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Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus

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ABSTRACT

Purpose: To assess the body-framed stereotactic body radiation therapy (SBRT) results and toxicity for medically inoperable stage I lung cancer adjacent to central large bronchus and then compare the results with those of SBRT in peripheral lung tumor in the aspects of survival and SBRT-related pulmonary toxicities.
Materials: From June 1999 to May 2006, 32 patients diagnosed as stage I, T1N0 or T2N0, resectable NSCLC were treated with body-frame based fractionated SBRT. Thirty-one patients had several medical problems conflicting surgical procedure. Stereotactic body frame was used for improving setup accuracy. Doses of 10–20 Gy per fraction were delivered to the planning target volume (PTV) up to a total dose of 40–60 Gy with three to four fractions on consecutive days. Centrally located tumor was defined as the tumor within 2 cm apart from large bronchial tree, and was subdivided into bronchial (main/lobar bronchus) and peribronchial (segmental or distal).
Results: Median follow-up was 26.5 months. The 6-month major response rate, including complete or partial response, was 53.1%. One patient showed progressive disease 1 month after SBRT. The 1- and 2-year actuarial local tumor control rates were both 85.3%. Overall survival was 70.9% at 1 year and 38.5% at 2 years, and survival was not correlated with SBRT dose. Of 9 patients with centrally located tumors, three (33%) experienced Grades 3–5 pulmonary toxicities. Eight patients showed partial or complete bronchial stricture and secondary loss of normal lung volume. Median time to bronchial stricture was 20.5 months. Overall survival did not differ by tumor location.
Conclusions: SBRT in this fractionation should not be given to central lung tumors because it can cause the late major airway toxicities in some patients. More protracted hypofractionated treatment regimen may be more safe than that used usually in SBRT for central lung tumors.

1. Introduction

Surgical resection with curative intent is the treatment of choice for patients with stage I early non-small cell lung cancer (NSCLC), with lobectomy showing good long-term survival rates [1–3]. Indications for surgery include good performance status, adequate expected lung function after surgery, and no medical problems that may complicate surgery. Some patients, however, cannot tolerate surgery or refuse the operation. Since the development of stereotactic body frames for extra-cranial high-precision therapy, stereotactic body radiation therapy (SBRT) has been tested in patients with early stage lung tumors [4] and frameless SBRT also is recently being used increasingly. Respiratory tumor motion and the uncertainty of tumor targeting due to respiration have been major drawbacks to the universal use of SBRT in these patients. Respiratory control systems, including active breathing-control, abdominal compressor, air-blanket [5,6] and a respiratory-gated system with four-dimensional computed tomography (CT) [7,8], have been utilized for radiation therapy in patients with lung tumors. Clinical trials have shown that, in patients with early stage NSCLC, outcomes of SBRT were similar to those of surgical treatment [9–30].

SBRT has been used primarily in patients with peripherally located lung tumors, because high-dose radiation treatment of centrally located tumors adjacent to critical organs may lead to severe toxicities in major organ like large bronchial tree, heart, esophagus and large vessel. The alternative for surgical treatment for inoperable central lung tumors was conventionally fractionated radiotherapy, but it had problem like the lower probability

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of tumor control and the elongated treatment period to the debilitated patients. SBRT approaches in central lung tumor were recently reported from several centers in the aspect of the treatment results and treatment-related toxicity [18,23,24].

We have assessed the body-framed SBRT results and toxicity for medically inoperable stage I lung cancer adjacent to central large bronchus and then compare the results with those of SBRT in peripheral lung tumor in the aspects of survival and SBRT-related pulmonary toxicities.

2. Methods and materials

2.1. Patients

Patients treated with SBRT in our institute were retrospectively analyzed. Eligibility criteria for SBRT included in our institute: (1) pathologically confirmed NSCLC, either squamous cell carcinoma, adenocarcinoma or not otherwise specified (NOS), (2) American Joint Committee on Cancer (AJCC) stage I (T1N0M0 or T2N0M0), (3) tumor size <5 cm in longest diameter and (4) Eastern Cooperative Oncology Group performance status 2 or below. Recurrent disease or new primary lung cancer with previous history of lung cancer was excluded from this analysis. All patients provided written informed consent and the treatment protocol was reviewed by the institutional review board of Asan Medical Center.

2.2. Treatment procedure

The technique used for SBRT in our institute was the same as in other reports in which the Stereotactic Body Frame (Elekta Oncology, USA) for linear accelerator was used. Patients were immobilized in the vacuum-fitted stereotactic body frame and the setup of the patient was marked on the chest and leg skin for reproducibility. Respiratory tumor movement was assessed fluoroscopically; if tumor motion was >5 mm, it was minimized through active breathing-control for 1 patient, abdominal compressor for 3 patients and respiratory-gated radiation therapy for 2 patients using Varian RPM-respiratory gating system (Varian, USA) and GE Lightspeed 4D CT (GE healthcare, USA). Five among 6 patients with breathing-control had a peripheral tumor and only 1 patient had a central tumor with the use of abdominal compressor. All patients who needed the breathing-control were educated and exercised before CT simulation, and patients, not suitable or intolerable to breathing-control, were treated without breathing-control. Actual treatment time with respiratory-gated therapy after completion of setup was about 10–15 min and was tolerable to all patients.

2.3. Target volume and irradiation dose

All patients underwent CT simulation with contrast enhancement. Gross tumor volume (GTV) was delineated on axial CT images in the mediastinal setting and then expanded the target volume to include the spiculated margin in the lung window setting. Clinical target volume (CTV) was identical to GTV because the latter encompassed enough microscopic tumors in the lung window setting. Planning target volume (PTV) was determined by adding a 5 mm margin to the axial plane and a 10 mm margin to the longitudinal direction of the GTV. For the authenticity of adequate margin for PTV, respiratory tumor movement was initially checked on anterior–posterior and lateral image of fluoroscopic simulator, and then verified through additional two-times of CT simulation at first and third day of treatment. We checked daily setup accuracy and real-time tumor mobility and intrafractional shift after the application of on-board imager with cone-beam CT. Treatment planning was formulated on the Render 3-D planning system (Elekta Oncology) or the Eclipse planning system (Varian, USA). Treatment dose was prescribed to the PTV margin such that 85% of the isodose curve of the isocenter dose volume would cover 95% of the PTV volume. SBRT was performed for 3 or 4 consecutive days, with each fractionated dose being 10, 12, or 20 Gy.

2.4. Pre- and post-treatment evaluation

All patients underwent pre-treatment chest CT, with SBRT started within 4 weeks. Post-treatment chest CT was performed 1, 6 and 12 months after SBRT. When indicated, additional CT, positron emission tomography (PET or PET/CT) or bronchoscopy was performed. Tumor response was evaluated as changes in maximal tumor diameter on axial chest image and determined by Response Evaluation Criteria in Solid Tumors (RECIST, uni-dimensional). Local tumor control was defined as a tumor response of stable disease (SD) or better. Pulmonary toxicity was scored by the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 2.0 [31,32]. Radiation-induced bronchial stricture was initially determined on scheduled follow-up CT scans or simple Chest X-ray by narrowing of bronchus or secondary collapsed lung parenchyma. Bronchoscopy, with or without biopsy, was done for discriminating radiation-induced stricture from tumor recurrence, and PET/CT was additionally examined in some patients. Some patients were observed with only follow-up CT scans without additional examination if the radiation-induced stricture was stable.

2.5. Tumor location

SBRT was performed independent of tumor location in our institute, but the risk of pulmonary toxicity was explained to the patient when the tumor was located close to the proximal large bronchial tree. Tumor location for SBRT was assessed according to the Radiation Therapy Oncology Group protocol [18]. Central tumor was defined as those within 2 cm from the distal part of large bronchial tree, actually segmental bronchus, and more peripherally located tumor was defined as peripheral tumor (Fig. 1A). Central tumors were subdivided into tumors located in the segmental bronchus within 2 cm of the proximal bronchial tree (peribronchial tumors) (Fig. 1B) and those located in the main or lobar bronchus with endobronchial mass (bronchial tumors) (Fig. 1C).

2.6. Statistical analysis

Survival time was measured from the date of SBRT to the date of last follow-up. Local progression free time was measured from the date of SBRT to the date of first recurrence. 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 for Windows (version 12.0; SPSS Inc., Chicago, IL) was used for all statistical analyses.

3. Results

3.1. Patient characteristics

Between June 1999 and May 2006, 32 patients diagnosed with stage I, T1N0 or T2N0, resectable NSCLC were treated with body-frame based fractionated SBRT. Their median age was 72.5 years (range, 58–89 years). Pathology was squamous cell carcinoma, adenocarcinoma or NOS. Thirty-one patients had medical problems that conflicted with surgical procedure, and 1 patient refused surgery. Twenty patients could not receive curative operation due to their poor lung function, and their median FEV_1 was 1.06 L, 44% (range: 0.66–2.54 L, 40–125%) and median measured DLCo

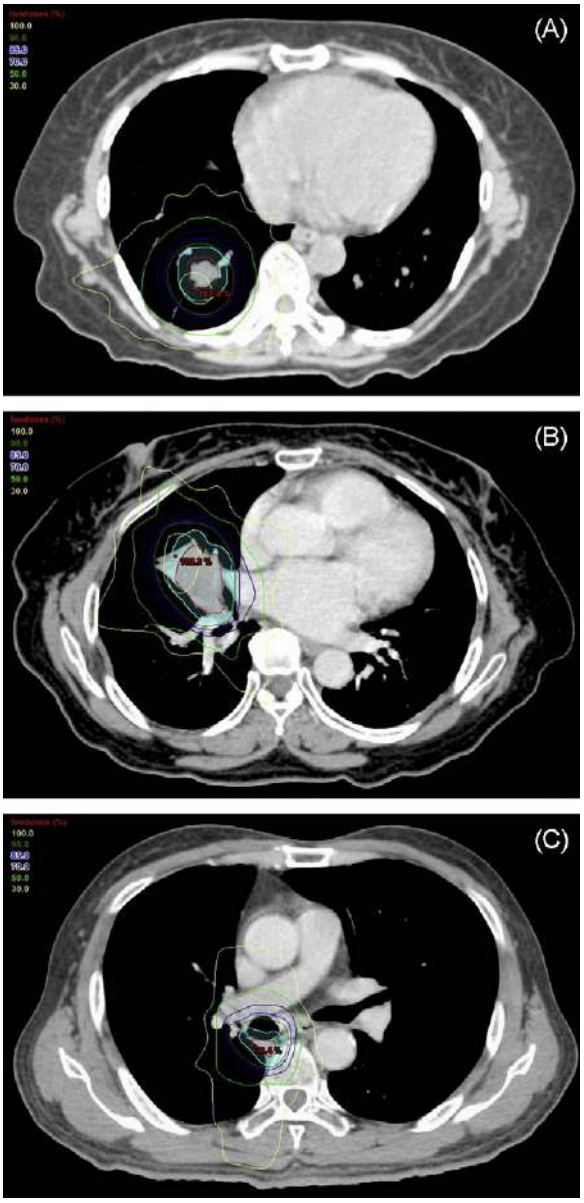

Fig. 1. Tumor location and isodose line of SBRT: (A) peripheral tumor; (B) peribronchial tumor; and (C) bronchial tumor.

was 11.0 ml/(min mmHg), 62%. No patients received chemotherapy before or after SBRT. Patient characteristics are summarized in Table 1. Median follow-up time was 26.5 months (range, 5.2–92.0 months).

3.2. Treatment procedure

The longest diameter of gross tumor was 12–45 mm (median: 23 mm) and median PTV was 43.5 cm^3 (range: 13.6–145.9 cm^3). The prescribe dose was 85% and covered successfully 95% of the PTV in all cases. Four to 8 (median: 6) beams with coplanar or non-coplanar beam were used. Average conformity index, referenced by RTOG, in our patients was 1.97 (range: 1.70–2.30). Nineteen (59%) patients had optimal conformity index below 2.0 and the other 13 patients had minor violation with the value below 2.5. For the reproducibility of treatment setup, CT simulation or cone-beam CT with daily verification film were checked and setup accuracy was within 4 mm (median: 1.54 mm, range: 0–4 mm) in all directions during treatment period. The dose constraint for the esophagus, heart and spinal cord in centrally located lung tumor was below 5 Gy in a fraction. Median time from diagnosis to treatment was 28 days (range: 4–41 days).

Table 1
Patient characteristics.

Characteristics	No. of patients
No. of patients analyzed	32
Gender	
Male	26
Female	6
Age (years)	
Median (range)	72.5 [58–89]
Performance status, ECOG[a]	
1	21
2	11
Histopathology	
Squamous cell carcinoma	18
Adenocarcinoma	11
Not other specified (NOS)	3
Stage	
T1N0	16
T2N0	16
Tumor size, long diameter (cm)	
Median (range)	2.3 [1.2–4.5]
Tumor location	
Central (bronchial[b]/peribronchial[c])	9 (6/3)
Peripheral	23
Reasons for SBRT[d]	
Poor lung function	20
Other medical problem	7
Age >80 years	4
Refused surgery	1
SBRT dose	
40 Gy/4 fractions	12
48 Gy/4 fractions	16
60 Gy/3 fractions	4

[a] Eastern Cooperative Oncology Group.
[b] Mass located on the main or lobar bronchus.
[c] Mass located on the segmental bronchus or within 2 cm of the proximal bronchus.
[d] Stereotactic Body Radiation Therapy.

3.3. Local tumor control and survival

The 6 month major response rate, consisting of all patients with complete (CR) or partial (PR) response, was 59.3% (19/32). Twelve patients (37.5%) showed SD and the remaining patient showed progressive disease (PD) 1 month after SBRT. Four patients had local tumor recurrences, at 1, 8, 9, and 10 months after SBRT; at 6 months, 1 showed PR, 2 showed SD and 1 showed PD. No patient showing CR at 6 months had a recurrence. The 1- and 2-year actuarial local tumor control rates were both 85.3%. Overall survival rates were 70.9% at 1 year and 38.5% at 2 years. Actuarial local tumor control and survival time did not differ according to SBRT dose and primary tumor stage.

3.4. Patterns of failure

Seven (21.9%) patients showed disease recurrences. Local tumor recurrence at the SBRT site developed in 4 (12.5%) patients and distant metastases in 5 (15.6%) patients, with 2 patients each experiencing both local recurrence and distant metastasis. The site of distant metastasis was the lung parenchyma in 3 patients, parotid gland in 1 and cerebrospinal fluid in 1.

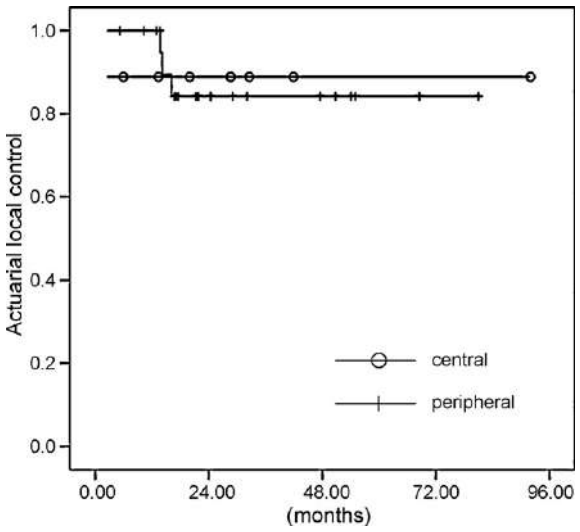

Fig. 2. Local progression-free survival.

3.5. SBRT results and tumor location

SBRT was performed in 9 patients with centrally located tumors, 6 of whom had bronchial tumors, with 1 of the latter having a mass on the main bronchial tree. In these patients, GTV or PTV included the whole circumference of the adjacent main or lobar bronchus. The remaining 3 patients had peribronchial tumors, with PTV partially including the lobar or segmental bronchus except the main bronchus. Twenty-three patients had peripheral tumors distant from the proximal bronchial tree. Baseline clinical and demographic characteristics did not differ between patients with centrally and peripherally located tumors.

SBRT doses in patients with centrally located tumors were 40 Gy in 2 patients, 48 Gy in 5 and 60 Gy in 2. The 2-year actuarial local tumor control rates were 88.9% in patients with centrally located tumors and 84.2% in patients with peripherally located tumors ($p = 0.97$, log-rank) (Fig. 2). The 2-year overall survival rates were 50.0% in patients with centrally located tumors and 35.4% in patients with peripherally located tumors ($p = 0.85$, log-rank).

3.6. SBRT-induced toxicity and tumor location

Toxicity was graded using NCI-CTC version 2.0. Pulmonary toxicity was evaluated through pulmonary function tests, medical need, dyspnea, pneumonitis and pleural effusion. Thirty-one (96.9%) patients experienced pulmonary toxicities, but most patients had mild symptoms. None of the patients with peripherally located tumors experienced a severe pulmonary toxicity, of G3 or above. Of the 9 patients with centrally located tumors, 3 patients had severe pulmonary toxicities, of G3 or above, and 8 patients experienced partial or complete bronchial strictures (Table 2). Time to development of bronchial stricture ranged from 2.0 to 39.6 months (median, 20.5 months). Bronchoscopy was done in 6 among 8 patients with bronchial stricture. Bronchoscopic biopsy was done in 5 patients without bleeding tendency and there was no tumor recurrence in any patients.

We attributed the death of 1 patient to bleeding, aspiration and pneumonia from an SBRT-induced complete bronchial stricture. This patient had a bronchial tumor in the main bronchus and the PTV volume included the entire circumference of the main bronchus. The SBRT dose to this patient was 48 Gy on 4 days. Pneumonectomy for the control of bleeding and pneumonia was done and we could not find the evidence of tumor recurrence at main bronchus. The patient was gone despite operation. Two patients with G3 or G4 pulmonary toxicity had partial bronchial strictures and secondary obstructive pneumonia induced by SBRT, and SBRT dose to them were 40 Gy on 4 days. Two patients having bronchial tumor and receiving 60 Gy on 3 days did not experienced severe pulmonary toxicity in NCI-CTC toxicity criteria, although they had a stricture of lobar bronchus and secondary lung collapse. Other SBRT-induced severe toxicity like skin reaction, esophagitis or rib fracture was not observed in all analyzed patients.

4. Discussion

Although surgery is the best treatment modality for patients with early stage NSCLC, co-morbid medical problems may restrict surgical procedures in some patients, especially in elderly patients with poor lung function. Fractionated SBRT or single dose radiation (SRS) has shown promising results in patients with lung cancer [9–30], including good local tumor control and minimal treatment-related toxicity, equal to that of surgery in patients with early stage NSCLC. Despite these good results, many investigations were limited to the peripheral lung tumors without any critical organ at risk in the target volume. More recently, however, SBRT/SRS has been assessed in patients with centrally located primary lung cancer [18,24] or metastatic lung tumor [20,23,33]. A phase II trial using the RTOG protocol reported that tumor location (hilar/pericentral vs. peripheral) was a strong predictor of pulmonary toxicity [18]. In this study, patients were treated with a total dose of 60 or 66 Gy in three fractions. Six patients had Grade 5 toxicities, including 4 with pneumonia, and 1 each with pericardial effusion and bleeding, with patients having hilar/pericentral tumors having an 11-fold increased risk of severe toxicities after SBRT. A phase I dose escalation study reported that 2 patients had major airway toxicities after SBRT [24]. One patient experienced Grade 2 bronchitis after 60 Gy in three fractions, and the other patient experienced Grade 3 tracheal necrosis after 72 Gy in three fractions. However, Joyner et al. [20] found that when SBRT of 36 Gy in three or six fractions was performed on centrally located primary or metastatic lung tumor, 1 patient experienced total occlusion of a major airway 36 months after SBRT, but that this did not lead to severe pulmonary toxicity, indicating that SBRT for centrally located lung tumors was feasible. Others have reported similar results with various SBRT schemes [23,33].

In our institute, fractionated SBRT for patients with early stage NSCLC was performed in medically inoperable patients, except for 1 who refused surgery. Of our 32 patients, 20 (62.5%) suffered from poor lung function and 4 (12.5%) were over 80 years old with other medical problems. We found that the 2-year actuarial local tumor control rate was 85.3% and the 2-year overall survival rate was 38.5%. Although the overall survival rate was disappointing, the local tumor control rate was similar to that of other studies of SBRT. None of the patients with peripherally located lung tumors experienced severe pulmonary toxicity (Grade 3 or above) after 48 Gy in

Table 2
Bronchial stricture after SBRT.

	Site of primary tumor		
	Bronchial tumor[a] (%)	Peribronchial tumor[b] (%)	Peripheral tumor[c] (%)
No stricture	0 (0)	1 (33)	23 (100)
Partial stricture	3 (50)	2 (67)	0 (0)
Complete stricture	3 (50)	0 (0)	0 (0)

[a] Mass located on the main or lobar bronchus.
[b] Mass located on the segmental bronchus or within 2 cm of the proximal bronchus.
[c] Mass located in the peripheral lung parenchyma.

four fractions, suggesting that more intensified SBRT may be safe in peripherally located lung tumors.

Unlike patients with peripherally located lung tumors, those with centrally located lung tumors had major airway toxicities after SBRT. Among 9 patients with centrally located tumors, 6 patients with bronchial tumors experienced airway strictures, with 3 each experiencing partial and complete strictures. One patient with a bronchial tumor showed bleeding and complete obstruction of the main bronchus at 13 months after SBRT, and then died despite pneumonectomy for the control of bleeding and secondary aspiration pneumonia. Two patients with bronchial tumors showed partial obstruction of the lobar bronchus and repeated obstructive pneumonia, and they needed interventional therapy like balloon dilatation or bronchial stent. They, however, could not have an opportunity for intervention due to death from extensive systemic metastasis in one and old age in other one patient. The other 3 patients with bronchial tumors also experienced bronchial strictures, but they did not suffer from respiratory difficulties. Actuarial local tumor control and overall survival did not differ by tumor location.

In summary, we found that SBRT was a feasible and effective treatment modality in patients with early stage NSCLC and medical problems conflicting with definitive surgery. Unlike in patients with peripheral lung tumors, SBRT in this fractionation, although less intensified fractionation schedule than other reports, should not be given to centrally located tumors because it can cause the late major airway toxicities in some patients and more protracted hypofractionated treatment regimen may be more safe than that used in this study. More data with more patients and maturing follow-up will be needed to confirm this study.

Conflict of interest

There is no conflict of interest, including any financial, personal or other relationships with other people of organizations that could inappropriately influence, in connection with this work.

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