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

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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.

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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

TABLE 2. Treatment Characteristics and Dose-Volume Analyses

Characteristics	T2aN0M0	T2bN0M0	Total
No. of patients	47	23	70
Proton dose (GyE/Fr)			
80 /20	10	4	14
60 /10	15	5	20
66 /10	5	3	8
70.2 /26	0	1	1
Carbon dose (GyE/Fr)			
52.8/4	11	5	16
66 /10	4	4	8
68.4 /9	2	1	3
Number of portals 1 / 2 / 3 / 4	11 / 24 / 11 / 1	3 / 14 / 5 / 1	14 / 38 / 16 / 2
PTV volume (cm^3)[a]	93.4 (43.0–178.3)	178.7 (81.1–315.2)	105.0 (43.0–315.2)
PTV coverage (%)	88.0 (36.0-98.0)	92.0 (38.0–99.0)	91.0 (36.0–99.0)
V20 Lung[b] (%)[a]	9.8 (4.9–21.0)	11.2 (5.0–24.1)	9.8 (4.9–24.1)
V5 Lung[b] (%)[a]	13.9 (6.1–27.8)	14.3 (8.1–33.0)	14.0 (6.1–33.0)

[a] Median (range).
[b] Percentage of lung volume receiving 20 (5) GyE or a higher dose.
GyE, Gray equivalent; Fr, fractions; PTV, planning target volume.

respiratory gating irradiation system developed at the National Institute of Radiological Sciences in Chiba[16] was used until April 2007, and AZ-733 (Anzai Medical Co. Ltd., Tokyo, Japan) was used from May 2007. The radiation treatment plans were performed using a CT-based three-dimensional treatment planning system (FOCUS-M; CMS, St. Louis and Mitsubishi Electric Corporation, Tokyo, Japan] until April 2008 and Xio-M [CMS, St. Louis, USA and Mitsubishi Electric Corporation, Tokyo, Japan] from May 2008). A collision detection system (Mitsubishi Electric Corporation, Tokyo, Japan) was improved to shorten the air gap from February 2010. All radiation doses were prescribed to the center of the tumor (isocenter). Initially, the clinical target volume was covered with at least 95% of the isocenter dose, and the goal of planning target volume coverage was also 95%. From May 2007, the planning target volume coverage was set as at least 95%, similar to photon SBRT studies. Dose-volume analysis results are summarized in Table 2.

Follow-Up Examinations and Statistical Analysis

After particle therapy, the patients were followed with physical examinations, diagnostic imaging, and blood tests, including tumor marker examinations. Follow-up studies and evaluation of tumor recurrence have been described in detail previously.[13] Toxicities were initially scored with the Common Terminology Criteria for Adverse Events, version 3.0, but were reclassified according to version 4.0. Grade 2 RP was defined as symptomatic, requiring medical management, but not interfering with activities of daily living. Grade 3 RP was defined as severely symptomatic, requiring oxygen administration and interfering with activities of daily living. Statistical analyses were carried out with SPSS 11.0J (SPSS Japan Inc., Tokyo, Japan) and StatView version 5 (SAS Institute Inc., Cary, NC). The overall survival, local control, progression-free survival, and regional recurrence rates were calculated using the Kaplan–Meier method. Differences between pairs of Kaplan–Meier curves were examined by the log-rank test. A p value less than 0.05 was considered statistically significant.

RESULTS

Dose Distribution

Figure 1 shows four examples of particle therapy planning for T2a NSCLC. Doses of the skin and ribs were relatively high, especially when treated with one portal, because of relatively high entry doses from the spread-out Bragg peaks (SOBP).

Survival and Local Control

All patients were observed for a minimum of 2 years or until death. The median duration of follow-up was 51 months (range, 24–103) for living patients and 44 months (range, 4–103) for all patients. For all 70 patients, the 4-year overall survival, local control, and progression-free survival rates were 58% (95% confidence interval [CI]: 46%–70%; T2a: 53%; T2b: 67%), 75% (95% CI: 63%–86%; T2a: 70%; T2b: 84%), and 46% (95% CI: 33%–59%; T2a: 43%; T2b: 52%), respectively (Fig. 2). The projected 5-year rates were 48%, 64%, and 36%, respectively. Local recurrence occurred in 19 patients (T2a: 13; T2b: 6); four patients with T2a disease and five patients with T2b developed local recurrence after 2 years. Eleven patients (9 with T2a and 2 with T2b disease) developed hilar and/or mediastinal lymph node metastases, and two of them also had lung metastases. The rate for developing regional lymph node recurrence was 15% at 3 years and 17% at 4 years. In addition, another 12 patients developed distant metastases. There were no significant differences according to the T stage. There were no isolated nodal failures in the 10 patients with a central legion.

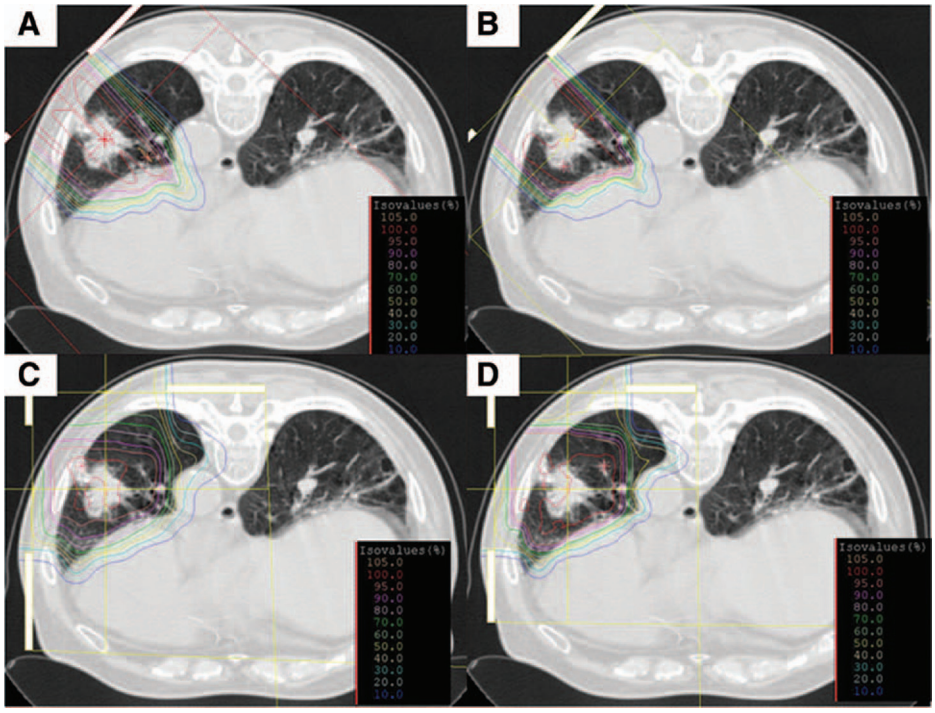

FIGURE 1. Example of particle therapy planning for T2a non–small-cell carcinoma. *A*, Proton therapy with one portal; (*B*), carbon-ion therapy with one portal; (*C*), proton therapy with coplanar two portals; and (*D*), carbon-ion therapy with coplanar two portals.

Figure 3 shows overall survival, local control, and progression-free survival rates according to medical operability for all patients. Operable patients had better survival rates than medically inoperable patients ($p = 0.018$), although local control and progression-free survival did not differ significantly. For the 30 operable patients treated with PT or CIT, the 4-year overall survival, local control, and progression-free survival rates were 72%, 73%, and 46%, respectively. The projected 5-year rates were 67%, 68%, and 40%, respectively. Figure 4 shows overall survival, local control, and progression-free survival curves according to the beam type. There were no significant differences between PT and CIT. Figure 5 shows the curves according to histology. There were significant differences in the overall survival between adenocarcinoma and squamous cell carcinoma ($p = 0.045$), but the local control rates did not differ significantly between the two subtypes ($p = 0.24$).

Complications

Table 3 summarizes adverse events according to T stage. Severe RP (grade 3 or higher) was noted in two patients (3%) receiving CIT (both with T2b disease), with idiopathic pulmonary fibrosis and very poor respiratory function. They received steroid pulse therapy, and continuous oxygen inhalation became necessary. Most symptomatic grade 2 or 3 RP occurred within 3 to 6 months after the start of irradiation. Severe dermatitis was noted in five patients (7%) (3 with T2a and 2 with T2b disease). For grade 3 and 4 dermatitis, wound care for skin ulcers (debridement, wound bed preparation, and moist wound healing, etc.) was required. In addition, they also received a few courses of hyperbaric oxygen therapy. The other main toxicities observed were a grade 2 rib fracture without the presence of cancer in 19 patients (27%) (13 with T2a, 6 with T2b disease) and grade 2 fibrosis of the thoracic wall soft tissue in five patients (7%; 3 with T2a, 2 with T2b disease). Most of grade 2 rib fractures developed in patients treated before 2006 (12 with T2a and 4 with T2b disease). Most of these toxicities were late toxicities seen after 6 months. Among the 10 patients with a central lesion, there was only one patient with rib fracture, none with severe dermatitis, and one patient with grade 2 RP. Although pneumothorax related to particle therapy arose in two patients at 7 and 35 months, respectively, it was resolved after conservative treatment.

DISCUSSION

Although clinical trials of dose escalation in SBRT for T2 patients are in progress, surgical resection remains the standard procedure of treatment for T2a or T2bN0M0 NSCLC patients. However, NSCLC patients over 70 years of age account for approximately one third of all patients at the time of diagnosis. Significant comorbid illness can also make them unfit for definitive surgery. Curative radiation therapy has emerged as a promising therapeutic option. Previous reports have shown the efficacy and safety of SBRT and particle therapy in stage I NSCLC patients.[8–11,17–22] For T2 patients, however, sufficiently high local control rates were not obtained.[10,11,20–22] Table 4 summarizes the results of SBRT and particle therapy for T2 NSCLC from other institutions.[10,11,20–22] Although dermatitis and rib fracture were frequently seen compared with SBRT, in the present study, PT and CIT were well tolerated and effective for T2a/bN0M0 NSCLC. Especially, T2b tumors larger than 5 cm in diameter not indicated for SBRT using photons could be successfully treated using PT or CIT with relatively low pulmonary toxicity compared with SBRT studies.[22,23] For inoperable patients,

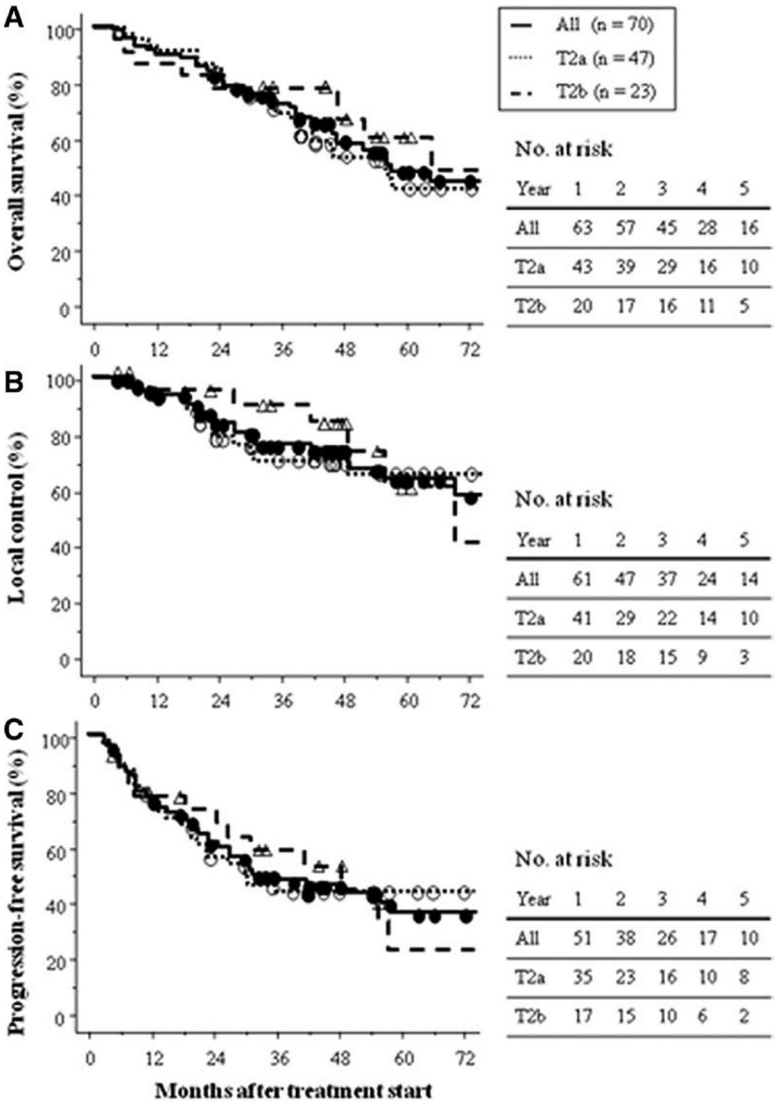

FIGURE 2. *A*, Overall survival; (*B*), local control; and (*C*), progression-free survival curves after particle therapy for all (•), T2a (○), and T2b (Δ) patients. *A*, $p = 0.65$; (*B*), $p = 0.75$; and (*C*), $p = 0.82$.

pulmonary toxicity was considered to be modest in both PT and CIT compared with other studies. As an advantage, PT and CIT can be delivered at a higher dose to the primary tumor, leading to improved local tumor control while simultaneously reducing the irradiated volume and doses delivered to the surrounding critical organs, regardless of the tumor size.[24] In our previous study, the local control rates were higher for adenocarcinoma than for squamous cell carcinoma,[13] contrary to experience with photons, suggesting similar radiosensitivity of the two histological subtypes.[25] However, there were no significant differences according to histology in the present study. The discrepancy may be because of improvement in planning and revision of the protocol. Further investigation about the differences according to the histology is warranted.

In this study, T2b patients tended to do better than T2a patients, although overall survival, local control, and progression-free survival did not differ significantly between T2a and T2b patients. This was considered to be because of the small patient number. Generally, selection biases may exist for patients undergoing particle therapy compared with those undergoing photon SBRT, and further analysis of the influences of selection biases may be necessary. An important outcome of our results may be that particle therapy can be effective against large tumors more than 5 cm in diameter. A high local control rate is also reported for large hepatocellular carcinomas treated by PT.[3]

In the present study, regional lymph node metastases were frequently observed. The rates were relatively high compared with those in some SBRT studies.[17,18] Possibly, occult lymph node metastases, not detected by diagnostic imaging, would increase in proportion to tumor size. In addition, it might also be related to the dose distribution of particle therapy with sharp dose fall-off and negligible incidental irradiation or none to the mediastinum. Moreover, we usually use positron emission tomography-CT to determine the clinical stage, but do not use endobronchial ultrasonography. This

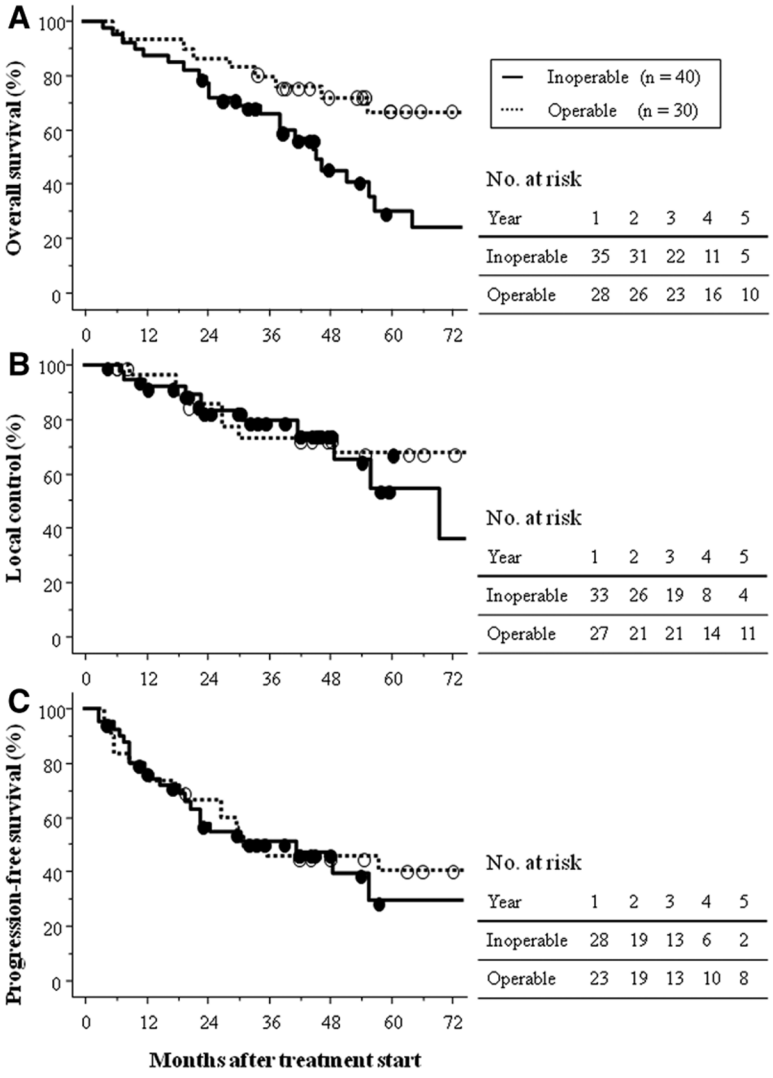

FIGURE 3. *A*, Overall survival; (*B*), local control; (*C*), and progression-free survival curves after particle therapy for operable (○) and inoperable (●) patients. *A*, $p = 0.018$; (*B*), $p = 0.54$; (*C*), $p = 0.82$.

might underestimate the incidence of lymph node metastasis at diagnosis. Further studies with more patients and more detailed analyses seem necessary.

In the present study, rib fracture and dermatitis (grade > 2) were also frequently seen, especially in patients treated between April 2003 and December 2006. During the early period, patients had been treated with only one portal to obtain enough SOBP.[13] These data are similar to the results of Japanese photon SBRT studies.[26,27] The low obesity rate in Japan might be associated with the high frequency of rib fracture. The skin and ribs are organs at risk in particle radiotherapy because of slightly higher entry doses regarding SOBP. In contrast, there were few adverse events for the patients with a central legion. These may be partly because chest-wall doses decrease with the increasing distance from the chest wall and unnecessary irradiation of the mediastinum can be minimized with particle radiotherapy. The previous protocol, 52.8 GyE delivered in four fractions, was stopped in January 2009. Since then, both PT and CIT protocols, 66 GyE delivered in 10 fractions, have been used. As for CIT, there may be no advantage to increasing fraction numbers in view of the low oxygen enhancement ratio.[28] However, the oxygen enhancement ratio of PT remains unclear, so we plan to conduct in vitro and in vivo studies on the issue in the future. In addition, treatment planning for the layer-stacking beam method and scanning method should also be studied in the future to reduce the dose to the skin and ribs, taking late toxicities into consideration.[29,30]

The new TNM classification may imply a potential change in adjuvant treatment indications because of stage migration. This change is especially relevant in patients with T2bN0M0 tumors, upstaged from stage IB to stage IIA. Patients with stage II NSCLC according to the 6th TNM classification are known to benefit from adjuvant chemotherapy after surgery.[31,32] It, therefore, seems reasonable to consider adjuvant chemotherapy or mediastinal radiation for T2bN0M0 patients. Several studies have investigated the efficacy of salvage RT after surgery.[33] Patients with hilar or mediastinal lymph node recurrence, who are not candidates for

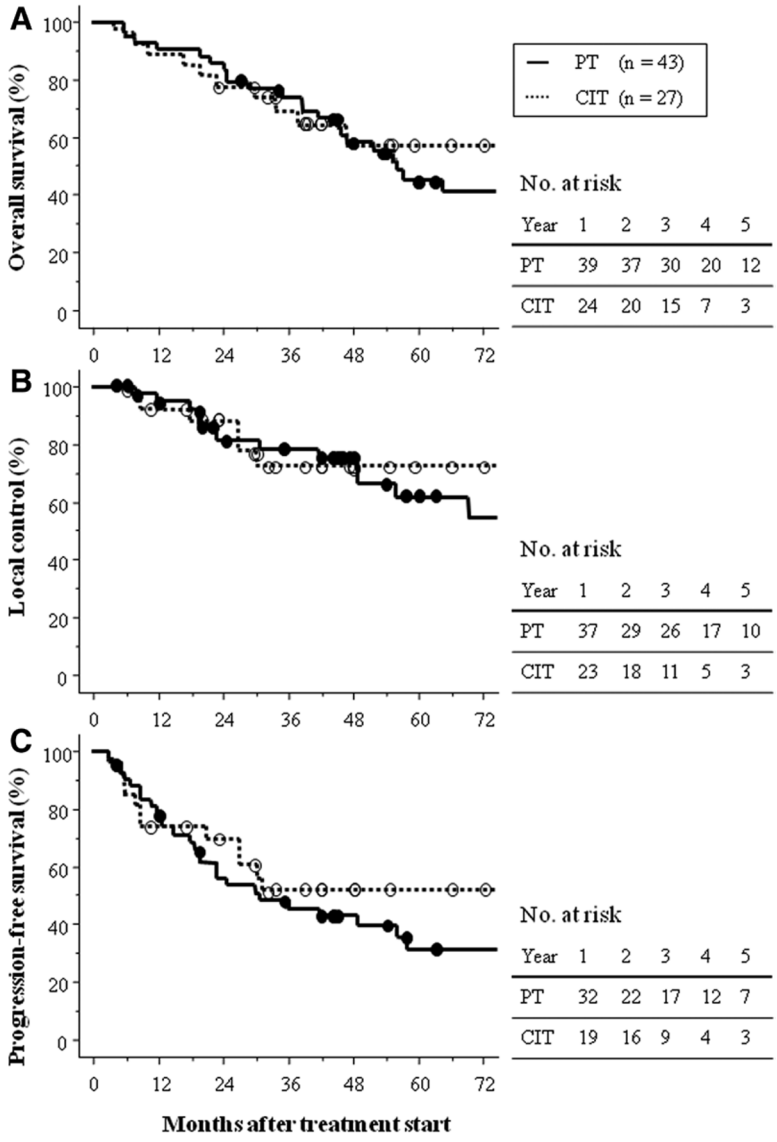

FIGURE 4. *A*, Overall survival; (*B*), local control, and (*C*), progression-free survival curves for patients receiving (•) or (○). *A*, $p = 0.80$; (*B*), $p = 0.85$; and (*C*), $p = 0.44$. PT, proton therapy; CIT, carbon-ion therapy.

chemotherapy, should be treated with radiation. As for mediastinal radiation after curative radiation to the primary lesion, to the best of knowledge, there is only one report regarding patients after SBRT.[34] In that study, conventional radiotherapy could successfully salvage lymph node relapses after SBRT in a proportion of patients, after surgery, and seemed reasonably well tolerated. PT and CIT can reduce pulmonary toxicity by reducing the mean lung dose and low dose regions compared with SBRT.[14,35,36] Moreover, PT and CIT stop just short of the mediastinum with the sharp distal fall-off of the Bragg peaks. Therefore, radiation for lymph node metastases after particle therapy may be safer than that after SBRT using photons. This could be a justification for further promotion of particle therapy for early-stage NSCLC. However, some patients are unfit for chemotherapy or mediastinal irradiation, so we will consider these adjuvant treatments for patients who can tolerate them.

Comparison of PT and CIT shows that low-dose regions spread into the surrounding normal lungs in PT because of the relatively large penumbra.[37,38] Although CIT is superior in a simple dose-volume histogram comparison under the same conditions, the air gap is currently made as small as possible because of the collision detection system. Moreover, the beam directions are limited to three fixed positions in CIT. With CIT, tumors located in the posterior thorax have to be treated in a prone position. We use a respiratory gating system, but the respiration curve is not stable in the prone position. Therefore, internal margins need to be added despite the use of a respiratory gating system. However, PT can use a rotational gantry and patients can be treated in the supine position. The high positioning accuracy and stable respiration curve in the supine position result in an advantage for PT in terms of dose-volume histograms. Moreover, we can also reduce the doses adjacent to organs at risk, especially to

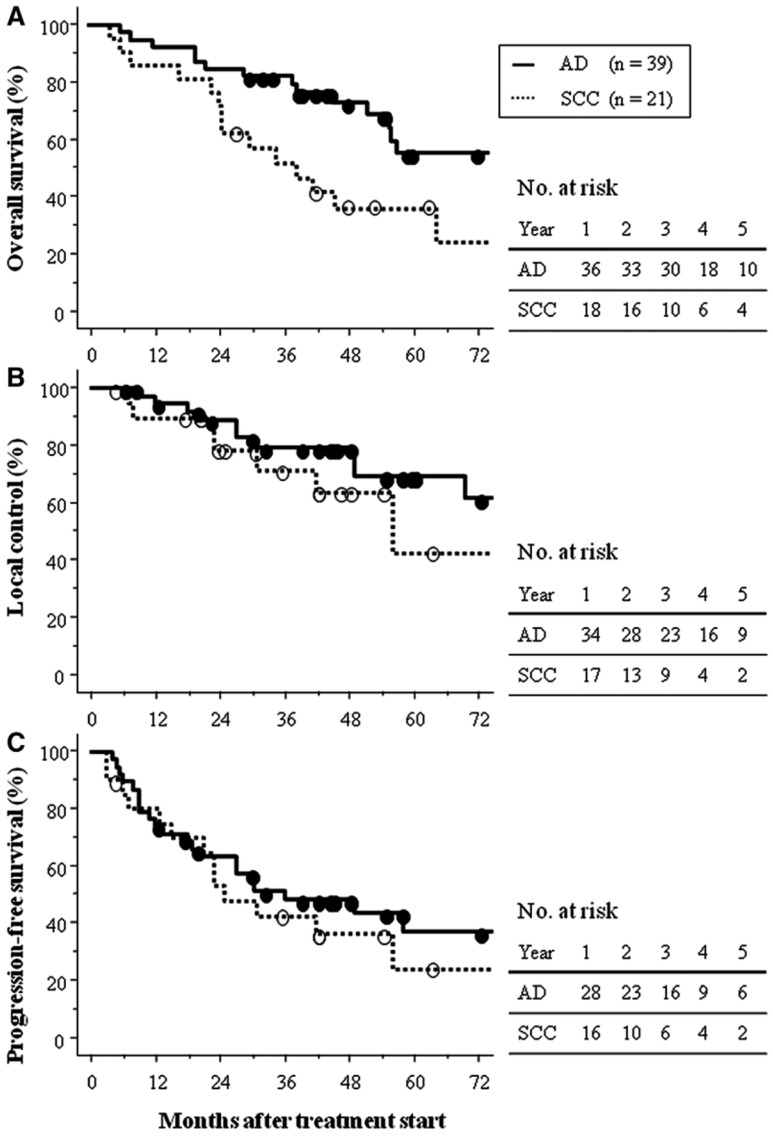

FIGURE 5. *A*, Overall survival; (*B*), local control; (*C*), and progression-free survival curves for patients with adenocarcinoma (•) and with squamous cell carcinoma SCC (○). *A*, $p = 0.045$; (*B*) , $p = 0.24$; (*C*), $p = 0.54$.

TABLE 3. Complications Related to Particle Therapy

Adverse Event	T2aN0M0	T2bN0M0	Total
No. of patients	47	23	70
Radiation pneumonitis			
Grade 2 / 3	7 / 0	3 / 2	3%[a]
Dermatitis			
Grade 2 / 3 / 4			7%[a]
All patients	7 / 3 / 0	3 / 1 / 1	6%[b]
Before 2006: T2a, 27; T2b, 9	6 / 2 / 0	2 / 0 / 0	
Rib fracture grade 2			
All patients	13	6	27%
Before 2006: T2a, 27; T2b, 9	12	4	44%[b]
Soft-tissue fibrosis grade 2	3	2	6%

The toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

[a] Data are a percentage of grade 3 or more.

[b] Before 2006, most patients were treated with 1 or 2 portals.

the esophagus and vessels, using a rotational gantry. We plan to install an automatic bone verification system in the near future. This would serve to better increase precision with stereotactic PT and CIT in combination with the respiratory gating system. Although there were no significant differences in the treatment results between PT and CIT in our previous and present studies,[13] these studies were not randomized, and the biological effectiveness of the dose-fractionation schedules used may not necessarily be comparable. In the near future, we plan to conduct a randomized controlled trial of PT versus CIT for stage I NSCLC.

In conclusion, particle therapy is well tolerated and effective for T2a/bN0M0 NSCLC. Especially, T2b tumors not indicated for SBRT might be a good indication of particle therapy. In patients with large tumors, however, regional lymph node metastases developed frequently. It therefore seems worthwhile to consider chemotherapy or mediastinal irradiation as adjuvant therapy whenever possible. Also, randomized studies comparing particle therapy and photon SBRT

TABLE 4. Representative Reported Results of Radiograph of Stereotactic Body Radiotherapy and Particle Therapy for T2 Non–Small-Cell Lung Cancer

Author, Yr	Therapy	No. of Patients	Total Dose, Prescribed	Treatment Outcome; OS, % Local Failure, Grade 3 RP (Nos.)	Median Follow-Up (Mo)
Dunlap, 2010[10]	SBRT	T2: 13	42–60 Gy/3–5 Fr, marginal	35% (2y, T2), 30% (2y, T2), 1 (T1-2)	13
Koto, 2007[11]	SBRT	T2: 12	45 Gy/3 Fr or 60 Gy/ 8 Fr, isocenter	72% (3y, T1–T2), 60% (3y, T2), 1 (T1–2)	32
Baumann, 2009[20]	SBRT	T2a: 17	45 Gy/3 Fr, marginal (67% IDL)	60% (3y, T1–T2a), 4 local failures (T2a), 1 (T1 or T2a)	35
Guckenberger, 2009[21]	SBRT	T2: 19	26–48 Gy/1–8 Fr, marginal (65%–80% IDL)	37% (3y, T1–T3), 1 local failure (T2), 1 (T1–T3)	14
van der Voort, 2009[22]	SBRT	T2: 31	36–60 Gy/3 Fr,marginal (70%–85% IDL)	62% (2y, T1–T2),4 local failures (T2),3 (T1 or T2)	15
Nakayama 2010[19]	PT	T2: 28	66–72.6 GyE/ 10–22 Fr, isocenter	98% (2y, T1–T2),0 local failure (T2),2 (T1–T2)	18
This study 2012	PT and CIT	T2a–b: 70 T2a: 47 T2b: 23	52.8–80 GyE/4–20 Fr, isocenter	T2a–b: 58% (4y), 25% (4y), 2 T2a: 53% (4y), 30% (4y), 0 T2b: 67% (4y), 16% (4y), 2	51

OS, overall survival; RP, radiation pneumonitis; SBRT, stereotactic body radiotherapy; Fr, fractions; y, years; IDL, isodose line; PT, proton therapy; GyE, Gray equivalent; CIT, carbon-ion therapy.

are desirable. Further investigation of particle therapy is warranted to define its role in T2a and T2bN0M0 NSCLC.

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