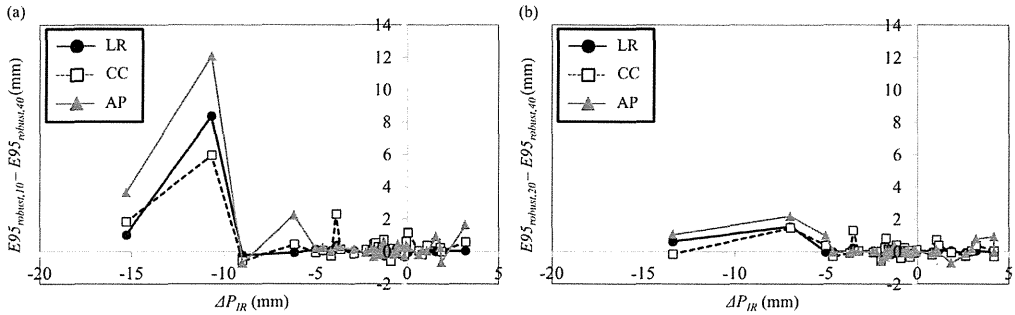

Figure 6. Relationship between ΔP_{IR} and $E_{robust,T}$-$E_{robust,40}$ ($T = 10$ and 20 s). (a) 10 s and (b) 20 s. The negative value of ΔP_{IR} indicated that the maximum amplitudes of P_{IR} for a modeling period of 10 or 20 s in the previous modeling were smaller than those for 40 s in the next modeling.

secondary cancers. The use of IR Tracking to treat liver and pancreatic cancer (unlike lung cancer) requires extra imaging doses to ensure that the signal-to-noise ratio between implanted fiducial markers and the surroundings is high. During the modeling period, the user cannot change the sampling frequency arbitrarily; therefore, a short modeling period is effective in reducing the imaging dose. This is of clinical importance, from the perspective of the "as low as reasonably achievable" principle and recommendations of the International Commission on Radiological Protection [21].

Recently, Poels et al. and Akimoto et al. developed an automatic CM updating method based on P_D on the monitoring images during beam delivery [22,23], concluding that the tracking accuracy improved for patients treated with IR Tracking without CM remodeling. We have shown that the robustness of CM parameters obtained over modeling periods of 10 s was lower than that over modeling periods of 20 and 40 s. However, a combination of a 10-s modeling period and the automatic CM updating methods could maintain tracking accuracy and improve the efficiency of a future workflow using the Vero4DRT.

Conclusions

We assessed the effect of the period of correlation modeling on prediction accuracy in 10 consecutive lung cancer patients who underwent IR Tracking. The accuracies of CMs derived using modeling periods of 20 s were almost identical to those obtained over a modeling period of 40 s, and superior to those obtained over 10 s.

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Original Study

Stereotactic Body Radiotherapy for Synchronous Primary Lung Cancer: Clinical Outcome of 18 Cases

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Abstract

For patients with synchronous primary lung cancer (SPLC), definitive surgical treatment is considered to be standard treatment. The clinical course after stereotactic body radiotherapy (SBRT) with or without surgery for these patients is not clear. This retrospective study showed SBRT yielded an excellent overall survival rate with limited toxicity. SBRT could be a good treatment option for frail patients with SPLC.

Background: Previous reports have shown that curative surgical approaches for synchronous primary lung cancer (SPLC) yielded excellent treatment outcomes. However, patients with SPLC are often unsuitable for such surgery as a result of poor general condition or other medical comorbidities. The effectiveness and feasibility of stereotactic body radiotherapy (SBRT) as a definitive treatment for SPLC are not well understood. **Patients and Methods:** We retrospectively reviewed the records of the patients who received lung SBRT between July 2007 and December 2012 at our institution and identified patients with SPLC. The clinical outcome was analyzed for each patient. The first progression site was classified as local, regional, distant, or new primary lung cancer. **Results:** A total of 18 patients were eligible. Fifteen patients received SBRT for both lesions, and 3 patients received surgery for one tumor and SBRT for the other. The median follow-up time was 34.3 months (range, 12.2-64.7 months). The median overall and progression-free survival was 45.6 months (95% confidence interval [CI] 21.0-60.6) and 25.3 months (95% CI, 13.1-50.6 months), respectively. The 3-year overall survival and progression-free survival rates were 69.1% (95% CI, 40.7-85.9) and 43.2% (95% CI, 20.2-64.4), respectively. Eleven patients (61%) experienced disease progression. The first progression site was local in 4 (22%), regional in 5 (28%), distant in 3 (17%), and new primary lung cancer in 2 patients (11%). Grade 3 radiation pneumonitis was observed in 2 patients (11%). **Conclusion:** SBRT for SPLC is a highly effective local treatment with limited toxicity, although the progression rate seems relatively high.

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Keywords: Multiple primary lung cancer, Non-small-cell lung cancer, Stereotactic ablative radiotherapy, Stereotactic body radiotherapy, Synchronous primary lung cancer

Introduction

Primary lung cancer with an additional nodule is not an uncommon clinical presentation. According to one study, staging computed tomography (CT) of operable lung cancer revealed additional pulmonary nodules in 16% of lung cancer patients, but only a small proportion of the additional nodules were found to be malignant.[1] Differential diagnosis of the additional nodule is a benign nodule, synchronous primary lung cancer (SPLC),[1] or an intrapulmonary metastasis. When an additional nodule is judged to be malignant from histopathologic or radiographic findings, the discrimination of SPLC from intrapulmonary metastasis is of critical importance because the prognosis and treatment strategy may be different in each clinical scenario.

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[1]SPLC = synchronous primary lung cancer.

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Martini and Melamed[2] proposed criteria for SPLC based on clinical and pathologic information, such as tumor histology and location. Several studies have also proposed using genetic analysis to identify SPLC.[3-6] However, no definitive criteria are available in daily clinical practice, and primary lung cancer with an additional nodule is usually treated as SPLC when there is no evidence of systemic disease spread.

SPLC is thought to be a potentially curable disease, and surgery is a standard treatment when patients are deemed operable. Indeed, surgical series have reported excellent treatment outcomes for patients with SPLC.[7-9] However, some patients with SPLC are not good candidates for surgery because of limited cardiopulmonary reserve, poor general condition, or other medical comorbidities. Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy, achieves high local control and overall survival (OS) rates with limited toxicity and is now regarded as an established treatment for medically inoperable early stage lung cancer.[10-12] Systemic review of SBRT studies reported that local control and 5-year OS rates were approximately 80% and 50%, respectively with less than 10% grade 3 or higher toxicity.[13] A head-to-head comparison of surgery and SBRT for operable patients does not exist, but a retrospective study revealed comparable survival rate of SBRT with surgery.[14]

When patients with SPLC are not candidates for surgery or refuse surgery, SBRT could be a good treatment alternative. To our knowledge, there are few publications discussing the use of SBRT for SPLC.[15-19] This study evaluates the OS, progression pattern, and toxicity of SBRT as a definitive treatment for SPLC.

Patients and Methods

Patients

We retrospectively reviewed the records of patients who received lung SBRT between July 2007 and December 2012 at the Institute of Biomedical Research and Innovation. The eligibility criteria for this study were as follows: (1) the patient had pathologically diagnosed primary lung cancer with an additional nodule; (2) histopathologic confirmation of an additional nodule was not mandatory but if there was no pathologic confirmation, radiologic finding indicated malignancy; (3) the location of an additional nodule was identified as being in the same lobe but another segment, in an ipsilateral or other lobe, or in the contralateral lung; (4) No evidence was present of lymph node involvement or distant metastasis; (5) Definitive treatment (surgery or SBRT) had been provided to both lesions; (6) No platinum-based chemotherapy was administered; (7) Patient had undergone at least 3 months of follow-up.

Patients were excluded if they had history of other malignancy and had not been disease-free for more than 3 years. All patients underwent a staging workup, including medical history, physical examination, CT scan of the chest and abdomen, and magnetic resonance imaging of the brain. Positron emission tomography (PET)/CT scan was done if available. This retrospective study was approved by the institutional review board.

Radiotherapy

Patients were positioned and immobilized in a supine position, and irradiation was performed under free shallow breathing, using 4 or 6 MV photons. Dose prescription was 48 Gy in 4 fractions, 60 Gy in 8 fractions, or 60 Gy in 10 fractions at the isocenter. Radiation dose prescription was determined, depending on the tumor location and proximity to the normal structures such as the main bronchus, large vessels, heart, and spinal cord.

Evaluation

Typically, CT scans of the chest and abdomen were taken every 4 to 6 months. If there were findings suspicious of disease recurrence or metastasis on CT scans, PET/CT was also performed at the discretion of the treating physician. First disease progression site was classified as local, regional, distant, or new primary lung cancer. Local failure was defined as the progression in the primary tumor and the involved lobe. Regional failure was defined as hilar, mediastinal, or supraclavicular lymph node metastasis. New primary lung cancer was defined as new solitary lung tumor in the uninvolved lobe without the evidence of locoregional failure and distant metastasis, and it was differentiated from lung metastasis by the multidisciplinary tumor board.

Statistical Analysis

Progression-free survival (PFS), OS, and time to progression were calculated from the first treatment day of SPLC by the Kaplan-Meier method. Primary tumor control rate by SBRT was also calculated from the initiation date of SBRT to each tumor. Toxicity was assessed by Common Terminology Criteria for Adverse Events, version 4.0. All statistical analyses were performed by EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Patient and Tumor Characteristics

The clinical characteristics for the patients are listed in Table 1. A total of 18 patients were eligible. The median age was 79 years (range, 71-86 years). Tumor histology was obtained for both lesions in 10 patients, and all of these 10 patients had adenocarcinoma. Out of pathologically confirmed 28 tumors, the most common histology was adenocarcinoma (n = 23), followed by squamous cell carcinoma (n = 4) and adenosquamous carcinoma (n = 1). The location of an additional nodule was the same lobe but other segment in 2 patients, an ipsilateral other lobe in 3 patients, and contralateral lung in 13 patients. Staging PET/CT was taken for 15 patients (83%).

Of the first treated lesions, 13 tumors were stage IA and 5 were stage IB according to American Joint Committee on Cancer, 7th edition, criteria.[20] Of the second treated lesions, 17 tumors were stage IA and 1 was stage IB. Fifteen patients received SBRT for both lesions, and 3 patients received surgery for one tumor and SBRT for the other.

A total of 33 tumors were treated with SBRT; the most common prescribed dose was 48 Gy in 4 fractions (n = 28), followed by 60 Gy in 8 fractions (n = 4) and 60 Gy in 10 fractions (n = 1) at the isocenter.

The median treatment interval between the local treatment for each lesion was 4.2 months (range, 0.0-12.3 months). This interval

Table 1 Characteristics of 18 Patients

Characteristic	Value
Age (years)	
Median (range)	79 (71-86)
≥75 years	15 (83%)
<75 years	3 (17%)
Sex	
Male	10 (56%)
Female	8 (44%)
Smoking History	
Former or current	10 (56%)
Never	5 (28%)
Not evaluated	3 (16%)
ECOG performance status	
0-1	15 (83%)
2	3 (17%)
Comorbidity	
Chronic heart failure/ischemic heart disease	4 (22%)
Diabetes mellitus	4 (22%)
COPD	7 (39%)
Interstitial pneumonia	1 (6%)
Renal failure	2 (11%)
Stage	
First treated lesion	
IA	13 (72%)
IB	5 (28%)
Second treated lesion	
IA	17 (94%)
IB	1 (6%)
Histologic Confirmation	
Both lesions	10 (56%)
One lesion	8 (44%)
Histology	
Adenocarcinoma	23 (64%)
Squamous cell carcinoma	4 (11%)
Adenosquamous cell carcinoma	1 (3%)
Not determined	8 (22%)
Tumor Location	
Same lobe	2 (11%)
Ipsilateral other lobe	3 (17%)
Contralateral lung	13 (72%)
Staging With PET	
Yes	15 (83%)
No	3 (17%)
Treatment	
Surgery/SBRT[a]	3 (17%)
SBRT/SBRT[b]	15 (83%)
Concurrent Chemotherapy	
Yes	2 (11%)
No	16 (89%)
Treatment interval (mo), median (range)[c]	4.2 (0.0-12.3)
SBRT Dose at Isocenter	
48 Gy/4 fractions	28 (85%)
60 Gy/8 fractions	4 (12%)
60 Gy/10 fractions	1 (3%)

Abbreviations: COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography; SBRT = stereotactic body radiotherapy.
[a]Surgery to one tumor and SBRT to the other tumor.
[b]SBRT to both tumors.
[c]Treatment interval between first day of definitive local treatment to each lesion.

was determined by the treating physician. In most cases, SBRT to the second lesion was initiated after ascertainment of no severe acute toxicity of surgery or SBRT to the first treated lesion, or after the tumor increased in size. Chemotherapy was used in 2 patients during and after the second course of SBRT. Pemetrexed was provided at 500 mg/m^2 every 3 weeks for 3 cycles in one patient and for 4 cycles in the other.

Clinical Outcome

At the time of this analysis, 4 patients were alive and free of lung cancer, 4 patients were alive with lung cancer, 7 patients died of lung cancer, and 3 patients died of other causes without the progression of lung cancer.

The median follow-up time was 34.3 months (range, 12.2-64.7 months) for all patients.

The median OS and PFS times were 45.6 months (95% confidence interval [CI], 21.0-60.6) and 25.3 months (95% CI, 13.1-50.6), respectively (Figures 1 and 2). The 3-year OS and PFS rates were 69.1% (95% CI, 40.7-85.9) and 43.2% (95% CI, 20.2-64.4). Primary tumor control rate per lesion treated with SBRT was 77.9% (95% CI, 56.9-89.5) at 3 years (Figure 3). Eleven patients (61%) experienced disease progression. The first progression site was local in 4 (22%), regional in 5 (28%), distant in 3 (17%), and new primary lung cancer in 2 (11%) (Table 2). The median time to disease progression was 18.1 months (range, 7.3-52.4 months).

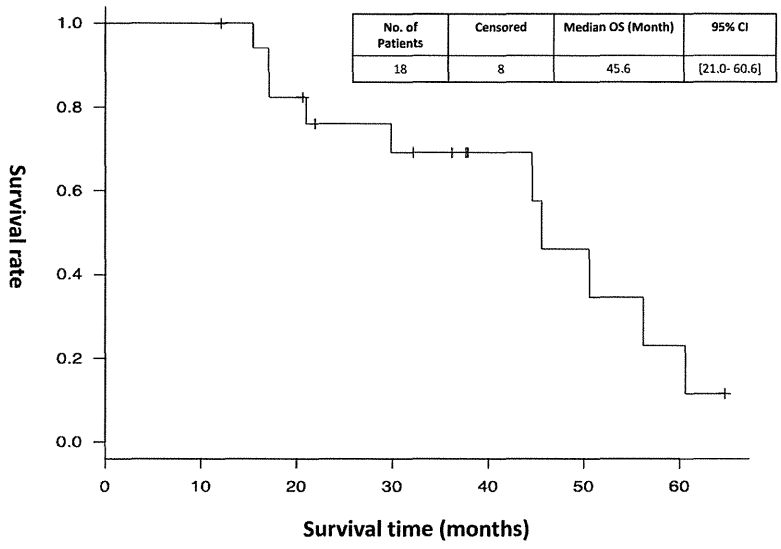
Toxicity

Three patients (16%) experienced grade 2 or higher radiation pneumonitis (RP). Among them, 2 patients experienced grade 3 RP. One patient had a history of interstitial pneumonia. He received SBRT for bilateral lung tumors and the interval between the first and second SBRT was 3.2 months. He developed grade 3 RP after 4.2 months from the second SBRT. The other patient underwent surgery for one tumor, then received SBRT for the other tumor located in the contralateral lung. At 7.5 months after SBRT, he experienced grade 3 RP. No other grade 3 or greater toxicity was recorded.

Discussion

The findings of this retrospective study showed that definitive treatment for SPLC using SBRT achieved a high OS rate (3-year OS of 69%) with limited toxicity (grade 3 toxicity of 11%).

Figure 1 Overall Survival of All Patients



Surgery is the standard treatment for patients with stage I and II lung cancer. According to the Japanese Lung Cancer Registry Study, the 5-year OS rate of clinical stage I to II lung cancer was 82.0% to 46.4%.[21] There are many reports addressing the outcome of the curative surgical approach of SPLC. Relatively large surgical studies reported that 5-year OS of patients with SPLC varied from 20% to 52%.[7-9,22] The population of patients is highly heterogeneous. A pooled analysis of surgical series on SPLC revealed that advanced age, male sex, nodal involvement, and unilateral tumor were adverse prognostic factors.[23] The 5-year OS was 82% among patients without risk factors versus 43% for patients with risk factors. These data showed that the outcome of surgical treatment of SPLC as a whole is not as good as that of single early stage lung cancer but is clearly better than that of patients with stage IV disease. Thus, the definitive treatment of every lesion for patients with SPLC is a justifiable approach.

If the tumor location is in the ipsilateral other lobe or contralateral lung, surgical resection usually included a lobectomy with

Figure 2 Progression-Free Survival Among All Patients

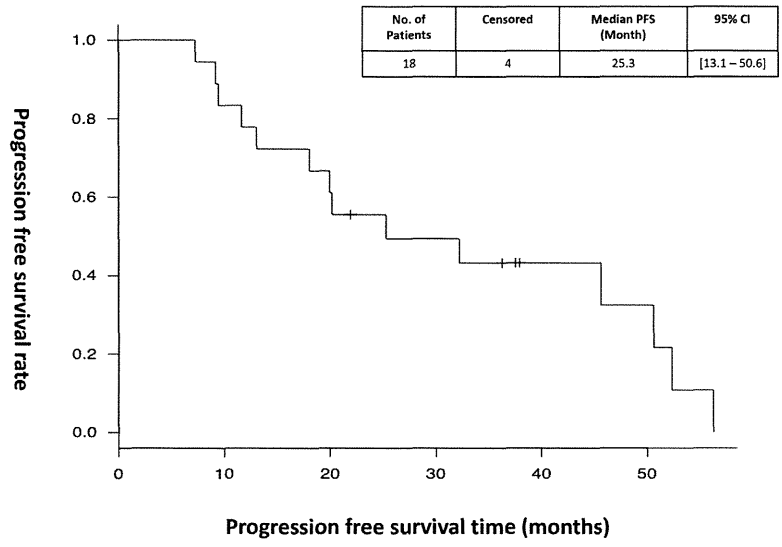
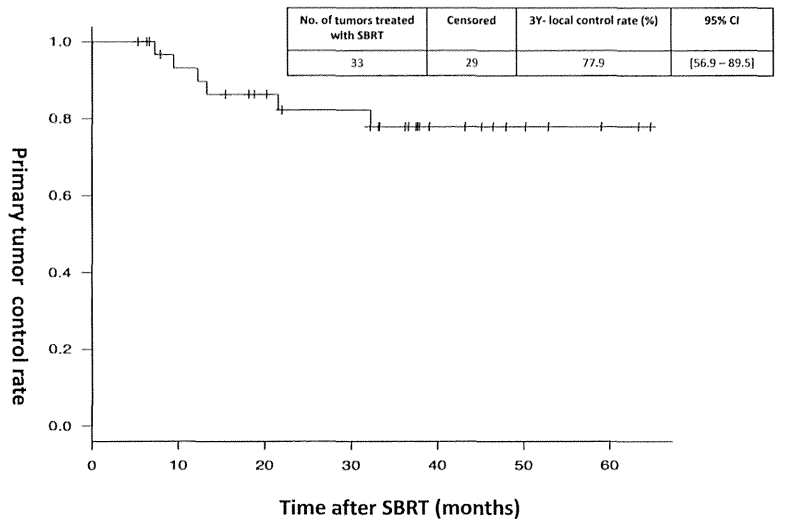


Figure 3 Primary Tumor Control Rate of Each Tumor Treated With Stereotactic Body Radiotherapy



limited resection (wedge resection or segmentectomy). Surgical series on SPLC reported that the postoperative complication and mortality rate was approximately 30% and 1% to 10%, respectively.[7-9] Patients with lung cancer are often older and have comorbidities such as chronic obstructive pulmonary disease and heart disease, similar to the patient population of this study. Because postoperative morbidity and mortality rates were shown to be high (complication rate, 48%; mortality rate, 6%) after surgery on single early stage lung cancer even in well-selected older patients,[24] surgery for SPLC is often too invasive for older, frail patients. Therefore, SBRT could be a good treatment option in such cases. Only a few SBRT studies have been published, with a relatively small number of patients.[15-19] According to previous reports on SBRT containing a relatively large number of SPLC patients, the 2-year OS was 56% to 61%,[18,19] which is comparable to this study. However, direct comparison between studies is difficult and of little meaning because of the small sample size and variation of the patient selection.

Whether the risk of RP increases when SBRT is provided in 2 separate courses or in the postoperative setting is a major concern. Only 11% of our patients experienced grade 3 RP. Considering that one of these patients had a medical history of interstitial pneumonia and increased risk of RP, grade 3 RP rate in our study was not much different from that of SBRT for single early stage lung cancer. Chang et al[19] reported a relatively high rate of grade 3 RP for patients who received conventionally fractionated radiotherapy and SBRT (13%), but the incidence of grade 3 RP in patients who received surgery and SBRT or 2 courses of SBRT is generally rare in SBRT studies (0-3%). This is possibly because SBRT is highly conformal and most of the normal lung tissue is spared, even after 2 courses of SBRT or in the postoperative setting.

The regional and overall recurrence rates after SBRT for single early stage lung cancer are reported to be up to 10% and 30%, respectively.[13,25] In our study, regional and overall recurrence rates were 28% and 61%, respectively, and were relatively high. SBRT without surgery for the treatment of SPLC has the disadvantage of not obtaining accurate pathologic mediastinal lymph node staging. Even though PET/CT has high sensitivity and specificity in detecting lymph node metastasis, the false-negative rate is reported to be 13% for clinical stage T1-2N0 non–small-cell lung cancer patients.[26] The regional recurrence rate (28%) of patients with SPLC in our study was about twice as much as that of patients with single early stage lung cancer. This is not surprising because each lesion has the risk of regional node micrometastasis not being detected by the imaging study. Adjuvant chemotherapy containing cisplatin has shown to increase survival in pathologic stage II and III patients.[27] Age-based analysis of the Lung Adjuvant Cisplatin Evaluation data also showed no major difference in OS and severe toxicity in subgroups aged older than 70 years, although it contained only a small number of patients older than 75.[28] Considering

Table 2 Precise Clinical Outcomes (n = 18)

Pattern of First Treatment Failure	n (%)
Local Recurrence	4 (22)
Isolated LR	2
LR and RR	1
LR and DR	1
Regional Recurrence	5 (28)
Isolated RR	3
RR and DR	1
Distant Recurrence	3 (17)
Isolated DR	1
New primary lung cancer	2 (11)

Abbreviations: DR = distant recurrence; LR = local recurrence; RR = regional recurrence.

that the median age of the patients in our study was relatively high (79 years) and most of them had other medical comorbidities or poor general condition, the benefit of adjuvant platinum-containing chemotherapy would be limited if provided after completion of local treatment.

There are limitations of this study. First, this is a retrospective study and includes only a small number of patients. Second, 8 out of 18 patients had only one lesion sampled. Third, selection bias exists, and we only had data for patients referring to our department. Fourth, chemotherapy was provided in 2 cases at the discretion of the treating physician. There are no data available for the role of adjuvant pemetrexed monotherapy for patients with SPLC. It might enhance the effect of radiotherapy and sterilize microscopic metastasis, but only a short course of pemetrexed monotherapy would not have major, if any, influence on the natural course of SPLC after definitive local treatment.

In conclusion, SBRT for SPLC is a highly effective local treatment with limited toxicity even for older, frail patients who are considered to be at high risk of morbidity and mortality after surgical procedures to each lesion.

Clinical Practice Points

- A definitive surgical approach is now regarded as standard treatment for SPLC patients. When both tumors are not located in the same lobe, definitive surgical approach usually consists of more than a lobectomy. However, elderly patients with other medical comorbidities are not good candidates for such surgical intervention.
- This study showed that SBRT achieved a high local control rate with limited toxicity and could be a treatment option for elderly, frail SPLC patients. This study also showed a relatively high incidence of regional and overall progression rate, compared with single early stage lung cancer.
- There may be a role for invasive mediastinal staging for more appropriate patient selection and of adjuvant chemotherapy for eradication of micrometastasis, although this was beyond the scope of our study.

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Disclosure

The authors declare that they have no conflict of interest.

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Original Research

Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: A propensity score matching analysis

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KEYWORDS
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Minimally invasive surgery
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Abstract ***Background:*** The aim of this study was to perform a survival comparison between stereotactic body radiotherapy (SBRT) and sublobar resection (SLR) in patients with stage I non-small-cell lung cancer (NSCLC) at high risk for lobectomy.
Methods: All patients who underwent SBRT or SLR because of medical comorbidities for clinical stage I NSCLC were reviewed retrospectively. Propensity score matching (PSM) was performed to reduce selection bias between SLR and SBRT patients based on age, gender, performance status, tumour diameter, forced expiratory volume in 1 second (FEV1) and Charlson comorbidity index (CCI).
Results: One hundred and fifteen patients who underwent SBRT and 65 SLR were enrolled. The median potential follow-up periods for SBRT and SLR were 6.7 and 5.3 years, respectively. No treatment-related deaths were observed. Before PSM, the 5-year overall survival (OS) was 40.3% and 60.5% for SBRT and SLR, respectively ($P = 0.008$). PSM identified 53 patients from each treatment group with similar characteristics: a median age of 76 years, a performance status of 0–1, a median tumour diameter of ~20 mm, a median FEV1 of

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~1.8 L and a median CCI of 1. The difference in OS became insignificant between the matched pairs (40.4% and 55.6% at 5 years with SBRT and SLR; $P = 0.124$). The cumulative incidence of cause-specific death was comparable between groups (35.3% and 30.3% at 5 years, $P = 0.427$).

Conclusion: SBRT can be an alternative treatment option to SLR for patients who cannot tolerate lobectomy because of medical comorbidities.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. The number of cases of stage I lung cancer is expected to increase when low-dose computed tomography (CT) screening is introduced because CT can detect more stage I cancer cases than chest radiography [2]. The U.S. Preventive Services Task Force recommends annual low-dose CT screening in individuals with a specific smoking history [3]. The treatment of stage I non-small-cell lung cancer (NSCLC) detected by CT screening is of increasing importance, particularly in high-risk operable patients [4–6]. Although lung cancer mortality has tended to decline over the last decade according to the age-adjusted incidence, the crude rate of lung cancer deaths remains high in the elderly [7,8]. As such the optimum treatment of early stage NSCLC in elderly individuals or those with medical comorbidities remains unclear.

Lobectomy remains the standard treatment for patients with clinical stage I NSCLC who can tolerate the type of surgery [9,10], even in the elderly. According to a recently updated opinion paper by the European Organisation for Research and Treatment of Cancer (EORTC) and the International Society of Geriatric Oncology (SIOG), surgical treatment should not be denied to elderly patients simply because of their age [11]. However, the percentage of patients undergoing surgery decreases with advancing age, even in patients with no comorbidities [12]. The EORTC/SIOG paper also refers to consideration of limited resections in the elderly, as well as stereotactic body radiotherapy (SBRT) in individuals who are medically inoperable.

Sublobar resection (SLR) is thought to result in inferior survival compared with lobar resection based on the results of a randomised trial [13]. This type of surgery is considered for patients with major comorbidities, and as well as individuals with a peripheral nodule of $\leqslant 2$ cm with favourable findings [10]. In addition, Rami-Porta and Tsuboi reported that lobectomy and wedge resection result in similar survival in patients aged $\geqslant 71$ years [14]. The American College of Surgeons Oncology Group (ACOSOG) Z4032 and Z4099 defined criteria of 'high risk' for lobectomy that included pulmonary function as the major criterion, and age and other medical comorbidities as minor criteria.

SBRT is being a standard treatment option for compromised patients who are medically unfit for any type of surgery due to advanced age or comorbidities [10]. Multicentre prospective trials revealed that SBRT was safe and effective in patients with inoperable stage I NSCLC [15–17]. The introduction of SBRT decreased the number of untreated elderly Dutch patients with early stage NSCLC [18].

The optimal treatment for high-risk operable patients who might tolerate surgical intervention but not lobectomy remains controversial [19,20]. To resolve this issue, an inter-group randomised trial (Radiation Therapy Oncology Group [RTOG] 1021/ACOSOG Z4099) comparing SBRT with SLR in high-risk patients with stage I NSCLC was initiated. However, it was closed in May 2013 due to slow patient enrolment. Therefore, there are no available data comparing SBRT and SLR based on a prospective randomised trial. The aim of the current study was to perform retrospective survival comparisons between SBRT and SLR in patients who underwent treatment due to medical comorbidities.

2. Methods

2.1. Patient population

This study retrospectively reviewed consecutive patients who underwent SBRT or SLR because of medical comorbidities for clinical stage I NSCLC. Data were obtained from databases maintained by the Departments of Radiation Oncology and Thoracic Surgery of Kyoto University Hospital. Clinical stage was determined using CT and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), or with CT alone. Patients with a tumour diameter >50 mm or those without histological confirmation of NSCLC were excluded. The type of recurrence was classified according to RTOG 1021/ACOSOG Z4099. Local recurrence (LR) included primary tumour recurrence and recurrence in the involved lobe. Regional recurrence (RR) was defined as ipsilateral nodal recurrence in hilum or mediastinum, or as recurrence in the ipsilateral lung. Distant recurrence (DR) was recurrence other than LR or RR. Primary tumour recurrence was diagnosed on the basis of histologic confirmation or enlargement of the local tumour on CT that continued for at least 6 months. FDG-PET was consid-

ered when primary tumour recurrence was highly suspected. When FDG-PET showed an intense uptake with a maximal standardised uptake value over 5 at 6 months or more after SBRT, primary tumour recurrence was definitely diagnosed [21,22]. Diagnosis of other types of recurrence was based on radiological findings of CT and/or FDG-PET.

The following data were extracted from the databases: age, gender, histology, ECOG performance status (PS), Charlson comorbidity index (CCI) [23], tumour diameter and forced expiratory volume in 1 second (FEV1) before the treatment. Follow-up data regarding overall survival (OS), LR, RR, DR and cause of death were also collected. The Institutional Review Board of Kyoto University Hospital approved this study.

2.2. Treatment procedures

SLR was performed via video-assisted thoracoscopic surgery under general anaesthesia with single-lung ventilation via a double-lumen tracheobronchial tube with the patient in a lateral decubitus position. Wedge resection or segmentectomy was performed at the discretion of the surgeon with generous margins. Systematic lymph node dissection was not performed, but lymph node sampling was performed in some patients.

Details regarding the SBRT planning and delivery at our institution were described previously [24,25]. The internal target volume was determined considering CT with slow scan or 4D CT, and tumour motion assessed using X-ray fluoroscopy. The planning target volume (PTV) was defined as the internal target volume plus a 5-mm margin. Irradiation was performed using 6-MV X-ray beams from a linear accelerator (Clinac 2300 C/D, Varian Medical Systems until April 2008; Novalis, BrainLab AG, Feldkirchen, Germany, thereafter) in multiple non-coplanar static ports. The prescribed dose was 48 Gy in four fractions to the isocentre for a peripheral tumour and 60 Gy in eight fractions for a centrally located tumour, respectively. Since June 2006, the dose was increased to 56 Gy in four fractions for a peripheral tumour with a diameter >30 mm.

2.3. Statistical analysis

Differences in patient characteristics between the treatment groups were evaluated using the Mann–Whitney U test for continuous data and with chi-square test for categorical data. Median follow-up was calculated using the reverse Kaplan–Meier method for potential follow-up [26]. OS was defined as the period between the start of treatment and the last follow-up, or death from any cause. Survival probability was estimated using the Kaplan–Meier method, and the survival difference between the treatment groups was evaluated using the log-rank test. Cause-specific death was defined as death from lung cancer or treatment-related mortality. The incidences of LR, RR, DM and cause-specific death were calculated using the cumulative incidence method with consideration of a competing risk of non-lung-cancer death. Differences in the cumulative incidence were evaluated using the Gray test.

Propensity score matching (PSM) was performed to reduce selection bias between patients with SLR and SBRT. PSM accounted for factors of age, gender, PS, tumour diameter, FEV1 and CCI. These were chosen according to the consensus of radiation oncologists and thoracic surgeons as the factors taken into consideration when selecting treatment options for patients with clinical stage I NSCLC.

Statistical analyses were performed using R (version 3.0.1), and PSM was done using a semi-automated method with the Matching package (version 4.8.3.4). Statistical significance was defined as $P < 0.05$.

3. Results

Between January 2003 and December 2009, 115 patients who underwent SBRT and 65 SLR were eligible for inclusion in the study. The patient characteristics are shown in Table 1. The clinical stage of T and N was determined with FDG-PET and CT in 56 SBRT patients, and 39 individuals who underwent SLR. Data regarding FEV1 were not available in 13 SBRT patients. NSCLC malignant histology was confirmed using pretreatment cytology or biopsy in all SBRT and 21 SLR patients, and using intraoperative biopsy before resection in 10 patients who underwent SLR. Pathology from the resection specimens confirmed the diagnosis of NSCLC in the remaining 34 SLR patients. Patients with SBRT exhibited significantly poorer PS, lower FEV1, larger tumour diameter and higher CCI than those with SLR. In contrast, a tendency for increased age was observed in patients who underwent SBRT.

The prescribed dose was 48 Gy in four fractions for most SBRT patients, except for five patients who received 60 Gy in eight fractions, one who received 56 Gy in four fractions and one who received 60 Gy in four fractions. Thirty-nine SLR patients underwent wedge resection, and the remaining 26 underwent segmentectomy. Two patients were up-staged to pathological IIIA after surgery because of mediastinal node metastasis that was identified after lymph node sampling. No patients received adjuvant chemotherapy until disease progression. No treatment-related death occurred in either group.

The median follow-up periods for patients in the SBRT and SLR groups were 6.7 and 5.3 years, respectively. Before PSM, OS was superior in SLR patients, who had a median survival time (MST) of 7.8 years compared with 3.6 years in the SBRT group ($P = 0.008$, Fig. 1). The 5-year OS was 40.3% (95%

Table 1
Characteristics of the whole patient cohort.

	SBRT ($n = 115$)	SLR ($n = 65$)	P-value
Age [year]	77 (56–88)	75 (50–88)	0.058
Gender (Male:Female)	83:32	43:22	0.498
PS (0:1:2)	56:47:12	36:29:0	0.026
Tumour diameter [mm]	25 (10–45)	20 (4–50)	<0.001
Histology (Ad:Sq:LC:Others)	58:41:4:12	39:22:1:3	0.393
FEV1 [L]	1.40 (0.60–2.96)*	1.77 (1.09–3.34)	<0.001
CCI	2 (0–8)	1 (0–6)	<0.001

Abbreviations: SBRT, stereotactic body radiotherapy; SLR, sublobar resection; PS, performance status; Ad, adenocarcinoma; Sq, squamous cell carcinoma; LC, large cell carcinoma; FEV1, forced expiratory volume in 1 second; CCI, Charlson comorbidity index.
Values are shown in median (range) for continuous data.
* FEV1 was not available in 13 SBRT patients.

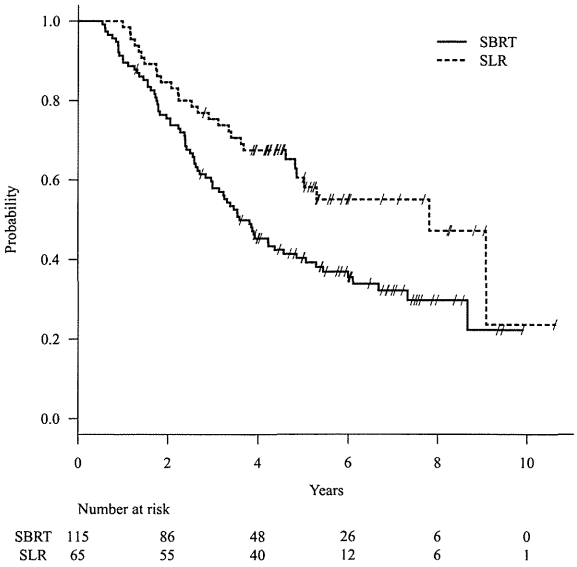

Fig. 1. Overall survival in the whole patient cohort. *Abbreviations:* SBRT, stereotactic body radiotherapy; SLR, sublobar resection.

confidence interval [CI], 31.1–49.3%) and 60.5% (95%CI, 46.7–71.8%) in the SBRT and SLR patient groups, respectively. Cause-specific death at 5 years was 33.8% (95%CI, 25.1–42.6%) and 26.3% (95%CI, 15.7–38.2%) in individuals who underwent SBRT and SLR ($P = 0.215$), respectively.

PSM identified 53 patients from each treatment group with similar characteristics: a median age of 76 years, a performance status of 0–1, a median tumour diameter of ~20 mm, a median FEV1 of ~1.8 L and a median CCI of 1 (Table 2). The difference in OS in the matched pairs became insignificant after PSM ($P = 0.124$, Fig. 2). MST and 5-year OS were 3.8 years and 40.4% (95%CI, 26.6–53.7%), and 5.3 years and 55.6% (95%CI, 40.2–68.5%) in the SBRT and SLR groups, respectively. Cause-specific death was similar between the two groups (35.3% [95%CI, 22.4–48.5%] and 30.3% [95%CI, 17.8–43.7%] at 5 years, $P = 0.427$; Fig. 3). Although LR tended to be higher in the SBRT group (28.3% and 14.1% at 5 years, $P = 0.059$), RR and DR were not significantly different between the two treatment groups (14.3% and 9.2% for RR, $P = 0.241$; 35.9% and 36.1% for DR, $P = 0.674$; Fig. 4).

4. Discussion

Limited data are available comparing the survival of patients who underwent SBRT or SLR for stage I NSCLC. Grills et al. compared the outcome after SBRT or wedge resection in 124 patients [27]. With a median potential follow-up of 2.5 years, OS was higher after wedge resection, but cause-specific survival (CSS) was identical. Parashar et al. reported no significant difference in local control, DM, OS or toxicity between 47 patients who underwent SBRT or SLR followed by radioactive seed implantation based on a mean follow-up of 1.5 years [28]. No matching method was applied in these two studies.

Two studies used PSM to compare SBRT with SLR. Varlotto et al. reviewed 48 SLR and 137 SBRT patients with a median follow-up of 2.2 years [29]. OS was superior in SLR compared with SBRT matched pairs based on pathology, age, gender, tumour diameter, aspirin use and CCI (86.3% and 31.7% for SLR and SBRT at 5 years, respectively, $P = 0.003$). However, a multivariate analysis that included propensity scores as a covariate revealed that the hazard ratio for OS was not significant. An additional study based on PSM was performed by Shirvani et al. [30]. They extracted 10,923 patients aged $\geqslant 66$ years with a median follow-up of 3.2 years from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to compare OS among the following five treatment groups: lobectomy, SLR, conventional radiotherapy, SBRT and observation. The unadjusted mortality at 2 years was lower for SLR (25.1%) compared with SBRT (41.1%). After PSM, OS and CSS in patients who underwent SBRT were similar to those with SLR, with hazard ratios of 0.82 ($P = 0.38$) for OS and 2.14 ($P = 0.10$) for CSS. The present study is consistent with the conclusions of these previous reports, in that OS after SBRT was not different from that after SLR after PSM. The

Table 2
Characteristics of patients in the matched cohort.

	SBRT ($n = 53$)	SLR ($n = 53$)	P-value
Age [year]	76 (58–86)	76 (50–88)	0.664
Gender (Male:Female)	42:11	37:16	0.373
PS (0:1)	27:26	30:23	0.697
Tumour diameter [mm]	22 (10–37)	20 (6–50)	0.236
Histology (Ad:Sq:LC:Others)	25:14:3:11	28:21:1:3	0.068
FEV1 [L]	1.87 (0.63–2.85)	1.75 (1.10–2.90)	0.800
CCI	1 (0–5)	1 (0–6)	0.233

The abbreviations used are the same as in Table 1.

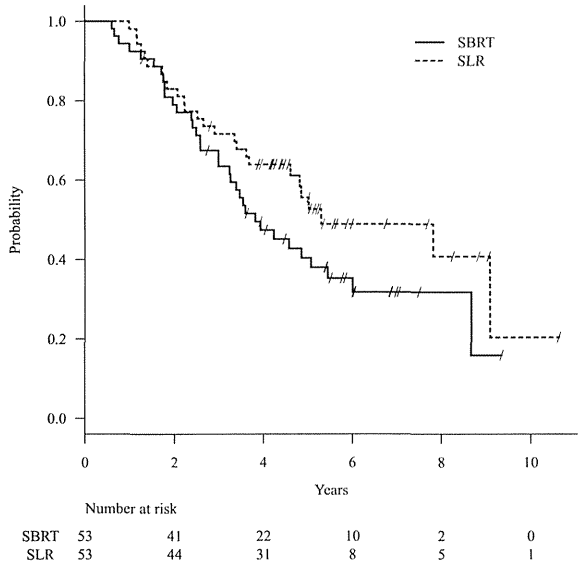

Fig. 2. Overall survival in the matched cohort. The abbreviations used are the same as in Fig. 1.

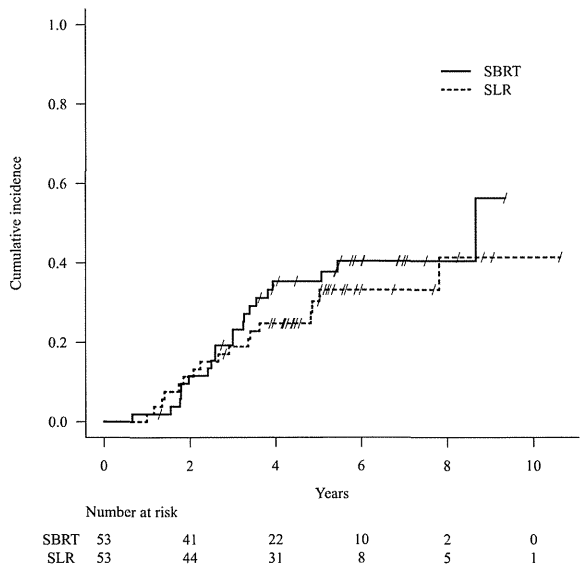

Fig. 3. Cumulative incidence of cause-specific death in the matched cohort.

number of patients in our study ($n = 180$) is comparable with previous studies, with exception of that using the SEER database [30]. Because the current study used a longer follow-up period (6.7 and 5.3 years for SBRT and SLR, respectively), our conclusions regarding long-term survival were likely to be more accurate.

Several limitations of the present study must be acknowledged. This study was based on a retrospective review of patient information. Some differences between the pre-treatment observations of the SLR and SBRT groups were observed. Histological confirmation of NSCLC was performed before treatment of all SBRT, but not SLR, patients. Because pulmonary nodules that were too small to be biopsied tended to be treated using SLR, the tumour diameter was smaller in the SLR group. Pulmonary function tests were performed in all SLR, but not SBRT patients. PSM was applied to the present study to reduce such differences between the two groups. Pre-treatment evaluation of the risk for surgery did not conform to such strict criteria as in the ACOSOG trials, but was based on the recommendations of a multidisciplinary tumour board. FDG-PET was not performed in all patients in the present study because it was not widely available throughout the study period.

Prospective randomised trials are preferable to generate convincing and reliable evidence. As described above, the RTOG 1021/ACOSOG Z4099 study was cancelled due to poor patient enrolment. The two similar trials, the ROSEL study conducted by the VU University Medical Center in the Netherlands, and the STARS study performed by the M.D. Anderson Cancer Center in the United States, were cancelled for similar reasons. This suggests that it will be challenging to perform a randomised control trial that compares different radiotherapy and surgical treatment modalities directly. Crabtree et al. compared the selection criteria and short-term outcomes of three prospective trials of stage I NSCLC, including RTOG 0236 for SBRT, ACOSOG Z4032 for SLR and ACOSOG Z4033 for radiofrequency ablation [31]. They found significant differences in patient age, clinical T-stage and the pretreatment percentage of predicted carbon monoxide diffusing capacity of the lungs among trials. PSM showed no difference between SBRT and SLR for 30-day adverse events of

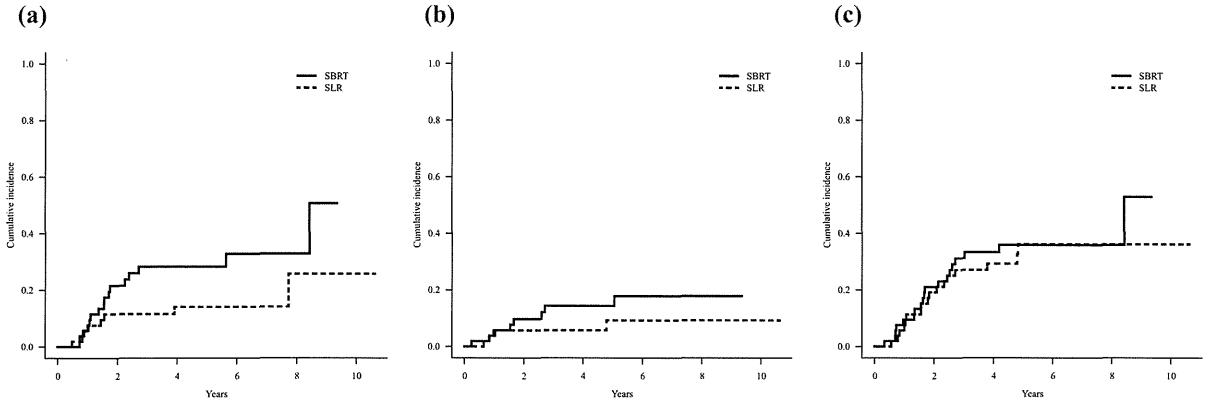

Fig. 4. Cumulative incidence of local recurrence (a), regional recurrence (b) and distant recurrence (c).

grade 3 or worse. A study that prospectively collects prognostic factors and survival data and compares outcomes among treatments using propensity scores could be an alternative to a randomised trial to compare SBRT and SLR.

Another criticism of the present study is the poor local control using SBRT. The 5-year LR of 28.3% is worse than the reported incidence of <20% [32]. Although we previously reported an LR of 13.2% [25], a longer follow-up revealed poorer LR, which might be explained to be an insufficient local tumour dose. The prescribed dose used in the present study was 48 Gy in four fractions at the isocentre, which corresponds to a biologically effective dose (BED) of 105.6 Gy. The dose covering 95% volume (D95) of PTV was a mean of 42.3 Gy using our SBRT procedures [33], which results in a BED of 87.0 Gy at the PTV periphery. Mehta et al. reported a relationship between BED at the isocentre and local control. They concluded that a BED of $\geqslant$159 Gy could achieve a local control rate of 90% [34]. Grills et al. reported a significant difference in LR between a BED at the PTV periphery of <105 Gy and $\geqslant$105 Gy (15% and 4%, respectively, at 2 years, $P < 0.001$) [35]. Both the isocentre and the PTV periphery doses were less in the present study than the doses recommended in these two studies. After this study, our prescription policy was changed to assure a BED of 106 Gy at the PTV periphery aiming further improvement of SBRT outcomes.

In conclusion, SBRT achieved comparable CSS to SLR in the PSM cohort. SBRT can be an alternative treatment option to SLR in high-risk patients who cannot tolerate lobectomy because of medical comorbidities.

Conflict of interest statement

Y.M. and M.H. receive a grant from a Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research. M.H. has a consultancy agreement with Mitsubishi Heavy Industries Ltd., Japan.

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Real-time tumor tracking

Evaluation of dynamic tumour tracking radiotherapy with real-time monitoring for lung tumours using a gimbal mounted linac

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ABSTRACT

Purpose: To evaluate feasibility and acute toxicities after dynamic tumour tracking (DTT) irradiation with real-time monitoring for lung tumours using a gimbal mounted linac.
Materials and methods: Spherical gold markers were placed around the tumour using a bronchoscope prior to treatment planning. Prescription dose at the isocentre was 56 Gy in 4 fractions for T2a lung cancer and metastatic tumour, and 48 Gy in 4 fractions for the others. Dose-volume metrics were compared between DTT and conventional static irradiation using in-house developed software.
Results: Of twenty-two patients enrolled, DTT radiotherapy was successfully performed for 16 patients, except 4 patients who coughed out the gold markers, one who showed spontaneous tumour regression, and one where the abdominal wall motion did not correlate with the tumour motion. Dose covering 95% volume of GTV was not different between the two techniques, while normal lung volume receiving 20 Gy or more was reduced by 20%. A mean treatment time per fraction was 36 min using DTT. With a median follow-up period of 13.2 months, no severe toxicity grade 3 or worse was observed.
Conclusions: DTT radiotherapy using a gimbal mounted linac was clinically feasible for lung treatment without any severe acute toxicity.
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Lung cancer is the leading cause of cancer-related deaths in most countries, including the US [1] and Japan [2]. There have been two trends in lung cancer in recent years. The first is the shift in the patient population to older ages [1,2], and the second is the gradual increase in the ratio of early stage lung cancer [3,4]. Thus, development of a new treatment modality that is appropriate for elderly patients with early stage lung cancer is desirable.

Stereotactic body radiotherapy (SBRT) was developed as a new treatment modality for early stage lung cancer in the late 1990s. Many retrospective studies and several multi-institutional prospective trials have demonstrated that excellent local control is obtained by SBRT, with acceptable toxicity [5–7]. Thus, SBRT is now an important treatment option for patients with early stage non-small-cell lung cancer who are medically inoperable and those who are elderly and relatively unfit for surgery.

The next innovation expected for lung SBRT is four-dimensional (4D) radiotherapy, which can cope with tumour movement. The lung expands periodically according to respiration and a lung tumour moves mainly in the craniocaudal direction. The amplitude of craniocaudal tumour motion is around 1 cm in mean, but can be 3–4 cm in some patients [8]. When the whole trajectory of a moving tumour is included in the irradiation field, larger volumes of healthy tissues are irradiated. The latter leads to a risk of toxicity [9–11], and accordingly, that might limit the indication of SBRT to smaller tumours. A new 4D irradiation technique that permits delivery of a dose to the tumour and limiting that to normal tissues by coping with respiratory motion may have the potential to improve the outcomes and to expand the indications of SBRT.

The Vero4DRT (formerly called the MHI-TM2000; Mitsubishi Heavy Industries Ltd., Tokyo, Japan, and BrainLab AG, Feldkirchen, Germany) [12] has two special features that allow dynamic tumour tracking (DTT) with real-time monitoring. One is two sets of kilovoltage (kV) X-ray imagers, that can monitor the three-dimensional position of the tumour in real-time via implanted fiducial markers, and the other is a gimbal mounted linac, enabling

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DTT. Extensive evaluation of the characteristics of this DTT system demonstrated high accuracies in treatment delivery to a moving target [13–17]. Previous experimental validation offered the required confidence for clinical implementation of DTT treatment in lung tumours. The purpose of this study was to evaluate feasibility and acute toxicities after DTT radiotherapy with real-time monitoring in SBRT for lung cancers using the Vero4DRT system.

Materials and methods

Patients

Eligibility criteria were as follows: (1) a single lung tumour with a diameter of 50 mm or less, (2) no nodal or distant metastasis, (3) respiratory tumour movement of 5 mm or more, (4) age of 20 years or above, (5) performance status of 0–2, (6) arms could be held over the head for 30 min or more, (7) doses to adjacent organs not exceeding the pre-determined constraints, which were the same as in the Japan Clinical Oncology Group protocol 0403 [18], and (8) written informed consent. This study was approved by the institutional review board. It was registered with the UMIN Clinical Trials Registry in Japan (UMIN000005324).

Pre-planning procedures

Prior to treatment planning, spherical gold markers with a diameter of 1.5 mm (Disposable Gold Marker [FMR-201CR]; Olympus Medical Systems, Tokyo, Japan) were placed around the tumour under bronchoscopic guidance as an internal surrogate for the tumour position. Treatment planning was carried out 1 week after insertion of the gold markers. At least 3 markers were required for the DTT irradiation to be performed.

On the simulation day, the patient was fixed in a supine position with both arms raised using an individualized vacuum pillow (BodyFIX; Elekta AB, Stockholm, Sweden, or ESFORM; Engineering System, Matsumoto, Japan). Ten respiratory phases of 4D CT were acquired in axial cine mode using a 16-slice CT scanner (LightSpeed RT16 or BrightSpeed Elite; GE Healthcare, Little Chalfont, UK) and a real-time positioning management system (Varian Medical Systems, Palo Alto, US). Immediately after the 4D CT scan, a breath-hold CT scan was also acquired at the end of exhalation. The breath-hold CT was sent to iPlan RT image (ver. 4.1; BrainLab AG) as a reference image. The coordinate for each phase image from the 4D CT was modified so that its centroid of the fiducial markers was matched with that in the breath-hold CT. Then, the 10 phase images were fused onto the breath-hold CT. After the CT scan, the patient was moved to the Vero4DRT to perform a 4D modelling [14], which correlates the external abdominal motion and the internal fiducial motion. The purpose of the modelling was to estimate the 4D modelling error and the peak-to-peak amplitude of tumour motion.

Treatment planning

Gross tumour volumes (GTVs) were delineated on the breath-hold CT and 10 phase images. An internal target volume for tracking (ITV) was defined as a composite of the eleven GTVs from the breath-hold CT and the 10 phase images (Supplementary Fig. 1). Because the phase images were registered based on the marker centroid, the ITV was supposed to compensate for tumour deformation and uncertainty in the positional relationship between the tumour and fiducial makers during respiration [19]. Planning target volume (PTV) for tracking was defined as the ITV plus setup error and additional margins to compensate the 4D modelling error, baseline drift of the abdominal position, and mechanical errors of the system. The setup error was estimated to be 2.5 mm in each direction as an inter-fraction positional variation between the fiducials and the tumour [19]. A margin for the 4D modelling error was defined as a mean plus 2 times of standard deviation in the 4D model on the simulation day. A margin for the baseline drift was estimated as 10% of the tumour motion amplitude. The mechanical errors were defined as 0.5 mm [12]. The PTV margin was defined as a linear sum of these errors. At least 5 mm was required for the margin.

Monitor units (MUs) for the treatment beams were calculated using the X-ray voxel Monte Carlo algorithm in iPlan RT dose (ver. 4.5.1; BrainLab AG) on the breath-hold exhale CT. The prescription dose was 48 Gy in four fractions for stage IA lung cancer, and 56 Gy in four fractions for stage IB lung cancer and metastatic lung tumour. This dose was prescribed at the isocentre. We typically arranged seven beams: four non-coplanar and three coplanar beams. 6-MV X-ray beams were collimated to the PTV plus 5-mm margin with a multi-leaf collimator. A static SBRT plan with non-tracking beams, based on the motion-encompassing method [8], was also prepared as a backup if DTT irradiation could not be achieved for some reason. Dose distributions were evaluated with an in-house developed software that allows 4D dose calculation considering the gimbal mounted linac [20]. The calculated dose distributions for the 10 phase CT images were accumulated into the exhale breath-hold CT with deformable image registration using MIM Maestro (ver. 5.2; MIM Software Inc., Cleveland, US). If the dose-volume metrics in the tracking plan were diagnosed to be superior to those in the static plan, the patient underwent DTT irradiation.

Irradiation of treatment beams

First, the patient was laid on the pre-formed vacuum pillow. Set-up error was corrected for bony structures using the ExacTrac X-ray system. Second, a 4D model was built to correlate the infra-red markers on the abdomen with the internal fiducial markers. Then, irradiation could start in dynamic tracking mode with the beam following a location predicted by the 4D model based on the infra-red markers placed on the patient's abdominal wall. During irradiation, the tumour and the internal fiducials were monitored visually every second with EPID and the kV imagers. If the fiducial markers were displaced from the predicted positions by 3 mm or more in 3 consecutive frames on the kV images, the irradiation was interrupted and rebuilding the 4D model was considered.

Follow-up after treatment

Follow-up visits were planned at 2, 4, 6, 9, and 12 months within the initial year after SBRT and every 3 months thereafter. A CT scan was performed at each visit. The follow-up period was defined as the duration between the first day of treatment and the last follow-up visit or the date of death. Acute toxicity was defined as any treatment-related toxicity during the initial 6 months after the treatment. Toxicity grading was according to the Common Terminology Criteria for Adverse Events v.4.0.

Results

Twenty-two patients were enrolled into this study between August 2011 and July 2013. No patients experienced toxicities related to the insertion of fiducial markers. Twenty-two of the 101 inserted markers were coughed out before the CT simulation. Consequently, the number of remaining makers in 4 patients decreased to two, which is insufficient for DTT to be performed. The planning procedures for DTT could not be performed in another two patients. One patient showed thoracic breathing that

Table 1
Patient characteristics for the patients undergoing dynamic tumour tracking.

Age [y]	83 (58–87)
Sex (male:female)	11:5
Performance status (0:1:2)	7:8:1
Primary cancer (yes:no)	13:3
Tumour diameter [mm]	20.5 (12–36)
Location (RML:RLL:LLL)	1:10:5
Respiratory motion [mm]	17 (10–46)
Prescribed dose (48 Gy:56 Gy)	12:4

Abbreviations: RML = right middle lobe, RLL = right lower lobe, LLL = left lower lobe.
Values are shown in median (range) for continuous data.

prevented the Vero system from tracking a tumour based on the abdominal motion (Supplementary Fig. 2). In the other patient with histology-unproven primary lung cancer, the tumour spontaneously regressed during 10 days between the fiducial insertion and the simulation. For the remaining 16 patients, the CT simulation for DTT was successfully performed. Characteristics of the 16 patients are shown in Table 1.

The mean PTV volume reduced from 56.2 cm^3 to 39.6 cm^3 for the static and tracking plans, respectively (Table 2). GTV doses were not spoiled by the tracking method (dose covering 95% volume of GTV, 93.4% vs. 93.7% of the prescription dose; $p = 0.323$ by paired t-test). Doses to the normal lung and liver were reduced in the 16 patients. Lung V20, the relative volume receiving 20 Gy or more, was reduced by 19.5%, from 5.5% to 4.4%. The tracking plan showed a higher maximal dose to the spinal cord than the static plan in 5 patients. However, the difference did not exceed 0.3 Gy and was considered to be clinically acceptable.

The DTT irradiation was completed for all 64 fractions for the 16 patients. Mean and standard deviation in treatment time per fraction were 36.2 and 8.8 min (range, 19–70 min), respectively. The treatment time exceeded 50 min in 5 fractions because of communication failures between the tracking system and the gimbal system requiring a restart of the tracking procedure. The gold markers were well recognized with kV X-ray imagers throughout all treatment fractions. The 4D modelling was performed as a mean of 1.9 times per fraction (range, 1–4).

With a median follow-up period of 13.2 months (range, 3.4–26.5 months), one patient experienced grade 2 radiation pneumonitis. No severe toxicity grade 3 or worse has been observed in any of the patients. Two patients died of cancer, and one died of infectious pneumonia. Local tumour control was achieved except one patient who developed local recurrence at 12.0 months.

Discussion

The Vero4DRT system has two major advantages. The first is that tumour position can be monitored in real time using kV imagers and an EPID. The second is that no extra treatment time over static SBRT and no special training for breath control are needed for the 4D treatment, which is clinically beneficial both for patient comfort and the throughput of the treatment system.

Several uncertainties are associated with 4D irradiation, including tumour position prediction errors and mechanical errors in beam delivery, which are problems to be overcome. In the Vero4DRT, kV imagers can ensure that the positions of the tumour and fiducial markers correspond to the predicted sites. EPID can be used to verify the tumour position in complement to the kV imagers [21]. Furthermore, log files allow retrospective confirmation of the accuracy in the delivery of tumour tracking after treatment. Our previous study, which evaluated the initial 10 patients from the present study cohort, confirmed high accuracies in the tracking performance. The 95th percentiles of overall tracking errors were 1.3 mm, 2.4 mm and 1.4 mm in left–right, cranio-caudal and anterior–posterior directions, respectively [22].

The Task Group 76 of the American Association of Physicists in Medicine classified motion management methods into five types: motion-encompassing, respiratory gating, breath-hold, forced shallow breathing with abdominal compression, and real-time tumour-tracking methods [8]. The motion-encompassing method is the most conventional and well-established. However, it uses the largest field of the five methods, with a large PTV. The breath-hold technique and abdominal compression are not always suitable for frail and elderly patients. Respiratory gating needs a longer treatment time than motion-encompassing methods. With a dynamic tracking method, patients do not need to hold or limit their breath, and the tumour is always irradiated by the treatment beams without intermittence, leading to a shorter treatment time than the breath-hold methods or the gating methods, and a comparable treatment time to the motion-encompassing methods. Dynamic tumour tracking is considered to be the favourable method among the five motion management methods from the patient compliance and comfort points of view. According to a Japanese survey of SBRT in 2009 [23], the most frequent response regarding the time needed for a single daily fraction was 30 min, followed by 40 min. Our result of 36.2 min for a single fraction was thus comparable with standard times for SBRT in Japan. In addition to patient comfort, a few studies have suggested that prolongation of the treatment time for a single fraction may reduce its biological effectiveness [24,25]. Unfortunately, considerable prolongation of treatment time over 50 min occurred in 5 fractions in the present study. The cause for the prolongation was immaturity of the tracking system including software. To realize DTT irradiation, the tracking software needed to communicate with other systems in real time and to command several operations including control of the gimbal motion, process of signals from the infra-red camera and analysis of images from the kV X-ray imagers. The tracking system had initial instability in the communication process where the system could not simultaneously execute such different tasks. Some adaptations to the tracking system have been introduced after the present study with the aim of improving stability. Volumetric modulated arc therapy, which can reduce total

Table 2
Comparison of dose-volume metrics between dynamic tracking and static method.

	DTT	Static	Difference	p-values*
PTV [cm^3]	39.6 (10.4–87.0)	56.2 (16.6–114.6)	−30.2%	<0.001
GTV D95 [%]	93.4 (89.9–98.0)	93.7 (89.5–99.3)	−0.4%	0.323
Lung V20 [%]	4.4 (1.9–13.7)	5.5 (2.2–17.2)	−19.5%	<0.001
Lung V5 [%]	18.2 (7.2–30.7)	20.4 (7.6–32.1)	−10.1%	<0.001
Spinal cord maximum [Gy]	7.1 (1.8–14.8)	8.4 (5.0–16.4)	−13.7%	0.028
Liver V15 [cm^3] ($n = 5$)	72.6 (3.8–162.3)	118.9 (16.5–230.8)	−49.6%	0.011

Abbreviations: DTT = dynamic tumour tracking method, PTV = planning target volume, GTV = gross tumour volume, Dx = dose covering x% of volume, Vx = volume covered by x Gy or more.
Values are shown in mean (range).
* p-Values by two-sided paired t-test.

MUs and consequently reduce treatment time, is being applied to SBRT of the lung [26]. Arc irradiation application to DTT is needed for reduction of treatment time with the Vero4DRT. The Vero4DRT achieved the same level of geometric and dosimetric accuracy with conformal arc DTT irradiation as that with fixed-port DTT [27]. A treatment planning system capable of VMAT plan is under development for the Vero4DRT.

The disadvantages of the current Vero4DRT system are its dependence on 4D modelling and fiducial marker insertion. If no appropriate 4D model is acquired, dynamic tracking cannot be performed, as occurred in one patient. One solution for this issue is to track a tumour based on real-time stereo fluoroscopy without any 4D model. However, this method introduces another problem of skin doses due to the continuous fluoroscopy during a treatment time. Another way to improve the 4D model is a training to encourage patients to perform periodical abdominal breathing [28].

The Vero4DRT currently requires fiducial markers with X-ray fluoroscopy monitoring to detect the tumour position and create the 4D model. Two types of fiducials are applicable to the Vero4DRT: one is a spherical marker, and the other is a cylindrical marker. We used the spherical gold markers that were inserted into a peripheral bronchiole under bronchoscopy. This method was reported in more detail by Imura et al. from the Hokkaido University [29]. All 57 patients in their report tolerated the marker implantation procedure and only one experienced pneumothorax, which resolved with bed rest. The toxicity rate was much lower than those of percutaneous insertion methods [30,31]. Trade-offs, however, for the reduced toxicity are marker dislocation between insertion and radiotherapy, and positional uncertainty between the tumour and markers. Imura et al. reported that 25% of the inserted markers could not be detected throughout the treatment period. Indeed, 22% of the markers in this study were coughed out before the CT simulation, and 4 of 22 (18%) patients could not undergo the DTT due to the marker dislocation. The reason why the Vero4DRT system requires 3 markers or more in the use of spherical markers is to detect the marker dislocation. Regarding the positional uncertainty between the tumour and markers, Ueki et al. evaluated intra- and interfractional variations [19]. Root mean squares in the intrafractional variations were 0.6 mm, 0.9 mm and 1.5 mm in the right-left, anteroposterior and craniocaudal directions, respectively. Moderate correlations of the intrafractional variation with tumour motion amplitude and tumour-marker distance were observed with correlation coefficients of 0.549–0.780. However, the intrafractional error did not always distribute symmetrically around zero, but often distributed in one side above or below zero. The direction and amplitude of the intrafractional variations varied between patients. Based on the results, we judged that a uniform isotropic margin was inadequate to cover the intrafractional variations, and that the fused CT approach as in the Method section was suitable for DTT planning. The interfractional variation could be covered by a 2.5-mm margin.

In conclusion, DTT radiotherapy with real-time monitoring using a gimbal mounted linac was clinically feasible for the lung without any severe acute toxicity.

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Conflict of interests

T.M., M.K. and M.H. have consultancy agreements with Mitsubishi Heavy Industries Ltd., Japan. A sponsored research programme is provided by Mitsubishi Heavy Industries Ltd.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.08.003.

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Development of a dose verification system for Vero4DRT using Monte Carlo method

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Vero4DRT is an innovative image-guided radiotherapy system employing a C-band X-ray head with gimbal mechanics. The purposes of this study were to propose specific MC models of the linac head and multileaf collimator (MLC) for the Vero4DRT and to verify their accuracy. For a 6 MV photon beam delivered by the Vero4DRT, a simulation code was implemented using EGSnrc. The linac head model and the MLC model were simulated based on its specification. Next, the percent depth dose (PDD) and beam profiles at depths of 15, 100, and 200 mm were simulated under source-to-surface distance of 900 and 1000 mm. Field size was set to 150×150 mm^2 at a depth of 100 mm. Each of the simulated dosimetric metrics was then compared with the corresponding measurements by a 0.125 cc ionization chamber. After that, intra- and interleaf leakage, tongue-and-groove, and rounded-leaf profiles were simulated for the static MLC model. Meanwhile, film measurements were performed using EDR2 films under similar conditions to simulation. The measurement for the rounded-leaf profile was performed using the water phantom and the ionization chamber. The leaf physical density and abutting leaf gap were adjusted to obtain good agreement between the simulated intra- and interleaf leakage profiles and measurements. For the MLC model in step-and-shoot cases, a pyramid and a prostate IMRT field were simulated, while film measurements were performed using EDR2. For the linac head, exclusive of MLC, the difference in PDD was < 1.0% after the buildup region. The simulated beam profiles agreed to within 1.3% at each depth. The MLC model has been shown to reproduce dose measurements within 2.5% for static tests. The MLC is made of tungsten alloy with a purity of 95%. The leaf gap of 0.015 cm and the MLC physical density of 18.0 g/cm^3, which provided the best agreement between the simulated and measured leaf leakage, were assigned to our MC model. As a result, the simulated step-and-shoot IMRT dose distributions agreed with the film measurements to within 3.3%, with exception of the penumbra region. We have developed specific MC models of the linac head and the MLC in the Vero4DRT system. The results have demonstrated that our MC models have high accuracy.

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