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Original Scientific Paper

FACTORS AFFECTING OUTCOME IN THE TREATMENT OF GLIOBLASTOMA

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SUMMARY – Treatment of glioblastoma is challenging due to its aggressive and highly invasive nature, and no significant advances in survival have been achieved recently. The aim of our retrospective study was identification of predictive factors and consequent survival outcome in patients who underwent surgical and oncologic treatment of glioblastoma. The study was conducted at the Department of Neurosurgery, Osijek University Hospital Centre. The authors designed a retrospective cohort study in 63 patients who underwent surgical and oncologic treatment between January 1, 2012 and December 31, 2017. Data were collected by reviewing medical records of the patients with histologically proven glioblastoma. Statistical analysis of study results revealed a significant impact of postoperative radiotherapy (p=0.002) and chemotherapy (p=0.016) on progression-free survival and overall survival (p=0.001 and p=0.009, respectively). Postoperative Karnofsky performance scale (p=0.027) was found to be significant in progression-free survival, and so was the interval between surgery and commencement of oncologic therapy (p=0.049). In conclusion, overall survival and prognosis in the treatment of glioblastoma remain poor, although prompt approach in postoperative adjuvant treatments improved progression-free survival.

Key words: *Brain neoplasms; Glioblastoma; Radiotherapy; Temozolomide; Procarbazine*

Introduction

Treatment of glioblastoma (GB) is a major challenge due to its aggressiveness and highly invasive nature, which prevents complete resection of the tumor and results in significant neurological morbidity and mortality[1,2]. Clinical presentation in patients with glioblastoma multiforme (GBM) is defined by three possible mechanisms, i.e. direct effect of tumor necrosis, which results in symptoms according to the affected region of the brain; secondary effect is described as a result of tumor growth and its surrounding edema, which results in increased intracranial pressure and brain shifting; third mechanism is defined upon tumor location resulting in focal onsets, therefore clinical

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presentation in GB patients is closely related to the stage and location of the tumor[3-5]. Standard treatment protocol includes maximal tumor resection followed by radiotherapy and chemotherapy; however, the prognosis remains extremely poor despite some advances in diagnosis and treatment[6]. According to its nature, the median survival of GB patients is up to 15 months and it remains important to investigate prognostic factors of the disease in order to improve overall survival of patients[7,8]. Several prognostic factors have been established in recent years such as age, Karnofsky performance status (KPS), and location of the tumor[9,10].

Besides the aforementioned factors, expression of methylguanine methyl transferase (MGMT) plays a major role in the treatment of glioblastoma. Temozolomide (TMZ) was introduced in 2005 as a new chemotherapeutic agent and as part of tri-modality treatment; neurosurgical and oncologic treatment consists of maximal surgical tumor reduction and concomitant chemo- and radiotherapy according to Stupp protocol. Stupp *et al*. found better overall survival (OS) in patients who underwent combined therapy regardless of MGMT, but significant advantage of progression-free survival (PFS) was found in patients with the methylated form compared to unmethylated gene[8]. MGMT is a major DNA repair protein that protects tumor cells against methylating chemotherapeutic agents[11]. According to health care system in the Republic of Croatia, TMZ has been granted as adjuvant chemotherapy since 2006.

In this study, the authors aimed to evaluate the effect of prognostic factors in GB patients having undergone surgical resection and oncologic treatment according to Stupp protocol at Osijek University Hospital Centre, Osijek, Croatia. The aim of our study was to estimate predictive factors in the preoperative and postoperative treatment period of GB, such as demographic data, extent of resection, performance status, and oncologic treatment.

Patients and Methods

We performed a retrospective cohort study in 63 patients who underwent surgical and oncologic treatment for histologically confirmed GB. The study was conducted during a five-year period, from January 1, 2012 until December 31, 2017 at Osijek University Hospital Centre, Osijek, Croatia. Patients were treated by a tri-modality protocol, which consisted of neurosurgical treatment and concomitant oncologic treatment at a single hospital center. Surgical treatment was performed in a regular fashion, i.e. general anesthesia and tumor removal. The extent of tumor removal depended primarily on the size of tumor and its location. The extent of tumor resection was described as gross total resection (GTR), subtotal resection (SR), partial resection (PR), and biopsy. Patients underwent oncologic treatment according to propositions of radiologic treatment, which included three-dimensional conformal radiotherapy with a median dose of 60 Gy. Supplementary oncologic treatment according to Stupp protocol with oral alkylating agent temozolomide was performed according to the patient postoperative clinical status based on predictive factors, i.e. KPS and Eastern Cooperative Oncology Group (ECOG) score. Besides TMZ, procarbazine, lomustine and vincristine (PCV), and nitrosourea (BCNU/CCNU) were administered as oncologic treatment. Study analysis also included assessment of factors such as gender, age, preoperative and postoperative Karnofsky performance status and ECOG, location of tumor, extent of resection (EOR), progression-free survival, and overall survival. The study was approved by the institutional Ethics Committee. The cohort sample was composed of adult patients operated on from January 1, 2012 until December 31, 2017 at a single institution. Patient database was assembled from archival documents at the Department of Neurosurgery and Department of Oncology, and also collected from the hospital electronic database. Stupp protocol was introduced as adjuvant BG treatment at the Osijek University Hospital Centre in 2012.

Statistical analysis

Data were analyzed using the SPSS 21.0 software package. Data were expressed as mean ± standard deviation or frequencies (%), as appropriate. We calculated the probability of progression-free survival and overall survival by using Kaplan-Meier curves. Univariate and multivariate Cox regression analyses were used to test the predictive potential of the selected factors with two outcomes, progression-free survival and overall survival. All $p<0.05$ values acquired from the long rank test were considered statistically significant.

Results

Demographic and clinical characteristics of patients are presented in Table 1. The patient mean age was 66.7±8.5 years. A slight male predominance was noted; there were 37 (58.7%) male patients and 26 (41.3%) female patients. The most common sites of single lobe tumor location in our study were frontal and parietal lobes. Most commonly, the presented type of tumor occupied two cerebral lobes (57.6%). Cox hazard regression analysis of overall survival revealed preoperative ECOG (p=0.029) and postoperative Karnofsky score (p=0.002) to be statistically significant in overall survival analysis (Table 2). Alongside Karnofsky score, younger age (p=0.025) was a significant predictor in progression-free survival analysis (Table 3). As expected, postoperative oncologic treatment also had a significant role in OS and PFS Cox hazard analyses (Tables 2 and 3). Besides, an indicative result was observed in Cox hazard regression on PFS in the interval between surgery and postoperative treatment (p=0.049) (Table 3). Cox hazard regression analysis of overall survival presented in Table 2 revealed better outcome in the group of patients treated with PCV (p=0.035). It was used in only seven (11.7%) patients, mostly as additional treatment after TMZ. Nevertheless, this number was statistically irrelevant and these patients had already received TMZ; better survival in this group might be possibly explained by positive MGMT promoter.

Table 1. Demographic and clinical data on patients with glioblastoma multiforme

Variable	n	%
Gender:		
male	37	58.7
female	26	41.3
Age group (years):		
≤65	28	44.4
≥66	35	55.6
ECOG performance status (preoperative)		
0	4	7.1
1	30	53.6
2	20	35.7
3	2	3.6
Karnofsky index (preoperative)		
50	2	3.6
60	0	0.0
70	20	35.7
80	18	32.1
90	12	21.4
100	4	7.1
Tumor location:		
one lobe only	21	35.6
two lobes	34	57.6
multicentric	4	6.8
Type of surgery (resection):		
complete	11	18.6
subtotal	37	62.7
partial	11	18.6
Karnofsky index (postoperative):		
50	3	6.4
60	0	0.0
70	16	34.0
80	18	38.3
90	8	17.0
100	2	4.3
Postoperative treatment:		
radiotherapy	52	82.5
chemotherapy	44	73.3
Type of chemotherapeutic agents:		
temozolomide	39	65.0
alkylating nitrosourea compounds (CCNU, BCNU)	8	13.3
PCV	7	11.7

ECOG = Eastern Cooperative Oncology Group score; CCNU = lomustine; BCNU = carmustine; PCV = procarbazine, lomustine, vincristine

Discussion

The authors conducted a single-center retrospective study during a five-year period. GB is the most malignant form of glial tumors with the highest mortality rate despite modern possibilities of treatment. Due to the high invasiveness of GBM, radical tumor resection is not considered curative, although it remains the primary goal of surgical treatment[12].

In 2005, Stupp *et al*. introduced a new therapy according to their study that included treatment with TMZ along with radiotherapy. The median survival changed significantly in 2-year and 5-year rates, but despite multidisciplinary treatments the median survival was only 14.6 months in GBM patients[8].

Treatment of GBM depends on many patient-related and disease-related factors which define the outcome of treatment[13]. These factors include age, gender, performance status (ECOG and Karnofsky), extent of

Table 2. Cox hazard regression analysis of overall survival

	Overall survival		
Variable	HR	95% CI	p
Gender	1.012	0.554-1.848	0.969
Age	1.489	0.808-2.744	0.201
Preoperative ECOG performance status	1.731	1.059-2.828	**0.029**
Preoperative Karnofsky index	0.973	0.943-1.004	0.087
Type of surgery (resection)	1.268	0.755-2.130	0.369
Tumor location	1.010	0.819-1.245	0.925
Postoperative Karnofsky index	0.938	0.901-0.977	**0.002**
Postoperative radiotherapy	0.128	0.056-0.293	**0.001**
Postoperative chemotherapy	0.419	0.217-0.807	**0.009**
Temozolomide	0.626	0.333-1.176	0.146
Alkylating nitrosourea compounds (CCNU, BCNU)	0.611	0.218-1.714	0.349
PCV	0.117	0.016-0.857	**0.035**
Interval between surgery and postoperative treatment	0.774	0.381-1.573	0.479

Bold = statistical significance; 95% CI = 95% confidence interval; HR = hazard ratio; p = p value; ECOG = Eastern Cooperative Oncology Group score; CCNU = lomustine; BCNU = carmustine; PCV = procarbazine, lomustine, vincristine

Table 3. Cox hazard regression analysis of progression-free survival

	Progression-free survival		
Variable	HR	95% CI	p
Gender	1.143	0.609-2.143	0.677
Age	0.537	0.312-0.925	**0.025**
Preoperative ECOG performance status	1.095	0.637-1.883	0.743
Preoperative Karnofsky index	0.996	0.963-1.030	0.824
Type of surgery (resection)	1.190	0.707-2.003	0.512
Tumor location	1.048	0.670-1.638	0.838
Postoperative Karnofsky index	0.963	0.930-0.998	**0.037**
Postoperative radiotherapy	0.187	0.065-0.541	**0.002**
Postoperative chemotherapy	0.411	0.199-0.849	**0.016**
Temozolomide	0.644	0.329-1.260	0.198
Alkylating nitrosourea compounds (CCNU, BCNU)	1.089	0.422-2.813	0.860
PCV	0.312	0.095-1.022	0.054
Interval between surgery and postoperative treatment	0.493	0.236-1.000	**0.049**

Bold = statistical significance; 95% CI = 95% confidence interval; HR = hazard ratio; p = p value; ECOG = Eastern Cooperative Oncology Group score; CCNU = lomustine; BCNU = carmustine; PCV = procarbazine, lomustine, vincristine

surgery, tumor location according to brain lobes and postoperative oncologic treatment, and they were thoroughly analyzed in our study. Comparing our study to recently published studies of GB treatment, we did not find any significant disparity in the results of surgical and oncologic treatment.

Overall survival in the treatment of GB remains poor despite recent possibilities of oncologic treat-

ment, i.e. the Stupp protocol. Postoperative treatment and follow-up should be focused on individual patient approach regarding their treatment course. Patients with less promising postoperative improvement should be treated less aggressively to obtain an acceptable quality of life[14]. Prognostic factors included in the treatment of GB should be managed as an algorithm of expected outcome in postoperative treatment; recent studies defined and included KPS, extent of resection and glioma grade as significant predictive markers of OS. The authors did not find any significant differences in PFS and OS according to the extent of tumor removal. Tumor location was defined as one lobe, two lobes, and multicentric tumor infiltration. Slightly better but not significant OS was noted in multicentric tumor invasion. A total of 82.5% of our patients underwent postoperative radiotherapy with a significant impact on PFS and OS outcome. Standardized postoperative radiotherapy included three-dimensional tumor dose of 60 Gy in 30 fractions with the target zone of 2 cm around the lesion. According to retrospective analysis by Álvarez de Eulate-Beramendi *et al*., survival rate in their group of patients was significantly increased with postoperative RT administration[15]. In a recent study, Katsigiannis *et al*. defined a timeframe of 48 postoperative days as being not associated with worsened survival; better results of RT treatment were recorded in shorter postoperative recovery period[16]. Our results also confirmed the necessity of starting RT during the earliest postoperative course. Standardized chemotherapy was applied in 65% of patients in our study, whereas alkylating nitrosourea compounds and PCV treatment were only used as second-line additional treatment in 13.3% and 11.7% of patients, respectively. As expected, Cox hazard analysis showed much better OS when using PCV after standard initial use of TMZ.

A limitation of our study was the impossibility of MGMT promoter methylation analysis at our institution, which would alleviate appropriate usage of TMZ. In a retrospective study conducted by Smrdel *et al.*, OS was significantly longer in the MGMT methylated group. Both PFS and OS were considerably increased in three-fold degree compared to unmethylated group[17]. Nevertheless, even though some limitations persisted, complete surgical resection of GBM is not always expected even if the best possible armamentarium is available. According to these restrictions, more extensive approach and tumor resection were achieved in patients where GBM had clear confinements and was located in a non-dominant brain area. Furthermore, future studies in our institution should be conducted using a wider array of predictive factors such as MGMT. Current limitations of our study did not reveal our results as insufficient and were in concordance with recently published studies, with no significant differences. Prognosis and survival in GB patients will certainly remain a challenge in the future. The modalities of postoperative treatment have not advanced greatly in the past few years.

In conclusion, scoring systems based on predictive factors are helpful in making prompt treatment decisions, even though further developments are needed to obtain a better personalized approach in each patient to achieve better long-term survival.

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Sažetak

PREDIKTIVNI ČIMBENICI U ISHODU LIJEČENJA GLIOBLASTOMA

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Liječenje glioblastoma je izazovno zbog njihove agresivne i vrlo invazivne prirode te u posljednje vrijeme nije postignut značajan napredak u preživljenju. Cilj našega retrospektivnog istraživanja bio je identificirati prediktivne čimbenike i posljedični ishod preživljenja kod bolesnika koji su bili podvrgnuti kirurškom i onkološkom liječenju glioblastoma. Studija je provedena na Klinici za neurokirurgiju Kliničkog bolničkog centra Osijek. Provedena je retrospektivna kohortna studija na 63 bolesnika koji su bili podvrgnuti kirurškom i onkološkom liječenju između 1. siječnja 2012. i 31. prosinca 2017. Podatci su prikupljeni pregledom medicinske dokumentacije bolesnika s histološki dokazanim glioblastomom. Statistička analiza rezultata istraživanja otkrila je značajan utjecaj poslijeoperacijske radioterapije (p=0,002) i kemoterapije (p=0,016) na preživljenje bez progresije bolesti i ukupno preživljenje (p=0,001, p=0,009). Poslijeoperacijska vrijednost na ljestvici Karnofsky (p=0,037) nađena je značajnom za preživljenje bez progresije bolesti, kao i kraći vremenski interval između operacije i početka onkološke terapije (p=0,049). Ukupno preživljenje, kao i prognoza liječenja glioblastoma i dalje su loši, iako pravodobni pristup poslijeoperacijskom adjuvantnom liječenju poboljšava razdoblje preživljenja bez progresije bolesti.

Ključne riječi: *Tumori mozga; Glioblastom; Radioterapija; Temozolomid; Prokarbazin*