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Source / Izvornik: **Acta clinica Croatica, 2019, 58., 221 - 228**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.20471/acc.2019.58.02.04>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:220:578857>

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Download date / Datum preuzimanja: **2024-09-10**



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CHARACTERISTICS OF TREATMENT AND OUTCOME IN ELDERLY PATIENTS WITH BRAIN GLIOBLASTOMA: A RETROSPECTIVE ANALYSIS OF CASE SERIES

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SUMMARY – Treatment modalities affecting quality of life and survival in elderly brain glioblastoma patients are not well defined. A single-institution data were analyzed during a 3-year period to disclose prognostic difference in management related to age. Karnofsky Performance Scale (KPS), overall survival (OS), and adjuvant therapy were evaluated. The case group comprised of elderly patients (>75 years), while the control group included those of younger age (<65 years). The investigated variables were correlated between the groups. Twenty elderly patients and a corresponding number of younger ones were analyzed. Preoperative KPS >70 indicated longer overall survival. Statistically significant correlation was recorded in both the control (p=0.036) and case (p=0.0053) groups. Lower postoperative KPS was significantly correlated with shorter OS in elderly patients (p=0.023). The correlation between the extent of tumor resection and OS was statistically significant in younger patients only (p=0.04). Overall survival was significantly shorter in elderly patients regardless of the extent of tumor resection (p=0.0057). Adjuvant therapy was significantly associated with longer OS in both the case (p=0.032) and control (p=0.013) groups. Elderly population is a more endangered group of surgical brain glioblastoma patients having lower quality of life and shorter overall survival. The management protocol should be personalized for each individual case in this age group of patients to reduce postoperative complications and grant a satisfactory quality of life.

Key words: Elderly patients; Glioblastoma; Management outcome; Prognosis; Treatment modalities

Introduction

Glioblastoma is the most common primary malignant intracranial tumor with the incidence of 4-5/100,000 *per year*^{1,2}. Despite advances in molecular diagnostics and therapy, overall survival (OS) of glioblastoma patients is poor, ranging from 8 to 11 months in many studies for most patients^{3,4}. In elderly patients, standard treatment (surgery-radiotherapy-chemotherapy) is not defined yet and there is little agreement

about the real benefit of specific treatment modalities affecting the quality of life^{5,6}.

Surgery is the first step of treatment of glioblastoma in resectable locations in younger patients, but many elderly patients have a poor clinical outcome without a chance of completing the standard protocol of therapy. Moreover, the selection of patients who may benefit from standard treatment is difficult and no validated stratification tools are currently available. Nevertheless, it appears that elderly patients benefit less from surgery regarding survival and quality of life.

For this purpose, the authors analyzed their institution experience in respect to treatment modalities applied, management outcomes and OS in a series of brain glioblastoma surgical patients aged over 75 years in comparison to younger ones.

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Received January 21, 2019, accepted March 14, 2019

Patients and Methods

We compared clinical and radiological data in 20 elderly patients (≥ 75 years) and 20 younger ones (≤ 65 years) affected by cerebral glioblastoma and operated on at the Department of Neurosurgery, University of Ancona, from January 2012 until January 2015. The groups were matched for clinical variables, surgical outcomes, adjuvant therapy, Karnofsky Performance Scale (KPS) and OS.

All procedures performed in the study were in accordance with ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. An informed consent was obtained from all participants included in the study.

Surgery was indicated for treatment of space-occupying and/or symptomatic tumor lesions. All patients underwent preoperative magnetic resonance imaging (MRI) study and brain computed tomography (CT) scan, which was repeated 24/48 hours after surgery and at 3-6-12-month follow-ups. Baseline demographic and medical data including patient gender and age at admission, major presenting symptoms, tumor location and grade of resection were evaluated. Histopathologic grading according to the World Health Organization (WHO) criteria and molecular markers (MGMT and IDH1/2) were determined from histopathological reports. Surgical resection was categorized as biopsy, subtotal tumor resection (STR) or total tumor macroscopic resection (TTR). Patients with no history of epileptic seizures were treated with prophylactic anticonvulsant therapy preoperatively (levetiracetam 500 mg twice a day for 2-4 weeks). In case of epileptic seizures, therapy was prolonged. To assess the quality of life, KPS was evaluated before surgery, 48 hours after surgery and at 2-month follow-up. Radiotherapy and chemotherapy adjuvant treatment, progression free survival (PFS) and OS were recorded and analyzed.

The PFS was defined as the interval between initial surgery and radiological progression of disease. The OS was defined as the interval between initial surgery and the date of death. The radiotherapy treatment consisted of conventional radiation therapy defined as 50-60 Gy delivered in 20-30 fractions. Chemotherapy protocol included temozolomide, which was administered at a dose of 75 mg/m² daily, followed by six cycles

of 200 mg/m² for 5 days every 4 weeks. All patients were screened for IDH1/2 mutations by direct sequencing, and for promoter status of MGMT gene by the methylation-specific polymerase chain reaction.

All data of elderly patients comprising the case group were compared with data from the control group of patients aged <65. Kaplan-Meier survival curves and univariate logistic regression were used on statistical analysis. The variables with $p < 0.05$ were considered statistically significant. The software used for analysis was the SPSS Version 19 (IBM, Armonk, New York, USA).

Results

From January 2012 until January 2015, we operated on 20 patients aged >75 affected by cerebral glioblastoma (case group) and 20 patients younger than 65 (control group). Baseline characteristics of the entire sample are summarized in Table 1. Univariate logistic regression of preoperative and postoperative variables tested for the entire sample are depicted in Table 2. Univariate logistic regression of preoperative and postoperative variables tested for the case and control groups separately are shown in Table 3.

In the case group consisting of 20 patients, the improvement on KPS 48 hours after surgery was by 10 points in four patients, 20 points in four patients and 30 points in one patient, while KPS was unchanged in seven patients. The KPS values worsened in four out of 20 patients. One patient died one week after surgery due to cardiovascular failure. At 2-month follow-up, systemic complications occurred in three out of 19 patients and KPS worsened in ten (52.6%) patients.

In the control group, median preoperative KPS was 65.2, postoperative 72.5, and 70.5 at 2-month follow-up. No systemic postoperative complications were recorded.

In 12 elderly patients having undergone TTR followed by oncologic standard treatment, the OS was 7.8 months *versus* 6.0 months only in eight patients having undergone STR. In the control group, median survival was 12.0 months in TTR patients and 5.9 months in STR patients. No mortality was documented in the control group.

A preoperative KPS >70 was associated with longer OS in both younger ($p=0.036$) and elderly ($p=0.0053$) patients, which was statistically significant.

Table 1. Baseline characteristics of the entire study sample

Patient characteristic	Case group (elderly) n (%)	Control group (younger) n (%)	p value
Total number of patients	20	20	
Age (years) (mean \pm SD) range	78 (\pm 3.15) 75-85	58.25 (\pm 3.71) 39-65	/
Gender			
Male	8 (40%)	9 (45%)	>0.05
Female	12 (60%)	(55%)	
Tumor location			
Frontal	5 (25%)	7 (35%)	>0.05
Parietal	7 (35%)	5 (25%)	
Temporal	5 (25%)	5 (25%)	
Occipital	3 (15%)	3 (15%)	
Preoperative KPS (mean \pm SD) \geq 70 <70	63 (\pm 8.87) 10 (50%) 10 (50%)	65.23 (\pm 7.57) 9 (45%) 11 (55%)	>0.05
Extent of resection			
TTR	12 (60%)	13 (65%)	>0.05
STR	8 (40%)	7 (35%)	
Adjuvant therapy			
RT + ChT	10 (50%)	15 (75%)	>0.05
RT	2 (10%)	4 (20%)	
None	8 (40%)	1 (5%)	
IDH1/2 mutation			
Yes	0	1 (5%)	>0.05
No	20 (100%)	19 (95%)	
MGMT promoter			
Methylated	7 (35%)	12 (60%)	0.19
Unmethylated	13 (65%)	8 (40%)	

SD = standard deviation; KPS = Karnofsky Performance Scale; TTR = total tumor resection; STR = subtotal tumor resection; RT = radiotherapy; ChT = chemotherapy

The correlation between the extent of tumor resection and OS was statistically significant in the control group of younger patients only ($p=0.04$) (Fig. 1AB). The correlation between postoperative KPS and OS was statistically significant in the case group of elderly patients only ($p=0.023$) (Fig. 2AB).

Table 2. Univariate logistic regression of preoperative and postoperative variables in the entire study sample

Variable	Overall (40 patients)			
	OS (months)	HR	95% CI	p value
Age (years)				
>75	7	2.51	1.48 to 10.3	0.0056
<65	12			
/	/			
Preoperative KPS				
\geq 70	11	0.39	0.09 to 0.66	0.0052
<70	7			
/	/			
Extent of resection				
TTR	9	0.47	0.11 to 0.92	0.034
STR	6			
/	/			
Postoperative KPS				
\geq 70	8.5	0.58	0.16 to 1.3	0.14
<70	7			
Adjuvant therapy				
RT + ChT	10	0.49	0.08 to 0.93	0.0001
RT	7			
None	3			
MGMT promoter				
Methylated	11	0.39	0.09 to 0.66	0.0052
Unmethylated	7			

OS = overall survival; HR = hazard ratio; CI = confidence interval; KPS = Karnofsky Performance Scale; TTR = total tumor resection; STR = subtotal tumor resection; RT = radiotherapy; ChT = chemotherapy

Adjuvant therapy was associated with longer OS in both groups of patients (Table 2). The OS was 7.0 months in the case group of elderly patients and 12.0 months in the control group of younger patients, yielding a statistically significant difference ($p=0.0057$).

Table 3. Univariate logistic regression of preoperative and postoperative variables in case group (elderly, age >75) and control group (younger, age <65)

Variable	Case group (elderly) (20 patients)				Control group (younger) (20 patients)			
	OS (months)	HR	95% CI	p	OS (months)	HR	95% CI	p
Preoperative KPS								
≥70	9				12			
<70	3	0.35	0.059 to 0.77	0.019	7.5	0.39	0.038 to 0.95	0.043
					/			
Extent of resection								
TTR	7.8				12			
STR	6	0.77	0.22 to 2.31	0.57	5.9	0.27	0.08 to 0.75	0.02
	/							
Postoperative KPS								
≥70	8.5				11			
<70	4	0.037	0.05 to 0.81	0.02	8.3	0.42	0.02 to 1.53	0.42
Adjuvant therapy								
RT + ChT	10				12			
RT	8	0.037	0.05 to 0.81	0.005	9			
None	2				3			0.0132
MGMT promoter								
Methylated	10				12.5			
Unmethylated	3	0.51	0.12 to 0.98	0.0001	5	0.39	0.18 to 0.85	0.0001

OS = overall survival; HR = hazard ratio; CI = confidence interval; KPS = Karnofsky Performance Scale; TTR = total tumor resection; STR = subtotal tumor resection; RT = radiotherapy; ChT = chemotherapy

Considering IDH1/2 mutations, they were detected in only one (5%) patient from the control group, whereas none of the case group patients presented with IDH1/2 mutations. Due to the almost complete absence of IDH1/2 mutations in our sample, statistical analysis of correlation between these molecular markers and OS was not possible.

Methylation of the MGMT gene promoter was found in 12 (60%) patients from the control group and seven (35%) patients from the case group. On univariate logistic regression, the OS was significantly longer in patients with methylation of the MGMT promoter in both groups ($p=0.0052$) (Table 2).

Discussion

Glioblastoma (WHO grade IV) is the most common malignant primary brain tumor in adults^{2,7}. Stan-

dard treatment for patients with glioblastoma is surgical resection with adjuvant therapy (radiotherapy and chemotherapy). Due to the presence of comorbidities in elderly patients, the benefit from standard treatment has been questioned^{5,6,8}. Accordingly, many studies have shown an increased postoperative mortality and morbidity in elderly patients⁹. However, the treatment of glioblastoma in elderly patients has become an everyday issue due to prolonged life expectation in the general population.

In this study, the modality and outcomes of treatment of 20 glioblastoma surgical patients aged >75 were evaluated and compared to a younger group of patients (≤ 65 years).

As previously reported in the literature, a statistically significant correlation between preoperative KPS and the length of OS was established regardless of pa-

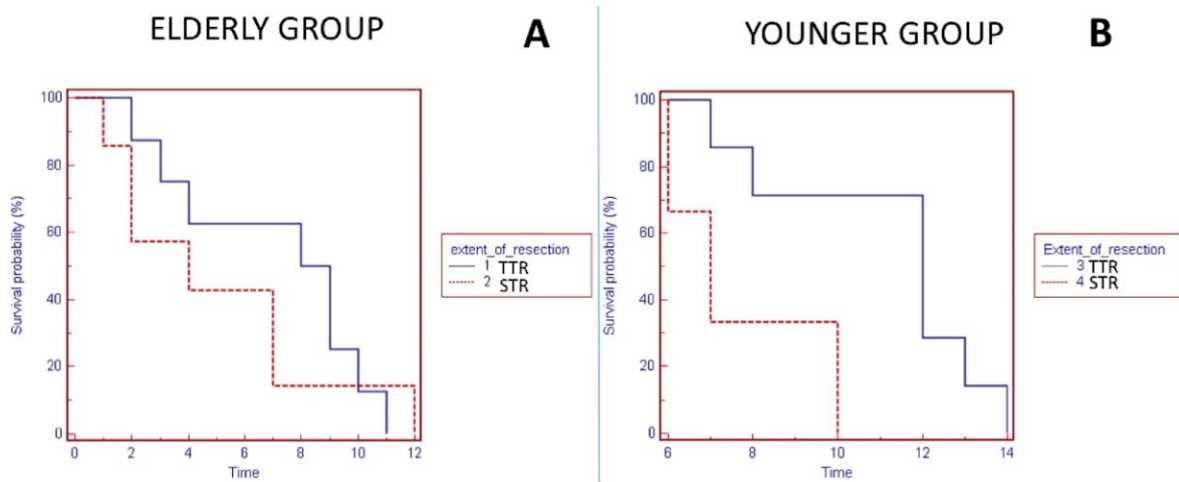


Fig. 1. Kaplan-Meier overall survival (OS) curves demonstrating significantly improved survival in patients having undergone total tumor resection (TTR). Improved survival was only observed in younger patients (B, control group) with subtotal tumor resection (STR) in contrast to elderly ones (A, case group).

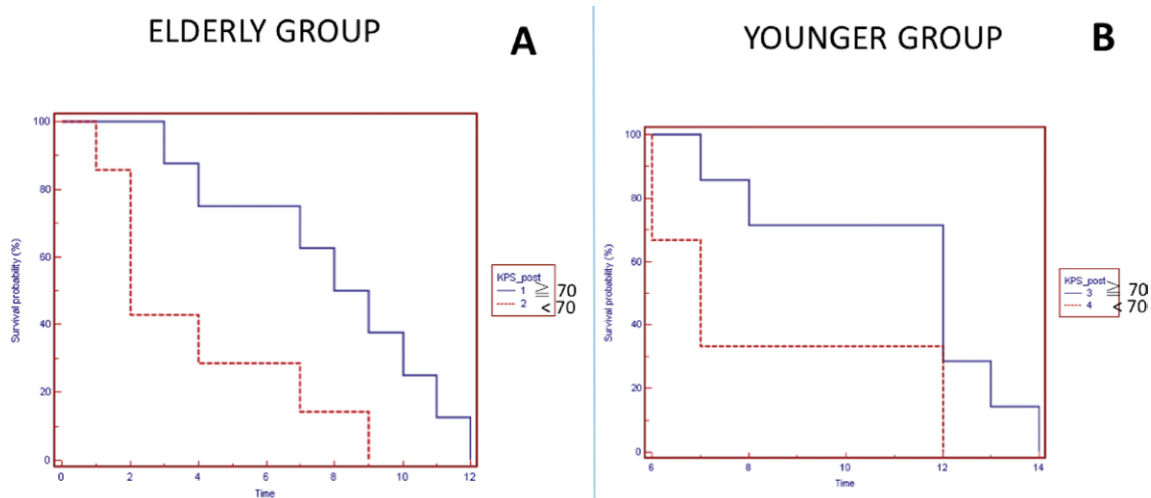


Fig. 2. Kaplan-Meier overall survival (OS) curves demonstrating significantly improved survival in patients with postoperative Karnofsky Performance Scale (KPS) >70 from both groups. Significantly improved survival was observed only in elderly patients (A, case group) with postoperative KPS <70 in contrast to the younger ones (B, control group).

tient age¹⁰. In our series, KPS values at 2-month follow-up were lower than the preoperative ones in more than half (10/19) of elderly patients. On the contrary, KPS values at 2-month follow-up obtained for younger patients were higher than the preoperative ones.

Data analysis showed that postoperative KPS values were significantly correlated to OS in the case group of elderly patients only ($p=0.023$), where postoperative neurological worsening appeared to be criti-

cal. In this group, new deficits were associated with poor quality of life and decreased survival. For these reasons, standard protocols of adjuvant radiotherapy and/or chemotherapy are often denied in such patients¹⁰⁻¹⁴.

In one elderly patient from our series, glioblastoma was asymptomatic and it was diagnosed after a polytrauma with vertebral fracture treated with screws and rods^{15,16}. This patient developed deep vertebral infec-

tion four months after surgery during radiotherapy and chemotherapy treatment, which was cured with broad-spectrum antibiotics eliminating the need of spinal instrumentation removal¹⁷⁻¹⁹.

Several relevant studies demonstrated that advanced age may be associated with poor prognosis in glioblastoma patients^{3,4,20-22}. The same was also observed in our series, where the group of elderly patients had significantly shorter OS when compared to the younger ones ($p=0.0057$).

Although some authors stress the importance of the extent of resection regardless of age¹², we found the extent of tumor resection (total or subtotal) to be significantly correlated with OS in younger patients only ($p=0.04$), whereas in elderly patients this correlation was not statistically significant. Accordingly, it seems that the extent of tumor resection is not an essential prognostic predictor in elderly patients. Since the presence of comorbidities and preservation of good clinical status are more relevant for elderly patients, the extent of tumor resection seems not to be a determining factor influencing OS. Hence, aggressive surgical treatment in elderly patients to achieve TTR is not always proposed, since it bears a high risk of neurological deterioration and/or complications, which in turn may preclude adjuvant therapy and early mobilization, leading to poor outcome. Accordingly, our data suggested that elderly patients who were able to complete standard treatment protocol (surgery, chemotherapy and radiotherapy) showed the best OS. In the light of this finding, minimally invasive treatment options may decrease the post-surgical complication rates²³, and early rehabilitation may help maintain intact neurological status in elderly patients²⁴.

Remembering our results, adjuvant therapy was associated with longer OS in elderly patients, which is consistent with other reports stressing that bimodal adjuvant treatment improves survival in the aging²⁵.

Nowadays, characterization of molecular biomarkers represents an integral part of modern neuro-oncology and can help in the management of glioblastoma patients too. Literature data indicate that IDH mutations, which are associated with secondary glioblastoma, are a consistent prognostic marker in low-grade and high-grade gliomas²⁶⁻²⁸. However, due to the almost complete absence of IDH1/2 mutations in our sample, statistical analysis of the correlation between these molecular markers and survival was not possible.

Another molecular marker investigated in this study was promoter status of the MGMT gene. Our study confirmed that OS was significantly longer in patients with methylation of the MGMT promoter in both groups of patients regardless of their age. Several clinical studies have shown that methylation of the MGMT promoter is a strong and independent prognostic factor associated with prolonged PFS and OS^{27,29-32}. However, this observation was not previously reported for patients over 75 years of age, which may be an original contribution of our study.

In conclusion, remembering the limited number of patients in our series, our results suggest that surgery can be successfully performed in selected glioblastoma patients in spite of their age, in respect to quality of life and OS. However, elderly population is a more endangered group of surgical brain glioblastoma patients having lower quality of life and shorter OS. Careful preoperative stratification, tailored surgical approach and balanced adjuvant therapy are beneficial for recovery and prognosis. Therefore, the management protocol should be personalized for each individual case in this age group of patients to reduce postoperative complications and grant a satisfactory quality of life.

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Sažetak

ZNAČAJKE LIJEČENJA I ISHODA U STARIJIM BOLESNIKA S GLIOBLASTOMOM MOZGA:
RETROSPEKTIVNA ANALIZA NIZA SLUČAJEVA

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Modaliteti liječenja od utjecaja na kvalitetu života i preživljavanje starijih bolesnika s glioblastomom još nisu jasno određeni. Kako bi se utvrdila prognostička razlika u primijenjenim oblicima liječenja u odnosu na dob bolesnika analizirani su podaci dobiveni trogodišnjim istraživanjem uzorka. Istraživani su sljedeći pokazatelji: Karnofskyjeva ljestvica (KPS), vrijeme ukupnog preživljavanja i primjena pomoćnog liječenja. Ogljednu skupinu činili su stariji bolesnici (≥ 75 godina), a kontrolnu skupinu oni mlađe dobi (≤ 65 godina). Međusobno su uspoređivani istraživani parametri iz obje skupine bolesnika. Promatrano je 20 starijih i odgovarajući broj mlađih bolesnika. Prijeoperacijski KPS >70 upućivao je na dulje sveukupno preživljavanje. Statistički značajna korelacija zabilježena je u bolesnika kontrolne ($p=0,036$) i ogledne ($p=0,0053$) skupine. Niže poslijeoperacijske vrijednosti KPS bile su značajno povezane s kraćim vremenom preživljavanja u starijih bolesnika ($p=0,023$). Korelacija između opsežnosti tumorske resekcije i sveukupnog preživljavanja bila je statistički značajna samo u mlađoj dobnoj skupini ($p=0,04$). Vrijeme sveukupnog preživljavanja bilo je značajno kraće u starijih bolesnika neovisno o stupnju kirurške resekcije ($p=0,0057$). Primjena pomoćne terapije bila je značajno povezana s duljim sveukupnim preživljavanjem u oglednoj ($p=0,032$) i kontrolnoj ($p=0,013$) skupini. U zaključku, starija je populacija ugroženija skupina kirurških bolesnika s glioblastomom u kojih je smanjena kvaliteta života i skraćeno vrijeme sveukupnog preživljavanja. Stoga je potrebno protokol liječenja prilagoditi svakom pojedinom bolesniku iz ove dobne skupine kako bi se smanjio udio poslijeoperacijskih komplikacija i poboljšala kvaliteta života.

Ključne riječi: *Glioblastom; Modaliteti liječenja; Prognoza; Stariji bolesnici; Uspješnost liječenja*