalda Shafizadeh[4] Ali Kazemian[3] Hooshang Saberi[1,2]

[1] Neurosurgery Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Neurosurgery, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Radiation Oncology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
[4] Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, USA

Address for correspondence Farshid Farhan, MD, Department of Radiation Oncology, Cancer Institute, Tehran University of Medical Sciences, P.O. Box: 14155-6447, Tehran, Iran (e-mail: farhan@sina.tums.ac.ir).

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Abstract

Objective Glioblastoma multiforme (GBM) is an aggressive primary tumor with frequent recurrences that leaves patients with a short survival time and a low quality of life. The aim of this study was to review the prognostic factors in patients with glioblastoma multiforme.

Material and Methods The focus of this retrospective study was a group of 153 patients with supratentorial GBM tumors, who were admitted to a tertiary-care referral academic center from 2005 to 2013. The factors associated with survival and local recurrence were assessed using the hazard ratio (HR) function of Cox proportional hazards regression and neural network analysis.

Results Out of the 153 patients, 99 (64.7%) were male. The average age of the patients was 55.69 ± 15.10 years. The median overall survival (OS) and progression-free survival (PFS) rates were 14.0 and 7.10 months respectively. In the multivariate analysis, age (HR = 2.939, $p < 0.001$), operative method (HR = 7.416, $p < 0.001$), temozolomide (TMZ, HR = 11.723, $p < 0.001$), lomustine (CCNU, HR = 8.139, $p < 0.001$), occipital lobe involvement (HR = 3.088, $p < 0.001$) and Karnofsky Performance Status (KPS, HR = 4.831, $p < 0.001$) scores were shown to be significantly associated with a higher OS rate. Furthermore, higher KPS (HR = 7.292, $p < 0.001$) readings, the operative method (HR = 0.493, $p = 0.005$), the use of CCNU (HR = 2.047, $p = 0.003$) and resection versus chemotherapy (HR = 0.171, $p < 0.001$) were the significant factors associated with the local recurrence of the tumor.

Conclusion Our findings suggest that the use of CCNU and TMZ, the operative method and higher KPS readings are associated with both higher survival and lower local recurrence rates.

Keywords
- glioblastoma multiforme
- survival
- local recurrence

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Resumo

Objetivo Glioblastoma multiforme (GBM) é um tumor primário agressivo com recorrências frequentes que deixam pacientes com uma curta sobrevida e baixa qualidade de vida. O objetivo deste estudo é rever fatores de prognóstico em pacientes com glioblastoma multiforme.

Material e Métodos O foco deste estudo retrospectivo foi um grupo de 153 pacientes com tumores GBM supratentoriais, os quais deram entrada em um centro acadêmico de atendimento de referência de 2005 a 2013. Fatores associados com a sobrevivência e a recorrência local foram avaliados usando a razão de risco (RR) da regressão de risco proporcional de Cox e análise de redes neurais.

Resultados Dos 153 pacientes, 99 (64,7%) eram homens. A média de idade foi de 55,69 $\pm$ 15,10 anos. A sobrevida geral (SG) mediana e a sobrevida de livre progressão (SLP) foram 14,0 e 7,10 meses, respectivamente. Na análise multivariada, idade (RR = 2,939, $p < 0{,}001$), método operatório (RR = 7,416, $p < 0{,}001$), temozolomida (TMZ, RR = 11,723, $p < 0{,}001$), lomustina (CCNU, RR = 8,139, $p < 0{,}001$), envolvimento do lobo occipital (RR = 3,088, $p < 0{,}001$) e Índice de Desempenho de Karnofsky (IDK, RR = 4,831, $p < 0{,}001$) foram identificados como significativamente associados a uma SG maior. Além disso, leituras maiores de IDK (RR = 7,292, $p < 0{,}001$), o método operatório (RR = 0,493, $p = 0{,}005$), o uso de CCNU (RR = 2,047, $p = 0{,}003$) e ressecção *versus* quimioterapia (RR = 0,171, $p < 0{,}001$) foram fatores significativos associados à recorrência local de tumor.

Conclusão Nossos resultados sugerem que o uso de CCNU e TMZ, o método operatório e leituras maiores de IDK estão associados tanto à maior sobrevida quanto à menor recorrência local.

Palavras-chave
- glioblastoma multiforme
- sobrevida
- recorrência local

Introduction

With an annual incidence rate of 3 to 4 cases per 100,000 persons[1], glioblastoma multiforme (GBM) is by far the most common malignant primary tumor of the brain in adults. The overall incidence of primary malignant brain tumors is reported to be around 2.74 per 100,000 persons in Iran.[2] Patients with GBM have a short survival term, and frequently present with tumor recurrence; therefore, an effective management of these patients is crucial. The longest reported survival terms, despite aggressive therapy, are lower than two years.[3–9] Aggressive therapies, including surgery, chemotherapy and radiation are not only costly, but bear additional complications.[10–12] Nearly all patients with GBM have a poor quality of life, and health related quality of life (HRQoL) is defined as a multidimensional concept covering physical, psychological, and social domains, as well as symptoms induced by the disease and its treatment.[13] Treating the tumor is intensive and time-consuming, and treatment complications, as well as tumor recurrences, are common. Effective treatment will improve the patients' performance status[14], neurocognitive function[15], overall quality of life[16] and overall survival.[4,17–19] In addition, the effective treatment will also improve the psychological health of the patients. Achieving high quality of life in patients with GBM requires the cooperation of various specialists, and certain loss of quality of life is intrinsic to cancer patients. However, one should identify and target the factors that will help the radiotherapists, oncologists, and neurosurgeons improve the overall survival of the patients without the recurrence of the tumor.

Our study assesses the factors that are associated with prolonged survival, improved quality of life and reduced tumor recurrence in patients with GBM.

Material and Methods

Patient Selection

A total of 153 patients with supratentorial GBM tumors were admitted to a referral tertiary academic center between 2005 and 2013 at a hospital in Tehran, Iran. In all cases, the GBM patients were diagnosed with the pathology, as confirmed by two senior neuropathologists, and the grading criteria was based on the classification system of the World Health Organization (WHO).[20,21] Patients at any age with a tissue-proven diagnosis of supratentorial GBM (WHO Grade IV) were included in the study. Patients who had serious concomitant malignant or chronic diseases, and patients with infratentorial gliomas and prior lower grade gliomas were excluded from the analysis to create a more uniform patient population.

Apart from the research's objectives, all patients received various management procedures depending on their preoperative assessment and on necessity indicators. Additionally, all patients were followed-up after undergoing the treatment.

Recorded Variables

The clinical, operative, and hospital course records of the patients who met the inclusion and exclusion criteria were retrospectively reviewed. The information was collected from neurosurgery and radiotherapy clinical notes, including the patients' demographics, presenting symptoms, neurological function and neurologic signs, as well as the neuroimaging perioperative course and the adjuvant therapy. The Karnofsky Performance Status (KPS) scale was used to specify the patients' preoperative functional status.[22] The KPS scores were collected during a physical examination by oncologists who were blind to the outcomes of the patients at the clinical visit, and prior to surgery. Preoperative sensory deficit was defined as decreased sensation to any stimulant. Motor deficit was defined as decreased force, as identified by a clinician during a physical examination. Language deficit was defined as any combination of receptive or expressive aphasia. Finally, cognitive deficits were defined as confusion or memory loss. The magnetic resonance imaging (MRI) characteristics were recorded, including the specific lobe location and eloquent brain involvement. This assessment was based on radiographic, not clinical, criteria. Unfortunately, the sizes of the lesions were not registered in the records. The geometric estimation of the volume of the resected tumor was based on the comparison of the enhanced tumor margin in the gadolinium-enhanced T1-weighted sequences of pre-op MRIs with those of post-op MRIs obtained less than 48 hours after tumor resection. The resections were then defined as either gross total resections (GTRs; $>$ 99% resection) or subtotal resections (STR; 90–99% resection) by an independent neuroradiologist who was blind to the outcomes of the patients. The patients who underwent biopsies were not classified as having undergone a resection. The date of death was recorded for any patient whose record was available in the hospital records. Time until death was defined as the time from the initial glioblastoma diagnosis (with the pathology) until death. Patients whose deaths were unconfirmed were classified as lost to the follow-up at the time of the last clinic visit. The concepts of stable disease, local recurrence and progression were defined according to the Response Assessment in Neuro-oncology (RANO) criteria. Briefly, the RANO criteria are based on the evaluation of the product of the maximal cross-sectional diameters of an enhancing lesion in the post-gadolinium enhanced T1-weighted MRI and/or T2-weighted /flair sequences before and 4 weeks after surgery. Depending on meeting a complex criteria comprised of the following, (i) postoperative radiographic assessment of tumor size based on the extent of the preoperative involvement (that is, disappearance, reduction or progression of all measurable and non-measurable lesions on gadolinium-enhanced T1-weighted images in addition to stable, regressing, or progressing tumor size in the T2-weighted/flair images), (ii) clinical status (stable, improved, or deteriorated condition), (iii) the use of corticosteroids (that is, none, stable/decreased or increased [conditional] dosage of medication), and (iv) the presence of new lesions (that is, none or present); the patients with glioblastoma were divided into 4 categories: "complete response," "partial response," "stable disease" or "progressive disease." For the present manuscript, the groups of patients with "complete response" and "partial response" on the RANO criteria were designated as having a "stable disease", and the group of patients with "stable diseases" and "progressive diseases" on the RANO criteria were defined as having "local recurrence."

Perioperative Treatment

All patients had been visited by neurosurgeons and radiation oncologists before surgery. The general aim of the neurosurgeons was to achieve GTR of the tumor when possible. Subtotal resection was achieved primarily when the tumor involved eloquent brain as confirmed by intraoperative mapping and/or monitoring, and surgical navigation (computed tomography [CT] and/or MRI wand) was used in all cases. Implant therapy was not performed in any of the patients. Radiation oncologists treated all the patients with 60 Gy 2-dimensional or 3-dimensional radiotherapy in 30 fractions. The patients were prescribed 6 sessions of adjuvant chemotherapy with 150 mg/m^2 over 5/28 days in 6 cycles of the first-line agent temozolomide (TMZ) in addition to the concurrent chemotherapy with 75 mg/m^2/day TMZ 1 hour prior to radiotherapy. A total of 6 cycles of 110mg/m^2 lomustine (CCNU) adjuvant chemotherapy was performed as the second-line agent because of inaccessibility to TMZ due to the cost of it and the lack of insurance coverage. Although procarbazine, CCNU and vincristine (PCV) remain the salvage chemotherapy regimen in patients with high-grade gliomas,[23] the alternative agent CCNU was used as an adjuvant chemotherapy regimen in this group of patients because of the lower complication rates, better tolerability and comparable survival rate to the use of PCV in our country.[24]

In this study, many patients were denied surgery or chemotherapy options, or both, because of the inability of the patients or their families to pay for the treatments. Therefore, apart from the study's objectives, some patients were treated depending on their preoperative assessment and based on necessity indicators depending on standard treatment options,[25,26] and some patients received incomplete treatments perforce. The decision involved input from a surgeon, a radiation oncologist and the patients themselves. Recurrent tumors were usually discovered on follow-up visits via postoperative MRI performed at 3-month intervals following surgery, or at the time that any symptoms developed.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp. Armonk, NY, US) software, version 20. Summary data was presented as mean $\pm$ standard deviation (SD) for parametric data, and nonparametric data, as median (interquartile range [IQR]). For the intergroup comparison, the Student's *t*-test was used for parametric data, and the Mann-Whitney U-test was used for nonparametric data. The percentages were compared using the chi-square test or Fisher's exact test where appropriate. Survival as a function of time was plotted using the

Kaplan-Meier method. Moreover, log-rank analysis was used to compare the Kaplan-Meier plots. The factors associated with overall survival were assessed using the Cox proportional hazard regression models for multivariate associations. For this purpose, all variables associated with survival in the univariate analysis ($p < 0.10$) were included.

The factors predicting the outcomes of survival and local recurrence were separately analyzed using the neural network analysis. For this purpose, two models for neural network analyses were developed to firstly predict the survival and secondly to predict local recurrence using selected baseline characteristics of the patients.

The analysis of a neural network uses a learning algorithm to define the nonlinear mathematical transfer functions to modify the synaptic weights of a network's processing units in an orderly fashion to obtain the desired outcome prediction (training datasets). Both the weights and the value of the activation functions can be adjusted during the training of an artificial neural network. However, this is impractical, as it would be simpler to only adjust for a single parameter. To surpass this problem, the bias neuron is generated. The bias neurons in layer 1 are connected to all the neurons in the following layer, but with none of the neurons present in the previous layer. The hidden layer contains unobservable network nodes (units). Each hidden unit is a function of the weighted sum of the inputs. It is similar to the correlation coefficient in the linear regression model. In all subsequent analyses, values of $p < 0.05$ were considered statistically significant.

Results

Preoperative, Perioperative and Postoperative Characteristics of the Patients

Among the 155 patients diagnosed with supratentorial primary GBM, 153 met the eligibility criteria and were included in the analysis. The pre-, peri- and postoperative characteristics of these 153 patients (99 men, 64.7% of the total study population) are summarized in ►**Table 1**. The mean $\pm$ SD age of the patients was 55.69 $\pm$ 15.10 years at the time of the diagnosis. In total, 40 patients (26.1%) were younger than 45 years, 88 patients (57.5%) were between 45 and 70 years old, and 25 patients (16.3%) were older than 70 years of age. The median preoperative KPS was 60 (IQR: 50–80, range: 20–100). A total of 52 patients did not express any neurologic symptoms at their consultations. Among 101 patients with neurologic signifiers, the major symptoms presented are described in declining order: seizures in 36 patients (23.5%); motor deficits in 21 patients (13.7%); sensory and language deficits in 15 patients (9.8%); visual deficits in 9 patients (5.9%); and cognitive deficits (memory loss/confusion) in 5 patients (3.3%). The median duration of the symptoms was 2 months prior to the diagnosis of the pathology. A total of 81 tumors (52.9%) were found in the right hemispheres, with the remainder involving the left hemispheres. Ninety-four tumors (61.4%) involved only 1 brain lobe, while all other tumors involved 2 brain lobes. Twenty-nine tumors (19.0%) involved the frontal lobe, 37 tumors (24.2%), the parietal lobe, 18 tumors (11.8%), the temporal lobe, 8 tumors (5.2%), the occipital lobe, 24 tumors (15.7%), the temporoparietal lobe, 16 tumors (10.5%), the parieto-occipital lobe and 21 tumors (13.7%) involved other areas. A total of 60 patients (39.2%) underwent biopsy, 91 patients (59.5%) underwent near total resection (NTR) or STR, and only 2 patients (1.3%) underwent GTR. There were no cases of perioperative mortality. Radiotherapy was performed in all patients (100%) with a median dose of 60 Gy in 30 fractions. A total of 100 patients (94.8%) underwent 2-dimensional radiotherapy, whereas 8 patients (5.2%) underwent 3-dimensional radiotherapy. Of the 153 patients, 78 (51%) underwent only radiotherapy, 57 (37.3%) underwent adjuvant chemotherapy, and 18 (11.8%) underwent concurrent + adjuvant chemotherapy. Concurrent + adjuvant chemotherapy was performed using TMZ. Among the 75 patients who underwent chemotherapy, TMZ was administered to 39 (25.5%), and CCNU was administered to 36 (23.5%). At the last follow-up, 136 (88.9%) patients had died, 10 patients (6.5%) were alive, and 7 patients (4.6%) did not make appointments, and had an unknown status. The median follow-up time for the surviving patients was 14 months (IQR: 10–20 months). The median overall survival rate of the patients was 14 months (IQR: 9–17 months). The median survival rates at 3, 6, 9, 12, 18, 24 and finally, 32 months of the patients in this study were 98.0%, 85.6%, 70.5%, 55.5%, 22.8%, 15.6% and 5.8% respectively. The patients were divided into certain categories to match case and controls for better analysis (►**Table 2**).

Factors Independently Associated with Survival

Univariate Analysis

We investigated the factors associated with the overall survival and progression-free survival using the Kaplan-Meier analysis. We found that age ($p = 0.005$), confusion and/or memory loss ($p < 0.001$), CCNU ($p < 0.001$), TMZ ($p < 0.001$), KPS ($p < 0.001$), operative method ($p < 0.001$), TMZ versus CCNU ($p = 0.007$), 2D versus 3D radiation protocol ($p < 0.001$), frontal lobe involvement ($p = 0.009$) and local recurrence ($p < 0.001$) had various degrees of impacts on both the overall survival and progression-free survival rates of our patients with glioblastoma multiforme (►**Table 3**).

Multivariate Analysis

All variables associated with survival in the univariate analysis ($p < 0.10$) and clinically important variables were included in the multivariate proportional hazards regression model. We found that age (hazard ratio [HR] [95% CI (confidence interval)], 2.939 [1.73–4.99], $p < 0.001$), operative method (HR [95% CI], 7.416 [3.81–14.42], $p < 0.001$), TMZ (HR [95% CI], 11.723 [5.46–25.13], $p < 0.001$), CCNU (HR [95% CI], 8.139 [4.04–16.38], $p < 0.001$), occipital lobe involvement (HR [95% CI], 3.088 [1.81–5.25], $p < 0.001$) and KPS (HR [95% CI], 4.831 [3.00–7.77], $p < 0.001$) had various degrees of impact on both the overall survival and progression-free survival rates of our patients with glioblastoma multiforme (►**Table 4**).

Table 1 pre-, peri- and postoperative characteristics of the patients

Study population → $N = 153$	
Characteristics	N (percent)
Age (mean ± SD)	55.69 ± 15.10
Male	99 (64.7%)
Preoperative factors	
KPS > 60	48 (31.4%)
KPS = 60	62 (40.5%)
40 < KPS < 60	35 (22.9%)
KPS < 40	8 (5.2%)
Neurologic sign	101 (66.0%)
Confusion/memory loss	5 (3.3%)
Language deficit	15 (9.8%)
Motor deficit	21 (13.7%)
Sensory deficit	15 (9.8%)
Seizure	36 (23.5%)
Visual deficit	9 (5.9%)
Mass location	
Right hemisphere	81 (52.9%)
Frontal lobe	29 (19.0%)
Parietal lobe	37 (24.2%)
Temporal lobe	18 (11.8%)
Occipital lobe	8 (5.2%)
Temporoparietal lobes	24 (15.6%)
Others	37 (24.2%)
Perioperative factors	
Operative method	
Biopsy	60 (39.2%)
Total and near total resection	93 (60.8%)
Chemoradiation plan	
Radiotherapy	78 (51.0%)
Radiotherapy + adjuvant chemotherapy	57 (37.2%)
Radiotherapy + concurrent chemotherapy + adjuvant chemotherapy	18 (11.8%)
Chemotherapy drugs	
TMZ	39 (25.5%)
CCNU	36 (23.5%)
Radiation method	
2D	145 (94.8%)
3D	8 (5.2%)
Postoperative factors	
Died at last follow-up, n	136 (88.9%)
Follow-up months (range)	49 (3–49)
Median survival (months)	14.0
Mean survival (months)	15.34 ± 9.63
3-month survival rate	98.0%
6-month survival rate	85.6%
9-month survival rate	70.5%
12-month survival rate	55.5%
18-month survival rate	22.8%
24-month survival rate	15.6%
32-month survival rate	5.8%
Recurrence	
Tumor recurrence, n	115 (75.2%)
progression-free survival (median)	7.1

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; CCNU, lomustine; KPS, Karnofsky Performance Status; TMZ, temozolomide.

Neural Network Analysis

The variables with the greatest impact on the survival rate of the included patients were considered for the neural network analysis (input variables for the outcome of survival: age, occipital lobe involvement, KPS, operative method and the use of CCNU and TMZ). We found the importance of the variables to predict survival in the following declining order: KPS = 30.6%, operative method = 20.4%, TMZ = 17.0%, CCNU = 15.0%, age = 13.5%, and occipital lobe involvement = 3.6% (►**Fig. 1**). In this model, four hidden layers and one bias neuron were germane to the calculation.

Factors Independently Associated with Local Recurrence

Univariate Analysis

Out of the 153 patients, 115 (75.2%) had one local recurrence. We analyzed the factors associated with local recurrence using the Kaplan-Meier analysis that defined time as progression-free survival, and status as occurrence of local recurrence. We found that CCNU ($p < 0.001$), TMZ ($p = 0.003$), chemotherapy versus resection ($p < 0.001$), operative method ($p = 0.016$) and KPS ($p < 0.001$) were each associated with local recurrence.

Multivariate Analysis

We identified the factors associated with local recurrence using the Cox regression model analysis that defined time as progression-free survival and status as occurrence of local recurrence. All variables associated with survival in the univariate analysis ($p < 0.10$), as well as the clinically important variables,

Table 2 Case control matching

Categorization of the patients	
Study population → $N = 153$	
Groups:	N (percent)
Age groups (two categories)	
• Age ≥ 70	28 (18.3%)
• Age < 70	125 (81.7%)
Age groups (three categories)	
• Age ≥ 70	28 (18.3%)
• 70 > Age ≥ 45	87 (56.9%)
• Age < 45	38 (24.8%)
Survival	
• More than 14 months	77 (50.3%)
• Less than 14 months	76 (49.7%)
TMZ versus without TMZ	
• Radiotherapy + resection + TMZ	28 (18.3%)
• Radiotherapy + resection	42 (27.5%)
TMZ	
• Using TMZ	39 (25.5%)
• Not using TMZ	114 (74.5%)
CCNU versus without CCNU	
• Radiotherapy + resection + CCNU	21 (13.7%)
• Radiotherapy + resection	42 (27.5%)
CCNU	
• Using CCNU	36(23.5%)
• Not using CCNU	117(76.5%)
TMZ versus CCNU	
• Radiotherapy + resection + TMZ	28 (18.3%)
• Radiotherapy + resection + CCNU	21 (13.7%)
Adjuvant versus concurrent chemotherapy	
• Radiotherapy + resection + adjuvant	33 (21.6%)
• Radiotherapy+resection + concurrent+ adjuvant	16 (10.5%)
Resection versus chemotherapy	
• Radiotherapy + resection	42 (27.5%)
• Radiotherapy + biopsy + chemotherapy	26 (17.0%)
Resection versus without resection	
• Radiotherapy + chemotherapy + resection	49 (32.0%)
• Radiotherapy + chemotherapy + biopsy	26 (17.0%)
Resection	
• Radiotherapy + resection	42 (27.5%)
• Radiotherapy + biopsy	34 (22.2%)

Abbreviations: CCNU, lomustine; TMZ, temozolomide.

were included in the multivariate proportional hazards regression model. We found that the operative method (HR [95% CI], 0.493 [0.30–0.80], $p = 0.005$), CCNU (HR [95% CI], 2.047 [1.27–3.29], $p = 0.003$), resection versus chemotherapy (HR [95% CI], 0.171 [0.08–0.33], $p < 0.001$) and KPS (HR [95% CI], 7.29 [4.77–11.12], $p < 0.001$) as significant risk factors for local recurrence (►**Table 4**). Interestingly, TMZ (HR [95% CI], 1.394 [0.75–2.58], $p = 0.292$) was not a significant predictor of local recurrence.

Neural Network Analysis

Significant variables from the multivariate model of local recurrence were included as input variables in the neural network analysis (input variables: KPS, operative method and the use of CCNU and TMZ). Subsequently, we found the importance of the variables to predict local recurrence in the following decreasing order: KPS = 41.5%, operative method = 21.8%, TMZ = 21.5%, and CCNU = 15.2% (►**Fig. 2**). In this model, four hidden layers and one bias neuron were generated.

Discussion

The Karnofsky Performance Status (KPS) scale was the most important factor associated with decreasing survival in this study (►**Fig. 3**). We categorized the patients in four groups for KPS. The first group was composed of patients with KPS > 60. The second group comprised patients with KPS = 60. The third group included patients with 40 ≤ KPS < 60. The fourth group featured patients with KPS < 40. It is interesting that survival decreased equiponderant with the decreasing KPS scores. Among all four groups, there is a statistically significant correlation ($p = 0.000$) between the KPS scores and decreased survival. Many studies have verified that a lower KPS score has a correlation with decreasing survival in GBM patients.[27–31] Abdullah Kalil et al conducted a study on factors associated with increased survival after surgical resection on GBM patients of more than 80 years of age in which they found a statistically significant correlation between the KPS and overall survival.[30] In another study, Chaichana et al considered preoperative factors associated with decreased survival for older patients who underwent resection of a GBM, and found that one of the preoperative factors that was independently associated with decreased survival was a KPS score of less than 80.[31] Chaichana et al, in another study, evaluated functional outcomes over time for patients with glioblastoma, and found that a preoperative KPS score of ≥ 90 is associated with a prolonged functional outcome. Their findings may help guide treatment strategies aimed at improving the quality of life of patients with glioblastoma.[32] The KPS was not statistically important in correlations with local recurrence in this study. Therefore, it seems that the KPS has a greater impact on quantity of life than on quality of life.

Age was another important factor associated with decreased survival in our study. We assessed the age effect on survival in two different ways. Initially, we found that the cut-off point for age in this study was 70 years. Patients with more than 70 years of age had significantly lower survival

Table 3 Univariate analysis of the pre- peri- and postoperative characteristics of the patients using the Kaplan-Meier analysis

Group:	A	B	C	D
Time: Status:	Overall survival Recurrence: No	Overall survival Recurrence: Yes	Overall survival Dead	Progression-free survival Recurrence: Yes
Age groups (two categories)	No# ($p = 0.532$)	Yes* ($p = 0.027$)	Yes ($p = 0.009$)	No ($p = 0.738$)
Age groups (three categories)	No ($p = 0.066$)	No ($p = 0.060$)	Yes ($p = 0.005$)	No ($p = 0.731$)
Motor deficit	No ($p = 0.300$)	No ($p = 0.910$)	No ($p = 0.584$)	No ($p = 0.052$)
Confusion and/or memory loss	Yes ($p < 0.001$)	No ($p = 0.222$)	No ($p = 0.307$)	No ($p = 0.855$)
Seizure	No ($p = 0.414$)	No ($p = 0.403$)	No ($p = 0.135$)	No ($p = 0.089$)
CCNU	No ($p = 0.114$)	No ($p = 0.108$)	No ($p = 0.144$)	Yes ($p < 0.001$)
TMZ	No ($p = 0.450$)	Yes ($p < 0.001$)	Yes (P <**0.001**)	Yes ($p = 0.003$)
Resection versus biopsy	No ($p = 0.085$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)
Resection versus chemotherapy	No ($p = 0.827$)	No ($p = 0.211$)	No ($p = 0.171$)	Yes ($p < 0.001$)
Resection versus without resection	No ($p = 0.306$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes ($p = 0.030$)
TMZ versus CCNU	No ($p = 0.249$)	Yes ($p = 0.007$)	No ($p = 0.315$)	No ($p = 0.935$)
CCNU versus without CCNU	No ($p = 0.237$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes ($p = 0.001$)
TMZ versus without TMZ	No ($p = 0.339$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes ($p = 0.003$)
Occipital lobe	No ($p = 0.053$)	No ($p = 0.067$)	No ($p = 0.685$)	No ($p = 0.468$)
Frontal lobe	No ($p = 0.051$)	Yes ($p = 0.009$)	Yes ($p = 0.034$)	No ($p = 0.912$)
Operative method	No ($p = 0.056$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes ($p = 0.016$)
KPS	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)
2D versus 3D radiation	Yes ($p < 0.001$)	Yes ($p = 0.004$)	No ($p = 0.547$)	–
Chemotherapy plan	No ($p = 0.090$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)	Yes ($p < 0.001$)
Recurrence	–	–	Yes ($p < 0.001$)	–

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; CCNU, lomustine; KPS, Karnofsky Performance Status; TMZ, temozolomide.
Notes: A: Time defined as overall survival and status defined as no tumor recurrence.
B: Time defined as overall survival and status defined as tumor recurrence.
C: Time defined as overall survival and status defined as death.
D: Time defined as progression-free survival and status defined as tumor recurrence.
*Yes means there is a significant correlation between an obvious factor and survival or recurrence.
#No means there is not a significant correlation between an obvious factor and survival or recurrence.

rates. Since the presence of other comorbidities in old age is more common, we assessed the correlation between age groups (age ≤ 45, $45 < \text{age} \leq 70$, age > 70) and survival. We found that there is a correlation between age and survival. Age and preoperative neurological function are the two factors most consistently associated with survival in several studies;[1,31–33] however, we could not find any correlation between age and local recurrence.

Chemotherapy, in the present study, was shown to decrease local recurrence and improve survival. Chemotherapy plans (radiotherapy alone versus radiotherapy + adjuvant chemotherapy versus radiotherapy + concurrent chemotherapy) cause a demonstrable statistically significant decrease in local recurrence ($p < 0.001$). Also, patients who received CCNU and TMZ had significant lower local recurrence rates and higher overall survival rates versus patients to whom CCNU or TMZ was not administered (►**Fig. 3A** and **B**). We compare two groups of patients: those who underwent radiotherapy + chemotherapy + biopsy versus the group of patients who underwent radiotherapy + resection. The interesting and important thing here is that chemotherapy was significantly more effective than resection in decreasing the local recurrence rate. Moreover, chemotherapy was effective on prolonging the overall survival. However, when we compared the efficacy of the TMZ versus the CCNU, for the first time, we found that patients who used TMZ had a higher overall survival than patients who used CCNU ($p = 0.007$). Johnson et al assessed the glioblastoma survival in the United States before and during the TMZ era.[34] They found that amongst patients treated with surgery and a radiation-containing regimen, the median survival rate was of 12.0 months during the period without TMZ against 14.2 months in the TMZ era. The survival of patients with newly diagnosed glioblastomas improved from one period to the other, likely due to the use of TMZ. In a recent experimental study, Harvey et al assessed the anticancer properties of CCNU in glioblastoma cell lines, and found that the combination of docosahexaenoic acid (DHA) and CCNU strongly induced Uppsala 87 malignant glioma (U87-MG0 apoptosis and necrosis as indicated by flow cytometric analysis.[35] They suggested a potential role for a

Table 4 Multivariate analysis of the factors associated with overall survival and local recurrence using the Cox regression models

Group:	A	B	C
Time: Status:	Overall survival Recurrence	Overall survival Death	Progression-free survival Recurrence
	Hazard Ratio (94% CI) *p-value*	*Hazard Ratio (95% CI)* *p-value*	*Hazard Ratio (95% CI)* *p-value*
Age groups (two categories)	2.939 (1.73–4.99) $p < 0.001$	3.081 (1.89–5.01) $p < 0.001$	–
TMZ	11.723 (5.46–25.13) $p < 0.001$	4.906 (2.51–9.56) $p < 0.001$	1.394 (0.75–2.58) $p = 0.292$
CCNU	8.139 (4.04–16.38) $p < 0.001$	4.155 (2.19–7.86) $p < 0.001$	2.047 (1.27–3.29) $p = 0.003$
Operative method	7.416 (3.81–14.42) $p < 0.001$	3.880 (2.00–7.50) $p < 0.001$	0.493 (0.30–0.80) $p = 0.005$
KPS	4.831 (3.00–7.77) $p < 0.001$	6.078 (3.85–9.57) $p < 0.001$	7.292 (4.77–11.12) $p < 0.001$
Occipital lobe	3.088 (1.81–5.25) $p < 0.001$	1.599 (0.95–2.69) $p = 0.077$	–
Resection versus chemotherapy	–	–	0.171 (0.08–0.33) $p < 0.001$

Abbreviations: 95% CI, 95% conficence interval; CCNU, lomustine; KPS, Karnofsky Performance Status; TMZ, temozolomide.
Notes: A: Time defined as overall survival and status defined as tumor recurrence.
B: Time defined as overall survival and status defined as death.
C: Time defined as progression-free survival and status defined as tumor recurrence.

combination therapy of CCNU and DHA for the treatment of glioblastomas. Other studies recommended using CCNU for recurrent GBMs.[36–38]

Among our patients, we found that if local recurrence did not occur, the patients experienced a higher overall survival time. This suggests the necessity of effective treatments to prevent local recurrence, leading to increasing survival rates.

The role of resection in prolonging survival in our patients appeared in the univariate and multivariate analyses (►**Fig. 3C**). The operative method had a statistically important role in increasing survival and decreasing local recurrence. Additionally, we compared patients in two groups: radiotherapy + resection versus radiotherapy + biopsy.

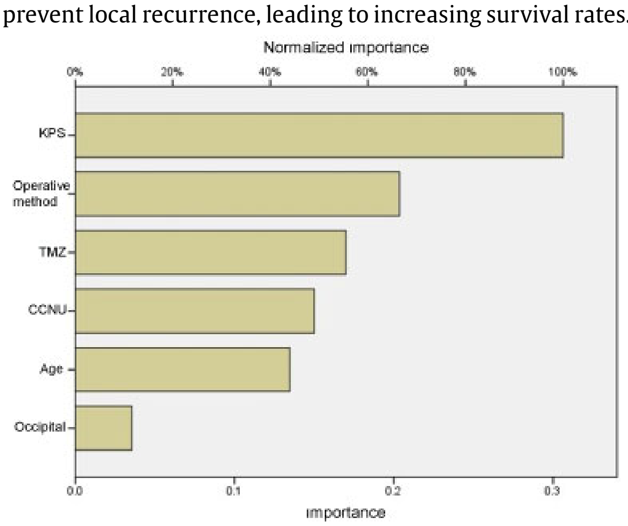

Fig. 1 Result of neural network analysis for predicting survival. The input variables are those that had an impact on survival on the multivariate analysis from Cox regression model analysis. We found the importance of the variables to predict survival as follows: KPS = 30.6%, operative method = 20.4%, TMZ = 17.0%, CCNU = 15.0%, age = 13.5%, and occipital lobe involvement = 3.6%. In this model, four hidden layers were included in the calculation.

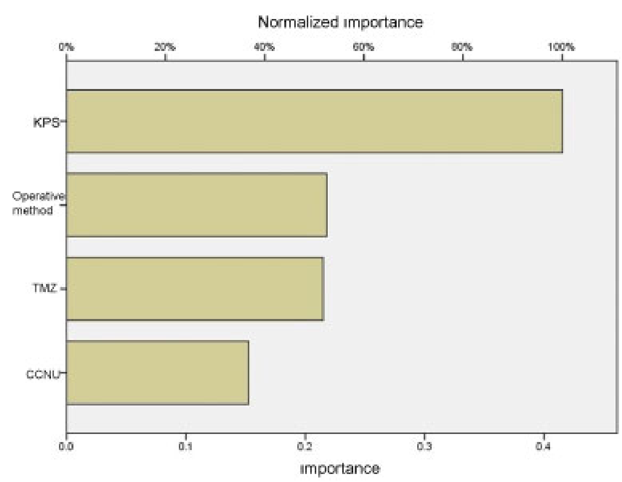

Fig. 2 Result of neural network analysis for predicting local recurrence. The input variables are those that had an impact on local recurrence on the multivariate analysis. We found the importance of the variables to predict local recurrence as follows: KPS = 41.5%, operative method = 21.8%, TMZ = 21.5%, and CCNU = 15.2%. In this model, four hidden layers were included in the calculation.

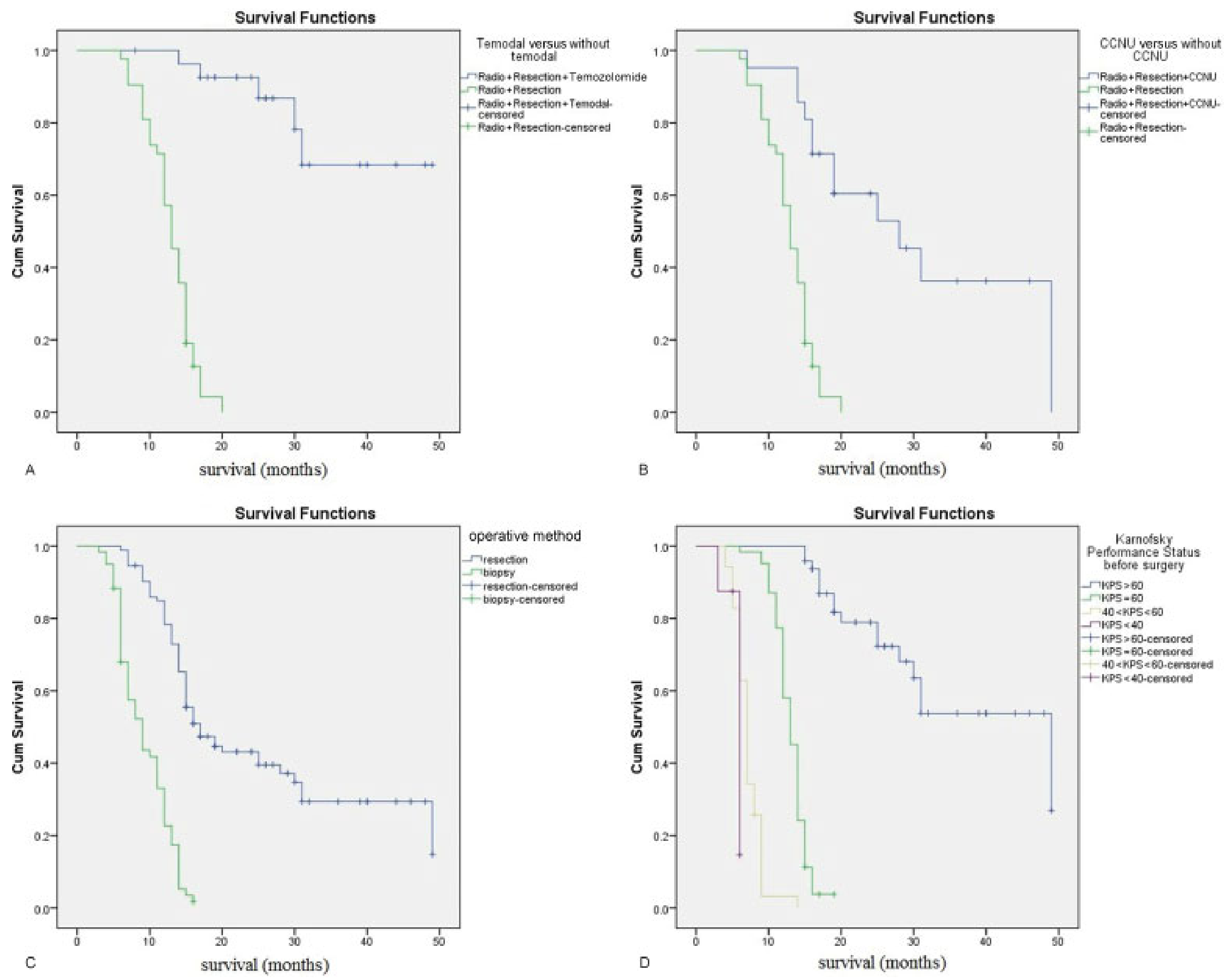

Fig. 3 (**A**) Kaplan-Meier curve suggesting the TMZ effect on overall survival ($p < 0.001$). (**B**) Kaplan-Meier curves suggesting the CCNU effect on overall survival ($p < 0.001$). (**C**) Kaplan-Meier curves suggesting the resection effect on overall survival ($p < 0.001$). (**D**) Kaplan-Meier curves for the overall survival of four groups of patients. The first group of patients had a KPS score > 60, the second group had a KPS score $= 60$, the third group had scores $40 \leq$ KPS < 60, and the last group had a KPS score < 40. There was a statistically significant difference ($p < 0.001$) among the four groups.

Patients who underwent radiotherapy + resection had higher survival and lower recurrence rates than the biopsy group. This observation clearly defined the important role of resection in prolonging survival among patients with poor prognoses, especially those with advanced ages. Chaichana et al assessed the factors associated with survival for 100 patients with glioblastomas with KPS scores ≤ 60.[39] They found that the factors associated with improved survival were age < 65 years, tumor size > 2 cm, radical tumor resection, and TMZ. Chaichana et al, in another study, assessed the effect of multiple resections on prolonging survival in 578 patients with GBM.[19] In their study 354, 168, 41, and 15 patients underwent 1, 2, 3, or 4 resections respectively. The median survival rate for patients who underwent 1, 2, 3, and 4 resections was of 6.8, 15.5, 22.4, and 26.6 months respectively, and that was statistically significant. Finally, they concluded that patients with recurrent glioblastomas can have improved survival rates with repeated resections.

Poor neurologic status before surgery was another factor associated with decreased survival and increasing local recurrence in our series. We found that confusion and/or memory loss will decrease survival, while motor deficit will probably increase local recurrence. In a different study, various neurologic signs have shown to decrease survival and increase local recurrence rates.[31,40–42] We designed a neural network analysis to predict the factors associated with decreasing survival, which we also found in the multivariate analysis, and the factors associated with local recurrence. The KPS was the most important factor to predict survival and local recurrence. We found the importance of each factor in predicting survival and local recurrence; however, future studies with larger sample sizes are recommended.

Strengths and Limitations

We believe that this study provides several useful insights to identify the factors associated with survival and local recurrence in patients with GBM. Firstly, the importance of quantity and quality of life in GBM is equal, and maybe quality of life is preferred, because of the overall short-term survival of the patients. There are many important factors associated with survival and local recurrence. The factors that are reversible are most important because they are the most effective at changing the fate of the patients.

This study confirms the associations of age, confusion and/or memory loss, CCNU, TMZ, KPS, operative method, TMZ versus CCNU, 2D versus 3D radiation and frontal lobe involvement in survival. It also confirms the association of CCNU, TMZ, chemotherapy versus resection, operative method and KPS with local recurrence. This study also confirmed that CCNU, TMZ, operative method and KPS are the factors associated with both survival and local recurrence.

Secondly, studies applying preoperative risk factors in a manner that provides useful prognostic information have yet to be established, both for survival and local recurrence. Lastly, this study provides a potentially useful guide that may prognosticate which GBM patients may benefit from chemotherapy as opposed to radiotherapy and resection. This means that the aggressive treatment is accompanied by higher survival and lower local recurrence rates.

This study, however, has some limitations. Firstly, the sample size is not large. A significantly larger sample size with exact sub-groups will allow a better analysis, especially for achieving neural network analysis. Secondly, we could not procure some necessary data from the records, perhaps most importantly the size of each tumor. Other MRI was missed in this study. Thirdly, some patients did not receive the full treatment, such as undergoing surgery and/or chemotherapy, because the treatments were cost-prohibitive. This study also does not account for the potential implication of molecular markers and genotypes, which may be associated with survival. Recent studies on GBM patients defined that O6-methylguanine–DNA methyltransferase (MGMT) promoter methylation leads to prolonged survival after TMZ and radiation therapy compared with patients without this molecular marker.[43] Additionally, Sanson et al indicated that isocitrate dehydrogenase 1 (IDH1) codon 132 mutation is closely linked to the genomic profile of the tumor, and constitutes an important prognostic marker in grade 2 to 4 gliomas.[44] These molecular markers, and perhaps other markers associated with survival, were not analyzed in this study. Additionally, this study was unable to evaluate the other prognostic factors associated with survival, such as marital status[45] and presence of a caregiver,[46] which have been found in other studies, because these were not consistently recorded in our patient records. Finally, this study is naturally limited because of its retrospective design, and, as a result, it is not appropriate to infer direct causal relationships. Furthermore, we performed multivariate and neural network analyses, and controlled for potential confounding variables. Given these statistical controls and a relatively precise outcome measure, we believe that our findings offer useful insights for the treatment of patients with primary GBM. Prospective studies with huge sample sizes are needed to provide better data to guide clinical decision making.

Conclusion

Almost all of the patients with GBM will benefit from aggressive therapy, including radiotherapy, chemotherapy and resection. We cannot guarantee the patients' survival or guarantee non-recurrence, but it is certain that patients with GBM should be managed with an effective therapy to reach two goals: higher survival and zero recurrence rates. These two goals will guarantee better quality and quantity of life for these patients. In this study CCNU, TMZ, operative method and KPS appear as factors associated with both increasing survival and decreasing local recurrence rates. A prospective study with a global partnership and a larger sample size is recommended for the future.

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