

Cyberknife® Radiosurgery and Fractionated Stereotactic Radiotherapy For Brainstem or Adjacent-to-Brainstem Metastases

Beyin Sapı veya Beyin Sapına Yakın Metastazlarda Cyberknife® Radyocerrahisi ve Fraksiyone Stereotaktik Radyoterapi

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ABSTRACT Objective: The objective of this small retrospective study is to report imaging and clinical outcomes of the patients with metastatic brain tumors in or adjacent (≤ 5 mm) to brainstem. The patients underwent both whole-brain radiotherapy (WBRT) and CyberKnife® fractionated stereotactic radiotherapy (FSRT)/or stereotactic radiosurgery (SRS). **Material and Methods:** Twenty-one patients with single or multiple brain metastases located in or adjacent to brainstem underwent FSRT/SRS between September 2007 and June 2011 at Ankara Oncology Hospital, Ankara, Turkey and Kartal Hospital, İstanbul, Turkey. Primary tumor locations were lung in 12 patients, breast in 7 patients, and other cancers in 2. All patients received WBRT, 17 before FSRT and 4 after. Median FSRT dose was 1600 cGy (range, 1200-2000 cGy) to the median isodose line 80% (range, 70-92%) in one to four fractions (median, two fractions). **Results:** Median follow-up after FSRT was 11 months (range, 1-25 months). Clinical response rate was 59.9%. Radiological response rate, which was available for 18 of 21 patients and defined as stable and regressive disease for Response Evaluation Criteria in Solid Tumors Version 1.1, was 61%. Acute complications (Grade 3, according to Radiation Therapy Oncology Group) observed in one patient. **Conclusion:** The combination of FSRT/SRS and WBRT appears to be an effective way of controlling brainstem and adjacent-to-brainstem metastases.

Key Words: Brain stem neoplasms; radiosurgery; radiotherapy; dose fractionation

ÖZET Amaç: Bu küçük çaplı retrospektif çalışmanın amacı beyin sapı içinde veya yakınında (≤ 5 mm) yerleşmiş metastatik beyin tümörlerinde radyolojik ve klinik sonuçları bildirmek. Hastaların tümü tüm beyin radyoterapisi (TBRT) ve CyberKnife® fraksiyone stereotaktik radyoterapi (FSRT)/ya da stereotaktik radyocerrahi (SRC) uygulandı. **Gereç ve Yöntemler:** Beyin sapı içinde veya yakınında yerleşmiş olan bir veya birden fazla beyin metastazı olan 21 hastaya Eylül 2007 ve Haziran 2011 tarihleri arasında FSRT/SRC uygulandı. Primer tümör yerleşimi 12 hastada akciğer, 7 hastada meme, 2 hastada ise diğer bölgelerdedi. Tüm hastalara TBRT uygulandı, 17 hastada FSRT öncesinde, 4 hastada ise sonrasında uygulandı. FSRT medyan dozu 1600 cGy (aralık, 1200-2000 cGy), medyan izodoz eğrisi %80 (aralık, %70-92) olup 1 ila 4 fraksiyonda (medyan, 2 fraksiyon) verildi. **Bulgular:** FSRT sonrası medyan takip süresi 11 aydı (aralık, 1-25 ay). Klinik yanıt oranı %59,9'du. Hastaların 18'inde radyolojik verilere ulaşılabildi, radyolojik yanıt oranı, Response Evaluation Criteria in Solid Tumors Version 1.1'e göre stabil ve gerilemiş hastalık olarak tanımlandığında %61'di. Hastaların birinde akut komplikasyon görüldü (Grad 3, Radiation Therapy Oncology Group). **Sonuç:** FSRT ve TBRT kombinasyonu beyin sapı içinde ve yakınında yerleşmiş metastazların kontrolünde etkili bir yol gibi gözükmektedir.

Anahtar Kelimeler: Beyin sapı neoplazmları; radyocerrahi; radyoterapi; doz bölünmesi

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Brain metastases are the most common intracranial neoplasms and affect 20-40% of all cancer patients.^{1,2} However, brainstem metastases are uncommon, comprising approximately 5-7% of intracra-

nial metastases and harbingers of poor prognosis.³⁻⁶ Successful surgical resection is difficult and may lead to significant neurologic sequelae. Therefore, treatment options for brainstem metastases are whole-brain radiotherapy (WBRT) or stereotactic radiotherapy or radiosurgery.⁷⁻¹⁰

Treatment of metastases to or adjacent to the brain stem with fractionated stereotactic radiotherapy (FSRT) or a combination of WBRT and FSRT is not well established and most radiosurgical series have been conducted using a single fraction delivered with Gamma Knife® (Elekta AG, Stockholm, Sweden).³⁻⁶ Therefore, the most beneficial treatment of brainstem metastases with surgery, radiosurgery, WBRT, FSRT, or combinations of these is controversial. A recent study concluded that fractionated stereotactic radiotherapy (FSRT) was a more effective and safe treatment compared to single dose radiosurgery.¹¹ In this small retrospective study, we report imaging and clinical outcomes of patients who underwent both WBRT and FSRT with CyberKnife® (Accuray Incorporated, Sunnyvale, CA) for metastatic brain tumors in or adjacent (≤ 5 mm) to brainstem.

MATERIAL AND METHODS

This is a retrospective study carried out in two centers. Between September 2007 and June 2011, 21 consecutive patients (13 men and 8 women) with metastases in or adjacent to brainstem, and who were determined to be inoperable by neurosurgeons, were treated with CyberKnife FSRT and WBRT in Ankara Oncology Hospital, Ankara, and Kartal Hospital, Istanbul, Turkey. The median age of patients at the time of stereotactic radiotherapy was 51 years (range, 39-69 years). Primary tumor locations were the lung in 12 patients, breast in 7, kidney in one, and rectosigmoid region in one patient. Twenty patients had initial symptoms and signs of amnesia, postural instability, headache, hemiparesis, visual defects, hearing loss, diplopia, while one patient was symptom-free. Before FSRT all patients received intramuscular dexamethasone (8 mg) as a premedication. Follow-up data were obtained from the medical records and/or by interviews with the patients.

The patient selection criteria in these two institutions, regarding CyberKnife stereotactic radiosurgery (SRS)/FSRT for brain metastases were as follows:

1. Patient's largest tumor dimension must be ≤ 5 cm
2. No contraindications for radiotherapy
3. Patients older than 18 years of age
4. Patients with sufficient a bone marrow reserve (Hb ≥ 8 g/dL, neutrophil count ≥ 1000 mm³, platelet $\geq 50\ 000$ /mm³)
5. Patients who signed the informed consent form

The median number of brain metastases was two (range, one to four). Four patients had one lesion, 7 patients had 2, 7 patients had 3, and 3 patients had 4 intracranial lesions. Median gross tumor volume (GTV) for metastases in or adjacent to the brainstem was 2822 mm³ (range, 199-24876 mm³). While 9 of the 21 patients had in-brainstem lesions, 12 patients had lesions adjacent to brainstem. The patients and tumor characteristics are summarized in Table 1.

For planning procedure, target volumes were defined on a computerized tomography (CT)/magnetic resonance imaging (MRI) fusion set, and the critical structures (eye bulb, optic nerve, optic chiasm, brainstem, and spinal cord) were delineated on CT images only. The planned tumor volume (PTV) was equal to GTV. Slice thickness for the CT scans was 1.5 mm, whereas it was 3 mm for MRI. All 21 patients received WBRT, either prior to (17 patients) or after (4 patients) FSRT. Median time between these two modalities was 3.0 months (range, 0.75-28 months). Except one patient who received 2,500 cGy, all other patients received 3000 cGy WBRT in 10 fractions.

If we are not concerned about the critical structures like brainstem, we have 3 different dose schedules after 3000 cGy in 10 fractions with only taking into account tumor dimension. According to this;

1. 21 Gy in 1 fraction or 26 Gy in 2 fractions for ≤ 2 cm tumors
2. 17 Gy in 1 fraction or 22 Gy in 2 fractions for 2.1-3 cm tumors
3. 14 Gy in 1 fraction or 18 Gy in 2 fractions for >3 cm tumors.

TABLE 1: Patients and tumor (in or adjacent to brainstem) characteristics.

Patients and tumor characteristics	
Patients	21
Gender	
Male	13
Female	8
Age (years)	
Median	51
Range	39-69
Primary site	
Lung	12
Breast	7
Kidney	1
Rectosigmoid	1
Initial symptoms	
Headache	
Dizziness-imbalance	
Right hemiparesis	
Amnesia	
Speech disorder	
Hearing loss	
Diplopia	
No symptom	
First treatment CKSR(n)	
	4
First treatment WBRT(n)	
	17
Location according to brainstem	
Mesencephalon	2
Pons	6
Medulla oblongata	1
Adjacent to brainstem (≤ 5 mm)	12

CKSR: CyberKnife stereotactic radiosurgery; WBRT: Whole-brain radiotherapy.

However, since brainstem is a dose limiting organ, clinicians in both oncology institutions preferred to administer different lower doses depending on their discretions. Therefore, there was no defined protocols for this specific group.

The median prescribed dose for CyberKnife, 1,600 cGy (range, 1,200-2,000 cGy), was delivered to a median 80% isodose line (range 70-92%) in median two fractions (range, one to four fractions). For 11 of the patients, the sequential planning algorithm was used; for the others, the simple or iterative planning algorithms were preferred. The median homogeneity index (HI), which was defined as the ratio of maximum plan dose to prescribed dose, was 1.25 (range, 1.08-1.59) and median coverage was 97% (range,

90-100%). The treatment characteristics are listed in Table 2.

Statistical analysis was performed using SPSS version 15.0 and survival outcomes were calculated using the Kaplan-Meier method. For univariate analysis, prognostic factors were analyzed by means of log-rank test. A value of $p < 0.05$ was accepted statistically significant.

RESULTS

In this retrospective study, 21 patients were evaluated. From the date of FSRT/SRS, the median follow-up time was 11 months (range, 1-25 months).

Initial symptoms improved in 11 of the 21 patients (52.4%), 2 patients (9.5%) were stable and 8 (38.1%) had progression based on clinical assessment. MRI follow-up was available for 18 patients. According to these, 8 lesions (44%) were in regression, 3 (17%) were stable, and 7 (39%) were progressive disease according to Response Evaluation Criteria in Solid Tumors Version 1.1.¹² Three patients could not have radiological imaging due to their poor performance status.

One year overall survival rate was 40%. Median survival was 11 months (CI 8.8-13.19). Several factors which were likely to effect survival were evaluated in a univariate analysis: age (< 50 vs. ≥ 50 , $p=0.900$), number of metastases (one to two vs. three to four, $p=0.661$), primary site (lung vs. other, $p=0.600$), gender (male vs. female $p=0.694$, systematic disease status (controlled or not $p=0.077$). Due to small patient number, univariate analysis was not performed for factors like GTV volume and localization of GTV. In this study, all patients with multiple brain metastases had only one brainstem or adjacent to brainstem metastasis. Since the number of patients with 1,2,3 and 4 brain metastases were 4,7,7,3 respectively, we could not compare patients having only one brain metastasis with multiple ones for overall survival.

One patient had partial motor dysfunction 1 month post-FSRT. This patient's symptoms improved upon further follow-up. This case was assessed as Grade 3 acute radiation toxicity (RTOG

TABLE 2: Treatment characteristics.

Patient No	WBRT Dose (cGy)	Time interval WBRT-CKSR	WBRT Time	GTV (mm ³)	Fraction of CKSR	Prescribed		HI	Coverage	Median brainstem dose (cGy)	Brainstem max. point dose (cGy)	Dose (cGy) received from ≤ 1cc volume of brainstem
						Dose (cGy)	isodose line (%)					
1	2500	3 week	Before CK	2822	3	1800	92	1,09	100	826	1956	1888
2	3000	2 months	Before CK	1185	3	1350	91	1,10	100	688	1471	1350
3	3000	2 months	Before CK	1393	1	1500	92	1,08	99,7	90,8	979	390
4	3000	3 months	Before CK	23810	1	1506	84	1,19	99,78	465	908	692
5	3000	1 months	Before CK	640	2	1500	84	1,19	98	389	1311	839
6	3000	10 months	Before CK	8028	1	1429	88	1,14	99	288	1354	772
7	3000	1 months	After CK	3172	3	1400	80	1,25	97	461	883	682
8	3000	6 months	Before CK	899	3	1680	84	1,19	100	1312	1999	1930
9	3000	2 months	Before CK	7514	3	1780	89	1,12	100	653	1971	1029
10	3000	2 months	Before CK	2074	3	1800	90	1,11	100	331	1401	830
11	3000	7 months	Before CK	19813	2	2000	82	1,22	94	554	1218	800
12	3000	6 months	Before CK	3220	2	1600	72	1,39	90	452	1794	1460
13	3000	1 months	After CK	399	2	1200	77	1,30	99	336	1592	935
14	3000	9 months	After CK	939	2	1200	73	1,37	95	424	1289	920
15	3000	2 months	Before CK	1131	2	1200	70	1,59	95	314	1138	590
16	3000	2 weeks	After CK	1088	4	1600	75	1,43	95	571	2216	1620
17	3000	15 months	Before CK	4868	3	1800	74	1,35	95	503	1844	1100
18	3000	23 months	Before CK	1534	2	2000	73	1,37	95	473	1347	830
19	3000	9 months	Before CK	24876	2	1600	70	1,43	95	216	947	450
20	3000	28 months	Before CK	2841	2	1600	79	1,27	95	365	959	658
21	3000	11 months	Before CK	199	1	1200	76	1,32	95	196	1420	1004

CKSR: CyberKnife stereotactic radiosurgery; WBRT: Whole-brain radiotherapy; CK: CyberKnife; GTV: Median gross tumor volume; HI: homogeneity index.

acute radiation morbidity). No other Grade 3 or 4 toxicities were observed.

DISCUSSION

Brainstem metastases are relatively uncommon lesions compared to metastases in other locations of the brain. However, their treatment options are limited, and surgery usually is not considered because of nearby critical structures. In the current literature, most of the studies have used Gamma Knife for the treatment of brainstem metastases using stereotactic radiosurgery.^{3,5,6,13-15} In addition, there are other studies in which linac-based systems were used as a means of SRS.^{16,17} All of these studies have shown that SRS is a safe, reliable, and efficient treatment method for brainstem metastases.^{3-6,13-17}

This study differs from others in reporting treatment results of not only metastases in the brainstem but also those that are adjacent to brainstem (≤ 5 mm) and using CyberKnife as an FSRT/SRS system. The CyberKnife SRT system has certain improved features of utility compared to the Gamma Knife radiosurgery system. First, while Gamma Knife treatment requires the implantation of a stereotactic frame, CyberKnife does not need this invasive procedure.¹⁸ By this way, CyberKnife is much more convenient to deliver fractionated treatment.¹⁸ Second, treatment plans are isocentric with Gamma Knife, whereas the CyberKnife System can also generate and deliver non-isocentric treatment plans.¹⁹ In addition, CyberKnife FSRT / SRS system gives us the facility of having real-time image guidance.^{16,20}

There is no consensus on marginal doses. There are two main factors affecting the choice of marginal dose prescription: tumor volume and previous radiotherapy. In most of the studies using SRS, a more conservative dose was used for the treatment of brainstem metastases compared to the doses normally prescribed for other brain metastases, because brainstem tissue is generally considered more radiosensitive. Dose range for different SRS series using Gamma Knife or a linac for the treatment of brainstem metastases were between 1,300 and 2,000 cGy, in one fraction.^{3-6,13,16} In the

final report of RTOG protocol 90-05, patients with cerebral or cerebellar solitary non-brainstem tumors with a maximum diameter of 40 mm were evaluated. Of 156 patients, 36% had recurrent primary brain tumors (prior median dose 60 Gy) and 64% had recurrent brain metastases (prior median dose 30 Gy). The authors reported the maximum tolerated dose of single fraction radiosurgery as 24 Gy, 18 Gy, and 15 Gy for tumors that were ≤ 20 mm, 21-30 mm, and 31-40 mm in their maximum diameter, respectively. The risk for developing grade 3-5 neurotoxicity was increased for tumors that were bigger than 20 mm in the maximum diameter.²¹

To our knowledge, no studies used CyberKnife as a means of FSRT/SRS for brainstem metastases. In the current study, our median prescribed dose was 1,600 cGy in a median two fractions, as biologically effective dose (BED) equal to 80 Gy ($\alpha/\beta=2$ Gy). This dose is relatively smaller than the doses mentioned above.

Nonetheless, Lorenzoni et al. have found that a marginal dose higher than 1,800 cGy is associated with longer survival, and Vogelbaum et al. have found that, for brain metastases, lower marginal doses result in lower local control rates.^{14,22} Besides, Valery et al. have showed that reduced doses can achieve the same local control in brainstem lesions.¹⁷ In their study, using linac radiosurgery, median radiosurgical dose was 13.4 Gy (BED: 103.2 for $\alpha/\beta=2$), median survival was 10 months and local control rates were 100%, 100%, and 79% at 3, 6, and 12 months, respectively.

In our study, the median survival for 21 patients was 11 months. Eighteen patients' follow-up MRI findings were available for a 6-months median follow-up after CyberKnife SRT. Of these 18 patients, 61% of the brainstem metastases were controlled (8 were in regression and 3 were stable) after FSRT/SRS.

In conclusion, Cyberknife FSRT/SRS as an adjuvant treatment to WBRT could yield a favorable response rate and low morbidity in the treatment of metastases inside or next to the brainstem.

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