

**5 cm ve Daha Büyük Beyin Metastazlarında Cyberknife® Fraksiyone Stereotaktik Radyoterapi**

**Cyber Knife® Fractioned Stereotactic Radiotherapy for Brain Metastases of 5 cm or Greater Dimensions**

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**Özet**

**Amaç:** Cyberknife® stereotaktik radyocerrahi (SRC) veya fraksiyone stereotaktik radyoterapi (FSRT), beyin metastazlarında önemli bir tedavi modalitesidir. Stereotaktik radyoterapi soliter beyin metastazlarında uygulandığı gibi büyük ve multiple beyin metastazları için de yararlıdır. Bu yazıda 5 cm üstünde beyin metastazlarında fraksiyone stereotaktik radyoterapi uyguladığımız 10 hastanın sonuçları sunulmaktadır.

**Gereç ve Yöntem:** Ankara Onkoloji hastanesinde Mayıs 2009-Nisan 2012 tarihleri arasında, beyin metastazı 5 cm üstünde olan 10 hastaya tüm beyin radyoterapisi ve Cyberknife (CK) uygulandı. Altı hastaya FSRT, 4 hastaya da SRC, ya palyatif tüm beyin radyoterapisine ek olarak ya da tüm beyin radyoterapisi sonrası yineleme için uygulandı. Hastaların medyan yaşı 58 (aralık, 26-67 yıl), medyan tümör çapı 53 mm (aralık, 50-69 mm), 1-3 fraksiyonda medyan toplam doz 1500 cGy (aralık, 1320-1800 cGy), medyan izodoz %91 (aralık %76-96) idi.

**Bulgular:** Cyberknife tedavisi sonrası ortalama takip zamanı 6.5 ay idi. Bir yıllık sağkalım oranı % 66.7, ortalama sağkalım 11.1 ay (aralık, 7.3- 14.9 ay) idi. Grad 3-4 herhangi bir akut toksite gözlenmedi.

**Sonuç:** Sonuçlarımız gösterdi ki FSRT 5 cm üstünde seçilmiş beyin metastazlarında güvenli olarak uygulanabilen ve etkili bir lokal tedavi modalitesidir. Büyük beyin metastazlı hastalarda Ck tedavisinin rolünü daha iyi tanımlamak için, uzun süre takipli daha çok çalışmaya ihtiyaç vardır.

**Anahtar Kelimeler:** Fraksiyone Stereotaktik Radyoterapi, Cyberknife, Beyin metastazı

## Abstract

**Objective:** CyberKnife® Stereotactic Radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) is an important treatment modality for brain metastases. As well as soliter brain metastasis Cyberknife® (CK) is also a useful stereotactic radiotherapy option for limited multiple or large metastases. Here we present our results of fractionated stereotactic radiotherapy (FSRT) for 10 patients with metastatic brain tumors greater than 5 cm.

**Material and Methods:** Between May 2009 - April 2012 in Ankara Oncology Hospital, Ankara, Turkey 10 patients with metastatic brain tumors greater than 5 cm in greatest dimension –were treated with whole brain radiotherapy (WBRT) and CK, FSRT. FSRT (6 patients) or SRS (4 patients) were applied to patients either as a part of initial palliative treatment with WBRT or for recurrent metastatic disease after WBR. The median patient age was 58 years (range 26 - 67 years). Median tumor diameter was 53 mm (range, 50 - 69 mm). Median total dose was 1500 cGy (range, 1320 - 1800 cGy) in 1-3 fraction. Median isodose was 91.0% (range 76 - 96%).

**Results:** After CK treatment, mean follow-up time was 6.5 months. 1-year overall survival rate was 66,7 %. Mean survival time was 11,1 months (range, 7,3-14,9 months). The treatment was well tolerated with no RTOG grade 3-4 acute toxicities.

## Conclusion:

Our results showed that FSRT is a safe and effective local treatment modality in selected patients with  $\geq 5$  cm diameter brain metastases with minimal serious adverse events. Further large studies with longer follow-up are needed to define the

role of CK in the treatment of large brain metastases as a part of initial palliative treatment or after progression.

**Key words:** Fractionated stereotactic radiotherapy, Cyberknife, brain metastasis

## Introduction

Among cancer patients, the incidence of brain metastasis is 20-40% and survival is only a few months. Treatment options of brain metastases include whole brain radiotherapy (WBRT), surgery and stereotactic radiosurgery (SRS) or combination of these (1-4). Nowadays patients with systemic cancer live longer and so this rate tends to increase. Prognostic factors associated with survival are age, extent of systemic disease, Karnofsky performance status (KPS) and number, size, location of brain metastases (2-4). Whole brain radiotherapy (WBRT) is the first and most common treatment option for brain metastases, especially for multiple and large-sized tumors (1,5). Whole brain radiotherapy improves survival from 3 to 5 months but can lead to short and long term side effects (eg: alopecia, fatigue, cognitive problems ) (6,7,8).

CyberKnife® is a new and non-invasive stereotactic radiotherapy method that can give a maximum dose to tumor precisely while preserving critical structures. Despite ideally CK is used for a single brain metastasis, it can also be used to treat multiple brain metastases (9-12). In general CyberKnife® SRS (only one fraction) or fractioned stereotactic radiotherapy (FSRT), (more than one fraction), is administered for lesions with a diameter of around 3 cm ( $\leq 4$ cm),  $\leq 3$

metastases and for patients having a good performance status (9,13). Treatment of large brain metastases even with FSRT results in low local control rate (14) and is not well defined treatment option yet.

Surgical resection is an effective and a safe treatment option for a large, single brain metastasis (15,16). However, treating ability for multiple lesions in one session and any location in the brain with FSRT has advantages in terms of side effects and survival compared to surgery (9,17,18,19). While for large tumors side-effects of FSRT, especially radiation-related necrosis is more frequent (9,14,20), there is no studies which showed the efficacy and safety of single-fraction radiosurgery for large brain metastases. Only one prospective RTOG trial established that 15 Gy in one session can be applied for tumors with volume between 14-33 cm<sup>3</sup> (20). It seems that doses must be reduced for larger brain lesions of about 30 cm<sup>3</sup> (21).

## **Patients and Methods**

Between May 2009 - April 2012, 10 patients with brain metastases equal or greater than 5 cm were treated with CK in Ankara Oncology Hospital, Ankara, Turkey. While 4 of these patients had only one, 5 patients had 2 and 1 patient had 3 metastases. All of the patients had only one large ( $\geq 5$ cm) metastatic brain tumour. The

median patient age was 58 years (rang, 26 - 67 years). Primary tumor locations were lung in four patients, breast in three, rectal malign melanoma in one, bone in one (osteosarcoma) and unknown primary for the remaining one patient. Three of them had also extracranial metastases. One patient had surrenal and liver metasteses and two had lung metastases before brain metastases diagnosed. Karnofsky Performance Scale score was  $\geq 70$  and recursive partitioning analysis (RPA) was class I-II for nine patients. For the remaining one KPS was below 70. Between initial symptoms were epileptic seizures, speech defects, headache, dizziness, amnesia, motor deficit. Also one of the patients was asymptomatic. Patient and tumor characteristics are shown in table 1.

**Table 1.** Patients and tumor characteristics

<b>Characteristic Value</b>	
<b>Patients</b>	<b>10</b>
<b>Gender</b>	
Male	7
Female	3
<b>Age (years)</b>	
Median	58
Range	26-67
<b>Primary site</b>	
Lung	5
Breast	2
Rektum	1
Bone	1
Primary unknown	1
First treatment CKSR(n)	1
First treatment WBRT(n)	9
<b>Tm diameter (mm)</b>	
Median	53
Range	50-69

Nine patients had treated with WBRT, 30 Gy in 10 fractions before CK. While three of these patients received radiosurgery or FSRT three weeks after WBRT, six patients received CK when progression occurred. For these six patients median time between WBRT and CK was 2.5 months (range, 1 – 13 months). Out of 10, remaining one patient initially was treated with CK and three weeks later received WBRT 25 Gy in 10 fractions. Median fraction number was 3 (3 fractions for 6 patients and 1 for the other 4 patients). Median prescribed dose was 1500 cGy (range, 1300 - 1800 cGy) and a

median isodose line was 91% (range, 76 - 96%). For the single fraction treatment (SRS) a median prescribed dose was 1500 cGy (range, 1400 - 1700 cGy), and for FSRT median prescribed dose was 1450 cGy (range, 1300 - 1800 cGy). Sequential planning algorithm was used for all patients. The median homogeneity index was 1.090 (range, 1.04 – 1.32) and the median of coverage was 99.80 % (range, 97 - 100 %). Median tumor volume was 40642 mm<sup>3</sup> (2184 - 77849 mm<sup>3</sup>) and the median tumor diameter was 53.0 mm (range, 50 - 69 mm). Treatment characteristics are shown in table 2.

**Table 2.** Treatment characteristics.

Patient No	WBRT Dose (cGy)	Time interval WBRT-CKSR	GTV Volume (mm <sup>3</sup> )	Fraction of CKSR	Prescribe Dose (cGy)	Prescribe Isodoseline (%)	HI	Coverage (%)	Tumor diameter (mm)
1	3000	3 months	44125	3	1300	76	1,32	99,8	54
2	3000	2 months	2184	1	1700	91	1,10	100,0	69
3	3000	7months	50623	1	1400	92	1,09	99,9	50
4	3000	3 weeks	5809	1	1400	89	1,12	99,9	57
5	3000	2 months	40642	3	1400	80	1,16	100,0	59
6	3000	3 weeks	77849	3	1400	80	1,25	97,0	50
7	2500	3 weeks	59335	3	1500	88	1,14	99,4	58
8	3000	4 weeks	20159	1	1600	92	1,09	99,0	52
9	3000	13 months	29545	3	1800	96	1,04	99,9	53
10	3000	3 weeks	12283	3	1800	94	1,06	99,9	51

Critical structures were delineated on computer tomography (CT); target volumes were defined on CT/ magnetic resonance imaging (MRI) fusion data set based on MRI images. The planning tumor volume (PTV) was equal to gross tumor volume (GTV) with no margin due to nearby critical structures. All patients received intramuscular dexamethasone (8 mg) before treatment.

## Results

We retrospectively analyzed 10 patients with brain metastases equal or greater than 5 cm who were treated with CK in addition to WBRT as an initial palliative treatment (4 patients) or because of progression after WBRT (6 patients) in Ankara Oncology Hospital between May 2009 - April 2012. The follow-up period after CK treatment ranged from 1 month to 15 months (median 4 months).

After stereotactic treatment, 1-year survival rate was found as 66,7% and mean survival time was 11,1 months (range, 7,3-14,9). Three of the patients died from systemic progression. Median time to death for these patients was 5 months (range, 4 - 8 months). Out of these 3 patients, at the time of death, one had a complete response, one had a partial response with 50% regression and the last one had 10% progression for brain metastases, radiologically. Remaining seven patients were still alive at the time of data collection. Three of these patients were alive with regression, three patients were alive with stable disease and one patient was alive with progression of brain metastases. Progression rate was radiologically 25 % for this patient. So crucial radiological response rate for brain metastases was 80% with four months median follow-up. All patients were

evaluated with MRI after CK treatment. Timing for follow-up images were variable for all patients depending on new symptom onset. The treatment was well tolerated with no grade 3-4 acute toxicities according to the RTOG acute toxicity criteria.

## Discussion

Although for patients with a large single brain metastasis surgical resection can be one of treatment options it may not be always feasible due to nearby critical structures. In this case FSRT with or without WBRT can be applied.

There are some studies which compared radiosurgery alone versus SRS and WBRT (19,22,23). While Chidel et al.'s study (22) there is a trend for survival benefit with only SRS over SRS+WBRT (10.5 vs. 6.4 months, respectively,  $p=0.07$ ), in other two studies overall survival (OS) was same (19,23). Although in Flickinger's study (23) local control (LC) was better with SRS+WBRT, in Sneed's study (19) it was same. In two of these studies it is also impressed that SRS alone and SRS+WBRT could not improve survival, because of progression of extracranial disease (22,23). Besides there are some studies conducted with FSRT and WBRT which recorded median survival as 11 and 12 months (24,25). So, despite slightly different conclusions SRS alone or combined with WBRT seems like promising for brain metastases in selected cases.

SRS is an optimal treatment option for patients with tumors large and/or close to nearby critical brain structures. In one study comparing SRS with a fractionated stereotactic radiotherapy (FSRT) for brain

metastases, it was concluded that while survival times were similar for both treatment regimens, lower toxicity rates were reported with FSRT treatment, although FSRT was used for large lesions and lesions in adverse locations (24). So the authors found that FSRT can be especially useful for patient with large lesions or lesions located near critical structures. In our study with large brain metastases we used SRS or FSRT. The treatment choice was depending on the clinician's discretion. With both treatment we didn't see any acute serious side effect.

In their prospective study Manning et al. revealed treatment results of 32 patients treated with FSRT of 27 Gy in 3 fractions and 30 Gy in 10 fractions with WBRT (25). They recorded median survival as 12 months.

Aoyama et al. performed FSRT with 35 Gy in 4 fractions and recorded median survival time as 8.7 months (26). In their study WBRT was used as a salvage treatment. Patients treated with FSRT, in this study, had similar tumor control and survival results with SRS given in the literature. They also suggested FSRT due to less toxicity compared to SRS.

Ernst-Stecken et al. performed FSRT to 51 patients who could not receive single fraction because of a tumor larger than 3 cm or closed to critical structures (27). Treatment was given as FSRT with 5 X 6 Gy if WBRT was added or as 5 X 7 Gy for FSRT only treatment. The median survival was 11 months. They suggested that FSRT is an effective and safe treatment when SRS could not be applied. They also recommend not exceeding 20 cc per fraction of  $>4$  Gy. In our current retrospective study, due to very large tumors we had to exceed this

recommandation for some of the patients. Although we didn't see any grade 3-4 acute side effects, due to very limited number of patients and retrospective nature of the study, we can't argue that large fraction doses or SRS is a safe for large brain metastases. Despite of larger tumour size in our study we found mean survival time as 11 months which is similar with their results.

There are very limited number of studies reporting FSRT results for patient with large (>3 cm) brain metastases. In one of these studies 150 patients with 250 brain metastases were treated with different fractionation schedules using FSRT and authors concluded that while longer fractionation (10 X4 Gy) is better tolerated than shorter ones (5 X 6-7 Gy, 7 X 5 Gy), response rate was higher with short fractionation (28). Complete response rates for 10 X 4 Gy, 7 x 5 Gy and 5 X 7 Gy were 31%, 47%, and 46%, respectively. Median follow up time for this study was 16 months. .

Additionally, Narayana et al. applied FSRT 30 Gy in 5 fractions to 20 patients for whom SRS could not be performed because of locations or size of tumors (29). Median survival was 8.5 months. Kwon et al. recorded that maximum tumor dimension and tumor volume were important factors improving local control (30). Finally authors concluded that FSRT can be effectively used for larger tumors and the risk of toxicity after FSRT was very small (25,29,30).

Surgical resection had an important role in the treatment of 1 or 2 brain metastases. For solitary metastases

resection plus WBRT had better survival and local control rates than WBRT alone (31,32). In a study, comparing resection versus resection plus WBRT brain recurrence rates were 85% and 21% respectively (33). Patchell et al. (34) showed that local control for patients who received postoperative WBRT was better (82% vs 30%). Schoggl et al. (35) retrospectively evaluated 133 patients comparing SRS plus WBRT with surgery plus WBRT. They reported that for median survival there was no difference, but local control rate was better in the SRS group. Rades et al. compared stereotactic radiosurgery versus surgical resection plus WBRT (36). They concluded that SRS alone is an alternative treatment to resection plus WBRT because of being less invasive, less time consuming and more cost –effective approach. In our study for all patients we used WBRT as a part of initial palliative treatment. Also majority of our patients had multiple brain metastases in addition to large ones. Our crude rate of progression was 20% and this is consistent with the other studies adding WBRT to surgery or stereotactic treatment.

**Table 3.** Table of studies.

Author	SRS	SRS+WBRT
Chidel et al. (22)	MS: 10.5 mos 2-y-DFS: 34%	MS: 6.4 mos (p:0.07) 2-y-DFS: 60% (P:0.03)
Sneed et al. (19)	MS: 11.3 mos 1-y-LC: 71%	MS: 11.1 mos 1-y-LC: 79%
	SRS	FSRT
Yean et al. (24)	MS: 6 mos 1-y-LPFS: 71% CR: 16% PR: 51% NC: 26% PD: 7%	MS: 8 mos (p:0.89) 1-y-LPFS: 69% CR: 15% PR: 68% NC: 17% PD: 0%

MS: Median Survival, DFS: Disease-Free Survival, LC: Local Control, LPFS: Local Progression-Free Survival, CR: Complete Response, PR: Partial Response, NC: No Change, PD: Progressive Disease

**Table 4.** Summary of studies.

Author	Dose	WBRT	Results	MS
Manning et al (25).	25 Gy/ 3 fx	30 Gy/ 3 fx	CR: 45% PR:- NC: 45% PD: 9%	12 mos
Aoyama et al (26).	35 Gy/ 4 fx	salvage	1-y-LC: 81%	8.7 mos
Ernst-Stecken et al (27).	30 Gy/ 5 fx 35 Gy / 5 fx	+ -	CR: 66.7% PR: 18.1% NC: 12.5% PD: 2.8%	11 mos
Fahrig et al (28).	30-35 Gy/ 5 fx 35 Gy/ 7 fx 40 Gy/ 4 fx	40 Gy/ 20 fx	CR: 42% PR: 30% NC: 21% PD: 7%	16 mos
Narayana et al (29).	30 Gy/ 5 fx	-	CR: 15% PR: 30% NC: 45% PD: 0%	8.5 mos
Kwon et al (30).	25 Gy/ 5 fx	37.5 Gy/ 5 fx	CR: 25% PR: 23% NC: 42% PD: 10%	10.8 mos

MS: Median Survival, CR: Complete Response, PR: Partial Response, NC: No Change, PD: Progressive Disease



We retrospectively analyzed a small group of patients who had  $\geq 5$  cm diameter brain metastases. To our knowledge, there is no study revealing stereotactic radiosurgery or radiotherapy results with CK for such a big metastases.

We concluded that CK, especially FSRT can be effectively and safely applied for large brain metastases in addition to WBRT. However we need longer follow up and larger series.

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