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RESEARCH

RADIOTHERAPY IN THE TREATMENT OF ELDERLY GLIOBLASTOMA PATIENTS

ABSTRACT

Introduction: The incidence of glioblastoma increases with advancing age. In this study we evaluated our therapeutic results in elderly patients with glioblastoma.

Materials and Method: The charts of 65 patients age ≥65 and treated between January 2002 and December 2011 in our department were assessed. Forty-five patients were male and the median age was 70 years (range, 65-84 years). Karnofsky performance status was ≥70 in 82% of the patients. Gross tumor resection was performed in 32 patients. The radiotherapy field was localized to the tumor (or tumor bed) in 59 patients and to the whole brain±localized field in the rest. The median treatment dose was 60 Gy(range, 20-60 Gy). Thirty-one patients received concomitant and 17 patients received adjuvant temozolomide.

Results: The median follow-up time was 5 months (range, 1-44 months). One and two-year survival rates for the whole group were 38.9% and 11.7%, respectively. Median survival times according to treatment fields were: 9 months in the localized group, 3 months in the whole brain group and 18 months in the whole brain+localized field group (p=0.04). Gender, performance status, radiotherapy dose, and the type of surgery did not significantly affect survival rates. Patients with midline tumors had poorer outcomes compared to other locations (p=0.01). Patients receiving adjuvant temozolomide had better overall survival (p=0.02).

Conclusion: Radiotherapy seems to be a feasible treatment strategy in elderly patients with glioblastoma. Although the patient number is small, the patients who received whole brain+localized field radiotherapy or adjuvant temozolomide had better survival in the current study.

Key Words: Glioblastoma; Radiotherapy; Temozolomide; Aged.

ARAŞTIRMA

YAŞLI GLİOBLASTOM HASTALARININ TEDAVİSİNDE RADYOTERAPİ

ÖZ

Giriş: Glioblastom insidansı yaşla artmaktadır. Bu çalışmada yaşlı glioblastom tanılı olguların radyoterapi sonuçları değerlendirilmiştir.

Gereç ve Yöntem: Haziran 2002 ve Aralık 2011 tarihleri arasında tedavi uygulanan 65 yaş ve üzeri 65 olgunun verileri değerlendirildi. Hastaların ortanca yaşı 70 olup (65-84 yaş) 45'i erkektir. Karnofsky performans durumu hastaların %82'sinde ≥70'tir. Otuz iki hastada gros tümör rezeksiyonu yapılmıştır. Radyoterapi 59 hastada lokalize alana (tümör/ tümör yatağı), 6 hastada tüm beyin ve lokalize alana yönelik uygulanmıştır. Tedavi dozu medyan 60 Gy'dir (20-60 Gy). Otuz bir hasta eşzamanlı, 17 hasta adjuvan temozolomide almıştır.

Bulgular: Ortanca izlem süresi 5 aydır (1-44 ay). Bir ve iki yıllık genel sağkalım oranları sırasıyla %38,9 ve %11,7'dir. Tedavi alanlarına göre bakıldığında ortanca sağkalım lokalize radyoterapi alan grupta 9 ay (7-11 ay), tüm beyin radyoterapisi alanlarda 3 ay (1-6 ay) ve tüm beyin ve lokalize alana yönelik radyoterapi alanlarda 18 aydır (3-18 ay) (p=0,04). Cinsiyet, performans durumu, radyoterapi dozu ve cerrahi tipi sağkalım oranlarını anlamlı olarak etkilememiştir. Orta hat yerleşimli tümörlerde diğer yerleşimli tümörlere göre hastalık daha kötü seyretmektedir (p=0,01). Adjuvan temozolamide alanlarda sağkalım daha iyi bulunmuştur (p=0,02).

Sonuç: Glioblastom tanılı yaşlı hastalarda radyoterapi uygun bir tedavi yaklaşımıdır. Bu çalışmada gruplarda hasta sayısı az olmakla birlikte tüm beyin ve lokalize radyoterapi alanlarda ve adjuvan temozolamide alan hastalarda sağkalım daha iyi bulunmuştur.

Anahtar Sözcükler: Glioblastom; Radyoterapi; Temozolomid; Yaşlı.

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Introduction

Glioblastomas (GB) account for 16% of all primary brain tumors. The incidence increases with advancing age, with the highest rates in those 75 to 84 years old. It is expected that in a few years, more than half of patients with GB will be over 65 years old (1). The current standard of care is surgery plus adjuvant concomitant temozolomide (TMZ) and radiotherapy (RT) followed by 6 cycles of adjuvant TMZ (2). It is known that age and performance status are the most important prognostic factors for GB (3-5). Furthermore, elderly patients generally have poor performance status and co-morbidities that interfere with their continuation with standard treatment. However, data related to the optimal management of elderly GB patients are still lacking. It has also been suggested that age alone should not disqualify patients from aggressive therapy with surgical resection, RT, and chemotherapy (6). To address the rarity of available data on elderly GB patients, we evaluated our therapeutic results in patients with GB older than 65 years, and assessed potential prognostic factors that impact on survival.

Materials and Method

The patient charts of all GB patients treated between January 2002 and December 2011 were assessed. Eligibility criteria were age older than or equal to 65 years, and confirmed histopathological or radiological diagnosis of GB. Patients who did not receive planned concurrent or adjuvant TMZ were included in the study. However, the patients who did not complete their planned RT sessions were excluded from the current study.

RT treatment field was localized to the tumor (or tumor bed) in 59 patients and to the whole brain (WB) ± localized field in the rest. The localized field involves the gross tumor volume (GTV) plus a margin for clinical target volume (CTV). For patients receiving 60 Gy localized RT, GTV was delineated using T1 contrast enhanced image sequences and CTV_{46Gy} was delineated using T2 or FLAIR sequences plus 2 cm on MRI. Subsequently, a 14 Gy additional dose was prescribed to GTV plus 1 cm (CTV_{60Gy}). The median treatment dose was 60 Gy (range, 20-60 Gy). In 6 patients, RT to the WB was delivered in 10 fractions to a total dose of 30 Gy. Three of these patients received an additional 15 Gy in 5 fractions as a booster dose to the tumor plus 1 cm. Thirty-one patients (31%) received concomitant TMZ and 6 patients received adjuvant TMZ. The concomitant TMZ dose was 75mg/m^2/day starting with the first day of RT. Adjuvant TMZ was delivered at 150 mg/m^2/day for 5 days in every 28-day period. Treatment characteristics are shown in Table 1.

Table 1— Treatment Characteristics of the Patients.

Characteristics	Patient Number = 65
Median (range) RT dose (Gy)	60 (20-60)
Treatment field	
Localized	59 (90.8%)
WB	3 (4.6%)
WB+ boost dose to tumor	3 (4.6%)
Concomitant TMZ	
Yes	31 (52%)
No	33 (48%)

Abbreviations: WB= Whole brain, TMZ= Temozolomide.

Overall survival was computed using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using SPSS 15.0 software (SPSS Inc., Chicago, IL).

Results

The data of 65 eligible GB patients formed the body of current analysis. The median age of the patients was 70 (range, 65-84 years). Forty-five (69%) of the patients were male and the Karnofsky performance status (KPS) was ≥70 in 82% of the cases. Gross tumor resection (GTR) was performed in 32 patients. Patients' characteristics are shown in Table 2.

Table 2— Characteristics of the Patients.

Characteristics	Patient Number= 65
Mean (range) age (years)	70 (65-84)
Median (range) tumor size (cm)	5 (3-8)
Gender	
Female	20 (31%)
Male	45 (69%)
KPS	
≥70	58 (90%)
<70	7 (10%)
Number of lesions	
Single	60 (92%)
Multiple	5 (8%)
Resection	
Complete	32 (49%)
Partial	19 (29%)
Biopsy	2 (3.0%)
No	12 (18%)

Abbreviations: KPS= Karnofsky performance status.

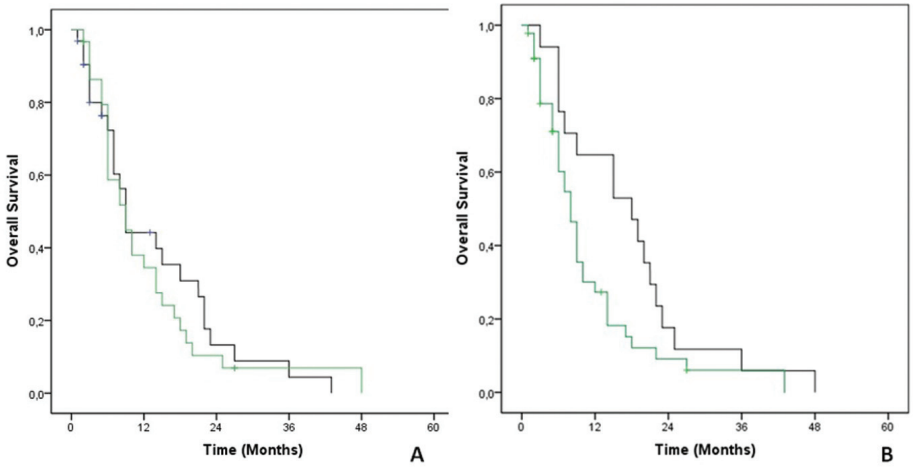

Figure 2— The effect of concomitant temozolomide (**A**), and adjuvant temozolomide (**B**) on survival (blue=with temozolomide, green=without temozolomide).

The median follow-up time was 5 months (range, 0-44 months). The tumor was unifocal in 60 patients (92%). Three patients had tumors located on the midline. KPS was ≥70 in 82% of the cases.

One and two year survival rates for the whole group were 38.9% and 11.7%, respectively. Median survival times according to treatment fields were: 9 months (range, 7-11 months) in the localized group, 3 months (range, 0-6 months) in the WB group and 18 months (range, 3-18 months) in the WB+ localized field group (p=0.04).

Gender, KPS, RT dose, number of tumors and the type of surgery did not significantly affect survival rates. Patients with midline tumors had poorer outcomes compared to other locations (p=0.01). Concomitant TMZ had no significant impact on survival; however, patients who received adjuvant TMZ had better survival (p=0.02) (Figure 1).

Discussion

In the current study we evaluated our treatment results in patients with GBM ≥65 years old and found that WB + localized field RT and adjuvant TMZ had a positive impact on survival; however, the addition of concurrent TMZ had no impact on survival.

It has been shown that older age and poor performance status are associated with poorer survival in patients with high grade glial tumors (3-5,7). However several studies have shown improved survival with treatment in elderly patients with GBM.

Iwamoto et al. reported their treatment results in 394 patients ≥65 years old. Approximately 82% of the patients underwent tumor resection; 81% received RT, and 43% received adjuvant chemotherapy. The median overall survival was 8.6 months. In the multivariate analysis, younger age, good KPS, single tumor, and surgical resection were found to affect survival. One hundred three patients who received adjuvant chemotherapy had a 55% decrease in the risk of death, compared with patients who had no additional treatment after RT (p<0.0001). They concluded that age alone should not disqualify patients from aggressive therapy with surgical resection, RT, and chemotherapy (6). Keime-Guibert et al. conducted a randomized trial comparing RT with supportive care alone for the management of GBM in patients 70 years of age or older (8). RT was delivered as a 1.8 Gy fraction dose to a total dose of 50 Gy. After 21 weeks of follow-up, the median survival for the 39 patients who received RT plus supportive care was 29.1 weeks, as compared with 16.9 weeks for the 42 patients who received supportive care alone (p=0.002). They concluded that RT improves survival without reducing the quality of life or cognition, in elderly patients with GBM. Scott et al. evaluated the role of RT in the treatment of GB in 2836 patients >70 years old from the SEER database. Multivariate analysis showed that RT improved CSS and OS, compared to patients who did not receive it (9). These studies have shown that RT should be delivered to elderly patients with GB, but they did not make any suggestions about the RT fields and doses.

Roa et al. randomized 100 patients with GBM, age 60 years or older, after surgery to receive either standard RT (60 Gy in 30 fractions over 6 weeks) or a shorter course of RT (40 Gy in 15 fractions over 3 weeks) (10). They found no difference in survival between the two RT arms. Median survival rates for the short and long course RT were 5.6 months and 5.1 months, respectively (p=0.63). There was an increase in post-radiotherapy steroids in the long course group. Malmström et al. randomized 291 patients who were over 60 years of age to receive TMZ (200 mg/m^2) on days 1-5 of every 28 days for up to six cycles, hypofractionated RT (34·0 Gy administered in 3·4 Gy fractions over 2 weeks), or standard RT (60·0 Gy administered in 2·0 Gy fractions over 6 weeks). For patients over 70 years of age, survival was better with TMZ and with hypofractionated RT than with standard RT (11).

In our study, 59 patients received the standard RT of 60 Gy in 30 fractions. However three patients who received a 30 Gy WB RT+ 15 Gy booster dose to the tumor had better survival. Although our patient group is too small to make a firm conclusion, hypofractionated RT might be a valid option for elderly patients with poor performance status. Concomitant TMZ did not affect the survival; however, 17 patients who received adjuvant TMZ had better survival. Iwamoto et al. also showed better survival in patients who received aggressive therapy including surgery, RT and chemotherapy. Furthermore, in the subgroup analysis of an EORTC/NCIC trial, patients older than 65 years had relatively diminishing benefits from the addition of TMZ to RT (12). It should also be kept in mind that those who received adjuvant chemotherapy were the ones with good performance status. Thus, this might be the reason for the long survival in this group of patients.

The retrospective nature of our study and the small number of patients in RT groups are both limitations of our study. However the number of elderly patients is increasing, leading to a challenge in making the proper treatment decisions. Prospective randomized studies should be carried out to form a guideline for this group of patients.

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