Oncological Results and Toxicities of Stereotactic Body Radiotherapy in Ultracentral Lung Tumors

Melek YAKAR, Durmus ETIZ

Eskisehir Osmangazi University Faculty of Medicine, Department of Radiation Oncology

ABSTARCT

Stereotactic body radiotherapy (SBRT) is an effective and safe treatment for early stage lung cancer and lung metastasis. However, SBRT dosing schedules are still controversial due to the risk of toxicity when considering the therapeutic index in ultracentral tumors. In the current study, patients with ultracentral tumors who underwent SBRT were evaluated retrospectively in terms of both oncological outcomes and toxicity. 34 patients who underwent SBRT due to ultracentral lung tumor between 2017 and 2023 were evaluated. It is considered as ultracentral if planning target volume (PTV) touched the proximal bronchial system, esophagus or pulmonary vein or pulmonary artery, and overall survival (OS), progression-free survival (PFS), SBRT oncological response and toxicities were evaluated. Median age is 66 years. The most common ultracentral location is that the PTV is on or in contact with the main airway in 30 patients. At a median follow-up of 24 months, 14 patients are alive and 20 (12 patients are metastatic, 8 patients are early stage) patients are dead. PFS after SBRT is median 12 (0-60) months and OS is median 23 (4-78) months. Median OS in early stage lung cancer and oligometastatic disease were 47 and 22 months, respectively (p= 0.65). There was local recurrence in 10 (29.4%) patients, regional recurrence in 14 (41.2%) patients, and distant recurrence in 14 (41.2%) patients. Toxicity developed in a total of 8 patients, 5 of whom were acute and 6 of whom were chronic. Grade 5 toxicity was observed in one patient. All patients with toxicity were male (p= 0.30). Considering the tumor type, 6 patients had metastatic and 2 patients had early stage lung cancer (p= 0.23). Six patients with toxicity had a history of chemotherapy in the last one month before SBRT (p= 0.25). There is no standard definition and treatment scheme for ultracentral lung SBRT. SBRT is a very effective treatment option in patients with early stage lung cancer and lung metastases who are medically inoperable or who do not accept surgery. However, ultracentrally located tumors have a high risk of toxicity due to their location close to organs at risk. Multicenter dose escalation studies are needed to create a SBRT scheme with an ideal therapeutic index, with both effective oncological treatment and acceptable side effects.

Keywords: Lung cancer, Stereotactic body radiotherapy, Ultracentral tumors, toxicity, Oncological results

INTRODUCTION

Surgery is the preferred method in early-stage lung cancer and oligometastatic disease with lung metastases, but there are patients who are elderly, medically inoperable, or who cannot undergo surgery due to the tumor's proximity to the mediastinal structures. Stereotactic body radiotherapy (SBRT) has become the standard treatment for both early-stage lung cancer and oligometastatic disease where surgery cannot be performed.[1-2] However, in ultracentrally located tumors, the definition of 'ultracentral tumor' and dose schedules are unclear. Some studies defined ultracentral tumor as the gross tumor volume (GTV) directly involving the proximal bronchial tree or trachea.[3-4] In another study by Tekatli et al., planning target volume (PTV) was defined as involving the trachea or main bronchial system.[5] Recently, a more consensual definition was introduced in the SUNSET study, a prospectively planned study that included patients with tumors whose PTV contacted or overlapped the central bronchial tree, esophagus, pulmonary vein, or pulmonary artery.[6]

Although SBRT fractions have been successfully determined for the treatment of central tumors, there is still no strong evidence or consensus for the treatment of ultracentral lesions.[7-8]

In the study conducted by Onishi et al., it was shown that BED10 should be ≥ 100 Gy to contribute to local control and overall survival.[9]

However, in the study conducted by Tekatli et al., a fatal mortality rate of 15% (the main cause was pulmonary hemorrhage) was reported with 60 Gy in 12 fractions.[5]

In addition to the increased incidence of bronchopulmonary hemorrhage, bronchial stenosis and lung volume loss are major concerns for SBRT in ultracentral tumors.[10] In the Phase II HILUS study, a 7 Gy x 8 fraction dose scheme was used and the rate of ≥ grade 3 toxicity was 34%, while grade 5 toxicity was 15%.[11] According to Expanded-Hilus study results, 13% grade 5 toxicity was reported and most of the patients suffered from fatal bronchopulmonary hemorrhage.[12] The aim of this study is to retrospectively evaluate the oncological results and toxicity rates of different SBRT regimens in ultracentrally located tumors.

PATIENTS AND METHODS

Patient Selection

Between 2017 and 2023, patients diagnosed with early stage lung cancer and isolated lung metastasis who underwent SBRT were evaluated retrospectively. Patients were selected based on the 'ultracentral definition' in the SUNSET study, that is, patients whose planning target volume (PTV) touched or overlapped the central bronchial tree, esophagus, pulmonary artery or pulmonary vein. Patients aged ≥ 18 and ≤ 85, who were medically inoperable and who attended regular follow-ups were included in the study. Tumor staging in early stage lung cancer was performed using 18F-fluorodeoxyglucose positron emission tomography (FDG-PET-CT) and contrast-enhanced thorax CT according to the AJCC Cancer Staging system, Eighth Edition.[13] Other patients were also evaluated and staged with FDG PET CT scans. Brain MRIs were also requested in patients where necessary. Tumor size was measured as its largest dimension in the axial, frontal, or sagittal plane during the end-inspiratory phase of CT. The patients were evaluated by the Chest Diseases Oncology Council before SBRT, and SBRT was recommended for cases deemed malignant or metastasis and medically inoperable (MI). First-second forced expiratory volume (FEV1) ≤ 40%, postoperative FEV1 ≤ 30% expected, carbon monoxide diffusion capacity (DLCO) ≤ 40% and hypoxemia/hypercapnia, severe pulmonary hypertension (HT), Diabetes Mellitus (DM) with end-organ damage.) cases with severe cerebral, cardiovascular and peripheral vascular disease, and serious chronic heart disease were accepted as MI. Biopsy could not be performed in some of the patients due to the risk of morbidity and mortality due to MI, and in these cases, after the follow-up thorax CT showed that the mass was enlarged and there was involvement in PET-CT, they were evaluated multidisciplinary and SBRT was planned. PET-CT scans were requested within 8 weeks before SBRT, especially in cases without biopsy, as recommended in the RTOG 0915 study.[14]

Target Volume, Dose Selection and Treatment Planning

Planning CT of the patients was obtained with 3-dimensional or 4-dimensional (4D)-CT. Patients were immobilized in a supine position with their arms raised above their heads on the T-bar / Wingboard, which was specially designed for lung treatments. A 1-3 mm thick image was obtained between the cricoid cartilage and the upper border of the L2 vertebra with the Siemens Somatom Definition AS® CT device. An external respiratory monitoring system (Real-time Position Management [RPM] System, Varian ® Medical Systems, Palo Alto, CA, USA) was used in 4D-CT. The RPM system uses an infrared tracking camera that monitors an external marker placed in the patient's upper abdomen to determine the phases of the respiratory cycle. The respiratory cycle is divided into a total of 10 segments, 10% of which are expiration and inspiration. Average CT (avgCT) and maximum intensity projection (MIP) datasets were created from phases. How many phases and which phases will be chosen in the treatment are determined by the doctor at the contouring stage. After the GTV was contoured in the phases to be used in the treatment, fusion of all GTVs was achieved. ITV was contoured via 4DCT MIP and PTV was obtained by giving a margin of 3-5 mm in all directions. In cases where 3D-CT was performed, the CT was taken during normal respiration, deep inspiration and deep expiration, and the GTV was contoured in all three CTs. ITV was determined by fusion of

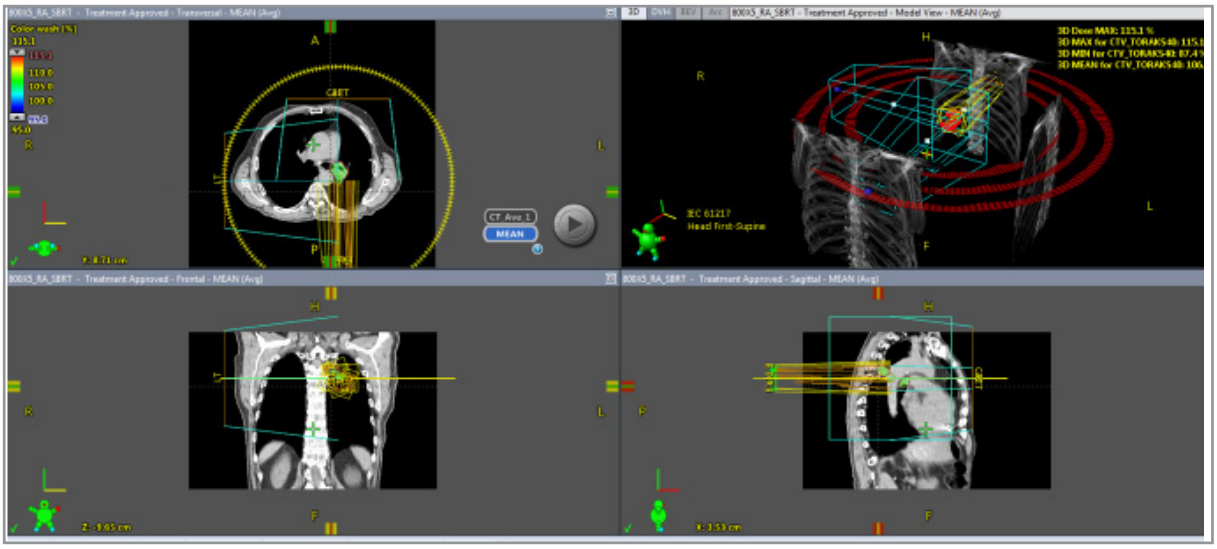

Figure 1. PTV and dose distribution of ultracentral tumor

all GTVs and a 3-5 mm margin was given to ITV. PTV was created by giving 3-5 mm margin in all directons.

The GTV was contoured using a lung window, and a soft tissue window was also used to avoid inclusion of vessels, atelectasis, or mediastinal and chest wall structures adjacent to the GTV.

Lungs, heart, main vessels, trachea, ipsilateral bronchial system, skin, ribs, brachial plexus, spinal cord, esophagus and, depending on the location of the tumor, liver and stomach are contoured as organs at risk. RTOG 0915 and RTOG 0813 studies were taken as basis for organs at risk doses.[7,14]

Treatment plans were created for Varian TrueBeam® with 6 MV FFF (flattening filter-free) or Varian Trilogy® linear accelerator with 6 MV. Planning criteria were established based on RTOG 0915 such that at least 95% of the PTV was covered by the prescription dose.[14] PTV maximum point dose (Dmax) not exceeding 140% of the prescribed dose was accepted. Figure 1 shows the PTV and dose distribution of the ultracentral tumor.

Different treatment schemes were used depending on tumor location, tumor size and the patient's karnofsky performance score (KPS). No concurrent chemotherapy was administered during SBRT. SBRT was applied with at least 48 hours between fractions. Patients were evaluated in the outpatient clinic at least once a week during treatment.

Oncological Results and Toxicity Follow-up

Clinical follow-up of the patients was performed 1 month after completion of SBRT, then every 3 months for the first 3 years, and every 6 months until the completion of 5 years. After 5 years, annual follow-up was started. During this period, contrast-enhanced thoracic CT scans were requested every 3-6 months, as per NCCN recommendation. FDG PET CT was requested at the 3rd month after SBRT and at the 12th month based on the RTOG 0915 study. Patients with symptoms were also asked for other tests regarding their symptoms. Tumor response was evaluated as changes in maximal tumor diameter on axial chest image and determined by Response Evaluation Criteria in Solid Tumors (RECIST).[15] Toxicity evaluation was made according to anamnesis, physical examination and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 during patient follow-ups.[16]

Ethical Approval was received from Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee before the study (Ethics Committee Approval No: E-25403353-050.99-2400074039).

Statistical Analysis

IBM SPSS for Windows 21 was used to analyze the data. Shapiro Wilk's test was used to determine the suitability of the variables for Normal distribution. Parametric and non-parametric tests were used to

compare the groups. Independent samples t test and Mann Whitney U test were used to compare independent groups (toxicity or no toxicity) according to distribution forms. Chi-square tests were used in the analysis of the created cross-tables. Kaplan-Meier survival analysis was performed to compare survival times according to toxicity, and Log-rank test statistics were calculated for comparisons between groups. In summarizing the data, number (%) was used for qualitative data and Mean value was used for quantitative data. ±SD or Median (minimum, maximum) statistics were used. $P<0.05$ was considered statistically significant.

RESULTS

Patient and Tumor Characteristics

Thirty four patients who underwent ultracentrally located lung SBRT between 2017 and 2023 were evaluated retrospectively. Median age is 66 (min: 52, max: 84). Median Karnofsky Performance score (KPS) is 80 (min: 60, max: 100). Twenty nine (85.3%) of the patients are male and 5 (14.7%) are female. The most common ultracentral location is that the PTV is on or in contact with the main airway in 30 patients. While 16 of the patients had early stage lung cancer, 18 had metastatic disease. Nineteen of the patients received systemic treatment within 1 month before SBRT. While there was a history of chronic disease in 20 patients, there was smoking history in 24 patients. There are 10 patients with chronic obstructive pulmonary disease, 3 with diabetes mellitus and 8 patients with cardiac diseases (coronary artery disease, hypertension). Some of the patients have multiple chronic diseases. Patient and tumor characteristics are given in Table 1.

Table 1. Patient and Tumor Characteristics

Features	Number of patients (%) or median (min-max)
Age	66 (52-84)
KPS	80 (60-100)
Gender	
Female	5 (14.7%)
Male	39 (85.3%)
Chronic Disease	
+	20 (58.8%)
-	14 (41.2%)
Smoking	
+	24 (70,6%)
-	10 (29,4%)
Tumor size (mm)	16,6 (2,2-50)
GTV volume (cc)	30 (13-55.8)
PTV volume (cc)	42.0 (22-88.2)
Tumor location	
Right	17 (50%)
Left	17 (50%)
Ultracentral location	
Main airway	17 (50.0%)
Main airway + PA	6 (17.6%)
Main airway + PV	4 (11.7%)
Main airway +esophagus	1 (2.9%)
Main airway + PA +PV	2 (5.8%)
P.A.	3 (8.8%)
PV	1 (2.9%)
Tumor Type	
Early Stage Lung Cancer	16 (47%)
Metastatic lung cancer	18 (53%)
Primary Tumor Location	
Lung	25 (73.5%)
Colon	3 (8.8%)
Breast	2 (5.9%)
Rectum	2 (5.9%)
Kidney	1 (2.9%)
Bladder	1 (2.9%)
Biopsy	
+	11 (32.4%)
-	23 (67.6%)
History of CT in the last month	
+	19 (55.9%)
-	15 (44.1%)

KPS: Karnofsky Performance Score, GTV: Gross Tumor Volume, PTV: Planned Target Volume, PA: Pulmonary Artery, PV: Pulmonary Vein, CT: Chemotherapy

Dosimetric Results

The median RT dose is 45 (min: 40-max:60) Gy, the fraction dose is 8 (min:7-max:10) Gy and the number of fractions is 5 (min: 5-max: 8). When the biological effective dose (BED)10 [n.d (1+d/(α/β))] (n: number of fractions, d: fraction dose, α/β: 10) is calculated, the median BED10 in all cases was 86.4 (min: 72-max:120) Gy. Median whole lung V12.5Gy in patients is 312 (min: 23, max 749)cc and V13.5Gy is 278 (min: 8, max 693) cc. D_{max} ipsilateral main airway median is 53 (min: 15, max: 61) Gy. The median D_{max} pulmonary artery and pulmonary vein doses are 21 (min: 0.4,

Table 2. Dosimetric results

Dosimetric Parameters	Median values (min-max) Toxicity + (Number of patients: 8)	Toxicity - (Number of patients: 26)
Total lung $V_{12,5Gy}$(cc)	304.5 (23.0- 749.0)	300 (94-662)
Total lung $V_{13,5Gy}$(cc)	278.5 (8.6- 693.0)	278 (8.2-587)
Total lung V_{20Gy}(%)	4.8 (0.9-8.2)	3.9 (1.3-9.1)
Total lung MLD (Gy)	4.1 (1.3-4.9)	3.3 (1.8-5.8)
Ipsilateral Main Bronchus D_{max}(Gy)	53 (15-61)	53 (29-59)
Pulmoner Arter D_{max}(Gy)	17 (0.7-44)	23 (0.4-56)
Pulmoner Ven D_{max}(Gy)	20 (0.68- 44)	12 (0.3-56)
Aorta D_{max}(Gy)	19 (6-46)	19 (5-56)
Vena Cava Superior D_{max}(Gy)	13 (0.2-49)	7 (0.3-54)
Trachea D_{max}(Gy)	11 (0.5-46)	17 (0.3-48)
Esophagus D_{max}(Gy)	15 (6-25)	14 (0.1-34)
Spinal cord D_{max}(Gy)	11 (2-17)	11 (6-24)
Heart D_{max}(Gy)	26 (0.8-37)	14 (0.2-43)

MLD: mean lung dose

max: 56) Gy and 16 (min: 0.3, max: 56)Gy, respectively. Trachea D_{max} median is 14 (min: 0.3, max: 48) Gy. Esophageal D_{max} median is 15 (min: 0.1, max 38) Gy. Dosimetric values in cases with and without toxicity are given in Table 2.

Survival and Disease Control

At a median follow-up of 24 months, 14 patients are alive and 20 (12 patients are metastatic, 8 patients are early stage) patients are dead. There were 8 (23.5%) complete responses, 18 (53%) partial, 6 (17.6%) stable and 2 (5.9%) progressive responses. Progression-free survival (PFS) after SBRT was accepted as the period from the first response evaluation to the last control, and overall survival (OS) after SBRT was accepted as the period from the end of SBRT to the last control. The date of first RT was defined as day 0 of follow-up. While PFS after SBRT was median 12 (0-60) months, OS after SBRT was median 23 (4-78) months. Median OS in early stage lung cancer and oligometastatic disease were 47 and 22 months, respectively (p= 0.65). The survival curve of the patients is available in Figure 2a.

Relapse Patterns

During a median follow-up period of 24 months, a total of 23 patients had one or multiple recurrences. Considering the recurrence patterns, 4 (11.7%) had only local, 4 (11.7%) only regional, 2 (5.8%) had only distant recurrence, 1 (2.9%) had local and regional, 3 (8%) had local and distant recurrence , 7 (20.5%) regional and distant, and 2 (5.8%) patients had local, regional and distant recurrence. Relapse distribution patterns are given in Figure-3. In total, 10 (29.4%) patients had local recurrence, 14 (41.2%) patients had regional recurrence, and 14 (41.2%) patients had distant recurrence. While the median RT dose was 42.5 Gy in cases with local recurrence, it was 48 Gy in cases without local recurrence (p= 0.861). While the BED10 was 78.7 Gy in cases with local recurrence, it was 86.4 Gy in cases without (p= 0.868). In cases without local recurrence, the RT dose and therefore the BED10 value were higher, but did not reach statistical significance.

Toxicity

During a median follow-up of 24 months, toxicity developed in a total of 8 patients, 5 of whom were acute and 6 of whom were chronic. Among the patients who developed acute side effects, three developed grade 3 toxicity and two developed grade 2 toxicity. Among the patients who developed chronic side effects, one developed grade 5 toxicity, two developed grade 3 toxicity, and three developed grade 2 toxicity. Information about patients who developed toxicity is available

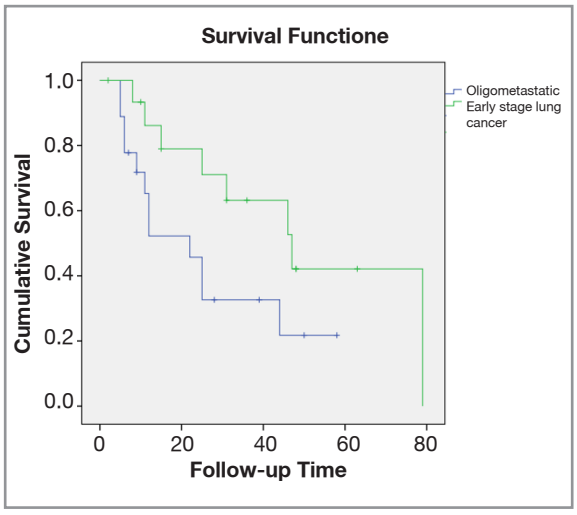

Figure 2a. The survival curve of the patients

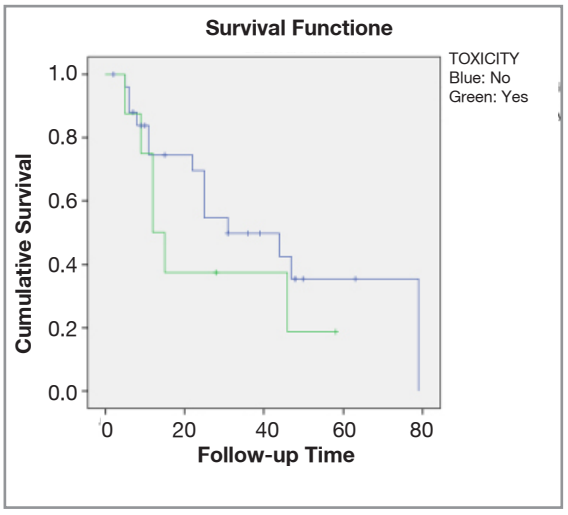

Figure 2b. The toxicity curve of the patients

in Table 3. All patients with toxicity were male (p= 0.309). 5 patients had a history of chronic disease (p= 1.00) and 6 patients had a history of smoking (p= 1.00). In 6 patients, PTV was on or adjacent to the main airway (p= 1.00). Considering the tumor type, 6 patients had metastatic and 2 patients had early stage lung cancer (p= 0.233). Six patients with toxicity had a history of chemotherapy in the last one month before SBRT (p= 0.257). In cases that developed toxicity, the median MLD was 4.1 Gy and lung V20Gy was 4.8%, while in cases that did not develop, MLD was 3.3 Gy and V20Gy was 3.9%, but it did not reach statistical significance due to the small number of patients. The median BED10 value in cases with and without toxicity is 85.5 (min: 72-max: 120) Gy and 86.4 (min: 72-max: 105) Gy, respectively. Bronchopulmonary hemorrhage developed in 2 of 34 patients during follow-up, and no statistically significant difference was found between the two groups between the doses of pulmonary artery Dmax, pulmonary vein Dmax, aorta Dmax and vena cava superior Dmax. In patients with bronchopulmonary hemorrhage, PTV does not invade the main vessels but is on the main airway. Pneumonia developed in 8 of 34 patients during follow-up. No statistically significant difference was found in lung V12.5 Gy (p= 0.910) and lung V13.5 Gy (p= 0.956) volumes, lung V20 Gy (p= 0.716) and MLD (p= 0.915) in cases with and without pneumonia.

The toxicity curve of the patients is available in Figure 2b. In the patient who developed grade 5 hemoptysis, the maximum dose to the ipsilateral bronchial system was 57 Gy, while V18 was 3.8 cc. Lung V20 value is 4.6% and MLD is 4.1 Gy. The patient has a diagnosis of COPD and a history of smoking. PTV is adjacent to the main airway and the SBRT dose is 7fr x 8 Gy and BED10 is 95.2 Gy.

DISCUSSION

SBRT is a standard and effective treatment method for medically inoperable early stage lung cancer. Studies have shown that SBRT is well tolerated even in patients with low KPS who have comorbidities. In the RTOG 0813 study, the maximum tolerated dose in central tumors was 12 Gy/fraction, while the dose-limiting toxicity rate was 7.2%.[7] The grade 3 and 4 toxicity rates recorded in RTOG 0236 are 12.7% and 3.6%, respectively.[17] In cases with oligometastatic disease, the use of ablative local treatments such as surgery, radiofrequency and SBRT can improve the oncological outcome.[18] SBRT is a treatment option recommended in guidelines for patients with medically inoperable early stage lung cancer and pulmonary oligometastases. While peripherally located lesions can be treated safely and result in excellent local control rates after SBRT, treatment of ultracentral lung tumors remains controversial due to the high reported rates of serious SBRT-related toxicities.

In the current study, 34 patients who underwent ultracentrally located SBRT were evaluated in

Table 3. Patients with chronic toxicity

Patient No:	Chronic
1	Grade 3 broncho-pulmonary hemorrhage
2	Grade 5 broncho-pulmonary hemorrhage
19	Grade 2 cough Grade 2 dyspnea
20	Grade 2 cough Grade 2 dyspnea
22	Grade 2 cough Grade 2 dyspnea
26	Grade 3 cough Grade 3 dyspnea

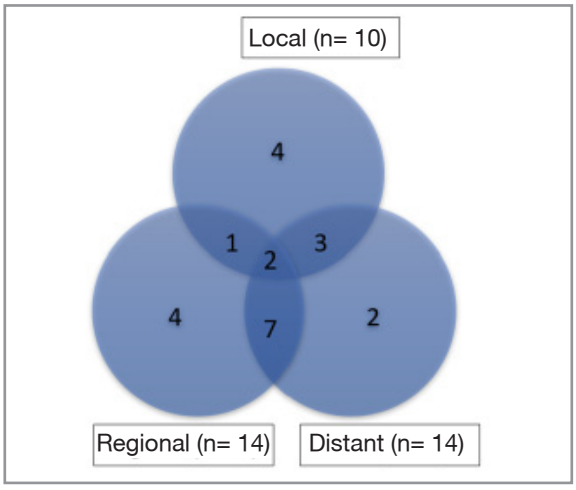

Figure 3. Relapse Patterns

terms of both oncological outcomes and toxicity rates. The median BED10 in the study was 86.4 Gy. The median follow-up was 24 months, the median PFS was 12 months, and the median OS was 23 months. Median overall survival in early stage lung cancer and oligometastatic disease was 47 and 22 months, respectively, and as expected, it was longer in early stage cases. In their study with 47 patients diagnosed with ultracentrally located primary or recurrent NSCLC, Tekatlı et al. applied 5 Gyx 12 fractions (BED10= 90), and the median OS was 15.9 months with a median follow-up of 29.3 months (5). Wang et al. applied median BED10= 100.8 Gy to 58 patients diagnosed with early-stage ultracentral lung cancer. In their study, the median OS was 58 months with a median follow-up of 57 months.[19] In our current study, the OS time is similar to Tekatlı et al., but appears to be shorter compared to the study by Wang et al. This may be due to the heterogeneity of our patient group, that is, the presence of both early stage and metastatic lung tumors, the median BED10 being below 100 Gy due to toxicity concerns, and the relatively short follow-up period.

In our current study, there were 8 (23.5%) complete responses, 18 (53%) partial, 6 (17.6%) stable and 2 (5.9%) progressive responses in SBRT response evaluation. In the study conducted by Song et al. with 32 patients diagnosed with early stage lung cancer, the tumor was located adjacent to the main bronchus. SBRT dose is 10-20 Gy per fraction and total dose is 40-60 Gy. At a median follow-up of 26.5 months, the response rates were 59.3% for complete response and partial response, while stable response was 37.5% and progressive response in the remaining cases.[10] Loi et al. used different SBRT schemes in 72 cases with ultracentrally located lung metastases, and the median SBRT dose was BED10 105 Gy. At a median follow-up of 17 months, SBRT response rates were 33%, 30%, and 27% for complete response, partial response, and stable disease, respectively. In the same study, it was shown that BED10 > 75 Gy increased local control in SBRT for lung metastasis.[20] In ultracentral disease, the standard dosing schedule and the BED10 value at which good oncological results can be achieved without causing serious toxicity are still unclear.

In the current study, a total of 23 patients had recurrence in one or multiple patterns during the follow-up period. Considering the recurrence patterns, 4 (11.7%) had only local, 4 (11.7%) only regional, 2 (5.8%) had only distant recurrence, 1 (2.9%) had local and regional, 3 (8%) had only distant recurrence. 8) local and distant, 7 (20.5%) regional and distant, and 2 (5.8%) patients had local, regional and distant recurrence. The most common recurrence pattern in the current study was distant metastasis and regional recurrence. In the study of Loi et al., in which they applied SBRT for ultracentral lung metastases, the most common recurrence pattern was distant metastasis and the 2-year distant metastasis-free survival was reported as 46%.[20] In studies applying SBRT to ultracentrally located early-stage lung cancer, recurrence rates are around 21.9% - 30%, and the most common recur-

rence pattern is distant metastasis.[5,10] According to the literature, the most common recurrence patterns are distant metastasis and regional metastasis. Therefore, the group to which adjuvant chemotherapy should be given must be well determined. At the same time, in ultracentrally located tumors, mediastinal/hilar lymph node staging should not be left solely to radiological examinations, but should also be evaluated with invasive methods, which may reduce regional recurrence rates.

Ultracentral tumors have a high risk of side effects with SBRT due to their proximity to organs at risk. In our current study, the acute toxicity rate is 14.7% and the chronic toxicity rate is 17.6%. Grade 3 and above toxicity rate is 8.8% in both acute and chronic. Grade 5 toxicity rate is 2.9%. In Tekatli et al.'s early-stage ultracentrally located lung cancer study, SBRT BED10 was 90 Gy, grade 3 and above toxicity rates were 38%, and fatal pulmonary hemorrhage was seen in 15% of the patients.[5] In the oligometastatic lung cancer study of Loi et al., in which they applied ultracentrally located SBRT, the SBRT BED10 was 105 (75-132) Gy. In this study, the incidence of toxicity was 27.7%, while the rate of grade 3 and above toxicity was 6.9% and the rate of grade 5 toxicity was 1.3% (20). In the RTOG 0813 centrally located early stage lung cancer SBRT study, acute grade 3 and above toxicity rates were 13.1% in the 11.5 Gy x 5 fr (BED10 123 Gy) arm and 10.5% in the 12 Gy x 5 fr (BED10 132 Gy) arm. Considering the chronic toxicity rates of Grade 3 and above, it is 5.2% in the BED10 123 Gy arm and 13.1% in the BED10 132 Gy arm.[7] According to the literature, acute and chronic toxicity rates vary greatly depending on the dose and tumor location.

Although it was thought that survival would be lower in ultracentral/central tumors, where serious side effects were expected, compared to peripherally located tumors, due to SBRT toxicity, Haasbeek et al. showed in their study that this was not true. 7.5 Gy/fr, a total of 63 Gy (BED10 105 Gy) was given to 63 ultracentrally located tumors, 20 Gy/fr, a total of 60 Gy (BED10 180 Gy) to 445 peripherally located T1 tumors, and 12Gy/fr, to T1 and T2 tumors located close to the chest wall. A total of 60 Gy (BED10 132 Gy) SBRT was applied. The 3-year OS rates for ultracentrally and peripherally located tumors were 64.3% and 51.1%, respectively, while the median OS was 47 and 36 months (p= 0.09). For ultracentrally and peripherally located tumors, 3-year local control rates are 92.1% and 90.2% (p= 0.9), regional control rates are 91.1% and 86.2% (p= 0.47), and 3-year DFS is 69.9% and 67.8% (p= 0.47). 0.91).[21]

The most important limitations of the current study are that it was retrospective, single-center, and the number of patients was small. At the same time, there is no standard in the dose and number of fractions per fraction, but comparisons were made with the BED10 value. Both early stage and oligometastatic patients were included in the study, and the patient group is heterogeneous. However, there is still no standard dosing schedule and the high expected grade 3 and above toxicity causes clinicians to choose more hypofractionated schemes in this patient group. For this reason, the number of patients who underwent ultracentrally located SBRT is quite low when looking at the literature. Standardization of dosage schedules, organs at risk doses and ultracentral definitions and finding the most appropriate therapeutic range in this patient group are very important in terms of reducing toxicity rates and improving oncological outcomes.

Conclusion

There is no standard definition and treatment scheme in ultracentral lung SBRT. SBRT is a very effective treatment option for early-stage lung cancer and lung metastases that do not require surgery. However, ultracentrally located tumors have a high risk of toxicity due to their location close to organs at risk. Multicenter dose escalation studies are needed to create an SBRT scheme with an ideal therapeutic index, both for an effective oncological treatment and with few side effects.

Acknowledgments

We would like to thank Professor Doctor Cengiz Bal from Eskişehir Osmangazi University Faculty of Medicine, Department of Biostatistics, for his statistical evaluation support.

REFERENCES

1. Guckenberger M, Wulf J, Mueller G, et al. Dose-response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4D dose calculation. Int J Radiat Oncol Biol Phys 74: 47-54, 2009.
2. Hörner-Rieber J, Bernhardt D, Blanck O, et al. Long-term follow-up and patterns of recurrence of patients with oligometastatic NSCLC treated with pulmonary SBRT. Clin Lung Cancer 20: e667-e677, 2019.
3. Chaudhuri AA, Tang C, Binkley MS, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultracentral lung tumors. Lung Cancer 89: 50-56, 2015.
4. Haseltine JM, Rimner A, Gelblum DY, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. Pract Radiat Oncol 6: e27-33, 2016.
5. Tekatli H, Haasbeek N, Dahele M, et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with "Ultracentral" non-small cell lung cancer. J Thorac Oncol 11: 1081-1089, 2016.
6. Giuliani M, Mathew AS, Bahig H, et al. SUNSET: Stereotactic Radiation for Ultracentral Non-Small-Cell Lung Cancer-A Safety and Efficacy Trial. Clin Lung Cancer 19: e529-e532, 2018.
7. Bezjak A, Paulus R, Gaspar LE, 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 37: 1316-1325, 2019.
8. Murrell DH, Laba JM, Erickson A, et al. Stereotactic ablative radiotherapy for ultra-central lung tumors: prioritize target coverage or organs at risk? Radiat Oncol 13: 57, 2018.
9. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 101: 1623-1631, 2004.
10. Song SY, Choi W, Shin SS, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer 66: 89-93, 2009.
11. Lindberg K, Grozman V, Karlsson K, et al. The HILUS-Trial-a Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Tumors Treated With Stereotactic Body Radiotherapy. J Thorac Oncol 16: 1200-1210, 2021.
12. Lindberg S, Grozman V, Karlsson K, et al. Expanded HILUS Trial: A Pooled analysis of risk factors for toxicity from stereotactic body radiation therapy of central and ultracentral lung tumors. Int J Radiat Oncol Biol Phys 117: 1222-1231, 2023.
13. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 67: 138-155, 2017.
14. Videtic MMG, Hu C, Singh AK, et al. NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase II study comparing 2 stereotactic body radiation therapy (SBRT) schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. Int J Radiat Oncol Biol Phys 93: 757-764, 2015.
15. Gulstene S, Lang P, Melody Qu X, et al. What is the predictive value of RECIST criteria following stereotactic lung radiation? Radiother Oncol 190: 109976, 2024.
16. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the common terminology criteria for adverse events (CTCAE - Version 5.0) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr (Engl Ed)112: 90-92, 2021.
17. Xiao Y, Papiez L, Paulus R, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 73: 1235-1242, 2009.
18. De Ruysscher D, Wanders R, van Baardwijk A, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol 7: 1547-1555, 2012.
19. Wang B, Dong Y, Yu X, et al. Safety and efficacy of stereotactic ablative radiotherapy for ultra-central lung cancer. Front Oncol 12: 868844, 2022.
20. Loi M, Franceschini D, Dominici L, et al. Stereotactic radiotherapy for ultra-central lung oligometastases in non-small-cell lung cancer. Cancers (Basel) 12: 885, 2020.
21. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. J Thorac Oncol 6: 2036-2043, 2011.

Correspondence:

Dr. Melek YAKAR

Eskisehir Osmangazi Universitesi Tip Fakultesi
Radyasyon Onkolojisi Anabilim Dali
Meselik Kampüsü
Büyükdere Mahallesi
26040 Odunpazari
ESKISEHIR / TURKIYE

Tel : (+90-538) 391 61 90

e-mail: myakar@ogu.edu.tr

ORCIDs:

Melek Yakar 0000-0002-9042-9489
Durmus Etiz 0000-0002-2225-0364