Journal of Izmir Chest Hospital 2022;36(2):92–98
DOI: 10.14744/IGH.2022.21033

RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

Stereotactic Body Radiotherapy in Non-Small Cell Lung Cancer Patients: Assessment of Response and Toxicity at Single İnstitution

Küçük Hücreli Dışı Akciğer Kanseri Olan Hastalarda Stereotaktik Vücut Radyoterapisi: Tek Kurumdaki Yanıt ve Toksisitenin Değerlendirilmesi

[1]Ali ÖLMEZOĞLU
[2]Berna KÖMÜRCÜOĞLU
[3]Kemal EKİCİ

[1]Department of Radiation Oncology, Istanbul Basaksehir Çam and Sakura City Hospital, İstanbul, Türkiye

[2]Department of Chest Diseases, Izmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Türkiye

[3]Department of Radiation Oncology, Istinye University, Bursa VM Medical Park Hospital, Bursa, Türkiye

ORCID ID
AÖ : 0000-0002-7809-9819
BK : 0000-0002-2877-242X
KE : 0000-0003-3222-9275

ABSTRACT

Objective: The aim of this study is to assess the efficacy and acute toxicity of stereotactic body radiotherapy (SBRT) for either primary or metastatic masses of lung tumors.

Material and Methods: Analysis was performed on 110 lung tumor masses (primarily non-small cell origin, a small proportion was metastatic) patients treated by CyberKnife® in our clinic between February 2010 and July 2015. Doses had been delivered ranged 20–60 Gy, in one to seven once-daily fractions, depending on tumor size and location.

Results: The median follow-up duration after SBRT was 29 months (range 14, 75–40 months). The median overall survival (OS) was 31.62 months (95% CI, 24.06–37.93 months). 3-year survival was 42% and 5-year survival was 22%.

Conclusion: Lung tumors (primary or metastatic) treated by SBRT had better treatment response and less toxicity compared with conventional radiotherapy schedules. If available-depending on size and location of the tumor(s) - SBRT is the most affordable; preferable option.

Keywords: CyberKnife, lung cancer, stereotactic body radiotherapy.

ÖZ

Amaç: Bu çalışmanın amacı, akciğer tümörlerinin primer veya metastatik kitleleri için stereotaktik vücut radyoterapisinin etkinliğini ve akut toksisitesini değerlendirmektir.

Gereç ve Yöntemler: Şubat 2010-Temmuz 2015 tarihleri arasında kliniğimizde CyberKnife® ile tedavi edilen 110 akciğer tümör kitlesi (esas olarak küçük hücreli olmayan, küçük bir kısmı metastatik) üzerinde analiz yapıldı. Hastalara 20–60 Gy arasında doz verildi, tümörün boyutuna ve konumuna bağlı olarak tedavi 1 ile 7 fraksiyonda yapıldı.

Cite this article as: Ölmezoğlu A, Kömürcüoğlu B, Ekici K. Stereotactic Body Radiotherapy in Non-Small Cell Lung Cancer Patients: Assessment of Response and Toxicity at Single İnstitution. Journal of Izmir Chest Hospital 2022;36(2):92–98.

Received (Geliş): January 12, 2022 **Accepted (Kabul):** March 10, 2022 **Online (Çevrimiçi):** July 29, 2022
Correspondence author (Sorumlu yazar): Kemal EKİCİ, MD. İstinye Üniversitesi, Bursa VM Medical Park Hastanesi, Radyasyon Onkolojisi Bölümü, Bursa, Türkiye.
Tel: +90 535 921 49 72 **e-mail:** drkemal06@hotmail.com

Bulgular: Stereotaktik vücut radyoterapisi sonrası medyan takip süresi 29 aydı (aralık 14,75–40 ay). Medyan genel sağkalım 31,62 aydı (%95 güven aralığı, 24,06–37,93 ay). Üç yıllık sağkalım %42 ve beş yıllık sağkalım %22 çıktı.

Sonuç: Stereotaktik vücut radyoterapisi ile tedavi edilen akciğer tümörleri (birincil veya metastatik), geleneksel radyoterapi programlarına kıyasla daha iyi tedavi yanıtına ve daha az toksisiteye sahipti. Eğer mümkünse, tümörlerin boyutuna ve konumuna bağlı olarak, stereotaktik vücut radyoterapisi en tercih edilen ve uygun maliyetli tedavi seçeneğidir.

Anahtar kelimeler: Akciğer kanseri, cyberKnife, stereotaktik vücut radyoterapisi.

INTRODUCTION

Lung cancer is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths. Cancer survival tends to be poorer in developing countries, most likely because of a combination of a late stage at diagnosis and limited access to timely and standard treatment.[1] Patients who are diagnosed at early stages can undergo surgical resection and account for 20–25% of cases. However, 20–30% of such patients are not surgical candidates or are unwilling to undergo surgery.[2] While anatomical resection is the standard treatment for early stage lung cancer, some patients cannot tolerate surgery due to comorbidities such as emphysema and heart disease. Median survival is 13 months for patients with untreated T1 tumors and 8 months for those with untreated T2 tumors, the 5-year cancer-specific survival rate being 16%.[3] Patients who are medically inoperable and receiving either no treatment or conventional radiotherapy are significantly less likely to survive than are those who receive surgery. Conventional radiation therapy involves fractionated radiation doses of 1.8–2.0 Gy/day for a total radiation dose of 60–70 Gy, corresponding to more than 6 weeks of treatment. Various techniques can be used, ranging from simple, two-dimensional techniques to sophisticated techniques such as three-dimensional radiation therapy and intensity-modulated radiation therapy. However, in patients with stage I lung cancer, the results of conventional radiation therapy are markedly inferior to those of surgery, with local recurrence rates of up to 70%.[4]

For the treatment of early-stage lung cancer, another strategy is to combine stereotactic localization techniques with high dose hypofractionation: Stereotactic body radiotherapy (SBRT). Various terms are used to describe stereotactic radiation therapy. For instance, in North America, it is referred to as SBRT, whereas the term radiosurgery continues to be used, especially by patients and the media. The principle remains the same: SBRT is a non-isocentric external beam radiation therapy method that delivers high-dose radiation. Biological aspects of high-dose radiation therapy consist of causing direct and indirect cell damage, delivery of ablative doses of radiation to neoplastic lesions prevents tumor repopulation. Furthermore, ablative radiation therapy causes vascular damage, which results in endothelial apoptosis and remodeling of the microvasculature and probably induces an immune response against the tumor as a result of the use of high radiation doses per fraction. In general, 1–5 fractions are delivered in a period of <2 weeks.[5] The use of SBRT requires a high level of accuracy throughout the treatment process. Such accuracy is achieved through the integration of modern imaging, simulation, planning, and dose delivery technologies. CyberKnife® (Accuray Inc., Sunnyvale, CA, USA) has been developed approximately 20 years ago for SBRT delivery as a compact linear accelerator mounted on a six-jointed robotic arm generating output of 6 MV X-ray. During planning, a highly conformal dose distribution around the target volume and the tolerance of neighboring organs has to be taken account. Specific objectives are established by protocols such as Radiation Therapy Oncology Group (RTOG) 0236,[6] RTOG 0813.[7] As the target motion amplitude is high in lung tumors, synchronization of radiation delivery with the respiratory cycle is crucial. The precision of up to 1200 spatial beamlets from so many different angles targeting the tumor was obtained by moving the radiation beam so as to follow the tumor motion trajectory in real time (tracking). Visualization of the tumor or of markers (fiducials) implanted during treatment allows tracking even millimetric internal tumor motion (interfraction motion) caused by breathing.

This study presents the treatment outcomes of the lung tumors irradiated by Cyberknife (SBRT) as a sole ablative treatment for curative intent or metastatic ones as palliative intent.

MATERIAL AND METHODS

Characteristics of Patients

Stage I-III non-small cell lung cancer (NSCLC) patients, who have no lymph node involvement and who are medically inoperable, constitute the target population. Cases of tumor recurrence and metastatic lesions were also included. This retrospective analysis was based on 110 patients treated in single institution with CyberKnife (Accuracy Inc., Sunnyvale, CA, USA) SBRT from February 2010 to July 2015. Although there have been reports of SBRT in patients with tumors of up to 10 cm in diameter,[8] in our study, median tumor volume was 9.92 cc (4.57–24.83). Patient demographics and clinical characteristics are summarized at Table 1. The median age was 61 (range 43–79). Of the 110 patients, 98 (89%) were men and 12 (11%) were women. Median SBRT doses were 50 Gy (range 20–60 Gy) and delivered in median 3 fractions (1–7), mostly the day-after-day depending on tumor size and location. Patients of peripherally localized tumors were 75 (68.2%) and central ones 35 (31.8%). Lung cancer stage was classified based on the tumor, node, and metastasis 7th edition by the American Joint Committee on Cancer. SBRT was administered for primary therapy in 62 cases (56%) and for recurrent tumors after surgery and/or chemotherapy in 43 cases (39%). Tumors of 5 cases (5%) were metastatic ones other than lung cancer primary. Eleven patients (10%) without histopathological confirmation because of comorbidities that increase biopsy risks, diagnosis was based on imaging only. Clinical diagnosis of lung cancer depended on consecutive increase in tumor size at computed tomography (CT) scans or increased pathological uptake of ^{18}F- flurodeoxiglucose (^{18}F-FDG) in tumor at positron emission tomography (PET) scan. Staging of negative N and M was based on con-

Table 1: Patient characteristics

Characteristics	No. of patients
Sex	
Male	98
Female	12
Stage	
Stage 1	106
Stage 4	5
Pathologic verification	
Yes	99
No	11
Tumor location	
Central	35
Peripheral	75
Tumor volume (cc)	
Median	17.8
Range	0.80–91.40
SBRT Doses (Gy)	
Median	50
Range	20-60
No. of Fractions	
Range	1–7
FDG-PET CT staging done	
Yes	77
No	34
Follow-up (months)	
Median	32
Range	21-64

SBRT: Stereotactic body radiotherapy, FDG-PET CT: Fluorodeoxyglucose positron emission tomography.

trast-enhanced CT or ^{18}F-FDG-PET CT in all patients. ^{18}F-FDG-PET-based staging was not mandatory but recommended and performed in 78 (71%) patients. Baseline spirometry-flow data were available in all patients as values of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC). Proportional predicted values (FEV_1/FVC) remained the same. All data were reviewed under an institutional review-approved retrospective protocol.

Treatment Planning and Delivery

From January 2011 to September 2015, SBRT was performed using CyberKnife (Accuracy Inc., Sunnyvale, CA, USA) radiosurgery system with 6-MV X-rays under respiratory gating. Gating system consists of an infrared tracking mechanism and X-ray imaging device. Infrared emitters mounted on the vest covering patients' chest wall correlate between breath and tumor motion detected by simultaneous imaging. In the case tumor superposed by neighboring organs and undetectable by X-ray imaging, internal fiducial markers implantation is essential for CyberKnife treatment. The correlation of motion between the external infrared emitters and internal fiducial markers will be updated periodically during treatment. Immobilization mostly was achieved with vacuum couch at supine position. Simulation CT (Toshiba Aquilion LB, Japan) was performed using 1-mm thick slices by administering intravenous contrast material simultaneously. Dose and fractionation schedules were chosen depending on size and location of the primary tumor and lung function parameters. In general, peripheral and small tumors were treated by preferentially with hypofractionated doses, whereas central, with close proximity to dose-limiting structures and relatively bigger ones, were treated with less likely with hypofractionated doses.

The primary tumor in the enhanced CT or ^{18}F-FDG-PET was delineated as gross tumor volume (GTV). The GTV was defined as the tumor visible in lung window of the planning CT scan without further margin contributing clinical target volume. The planning target volume (PTV) was generated by adding a 1–5 mm margin to GTV. The SBRT doses were prescribed to the 85% covering the PTV. Evaluation of the final treatment plan depended on factors such as the homogeneity and conformality index (Fig. 1). The ^{18}F-FDG-PET-guided planning could be possible for 78 patients (71%). During the follow-up, 56 of these patients (51% of all cases) for metabolic response assessment were administered to ^{18}F-FDG-PET CT after SBRT.

Follow-up

The median follow-up duration after SBRT was 29 months (range, 14–39 months) and was complete in 96.4% of patients. Clinical and radiographic assessments were performed every 3 months after SBRT for the first 2 years, every 6 months for the first 3 years, and annually thereafter. Post-treatment imaging assessment included contrast-enhanced CT or ^{18}F-FDG-PET for metabolic response if available. ^{18}F-FDG-PET follow-up was done in 56 patients (51%) to assess metabolic response regarding tumor maximum standardized uptake value ($SUV_{[max]}$) decrease at tumors. Local responses relating to treatment were classified according to the modifications of the Response Evaluation Criteria in Solid Tumors. Acute and late toxicities associated with treatments were evaluated by the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0.[8,9]

Statistical Analysis

Survival time was measured from the date of SBRT to the date of death or lost follow-up. The Kaplan–Meier method was used to measure survival time, and the log-rank test was used for comparison by risk factors. A probability level of 0.05 was considered statistically significant. SPSS software, version 21.0.0, was used for the statistical analyses (SPSS Inc., Chicago, III, USA).

RESULTS

Survival

All patients completed their treatment as planned. The median follow-up duration after SBRT was 29 months (range 14–39 months).

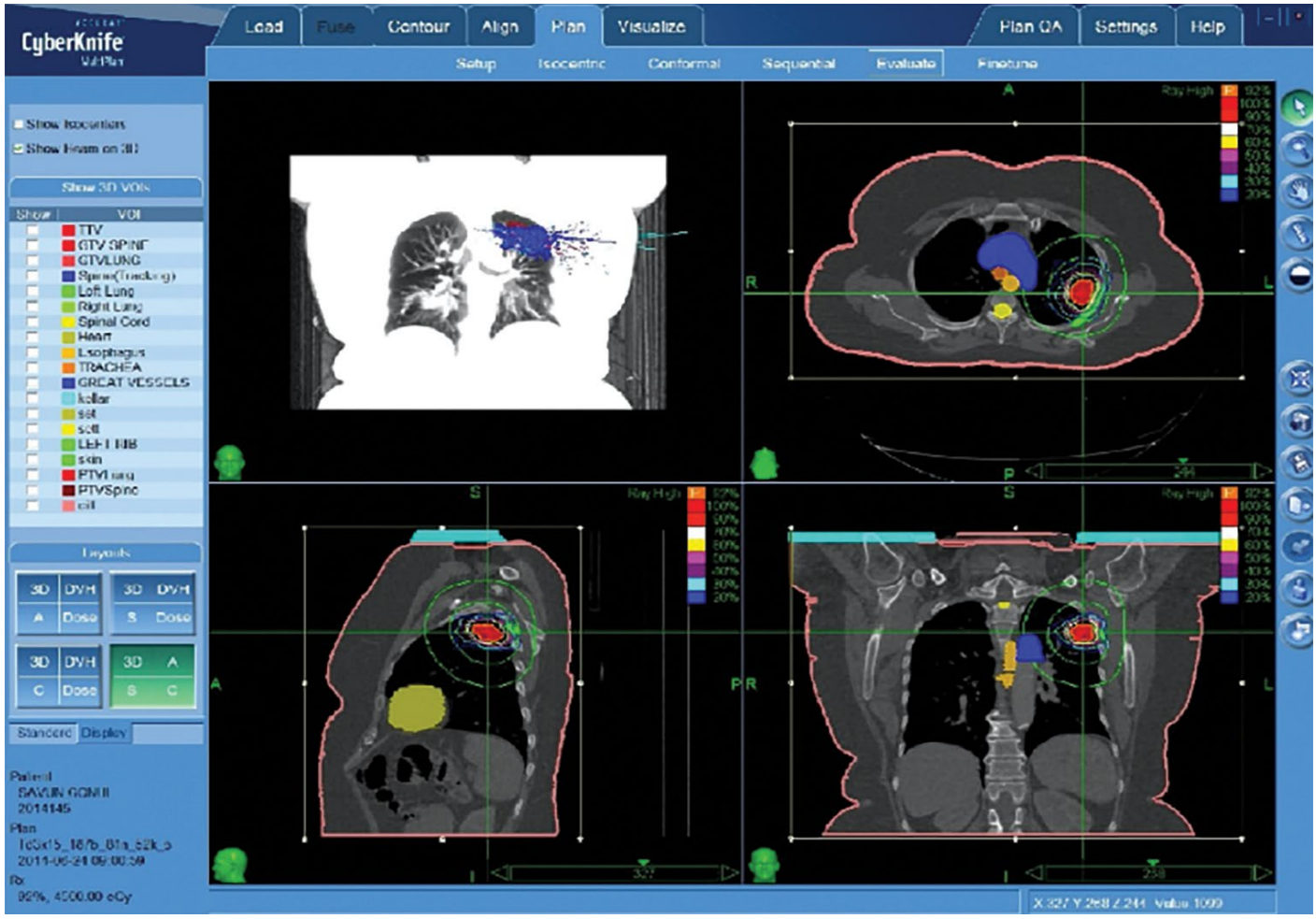

Figure 1: Stereotactic body radiotherapy treatment planning in a single patient.

The median tumor $SUV_{(max)}$ before SBRT was 11.7 (7.5–15.5). After SBRT, median $SUV_{(max)}$ value was 3.5 (2.7–4.9). The metabolic response rate was 58% ($p<0.01$) for patients who underwent ^{18}F-FDG-PET median 6 months (3–8) after SBRT. 3-year survival was 42% and 5-year survival was 22%. The median of OS was 31.62 months (95% CI, 24.06–37.93 months) (Fig. 2).

Toxicity

SBRT was generally well tolerated and all patients completed therapy as planned. Five patients (4.5%) had grade 2 and 9 (8.2%) patients had grade 1 acute radiation pneumonitis demonstrated by CT scans and clinical examination. All of these patients (12.7%) underwent flow-spirometry after SBRT. There has been <10% decrease in FEV_1 and FVC between baseline and later obtained values. This has no impact on quality of life contributing grade 3 or higher toxicity. No patient reported chest pain, rib fracture, and hematological toxic effects. Blood routine tests were normal before and after SBRT.

DISCUSSION

Conventional radiation therapy has traditionally been offered to non-operable patients with suboptimal results. With the advent of SBRT, patients are able to achieve long-term outcomes, with reported 3-year survival of 56.6%. In the meta-analysis by Zheng et al.,[9] all the studies published between 2000 and 2012, the results obtained with SBRT were compared with those obtained with surgery in operable patients with stage I NSCLC. Forty SBRT studies-30 of which were retrospective-comprising a total of 4850 patients and 23 surgery studies-all of which were retrospective-comprising a total of 7051 patients were selected for inclusion. In the present study, median follow-up duration was 29 months while in the meta-analysis of 4850 patients reported as 28 months. The meta-analysis had included studies of 4850 SBRT patients with stage I NSCLC and the overall survival rates at 1, 3, and 5 years were 83.4%, 56.6%, and 41.2%, respectively. The present study constituting 62 stages I-III NSCLC patients (56%) for primary therapy and 43 patients (39%) with recurrent disease after surgery and/or chemotherapy had overall survival rates at 1, 3, and 5 years as 83%, 42%, and 22%, respectively. Local control is not only defined as disappearance of the lesion but also as a decrease in size or no increase in size of the lesion. There is variability in the definition of local recurrence (failure of local control). Several studies consider recurrence only in the treatment bed while some others as any disease in lungs away from the treatment bed. As in our study, 43 patients (39%) who have previously been treated with

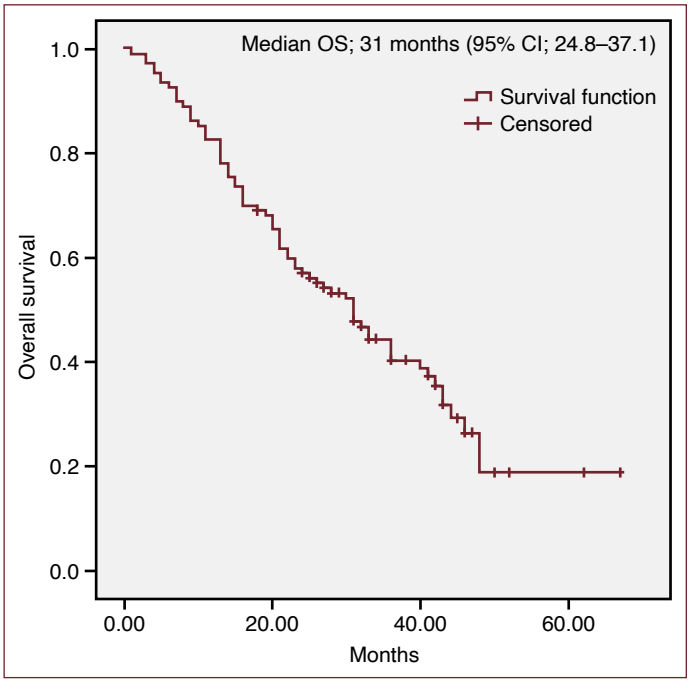

Figure 2: Overall survival curves of the patients treated with stereotactic body radiotherapy.

CI: Confidence interval.

surgery and/or chemotherapy could have better locoregional control than 62 patients constituting 56% of our principal study population that administered for primary therapy. Therefore, overall survival data might be preferable to assess the treatment response as in our study.

Metabolic imaging with PET using ^{18}F-FDG has been accepted as an important imaging modality in lung cancer. ^{18}F-FDG-PET provides information on the mediastinum and extrathoracic staging (nodal and metastatic status). A meta-analysis of studies investigating the accuracy of FDG-PET in diagnosing malignant pulmonary lesions estimated the sensitivity and specificity to be 96.8 and 77.8%, respectively. A separate meta-analysis by Hellwig et al.[10] found the sensitivity and specificity of ^{18}F-FDG-PET in the diagnosis of lung lesions to be 96 and 80%. Furthermore, ^{18}F-FDG-PET, in the response assessment to SBRT, has greater prognostic significance than that obtained by conventional imaging methods. The $SUV_{(max)}$ of ^{18}F-FDG-PET may predict the outcome after SBRT. Among 195 NSCLC patients, a multivariate analysis done by Takeda et al.,[11] only the $SUV_{(max)}$ of a primary tumor was a significant predictor. A prospective study by Mohammed et al.[12] to evaluate radiographic and metabolic response after SBRT for early lung tumors yielded metabolic response is rapid than radiographic response which occurs even after 1-year post-treatment. In the present study, the metabolic response rate based on $SUV_{(max)}$ decrease after SBRT was 58% ($p<0.01$) for patients who re-underwent ^{18}F-FDG-PET CT median 6 months (3–8) following SBRT.

Nowadays, a rapid increase in the use of SBRT early-stage NSCLC patients, especially in the USA, has been accompanied by an increasing number of patients receiving SBRT solely on the basis of a clinical diagnosis.[13] Such patients currently account for less than 10% of all cases, as in our present study, 11 patients (10%) without histopathological confirmation had been treated. In a prospective study evaluating the impact of adding positron emission tomography (PET) to conventional staging, thoracotomy was found to have been "futile" (i.e., was performed in patients with benign disease) in less than 10% of cases.[14] In a large study conducted in the Netherlands (n=676), in which all patients were staged by ^{18}F-FDG-PET CT, 65% had no histological diagnosis.[15] A trend toward increased SBRT use without biopsy (histopathological confirmation) may lead a new model to treat early NSCLC.

Lower toxicity profile observed in many retrospective studies for peripheral tumors.[15,16–21] In RTOG 0236 (a multicenter phase II study), 52 patients with medically inoperable T1-3 NSCLC (<5 cm) were treated with 60 Gy delivered in 3 fractions. Long-term results showed an overall survival of 40% after a median follow-up of 4 years. Grade 3 toxicity was reported in 15 patients, and grade 4 toxicity was reported in 2, with no reports of grade 5 toxicity.[22] On the other hand, the use of SBRT to treat patients with central lung lesions began to be questioned after the publication of results showing severe toxicity rates of 17% and 46% at 3 years for peripheral and central lesions, respectively, 6 deaths having been related to the treatment of central lesions.[23,24] Thereafter, toxicity is always a concern in patients with central lesions. It was suggested that it would be safer and more appropriate to use a larger number of fractions (5 or more fractions) and smaller doses per fraction to treat patients with central lesions. Systematic review of 20 studies consisting 563 central lung lesions treated with SBRT reported grade 3/4 toxicity 8.6% of cases, and SBRT-related mortality was 2.7%. 3-year overall survival rates were 50–75%.[25,26]

In the present study, median tumor volume for peripheric lesions was 8.63 cc (range, 4,56–19,90 cc). For central ones, median tumor volume was almost double: 17, 95cc (range,5,82–32,93 cc). Median fractions were 3 both for peripheric and central lesions but tumor doses differed as median 54 Gy for peripheric and median 45 Gy central ones. Significant volume difference in median tumor volumes (8,63 cc peripheral, 17,95 central) contributing dose limits for adjacent organs and normal structures forced us the dose escalation of 20% decrement for the central tumor doses. However, overall survival median 31 months for both tumor localization were same as well.

Most of the lung cancer patients who are candidates for SBRT are not surgical patients as in present study; it should be taken into consideration to evaluate the pulmonary toxicity of SBRT in this group of patients. Several studies have evaluated lung function changes in patients undergoing SBRT. Although FEV_1 and FVC are generally reduced and can decrease further over time, this has no impact on patient quality of life or survival.[27–29] No clinical or spirometric risk factors for pulmonary toxicity were identified.[29–35] RTOG 0236 protocol consisting of 55 patients received SBRT for peripheral tumors showed a 5.8% decrease in FEV_1.[32] In the present study, 5 patients (4,5%) had grade 2, 9 (8.2%) patients had grade 1 acute radiation pneumonitis demonstrated by CT scans and clinical examination. All of these patients (12.7%) underwent flow-spirometry after SBRT. There has been less than 10% decrease in FEV_1 and FVC between baseline and later obtained values.

In view of the promising results obtained with SBRT for early-stage lung cancer, the idea of substituting this noninvasive technique for

surgery, which is the standard treatment, led to randomized studies comparing SBRT with surgery. Two prospective phase II trials reported 76–84% 2–3-year overall survivals for operable stage I disease after SBRT, which compare favorably with surgical outcomes. Two phase III randomized trials (STARS and ROSEL) to compare SBRT with surgery in operable stage I NSCLC were prematurely terminated due to poor accrual.[35–39] The investigators of two of the aforementioned studies[36,37] performed a pooled analysis of the collected data.[38] Eligible patients were those with clinical T1-2a (<4 cm), N0M0, operable NSCLC. A total of 58 patients were enrolled and randomly assigned to SBRT (n=31) or surgery (n=27). The median follow-up duration was 40.2 months for the SBRT group and 35.4 months for the surgery group. Only 1 patient in the SBRT group died, compared with 6 in the surgery group. Estimated overall survival at 3 years was 95% in the SBRT group and 79% in the surgery group. Grade 3 treatment-related adverse events were observed in 3 (10%) of the patients in the SBRT group, no grade 4 events having been observed in that group. In the surgery group, 1 (4%) of the patients died of surgical complications and 12 (44%) had grade 3/4 treatment-related adverse events. The authors of this publication concluded that SBRT is at least equivalent to surgery in terms of survival and local control and has reduced toxicity.[39–42]

In our study, as data had been obtained as retrospective design, tumors of varying stages (NSCLC stages I-II) and tumors of patients who have previously been treated with surgery and/or chemotherapy have taken into consideration. Therefore, we have focused at overall survival rather local control to maintain comparable results in previosly published data. 1- and 3-year OS rates in our series could yield 82% and 42%, respectively. Especially when standard treatment "surgery" could not be done because of poor pulmonary function or comorbid diseases, SBRT is the most affordable; preferable option rather than "doing nothing."

Disclosures

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.Ö.; Design – A.Ö.; Supervision – K.E.; Fundings – A.Ö.; Materials – A.Ö.; Data Collection and/or Processing – B.K.; Analysis and/or Interpretation – B.K.; Literature Search – K.E.; Writing – K.E.; Critical Reviews – B.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
3. Raz DJ, Zell JA, Ou SH, Gandara DR, Anton-Culver H, Jablons DM. Natural history of stage I non-small cell lung cancer: Implications for early detection. Chest 2007;132:193–9.
4. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable). Cochrane Database Syst Rev 2001;CD002935.
5. Zeng J, Baik C, Bhatia S, Mayr N, Rengan R. Combination of stereotactic ablative body radiation with targeted therapies. Lancet Oncol 2014;15:e426–34.
6. Radiation Therapy Oncology Group [Internet]. Philadelphia: RTOG. 2011 Feb 9 - RTOG 0236 Protocol Information, A phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I/II non-small cell lung cancer; 2009. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable. Accessed Sep 25, 2014.
7. Radiation Therapy Oncology Group [Internet]. Philadelphia: RTOG. 2015 Jun 22 - RTOG 0813 Protocol Information, Seamless phase I/II study of stereotactic lung radiotherapy (SBRT) for early stage, centrally located, non-small cell lung cancer (NSCLC) in medically inoperable patients; 2015 Jun 8. Available at: http://www.rtog.org/ClinicalTrials/Protocol Table. Accessed Sep 25, 2014.
8. Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: Clinical implications. Radiother Oncol 2010;94:1–11.
9. Zheng X, Schipper M, Kidwell K, Lin J, Reddy R, Ren Y, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: A meta-analysis. Int J Radiat Oncol Biol Phys 2014;90:603–11.
10. Hellwig D, Ukena D, Paulsen F, Bamberg M, Kirsch CM. Metaanalysis of the efficacy of positron emission tomography with F-18-fluorodeoxyglucose in lung tumors. Basis for discussion of the German Consensus Conference on PET in Oncology 2000. Pneumologie 2001; 55: 367–77.
11. Takeda A, Yokosuka N, Ohashi T, Kunieda E, Fujii H, Aoki Y, et al. The maximum standardized uptake value (SUV_{max}) on FDG-PET is a strong predictor of local recurrence for localized non-small-cell lung cancer after stereotactic body radiotherapy (SBRT). Radiother Oncol 2011;101:291–7.
12. Mohammed N, Grills IS, Wong CY, Galerani AP, Chao K, Welsh R, et al. Radiographic and metabolic response rates following image-guided stereotactic radiotherapy for lung tumors. Radiother Oncol 2011;99:18–22.
13. Rutter CE, Corso CD, Park HS, Mancini BR, Yeboa DN, Lester-Coll NH, et al. Increase in the use of lung stereotactic body radiotherapy without a preceding biopsy in the United States. Lung Cancer 2014;85:390–4.
14. Herder GJ, van Tinteren H, Golding RP, Kostense PJ, Comans EF, Smit EF, et al. Clinical prediction model to characterize pulmonary nodules: Validation and added value of ^{18}F-fluorodeoxyglucose positron emission tomography. Chest 2005;128:2490–6.
15. Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: A retrospective analysis. Lancet Oncol 2012;13:802–9.
16. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833–9.
17. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94–100.
18. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys 2015;93:989–96.
19. Baumann P, Nyman J, Lax I, Friesland S, Hoyer M, Rehn Ericsson S, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. Acta Oncol 2006;45:787–95.

20. Brown WT, Wu X, Fayad F, Fowler JF, Amendola BE, García S, et al. CyberKnife radiosurgery for stage I lung cancer: Results at 36 months. Clin Lung Cancer 2007;8:488–92.
21. van der Voort van Zyp NC, Prévost JB, Hoogeman MS, Praag J, van der Holt B, Levendag PC, et al. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: Clinical outcome. Radiother Oncol 2009;91:296–300.
22. Timmerman RD, Hu C, Michalski J, Straube W, Galvin J, Johnstone D, et al. Long-term results of RTOG 0236: A phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically ınoperable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014;90:30.
23. McGarry RC, Papiez L, Williams M, Whitford T, Timmerman RD. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: Phase I study. Int J Radiat Oncol Biol Phys 2005;63:1010–5.
24. Timmerman R, Papiez L, McGarry R, Likes L, DesRosiers C, Frost S, et al. Extracranial stereotactic radioablation: Results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946–55.
25. Baba F, Shibamoto Y, Ogino H, Murata R, Sugie C, Iwata H, Otsuka S, et al. Clinical outcomes of stereotactic body radiotherapy for stage I non-small cell lung cancer using different doses depending on tumor size. Radiat Oncol 2010;5:81.
26. Bezjak A, Paulus R, Gaspar LE, Timmerman RD, Straube WL, Ryan WF, et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG oncology/RTOG 0813 trial. J Clin Oncol 2019;37:1316–25.
27. Zheng X, Schipper M, Kidwell K, Lin J, Reddy R, Ren Y, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: A meta-analysis. Int J Radiat Oncol Biol Phys 2014;90:603–11.
28. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: A pooled analysis of two randomised trials. Lancet Oncol 2015;16:630–7.
29. Guckenberger M, Kestin LL, Hope AJ, Belderbos J, Werner-Wasik M, Yan D, et al. Is there a lower limit of pretreatment pulmonary function for safe and effective stereotactic body radiotherapy for early-stage non-small cell lung cancer? J Thorac Oncol 2012;7:542–51.
30. Stanic S, Paulus R, Timmerman RD, Michalski JM, Barriger RB, Bezjak A, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: An analysis of RTOG 0236. Int J Radiat Oncol Biol Phys 2014;88:1092–9.
31. Takeda A, Enomoto T, Sanuki N, Handa H, Aoki Y, Oku Y, et al. Reassessment of declines in pulmonary function ≥1 year after stereotactic body radiotherapy. Chest 2013;143:130–7.
32. Bishawi M, Kim B, Moore WH, Bilfinger TV. Pulmonary function testing after stereotactic body radiotherapy to the lung. Int J Radiat Oncol Biol Phys 2012;82:e107–10.
33. Stephans KL, Djemil T, Reddy CA, Gajdos SM, Kolar M, Machuzak M, Mazzone P,et al. Comprehensive analysis of pulmonary function Test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. J Thorac Oncol 2009;4:838–44.
34. Henderson M, McGarry R, Yiannoutsos C, Fakiris A, Hoopes D, Williams M, et al. Baseline pulmonary function as a predictor for survival and decline in pulmonary function over time in patients undergoing stereotactic body radiotherapy for the treatment of stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:404–9.
35. Palma D, Lagerwaard F, Rodrigues G, Haasbeek C, Senan S. Curative treatment of Stage I non-small-cell lung cancer in patients with severe COPD: Stereotactic radiotherapy outcomes and systematic review. Int J Radiat Oncol Biol Phys 2012;82:1149–56.
36. Clinical Trials. Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer (ROSEL);2008 May 28 Available at: https://clinicaltrials.gov/ct2/show/NCT00687986. Accessed Jun 15, 2022.
37. Randomized study to compare cyberknife to surgical resection in stage I non-small cell lung cancer (STARS). 2009 Feb 7. Available at: https://clinicaltrials.gov/ct2/show/NCT00840749. Accessed Apr 13, 2015.
38. ACOSOG PROTOCOL Z4099; RTOG PROTOCOL 1021. A randomized phase III study of sublobar resection (+/- brachytherapy) versus stereotactic body radiation therapy in high risk patients with stage I non-small cell lung cancer (NSCLC); 2011 May 2. Available at: http://rpc.mdanderson.org/rpc/credentialing/files/Z4099-1021%20A0%2005-02-2011.pdf. Accessed Mar 18, 2022.
39. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: A pooled analysis of two randomised trials. Lancet Oncol 2015;16:630–7.
40. Lin Q, Zhou N, Zhu X, Lin J, Fang J, Gu F, et al. Outcomes of SBRT for lung oligo-recurrence of non-small cell lung cancer: A retrospective analysis. J Radiat Res 2021:rrab118.
41. Andruska N, Stowe HB, Crockett C, Liu W, Palma D, Faivre-Finn C, et al. Stereotactic radiation for lung cancer: A practical approach to challenging scenarios. J Thorac Oncol 2021;16:1075–85.
42. Videtic GMM, Reddy CA, Woody NM, Stephans KL. Ten-Year experience in implementing single-fraction lung SBRT for medically inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 2021;111:436–42.