Stereotactic body radiotherapy for lung tumors: Preliminary results from a single institution

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ABSTRACT Stereotactic body radiotherapy (SBRT) for small lung tumors has been reported to achieve very promising treatment outcomes. At our institution, 25 lesions in 22 patients were treated with this technique over a 5-year period. All patients had medically inoperable lung tumors ≤ 5 cm in size or had refused surgery. In cases of metastatic tumors, the number of lesions did not exceed 2. Radiotherapy was performed under strict patient immobilization with an exclusive fixation device. Tumor volumes were determined by 4-dimensional computed tomography, under free breathing, and the position of the radiation field was verified by linac graphy at each treatment. A total of 48 Gy in 4 fractions was delivered by 6–10 non-opposed beams. The 3-year local control rate was 92% for primary lung cancer and 75% for metastatic lung cancer. The 3-year overall survival rate for primary and metastatic lung cancers were 65% and 56%, respectively. Metastasis from colorectal cancer was associated with poor local control. Severe adverse effects were not observed. The SBRT method used provided safe and effective treatment.

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Key words：**Stereotactic body radiotherapy, Conformal radiotherapy, Lung tumor**

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a treatment method that can be carried out with strict immobilization of the patient and accurate geometrical targeting using an image-guided radiotherapy system. Although amazing treatment results have been reported for small lung tumors, the detailed procedure of SBRT varies according to the institution at which it is performed. We introduced the use of SBRT for lung tumors in 2007 and, herein, present the procedure used for SBRT and confirm the treatment results obtained with the method at our institution.

MATERIALS AND METHODS

Since July 2007, 28 lung lesions in 25 patients

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have been treated by SBRT at our institution; 3 patients who had follow-up periods of <6 months were excluded from this analysis. Therefore, 25 lesions in 22 patients were included in the present study. Two of the patients had 2 metastatic lesions each, and 1 patient received a second SBRT treatment for asynchronous primary lung cancer.

The criteria used to define patients eligible for SBRT included Stage I primary lung cancer or metastatic lung cancer with up to 2 lesions; a major axis of the lesion of ≤ 5 cm; absence of active lesions outside of the lung; a high suspicion of malignancy based on diagnostic imaging or clinical course when not proven by pathologic findings; medically inoperable lesions or patient refusal for surgery; a forced expiratory volume in 1 sec of ≥ 700 ml; absence of active interstitial pneumonitis and pulmonary fibrosis; and willingness to provide written informed consent.

The radiotherapy equipment consisted of a computed tomography (CT) scanner (Asteion 4, Toshiba, Tokyo, Japan), a 3-dimensional radiation treatment planning (RTP) system (XiO, Elekta, Stockholm, Sweden), and a linac machine (PRIMUS MD2, Siemens, Munich, Germany). Radiotherapy was planned according to CT images. Before acquiring CT images, the patient was strictly immobilized with an exclusive device (ESFORM Body Support System®, Engineering System, Nagano, Japan) (Fig. 1), under oxygen inhalation, to minimize the patient's respiratory movement. Two series of CT scans during free breathing were obtained. The first series included the entire lung and adjacent parts of the body. In the second series, thin slice images around the lesion were acquired using 4-dimensional CT. During the 12-sec scan, 12 consecutive images were acquired at each slice. These images, including those taken during the inspiratory and expiratory phases, were digitally added and reproduced into a new series (1 image per slice). This digitally reproduced series was called, "dynamic CT". The first and second series were integrated on the RTP system using a CT-CT fusion technique. The tumor volume was contoured on the "dynamic CT" series to yield an internal target volume (ITV), and a planning target volume (PTV) was created by adding a 5-mm setup margin to the ITV. Organs at risk were contoured on the first CT series. Six to ten radiation beams were arranged in a non-opposing fashion to deliver a total dose of 48 Gy in 4 fractions at the center of the PTV for peripheral lesions with aperture margins of 5–7 mm (Fig. 2). For central lesions, when dose constraints for the central organs at risk could not be cleared, an altered dose fractionation of 60 Gy in 10 fractions was applied. Dose constraints for the organs at risk are listed in Table 1. Dose distributions were calculated using the Clarkson algorithm with heterogeneity correction. At the time of each treatment, verification films (linac graphy) were obtained and the position of the isocenter was corrected, if necessary.

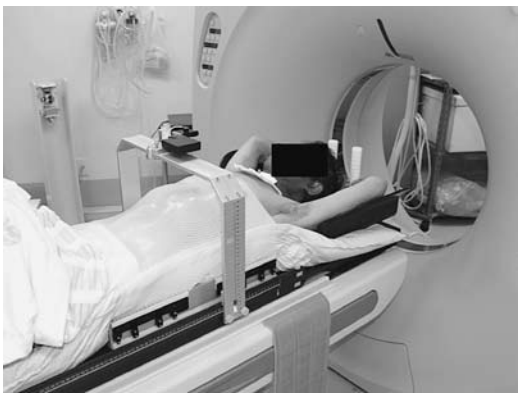

Fig. 1 Patient set-up with the exclusive immobilization device.

Tumor response was classified as either "uncontrolled," characterized by apparent tumor enlargement or regrowth, or "controlled," characterized by a decreased or unchanged tumor size or uncertain findings masked by radiation fibrosis. Local control and survival from the initiation of radiotherapy were calculated using the

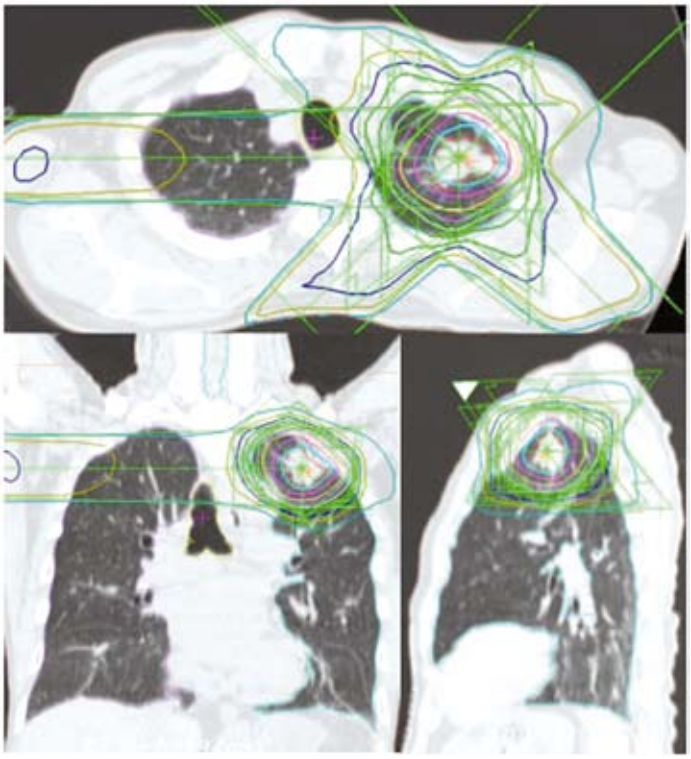

Fig. 2 An example of beam arrangement and dose distribution.

Table 1. Dose constrains for organs at risk

Lung (Lung – PTV)	$V_{40} \leq$ 100 ml Mean dose $\leq$ 18 Gy $\%V_{15} \leq$ 25% $\%V_{20} \leq$ 20%
Spinal cord (+ 3 mm margin)	Maximal dose $\leq$ 25Gy
Pulmonary artery (+ 5 mm margin)	$V_{40} \leq$ 1 ml $V_{35} \leq$ 10 ml
Esophagus (+ 5 mm margin)	$V_{40} \leq$ 1 ml $V_{35} \leq$ 10 ml
Stomach and intestine (+ 5 mm margin)	$V_{36} \leq$ 10 ml $V_{30} \leq$ 100 ml
Bronchus (+ 5 mm margin)	$V_{40} \leq$ 10 ml

PTV; Planning target volume, Vx; Volume of the organ receiving at least X Gy, %Vx; percent volume of the organ receiving at least X Gy

Kaplan-Meier method. Statistical analyses were performed using JMP version 10 (SAS institute, Tokyo, Japan).

The study was approved by the ethics committee of Kawasaki Medical School.

RESULTS

The patient and tumor characteristics are summarized in Table 2. The median age of the patients was 74 years (range, 39–92 years), and the median follow-up period was 18 months (range, 8–59 months). Tumors were classified as

"controlled" in 21 of the 25 lesions. Four patients developed local recurrence, with 2 primary lung adenocarcinomas recurring 8 and 47 months after treatment and 2 metastatic lung carcinomas, derived from colorectal cancer, recurring 12 and 22 months after treatment. The cumulative control rate is shown in Fig. 3. The 3-year local control rates for all lesions, primary lung cancer lesions, and metastatic lung cancer lesions were 82%, 92%, and 75%, respectively.

Of the 14 patients with primary lung cancer (1 patient developed primary lung cancer after SBRT for metastatic cancer and was counted as "overlapping"), 2 died as a result of the disease, 1 died of heart disease, 3 were alive with persistent cancer, and 8 were disease-free at the last follow-up visit. Of the 9 patients with metastatic lung cancer, 1 died of the disease, 1 died of other causes

Table 2. Patient characteristics

Number of Patients	
Male	16
Female	6
Age (y), median (range)	74 (39-92)
Number of lesions	
Primary lung cancer	14
Metastatic lung cancer	11
Histology	
Adenocarcinoma	11
Squamous cell carcinoma	8
Adenoid cystic carcinoma	1
Not proven	5
Tumor diameter (mm), median (range)	20 (3-50)
Stage of primary lung cancer	
IA	11
IB	3
Primary site of metastatic lung cancer	
Lung	6
Colorectal	2
Submandibular gland	1
Esophagus	1
Unknown primary	1

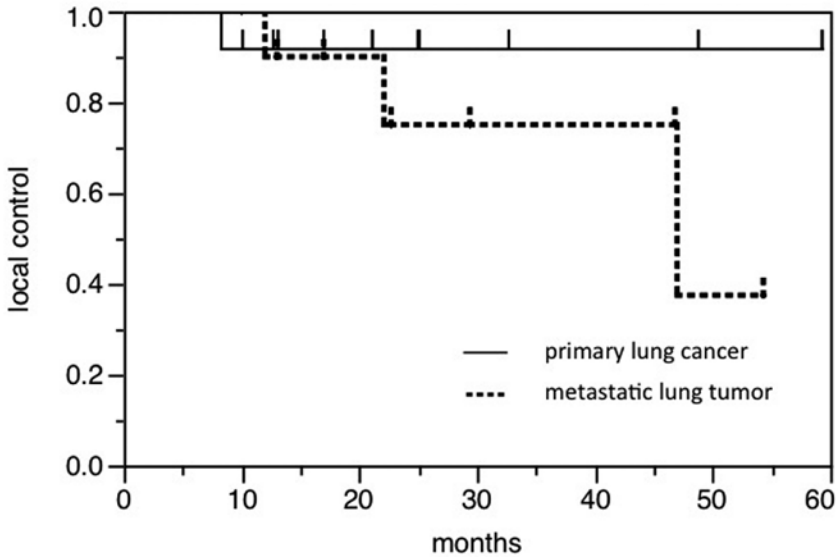

Fig. 3 Local control rates after stereotactic body radiotherapy according to tumor origin.

(unidentified), 4 were alive with persistent cancer, 1 was salvaged by surgery, and 2 were alive and disease-free at the last follow-up. The cumulative survival rate is shown in Figs. 4 and 5. The overall 3-year survival rates were 65% and 56% for primary and metastatic cancer, respectively. The cause-specific 3-year survival rates were 78% and 67% for primary and metastatic lung cancers, respectively.

No severe adverse effects were observed, and none of the patients developed symptomatic radiation pneumonitis or had worsened dyspnea after SBRT.

DISCUSSION

Stereotactic body radiotherapy (SBRT) for small lung tumors has recently become available, with the development of the necessary treatment equipment.

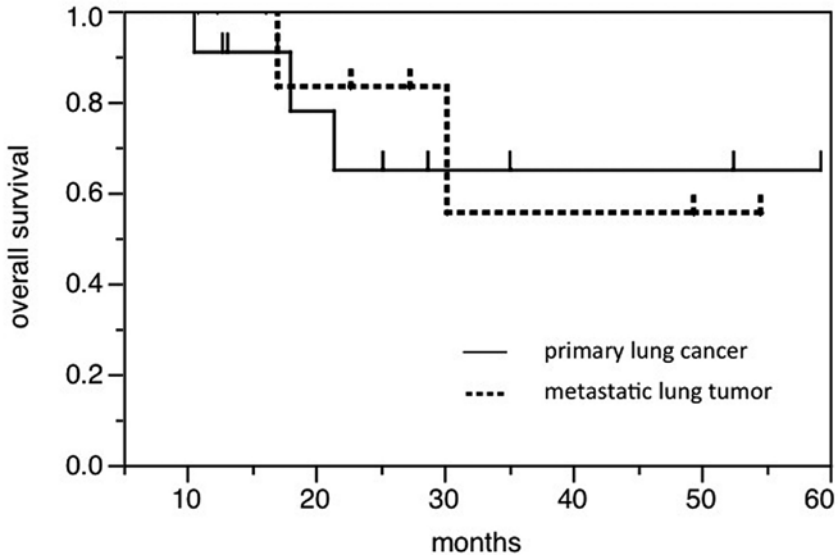

Fig. 4 Overall survival rates after stereotactic body radiotherapy according to tumor origin.

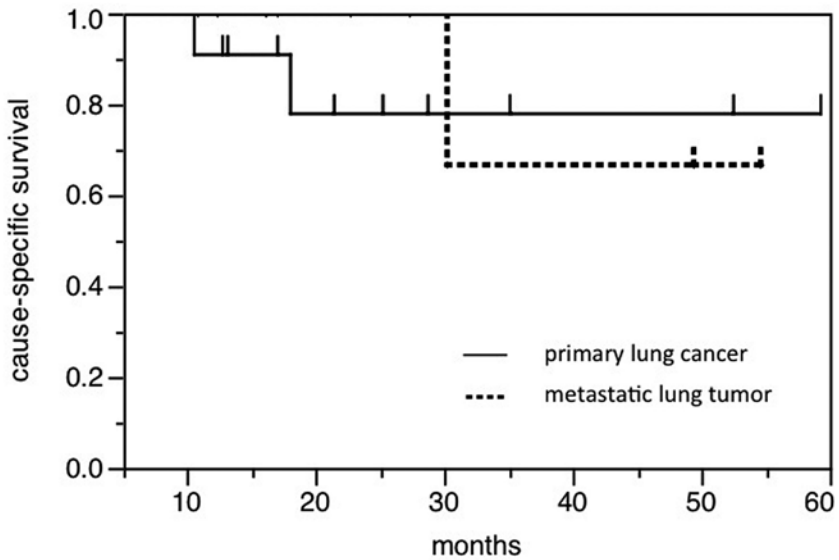

Fig. 5 Cause-specific survival rates after stereotactic body radiotherapy according to tumor origin.

This modality achieves a large biological effect by applying hypofractionated radiotherapy to a precise anatomic location, resulting in very promising treatment outcomes. The reported 5-year local control and overall survival rates reach up to 92% and 72%, respectively, for Stage IA lung cancers and up to 73% and 62%, respectively, for Stage IB lung cancers[1]. These results are similar to those obtained with surgery, and yet, SBRT can be performed safely without a resultant deterioration in pulmonary function, even in patients with chronic obstructive pulmonary disease[2,3]. Given these results, SBRT has become a primary strategy for treating medically inoperable lung cancer and for treating lung oligometastasis[4].

The SBRT results observed at our institution were comparable to other reported outcomes, showing that our treatment policy and procedures are acceptable. Local control of metastatic lung tumors was worse than that observed for primary lung cancers; this tendency seemed especially apparent in cases of metastasis from colorectal cancers, which also in agreement with previously published reports[5,6].

Technically, 2 important aspects must be taken into account for the successful treatment of patients with SBRT. The first is the precise immobilization of the patient and the second is the control of tumor movement resulting from breathing. These 2 considerations are very important in this modality because geometric errors are critical to the highly precise irradiation that is required. The procedure described here employs a body frame system for patient immobilization and 4-dimensional CT with oxygen inhalation to minimize and optimize the target volume. Although other technical approaches to minimize tumor movement, including breath-holding or respiratory-gated irradiation have been reported[7], the described method is convenient and may be implemented without special devices. These attributes make this method one of the most popular in Japan[8,9].

The SBRT technique has some deficiencies that will need to be addressed in the future. First, judging the treatment effect is difficult because of radiation-induced fibrosis, which frequently appears and remains in the irradiated lung[10]. Radiation-induced lung fibrosis often presents as a mass-like consolidation that mimics residual or recurrent tumors. A long follow-up period with no evidence of tumor regrowth is the only way to diagnose a complete response. For this reason, residual tumor shadows without enlargement were defined as "controlled." Second, optimal dose-fractionation is not clear, especially in centrally located tumors. A biologically effective dose (BED) of 83.2–146 Gy has been reported to result in superior overall survival, compared with higher or lower doses[11]. The 48-Gy radiation dosing in 4 fractions resulted in a BED of 106 Gy, which appeared reasonable for peripheral tumors. For centrally located tumors, however, some literature reports severe toxicity[12,13], and we should recognize that the safety of SBRT for these tumors has not yet been established. Finally, despite the high rate of local control, this method has limited effect in terms of patient survival. Overall survival is reported to correlate with the development of distant metastasis[14]. Although future challenges include additional concurrent or adjuvant systemic therapy, these combined modalities have latent risks of increasing adverse effects. Well-controlled prospective studies are required to evaluate these risks.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no competing financial interests.

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