

Stereotactic Body Radiation Therapy for Stage I Non-small Cell Lung Cancer Patients with Chronic Respiratory Insufficiency Requiring Domiciliary Oxygen Therapy

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Abstract. *Background: The efficacy of stereotactic body radiation therapy (SBRT) for patients treated with domiciliary oxygen therapy is not well-known. Patients and Methods: We collected the clinical records of 15 patients with chronic respiratory insufficiency requiring domiciliary oxygen therapy at 1-3 l/min who were treated with SBRT for stage I non-small cell lung cancer. All patients were fixed with a thermoplastic body cast system. SBRT was given in 7-8 fields with an isocenter dose of 40-60 Gy in 4-10 fractions (median, 48 Gy in 4 fractions). Results: The overall 2-year and 5-year survival rates for all patients were 67.4% and 34.7%, while the disease-specific 2-year and 5-year survival rates were 90.0% and 72.0%, respectively. Pulmonary adverse effects were mild in the majority of the patients, although two patients had grade 2 radiation pneumonitis. The oxygen flow required increased slightly at follow-up periods greater than one year, but was still at an acceptable level. Conclusion: SBRT was feasible for patients requiring domiciliary oxygen therapy.*

Although surgical resection remains the present standard-of-care for early-stage non-small cell lung cancer (NSCLC), stereotactic body radiation therapy (SBRT) is a worthwhile alternative. In particular, SBRT for NSCLC is considered for patients who are medically inoperable because of pulmonary co-morbidities or other medical conditions (1-6). If a patient has severe lung function impairment, observation is a viable

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non-surgical option (7) because possible radiation-induced pneumonitis or fibrosis may be critical for such patients. However, medically inoperable patients with untreated early-stage lung cancer have a poor prognosis, with >50% of patients dying of lung cancer (7). Although it has been recently shown that poor pulmonary function does not predict reduced survival or pulmonary function after SBRT (8, 9), the efficacy of SBRT for patients treated with domiciliary oxygen therapy is not been well-known.

In this retrospective study, we investigated the feasibility of using SBRT to treat patients with stage I NSCLC with chronic respiratory insufficiency requiring domiciliary oxygen therapy, particularly in focusing on changes in oxygen flow rate.

Patients and Methods

Patients. From April 2004 to April 2010, 259 patients with early-stage lung cancer were treated with SBRT at the Department of Radiology of Kyushu University Hospital. Out of these, we retrospectively collected the clinical records of 15 patients (5.8%) with chronic respiratory insufficiency, requiring domiciliary oxygen therapy before SBRT. These patients had been treated with 1-3 l/min of oxygen to maintain an oxygen saturation of $\geq 88\%$, as measured by pulse oximetry.

Patients' characteristics are presented in Table I. Pulmonary function tests were performed before treatment, and results are shown in Table II.

Treatment. The SBRT technique has been previously described (10). Briefly, the patients were fixed with a body cast system composed of a thermoplastic body cast, a vacuum pillow, arm and leg support, and a carbon plate (Engineering Systems Co., Matsumoto, Japan). The body cast restricted the chest and abdominal wall movement in order to immobilize the patients during planning and treatment. Respiratory movement was evaluated with an X-ray simulator for the diaphragm and the tumor. CT scans were performed at 2-mm intervals on the day of planning and the first treatment day for verification. CT volume data were transferred to a three-dimensional radiotherapy treatment planning (3D-RTP) system (Eclipse; Varian Medical Systems, Inc., Palo Alto, CA, USA). Seven to eight multi-leaf collimator-shaped static ports of 4- or 6-MV X-rays were selected. To maintain the

Table I. Patients characteristics (n=15).

	Number
Gender	
Male:female	10:5
Age	
Median, range (years)	75 (60-83)
Performance status	
0	0
1	3
2	8
3	3
4	1
Underlying disease	
COPD	12
Post-operative respiratory failure	1
Chronic pulmonary tuberculosis	1
Chronic heart failure	1
Histology	
Squamous cell carcinoma	8
Adenocarcinoma	1
Unknown	6
Clinical stage	
T1aN0M0	7
T1bN0M0	5
T2aN0M0	8
Tumor size	
Median, range (mm)	20 (8-48)

COPD, Chronic obstructive pulmonary disease.

isocenter setup accuracy, a comparison of the anterior, posterior (AP) and lateral digital portal images with the planning AP and lateral digitally reconstructed radiographs was performed daily. The dose was 48 Gy in four fractions to the isocenter for 13 of the tumors, 60 Gy in 10 fractions for one tumor, and 40 Gy in 4 fractions for 1 tumor. The linear accelerator used was a Clinac-21Ex (Varian Medical Systems, Inc.). The median percentage of total lung receiving more than 20 Gy (V20) was 4.8% (range 2.2-8.7%).

Follow up. In principle, patients were assessed after completion of SBRT every four weeks for the first six months, every three months for the next 36 months, and every six months thereafter. Toxicity was graded according to the Common Terminology Criteria Adverse Events version 3 (CTCAE v3.0) (11), and chest CT or x-ray was performed at every follow-up. Oxygen therapy continued after SBRT. Oxygen flow was moderated to achieve target oxygen saturation levels of $\geq 88\%$, based on pulse oximetry.

The overall and disease-specific survival rates were calculated using the Kaplan Meier method. The median follow-up was 23 months (range 6-69 months).

Results

Survival and patterns of failure. The overall 2-year and 5-year survival rates for all patients were 67.4% and 34.7%, while the disease-specific rates were 90.0% and 72.0%, respectively (Figure 1).

Table II. Pulmonary function test values before stereotactic body radiotherapy.

Test	Median, range
FEV ₁ (l)	0.74 (0.38-1.85)
FEV ₁ (%)	43.1 (21.1-77.7)
FVC (l)	1.81 (0.87-3.58)
FVC (%)	63.3 (43.3-116.2)

FEV, Forced expiratory volume in 1 second; FVC, forced vital capacity.

Six patients (40%) had disease recurrence. Three patients (20%) had a local recurrence, and one had a pleural dissemination. Two patients experienced disease relapse in the hilar lymph nodes. No patient developed distant metastases. During the observation time, three patients died of lung cancer; five patients died of concurrent disease (chronic obstructive pulmonary disease (COPD) in four patients, cardiovascular disease in one patient).

Adverse effects. Pulmonary adverse effects were mild in the majority of the patients. Although two patients had grade 2 radiation pneumonitis, medical management including steroid administration improved their symptoms. There were no severe complications for the remaining 13 patients.

Oxygen flow before and after treatment, used to maintain oxygen saturation levels of $\geq 88\%$ are shown in Figure 2. No patient exhibited reduced oxygen flow levels after SBRT. Out of five patients whose oxygen flow levels were evaluated at an interval less than one year after SBRT, only one patient exhibited an increase in the oxygen flow required. In contrast, the necessary oxygen flow increased slightly with follow-up periods of more than one year.

Discussion

To our knowledge, this is the first report of the feasibility of SBRT for patients with stage I NSCLC with chronic respiratory insufficiency requiring domiciliary oxygen therapy. Although the sample size was small, the treatment was well-tolerated and the tumor control rate was high.

Recently, several reports have been published regarding pulmonary function after SBRT for patients with early-stage NSCLC. Henderson *et al.* reported that poor baseline pulmonary function did not predict reduced survival or pulmonary function after SBRT for patients with stage I NSCLC treated with a dose of 60–66 Gy in three fractions (9). Bishawi *et al.* reviewed collected data of stage I-II lung cancer prospectively, and demonstrated that SBRT did not have an effect on forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) at a mean follow-up time of four months (8). In our study, the oxygen flow

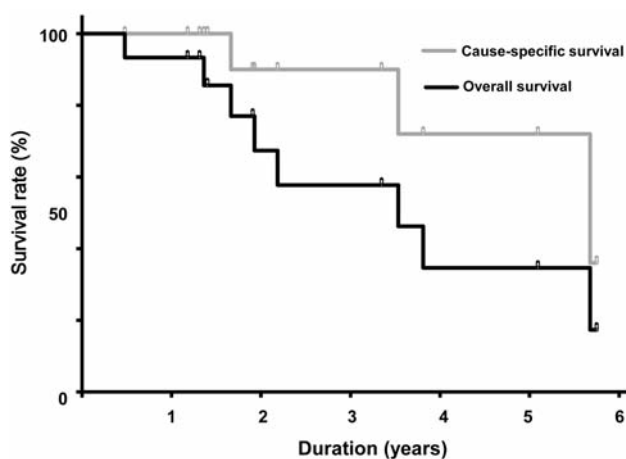


Figure 1. Overall and disease-specific survival rates for 15 patients treated with stereotactic body radiation therapy for stage I non-small cell lung cancer.

required to maintain oxygen saturation levels of $\geq 88\%$ increased slightly in most cases with follow-up periods of more than one year, but was still at acceptable levels.

In this study, we used a median total dose of 48 Gy with four fractions, which is the most frequently used schedule of SBRT for primary lung cancer in Japan (12), although it is smaller than the doses used in the United States (5). We were able to achieve very low V20 values for the lungs, but three patients (20%) had a local recurrence. Multi-institutional phase II trials of SBRT are currently underway in Japan (13), and patient enrollment for these trials has already closed. The results will hopefully validate the efficacy of this schedule of SBRT for NSCLC.

Patients with chronic respiratory insufficiency requiring domiciliary oxygen therapy have a poor prognosis. Crockett *et al.* examined the prognosis of patients treated with domiciliary oxygen therapy for COPD, and demonstrated that the overall crude survival was 75.1%, 51.3%, and 18.9% at 1, 2, and 5 years respectively (14). Therefore, observation alone may be a non-surgical option for patients with severe lung function impairment (7). In our study, five patients (26.7%) died of concurrent diseases, and the overall 2-year and 5-year survival rates for all patients were 67.4% and 34.7%, respectively. However, McGarry *et al.* reported that medically inoperable patients with untreated stage I-II NSCLC have a poor prognosis, with $>50\%$ of patients dying of lung cancer; the median survival time for such patients with no treatment was 14.2 months (7). Therefore, based on the fact that poor pulmonary function does not predict reduced survival or pulmonary function after SBRT (8, 9), SBRT may be a treatment option for patients already requiring domiciliary oxygen therapy.

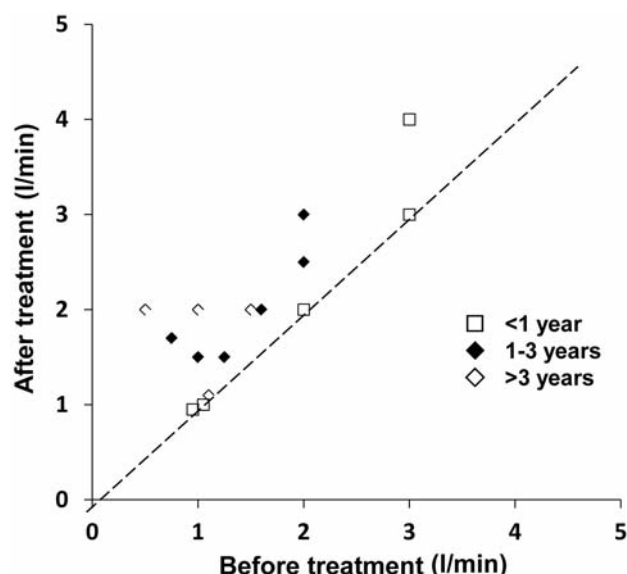


Figure 2. Oxygen flow before and after stereotactic body radiation therapy (SBRT) to maintain oxygen saturation levels of $\geq 88\%$. In one patient, chronic respiratory failure acutely worsened; the oxygen flow levels necessary for this acute-on-chronic form of respiratory failure were excluded. The plots are divided into three categories according to the period between SBRT and the follow-up evaluation of oxygen flow (<1 year, 1-3 years, >3 years). The median follow-up period was 1.2 years (range 0.1-5.7 years).

In this retrospective study, SBRT proved feasible for patients requiring domiciliary oxygen therapy. However, the number of patients was small, and this finding is in contrast to the situation after conventionally fractionated radiotherapy, where COPD and reduced FEV1 were associated with severe acute radiation pneumonitis (15). The exact benefit of SBRT for patients with domiciliary oxygen therapy may be elucidated by larger prospective observational studies.

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