Robotic Stereotactic Radiotherapy Results and Treatment Compliance of Patients Aged 65 and Over

Altmış Beş Yaş ve Üstü Hastaların Robotik Stereotaktik Radyoterapi Sonuçları ve Tedaviye Uyumu

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ABSTRACT Objective: This study aims to report the robotic fractionated stereotactic radiotherapy (FSRT) results and treatment compliance in patients ≥65 years of age. **Material and Methods:** Retrospective reviews of 39 patients aged 65 years and older treated with CyberKnife® FSRT were performed. Karnofsky Performance Status (KPS) of 72% of the patients were ≥70, and 33% of the patients had comorbid illnesses. Patients were classified according to diagnosis: brain metastasis (n=22), primary brain tumor (n=6), vertebral metastasis (n=4), locally recurrent nasopharyngeal cancer (n=3), orbital tumor (n=3), and early-stage lung cancer (n=1). Median age was 69 years (range, 65-81 years). FSRT was performed as a re-irradiation in 62% of all patients. **Results:** Median follow-up for all groups of patients was 6 months (range, 1-36 months). In all groups, one patient presented with grade 2 hearing impairment during the 16-month follow-up (Common Terminology Criteria for Adverse Events, v 3.0). For one patient in the brain metastasis group, the treatment was delayed for 3 days because of neutropenia. There were no acute grade 3-4 toxicities. In the brain metastasis group, median overall survival was 5 months (CI: 1.2-8.7); 5-month and 7-month overall survival rates were 50% and 33%, respectively. One-year progression-free survival rate of the 14/22 evaluable patients with brain metastases was 63.5%. **Conclusion:** Robotic FSRT is a non-invasive and well tolerated treatment modality for this age group of patients.

Key Words: Aged; radiosurgery; compliance

ÖZET Amaç: Yaşlı hastaların (≥65 yaş), fraksiyone stereotaktik radyoterapiye (FSRT) uyumu ve tedavi sonuçlarının bildirilmesi. **Gereç ve Yöntemler:** Altmış beş yaş ve üzeri, CyberKnife® ile FSRT uygulanan 39 hasta retrospektif olarak incelendi. Hastaların %72'sinin Karnofski performans durumu (KPS) >70 idi ve %33'ünün komorbid hastalığı vardı. Hastalar tanılarına göre sınıflandırıldı; beyin metastazları (n=22), primer beyin tümörü (n=6), vertebra metastazı (n=4), lokal rekürren nazofarenks kanseri (n=3), orbita tümörleri (n=3), erken evre akciğer kanseri (n=1). Ortanca yaş 69 (aralık, 65-81) yıl idi. FSRT, hastaların %62'sine yeniden ışınlama amacı ile uygulandı. **Bulgular:** Tüm gruplar için ortanca takip zamanı 6 ay (aralık, 1-36 ay) idi. Bir hastada, 16 aylık takip süresinde evre 2 duyma kaybı (Common Terminology Criteria for Adverds Events, v 3,0 göre) gözlendi. Beyin metastazlı grupta bir hastada tedavi nötropeni nedeni ile üç gün ertelendi. Hiçbir hastada uygulama sırasında ve sonrasında evre 3-4 toksisite görülmedi. Beyin metastazlı grup için ortanca genel sağkalım 5 ay (CI: 1,2-8,7), 5 ve 7 aylık genel sağkalım oranları sırası ile %50 ve %33 idi. Bir yıllık progresyonsuz sağkalım oranı değerlendirilebilinen 14/22 beyin metastazlı hasta için %63,5 idi. **Sonuç:** Robotik FSRT, bu yaş grubu için iyi tolere edilebilen ve non-invaziv bir tedavi yaklaşımıdır.

Anahtar Kelimeler: Yaşlı; radyocerrahi; uyum

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Although the incidence of cancer in elderly patients is high, there are few clinical trials dedicated specifically to this age group.[1,2] In most studies, older patients are excluded owing to concerns with

toxicity and potential lack of benefit from the treatment.[1,3] This group of cancer patients should be evaluated with particular attention to their comorbid conditions and performance status.[1,3]

Cancer treatment often involves more than one mode of therapy including surgery, chemotherapy, and radiotherapy (RT). Older patients are less likely to cope with the increased difficulties caused by a combination treatment.[1,4] Surgery and RT are commonly utilized treatment modalities to control local disease, whereas chemotherapy is less frequently offered to elderly cancer patients.[5] Compared with surgery, the risk of mortality following RT is much lower. Organ and function preservation is an advantage of RT.[1] Conventional fractionation with curative intent usually lasts 5-7 weeks.[5] Increased number of fractions with conventional radiotherapy can cause the elderly to give up on treatment before its completion.[1,5,6]

It is possible to reduce treatment durations in many diseases by fractionated stereotactic radiotherapy (FSRT).[7] The use of robotic FSRT with CyberKnife® (CK) (Accuray Incorporated, Sunnyvale, CA) also offers a frameless non-invasive treatment option.[7]

FSRT with CK reduces the number of fractions at the expense of increase in the duration of a fraction which can cause inconvenience during the treatment of a frail patient.[5,7]

This retrospective study aims to report treatment results with robotic FSRT in ≥65 year old patients.

MATERIAL AND METHODS

PATIENT CHARACTERISTICS

A total of 400 patients were treated with robotic FSRT between May 2009 and June 2011 at the Oncology Education and Research Hospital, Radiation Oncology Department, Ankara University. Thirty nine patients (24 men and 15 women) aged 65 years and older (according to the World Health Organization, the lowest age limit for "old age" is 65 years) were analyzed. Median age was 69 years (range 65-81 years). Patients were classified according to diagnosis: brain metastasis (n=22), primary brain tumor (n=6), vertebral metastasis (n=4), locally recurrent nasopharyngeal cancer (n=3), orbital tumor (n=3), and early-stage lung cancer (n=1). Karnofsky Performance Status (KPS) of 72% of the patients were ≥70 and 33% of the patients had comorbid illnesses. Robotic FSRT was performed as re-irradiation in 62% of cohorts. The prescribed dose range was 1100-6000 cGy (median, 1800 cGy). Patients with brain metastases constituted the largest portion of this group. Patient characteristics are shown in Table 1.

TREATMENT PROCEDURE

Robotic FSRT consisted of three steps: Computed tomography (CT) acquisition, treatment planning, and treatment delivery. Patients were immobilized non-invasively using a rigid thermoplastic mask in the supine position for brain irradiation. The tumor was marked with three gold fiducials implanted percutaneously with CT guidance for the lung cancer patient. Simulation (planning) CT scans were

TABLE 1: Patient characteristics.

Characteristics	No of Patients(%)	Median (Range)
No of patients	39	
Female	15 (38.5)	
Male	24 (61.5)	
Age		69 (65-81)
KPS		
≥ 70	28 (72)	
< 70	11 (28)	
Comorbidity		
Yes	13 (33.3)	
No	26 (66.7)	
Subgroup of diagnosis		
Brain metastases	22 (56.4)	
Primary brain tm	6 (15.4)	
Vertebral metastases	4 (10.3)	
Recurrent NF CA	3 (7.7)	
Orbital tm	3 (7.7)	
Lung cancer	1 (2.6)	

KPS: Karnofsky Performance Status; tm: tumor; NF CA: Nasopharyngeal Cancer; RT: Radiotherapy.

acquired using 1.5-mm-thick slices in the standard manner, covering a certain safety margin around the target volume. Magnetic resonance imaging (MRI) with 3-mm slice thickness was also used for fusion. The gross tumor volume (GTV) and critical structures were delineated following the transfer of CT and MRI fusion to the system.

The second step was treatment planning. An inverse treatment planning technique was used to ensure that the tumor received the maximum dose permissible with the restrictions imposed by the maximum normal structure tolerance doses. During treatment, two orthogonally positioned diagnostic X-ray cameras provided real-time images of the patients' internal anatomy. Skull, spine, and fiducial tracking techniques were used to identify the tumor location and automatically redirect the radiation beam to the tumor's current location.

The patients were informed about the potential risks and benefits of robotic FSRT, and their informed consents were obtained. In our study, treatment duration ranged from 12 to 75 minutes per fraction (median, 38 min), depending on the number of beam nodes. Treatment characteristics are shown in Table 2. All patients completed the planned treatment course without interruption. The treatment of one patient was delayed for 3 days due to neutropenia.

STATISTICAL ANALYSIS

The Kaplan-Meier method was used to estimate overall survival.

TABLE 2: Treatment characteristics.

Characteristics	No
Prior RT dose (cGy)	
Median (range)	3000 (2000-7000)
Gross total volume (cm^3)	
Median (range)	8,6 (0.9-89.4)
Prescribed dose (cGy)	
Median (range)	1800 (1100-6000)
Treatment duration per fraction (min)	
Median (range)	38 (12-75)

RT: Radiotherapy.

RESULTS

BRAIN METASTASES

The median age at the time of robotic FSRT was 69 years (range, 65-78 years) for the 22 patients with brain metastases. KPS was ≥70 in 68% of the patients (n=15). The majority of the patients' primary diagnoses were lung cancer (64%). In this cohort, 55% of the patients did not have any comorbidities (n=12). Thirty four lesions were treated in 22 patients, 15 of whom had single metastatic lesions. Median gross tumor volume was 3.9 cm^3 (range, 0.2-37.4 cm^3). The prescribed dose range was 1300-4200 cGy (median 1800 cGy). The median treatment duration per session was 34 min (range, 13-68 min). In our study, 18% of the brain metastases (n=4) were recurrences following whole brain radiotherapy (WBRT); 59% (n=13) were treated as a boost after WBRT; and 23% (n=5) received robotic FSRT only. The intervals between FSRT and WBRT are shown in Table 3. All patients completed the planned treatment course without interruption. One year progression-free survival (PFS) rate of the 14/22 evaluable patients was 63.5%. Median overall survival was 5 months (range, 1-25 months) (CI: 1.2-8.7). 5-month and 7-month overall survival rates were 50% and 33%, respectively.[Isodose curves (a, b) and dose-volume histogram (c) for a patient with brain metastases were shown in the Figure 1].

PRIMARY BRAIN TUMORS

The distribution of the radiological and/or histological diagnoses of the 6 patients with primary brain tumors were as follows: schwannoma (n=3), meningioma (n=1), recurrent glioblastoma multiforme (GBM) (n=1), and glomus jugulare (n=1). Median age was 70 years (range 66-81 years). Half of the patients (n=3) had comorbidities and their KPS was under 70. Median target volume was 9 cm^3 (range 0.7-18.2 cm^3). The prescribed dose range was 1100-2400 cGy (median 1700 cGy) in one to three fractions. The median treatment duration per session was 34.5 min (range 28-47 min). With the exception of the patient with GBM, none of patients in this group had a history of RT. The

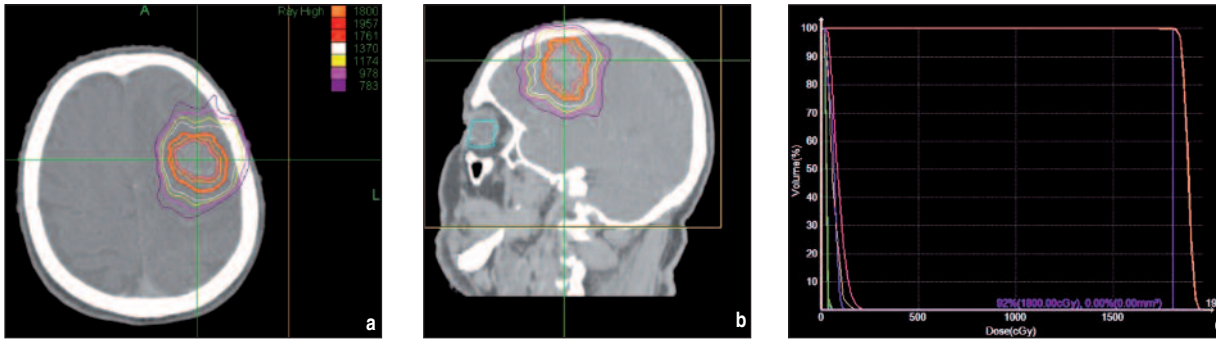

FIGURE 1: Isodose curves **(a, b)** and dose-volume histogram **(c)** for a patient with brain metastasis.
(See color figure at http://tipbilimleri.turkiyeklinikleri.com/)

TABLE 3: Interval between CK and WBRT.

CK Purpose	Patient number	CK-WBRT interval time median (range)
WBRT boost	13	4 weeks (3-8 weeks)
Recurrent	4	14 weeks (12-24 weeks)
Only CK, SRS	5	-

CK: Cyberknife; SRS: Stereotactic Radiosurgery; WBRT: Whole Brain Radiotherapy.

GBM patient had received 6000 cGy with conventionally fractionated 3D-conformal RT and the interval between RT and FSRT was 20 months. Median overall survival was 7 months (range, 3-25 months) (CI: 4.7-9.2). There were no cases of treatment-related toxicity or inability to sustain treatment in this group of patients.

VERTEBRAL METASTASES

Robotic FSRT with CyberKnife was indicated for 4 patients with vertebral bone metastases due to a history of RT in the same region. The primary diagnoses were carcinoma of lung (n=1), endometrium (n=1), cervix (n=1), and stomach (n=1). Median age was 69 years (range 66-73 years). None of patients had comorbidities and their KPS were ≥70 except one patient. Median prescribed dose was 1750 cGy (range, 1100-2000 cGy) in three to five fractions. Previous irradiation dose ranged from 3000-6000 cGy (median 3300 cGy). The median interval between prior RT and robotic FSRT was 18.5 months (range, 7-28 months). Median target volume was 46.9 cm^3 (range 31-60.7 cm^3). Median treatment duration per session was 56 min (range 46-69 min). In spite of the longer treatment durations in this group, all patients completed the planned treatment course without interruption. Due to the small number of patients, survival could not be evaluated.

RECURRENT NASOPHARYNGEAL CANCER

Three recurrent nasopharyngeal cancer patients who had previously received full-dose RT were treated with FSRT. Histopathological diagnosis of all three patients was undifferentiated carcinoma. Median age was 65 years (range 65-70 years). There were no comorbidities and KPS was ≥70. Previous irradiation dose was 7000 cGy in all patients. The median interval between prior RT and FSRT was 39 months (range 26-46 months). Median target volume was 23.7 cm^3 (range 4.9-36.6 cm^3). The prescribed dose range was 2400-3000 cGy in five fractions (median dose 2500 cGy). Median fraction time was 46 min (range 22-75 min). The median follow-up of 15 months (range, 7-16 months) showed that all patients were alive with stable disease. One patient presented with grade 2 hearing impaired during 16-month follow-up (according to Common Terminology Criteria for Adverse Events, v 3.0). The treatment of one patient with a KPS below 70 was delayed for 3 days due to neutropenia.

ORBITAL TUMORS

There were three patients with orbital tumors, two with the histology of malignant melanoma and one with squamous-cell carcinoma. The melanoma patients were prescribed 3000 cGy and 3200 cGy in five fractions. Target volumes were 1.6 cm^3 and 1 cm^3, fraction durations were 12 and 14 minutes. They were assessed as locally stable (according to Resist Criteria v 1.1) with MRI after FSRT, at 22-months follow-up times for both patients.

Regarding the case with squamous-cell carcinoma histology, prescribed dose was 2800 cGy in six fractions, target volume was 89 cm^3, and the treatment duration per fraction was 52 minutes. A partial response was achieved at 28-months follow-up (according to RECIST Criteria, v 1.1).

LUNG CANCER

There was only one patient with lung cancer (early-stage non-small-cell lung carcinoma). She was 78 years old. Her prescribed dose was 6000 cGy in three fractions, and the fiducial-synchrony® respiratory tracking system was utilized. Treatment duration per fraction was 68 minutes. She completed the planned treatment course without interruption. She died at the end of the 18-month follow-up because of progressive systemic disease.

DISCUSSION

Selecting a treatment modality for elderly patients with cancer can be a difficult decision because of the often-present concomitant diseases.[5,7] Although long courses of external-beam radiation are commonly utilized to obtain local tumor control, these prolonged courses may not be the most suitable treatment modality for elderly patients due to their lower tolerance and relative frailty.[8] While diseases such as hypertension, diabetes, cardiac, and pulmonary problems exist in 35% of patients aged under 70, they are present in 90% of the elderly.[9] Owing to the high prevalence of comorbidity in elderly patients, outcomes and side effects of treatments may also be complex; therefore, shorter courses of RT can be more appropriate and effective in the elderly.[5,10] In a retrospective trial which compared conventional fractionation with hypofractionation in patients with GBM, patients in the hypofractionation group (4 χ7 Gy), who had far worse prognostic factors, obtained median survival similar to the conventional RT group (33 χ2 Gy).[10] Phase II multicenter study from Minniti et al. evaluated the efficacy and safety of a short course radiotherapy plus concomitant and adjuvant temozolomide (TMZ) in 70 years of age or older with newly-diagnosed GBM.[11] All patients completed the planned course of RT. Abbreviated course of RT is well tolerated in elderly patients with GBM.

Rades et al. compared WBRT 10χ3 Gy with 5χ4 Gy in brain metastases in elderly patients (≥ 65 years).[12] The 6- month overall survival rates and local control rates were better in 5χ4 Gy arm, but this was not significant. Shorter course WBRT with 5χ4 Gy was superior to 10χ3 Gy regarding local control and overall survival in patients at this age.

Schild et al. observed higher RT-related toxicity in elderly patients with limited stage small cell lung cancer, as increased rates of pneumonitis and treatment-related death in patients aged >70 years.[13] A recently-publishd study has demonstrated that hypofractionated radiotherapy is an effective and safe treatment for older patients with stage I non-small cell lung cancer. Median age was 74, all patients (n:75) were over 60 years old. Patients received a median total dose of 65 Gy with a daily dose fraction of 2.5 Gy. Radiation-related toxicity grade 3 or over was seen in only 3 patients and there were no treatment-related deaths.[14] Similar study from Haasbeck et al. demonstrated that stereotactic radiotherapy achieved high local control with minimal toxicity in elderly patients despite their significant comorbidities in early stage lung cancer patients who were 75 years and older.[15]

There are a few clinical trials in the literature concerning older patients and FSRT in elderly. Dewas et al. have demonstrated similar outcomes with our study, having analyzed 345 patients of all ages who underwent FSRT with CyberKnife.[7] Ninety eight patients were aged over 70. Treatment could not be completed in 2% (2/98) of the patients aged over 70 years vs. 3.6% (9/247) among the

younger. Treatment was discontinued for two patients because of the difficulty in maintaining the treatment position in one case, and due to progressive disease in the other. No significant differences were found in terms of treatment feasibility and toxicity between the two groups.

Van der Voort van Zyp et al. have reported that local control rate was excellent (100%) and treatment-related toxicity was low in octogenarians with stage I non-small cell lung cancer after CyberKnife FSRT.[16]

In the current retrospective study, 39 patients who were at least 65 years old with a variety of diagnoses underwent FSRT with CyberKnife. All patients showed compliance to the treatment. There were no acute grade 3 or 4 toxicities. Nine of 11 patients with KPS below 70 were treated for palliation (brain metastases, vertebral metastases). Robotic FSRT is well-tolerated by patients with poor performance status due to palliative treatment volume and doses. CyberKnife FSRT appears to be a non-invasive and readily tolerable treatment modality for this age group of patients.

This study has certain limitations. It was a retrospective study with the inherent selection bias. Distribution of patient diagnoses was very heterogeneous and overall survival could not be evaluated due to the small number of patients in the groups.

Advanced age is associated with poor performance status, increased comorbidity, and suboptimal treatment. Fractionated stereotactic radiotherapy with CyberKnife is preferable in selected senior patients due to the small number of fractions, well-tolerable non-invasive nature of the treatment, and good tumor control.

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