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Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the Japanese experience

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Abstract Stereotactic body radiation therapy is a new treatment modality for early-stage non-small-cell lung cancer, and is being intensively investigated in the United States, the European Union, and Japan. We started a feasibility study of this therapy in July 1998, using a stereotactic body frame. The eligibility criteria for primary lung cancer were: (1) solitary tumor less than 4 cm; (2) inoperable, or the patient refused operation; (3) histologically confirmed malignancy; (4) no necessity for oxygen support; (5) performance status equal to or less than 2, and (6) the tumor was not close to the spinal cord. A total dose of 48 Gy was delivered in four fractions in 2 weeks in most patients. Lung toxicity was minimal. No grade II toxicities for spinal cord, bronchus, pulmonary artery, or esophagus were observed. Overall survival for 29 patients with stage IA, and 14 patients with stage IB disease was 87 % and 80 %, respectively. No local recurrence was observed in a follow-up of 3–50 months. Regional lymph node recurrence developed in 1 patient, and distant metastases developed in 4 patients. We retrospectively analyzed 241 patients from 13 Japanese institutions. The local recurrence rate was 20% when the biological equivalent dose (BED) was less than 100 Gy, and 6.5% when the BED was over 100 Gy. Overall survival at 3 years was 42% when the BED was less than 100 Gy, and 46% when it was over 100 Gy. In tumors which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients. Long-term results, in terms of local control, regional recurrence, survival, and complications, are not yet evaluated. However, this treatment modality is highly expected to be a standard treatment for inoperable patients, and it may be an alternative to lobectomy for operative patients. A prospective trial, which is now ongoing, will, answer these questions.

Key words Non-small-cell lung cancer · Stereotactic radiation therapy

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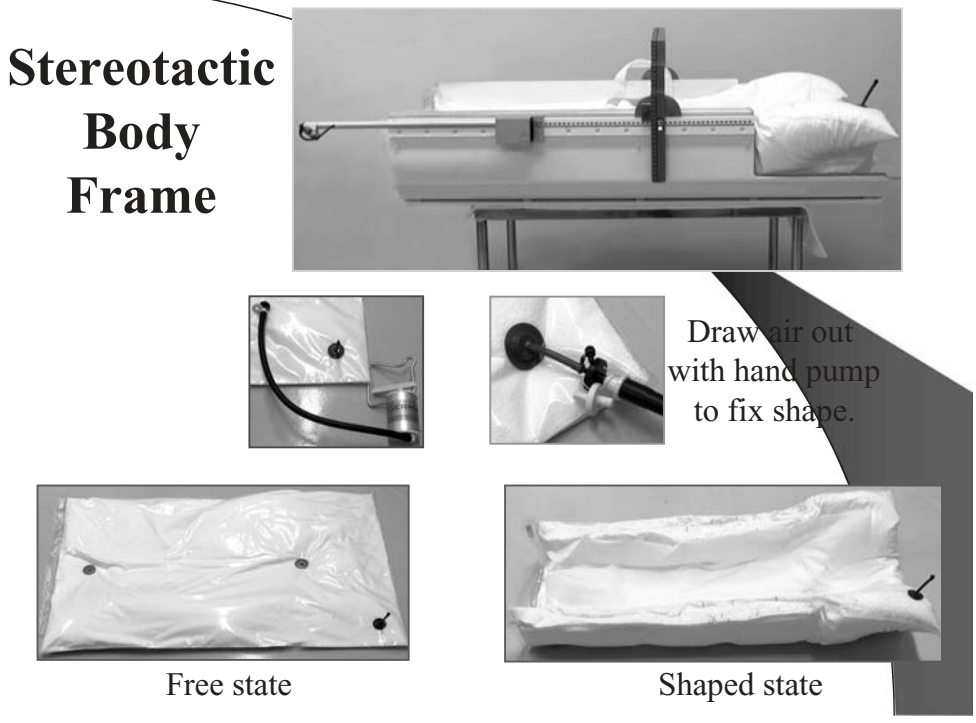
Stereotactic body radiation therapy for early-stage non-small-cell lung cancer (NSCLC) is a new treatment modality, and Japan is one of the leading countries in using three-dimensional radiation therapy. The background of this treatment is the great success of stereotactic irradiation for intracranial tumors, in terms of the technologies used, quality assurance (QA) and quality control (QC), and clinical outcomes. That is, a high local control rate has been shown with minimal toxicities. The success has caused much interest in the application of this treatment for extracranial regions. Why use stereotactic radiation irradiation (SRI) for lung cancer? The number of patients detected at an early stage has been increased by screening examinations. Accordingly, the number of older patients with early-stage lung cancer who are not amenable to operation has increased, and the clinical results of conventional radiation therapy are not satisfactory. In regard to technical aspects, the application of this new technique is easier for lung cancer, because it is visible on fluoroscopy and because normal tissue toxicities to radiation are relatively well described compared with other normal tissues.

For the management of stage I NSCLC, surgical resection alone is the standard treatment, and lobectomy is generally accepted as the optimal surgical procedure. Survival outcomes of surgical treatment have recently been reported by the Japanese Association for Chest Surgery. According to these data, the overall survival of patients in clinical stage IA is 81.3% at 3 years, and 71.5% at 5 years, and that of patients in clinical stage IB is 62.9% at 3 years, and 50.1% at 5 years.

What about radiation therapy alone for stage I NSCLC? As is known, radiation therapy has been used primarily for those patients who are not considered to be surgical

Fig. 1. Stereotactic body frame



candidates; that is, those who refuse surgical intervention, and those who are medically inoperable. The reported 5-year survival rate is around 8%–27%, and is not satisfactory. Several prognostic factors, such as T stage and total dose, have been reported, and doses higher than 65 Gy did show higher survival rates, which can be a rationale for dose escalation.

However, there remain several problems with stereotactic radiation therapy for lung cancer compared to its use in intracranial tumors. (1) How should the body be fixed with high accuracy? (2) How do we cope with the movement of the tumor caused by respiration? (3) What are the optimal treatment regimens? (4) Toxicities to normal tissue caused by large-fraction size irradiation have not been examined. (5) Fractionated stereotactic radiation therapy is considered to be appropriate for lung cancer, but the optimal fractionation scheme has not yet been decided.

We started a feasibility study of this stereotactic body radiation therapy for small lung tumors in July 1998. The stereotactic body frame shown in Fig. 1 was used. The patient was placed in this body frame, and immobilized. We used both X-ray and computed tomography (CT) simulators, with the same table, to improve the accuracy of the set-up. The movement of the tumor caused by respiration was estimated using fluoroscopy, and if that movement in the craniocaudal (CC) direction was greater than 8 mm, a diaphragm control was employed to suppress the movement of the chest wall. Then the three-dimensional treatment planning was carried out. We verified the tumor location in each treatment. As regards the movement of the tumor caused by respiration, the largest movement was in the CC direction. It was 0–22 mm, and movement of less than 15 mm occurred in 90% of all tumors. When that movement was over 20 mm, we used the diaphragm control, and, with the use of this device, the movement of the respiration decreased significantly. The set-up error with patients was greater than 3 mm in at least one direction. Patient repositioning had to be undertaken in 21.6% of all treatments.

The eligibility criteria for primary lung cancer were as follows: solitary tumor less than 4 cm; inoperable, or the patient refused operation; histologically confirmed malignancy; no necessity for oxygen support; performance status equal to or less than 2; and the tumor was not close to spinal cord.

The eligibility criteria for metastatic lung cancer were as follows: one to two tumors less than 4 cm each, primary tumor controlled, no other metastasis, no necessity for oxygen support, performance status less than 2, and tumors not close to the spinal cord. Between July 1998 and September 2002, a total of 70 patients received this treatment modality. Their ages ranged from 70 to 87 years, with a mean of 71 years. Fifty patients had primary tumors, and 20 patients had secondary tumors. Seven of the 20 secondary tumors were solitary. In 57 tumors, a total dose of 48 Gy was delivered, in four fractions in 2 weeks. Ten tumors were treated with a total dose of up to 60 Gy. In the initial three tumors, a total dose of 40 Gy was administered.

We examined the toxicity by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2. Lung toxicity was grade II in 4%, grade I in 92 %, and grade 0 in 4 %. No grade II toxicities for spinal cord, bronchus, pulmonary artery, or esophagus were observed. The clinical course of 1 patient who responded well to this treatment is shown in Fig. 2.

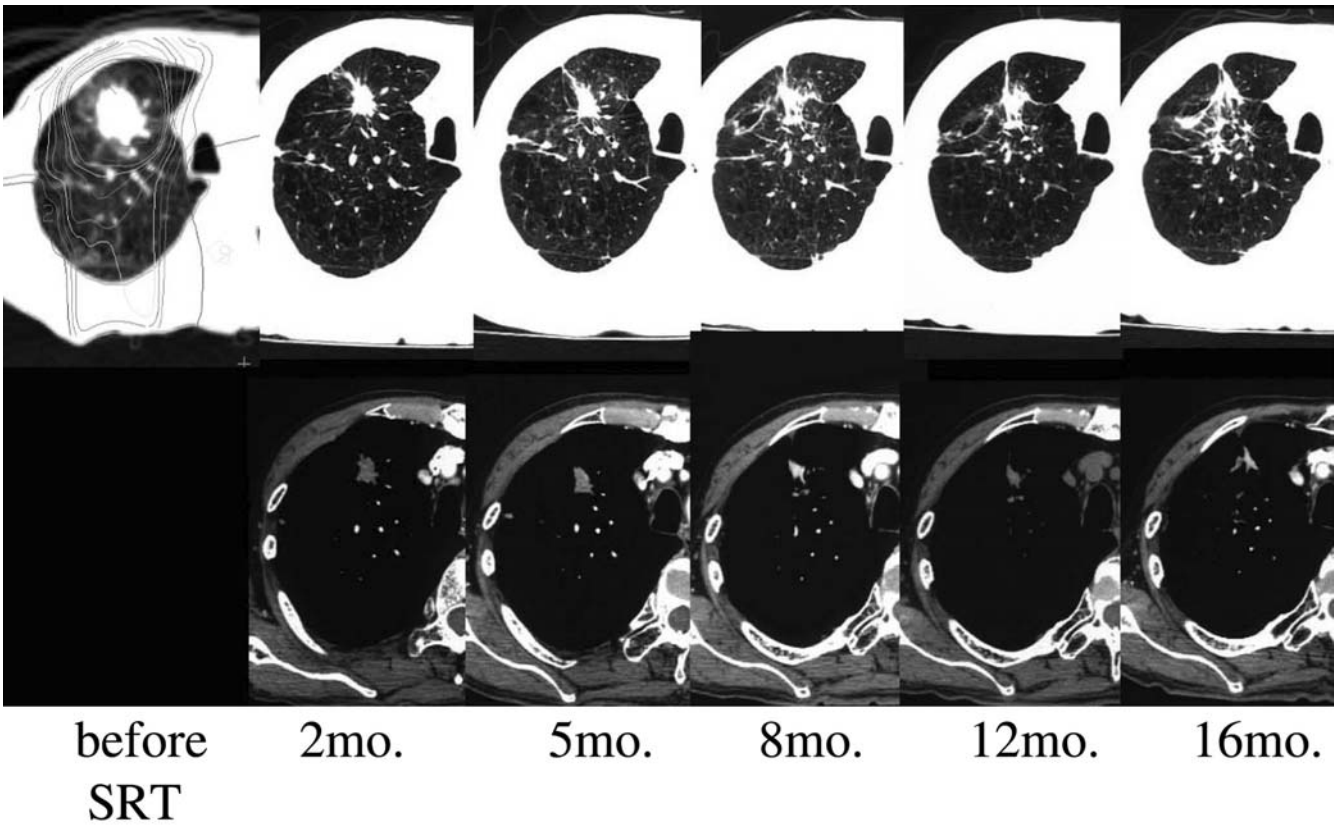


Fig. 2. Clinical course of a patient treated with stereotactic radiation therapy (*SRT*). The patient, a 71-year-old man, had primary lung cancer (squamous cell carcinoma; T2N0M0). *mo.*, months

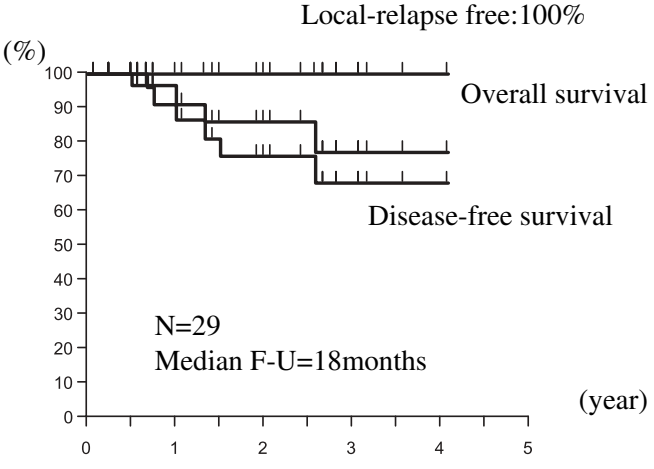


Fig. 3. Survival curves of patients with stage IA: T1N0M0 non-small-cell lung cancer (NSCLC) treated with SRT. *F-U*, follow-up

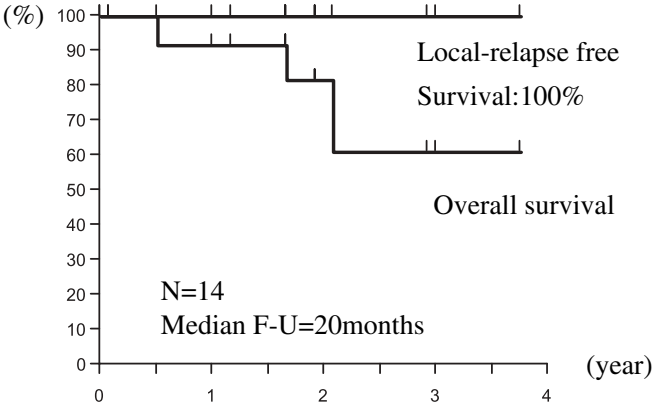


Fig. 4. Survival curves of patients with stage IB: T2N0M0 NSCLC treated with SRT

Survival curves for 29 patients with stage IA, T1N0M0 NSCLC are shown in Fig. 3. No local recurrence was observed in a follow-up of 6–50 months (median, 18 months). Regional lymph node recurrence developed in 1 patient, and bone metastases developed in 2 patients.

Survival curves for 14 patients with stage IB, T2N0M0 NSCLC are shown in Fig. 4. No local recurrence was observed at a follow-up of 3–45 months (median, 20 months). Liver and bone metastases developed in 1 patient each.

We retrospectively analyzed data from 241 patients from 13 Japanese institutes. Their ages ranged from 35 to 92 years, with a median of 76 years. Histology was sqnamous cell carcinoma in 106 patients, adenocarcinoma in 102 patients, and "others" in 33 patients. As regards clinical stage, 153 patients were stage IA, and 88 patients were stage IB. Tumor diameter ranged from 7 to 58 mm, with a median of 28 mm. One hundred and sixty-one patients were inoperable, and 80 patients were operable. The biological equivalent dose (BED) was 57–180 Gy, with a median of 108 Gy.

Lung toxicities were minimal, with grade II in only 2.2 % and no grade III. Local response to the treatment was complete response (CR) in 23%, and partial response (PR) in 62%. The local recurrence rate was 20% when BED was less than 100 Gy, and 6.5% when BED was over 100 Gy, at follow-up periods of 4–72 months (median, 18 months). Overall survival at 3 years was 42% when BED was less than 100 Gy, and 46% when BED was over 100 Gy. For tumors which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients.

We are going to start a prospective multiinstitutional phase II study with a grant from the Health and Welfare Ministry of Japan. The target is stage IA NSCLC. A total dose of 48 Gy in four fractions will be delivered in 4 to 8 days. Entry of 150 patients from 15 institutes in 3 years is expected. The primary endpoint is survival. This is the first trial of the Radiation Therapy Study Group (RTSG), which is the newest group in the Japanese Clinical Oncology Group (JCOG). We hope that this trial will provide more conclusive data on stereotactic body irradiation for early-stage NSCLC.

In summary, regarding stereotactic body radiation therapy for early-stage NSCLC, (1) long-term results, in terms of local control, regional recurrence, survival, and complications are not yet evaluated. (2) Technologies to cope with tumor movement, gauging tracking, need to be improved. (3) This treatment modality is highly expected to be a standard treatment for inoperable patients, and may be an alternative to lobectomy for operative patients. A prospective trial ongoing is expected to resolve these matters.