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Research Article

Effect of Reoperation on Survival of Patients With Glioblastoma

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Summary

Objective: Surgical resection is the most important part of glioblastoma treatment. The objective of this study was to determine the effect of reoperation on survival of patients with glioblastoma.
Methods: Records of the glioblastoma patients operated between 2001 and 2010 by the senior author were analyzed retrospectively. Comparisons were made between patients who received (Reoperation group, n=50) and who did not receive (Monooperation group, n=111) reoperation with regard to age, gender, tumor localization, number of operations and length of survival.
Results: No significant difference was found between two groups in terms of age, gender, and tumor localization. Mean follow-up duration was 12.7 months (range: 1-96 month). Mean lengths of survival after the first operation were 26.7 ±4.0 months and 12.2 ±1.6 months in the reoperation and monooperation groups, respectively ($p<0.001$). Regression analysis revealed that reoperation was the only prognostic factor determining the survival in recurrent malignant glial tumors. Moreover, surgical site was shown to affect survival; rate of mortality in patients operated on temporal side was statistically greater than that in patients operated on parietal side ($p=0.01$).
Conclusion: Despite modern treatment strategies, reoperation is still the most important factor determining the length of survival in recurrent glioblastoma.

Key words: Glioblastoma, reoperation, survival

Tekrarlayan Ameliyatların Glioblastoma Hastalarında Sağkalıma Etkisi

Özet

Amaç: Cerrahi rezeksiyon glioblastoma tedavisinin en önemli kısmını oluşturmaktadır. Bu çalışmanın amacı reoperasyonun glioblastomalı hastaların sağkalımı üzerine etkisini belirlemektir.
Araçlar: 2001- 2010 yılları arasında aynı cerrah tarafından opere edilen glioblastoma hastalarının dosyaları retrospektif olarak incelendi. Birden fazla defa opere edilen (reoperasyon grubu, n=50) ve bir kez opere edilen (monooperasyon grubu, n=111) hastalar yaş, cinsiyet, tümör lokalizasyonu, operasyon sayısı ve sağkalım süresi açısından karşılaştırıldı.
Sonuçlar: Gruplar arasında yaş, cinsiyet, tümör lokalizasyonu açısından anlamlı farklılık saptanmadı. Ortalama takip süresi 12.7 ay (1-96 ay); ilk operasyondan sonra ortalama sağkalım süresi reoperasyon grubunda 26.7 ±4.0 ay, monooperasyon grubunda 12.2 ±1.6 ay ($p<0.001$) idi. Regresyon analizine göre tekrarlayan malign glial tümörlerde sağkalımı belirleyen tek prognostik faktör reoperasyon idi. Cerrahi yapılan bölgenin sağkalıma etkisi olduğu gösterildi. Temporal bölgeden opere olan hastalarda mortalite oranı parietal bölgeden opere olanlardan anlamlı olarak yüksek ($p=0.01$) idi.

Sonuç: Modern tedavi stratejilerine rağmen tekrarlayan glioblastomalı hastalarda sağkalım süresini belirleyen en önemli faktör reoperasyondur.

Anahtar Kelimeler: Glioblastoma,reoperasyon, sağkalım

INTRODUCTION

Glioblastoma, the most malignant primary neoplasm of the central nervous system, constitutes 25% of all malignant nervous system tumors[15]. Nearly all glioblastoma patients die within two years despite using multimodal treatments (maximum surgical resection, irradiation and chemotherapy)[22]. After 2005, the recommended treatment of glioblastoma has become to be consisted of surgery and postoperative radiotherapy (RT), with concomitant and adjuvant chemotherapy[27]. Maximal tumor resection is the principle during surgery[1,5,12,13,14,19,24,30].

Patient age, functional status, grade of resection, type of oncological treatment, and methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) gene are among prognostic factors that have been identified[7,9,10].

Glioblastoma recurrence is inevitable after a median survival time of 32 to 36 weeks[11]. Reoperation which has been described in 10–30% of glioblastoma patients is one of the studied prognostic factors[3,23,26]. There is neither enough data about the role of the number of reoperations as a prognostic factor nor a consensus about its ideal timing. A period greater than 6 months between the initial surgery and recurrence has been associated with longer survival[2,4,7,10,29]. Durmaz et al. reported no significant difference in length of survival after the first reoperation[6]. Indications for reoperation are also debatable. Glioblastoma patients in good health, younger than 65 years, or able to function independently have been selected for reoperation in the literature[2,4,7,29,31].

In this retrospective study, we aimed to investigate the effect of reoperation on the survival of 161 glioblastoma patients.

MATERIAL AND METHODS

The data for this retrospective study were retrieved from medical reports of patients who were admitted to the Neurosurgery Department in Uludag University Medical School between January 2001 and January 2010 and operated by the senior author.

Within this time period, 161 patients underwent surgery for glioblastoma. Patients who had (i) a Karnofsky Performance Status (KPS) scale of greater than 60, (ii) tumor progression verified on MRI without clinical sign or symptoms and, (iii) signs of raised intracranial pressure or increasing neurological deficits were reoperated.

Sex, age at surgery (years), tumor localization, clinical presentations, preoperative Karnofsky performance score, primary oncological treatment (temozolomide chemoradiotherapy, RT with adjuvant chemotherapy, RT alone, chemotherapy alone, or no primary oncologic treatment), vital status (alive or dead) and time of death were recorded for all patients. For patients undergoing reoperation, dates of repeated surgery were also recorded.

The patients were divided into two groups: patients who received (Reoperation group, n=50) and who did not receive (Monooperation group, n=111) reoperation. Two groups were compared with regard to age, gender, tumor localization, number of operations and survival. Length of survival from time of surgery to time of death was analyzed using the method described by Kaplan and Meier, and the significance of differences among the survival curves for each parameter was tested using the log-rank test. A multivariate analysis was performed with the Cox proportional hazard regression model.

RESULTS

The study included 161 glioblastoma patients (88 males, 73 females) within a period of 9 years (from 2001 to 2010). Mean age of patients was 54.8±12.77 (range: 15-95) years. No significant difference was found (p=0.087) between mean age of females (56.6±13.6 [range: 15-84] years) and that of males (53.4±11.9 [range: 25-95] years) by Mann Whitney U test. Patient demographics, tumor characteristics, presenting symptoms have been listed in Table 1.

One hundred eleven patients underwent only one operation, while 50 patients were reoperated upon tumor recurrence. No significant difference was found between two groups in terms of age, gender, and tumor localization.

Five patients received RT, while rest of the patients received a combination of chemotherapy and RT, after surgery.

Patients in the reoperation group underwent operations for several different times: one patient was operated 6 times, one patient was operated 4 times, 6 patients were operated 3 times and rest of the patients was operated twice.

Mean follow-up duration was 12.7 (range: 1-96) months. One hundred twenty three patients died while 38 of them are still being followed-up.

Mean length of survival after the first operation was 26.7 ±4.0 months and 12.2 ±1.6 months in the reoperation and monooperation groups, respectively (p<0.001). Regression analysis revealed that reoperation was the only prognostic factor determining the survival in recurrent malignant glial tumors (Fig 1).

Moreover, surgical site was shown to affect survival; rate of mortality in patients operated on temporal side was statistically greater than that in patients operated on parietal side (p=0.01).

Table 1: Patient demographics, tumor characteristics and clinical presentation

		Group 1 n(%)	Group 2 n(%)
sex			
	male	58(36.02)	30(18.63)
	female	53(32.92)	20(12.42)
age			
	<40	2(1.24)	11(6.83)
	40-60	50(31.06)	31(19.25)
	>60	59(36.65)	8(4.97)
presenting symptoms			
	headache	37(17.05)	13(5.99)
	nausea/vomiting	6(2.76)	4(1.84)
	seizures	27(12.44)	20(18.69)
	cognitive changes	7(3.23)	3(1.38)
	neurological deficit	52(23.96)	21(9.68)
tumour location			
	right	61(37.89)	24(14.91)
	left	50(31.06)	26(16.05)
surgery			
	gross total resection	74(45.96)	27(16.77)
	subtotal resection	37(22.98)	23(14.29)
side			
	frontal	39(24.22)	12(7.45)
	temporal	42(26.08)	19(11.80)
	occipital	9(5.59)	5(3.10)
	parietal	21(13.04)	14(8.69)

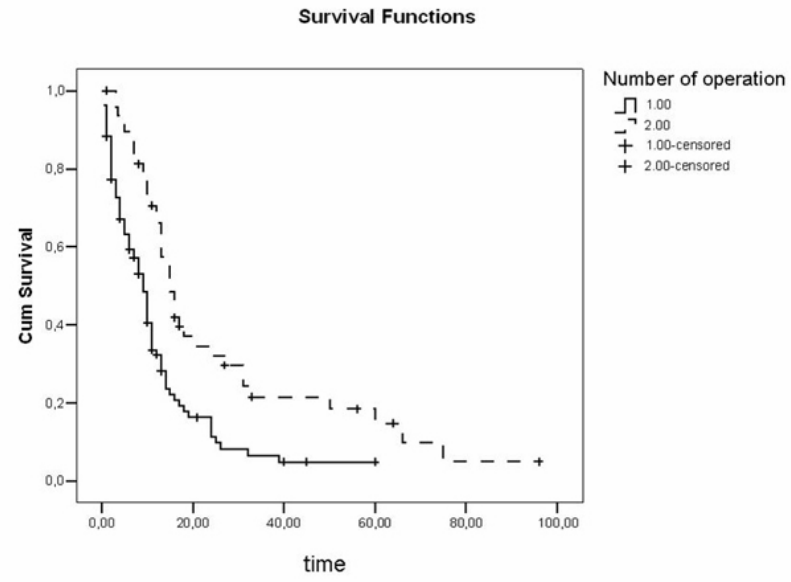

Figure 1: *Kaplan Maier graphics shows the survival difference between mono and reoperation groups*

DISCUSSION

The aim of this retrospective analysis was to evaluate the effect of reoperation on the treatment of recurrent glioblastoma. In the selected patients, reoperation can confirm tumor recurrence, reduce intracranial pressure, improve neurological status, and possibly improve efficacy of adjunctive therapy[11]. The major advantages of re-resection are rapid palliation of symptoms and histological diagnosis[18].

The rate of glioblastoma patients who were reoperated in our study (50 out of 161; 31%) is higher than that reported in the literature but similar to that found by Durmaz et al.[6]. This difference probably resulted from the differences in the indications for reoperation.

Studies investigating the number of reoperations as a prognostic factor are limited in the literature however, up to five times of reoperation has been reported[16]. In our study, 37 patients were operated twice while 6 patients were operated 3 times, one patient was operated 4 times, and one patient was operated 6 times.

Although individually variable, length of survival for patients with glioblastoma changes from an average of 10 to 14 months after diagnosis[13,14,27,28]. Mandl et al pointed that the survival after repeated surgery was dependent on the extent of resection at the first operation and repeated surgery after a radical first resection has a limited additional effect on survival[17]. Pinsker et al reoperated 38 glioblastoma patients and in contrast to Mandl et al, they conclude that increased survival with high quality of life can be achieved by repeated surgery only[20]. The authors showed a significant prolonged survival time by reoperation in the literature[8,18]. In a retrospective review, Barker et al showed that 46 patients who underwent secondary surgery and adjunctive therapy demonstrated a median survival time of 36 weeks following resection which was 12 weeks longer than the chemotherapy and/or radiation therapy group[3]. Reoperation improved the overall mean length of survival to 26.7 ±4.0 months in our study.

Similar to previous studies[15], we demonstrated in our study that, glioblastoma located on the temporal lobe was associated with poor prognosis. However, contrary to the previous finding that glioblastoma located on the frontal

region was a positive prognostic factor[15], we found that, parietal lobe tumor location was associated with prolonged survival.

Age at the time of diagnosis, preoperative KPS score, KPS score change at 2 weeks postoperation, involvement of brain lobe (diffuse or focal), involvement of the eloquent cortex or deep structure, Ki-67 expression level and adjuvant chemotherapy have been found to correlate significantly with the prognosis of glioblastoma patients[23]. Stark concluded that a) age younger than 61 years, b) preoperative and, c) postoperative KPS score equal to or greater than 70, d) total tumor resection, e) radiotherapy of at least 54 Gy in total, f) recraniotomy for recurrence, g) applied chemotherapy were significantly associated with prolonged survival[25]. The prolongation of survival time was found statistically significant in the Karnofsky Performance subgroup (KPS $\geq$ 90 at the time of re-operation) by Pinsker et al[20]. Also, Barker et al showed that the KPS were improved 28% in the repeat resection group. The authors concluded that although the results were likely secondary to selection bias, a subset of patients with recurrent glioblastoma might potentially benefit from repeated resection[3]. We were unable to analyze the role of KPS score as a prognostic factor since only patients with KPS > 60 were reoperated.

Resection in cases of recurrent glioblastoma may provide a modest benefit in survival and/or improvement in quality of life within a subset of patients[11]. Extent of initial resection, performance status, patient age were found to be a significant predictor of outcome. Although minor discrepancies exist among different studies, the general consensus is that resection should be seriously considered in those with a high KPS score (>70) and whose lesions are in a favorable location[11]. All the patients at reoperation group had KPS score of >60 and KPS were unchanged or improved after the reoperations.

The advantage of surgery on the survival of glioblastoma patients is controversial[1,15]. Mandl et al. suggested that patients with mild to moderate symptoms of glioblastoma relapse should be subjected to salvage therapies like chemotherapy or RT without recraniotomy because they claimed preservation of the quality of life to be the aim of the treatment of glioblastoma relapse[17]. Pinsker et al mentioned the same goal but they concluded that prolongation of survival time after reoperation was statistically significant[20]. Different authors offered different chemoradiotherapy regiments combined with the repeatsurgery but there is no conscenscus with the regiment[21,29]. However, we found in our study that, reoperation was the only prognostic factor determining survival in recurrent glioblastoma cases. Our add-on therapies were determined by the oncology team.

The efficacy and utility of repeated resection alone in cases of recurrent glioblastoma remains controversial due to a lack of randomized clinical trials[11]. The advantage of this study is that the results reflected the experience of the same surgeon. Involvement of more than one surgeon in other studies may cause differences in the surgical techniques which might be the reason for bias.

Major limitations of the present study include: (i) the study is retrospective in nature, and (ii) prognostic factors of survival in glioblastoma patients such as methylation status of the MGMT gene and pre- and post-operative tumor volumes have not been assessed. Studying both of these factors would have improved the study.

In conclusion, despite modern treatment strategies, reoperation is still the most important factor determining the length of survival in recurrent glioblastoma.

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