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The role of stereotactic body radiotherapy (SBRT) in the treatment of recurrent / progressive lung lesions after primary treatment

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ABSTRACT

Background: To evaluate treatment outcomes and toxicity of pulmonary SBRT for intrathoracic recurrence in patients with locally advanced NSCLC treated as a combination of surgery, radiotherapy or chemotherapy. ***Materials and Methods:*** A total of 46 patients with NSCLC who received thoracic SBRT for local or non local intrapulmonary recurrent lesions in our department from 2009 to 2019 were retrospectively enrolled in this study. The patients received median 43.4 Gy (25 Gy -60 Gy) radiotherapy using the CyberKnife radiosurgery system in median 3.6 fractions (range, 1-8).Univariate and multivariate Cox regression analyses were performed on the factors predicting outcomes. ***Results:*** The median follow up time after SBRT was 23.5 months. Treatment of the primary tumor consisted of surgical resection, radiochemotherapy, and systemic therapy in 25, 8 and 13 patients, respectively. İsolated local recurrence, intrathoracic recurrence and distant metastasis were detected in 5 (10.9%), 12 (26.1%) and 8 (17.4%) patients, respectively. Kaplan-Meier analysis of 2 year OS, PFS and LC for all tumors treated after SBRT were; 51%, 56% and 91%, respectively. In parameters related to patient and treatment; no statistical significance was found affecting local control and survival.(p>0.05). Grade 2 radiation pneumonitis and chest wall pain were observed in 2 (4.3%) and 1 (2.1 %) patients. Grade 3 toxicity was detected in 3 (6.5%) cases. ***Conclusion:*** Pulmonary SBRT for recurrent NSCLC is a good treatment option with favourable LC and promising survival. SBRT can be an effective treatment modality in the treatment of patients with local/ limited pulmonary relapses with acceptable toxicity rates.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) can deliver ablative radiation doses in few fractions by using advanced imaging techniques [1, 2]. The main difference between SBRT and conventional radiotherapy is the ability to deliver significantly higher doses during each treatment session in SBRT.Delivery of such high doses using SBRT offers high probability of tumour control without compromising the surrounding organs at risk [3].

Thoracic SBRT shows a similar survival rate to surgical therapies in the treatment of early stage inoperable non-small cell lung cancer (NSCLC) [4, 5].

However, in the follow up patients whose first treatment is surgical resection, definitive radiotherapy (RT) or chemoradiotherapy (CRT), diffuculties are experienced in the management of local and regional recurrences or new lesions with the diagnosis of second primary NSCLC.

Surgical approach may not always be possible due to the location or extent of the newly developed lesion and/or the functional status of the patient. SBRT is an option in such patients[6]. Reirradiation is associated with extra toxicity risks, which need to be weighed against the benefit of salvage radiation therapy for patients previously treated with conventionally fractionated radiation therapy [7]. A recent American Society of Radiation Oncology consensus statement discussed the role of SBRT for salvage therapy after 3 scenarios: prior conventionally fractionated radiation, prior SBRT and prior sublobar resection [8]. The level of evidence was considered low in all scenarios and individualization of treatment for each patient was recommended.

In this study, we examined the safety and efficacy of thoracic stereotactic body radiation therapy in patients with NSCLC treated with a combination of surgery, radiotherapy or chemotherapy, in the light of current literature.

MATERIALS AND METHODS

Study design and eligible patients

A retrospective cross-sectional study was conducted in forty-six patients treated with an initial diagnosis of NSCLC between January 1995 and March

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2019 and undergoing thoracic SBRT for newly developed lesions during follow-up.

These lesions were detected by thoracic CT and FDG-PET images obtained during patient follow-up.Thoracic SBRT decision was made for all cases of the study after evaluation by the multidisciplinary lung tumor council (consisting of pulmonologist, thoracic surgeon, radiologist, nuclear medicine specialist, medical oncologist and radiation oncologist). All lesions of the patients were evaluated as malignant radiological images. While diagnostic biopsy was performed on 8 patients, this was not possible for the remaining 38 patients. When the patients who were not biopsied were assessed; most were stage IV patients evaluated as oligoprogression and oligoresidual disease. Therefore histopathological confirmation was not considered necessary. In addition fewer patients did not undergo biopsy due to medical problems.

Pathology results of the patients who underwent biopsy were consistent with their primary histology.In patients whose histopathological diagnosis could not be reached, the treatment decision was made after examining the clinical findings and imaging results such as contrast-enhanced CT and PET/CT. Patients were evaluated for salvage SBRT based on tumor size, localization (peripheral/ultracentral), performance status, and overlap with previous radiotherapy site. Patient and tumor characteristics are summarized in table 1.

SBRT planning and delivery

Patients underwent SBRT using the CyberKnife (Accuracy, Sunnyvale, CA, USA) radiosurgery system between June 2009 and July 2019. CyberKnife system is a computer-controlled robot that provides high-dose treatments using focused radiation beams on target tissues. This system monitors tumors with real-time fiducial and breath tracking (XSight Lung Tracking System) techniques during SBRT. Thus minimizing toxicity, more accurate dose distribution and safe dose increase with high conformity. Fiducial Tracking (n = 14) tracks reference marks which are tiny 1–4 gold seeds implanted near or within the tumor. Besides, the other Xsight Lung Tracking System (n = 32) tracks the soft tissue (tumor) target without the need for reference markers.

After immobilization of the patients in supine position with vacuum couch, simulation CT (GE Healthcare, WI, USA) was obtained with 1.25 mm slice thickness. A combination of CT and PET CT was used to create the gross target volume (GTV). The planning target volume (PTV) were determined by adding a 5 mm isotropic margin to the GTV. Time interval between treatments, the previous radiation dose to critical organs and the site of recurrence were factors considered in determining the SBRT dose and fractionation number. Homogeneity and conformality index were taken into account in the evaluation of the selected treatment plan.

Table 1. Demographic, clinical and treatment characteristics of the patients.

		Number of Patients	Percent (%)
Age (years)	Median (range)	65 (46-85)	
Sex	Men	39	84,8
	Women	7	15,2
ECOGPerformance Status	0	17	37,0
	1	22	47,8
	2	7	15,2
	3-4	0	0
First histology	Carcinoma (not classified)	12	26.1
	SCC	22	47,8
	Adenocarcinoma	10	21,7
	Large cell carcinoma	2nd	4.3
First stage	Stage 1	12	26.1
	Stage 2	10	21,7
	Stage 3	5	10.9
	Oligometastasis	13	28,3
	Other stage 4	6	13,0
First treatment	Surgery ± adjuvant therapy	25	54,3
	Radical RT-chemo	8	17,4
	Chemotherapy alone	13	28,3
First RT	No	24	52,2
	Yes	22	47,8
Number of metastatic patients receiving systemic therapy after SBRT*	Chemotherapy	9	47.3
	Targeted therapy	2	10.5
Recurrence location	Peripheral	39	84.89
	Central	7	15.2
Recurrence type	Local	9	19,6
	Lung (same-opposite lung)	36	78,2
	Other sites	1	2.2

*Oligometastic and other stage IV includes a total of 19 patients. ECOG, Eastern Cooperative Oncology Group ; SCC: Squamous cell carcinoma; RT, radiotherapy; SBRT, stereotactic body radiotherapy

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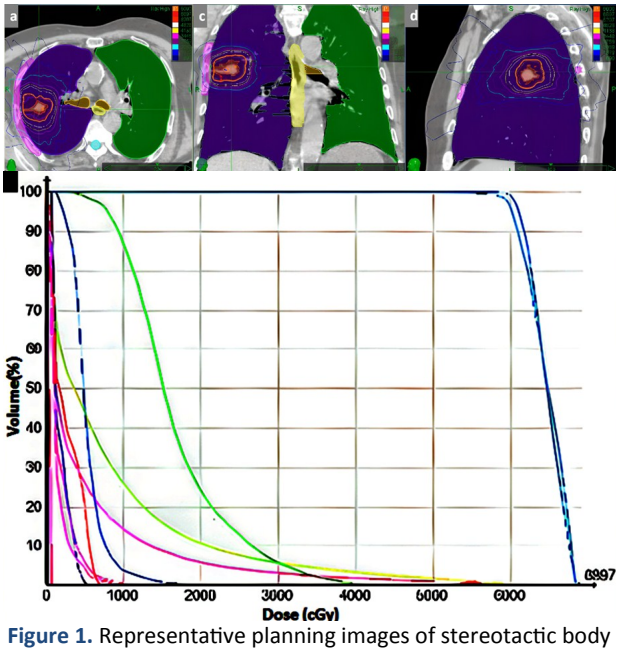

Figure 1. Representative planning images of stereotactic body radiotherapy planning with 60 Gy in 5 fractions on a sample patient. **a, c ,d** Axial ,coronal and sagittal images illustrating the dose distribution of SBRT. **b,** Dose-volume histogram of the plan.

Follow up

PET-CT scanning was performed approximately 3 months after treatment to determine the initial response to SBRT. Patients were followed up every 3-6 months for the first 2 years, and annually thereafter. Response Evaluation Criteria in Solid Tumors (RECIST) was used to determine treatment response [9].

Local recurrences were defined as greater than 20% increase in treated tumor size on CT or an increase in the maximum standard uptake value on PET. Regional recurrences were defined as new lesions detected by PET/CT or biopsy in the ipsilateral lung or mediastinal lymph nodes outside the PTV.

Statistical analysis

The survival outcomes were estimated by the Kaplan-Meier methods. Univariable and multivariable Cox regression analyses were performed to identify variables associated with OS (overall survival), PFS (progression free survival) and LC (local control). Statistical analyzes were performed using SPSS software, version 17.0.0 (SPSS Inc., Chicago, III, USA).

Both acute and late toxicities associated with treatments were evaluated retrospectively with the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. [10]. Institutional ethics committee approval was obtained for the study.

RESULTS

The median follow-up after the first diagnosis is 61.3 (9-222) months, median follow-up after SBRT is 23.5 (1.5-104) months. While 28 patients (60.9%) had a single lesion, remaining 18 patients (39.1%) had multiple lesions. Patients with ECOG (Eastern Cooperative Oncology Group Performance Status) 0-1 were classified as the group with good performance, and patients with ECOG 2 were classified as the group with poor performance. Nineteen out of 46 patients were stage IV disease (7 patients had regional metastatic disease, 8 patients had solitary extrathoracic metastases,4 patients had multiple extrathoracic metastases) at the time of SBRT.

Oligometastatic disease was defined as up to 5 extrathoracic lesions in up to 3 organs at the time of diagnosis.[11] Six patients with extensive stage (non-oligometastatic) underwent SBRT because their lung lesions showed symptomatic progression under chemotherapy.Treatment of the primary tumor consisted of surgical resection, radiochemotherapy, and systemic therapy in 25, 8 and 13 patients respectively (table 1).Oligometastatic and other stage IV patients with good systemic treatment response were evaluated in the multidisciplinary council within our institution and a curative approach was recommended forrecurrent lung lesions.The distrubition of 29 patients who received systemic therapy was as follows; 28 patients received chemotherapy, 1 patient targeted therapy and none of the patients received immunotherapy.

Thoracic SBRT was performed for synchronous oligometastasis in one patient,local recurrence in 9 patients and intrapulmonary recurrence in the remaining 36 patients (same or opposite lung).The mean time from the first diagnosis to recurrence is 37.2 months (range, 3 to 190 mo). The median duration from prior thoracic radiotherapy to SBRT was 27.8months (range, 2 to 75mo). Among 46 recurrent lesions, 39 (84.8%) lesions were peripherally located and 7 (15.2%) were centrally located. The patients received median 43.4 Gy (25 Gy -60 Gy) radiotherapy in median 3.6 fractions (table 2).

Table 2. Treatment characteristics.

SBRT dose (Gray)	Median (range)	43.4 (25-60)
SBRT fraction number	Median (range)	3.6 (1-8)
SBRT tumor volume (cc)	Median (range)	27.4 (9.3-82.0)
SBRT max . dose (Gray)	Median (range)	51.33 (26.6-69.7)
SBRT BED10 value	Median (range)	(60-180)

BED, biological equivalent dose;SBRT, stereotactic body radiotherapy

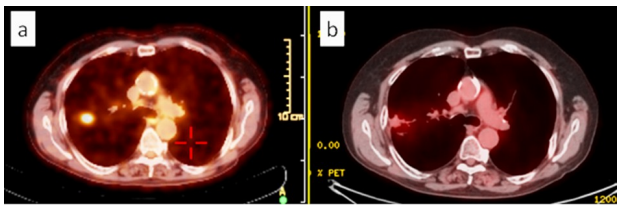

Figure 2. Representative planning axial images showing PET CT change in intensity of FDG uptake -**a**- before/ -**b**- after (18 month) SBRT.

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Survival

Isolated local recurrence developed in 5 patients (10.9%) during amedian follow-up of 23.5 months.In addition12 patients (26.1%) had intrathoracic recurrenceand 8 (17.4%) patients had distant metastasis.

When survival analysis was evaluated for all patients, 2 year overall survival, progression free survival and local control rates were 51%, 56% and 91%, respectively.The OS, PFS and LC curves are summarized in figures 3.When survival analysis was evaluated for 27 patients who were not at an advanced stage initially, 2 year overall survival, disease-free survival and local control rates were 52%, 53% and 95%, respectively. Age and gender of the patient, prior RT dose, prior chemotherapy, weight loss, time between treatments, location of the target lesion, performance status, systemic therapy, number of lesions, metastatic diseaseand tumor size were analized as factors effecting survival and local control. We did not find any significant prognostic factors for LC and survival rates on univariable and multivariate analysis.

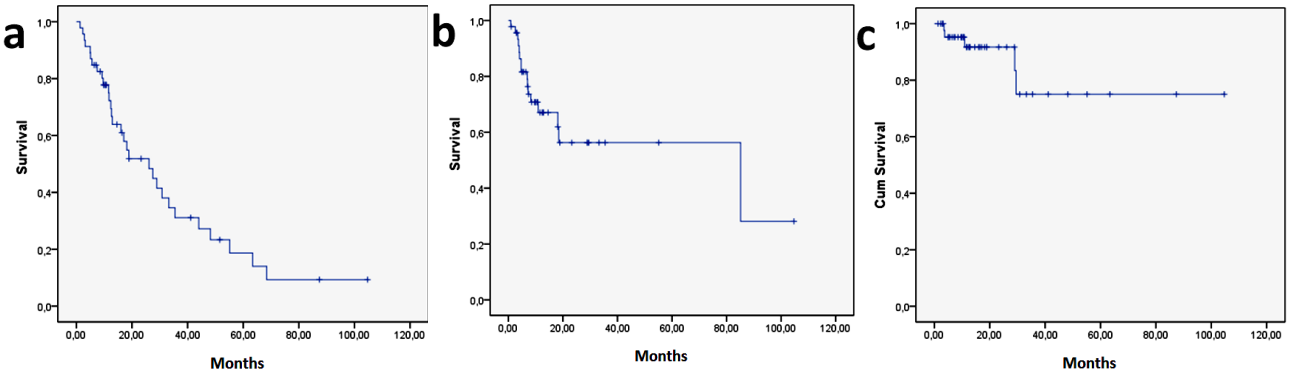

Figure 3. Kaplan-Meier analysis of overall survival **(a)**, progression-free survival **(b)** and local control **(c)** for patients treated with stereotactic body radiotherapy.

Toxicities

Acute toxicity after thoracic SBRT for recurrent lung lesions was tolerable. Among 46 patients 8 (17.3%) patients developed grade 1 fatigue. Grade 2 radiation pneumonitis and chest wall pain were observed in 2 (4.3%) and 1 (2.1 %) patients respectively. Grade 3 toxicity was observed in 3 (6.5%) cases, 2 patient with radiation pneumonitis and 1 patient with fatigue. No grade 4 or 5 toxicity was observed (table 3).

Table 3. SBRT Toxicity.

Side effect	Degree	Number of patients	Percent (%)
Fatigue	grade 1	8	17.3
	grade 2	2	4.3
	grade 3	1	2.1
	grade 4-5	0	0
Radiation Pneumonitis	grade 1	1	2.1
	grade 2	2	4.3
	grade 3	2	4.3
	grade 4-5	0	0
Chest Wall Pain	grade 1	1	2.1
	grade 2	1	2.1
	grade 3	0	0
	grade 4-5	0	0
Total		18	39

DISCUSSION

Treatment options for patients with recurrent or second primary NSCLC are very limited. The main treatment methods are surgical resection and radiotherapy. Surgical resection may not always be possible due to lesion and/or patient-related factors. In such cases, radiotherapy may be the appropriate treatment for selected patients. New technologies are used in radiotherapy to minimize the toxicity risks associated with the treatment. One of these, the SBRT method, provides dose reduction in critical structures by using image guidance, while allowing much higher dose levels in the target volume [12]. Another advantage of SBRT is that it can deliver high doses of radiotherapy to the tumor in a short time, without the risk of postoperative complications and mortality.

There are studies in the literature showing SBRT results after primary radiotherapy in NSCLC patients. Kelly *et al.* studied 36 patients who received SBRT (40 -50 Gy / 4-5 fractions) as salvage therapy after conventional radiotherapy with stage I-III NSCLC. Twenty-four patients had received definitive *external beam radiation therapy* (*EBRT*), seven had received postoperative adjuvant EBRT, and five patients had received palliative EBRT. The median dose delivered at the time of initial treatment was 61.5 Gy (range, 30 –79.2 Gy). Most patients (28, or 78%) had received chemotherapy at some point during the treatment of the primary lung tumor, with 14 (38%) patients receiving concurrent chemoradiation.In an average of 22 months after treatment, 11 patients had in-field recurrence and 25 patients had out of field failure. The 2-year overall and progression-free survival rates were 26% and 92%, respectively, and the local control rate was 59%[13].Ceylan *et al.* performed thoracic SBRT (dose ranging from 30-60 Gy in 3-9 fractions) to 34 target volumes (21 in-field and 13 out -of-field) of 28 patients with recurrent NSCLC. Twenty

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two patients had received definitive EBRT with a median delivered dose of 59.4 Gy (range 47.5–66 Gy), 5 patients had received postoperative adjuvant EBRT with a median delivered dose of 56 Gy (range 50.4-60 Gy), and 1 patient had been treated with SBRT at 60 Gy. The patients receiving chemotherapy are distributed as follows; 2 patients concurrent with SBRT, 2 patients sequential, 8 patients 2nd-line chemotherapy, 2 patients 3rd-line chemotherapy. They reported two-year overall survival and local control rates of 42% and 37%, respectively [14]. In our study, relatively higher 2-year overall survival and local control rates were observed.The fact that more than half of the patients did not receive radiotherapy in their initial treatment and the number of operated patients was high suggests that SBRT may be associated with better treatment outcomes in postoperative recurrences. This may be related to the fact that the patients who were suitable for surgery in their initial treatment were in the early stages and did not have any medical problems.

Although high regional control was achieved with salvage SBRT in this study, the rate of distant metastases (17.4 % at 2 years) appears to be higher than in patients definitively treated for primary early stage disease [15]. Additionally, a shorter median interval for relapse has been reported after salvage SBRT compared with primary early-stage NSCLC treated with SBRT [16, 17]. In this context, the importance of systemic treatment after salvage SBRT is better understood. However, it is not clear whether adding systemic therapy would be beneficial for all patients and which agents should be used.

The most important prognostic factors in recurrent NSCLC arethe total dose and the fraction dose of previous radiotherapy, the time between treatments, the location of the target lesion, the performance status of the patient and whether treatment is performed for curative or palliative purposes [7].

There are several studies analyzing the factors associated with treatment outcomes in patients who underwent SBRT after primary radiotherapy. In the study of Parks *et al.*, salvage SBRT (in doses of 30-54 Gy and in 3-5 fractions) was administered to 27 patients(29 lesions) with recurrent stage II-III NSCLC who received mean 64.8 Gy conventional radiotherapy at baseline. The location of the recurrent lesions was as follows; hilum (n: 9), mediastium (n: 8) lung parenchyma (n: 12) [central (n: 1), peripheral (n: 11)] Twenty patients were treated with concurrent chemotherapy. The median time from prior thoracic radiotherapy to SBRT was 13.4 months (range, 2.6 to 112.6 mo)an average of 12 months of follow-up. Longer smoking duration and in-field recurrence are among the factors that negatively affect local control[18]. When we evaluated the factors affecting survival in the current study;wecould not find any significant prognostic factor for LC and survival rates on univariate and multivariate analysis.There is only one patient alive in ECOG 2 group and this patients has a very short follow up period. It seems to be an important factor influencing the results.

Kilburn *et al.*, including 33 patients [total 33 lesions; central (n:17), peripheral (n:16)] with recurrent NSCLC (n=29) or small cell lung cancer (SCLC) (n=3), found that larger tumor size was associated with poorer local control [19]. In our study, no effect of tumor size on survival and local control was found. Patel *et al.* studied 26 patients with 29 tumoral lesions, most of them diagnosed with NSCLC, who underwent salvage SBRT.The majority, 19 patients, previously received definitive external beam radiation therapy.Initial chemotherapy was administered to 24 patients: concurrently with radiation in 21 and adjuvantly in three patients.Twelve tumors were treated with biologically equivalent dose (BED)<48 Gy10 with a median BED dose of 36.6 Gy10 (9.5-42 Gy), and 17 tumors were treated with BED ≥ 48 Gy10 with a median BED dose of 72.2 Gy 10 (48-112.5 Gy). There were 17 peripheral tumors and 12 central tumors.They reported that local control rates were not significantly affected by the biological effective dose and the peripheral or central location of the target.(20)Likewise, in the present study, most of the recurrences are peripherally located, and the location of lesions did not appear to be a factor affecting survival and local control. Horne *et al.* reported outcomes of 72 patients with recurrent / residual (n=39) or second primary (n=33) NSCLC who underwent thoracic SBRT after primary radiotherapy. Initial treatments varied, 59.7% received CRT, 15.3% patients EBRT alone, and 25.0% SBRT. For patients undergoing conventionally fractionated RT, the median dose was 69Gy in 33 fractions and for SBRT was 60Gy in 3 fractions.Two year overall survival and local control rates are 46% and 78%, respectively. In addition, larger target tissue size was associated with poorer overall survival in multivariate analysis [21].

In several studies, treatment toxicity has been reported in patients diagnosed with NSCLC who underwent SBRT for recurrence. Agolli *et al.* reported that 10% of 28 patients with NSCLC who underwent SBRT for recurrent lesions after primary surgery had grade 2–3 radiation pneumonia and 7% had grade 2 fibrosis.Treatment-related toxicity was graded according to CTCAE v 4.0. [22] Similarly; in another study including 27 patients with NSCLC treated with primary thoracic radiotherapy who underwent SBRT for subsequent relapses, 11 patients developed grade 2 pneumonia, 6 patients had grade 3 pneumonia, and 2 patients developed grade 2 esophagitis. Chest wall pain was reported as grade 2 in 2 patients, grade 3 in 1 patient, and grade 4 in 1 patient [18]. In the present study, grade 4 and 5 toxicity was not observed, while

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grade 3 side effects were observed in 3 patients. In terms of toxicity, our study showed that salvage SBRT was well tolerated and had a very low toxicity profile.

The current study has some limitations. This was a retrospective study with a heterogeneous patient group. Another limitation is the lack of histopathological diagnosis in most of the cases. Biopsy cannot be performed in manycases with suspected recurrence for many reasons, such as the patient's medical problems, tumor location and lack of consent from the patient. Therefore the treatment decision was made by the relevant clinical team based on clinical findings and imaging results. Keidar *et al.* evaluated the diagnostic value of PET/CT and its impact on patient management in 42 patients with suspected NSCLC recurrence. The study demonstrated the potential value of PET/CT in patients with suspected recurrent NSCLC. [23]

As a result; pulmonary SBRT for recurrent NSCLC is a good treatment option with favorable LC and promising survival. SBRT could be an effective treatment modality in the treatment of patients with recurrent NSCLC with acceptable toxicity rates.

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