Original Article

Salvage Treatment Options for Glioblastoma: Is Re-Operation Beneficial in Early Recurrence?

Glioblastomda Kurtarma Tedavi Seçenekleri: Erken Nükslerde Re-Operasyon Katkı Sağlar mı?

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ABSTRACT

Introduction: We aimed to investigate salvage treatment options for glioblastoma and to explore the role of surgery in early progression.

Methods: The study was designed as a retrospective review of 73 recurrent glioblastoma patients treated between July 2011 and March 2016. Patients were divided into two groups according to time of progression and re-treatments were analyzed for each. Early and late progressions were defined as progression before and after completion of the standard treatment package (≤9 months versus >9 months). Survival analysis were made with Kaplan-Meier method. Survival time comparisons between groups were made with Log-Rank test. Effect of variables on survival times were evaluated with Cox-Regression Analysis.

Results: Median overall survival time from the first diagnosis was 20 months (95% CI 17.0-22.9) and 2-year survival rate was 32.9%. Median time to progression was 10 (1-42) months. Median post progression survival (PPS) time was 8 months (95% CI 6.2-9.8). In multivariable analysis, we found early progression (9 months or less, $p<0.001$) and the use of supportive care after progression ($p<0.001$) as negative prognostic factors for PPS. In late progression, re-operation provided higher rates of PPS than systemic therapy (median 27 vs 10 months, p: 0.005) and supportive care (median 27 vs 3 months, $p<0.001$). However, no significant difference was found between reoperation and supportive care in case of early progression (median 3 vs 1 months, $p=0.143$).

Discussion and Conclusion: Progression is inevitable after standard treatment of glioblastoma. Survival after relapse is considered to be shorter than a year and appropriate patient selection is crucial when deciding on re-treatments. Survival rates of patients with progression earlier than 9 months are lower, and reoperation may not be an ideal option for this group.

Keywords: glioblastoma, reoperation, re-irradiation, temozolomide, bevacizumab

ÖZET

Giriş ve Amaç: Glioblastom, kötü seyirli, erişkinlerde en sık görülen primer beyin tümörüdür. Standart tedavi sonrası hastaların hemen hepsinde progresyon gelişmektedir. Progresyonda re-operasyon, sistemik tedaviler ve re-irradyasyon uygulanabilmektedir. Erken progrese olanların prognozu geç progrese olanlara göre daha kötüdür. Bu çalışmada progresyon zamanına göre kurtarma tedavi seçeneklerinin irdelenmesi amaçlandı.

Yöntem ve Gereçler: Temmuz 2011-Mart 2016 arasında tedavi edilmiş 73 nüks glioblastom tanılı hasta restospektif olarak değerlendirildi. Standart tedavi programı tamamlanmadan önce (≤9 ay) progrese olanlar 'ERKEN', tamamlandıktan sonra (>9 ay) progrese olanlar 'GEÇ' progresyon olarak tanımlandı.

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Her iki grup için kurtarma tedaviler irdelendi. Sağkalım analizleri için Kaplan-Meier metodu kullanıldı. Tek değişkenli analizlerde log rank, çok değişkenli analizde cox-regresyon testi kullanıldı.
Bulgular: İlk tanıdan itibaren genel sağkalım 20 ay (%95 CI 17.0-22.9), 2 yıllık genel sağkalım %32.9 olarak bulundu. Medyan progresyon zamanı 10 (1-42) aydı. Progresyon sonrası genel sağkalım 8 ay (%95 CI 6.2-9.8) olarak saptandı. Çok değişkenli analizde, 9 aydan erken progresyon ($p<0.001$) ve destek tedavi ($p<0.001$) sağkalımı negatif yönde etkileyen faktörler olarak bulundu. Geç progresyonda cerrahinin, sistemik tedaviden (medyan 27'ye karşı 10 ay, p: 0.005) ve destek tedavisinden (medyan 27'ye karşı 3 ay, $p<0.001$) daha iyi sağkalım sağladığı gözlendi. Erken progresyonda ise re-operasyon ve destek tedavisi arasında fark saptanmadı (medyan 3'e karşı 1 ay, p: 0.143).
Tartışma ve Sonuç: Glioblastomda standart tedaviler sonrası progresyon kaçınılmazdır. Progresyon sonrası sağkalım 1 yıldan kısadır ve kurtarma tedavi seçenekleri için uygun hasta seçimi önemlidir. Erken progresyon gösteren hastaların sağkalımı düşüktür ve re-operasyon bu hastalar için uygun olmayabilir.

Anahtar Kelimeler: glioblastoma, re-operasyon, re-irradyasyon, temozolomid, bevasizumab

Introduction

Glioblastoma, also known as Glioblastoma multiforme (GBM) is the most common central nervous system tumor in adults. At present, the standard treatment of GBM is maximal safe resection followed by 60 Gy conventional radiotherapy concurrently with temozolomide (TMZ) and adjuvant maintenance TMZ. Despite the current protocol, most patients progress within a year and have a median survival of 14.6 months [1].

After progression, current treatment options are limited and often ineffective. Surgery is always a tried-out option in selected patients if the tumor is well-suited for surgery [2]. Numerous studies published assessing the role of chemotherapeutic agents and their combinations such as nitrosoureas, TMZ, bevacizumab (BVC), immunotherapeutics and targeted therapies [3,4]. Re-irradiation is also a safe option with the advances of technology. Particularly, fractionated stereotactic radiotherapy has been shown to be useful in progression [5]. However, improvements on survival are insufficient and standard therapy currently is lacking.

Various studies support the conclusion that progressive glioblastoma (pGBM) treatment should be determined on a patient-to-patient basis and careful consideration of factors such as clinical/performance status, age, and quality of life is vital to deciding on treatment [6]. The most discussed topic of pGBM management is the usefulness of re-operation. Concerns about the additional morbidities of surgery, and short survival rates of the disease complicate the decision. Recently, a meta-analysis highlighted the timing of re-operation and showed that early re-intervention is associated with a higher risk of death than late re-intervention [7]. Patients with early progression may have an aggressive tumor moleculer profile, and this may be more important than the therapy itself. The progression time can have a significant impact on the treatment decision of pGBM.

The aim of the study is to demonstrate the prognostic role of the progression time and to investigate time-dependent salvage treatment options for pGBM.

Materials and Methods

Study Design

We retrospectively reviewed the medical records of patients treated for glioblastoma between July 2011 and March 2016. Inclusion criteria were as follows: (1) Patient had to have a radiologically proven progression after 1st treatment according to Response Assessment in Neuro-Oncology (RANO) Criteria [8], (2) patient had to attend follow-

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up. Patients who could not be operated and only biopsied were excluded. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by The Ethics Committee of Cerrahpaşa Medical Faculty (21.02.2020/30332) and all patients had written informed consent.

Initial treatment

All patients underwent maximal debulking surgery, followed by radiotherapy plus TMZ. Total resection was achieved on 35 (48%) patients, while 38 (52%) patients had subtotal resection. Radiotherapy (RT) was administered 60 Gy with conventional fractionation in 6 weeks. RT planning was done in a single-phase treatment plan with a 2-2.5 cm Clinical Target Volume (CTV) and 5mm Planning Target Volume (PTV) margin, including peritumoral edema. TMZ 75 mg/m^2 oral capsule was taken every day during RT. Eight patients (11%) received hypo-fractionated radiotherapy (40 Gy in 3 weeks) due to lower performance status and/or older age. Of these, four patients were administered with concomitant TMZ. After radiochemo-therapy, 6 cycles of adjuvant TMZ (150- 200 mg/m^2) were administered over a 28-day cycle for 5 days (1). Adjuvant TMZ was given 12 cycles in 2 (2.73%) patients and lower than 6 cycles (median 3) in 31 (42.5%) patients. It was stopped earlier due to hematological toxicity in four patients and rapid progression in 27 patients. After completion of treatment, the patients were followed up with a clinical examination and magnetic resonance imaging (MRI) every 2 months. Tumor progression was defined as the evidence of a new contrast-enhancing lesion or a ≥25% increase in size of a known contrast-enhancing lesion or remarkable increase T2/FLAIR abnormality on MRI.

Treatment after progression

Patients eligible for surgery after recurrence were operated as a first option, others were considered for chemotherapy firstly. TMZ was used as in the initial treatment dose, 150-200 mg/m^2, 5 days in every 4 weeks until progression. BVC was administered 10 mg/m^2 every two weeks. Reirradiation was used only in two patients with a hypofractionated scheme (6x5 Gy). Twenty patients were not eligible for any treatment and received only supportive care.

Data Collection

Data collection form includes age (at diagnosis), gender, tumor location, extent of resection, Karnofsky performance score (KPS), initial treatments, date of progressions, salvage treatments, date of death or last follow-up. The progression time was defined as the time from the first surgery to the first evidence of progression. Overall survival (OS) was defined as the time from the surgery to the last follow up or patient's death. Post progression survival (PPS) was defined as the time from the first evidence of progression to the last follow up or patient's death.

Statistical Analysis

All analyses were performed on SPSS package (SPSS 22.0 for Windows; SPSS Inc, Chicago, IL). Imbalances in categorical variables were tested using the Chi-square test. Survival analysis were made with Kaplan-Meier method. Differences were compared with Log-Rank test. Pairwise comparisons were made with Bonferroni correction method. Effect of variables on survival times evaluated with Cox-Regression Analysis with Backward Conditional method. $p<0.05$ values were accepted as statistically significant.

Results

A total of 147 patients were screened. We enrolled 73 eligible cases into our study,

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Table 1. Patient and tumour characteristics

	Early progression, ≤9 month, n (%)	Late progression, >9 month, n (%)	All n (%)	p
Age				
<60	20 (64.5)	29 (69.0)	49 (67.1)	0.684
≥60	11 (35.5)	13 (31.0)	24 (32.9)	
Sex				
Male	15 (48.4)	24 (57.1)	39 (53.4)	0.459
Female	16 (51.6)	18 (42.9)	34 (46.6)	
Initial KPS				
≤70	12 (38.7)	9 (21.4)	21 (28.8)	0.107
>70	19 (61.3)	33 (78.6)	52 (71.2)	
Main Location				
Frontal	11 (35.5)	18 (42.9)	29 (39.7)	
Temporal	8 (25.8)	11 (26.2)	19 (26.0)	0.828
Parietal	8 (25.8)	10 (23.8)	18 (24.7)	
Occipital	4 (12.9)	3 (7.1)	7 (9.6)	
Extensiveness				
Single lobe	21 (67.7)	31 (73.8)	52 (71.2)	0.571
Multiple lobes	10 (32.3)	11 (26.2)	21 (28.8)	
First surgery type				
Total	13 (41.9)	22 (52.4)	35 (47.9)	0.377
Subtotal	18 (58.1)	20 (47.6)	38 (52.1)	
Treatment after progression				
Surgery	8 (25.8)	7 (16.6)	15 (20.6)	
Temozolomide	6 (19.4)	19 (45.2)	25 (34.2)	0.227
Bevacizumab	6 (19.4)	7 (16.7)	13 (17.8)	
Supportive care	11 (35.5)	9 (21.4)	20 (27.4)	

median age was 53 (24-79) years. Median overall survival time from the first diagnosis was 20 months (95% CI 17.0-22.9) and 2-year survival rate was 32.9%. Median time to progression was 10 (1-42) months. Median survival time after progression was 8 months (95% CI 6.2-9.8), 6- months and 1-year PPS rate was 58.9% and 30.1%, respectively. The patients were dichotomized into two groups according to the time of progression. Early progression, which was defined progression before completion of the standard treatment package (≤9 months), was seen in 31 patients. Late progression, which was defined progression after completion of the standard treatment package (>9 months), was detected in 42 patients. Two patients were still alive at the time of our review. Isocitrate dehydrogenase (IDH) mutations were positive in five patients, negative in 30 patients and missing in 38 patients. Five of the seven samples examined had methyl guanine methyl transferase (MGMT) promoter-methylation. MGMT status was missing in 66 patients. Demographic characteristics were given in Table 1.

After first progression, the most common treatment was TMZ in 25 (34%) patients. The second and third progressions were demonstrated radiologically with only 16 and 5 patients, respectively. Others experienced rapid clinical deterioration without an MRI diagnosis and did not receive tertiary treatments. (Table 2).

In univariable analysis, male patients had significantly higher PPS times than females (p=0.030). Patients with a score equal to or less than 70 KPS had a shorter PPS time than patients with a score higher than 70 KPS (p=0.088), and patients who had progression after 9 months had higher PPS times than those who did not (p<0.001). When we evaluated the type of treatment after relapse, the supportive care arm had a significantly shorter PPS than the others (p<0.001) (Table 3).

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Table 2. Treatment methods after relapse

	First relapse (n=73)	Second relapse (n=16)	Third relapse (n=5)
Temozolomide	25 (34%)	2 (12%)	
Supportive care	20 (27%)	2 (12%)	1 (20%)
Surgery	15 (21%)	3 (19%)	
Only Surgery	8 (11%)		
Surgery + TMZ	3 (4%)		
Surgery + BVC	2 (3%)		
Surgery + RT + TMZ	2 (3%)		
Bevacizumab	13 (18%)		
BVC	11 (15%)	2 (12%)	2 (40%)
BVC + IRI	2 (3%)	6 (38%)	1 (20%)
PCV		1 (6%)	1 (20%)

TMZ:Temozolomide, BVC: Bevacizumab, RT: Radiotherapy, IRI:Irinotecan, PCV: Procarbazine, lomustine, vincristine.

Table 3. Survival rates after progression

	n	Median Survival (Month)	95% Confidence Interval		1- year Survival Rate (%)	p
			Lower	Upper		
Overall Survival after progression	73	8	6.2	9.8	30.1± 5.4	N/A
Age						
<60	49	9	7.0	10.1	32.7 ±6.7	0.642
≥60	24	6	1.2	10.8	25.0 ±8.8	
Gender						
Male	39	10	6.7	13.0	38.5 ± 7.8	0.030
Female	34	6	3.1	8.9	20.6 ± 6.9	
Initial Karnofsky Performance Status						
≤ 70	21	7	2.5	11.5	19 ± 8.6	0.088
> 70	52	9	5.9	12.1	34.6 ± 6.6	
Main Location						
Frontal	28	9	6.9	11.0	32.1 ± 8.8	
Temporal	20	7	6.0	8.0	26.3 ± 10.1	0.516
Parietal	18	9	3.7	14.3	35.3 ± 11.6	
Occipital	7	3	0.4	5.6	14.3 ± 13.2	
Extensiveness						
Single lobe	52	8	5.2	10.8	30.8 ± 6.4	0.658
Multipl lobes	21	9	5.7	12.3	28.6 ± 9.9	
First Surgery						
Total resection	35	9	6.7	11.3	31.4 ± 7.8	0.218
Subtotal resection	38	7	3.6	10.4	28.9 ± 7.4	
Progression time						
≤9 month	31	5	1.9	8.1	9.7 ± 5.3	<0.001
>9 month	42	10	6.0	14.0	45.2 ± 7.7	
Treatment After Relapse						
Temozolomide	24	9	6.6	11.4	36.0 ± 9.6	<0.001
Bevacizumab	13	9	6.9	11.1	30.8 ± 12.8	
Surgery ± adjuvant	15	13	1.6	24.4	53.3 ± 12.9	
Supportive care	20	2	0.7	3.3	5 ± 4.9	

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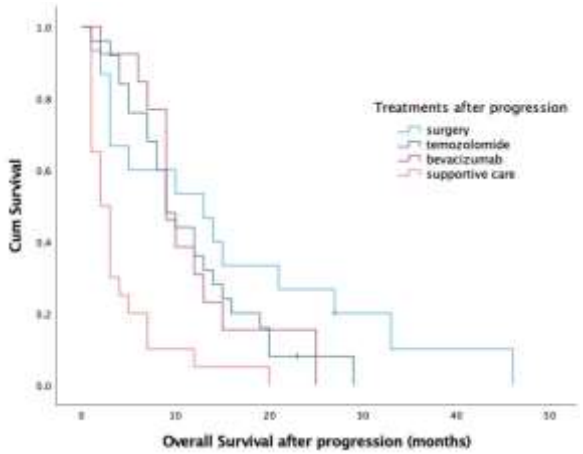


Figure 1. Survival curves of treatment groups after progression

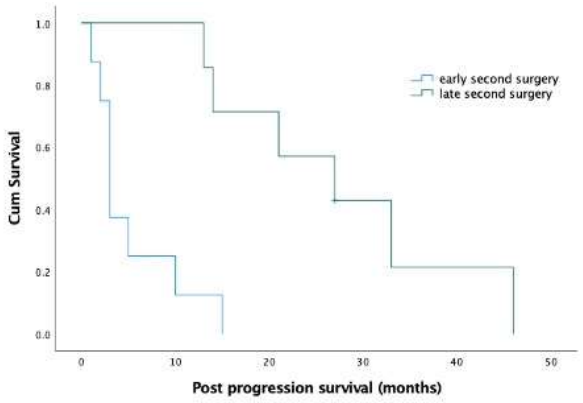
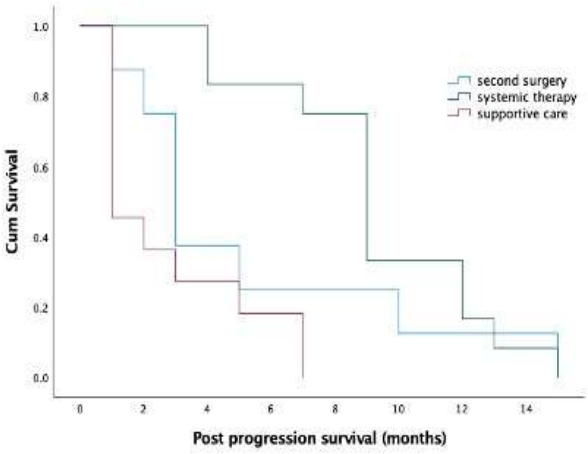


Figure 2: Kaplan Meier curves of surgery in early vs late progression

In multivariable analysis with factors with a p value of <0.05, we found progression time 9 months or less (p<0.001) and the use of supportive care after progression (p<0.001) as negative prognostic factors. Risk of death after progression was increased by a coefficient of 2.8 (95% CI: 1.6-5.0) in individuals who progressed ≤9 months in comparison to those who progressed later than 9 months. Re-operation (HR:0.20, 95% CI: 0.10-0.44), TMZ treatment (HR:0.37, 95% CI: 0.20-0.69) and BVC treatment arms (HR:0.26, 95% CI: 0.12-0.55) were associated with a lower risk of death after progression in comparison to supportive care arm (Figure 1).

Patients who underwent re-operation with or without adjuvant treatment had the longest



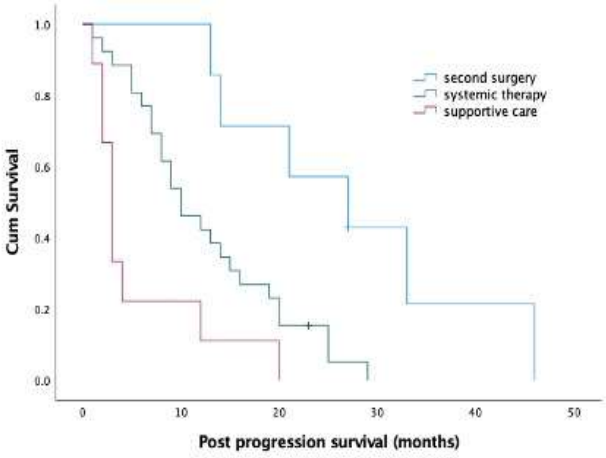


Figure 3: Kaplan Meier curves of treatments in a) early and b) late progression

PPS times (median 13 months, 95% CI: 1.6-24.4). However, when we consider the timing of re-operation; there was a significant PPS difference between early and late resections (median 3 months (95% CI:2.1-3.9) vs median 27 months (95% CI:11.6-42.4), p:0.001) (Figure 2).

In case of early progression; systemic therapy had a longer PPS than supportive care (median 9 vs 1 months, p<0.001). However there was no significant difference between re-operation and supportive care (median 3 vs 1 months, p=0.143) (Figure 3A).

In case of late progression; re-operation provided rates of PPS than systemic therapy (median 27 vs 10 months, p=0.005) and

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supportive care (median 27 vs 3 months, p<0.001) (Figure 3B).

Discussion

Progression is inevitable after initial treatment of GBM. Today, however, there is no standard treatment for pGBM. In daily practice, if the clinical status of patient is suitable, the first option in mind is re-operation. However, re-operation is a highly controversial issue which has not been proven by randomized clinical trials. Analysis of 19 phase 2 studies by the North American Brain Tumor Consortium revealed no benefit of additional operations [9]. Nevertheless, the vast majority of literature supports the benefit of re-operation in pGBM [10-12]. A recent systemic review and a meta-analyse also advocates re-operation for progression [7,13]. Moreover, multiple resections have been found to increase survival. Chaichana et al. reported overall survival of 6.8, 15.5, 22.4 and 26.6 months after resections 1, 2, 3 and 4th, respectively [14]. In contrast, a study conducted in TMZ era revealed that patients with multiple resections were much younger and had higher perpormance status. And once adjusted for age, the benefit of multiple resections was no longer significant [15]. Recent data from the DIRECTOR cohort conclude that the benefit of re-operation is only with the removal of complete resection of the contrast-enhancing lesion [16]. Another study suggested that neutrophil/lymphocyte ratio (NLR) is a prognostic factor for PPS. The authors reported a median PPS of 9.7 months for NLR ≤ 4 and 5.9 months for NLR > 4 [17].

All these studies demonstrate the need for appropriate patient selection for re-treatments. Two studies analyzing data from phase 1 and 2 trials in North America and Europe reported that prognostic factors affected survival outcomes more than treatment modalities [18, 19]. Carson et al. identified age (≥50 vs. <50), 10 points increase in KPS and corticosteroid use in their recursive partitioning analysis for GBM. Gorlia et al. found World Health Organization (WHO) performance status, baseline steroids, tumor size (≤42mm vs. >42mm) and number of target lesions (1 vs. more than 1) as prognostic calculators. These prognostic factors are important to decide which treatment is avaliable for which patient. Several other studies also suggest that preoperative KPS scores are associated with higher OS time [20]. We have inadequate data of KPS at the time of first progression. However, an initial score higher than 70 to be correlated with better PPS trend after progression.

In this study, progression time greater than 9 months and re-treatment instead of supportive care were associated with longer survival after progression. Systemic therapies have similar PPS (9 and 10 months) when administered in case of early or late progression. However the benefit of re-operation reversed when it was incorporated into early progression. McGirt et al. emphasized the importance of gross total resection in both primary and secondary resections and found the benefit of a second surgery after 12 months of primary resection, but not earlier [21]. In a radiosurgery trial from Korea, radiosurgery and TMZ had a 15.5 month survival after progression. They also concluded that patients who progressed late, had better survival rates [22]. Conversely, Nava et al. and Ringel et al. found no prognostic effect of the progression time [23, 24]. The first found no benefit of reoperation in patient cohorts both before and after 2005. In addition, there was no 9-month threshold difference for resection results. However lower OS in the study (11.7 before TMZ and 12.9 after TMZ) may affect the outcomes. The latter found high survival rate (25 months), and good response to re-operation not dependent on the progression time. This may be due to the inclusion of well-selected patients with high KPS (median 90%) and low rapid progression rate (19% of patients had progression earlier than 5 months).

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A recent study by Goldman et al pointed out the importance of time-dependent methodology for oncologic treatments [25]. They found that, re-operation was associated with a lower risk of death when timing was ignored (HR:0.62, 95% CI: 0.43-0.90, p=0.01). However, re-operation was associated with a higher risk of death after timing was taken into account (HR:2.19, 95% CI:1.47-3.28, p<0.001). This was also confirmed in a meta-analysis by Zhao et al. and a more recent single-instution study [7,26].

The evidence about the outcomes of surgical intervention are commonly from retrospective investigations. We need further researches to come to a conclusion and obtain higher-level evidence on the impact of surgery. The rate of re-operation in previous studies is 10-30%. More recent studies have reported higher rates of re-operation, possibly with improved surgical technics. However, care should be taken when making decisions in rapidly progressive cases. Second surgery can be considered in young patients with good performance status and progressive disease location that can be safely resectable in non-eloquent brain area. It helps relieving of symptoms quickly and may serve a better quality of life. In addition, information about the histopathological features of progressive disease may shed light on new therapeutic pathways.

Recently, improvements in radiotherapy setting allows a secondary radiation in the selected pGBM. A variety of re-irradiation studies have shown results comparable to other treatment modalities. Skeie et al. reported 12-month survival with radiosurgery [27]. Two studies from North America reported that 11-month survival with re-irradiation and no benefit of additional surgery before or after hypofractionated stereotactic radiation therapy [5, 28]. In our study population, only 2 patients were re-irradiated. This may be a result of primarily consideration of re-operation and systemic treatments and keeping radiation for residual tumors. However, the worsening of the patients' symptoms led to a decrease in the radiological detection rate of second relapses. Irradiation can be a good non-invasive option in both early and late progression.

Bevacizumab is a vascular endothelial growth factor inhibitor. We observed that BVC has similar efficiency with other treatment options. It may provide a better quality of life, particularly in early progression and when high doses of corticosteroid needed.

Our study has various limitations, one is that while chemotherapy efficacy has been shown to be dependent on the methylation of the promoter for MGMT, we did not have results for all of our patients and thus, we evaluated chemotherapy effectiveness without taking this factor into account. Similarly, IDH-1 status was unknown in half of the patients. Further studies will clarify the role of underlying molecular profiles in the pGBM treatment setting. Another limitation is the presence of combination therapies after progression, making it difficult to assess the efficacy of each. Finally, although some studies proposed 6-month progression free survival is a critical end point for evaluating the effectiveness of treatment [29], we were only able to prove a second relapse in 16 patients, and used PPS in this comparison.

Conclusion

In conclusion, Glioblastoma is a tumor with dismal survival even though efforts to increase treatment options and their effectiveness are being made. Standard treatments in progressive GBM are lacking. Survival after progression is considered to be shorter than a year and proper patient selection is crucial when deciding to proceed re-treatments. In particular, re-operation may not be a viable option for early progression, and should be discussed in multidisciplinary boards.

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