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The Impact of Surgery on the Efficacy of Adjuvant Therapy in Glioblastoma Multiforme

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Glioblastoma multiforme (GBM) is the most malignant brain tumor. Surgery still remains a fundamental part of treatment in GBM, followed by radiotherapy and chemotherapy.
Objectives. The aim of the study was to assess the impact of surgery on the efficacy of adjuvant therapy in patients with glioblastoma multiforme.
Material and Methods. The study involved 181 patients: 50 treated with adjuvant radiotherapy (RTH) only (60 Gy in daily 2Gy fractions) and 131 treated with postoperative radiochemotherapy (RTH-CHT) (60 Gy, 2Gy/d) + 75 mg/m^2 temozolomide for 42 days of radiotherapy, followed by 6 courses every 28 days; the first course was 150 mg/m^2 for 1–5 days, and the subsequent courses were 200 mg/m^2 for 1–5 days). Overall survival (OS) and disease-free survival (DFS) were assessed. The statistical analysis entailed the log-rank test, Kaplan-Meier curves and Cox proportional hazards regression; the threshold of statistical significance was set at $p = 0.05$.
Results. Median OS and DFS were significantly increased ($p = 0.001$) in the RTH-CHT group compared with the RTH group: 9.77 months vs 6.38 months for OS, and 8.4 months vs 4.33 months for DFS. After radical surgery, RTH-CHT extended OS by 5.3 months and DFS by 4.5 months in comparison to RTH. In patients who underwent non-radical surgery, the type of adjuvant therapy made no difference in either OS or DFS. In the RTH-CHT group, OS and DFS depended on the extent of the surgery, and were significantly longer in patients who underwent radical surgery (OS: $p = 0.03128$; DFS: $p = 0.01206$). In the RTH group, the type of surgery had no effect on survival.
Conclusions. Radiochemotherapy significantly prolongs OS and DFS compared with radiotherapy alone in GBM patients who have undergone radical removal of the tumor. Among patients who had non-radical surgery, the type of adjuvant treatment has no effect on OS or DFS (**Adv Clin Exp Med 2015, 24, 2, 279–287**).

Key words: glioblastoma multiforme, adjuvant treatment, surgery.

Glioblastoma multiforme (GBM) is a brain tumor with an especially adverse prognosis. Despite the use of modern methods of surgical treatment supplemented with radical postsurgical radiotherapy combined with the administration of temozolomide, the average overall survival time still does not exceed 2 years [1]. The main prognostic factors described in the literature are the patient's age, the patient's general condition, the adjuvant therapy method and the tumor resection margin [2, 3].

According to the most recent studies, the extent of surgery in GBM patients affects not only the patient's neurological condition and the survival time, but also the efficacy of the postsurgical systemic treatment [26]. The published data show that the more radical the surgery is, the more effective postsurgical radiochemotherapy combined with temozolomide will be [27].

The aim of this study was to evaluate and compare the effectiveness of postsurgical radiotherapy and radiochemotherapy as adjuvant treatment of patients with glioblastoma multiforme and the influence of the extent of surgery on the treatment outcome. The prognostic value of such factors as age, general condition, the waiting time for the initiation of adjuvant therapy and the length of time before disease progression or relapse were also evaluated.

Material and Methods

The study involved 181 patients radically treated for GBM at St. John's Cancer Center in Lublin, Poland, from 2004 to 2010. Among them, 50 patients underwent only postsurgical radiotherapy in the years 2004–2006, while 131 patients treated between 2006 and 2010 were treated with radiotherapy combined with temozolomide. The analysis did not include patients with a relapse of GBM who underwent only tumor biopsy or were undergoing palliative treatment (Table 1).

All the patients underwent surgery and the clinical diagnosis of GMB was confirmed by histopathological examination. The evaluation of the extent of surgery was based on the description of the surgery and the results of computer tomography examinations conducted after the surgery; on these bases, the operations were categorized as total or partial resections. Radical radiotherapy was performed on all patients. A total dose of 60 Gy in 30 fractions of 2 Gy was applied. In the course of radiotherapy, the group of 131 patients additionally received 75 mg/m^2 temozolomide daily, 7 days a week, for 42 days commencing from the first day of radiotherapy. Next, upon the completion of radiotherapy, 1 to 6 courses of temozolomide were administered at a dosage of 150 mg/m^2 (1–5 days) in the first course and 200 mg/m^2 (1–5 days) in subsequent courses every 28 days. The number of administered courses depended on the response to treatment. Observed progression or relapse of the neoplasm disqualified patients from further treatment. Almost all the patients were additionally treated, depending on the indications, with decongestants, anti-emetic and anti-convulsant medicines.

Progression or relapse of GBM was diagnosed on the basis of clinical symptoms and confirmed with computer tomography. Tumor relapse was treated surgically or symptomatically. Disease-free survival (DFS) time and overall survival (OS) time were calculated from the beginning of radiotherapy to progression/relapse (DFS) or death (OS). Data concerning the progression/relapse date or time of death were based on medical records and death registries, respectively.

In the first part of the statistical analysis, the differences between OS and DFS were examined using the log-rank test. Kaplan-Meier curves were used to illustrate the differences. The Cox proportional hazards regression model was used to evaluate the influence of quantitative factors on overall survival and disease-free survival, as well as to calculate the relative risk for qualitative variables. The threshold of statistical significance adopted was $p = 0.05$. The statistical analysis of the data was carried out using STATISTICA 8.0 software.

Results

Patients' Characteristics

Both of the groups studied consisted mainly of men of about 50 years of age with a WHO performance level of 1. A significant majority of the patients in the group treated with radiochemotherapy had had radical surgery with total tumor excision, while in the group receiving only radiotherapy most of the patients had undergone only partial tumor excision. The median waiting time for radiotherapy, measured from surgery to the commencement of irradiation, was 7 weeks for the patients undergoing radiotherapy with temozolomide, and 6 weeks for the patients receiving radiotherapy alone. In course of radiotherapy, steroids were administered to most patients (Table 1).

Treatment

In the group that underwent only radiotherapy, the radiation was discontinued in 4 patients (8%) due to disease progression. The applied doses in those 4 patients were 50 Gy, 36 Gy, 48 Gy

Table 1. Patient characteristics

Characteristics	Radiotherapy number of patients (%)	Radiotherapy + temozolomide number of patients (%)
Age		
median	54	52
interval	26–70	28–72
Sex		
men	30 (60)	71 (54)
women	20 (40)	60 (46)
WHO		
0	6 (12)	11 (9)
1	30 (60)	92 (70)
2	14 (28)	28 (21)
Extent of surgery		
partial resection	34 (68)	36 (27.5)
radical resection	16 (32)	95 (72.5)
Surgery to radiotherapy time (weeks)		
median	7.0	6.0
interval	2.1–23.4	0.8–45.8
Steroid usage		
yes	45 (90)	113 (86)
no	5 (10)	18 (14)

and 28 Gy, respectively. In the group of 131 patients, the concurrent radiochemotherapy course was completed by 122 patients (93%) and the full treatment was completed by 64 patients (49%). The reasons for discontinuing radiochemotherapy were disease progression and hematological toxicity of the 3rd or 4th degree due to the administration of temozolomide.

Overall Survival and Disease-Free Survival in the Study Subjects

During follow-up periods lasting from 1 to 26 months all the study subjects died. Both the OS (Fig. 1) and DFS (Fig. 2) of the patients who underwent radiochemotherapy were significantly longer ($p < 0.001$) than in patients who were treated solely with radiotherapy (Table 2).

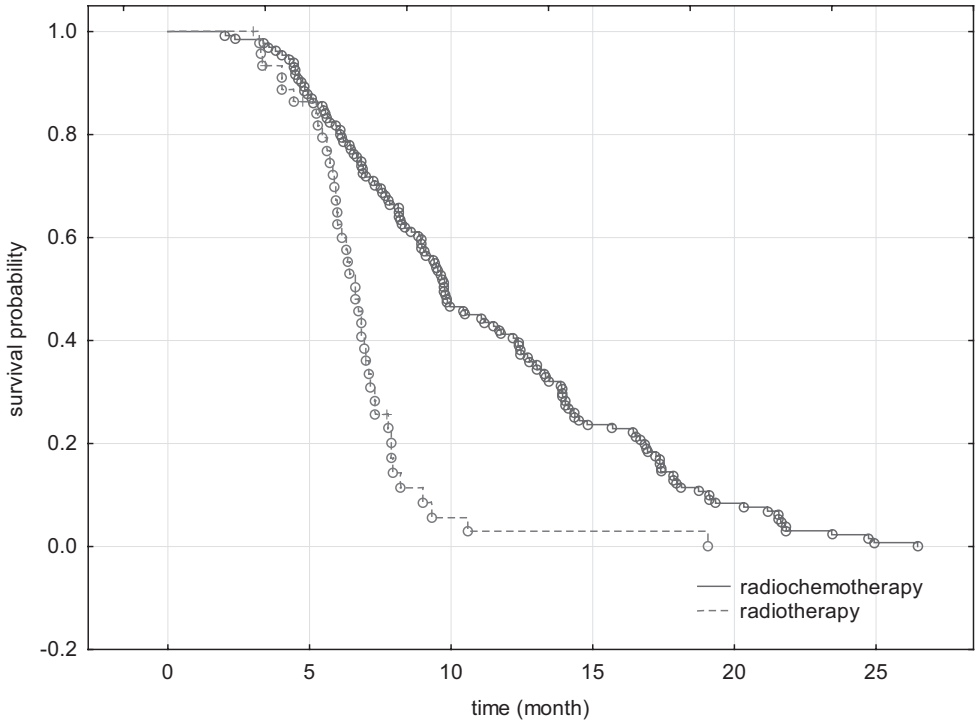

Fig. 1. Kaplan-Maier curve of overall survival in relation to the method of treatment ($p < 0.001$)

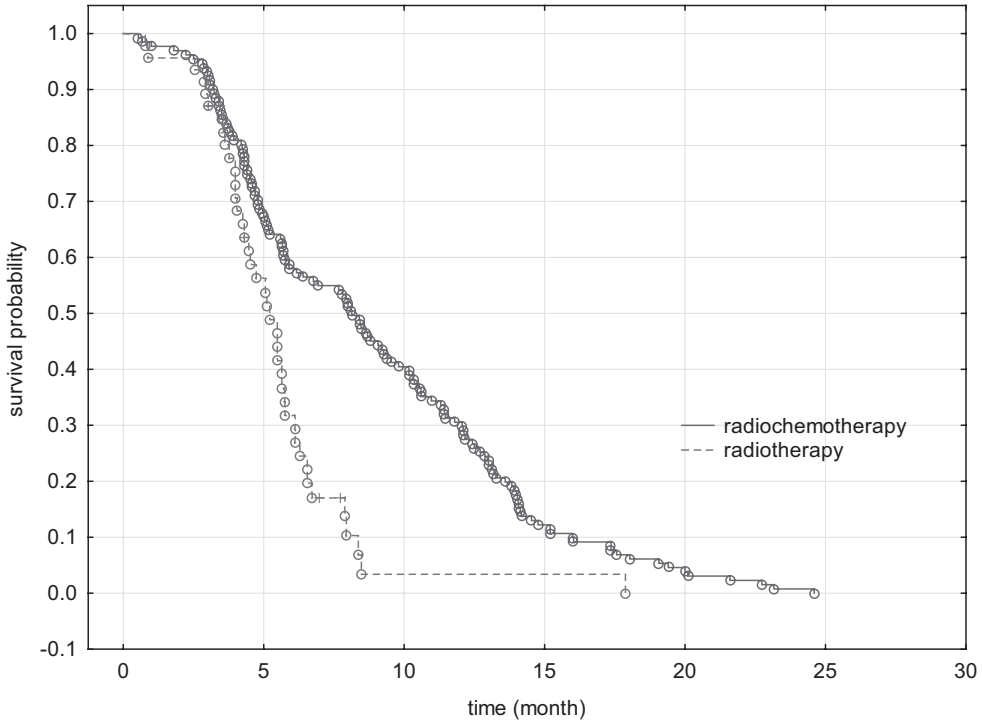

Fig. 2. Kaplan-Maier curve of disease-free survival in relation to the method of treatment ($p < 0.001$)

Table 2. The patients' overall survival and disease-free survival

Variable	Radiotherapy (95% CI)	Radiochemotherapy (95% CI)
Overall survival median in months	6.38 (5.81–6.93)	9.77 (8.92–11.76)
Overall survival (%) 6 months 12 months 24 months	 62.85% 3.69% 0%	 81.7% 41.2% 2.3%
Disease-free survival median in months	4.33 (3.77–5.47)	8.4 (5.91–9.83)
Disease-free survival (%) 6 months 12 months 24 months	 29.4% 2.4% 0%	 58.8% 31.3% 1.5%

Prognostic Factors in the Study Subjects

Unifactorial Analysis

In both study groups the patients' age, sex, general condition according to WHO criteria and waiting time for radiotherapy had no significant effect on OS and DFS. The only factor with significant influence on OS ($p = 0.03$) and DFS ($p = 0.008$) was the extent of surgery, but only in patients who underwent postsurgical radiochemotherapy.

Multifactorial Analysis

In the group of patients who underwent radiochemotherapy, as many as 3 factors influenced the mortality risk value. Patients with time to relapse or progression equal to or longer than the median (8.4 months) had a 19.29% lower risk of death compared to other patients from this group. Also, a waiting time for radiotherapy equal to or longer than the median (6 weeks) increased the risk of death by 5.5% in these subjects. Furthermore, a less than radical surgical excision of the tumor resulted in an increase in the mortality risk increase by as much as 61.9% (Table 4). Among the patients who underwent postsurgical radiotherapy only, without the administration of temozolomide, only the length of the time to relapse/progression was a significant factor affecting the mortality risk: patients whose time to relapse/progression was equal to or longer than the median (5.18 months) had a 17.9% lower mortality risk than the remaining patients (Table 3).

Survival Time in Relation to the Extent of Surgery

Among the patients who underwent non-radical surgery, the OS and DFS medians were comparable regardless of the method of postsurgical treatment. Administration of temozolomide during and/or after radiation therapy did not prolong these patients' survival time (Table 4). However, the patients who underwent radical surgery benefited from the administration of temozolomide combined with postsurgical radiotherapy. Among the patients treated with the combined method,

Table 3. Multifactorial analysis of the influence of the evaluated factors on the patients' overall survival

Treatment method	Prognostic factors	Relative risk	P-value	95% confidence interval
Radiochemotherapy	time to relapse	0.8071	0.0000	0.777–0.837
	surgery to radiotherapy time	0.945	0.007	0.906–0.985
	extent of surgery	1.000 1.619	 0.016	 1.093–2.396
Radiotherapy	time to relapse	0.821	0.003	0.677–0.904

Table 4. The patient's overall survival and disease-free survival in relation to the extent of surgery

Variable	Radiotherapy	Radiochemotherapy
	(95% CI)	(95% CI)
Overall survival median (months) after non-radical surgery	6.35 (5.34–6.67)	7.36 (6.48–8.24)
Overall survival (%) 6 months 12 months 24 months	 71.42% 0% 0%	 69.43% 19.48% 0%
Disease-free survival (months) after non-radical surgery	5.12 (4.34–5.62)	4.81 (4.56–5.66)
Disease-free survival (%) 6 months 12 months 24 months	 28.57% 0% 0%	 22.56% 13.60% 0%
Overall survival median (months) after radical surgery	6.43 (5.63–6.85)	11.72 (9.77–13.04)
Overall survival (%) 6 months 12 months 24 months	 55.8% 3.5% 0%	 85.3% 49.4% 3.2%
Disease-free survival (months) after radical surgery	5.06 (3.64–5.75)	9.53 (8.42–11.37)
Disease-free survival (%) 6 months 12 months 24 months	 31.9% 3.5% 0%	 71.6% 35.8% 1.1%

the OS median increased by 5.3 months and the DFS median increased by 4.5 months compared to patients who underwent postsurgical radiotherapy only (Table 4). The analysis of the survival time of patients who underwent only postoperative radiotherapy showed that the extent of surgery did not affect the OS and DFS ($p > 0.05$); the survival times of all the patients were similar regardless of the extent of surgery. The probability of surviving 6 months without relapse in patients treated radically and non-radically was 30% and 28%, respectively. The probability of 6-month overall survival in these groups was 50% and 48%, respectively. The probability of 12-month and 24-month OS or DFS was 0%. Significant differences in OS and DFS were observed in the group of patients who underwent radiation therapy combined with the administration of temozolomide. Patients who had undergone radical resection were characterized by significantly longer OS and DFS than patients who had had non-radical surgery. The probability of 6-month and 12-month overall survival was almost 40% higher in radically treated patients (Fig. 3). Similarly, in patients who had had radical tumor resections there was an almost 50% lower probability of relapse within 6 months, and about a 30% lower probability of relapse within 12 months (Fig. 4).

Discussion

Because there is no highly effective method of treating GBM patients, one of the main aims of the current study was to find factors that can modify existing therapeutic methods. This study has proven that the presence of a tumor after non--radical surgical treatment is a factor significantly affecting the efficacy of adjuvant treatment using temozolomide.

In the study group, the median overall survival was lower than in most available studies, in which the median OS was 7.7 to 12.1 months in cases of radiation therapy alone and 12.0 to 14.6 months in cases of combined treatment [8–11, 20]. However, the disease-free survival of the subjects of the current study was comparable with published data [8]. The reason for the shorter relapse-to-death

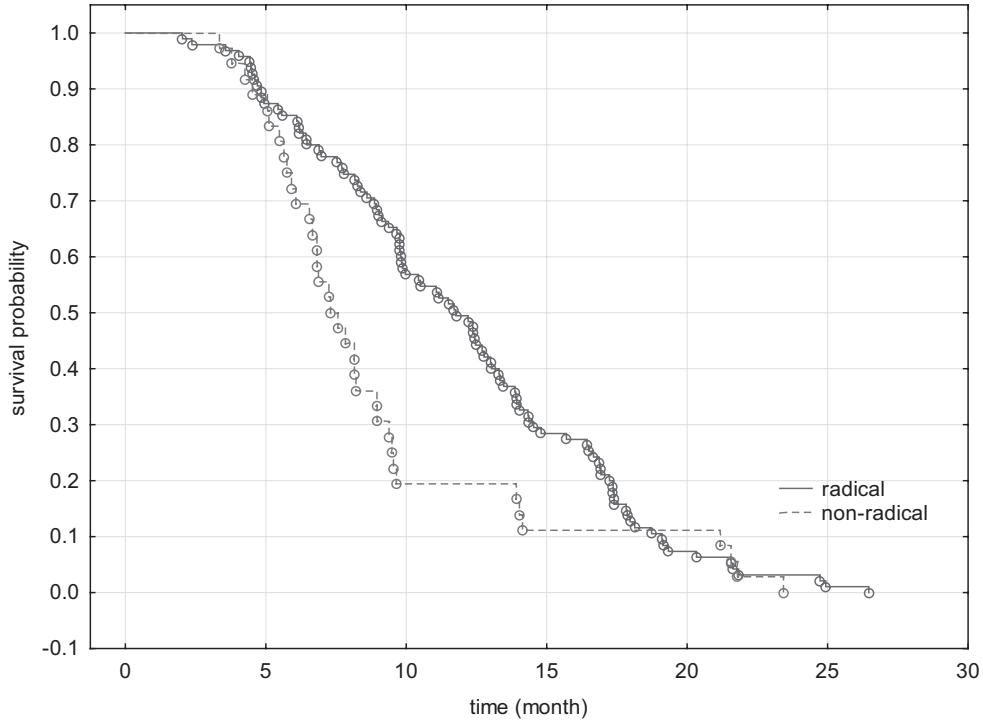

Fig. 3. Kaplan-Maier curve of overall survival of the patients in the chemoradiotherapy group in relation to the extent of surgery (p = 0.03128)

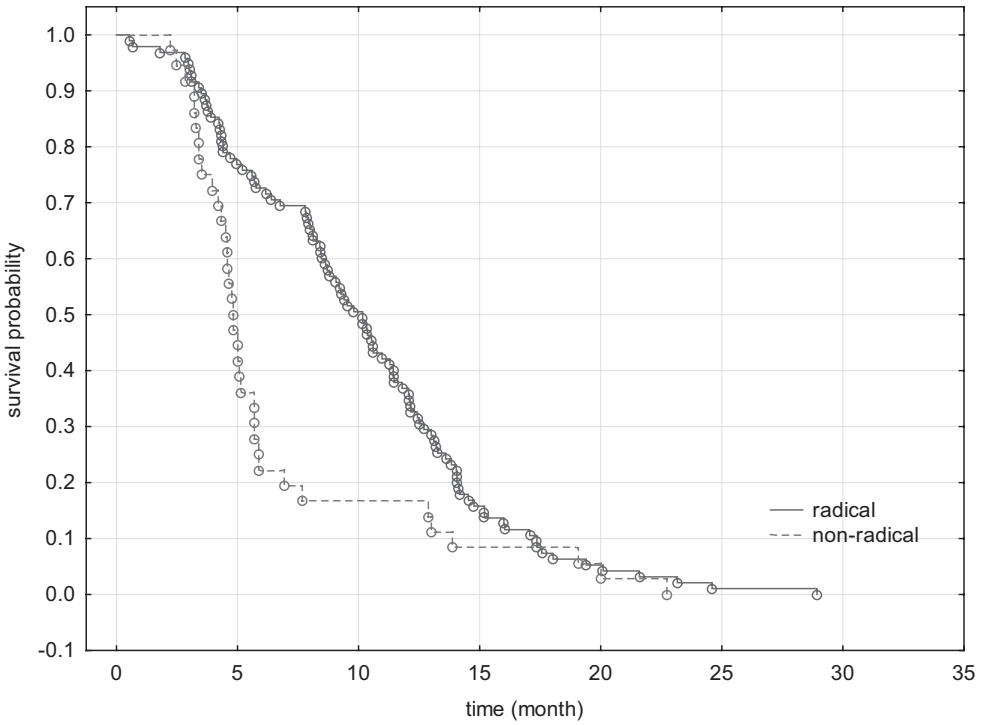

Fig. 4. Kaplan-Maier curve of disease-free survival of the patients in the chemoradiotherapy group in relation to the extent of surgery (p = 0.0084, t = 2.635)

time in the current study compared to literature data may be the different relapse treatment scheme used in this study. In the present study, subjects with tumor relapse were surgically treated, but second-line chemotherapy was not used, while in the EORTC/NCIC study second-line chemotherapy was used in 72% of the patients treated with radiotherapy and 58% patients treated with radiochemotherapy [8]. Among the evaluated prognostic factors, only the time to relapse, the waiting time for radiotherapy and the extent of surgery had prognostic value, which is compatible with most literature data. Delays in starting radiotherapy after surgery shorten patients' overall survival to a statistically significant degree [16–19]. Each day of waiting for radiotherapy increases the risk of death by 2%, and each week by 8.9% (95% CI: 2.0–16.1%) [16, 17]. It is difficult to precisely establish the optimal moment for initiating radiotherapy but it has been demonstrated that waiting

times longer than 3 weeks significantly (p = 0.01) shorten survival time, and over 10 weeks the statistical significance is high (p = 0.0072) [21].

The radicality of surgery in GBM patients has been long considered one of the most important prognostic factors [8, 12–15], which was confirmed by the present analysis. However, there are still many controversies concerning the role of the radicality of surgery as prognostic factor due to the recognized distribution bias. Many patients qualified for surgical procedures are younger and often in better general condition than others [3]. The tumor location is also prognostically important. It is well known that small tumors are located superficially and can be removed more radically [23]. Moreover, in most studies, the evaluation of the extent of surgery was made intraoperatively by the surgeon, rather than on the basis of post-surgical imaging. The current analysis showed that post-surgical radiochemotherapy successfully prolonged survival time only in patients who had undergone radical tumor resection. Among the patients with residual tumor, the efficacy of radiochemotherapy combined with temozolomide was comparable with that of radiotherapy alone.

The results obtained in the present study demonstrate the importance of the extent of surgery not only as a factor improving the overall survival of GBM patients treated with the combined method, but also influencing the efficacy of treatment using temozolomide. The concept that the efficacy of post-surgical treatment may be strictly connected with the type of surgery performed in GBM patients is a new one. So far, similar correlations have been presented in just a few reports [22, 24–26]. Those studies described not only the influence of the extent of surgery on the patients' survival, but also the efficiency of the adjuvant treatment: temozolomide and intraventricular chemotherapy using carmustine (BCNU). In a study conducted by Westphal et al., the median overall survival of patients who underwent radical surgery was 14.5 months in the BCNU group and 12.4 months in the placebo group (p = 0.02); in patients who had undergone non-radical surgery, the medians were 11.7 and 10.6 months, respectively (p = 0.98) [22]. In the EORTC-NCIC study the prolongation of survival time in the group receiving temozolomide compared to the group receiving only radiotherapy was 4.1 months among radically treated patients, 1.8 months in patients who had had non-radical resections and 1.5 months in patients who only had biopsies [24]. In a prospective study published in 2012 involving 143 GBM patients, Stummer et al. also found a statistically significant correlation (p < 0.001) between the extent of surgery and the response to radiochemotherapy. The radicality of surgery was evaluated on the basis of postsurgical MRIs. Median survival time was 16.9 months (95% CI: 13.3–20.5, p = 0.039) for patients with residual tumors up to 1.5 cm in diameter and 13.9 months (95% CI: 10.3–17.5, p < 0.001) for those with residual tumors larger than 1.5 cm in diameter [25].

The mechanism responsible for this pattern is unknown. One theory is that the effect of hypoxia characterizing the peripheral tumor fragments probably plays the main role in the phenomenon described. Hypoxia causes the activation of associated genes, which leads to an aggressive course of the disease, metastasis and a worse response to systemic treatment [27]. The peripheral tumor fragments are also characterized by augmented angiogenesis [28], and the cells in this region have more migratory capabilities, resistance to apoptosis and to chemical treatment [29]. Removal of these parts of the tumor decreases the number of the most resistant tumor cells and facilitates better penetration of medicine. A second theory explaining this phenomenon is associated with changes in the interstitial fluid pressure in GBM patients. Increased pressure leads to better penetration of medicine in the necrotic tissues and the tissues surrounding the tumor. Following surgery there is a short spell of pressure increase caused by edema. After detumescence, the interstitial fluid pressure decreases and the administered medicines probably persist longer in the tissues surrounding the postsurgical tumor bed [30].

Evaluating the impact of the extent of surgery in GBM patients on the postsurgical combined treatment is a very important issue because radical surgery is always risky and is associated with many complications. Everyday practice would significantly benefit from definite confirmation that in non-radically treated patients the prognosis is unfavorable even when temozolomide is administered.

This study has confirmed that the degree of surgery radicality in GBM patients plays a much more important role than was previously believed. Postsurgical radiochemotherapy is much more efficient in patients who have undergone radical tumor excision than in patients with residual tumors. This means that surgery should be as radical as possible, not only in order to eliminate tumor symptoms but also – and importantly – due to its significant impact on the effect of subsequent treatment and the prognosis.

The prognosis in GBM patients is still very unfavorable despite modern treatment methods. The present study shows that combined post-surgical radiochemotherapy significantly prolongs patients' survival time compared to post-surgical

radiotherapy alone, and that the efficacy of post-surgical treatment depends considerably on the extent of surgery and the degree of tumor resection. The presence of residual tumor is probably a factor significantly modifying the activity of temozolomide. Thus, the quality of the surgical procedure is a key element in the treatment of patients with GBM.

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