

## HYPERFRACTIONATED RADIOTHERAPY IN MALIGNANT ASTROCYTOMAS

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### ABSTRACT

**Purpose:** After conventional doses of 55 to 65 Gy of fractionated irradiation, anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) usually recur at its original location. The present study was designed to determine whether hyperfractionated radiotherapy (HFRT) would improve local tumor control and patients' survival. Also the factors effecting the prognosis in high grade astrocytoma were detected.

**Materials and Methods:** Between December 1994 and January 1996, 24 patients were enrolled to a prospective study. Patients were histologically confirmed with AA and GBM and previously untreated. A total dose of 69.6 Gy was delivered in 1.2 Gy fractions twice daily with an interval of 6 to 8 hours, 5 days per week. Clinical Target Volume (CTV) was established as Gross Tumor Volume (GTV) plus 2-2.5 cm and 0.5 cm was added as safety margin for Planning Target Volume (PTV).

**Results:** The overall median survival was 51 weeks, 54 weeks for AA, 45 weeks for GBM. Time to progression was 24 weeks. Age, performance status and histological subtype were significant predictors on survival. We did not observe any late toxicity depending HFRT.

**Conclusion:** Although we observed prolonged survival in our study compared with the conventional radiotherapy results in the literature, hard to say it is related to HFRT due to small number of patients. Our study gives an idea that HFRT can be easily applied and side effects are well tolerated.

**Key Words:** Radiotherapy; hyperfractionated, malign astrocytomas.

### MALİGN ASTROSİTOMLARDA Hİ- PERFRAKSİYONE RADYOTERAPİ

#### ÖZET

**Amaç:** Anaplastik astrositoma (AA) ve glioblastome multiforme (GBM), 55-65 Gy konvansiyonel radyoterapi sonrası orjinal lokalizasyonunda yinelemektedir. Bu çalışmada hiperfraksiyone radyoterapinin (HFRT) lokal tümör kontrolü ve sağkalım üzerine etkisi araştırılmıştır. Ayrıca yüksek grad astrositomalarda prognostic faktörler de incelenmiştir.

**Gereç ve Yöntemler:** Aralık 1994- Ocak 1996 tarihleri arasında daha önce tedavi almamış histolojik olarak AA veya GBM tanılı 24 hasta çalışmaya dahil edilmiştir. Günde 2 kez, 6-8 saat aralarla 1.2 Gy/fraksiyonlarda toplam 69.6 Gy uygulanmıştır. Klinik Hedef Volüm, Gros Tümör Hacmine 2-2.5 cm eklenerek hesaplanmıştır.

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**Bulgular:** Ortalama sağkalım 51 hafta, AA için 54 hafta, GBM içinse 45 haftadır. Progresyona kadar geçen süre 24 haftadır. Yaş, performans durumu ve histolojik alttip sağkalım için anlamlı belirteçlerdir. Çalışmamızda HFRT'ye bağlı geç yan etki gözlemlenmedi.

**Sonuç:** Literatürde konvansiyonel RT uygulanmış çalışmaların sonuçları ile karşılaştırıldığında, bizim çalışmamızdaki sağkalım süreleri daha uzundur ancak hasta sayısı az olduğu için bu sonuçlar HFRT ile ilişkilendirilememiştir. Çalışmamızın sonuçlarına göre, HFRT kolay uygulanabilen ve yan etkileri iyi tolere edilebilen bir tedavi şeklidir.

**Anahtar Kelimeler:** Radyoterapi, hiperfraksiyone; malign astrositom.

## INTRODUCTION

Primary brain tumors account for one percent of all types of cancers. They are more common in man than woman with the ratio of 3/2. The frequency of intracranial tumors is increasing with age.

Malign astrocytomas are primary brain tumors in adults. They have a well established propensity for local invasiveness and tumor recurrence at or adjacent to, their original location. Median survival is generally less than one year from the time of diagnosis, and even in the favorable situations, most patients die within two years (1). Standard therapy consists of surgical resection to the extent that is safely feasible, followed by radiotherapy. Chemotherapy is added to the management in some cases. Many approaches have been used including different fractionation models (2,3) radiosensitizers (4), interstitial brachytherapy (5), radiosurgery (6), adjuvant, neoadjuvant and concomitant chemotherapy (7,8,9).

HFRT involves the use of smaller than standard fractions given several times per day. Higher total doses are given in a similar overall treatment time as standard single fractionated radiation. The theoretical benefits of HFRT are: an increase tumor killing while late tissue effects are equivalent, for lower RT fraction sizes, oxygen enhancement ratio is lower so reducing hypoxia to radioresistance and this approach let the total dose increase, it doesn't cause additional toxicity (10,11). A strong relationship appears to exist in central nervous system (CNS) irradiation between RT fraction

size and the risk of the late CNS injury, especially radiation necrosis (12). There are both laboratory and clinical data demonstrated a larger sparing of late CNS RT effects for the same total dose when smaller fraction sizes are utilized. Because of this reason, CNS tumors are relatively radioresistant lesions, well suited to use HFRT (11).

According to these informations, the objective of this study is to evaluate the tolerability of HFRT with higher biologically effective doses (BED) in comparison with conventional radiotherapy and analyze the prognostic factors in high grade astrocytomas.

## MATERIAL AND METHOD

Twenty six patients diagnosed with AA and GBM were enrolled to HFRT schedule. Two of them died with another illness during the therapy. Median follow-up period was 39.5 week. The median symptom period before diagnosis was 32 days (3 days - 6 months). Karnofsky Performans Status (KPS) was used to appraise the performance of patients, where it was between 80-100 in 6 (25%) cases and 70-30 in 18 (75%) cases.

Histopathological test results revealed that 12 (50%) cases had GBM and the other 12 (50%) had AA. Lesions were placed infratentorial in 4 (16.6%) cases and supratentorial in 20 (83.4%) cases. 22 patients (91.6%) underwent to surgery. Only 2 (8.4%) of them had diagnosis with biopsy. In 7 (29.16%) patients 80-100% of tumor was removed and 79% or less in 17 (70.8%) patients.

All cases had taken a local therapy. Clinical Target Volume (CTV) was established as Gross Tumor Volume (GTV) plus 2-2.5 cm and 0.5 cm was added as safety margin for Planning Target Volume (PTV). Twice daily fractions of 1.2.Gy were delivered 5 days per week up to a total dose of 69.6 Gy radiotherapy was delivered with 6-8 hours interval using gamma rays of Co 60 and isocentric (SAD) technique. The biological effective doses applied to tumor and normal brain tissue was calculated according to linear quadratic model.

For the purpose of evaluation of response to RT, CT or magnetic response imaging (MRI), are done before operation, pre-RT and two months after RT. Before RT, patients routinely underwent complete blood counts,

biochemical tests and neurological testing. During RT, patients were to be seen every week. After the end of RT, patients were seen in the first month. Then, they were seen at 2-month intervals during the first year.

Response criteria were as follows: complete response (CR) was defined as the disappearance of all enhancing tumors on CT scans, off steroids and neurologically stable. Partial response (PR) was defined as 50% or greater reduction in the size of the enhancing tumor on CT scans, stable or reduced steroids and neurologically stable. Progressive disease (PD) was defined as 49% or less reduction in the size of the enhancing tumor or neurologically worse.

Survival rates were determined with Kaplan-Meier analysis dating from operation date to last control date, and log-rank test was

used to determine the distinction between the groups. A p value of less than 0.05 was considered statistically significant.

## RESULTS

HFRT was used for 24 patients with AA and GBM. Median follow-up period was 39.5 weeks. Overall the median survival time was 51 weeks and the expected survival ratio at one year was found as 52% (Fig. 1). At two months follow up control CT was asked for every patient and CR was observed in 10 patients (41.7 %) while PR in 8 (33.3 %) and PD in 6 patients (25%). Complete and partial response patients showed 52.3 weeks median survival, while patients who had no response showed 46 weeks. No significant differences in these outcomes were found between the two groups ( $p > 0.05$ ). Median time to progression was 24 weeks.

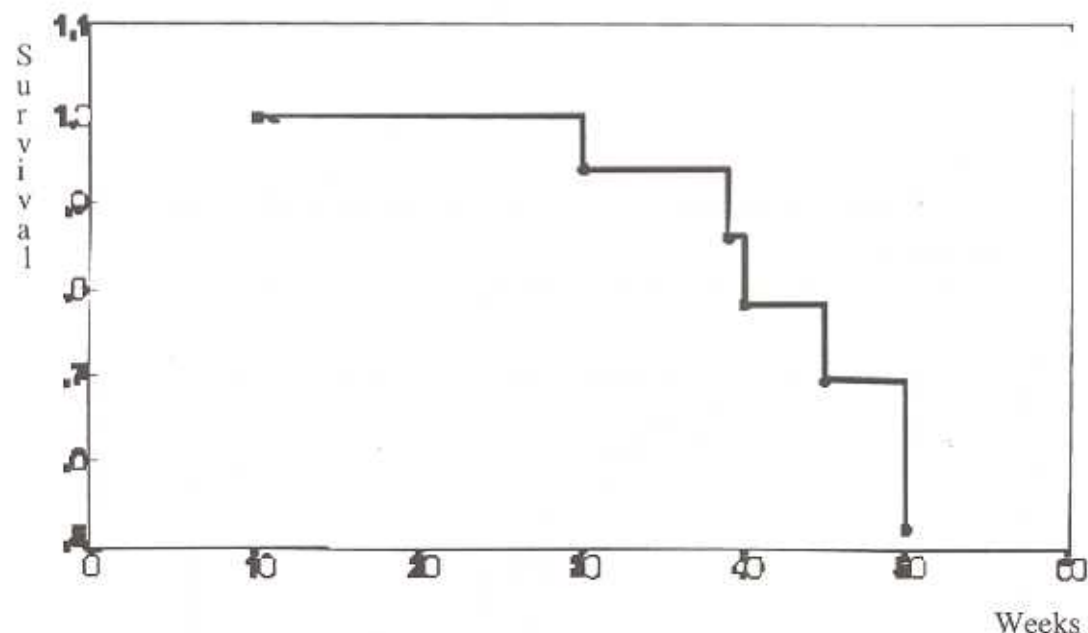


Figure 1. Overall survival of all patients.

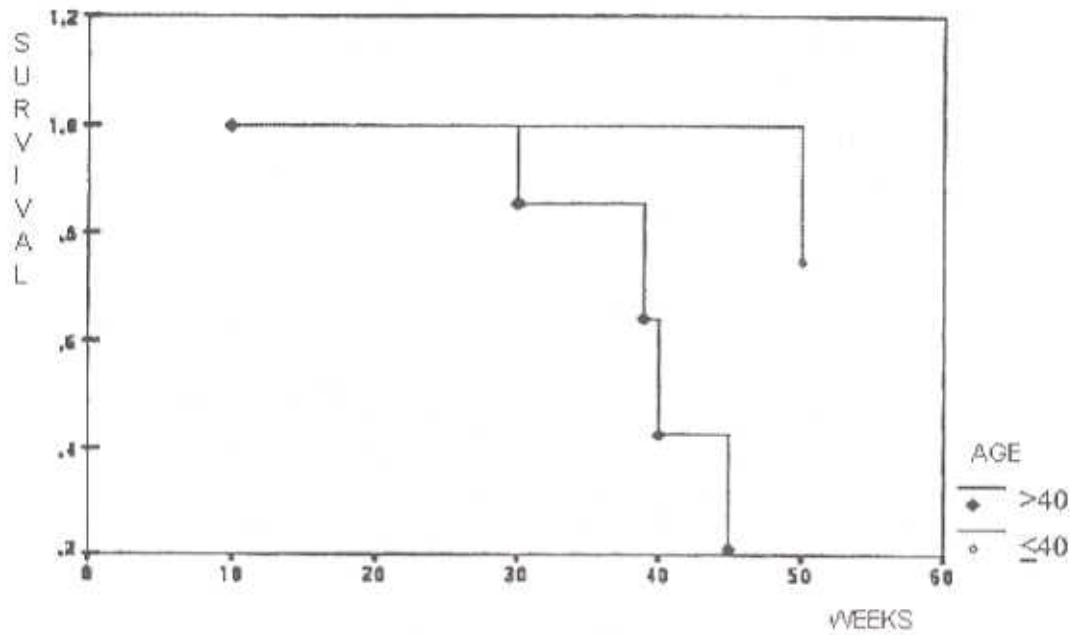


Figure 2 . Survival according to age ( p<0.05).

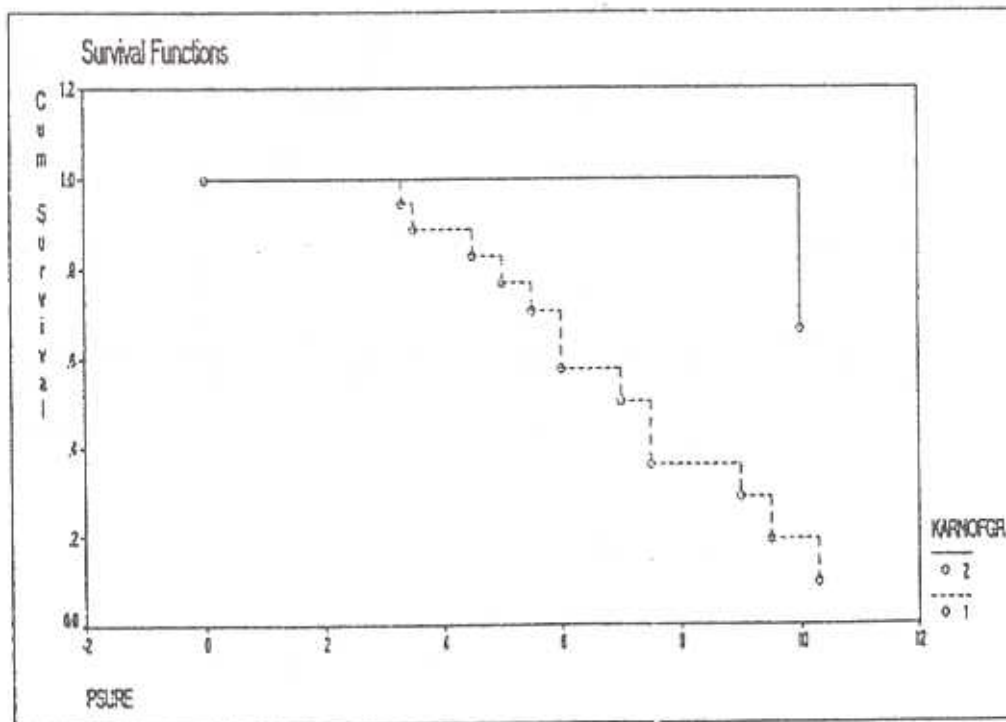


Figure 3. survival according to KPS ( p<0.05).

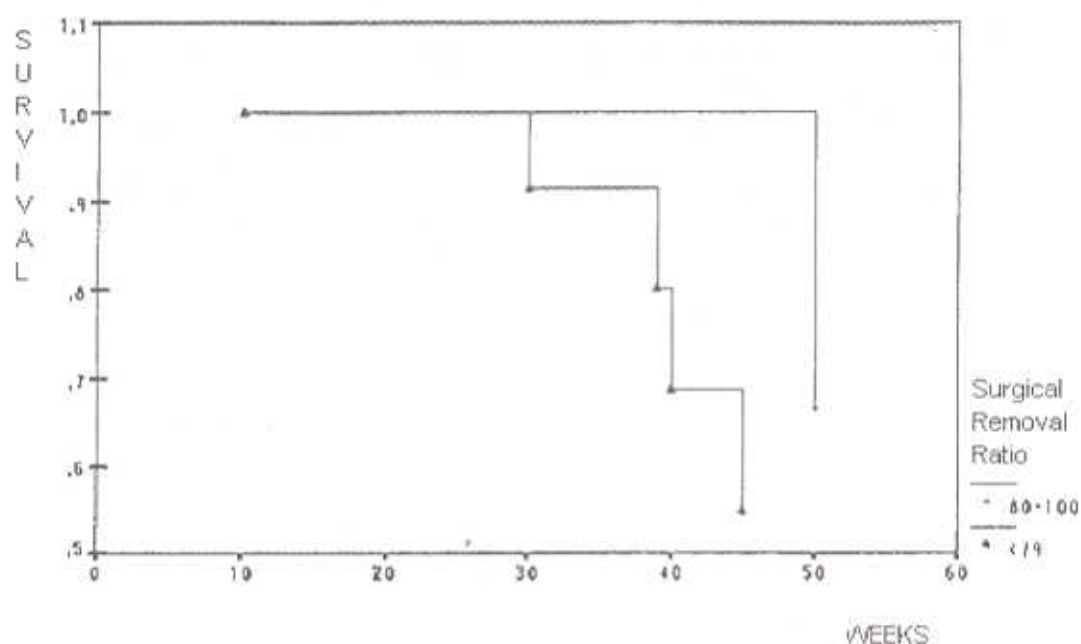


Figure 4. Survival according to surgical removal proportion ( $p < 0.05$ )

We also investigated the effect of patients' age at diagnosis to the median period to progress and median survival, we found that survival in younger than 40 years old and older patients than this were 58 weeks and 40 weeks, respectively ( $p < 0.01$ ) (Fig. 2). Gender had no meaningful effect on median period until progression and survival ( $p > 0.005$ ). The median period to progress in AA was 40 weeks, compared with 20 weeks for the GBM, which shows a significant difference between the two histopathologic subtypes. Median survival in AA was 54 weeks, while it was 45 weeks in GBM ( $p < 0.05$ ). Patients were divided into two groups according to KPS values: In the first group KPS values were between 80-100 and those in the second group had 30-70. In the second group where KPS values were equal or less than 70, median survival was significantly shorter than the first group ( $p < 0.05$ ) (Fig. 3). Tumor volume before operation was 9.6 cm on an average. There was no clear distinction between the patients with tumor volume of  $< 16$  cm or  $> 16$  cm ( $p > 0.005$ ). The effect of surgery on prognosis was evaluated and concluded that in cases with 80-100% of tumor removal median survival was 55.3 weeks, compared to 47.4 weeks in cases with less than 80% removal. This finding suggests that surgical removal proportion had

no significant effect on median survival (Fig. 4).

The patients' characteristics and the effects of prognostic factors on median survival is shown in Table-I.

Table I. Patients' characteristic and analysis of prognostic factors

COVARIATE	NUMBER	P VALUE	MEAN SURVIVAL WEEK
AGE			
13-40	14		58
41-65	10	$P < 0.01$	40
SEX			
female	9		49.5
male	15	$p > 0.05$	50
KPS			
100-80	6		53
70-30	18	$p < 0.05$	43
PREOP TUMOR VOLUME			
$> 16$ cm	7	$p > 0.05$	52.1
$< 16$ cm	17		48.2
HISTOLOGY		$p < 0.05$	
AA	12		54
GBM	12		45
EXTEND OF SURGICAL RESECTION			
Subtotal	17	$p > 0.05$	47.4
Gross total	7		55.3

Alopecia and mild to moderate hyperemia within the treatment volume were observed in all patients. Also, there was dry desquamation in 3 (12.5%) cases and wet desquamation at retroauricular area in 1 (4.16%) patient. 4 (16.6%) patients suffered from nausea and vomiting responded well to standard antiemetic treatment without any interruption. 1(4.16%) patient had high blood glucose level because of steroid treatment and turned to normal levels with antidiabetics. Serous otitis media was seen in 1(4.16%) case. There was brain edema in 1(4.16%) case, causing deferral of RT for one week. Overall no patient showed atrophy or brain necrosis in controls.

### DISCUSSION

High grade astrocytomas are the most common brain tumors in adults. But according to many studies their treatment results are not successful. Kernohan classification has been used to classify malign gliomas for many years. Grade 4 tumor prognosis is worse than grade 3 tumor (13,14). Necrosis is accepted as a prognostic factor in malign astrocytomas. Malign astrocytomas with necrosis are assessed as GBM, while the other high grade astrocytomas without necrosis are classified as AA. Median survival in GBM and in AA has been found 32 and 72 weeks respectively (15). Since long term tumor control and survival were not achieved with conventional RT in high grade astrocytomas, in this current study, HFRT was used to overcome the poor results of high grade astrocytomas and to evaluate the tolerability of this altered fractionation schedule. Walker et al. (16), showed that increasing of total dose, resulted in survival improvement in supratentorial malign astrocytomas. HFRT involves the use of smaller than standard fractions given more than one times per day. Higher total doses are given in the same overall treatment time when compared with conventional radiotherapy. This schedule, reduces the risk of late radiation injury while at the same time it increases the chance for tumor cell killing (3). In HFRT it is possible to increase the effective dose applied to tumor without exceeding the brain tolerance dose.

Several studies have been reported using different fraction schedule with concomitant chemotherapy. In RTOG 83-02 study, evaluating 64.8Gy, 72.0Gy, 76.8Gy and 81.4Gy using twice-daily fractions of 1.2 Gy

and all patients received adjuvant BCNU chemotherapy. While 72 Gy tended to have benefit in the beginning, it didn't show survival advantage to 60 Gy standard RT (17). In prospective phase II study conducted by EORTC included 66 patients, applied accelerated hyperfractionated RT. Total doses used were 42 Gy, 48 Gy, 54 Gy, 60 Gy using 3 fractions per day of 2 Gy. Median survival was determined as 8.7 months. Any of the groups was not superior to the others and they didn't overwhelm fractionated treatment scheme. It was also suggested that tumor repopulation was not a major factor in radioresistant property of GBM (18).

In patients with malign glioma chemotherapy given as an adjunct to RT or before RT for several years but such treatment has had limited success. (19,20).

Stupp et al. (9) had determined a randomize prospective study, for newly diagnosed and histologically confirmed glioblastoma. Patients were divided into two groups. The control group received standart local radiotherapy alone, the patients in the other group were received standart radiotherapy plus concomitant daily temozolomide, followed by adjuvant temozolamide. According to this study, addition of temozolomide to radiotherapy early in course of glioblastoma provides a statistically significant and clinically meaningful survival benefit.

In our study median survival was 51 weeks and median time to progression was 24 weeks. Median survival in GBM was 45 weeks, while it was 54 weeks in AA. We conclude that HFRT might be the choice to prefer, because the therapy was well tolerated by the patient. The most common acute toxicity in our study was skin reaction. There was only one side effect to discontinue the treatment and no additional late adverse events.

In the present study, the most important prognostic factor was age, histological subtype and performance status as confirmed in the literature (21,22). The median survival in patients, younger and older the age of 40 years, are 58 and 40 weeks, respectively. There are some studies in literature showing that the older ages lower the life duration (23,24,25,26).

Whittle et al. (27) had demonstrated the importance of preoperative clinical grade and radiation treatment in determining outcomes in patients over 60 years. KPS was also observed as a prognostic factor effecting survival. Brandes et al. (28) had determined in a prospective study for elderly patients with good performance status definitive radiation therapy and adjuvant chemotherapy with temozolamide was advised.

There was no relationship between preoperative tumor size and prognosis. Although Jonathan et al. (29) showed a strong relationship between postoperative tumor size and survival, we didn't observe a meaningful effect of surgical removal on survival.

In our study, median survival in patients with complete and partial response was 52.3 weeks, while in patients with less than 50%

reduction in tumor or progression was 46 weeks but it was not statistically significant. Andreou et al. (30) showed that the reduction in tumor size after RT prolonged the survival, in 115 cases. In another study, it was shown that 50% or more reduction in tumor size after RT prolonged survival (16).

In conclusion, although our results are better than literature results, it is hard to say HFRT is superior, because of the small number of patients. Our study gives an idea that HFRT can be easily applied and side effects are well tolerated. Considering the prognostic factors, randomized studies with different fraction models, radiosensitizers and newer chemotherapy strategies are warranted to reach clear results about survival and late side effects.

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