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Research

Stereotactic Body Radiation Therapy For Medically Inoperable Stage I Non-small Cell Lung Cancer

Medikal İnoperabl Evre I Küçük Hücreli Dışı Akciğer Kanserinde SBRT Sonuçları

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ABSTRACT

Objective: The primary treatment for stage I non-small cell lung cancer (NSCLC) in medically inoperable patients is stereotactic body radiation therapy (SBRT). The current study aimed to retrospectively analyze patients who underwent SBRT.

Methods: A total of 188 patients with stage I NSCLC treated with SBRT between 2014 and 2020 were enrolled. Local control (LC), progression-free survival (PFS), overall survival (OS), and treatment-related toxicities were analyzed.

Results: Patients were mostly male (65.7%, n=71), with a median age of 68 (56-88). Based on tumor size and location, 69 patients (63.9%) received between 50 and 60 Gy in 5 fractions, 26 patients (24.1%) received 54 Gy in 3 fractions, 11 patients (10.2%) received 60 Gy in 8 fractions, and 2 patients (1.8%) received 60 Gy in 3 fractions. The median follow-up time was 32 months (12-47 months). Locoregional relapse occurred in 11 patients, among whom 4 (3.7%) developed distant metastasis. The 3-year LC, OS, and PFS rates were 89.5%, 83%, and 72%, respectively. Advanced age and presence of chronic obstructive pulmonary disease were associated with a decreased 3-year OS. In smokers and those with large tumor volumes, PFS decreased to 3 years. No grade 3 or 4 treatment-related toxicities were observed.

Conclusion: SBRT is a fast, safe, and valuable therapeutic approach for patients with early-stage medically inoperable NSCLC, providing significant tumor control rates with low toxicity.

Keywords: Stereotactic body radiation therapy, radiotherapy, non-small-cell lung cancer, SBRT, NSCLC

ÖZ

Amaç: Stereotaktik vücut radyoterapisi (SBRT), medikal inoperabl evre I küçük hücreli dışı akciğer kanseri (KHDAK) tedavisinde ana yaklaşımdır. Bu çalışmada, SBRT ile tedavi edilen medikal inoperabl evre I KHDAK hasta sonuçlarını retrospektif olarak analiz etmeyi amaçladık.

Gereç ve Yöntem: 2014 ile 2020 tarihleri arasında SBRT uygulanan evre I KHDAK tanılı 108 hastanın lokal kontrol, progresyonsuz sağkalım, genel sağkalım ve tedaviye bağlı toksisite sonuçları analiz edildi.

Bulgular: Hastaların %65,7'si erkek ve ortalama yaş 68 (56-88) idi. Tümör büyüklüğü ve lokalizasyonuna göre; 69 hastaya (%63,9) 5 fraksiyonda 50-60 Gy, 26 hastaya (%24,1) 3 fraksiyonda 54 Gy, 11 hastaya (%10,2) 8 fraksiyonda 60 Gy, 2 hastaya (%1,8) 3 fraksiyonda 60 Gy radyoterapi uygulandı. Ortalama takip süresi 32 aydı (12-47 ay). On bir hastada lokal nüks ve 4 hastada (%3,7) uzak metastaz gelişti. Üç yıllık lokal kontrol, progresyonsuz sağkalım ve genel sağkalım oranları sırasıyla %89,5, %72 ve %83 idi. İleri yaş ve kronik obstrüktif akciğer hastalığı varlığı azalmış 3 yıllık genel sağkalım ile ilişkili bulundu. Sigara içme öyküsü ve büyük tümör volümü ise azalmış 3 yıllık progresyonsuz sağkalım ile ilişkili idi. Tedaviye bağlı 3. ve 4. derece toksisite gözlenmedi.

Sonuç: SBRT erken evre medikal inoperabl KHDAK hastaları için yüksek tümör kontrol oranları ve düşük toksisite sonuçları ile hızlı ve güvenli bir tedavi yaklaşımıdır.

Anahtar Kelimeler: Stereotaktik vücut radyoterapisi, radyoterapi, küçük hücreli dışı akciğer kanseri, SBRT, KHDAK

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INTRODUCTION

Lung cancer is the second most common type of cancer in both women and men (1). Despite progress in diagnosis and treatment approaches. Non-small cell lung cancer (NSCLC) is the most frequent type of lung cancer and has multiple histological subtypes. It accounts for approximately 85% of all diagnosed lung cancer cases, with a 5-year survival of approximately 25% (2). Although the typical treatment for early-stage NSCLC is surgical resection, a notable percentage of these patients are not suitable for surgery due to comorbidities, such as heart disease, loss of pulmonary parenchyma, and chronic obstructive pulmonary disease (COPD), particularly among heavy smokers and the elderly.

Stereotactic body radiation therapy (SBRT) has become the standard of care for patients with early-stage NSCLC who are medically inoperable, after a series of trials proved its effectiveness and safety profile (3). SBRT allows reaching high radiation doses. In this way, it is possible to achieve lower rates of normal tissue complications along with improved local control (LC) and survival outcomes (4-7). In the SPACE trial comparing conventional fractionated radiotherapy to SBRT, no differences were observed in overall survival (OS) and progression-free survival (PFS), despite the imbalances in terms of known prognostic factors between the two treatment arms, which favored the conventional radiotherapy arm (8). Moreover, quality of life was better and toxicity was lower with SBRT. On the other hand, the positive effects of SBRT compared with conventional radiotherapy have been confirmed by other studies and meta-analyses (9,10).

In the current study, we retrospectively analyzed the LC, PFS, OS, and treatment-related adverse events (AEs) in patients with medically inoperable early-stage NSCLC who underwent SBRT.

METHODS

Patient Selection and Follow-up

In this retrospective study, patients with medically inoperable T1-2aN0M0 NSCLC who received SBRT between 2014 and 2020 were examined. The multidisciplinary team ascertained inoperability based on the presence of medical comorbidities and pulmonary function tests. Diagnosis, in cases in which biopsies are not feasible, are non-diagnostic results or are declined by the patient, was made using clinical and imaging findings by the multidisciplinary team.

Positron emission tomography computed tomography (CT) scans were obtained 3-4 months after the completion of SBRT for each patient. Patients were followed for a 3-month period during first 2-years then 6-months period, including physical examination and thorax CT in each follow-up visit. Treatment-related AEs were documented in accordance with the common terminology criteria for adverse events version 5 (CTCAEv5).

Radiotherapy Specifications

Breath-hold CT, slow CT, and 4D CT methods with 1-2 mm slice thickness scanning were used for treatment planning. Additionally, the breath-hold technique was primarily employed in lower lobe tumors. Planning target volume (PTV) margins from the internal target volume were customized from 5 mm to 10 mm in all directions based on tumor location and CT technique. Treatment was administered with Truebeam linac (Varian Systems, USA) or volumetric modulated arc therapy on a Synergy® Linac (Elekta AB, Stockholm, Sweden). According to the American Association of Physicists in Medicine study, dose fractionation plans were prescribed to achieve a biologically effective dose (BED) of at least 100 Gy (alpha/beta ratio=10), and it was chosen based on target location and size (4). All BED calculations were based on the prescribed dose, with the entire PTV receiving at least 95% of the prescribed dose. 54 Gy in 3 fractions or 60 Gy in 5 fractions or 60 Gy in 3 fractions were prescribed for peripheral locations, whereas 50-60 Gy in 5-8 fractions for larger peripheral and central locations. Treatment was delivered every other day. All patients were treated using stereotactic radiation techniques under an image-guided radiation treatment protocol (5).

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences software. Descriptive statistical methods were used to evaluate the data. Fisher's exact test and Fisher-Freeman-Halton exact test were used to compare qualitative data. The conformity of quantitative data to the normal distribution was assessed using graphical inspections and the Shapiro-Wilk test. If the two groups did not have a normal distribution, the Mann-Whitney U test was used for comparison. Kaplan-Meier analysis was used for survival analysis. Statistical significance was defined as $p<0.05$.

This retrospective study was approved by the İstanbul University Ethics Committee (decision no: 2020/11, date: 02.07.2020).

RESULTS

In total, 108 patients with a median age of 68 (56-88 years) were examined in this cohort. Of the patients, 65.7% (n=71)

were male, 82.4% (n=89) were smokers, and 21.3% (n=23) had COPD. The eastern cooperative oncology group performance status was evaluated; 37 (34.3%) had a score of 0, and 68 (63%) had a score of 1. In 70 patients (64.8%), biopsies were performed, and histological analysis revealed that 29.6% (n=32) had squamous cell carcinoma and 35.2% (n=38) were diagnosed with adenocarcinoma. Among the 38 patients (35.2%) who could not undergo biopsy, treatment decisions were made by the multidisciplinary team as previously described (Table 1).

The median gross tumor volume (GTV) (in cc) was 8.9 cc (0.3-77 cc), and the median PTV (in cc) was 16.35 cc (0.4-94.6 cc). Radiotherapy was administered with 54 Gy given in 3 fractions for small peripherally located lesions in 26 patients (24.1%) and 60 Gy given in 3 fractions for small peripherally located lesions to 2 patients (1.8%). 50-60 Gy in 5 fractions (50 Gy in five fractions for one patient, 55 Gy in five fractions for one patient, 60 Gy in five fractions for 67 patients) for larger peripherally located tumors and small centrally located tumors in 69 patients (63.9%), and 11 patients (10.2%) with centrally located tumors total dosed 60 Gy with 8 fractions. The breath-hold technique was used in 52 patients (48,1%), 4D CT in 30 patients (27.8%), and slow CT in 26 patients (24.1%).

The median follow-up time was 32 months (12-47 months). Twenty-four deaths (22.2%), comprising twelve cases from intercurrent disease (not related to radiation-induced toxicity), 1 case of lung cancer, and 11 cases of unknown cause. Eleven patients developed locoregional relapse (seven with local relapse only, three with regional relapse only, and one with both local and regional relapse), and the local control rate was 89.5%. Four patients (3.7%) developed distant metastasis. OS and PFS at 3 years were 83% and 72% respectively (Figure 1,2).

In the univariate analysis, sex, smoking history, tumor location, tumor volume, and radiation therapy (RT)

Table 1. Patient characteristics and tumor characteristics

		n (%)
Gender	Male	71 (65.7)
	Female	37 (34.3)
Age	Mean ± SD	69.43±6.36
	Median (min-max)	68 (56-88)
Performance status (ECOG)	0	37 (34.3)
	1	68 (63)
	2	3 (2.8)
Family History	Yes	51 (47.2)
	No	57 (52.8)
Smoking history	Yes	89 (82.4)
	No	19 (17.6)
Biopsy	No	38 (35.2)
	Yes	70 (64.8)
Histology	Adenocarcinoma	38 (35.2)
	SCC	32 (29.6)
	No biopsy	38 (35.2)
COPD	No	85 (78.7)
	Yes	23 (21.3)
Tumor location	Peripheral	60 (55.6)
	Central	48 (44.4)
Tumor location (Lobe)	RUL	30 (27.8)
	RML	8 (7.4)
	RLL	24 (22.2)
	LUL	29 (26.9)
	LLL	17 (15.7)

ECOG: Eastern cooperative oncology group, SD: Standard deviation, SCC: Squamous cell carcinoma, COPD: Chronic obstructive pulmonary disease, RUL: Right upper lobe, RML: Right Middle lobe, RLL: Right lower lobe, LUL: Left upper lobe, LLL: Left lower lip, min-max: Minimum-maximum

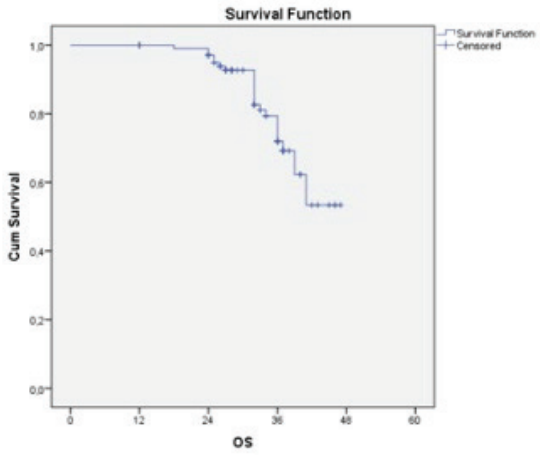

Figure 1. Overall survival analysis
OS: Overall survival

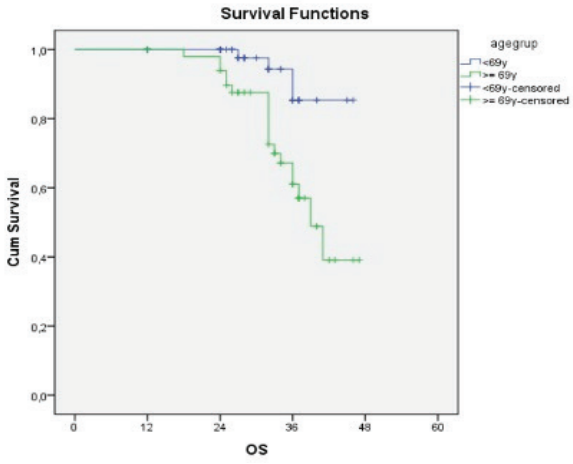

Figure 3. Association between age and overall survival
OS: Overall survival

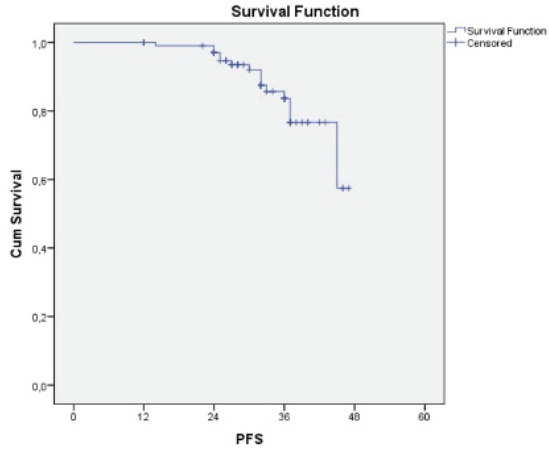

Figure 2. Progression-free survival analysis
PFS: Progression-free survival analysis, cum: Cumulative

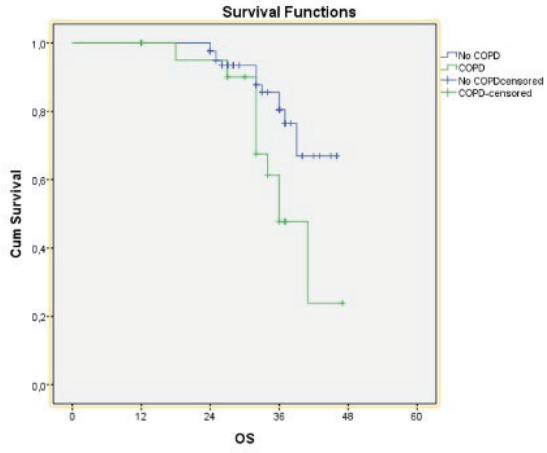

Figure 4. Association between COPD and overall survival
OS: Overall survival, COPD: Chronic obstructive pulmonary disease

technique had no statistically significant impact on 3-year OS. However, patients ≥69 years of age had lower 3-year OS rate than<69 years of age (61% vs 85%, p=0.04) (Figure 3). Additionally, the 3-year OS rates of those with COPD were 47% and 85% in patients without COPD, which was found to be statistically significant (p=0.013) (Figure 4).

In the univariate analysis, age, sex, COPD, tumor location, and RT technique had no statistically significant impact on 3-year PFS rate. However, 3-year PFS was significantly associated with tumor volume and smoking history. Tumor volumes ≥9 cc had a lower 3-year PFS compared to those <9 cc (70% vs 94%, p=0.004). Patients with a smoking history had a lower 3-year PFS (69% vs 87%, p=0.002).

There were no grade 3 and 4 treatment-related AEs, and in 60.2% (n=65) of the cases, no side effects were observed according to the CTCAEv5. Mild esophagitis (grade I) was observed in 16 patients (14.8%), whereas 26 (24.1%) experienced mild fatigue during treatment. Grade 2 radiation pneumonia was observed in 20.4% (n=22) of cases, with seven cases being radiologically proven and 15 cases presenting both symptomatic and radiologically proven. Among these 22 patients, 15 had centrally located tumors and seven had peripherally located tumors (p=0.042). Chest wall pain was observed in only one patient. 4D-CT, breath-hold CT, and slow CT showed no differences in efficacy and side effects.

DISCUSSION

In this retrospective analysis, the OS and PFS at 3 years were 83% and PFS at 3 years was 72%. These results indicate

that SBRT for medically inoperable patients is a safe and effective treatment method, with high rates of survival and disease control, high tolerability, and low rates of treatment-related AEs.

Kann et al. (6) reported local failure rates of 8.2% and 9.7% at 2-years for inoperable and operable early stage NSCLC in a comprehensive study involving 952 patients from five institutions. Kestin et al. (11) also reported a 9% local failure rate in a retrospective analysis of 483 patients with early-stage NSCLC treated with SBRT. One of the factors that may affect local control is tumor size. Kestin et al. (11) found an association between GTV size and local recurrence (LR) (p=0.02), with a 2-year LR rate of 3% for sizes <2.7 cm, vs. 9% for those 2.7 cm (p=0.03). Although statistically insignificant, Kann et al. (6) reported a higher LR rate for T2 tumors than for T1 tumors. Similarly, we observed a relationship between 3-year PFS rates and tumor volume, with a 94% PFS rate for tumor volumes <9 cc in contrast to 70% for those ≥9 cc (p=0.004).

Another component that may be associated with local control and survival rates is BED 10. Previous studies have demonstrated better oncological outcomes with a BED ≥100 Gy in contrast to <100 Gy across various treatment methods and schedules (12-17). On the other hand, higher doses achieved with SBRT do not appear to be associated with high levels of toxicity, and BED <180 Gy was shown to be safe for stage I NSCLC (15). In our study, we used BED >100 Gy for all patients 3 or 5 or 8 fractions, and observed very low rates of toxicities. Furthermore, we observed no differences in side effects and efficacy among breath-hold, 4D CT, and slow CT techniques. Although breath-hold techniques were generally expected to result in fewer side effects, the lack of difference in our study may be attributable to low tumor volumes.

A phase II prospective study at MD Anderson Cancer Center reported the 7-year results of 65 patients with medically inoperable stage I NSCLC who were treated with 50 Gy in 4 fractions. The 7-year PFS and OS were 38.2% and 47.5%, respectively. Moreover, only three patients (4.6%) developed grade 3 treatment-related AEs (18). Notably, this represents the longest follow-up data in a prospective SBRT trial. In our study, the 3-year-OS and PFS were 83% and 3-year PFS was 72%.

COPD, which is an independent risk factor for lung cancer, also represents a negative prognostic factor in these patients. In a single-center cohort of 176 patients with stage I NSCLC and severe COPD, Palma et al. (19) reported a 3-year OS of 47% after SBRT. We demonstrated that the 3-year-OS of patients with COPD was 47%, which was significantly lower than that of patients without COPD (85%) (p=0.013). However, a retrospective study in Japan reported no significant difference in OS or cause-specific survival between patients with and without COPD after SBRT (20).

Smoking is the most significant preventable risk factor for lung cancer as known. Furthermore, it may impact survival time. Previous studies have shown that survival rates may decrease with smoking, and quitting smoking, even at the time of diagnosis, may improve survival. We found a significant association of 3-year PFS rates but not OS. Therefore, it is crucial to follow up on patients' smoking status during treatment and encourage active smokers to be quit.

Radiation pneumonitis (RP) developed in 22 of the patients in our cohort, which is consistent with the findings of a previous study (21). Additionally, we found that central tumor location was a significant predictor of RP. However, there are conflicting data regarding the relationship between RP and tumor location; Kita et al. (22) identified central tumor location as an independent risk factor for developing RP, whereas Yamashita et al. (23) did not find any such correlation. In other studies, tumor size was shown to be an important factor for the development of RP (24).

This study has several limitations. Due to its retrospective nature, these data is prone to limitations and potential biases. In addition, lacking a comparative group, the observed outcomes may be influenced by various factors, increasing the risk of bias. Moreover, more than a quarter of patients were treated without biopsy confirmation. Consequently, while the trial can provide insights into the benefits and risks of treatment, its findings should be interpreted with caution.

CONCLUSION

SBRT remains a valuable therapeutic approach for patients with early-stage medically inoperable NSCLC, with high tumor control rates and minimal toxicity.

ETHICS

Ethics Committee Approval: This retrospective study was approved by the İstanbul University Ethics Committee (decision no: 2020/11, date: 02.07.2020).

Informed Consent: Since it was a retrospective study, no consent was required.

Authorship Contributions

Surgical and Medical Practices: E.K.U., Concept: E.K.U., H.M., Design: E.K.U., H.M., Data Collection or Processing: E.K.U., H.M., Analysis or Interpretation: E.K.U., H.M.,

Literature Search: E.K.U., M.B.K., M.F., M.K.B., Writing: E.K.U., M.B.K., M.F., M.K.B., Ö.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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