Long-Term Outcome of Proton Therapy and Carbon-Ion Therapy for Large (T2a–T2bN0M0) Non–Small-Cell Lung Cancer

Hiromitsu Iwata, MD, PhD,†‡ Yusuke Demizu, MD, PhD,† Osamu Fujii, MD, PhD,† Kazuki Terashima, MD, PhD,† Masayuki Mima, MD,† Yasue Niwa, MD,† Naoki Hashimoto, MD, PhD,† Takashi Akagi, PhD,§ Ryohei Sasaki, MD, PhD,|| Yoshio Hishikawa, MD, PhD,† Mitsuyuki Abe, MD, PhD,† Yuta Shibamoto, MD, PhD,* Masao Murakami, MD, PhD,¶ and Nobukazu Fuwa, MD, PhD†*

Introduction: Although many reports have shown the safety and efficacy of stereotactic body radiotherapy (SBRT) for T1N0M0 non–small-cell lung cancer (NSCLC), it is rather difficult to treat T2N0M0 NSCLC, especially T2b (>5 cm) tumor, with SBRT. Our hypothesis was that particle therapy might be superior to SBRT in T2 patients. We evaluated the clinical outcome of particle therapy for T2a/bN0M0 NSCLC staged according to the 7th edition of the International Union Against Cancer (UICC) tumor, node, metastasis classification.

Methods: From April 2003 to December 2009, 70 histologically confirmed patients were treated with proton (n = 43) or carbon-ion (n = 27) therapy according to institutional protocols. Forty-seven patients had a T2a tumor and 23 had a T2b tumor. The total dose and fraction (fr) number were 60 (Gray equivalent) GyE/10 fr in 20 patients, 52.8 GyE/4 fr in 16, 66 GyE/10 fr in 16, 80 GyE/20 fr in 14, and other in four patients, respectively. Toxicities were scored according to the Common Terminology Criteria for Adverse Events, Version 4.0.

Results: The median follow-up period for living patients was 51 months (range, 24–103). For all 70 patients, the 4-year overall survival, local control, and progression-free survival rates were 58% (T2a, 53%; T2b, 67%), 75% (T2a, 70%; T2b, 84%), and 46% (T2a, 43%; T2b, 52%), respectively, with no significant differences between the two groups. The 4-year regional recurrence rate was 17%. Grade 3 pulmonary toxicity was observed in only two patients.

Conclusion: Particle therapy is well tolerated and effective for T2a/bN0M0 NSCLC. To further improve treatment outcome, adjuvant chemotherapy seems a reasonable option, whenever possible.

*Department of Radiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; †Department of Radiology, Hyogo Ion Beam Medical Center, Tatsuno, Japan; ‡Department of Radiation Oncology, Nagoya Proton Therapy Center, Nagoya City West Medical Center, Nagoya, Japan; §Department of Radiation Physics, Hyogo Ion Beam Medical Center, Tatsuno, Japan; ||Divisionof Radiation Oncology, Kobe University Graduate School of Medicine, Kobe, Japan; and ¶Center for Radiation Oncology, Dokkyo Medical University, Tochigi, Japan.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Hiromotsu Iwata, MD, PhD, Department of Radiology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467–8601, Japan. E-mail: h-iwa-ncu@nifty.com

ISSN: 1556-0864/13/0806-0726

Key Words: Proton therapy, Carbon-ion therapy, Non–small-cell lung cancer, T2a/2b, 7th edition International Union Against Cancer, tumor, node, metastasis classification.

(*J Thorac Oncol.* 2013;8: 726-735)

Tumor size is an important factor influencing the local control probability by radiation therapy. Generally, as the tumor becomes larger, the clonogenic cell number, hypoxic fraction, and quiescent cell fraction increase,[1,2] leading to elevated resistance to photon radiotherapy. However, biological and clinical evidences suggest that particle therapy may be useful for relatively large but localized tumors, such as hepatocellular carcinoma larger than 5 cm.[3,4] Therefore, stage I non–small-cell lung cancer (NSCLC) larger than 3 cm in diameter (T2) may also be a good indication of particle therapy.

The 7th edition of the tumor node metastasis (TNM) staging system for NSCLC proposed by the International Association for the Study of Lung Cancer and approved by the International Union Against Cancer and the American Joint Committee on Cancer has been in use since 2010.[5] The changes between the 6th and 7th editions were the new cutoff sizes for primary tumors, subdivisions of the T and M categories, and reclassification of malignant pleural effusions and separate tumor nodules. As for the T category, T1 tumors were subdivided into T1a (≤ 2 cm) and T1b (> 2 to ≤ 3 cm), T2 tumors into T2a (> 3 to ≤ 5 cm) and T2b (>5 to ≤7 cm), and T2 tumors more than 7 cm were reclassified as T3.[6,7] In addition, T2bN0M0 cases were classified from stage IB to stage IIA. The proposed changes to the 7th edition of the TNM classification of NSCLC emphasize the prognostic relevance of tumor size much more than in previous editions. Tumor size correlated with the prognosis of patients clinically staged as N0. In recent years, stereotactic body radiotherapy (SBRT) has been gaining popularity worldwide as a new treatment modality for stage I NSCLC.[8,9] Many reports have shown that SBRT is safe and effective for T1N0M0 NSCLC. However, it is difficult to treat T2N0M0 NSCLC, especially T2b (>5 cm), with SBRT.[10,11] Compared with conventional radiation, SBRT produces superior dose distribution at the

target while simultaneously reducing the irradiated normal tissue volume. However, with an increase in tumor size, local control becomes poorer and the risk of high-grade radiation pneumonitis (RP) increases. Previous reports have shown a correlation between severe RP and dose-volume parameters such as the mean lung dose.[12] Obviously, with the increase in tumor size, the dose to normal lung increases and the risk of RP becomes high. Therefore, particle therapy is considered to be indicated for larger lesions.

We previously reported the results of proton therapy (PT) and carbon-ion therapy (CIT) for 80 stage I NSCLC patients, including 38 T2 cases, staged according to the 6th edition of TNM classification, between April 2003 and April 2007 at Hyogo Ion Beam Medical Center (Tatsuno, Japan).[13] In our previous study, particle therapy was safe and effective for both T1N0M0 and T2N0M0 NSCLC. Particle therapy can preserve the homogeneity to a target and lower the low-dose region in the lung and the mean lung dose compared with SBRT using photons.[14] Moreover, particle therapy, especially CIT, has high relative biological effectiveness and an advantage against hypoxic tumor cells in terms of a lower oxygen enhancement ratio. Therefore, it was hypothesized that particle therapy might be superior to SBRT in T2 patients. In the present study, we restaged the patients with early NSCLC based on the 7th edition of the TNM classification and analyzed the clinical outcome of particle therapy for T2a and T2bN0M0 NSCLC.

MATERIALS AND METHODS

Study Design and Patient Eligibility and Characteristics

Particle therapy was performed in clinical studies based on protocols determined by the particle therapy committee of Hyogo prefecture and approved by the Institutional Review Board. Early clinical results of the study were reported previously.[13] The eligibility criteria for the clinical studies were as follows: (1) histologically confirmed primary NSCLC staged as T1N0M0 or T2N0M0 by the 6th UICC TNM classification using computed tomography (CT) scans, bone scans, brain magnetic resonance imaging, and 18-fluoro-deoxyglucose-positron emission tomography; (2) medical inoperability or refusal of surgical resection; (3) World Health Organization performance status of 2 or less; (4) no history of lung cancer; (5) no previous chest radiotherapy or chemotherapy; and (6) written informed consent. Of the 139 patients treated between April 2003 and December 2009, 70 patients, restaged as T2aN0M0 or T2bN0M0 according to the 7th UICC classification, were the subject of this study. Forty-seven patients had a T2a tumor and 23 had a T2b tumor. No tumors lesser or equal to 3 cm, in their greatest dimension, invaded the main bronchus (< 2 cm from the carina) or the visceral pleura, and no tumors were associated with atelectasis or obstructive pneumonitis extending to the hilar region. Therefore, all tumors had a diameter of more than 3 cm. Fifty-one patients were men and 19 were women. Patient age ranged from 57 to 92 years (median, 75 years). Forty patients were medically inoperable and 30 refused surgery. Patient and tumor characteristics are summarized in Table 1.

TABLE 1. Patient and Tumor Characteristics

Characteristics	T2aN0M0	T2bN0M0	Total
No. of patients	47	23	70
Age (yr)[a]	75 (57–87)	76 (60–92)	75 (57–92)
Sex male / female	31 / 16	20 / 3	51 / 19
PS 0 / 1 / 2	25 / 16 / 6	8 / 10 / 5	33 / 26 / 11
Refusal / medical inoperability	23 / 24	7 / 16	30 / 40
Pulmonary comorbidity	14	10	24
Longest tumor diameter (mm)[a]	38 (31–48)	56 (51–70)	41 (31–70)
Histology AD / SQ / other	27 / 14 / 6	12 / 7 / 4	39 / 21 / 10
Smoking history (+ / −)	33 / 14	19 / 4	52 / 18
Peripheral / central	42 / 5	18 / 5	60 / 10

[a] Median (range).
PS, performance status; AD, adenocarcinoma; SQ, squamous cell carcinoma.

Treatment Protocols and Treatment Systems

The treatment protocols have been evaluated by the committee and subjected to minor modifications whenever necessary. Our treatment protocols, used from April 2003 to 2007, were described in detail previously.[13] In brief, three treatment protocols were prepared by referring to those of other facilities. The first PT protocol, 80 Gray equivalent (GyE) delivered in 20 fractions, was set on the basis of earlier experiences at the National Cancer Center East (Kashiwa, Japan). After evaluating acute and medium-term toxicity in 15 patients, the second PT protocol, 60 GyE delivered in 10 fractions based on the protocol of Proton Medical Research Center (Tsukuba, Japan), was started to shorten the overall treatment time. The CIT protocol was 52.8 GyE delivered in four fractions, based on the National Institute of Radiological Sciences protocol (Chiba, Japan). After this period, the following new protocols were used. In May 2007, a revision of one of the PT protocols (from 60 to 66 GyE in 10 fractions) was started after 37 patients, with stage I NSCLC, had accrued at the time of a minor update to the system (improvement in the respiratory gating system) after we evaluated the toxicity and efficacy of this protocol (at least 35 patients) in our previous study.[13] In January 2008, a new CIT protocol, 66 GyE in 10 fractions was started on the basis of our previous results.[13] The previous CIT protocol, 52.8 GyE delivered in four fractions, was stopped in January 2009, taking into consideration late toxicities of hypofractionation. As an exception, three patients were treated with other fractionation schedules, considering the proximity to risk organs in this study. The dose-fractionation schedules used are shown in Table 2. All radiation doses were delivered to the center of the tumor. All irradiation was given once a day, 5 days a week. The policy for selecting beam type was based partly on the availability of the particle beams; between April 2004 and March 2005, only PT was available. In April 2005, CIT became available, and thereafter, treatment plans for both PT and CIT were made for every patient. Then, the dose-volume histograms were compared, and a more suitable modality (PT or CIT) was determined and was then actually used for each patient. Chemotherapy was not included in these protocols. Our treatment systems at Hyogo Ion Beam Medical Center have been described in detail previously.[13,15] A

