Stereotactic Body Radiotherapy Using a Radiobiology-Based Regimen for Stage I Non–Small-Cell Lung Cancer

Five-Year Mature Results

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Introduction: Although the protocol of 48 Gy in four fractions over 4 days has been most often employed in stereotactic body radiotherapy (SBRT) for stage I non–small-cell lung cancer in Japan, higher doses are necessary to control larger tumors, and interfraction intervals should be longer than 24 hours to take advantage of reoxygenation. We report the final results of our study testing the following regimen: for tumors less than 1.5, 1.5–3, and greater than 3 cm in diameter, 44, 48, and 52 Gy, respectively, were given in four fractions with interfraction intervals of greater than or equal to 3 days.

Methods: Among 180 histologically proven patients entered, 120 were medically inoperable and 60 were operable. The median patient age was 77 years (range, 29–89). SBRT was performed with 6-MV photons using four noncoplanar and three coplanar beams. Isocenter doses of 44, 48, and 52 Gy were given to four, 124, and 52 patients, respectively.

Results: The 5-year overall survival rate was 52.2% for all 180 patients and 66% for 60 operable patients. The 5-year local control rate was 86% for tumors less than or equal to 3 cm (44/48 Gy) and 73% for tumors greater than 3 cm (52 Gy; $p = 0.076$). Grade greater than or equal to 2 radiation pneumonitis developed in 13% (10% for the 44/48-Gy group and 21% for the 52-Gy group; $p = 0.056$). Other grade 2 toxicities were all less than 4%.

Conclusions: Our first prospective SBRT study yielded reasonable local control and overall survival rates and acceptable toxicity. Refinement of the protocol including dose escalation may lead to better outcome.

Key Words: Lung cancer, Stereotactic body radiotherapy, Stage I, Dose, Fractionation, Reoxygenation.

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Stereotactic body radiotherapy (SBRT) is now the first choice of treatment for medically inoperable patients with stage I non–small-cell lung cancer (NSCLC) and operable patients who refuse surgery.[1–3] Recently reported results suggest that SBRT and surgery yield nearly equivalent outcome.[4–7] Owing to the relatively short history, however, the vast majority of previously published data of SBRT, including those in very recent publications, are middle-term 3-year data.[3,7–10] To compare the two modalities, however, longer-term results, at least 5-year data, are necessary.

In our previous publication, we reported 3-year results of a prospective SBRT study involving three institutions for histologically confirmed stage I NSCLC.[11] Total doses were 44–52 Gy in four fractions; larger tumors were treated with higher doses, and interfraction intervals of at least 72 hours were adopted to efficiently utilize the reoxygenation phenomenon. The rationale for this protocol was discussed in detail previously.[11] Nearly 6 years have passed since the last patient was treated with this protocol, so we analyzed the long-term results.

PATIENTS AND METHODS

Eligibility Criteria and Patients

Approval was obtained from the institutional review boards and informed consent was obtained from all patients. Eligibility criteria were: (1) histologically confirmed stage I NSCLC diagnosed by chest and upper abdomen computed tomography (CT), brain MRI, and bone scintigraphy or fluorodeoxyglucose positron emission tomography (FDG-PET); (2) greatest tumor diameter less than or equal to 5 cm; (3) World Health Organization performance status less than or equal to two or performance status three when its cause was not a pulmonary disease; (4) no prior therapy and no concurrent malignancy; and (5) arterial oxygen pressure greater than or equal to 60 mmHg and forced expiratory volume in 1 second greater than or equal to 700 ml.

Between May 2004 and November 2008, 180 eligible patients entered the study. All completed the planned treatment. Patients were deemed medically inoperable when they had a poor pulmonary function (the ratio of forced expiratory volume in 1 second to forced vital capacity less than 60% and/

or the percent vital capacity less than 75%) or other debilitating conditions that preclude surgery. The patient and tumor characteristics are shown in Table 1. Ages ranged from 29 to 89 years, with a median of 77 years. The longest tumor diameter ranged from 12 to 50 mm, with a median of 27 mm. The tumor location was classified into central or peripheral according to the Radiation Therapy Oncology Group criteria.

Treatment and Evaluation

Our treatment methods were previously described.[11,12] The visible gross tumor volume on CT during three phases (under normal breathing, and with breath holding during the expiratory and inspiratory phases) was superimposed to represent the internal target volume (ITV). The planning target volume (PTV) margin for the ITV was 5 mm in the lateral and anteroposterior directions and 10 mm in the craniocaudal direction.

SBRT was delivered with four fractions using static three coplanar and four noncoplanar 6-MV photon beams. In principle, respective fractions were delivered at intervals of greater than or equal to 72 hours, but owing to national holidays, patient schedule convenience, and machine availability, the actual overall treatment period was 9–21 days (median, 12 days); in 92% of the patients, it was 10–14 days. The total dose at the isocenter was 44 Gy for tumors with a maximum diameter less than 1.5 cm, 48 Gy for tumors of 1.5–3 cm, and 52 Gy for those greater than 3 cm. The dose calculation algorithm was pencil beam convolution with Batho power law correction. It was recommended to cover 95% of the PTV with at least 90% of the isocenter dose, and, in all cases, 95% of the PTV received at least 80% of the prescribed dose. Consequently, 95% of the ITV was covered with greater than or equal to 94% of the prescribed dose in all but one case. Dose constraints for normal tissues were: (1) volume of the lung receiving 20 Gy, less than or equal to 20%; (2) 40 Gy for less than 1 cc of the pulmonary artery and esophagus; (3) 36 Gy for less than 10 cc of the stomach; and (4) maximum cord dose less than 18 Gy. Central and peripheral lesions were treated in the same way.

Chest and upper abdominal CT was performed at 2-month interval until 6 months, and every 2–4 months thereafter. FDG-PET was performed whenever necessary. Local recurrence was diagnosed by serial CT examinations combined with FDG-PET and/or biopsy (two patients). Pleuritis carcinomatosa unaccompanied by local recurrence was regarded as distant metastasis. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 3. Follow-up after 5 years was conducted at the discretion of the attending radiation oncologist.

Statistical Analysis

For survival and failure-free rate analyses, the Kaplan–Meier method (from SBRT start) and log-rank test were employed. To evaluate isolated lymph node (regional) failure, patients were censored when they developed local recurrence or pulmonary metastasis. To evaluate isolated distant metastasis, patients were censored when they developed local and/or regional recurrence. The local status was followed until death and patients were not censored even when they developed regional or distant metastasis. Multivariate analysis of potential prognostic factors was carried out using the Cox proportional hazards model. In doing multivariate analysis, patients were divided into two groups and all the parameters were entered as dichotomous variables. Incidences of adverse events were compared using Fisher's exact and χ^2 tests. Statistical softwares used were StatView version 5.0 (SAS Institute, Cary, NC) and HALWIN (Gendaisuugakusha, Kyoto, Japan).

RESULTS

Efficacy

The median follow-up period was 52.5 months for all patients and 72.5 months for living patients. Only one patient

TABLE 1. Patient and Tumor Characteristics

		Stage IA		Stage IB
Characteristic	**All**	**44 Gy**	**48 Gy**	**52 Gy**
Maximum tumor diameter (cm)	1.2–5.0	<1.5	1.5–3	>3
Patient number	180	4	124	52
Age (years)				
Range (median)	29–89 (77)	67–81 (74)	55–87 (77)	29–89 (78)
Sex				
Men/women	123/57	2/2	79/45	42/10
Performance status				
0/1/2/3	87/69/21/3	3/0/1/0	63/47/13/1	21/22/7/2
Operability				
Operable/inoperable	60/120	2/2	43/81	15/37
Histology				
Adeno/squamous/NSCLC	104/60/16	4/0/0	74/37/13	26/23/3
Tumor location				
Center/periphery	35/145	0/4	23/101	12/40

Adeno, adenocarcinoma; squamous, squamous cell carcinoma; NSCLC, unclassified non–small-cell lung cancer.