Acta Oncologica, 2015; 54: 315–321

informa
healthcare

ORIGINAL ARTICLE

Particle therapy for clinically diagnosed stage I lung cancer: Comparison with pathologically proven non-small cell lung cancer

OSAMU FUJII[1], YUSUKE DEMIZU[1], NAOKI HASHIMOTO[1], MASARU TAKAGI[1], KAZUKI TERASHIMA[1], MASAYUKI MIMA[1], DONGCUN JIN[1], FUMIKO NAGANO[1], KUNIAKI KATSUI[1], TOMOAKI OKIMOTO[1], HIROMITSU IWATA[1,2,3], YASUE NIWA[4], TOMOHIRO YAMASHITA[1], TAKASHI AKAGI[1], TAKASHI DAIMON[5], RYOHEI SASAKI[6], YOSHIO HISHIKAWA[7], MITSUYUKI ABE[1], MASAO MURAKAMI[8] & NOBUKAZU FUWA[1]

[1]*Department of Radiology and Radiation Physics, Hyogo Ion Beam Medical Center, Tatsuno, Japan,* [2]*Department of Radiation Oncology, Nagoya Proton Therapy Center, Nagoya City West Medical Center, Nagoya, Japan,* [3]*Department of Radiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan,* [4]*Department of Radiology, Hyogo College of Medicine, Nishinomiya, Japan,* [5]*Division of Biostatistics, Hyogo College of Medicine, Nishinomiya, Japan,* [6]*Division of Radiation Oncology, Kobe University Graduate School of Medicine, Kobe, Japan,* [7]*Medipolis Proton Therapy and Research Center, Ibusuki, Japan and* [8]*Center for Radiation Oncology, Dokkyo Medical University, Tochigi, Japan*

ABSTRACT

Background. The purpose of the present study was to present the treatment outcomes of particle therapy for indeterminate pulmonary nodules (IPNs) diagnosed as stage I non-small cell lung cancer, including a comparative analysis involving pathologically proven lung cancer (PPLC).

Material and methods. A total of 54 patients (57 lesions) who underwent particle therapy for IPNs were enrolled in this study. Median patient age was 76 (range 52–87) years. T-classification was: T1a, 30; T1b, 16; and T2a, 11. Particle therapy using protons or carbon ions was delivered at total doses of 52.8–80 Gy equivalent in 4–26 fractions. The PPLC cohort included 111 patients.

Results. The median follow-up time was 41 (range 7–90) months. For all IPN patients, the three-year overall survival, progression-free survival, local control and distant progression-free survival rates were 90%, 72%, 94% and 79%, respectively. Grade 2 toxicities were radiation pneumonitis (19%), dermatitis (9%), rib fracture (2%), chest wall pain (2%) and neuropathy (2%). No ≥ grade 3 toxicities were observed. In univariate analysis, the IPN group showed significantly better survival relative to the PPLC group. However, after adjustment for baseline imbalances between these two groups in multivariate analysis, pathological confirmation did not correlate with survival.

Conclusions. Particle therapy for IPNs provided favorable outcomes with minimal toxicities, which may be comparable to those for PPLC patients. Further studies are needed to clarify the optimal management of IPN patients.

Lung cancer is the most common cause of cancer death worldwide. Surgical resection remains the mainstay of care for stage I non-small cell lung cancer (NSCLC). Stereotactic body radiation therapy (SBRT) has been widely used in the management of stage I NSCLC, especially for patients in whom medical comorbidities preclude surgical resection [1,2]. Furthermore, particle therapy is a newly emerging treatment option for the achievement of higher local tumor control with minimal toxicity in early-stage NSCLC patients [3–5].

For the majority of NSCLC patients, pathological confirmation should be made so that appropriate treatment can be given. The American College of Chest Physicians (ACCP) clinical guidelines recommend non-surgical biopsy be performed when the probability of malignancy is low to moderate, and surgical diagnosis be undertaken when the clinical

Correspondence: O. Fujii, Department of Radiology, Hyogo Ion Beam Medical Center, 1-2-1 Koto Shingu-cho, Tatsuno, Hyogo 679-5165, Japan. Tel: +81 791 58 0100. Fax: +81 791 58 2600. E-mail: osfujii@aa.cyberhome.ne.jp

(Received 10 July 2014; accepted 3 October 2014)

ISSN 0284-186X print/ISSN 1651-226X online © 2014 Informa Healthcare
DOI: 10.3109/0284186X.2014.974828

probability of malignancy is high in patients with an indeterminate nodule that measures >8 mm [6]. However, non-surgical biopsy has the associated potential risk of causing complications, such as pneumothorax and hemorrhage [7]. In addition, surgical resection runs the risk of fatal and non-fatal complications [8]. Therefore, in some cases it is difficult to perform these procedures and not all patients will benefit from a pathological confirmation, as it will not influence clinical management.

For indeterminate pulmonary nodules (IPNs) that are not suitable for non-surgical biopsy and/or surgical resection, SBRT is often used in clinical practice. Favorable outcomes have been reported especially in several European and Japanese studies [9–11]. However, there is little information available regarding non-surgical treatments with the exception of SBRT, and optimal management of IPNs remains controversial. Therefore, it is imperative to formulate a therapeutic strategy for IPN patients.

In the present study, we performed a retrospective and single-institutional review of 54 patients treated with particle therapy for IPNs clinically suggestive of stage I NSCLC. We also compared the treatment outcomes with those of pathologically proven lung cancer (PPLC), which had been analyzed in our previous study [5].

Material and methods

Study design and patients

Between April 2003 and December 2012, a total of 91 patients (94 lesions) with IPNs highly suggestive of stage I NSCLC underwent particle therapy at Hyogo Ion Beam Medical Center. Among these patients, 37 were excluded from this study because similar patients were excluded from the PPLC population (111 patients with 111 lesions) [5]; 28 had a history of previously treated lung cancer, five were lost to follow-up (<5 months) and four were diagnosed as having lung cancer coexistent with interstitial pneumonia. The remaining 54 patients (57 lesions) were identified and were retrospectively analyzed. Thirty-five patients were male and 19 were female, with a median age of 76 years. Thirty cases were staged as T1aN0M0, 16 as T1bN0M0 and 11 as T2aN0M0 according to the 7th International Union Against Cancer TNM classification [12]. Patients either refused surgery (n = 38) or had medical contraindications that precluded surgery (n = 19). Each patient involved in the study gave his or her written informed consent, and the study was approved by the Ethics Committee at our institute.

All patients underwent pre-treatment imaging consisting of chest computed tomography (CT) and fluorodeoxyglucose (FDG)-positron emission tomography (PET). IPNs were clinically diagnosed as highly suggestive of stage I NSCLC when there were principally two or three combinations of radiographic findings: 1) morphologic CT features (n = 57); 2) enlargement of the lesion on serial CT (n = 34); and 3) an increased SUV on FDG-PET (n = 39). Morphologic characteristic CT features compatible with NSCLC included pure or part solid ground glass opacity (GGO), a spiculated margin, vascular convergence and a dilated bronchus leading into the nodule or the presence of pseudo-cavitation [6]. Serial CT scans at ≥3 month interval were performed to confirm the enlargement of lung nodules for at least three years.

The reasons for the lack of pathological diagnosis were as follows: 1) negative biopsy results and patient refusal to undergo further examinations (n = 23); 2) initial refusal to undergo the biopsy procedure (n = 12); 3) no indication requiring biopsy because of the tumor's small size and location (n = 10); and 4) a high risk of morbidity related to biopsy because of patient or tumor characteristics (n = 9). While taking into consideration patient preferences, comorbidities and the risk of tumor growth using the watch-and-wait approach, all IPN patients were judged as candidates for particle therapy by two or more radiation oncologists.

Treatment methods and follow-up

Our treatment methods and follow-up procedures were identical to those for PPLC, and have been described in detail previously [4,5]. Briefly, each patient was immobilized using a custom-made thermoplastic cast and 2-mm-thick CT images were obtained during the exhalation phase using the respiratory gating system. The gross tumor volume (GTV) was defined as the visible tumor on CT imaging, and the clinical target volume (CTV) was defined as the GTV plus a margin of 5 mm in all directions. The planning target volume (PTV) was defined as the CTV plus a setup margin of 5 mm and an internal margin of 1–4 mm, depending on the stability of respiration under the respiratory gating system. Radiation doses were delivered to the center of the PTV. One to four portals were used in the proton therapy and carbon ion therapy treatments. A respiratory gating system developed at the National Institute of Radiological Sciences in Chiba was used until April 2007, and an AZ-733 (Anzai Medical, Tokyo, Japan) was used from May 2007 for beam irradiation during the exhalation phase. Carbon ion beams of 320 MeV or proton beams of 150 MeV generated using a synchrotron accelerator (Mitsubishi Electric Corporation, Tokyo, Japan) were used for treatment.

The proton therapy protocols involved the delivery of total doses of 66 Gy equivalent (GyE) in 10 fractions (n = 10), 60 GyE in 10 fractions (n = 9), 52.8 GyE in 4 fractions (n = 8) and 80 GyE in 20 fractions (n = 1). The carbon ion therapy protocols involved the delivery of total doses of 66 GyE in 10 fractions (n = 14), 52.8 GyE in four fractions (n = 12), 68.4 GyE in nine fractions (n = 1), 76 GyE in 20 fractions (n = 1) and 70.2 GyE in 26 fractions (n = 1). The centrally located tumors were basically treated with 20 or 26 fractions because of their proximity to critical organs. Biological effective dose (BED_{10}) was calculated using the linear quadratic (LQ) model [13] to compare the effect of treatments with different fraction sizes and total doses. The BED_{10} was calculated as follows: BED_{10} (GyE) = nd $[1 + d/(\alpha/\beta)]$, where n is the number of fractions, d is the dose/fraction and the α/β ratio = 10 Gy. No patients received chemotherapy before and/or during particle therapy.

Follow-up imaging and toxicity evaluations were obtained at three-month intervals. Local recurrence was defined as an increase in radiographic abnormality within the irradiated area. If there was a possibility of tumor recurrence, FDG-PET was performed to assess the extent of locally recurrent lesions and to detect distant metastases. Radiation-induced late toxicities were assessed using version 4 of the National Cancer Institute-Common Toxicity Criteria.

Statistical analysis

The baseline characteristics of the patients were compared between the IPNs and PPLC groups using the Mann-Whitney rank-sum test for continuous variables and Fisher's exact test for categorical variables. Follow-up began on the date of the first particle therapy to determine median follow-up and time-to-event estimates. Survival and local control curves were estimated using the Kaplan-Meier method, and compared using the log-rank test. The Cox proportional-hazards regression model was also used to simultaneously adjust for baseline characteristics that included smoking history, tumor diameter, type of opacity, operability, treatment beam and the number of portals; this was because there were statistically significant differences regarding tumor diameter, opacity, operability and the number of portals required. There were no statistically significant differences regarding smoking history and beam type but some imbalances ($p < 0.15$) in these baseline characteristics between the IPN and PPLC groups. All p-values were two-sided, and values of $p < 0.05$ were considered to indicate statistical significance. Data were analyzed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient and tumor characteristics

Relevant baseline characteristics for the IPNs and PPLC groups are summarized in Table I. Among these, the median tumor diameter in the PPLC group was significantly larger at 29 mm as compared with 19 mm in the IPN group ($p < 0.001$). The proportion of GGO and medically operable lesions were significantly higher in IPN patients. In the IPN and PPLC groups, 18 (32%) and 10 (9%) lesions were diagnosed on CT scans as pure GGO or part-solid GGO, respectively ($p < 0.001$). Furthermore, there was a significant difference regarding the number of

Table I. Patient characteristics.

	IPNs	PPLC	p-Value
No. of patients (lesions)	54 (57)	111 (111)	
Median follow-up	41 (7–90) months	42 (5–103) months	0.900
Median age (range)	76 (52–87) years	76 (39–89) years	0.242
Male/female	35 (65%)/19 (35%)	76 (68%)/35 (32%)	0.724
Smoking: yes/no	30 (56%)/24 (44%)	80 (72%)/31 (28%)	0.052
Performance status: 0/1/2	33 (61%)/18 (33%)/3 (6%)	58 (52%)/42 (38%)/11 (10%)	0.482
Median tumor diameter (range)	19 (8–45) mm	29 (11–48) mm	<0.001
T-classification: T1a/T1b/T2a	30 (53%)/16 (28%)/11 (19%)	17 (15%)/45 (41%)/49 (44%)	<0.001
Histology: AD/SQ/UN		70 (63%)/36 (62%)/5 (5%)	
Tumor location:			
Central/Peripheral	5 (9%)/52 (91%)	6 (5%)/105 (95%)	0.299
Opacity:			
GGO/Solid	18 (32%)/39 (68%)	10 (9%)/101 (91%)	<0.001
Operability: yes/no	38 (67%)/19 (33%)	53 (48%)/58 (52%)	0.015
No. of portals: 1/2/3/4	3/25/17/12	21/55/29/6	0.003
Median BED_{10} (range)	110 (89–122) GyE_{10}	112 (89–122) GyE_{10}	0.573
Treatment beam: carbon/proton	29 (51%)/28 (49%)	41 (37%)/70 (63%)	0.059

AD, adenocarcinoma; BED, biological effective dose; IPNs, indeterminate pulmonary nodules; PPLC, pathologically proven lung cancer; SQ, squamous cell carcinoma; UN, unclassified non-small cell lung cancer.

portals used between the two groups ($p = 0.003$). No statistical differences in the other baseline characteristics could be found, but some imbalances were recognized with respect to smoking history ($p = 0.052$) and beam type ($p = 0.059$). The median follow-up time for the IPN patients was 41 (range 7–90) months for all patients and 43 (range 7–90) months for survivors. The median follow-up time for the total PPLC patient population was 42 (range 5–103) months and 49 (range 16–103) months for the surviving patients.

Survival and local control

Of all the IPN patients, five died from lung cancer and three from other diseases. Forty-six patients were alive at the last follow-up, but 11 of these exhibited lung cancer recurrence. Overall, five patients (9%) experienced local recurrence, 10 patients (19%) developed regional lymph-node recurrence and 10 patients (19%) developed distant metastases. Of five patients who had local recurrence, one patient experienced regional lymph-node recurrence and another experienced distant metastases. The median time to local recurrence for the IPN group was 29 (range 11–69) months. In addition, 11 patients had regional lymph-node and/or distant metastases without local progression.

According to the log-rank test, there were significant differences between the IPN and PPLC groups in terms of overall survival (OS), progression-free survival (PFS) and distant progression-free survival (DPFS) (Figure 1). The three-year OS, PFS, local control (LC) and DPFS rates in the IPN group were 90% [95% confidence interval (CI) 81–98%], 72% (95% CI 59–84%), 94% (95% CI 86–100%) and 79% (95% CI 68–90%), respectively; in the PPLC group they were 73% (95% CI 65–82%), 47% (95% CI 38–57%), 80% (95% CI 71–88%) and 63% (95% CI 60–73%), respectively.

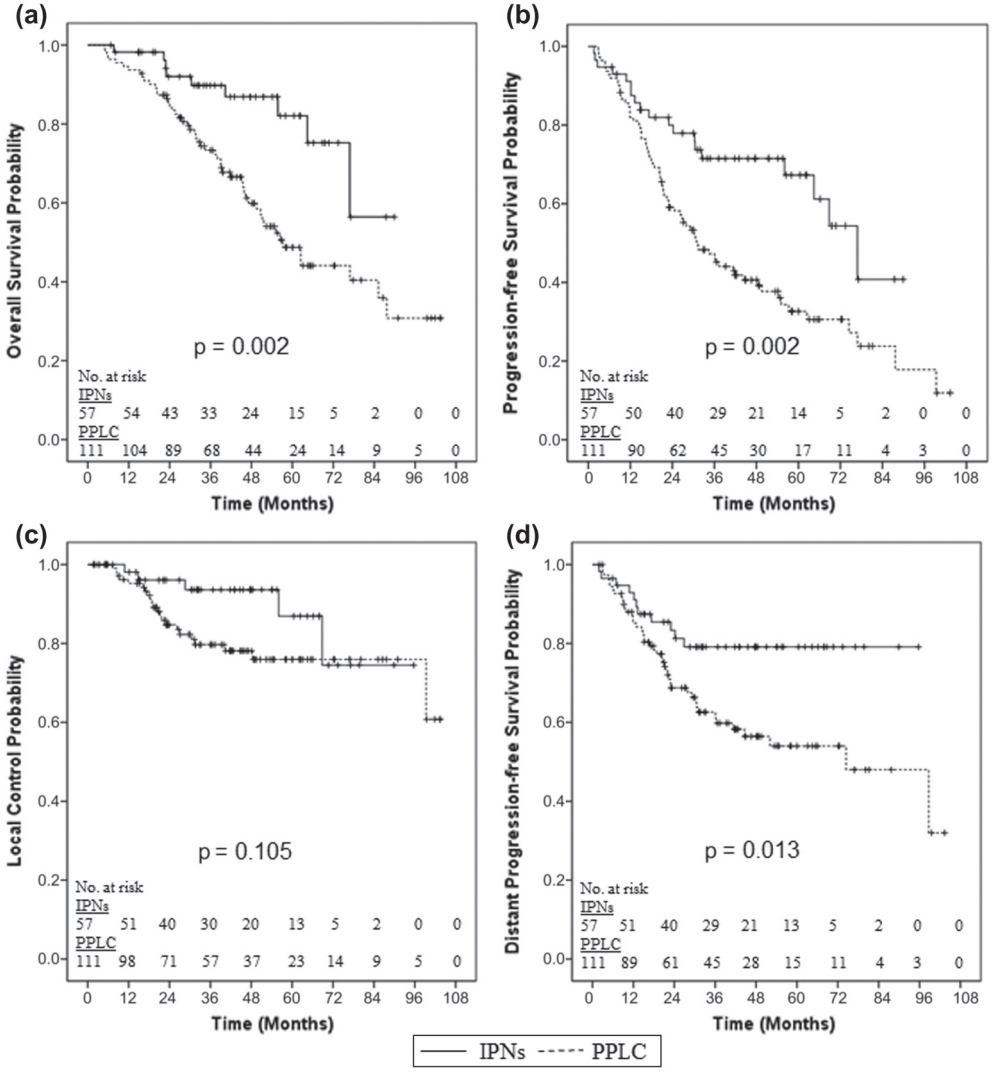

Figure 1. Overall survival (a), progression-free survival (b), local control (c) and distant progression-free survival (d) are shown for the IPN and PPLC groups. IPNs, indeterminate pulmonary nodules; PPLC, pathologically proven lung cancer.

Table II. Multivariate analysis of potential prognostic factors for survival and local control in IPN/PPLC patients.

	OS		PFS		LC	
Factor	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Pathological confirmation (No)	0.598 (0.277–1.290)	0.190	0.719 (0.414–1.248)	0.719	0.776 (0.275–2.191)	0.632
Smoking (No)	0.338 (0.157–0.728)	0.006	0.848 (0.513–1.400)	0.519	0.670 (0.262–1.715)	0.404
Tumor diameter	1.033 (1.002–1.066)	0.038	1.033 (1.008–1.059)	0.009	1.028 (0.985–1.073)	0.212
Opacity (GGO)	0.275 (0.065–1.172)	0.081	0.214 (0.076–0.607)	0.004	0.200 (0.025–1.574)	0.126
Operability (Yes)	0.422 (0.240–0.741)	0.003	1.271 (0.919–1.756)	0.147	0.780 (0.347–1.756)	0.548
Treatment beam (carbon)	0.608 (0.299–1.238)	0.170	0.796 (0.464–1.366)	0.408	2.170 (0.854–5.518)	0.104
No. of portals	1.256 (0.805–1.959)	0.315	1.271 (0.919–1.756)	0.147	1.006 (0.576–1.757)	0.984

CI, confidence interval; GGO, ground glass opacity; HR, hazard ratio; IPN, indeterminate pulmonary nodule; LC, local control; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PPLC, pathologically proven lung cancer.

Multivariate analysis to adjust for baseline imbalances revealed the following significant prognostic factors (Table II): smoking history; tumor diameter and operability for OS; and tumor diameter and tumor opacity for PFS. The other factors including pathological confirmation, treatment beam and number of portals were found to have no significant relationship with the OS, PFS and LC endpoints.

Toxicity

Treatment-related toxicity was limited (Table III). None of the IPN patients experienced ≥ grade 3 toxicities. With regard to grade 2 toxicity a total of 11 patients (19%) developed radiation pneumonitis (RP), five patients (9%) had acute dermatitis, one patient (2%) had rib fracture and one patient (2%) experienced chest wall pain. Most instances of grade 2 pneumonitis were in the form of a mild cough and slight fever, and were relived without steroids at the outpatient clinic. In addition, one patient (2%) whose tumor was initially situated at the apex of the lung had received carbon ion therapy at a total of 52.8 GyE in four fractions, and developed grade 2 brachial plexopathy at 72 months after treatment. A review of the three-dimensional treatment plan revealed that the maximal brachial plexus dose was 53.0 GyE.

Table III. Treatment-related toxicities in IPN patients (n = 57).

	Grade 1	Grade 2	Grades 3–5
Acute			
Dermatitis	37 (65%)	5 (9%)	0
Late			
Pneumonitis	44 (77%)	11 (19%)	0
Rib fracture	12 (21%)	1 (2%)	0
Chest wall pain	0	1 (2%)	0
Neuropathy	0	1 (2%)	0

IPN, indeterminate pulmonary nodule.

Discussion

In the present study, favorable outcomes with minimal toxicity were achieved with particle therapy using protons or carbon-ions for the IPNs diagnosed as stage I NSCLC. The three-year OS and LC rates were 90% and 94%, respectively, and no toxicity of ≥ grade 3 was observed. Therefore, particle therapy can be employed as a safe and effective treatment modality for IPNs. To our knowledge, ours is the first report describing the treatment outcomes of particle therapy for IPNs.

Several reports have been published regarding the outcome of SBRT for IPNs. The three-year OS and LC rates were approximately 54–90% and 80–91%, respectively (Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.974828). Our results seem to be similar to those of past studies. However, since all of these studies involved retrospective analysis and patient characteristics varied among the institutions, a precise comparison would be difficult. Several factors, such as gender, tumor size and radiation dose have been considered as significant prognostic factors in the treatment of NSCLC [1,14,15]. In the present study, smoking history, tumor size and operability were also found to be significant prognostic factors for OS. It should be noted that the median tumor size in the IPN group was significantly smaller than that in the PPLC group. This suggests that the IPN cohort might have included patients with relatively early stage lung cancer. Thus, our favorable outcome could be attributable in part to bias associated with patient selection criteria.

Univariate analysis using the log-rank test revealed that there were significantly differences in OS and PFS between the IPN and PPLC groups. However, in multivariate analysis adjusted for some characteristic imbalance between the two groups, pathological confirmation did not significantly correlate with survival. Previous reports concerning SBRT for stage I NSCLC have indicated that there was no difference

in outcome between the two groups [10,11]. A multi-institutional review of SBRT involving a total dose of 60 Gy delivered in 3–8 fractions revealed no survival differences among the 233 IPN and 122 PPLC patients [11]. Another recent retrospective review of SBRT involving 40–50 Gy delivered in five fractions, comparing 58 IPN and 115 PPLC patients, also showed no significant differences in terms of the three-year OS, PFS and LC [10]. Our data support the findings of these two reviews.

Particle therapy can theoretically produce a superior dose distribution in the target using the sharp distal falloff of the Bragg peaks produced using these modalities, than is the case using photon irradiation [16]. Concerning particle therapy for stage I PPLC, several studies have reported promising local control rates ranging from 78% to 98% [3–5]. However, these seem to be comparable to the control rates achieved in the SBRT series [1,2]. Furthermore, comparison of pulmonary toxicity is difficult because of the low incidence of this complication; the rate of $\geq$grade 3 RP has been reported to range from 0% to $<10\%$ in most SBRT and particle therapy studies [1,3–5]. Therefore, the clinical benefit of particle therapy over photon treatment modalities remains unclear. Nevertheless, the theoretical advantages offered by particle beam therapy might make it useful, particularly for patients with relatively large or several tumors [17,18]. Indeed, no severe ($\geq$grade 3) RP was observed in our series, while 3–9% of patients developed severe RP in the SBRT series [9–11]. Further studies are needed to clarify the subset of patients who would benefit from particle therapy.

As a result of several medical problems, it is often difficult to obtain a pathological diagnosis with a clinical workup including bronchofiberscopy and CT-guided needle biopsy. In the present study, the reasons for the lack of pathological confirmation were classified into four groups as stated in Material and Methods section. In any case, careful observation using serial CT is usually warranted for patients with a very low probability of cancer, whereas, for those with a high probability of cancer surgical resection is usually indicated in clinical practice. However, some of the former group may be at risk of tumor growth under the watch-and-wait approach, and some of the latter group may be unfit for surgery because of either patient preference or co-morbidities. In some very limited cases without pathological confirmation, clinicians might be justified in attempting a potential toxic cancer treatment. Optimal management for IPN patients remains controversial and depends largely on the individual clinician's approach.

A higher proportion of patients treated in European studies involving SBRT have no pathological diagnosis [11,19,20]. This approach to SBRT mainly depends on the suggestion that the diagnosis of benign disease is typically made in only 1–4% of patients undergoing surgery for an FDG-PET positive lesion in the Netherlands [21–23]. Indeed, improvement in imaging modalities has made it possible to diagnose small peripheral lesions much more precisely than was possible previously. However, the sensitivity and specificity of FDG-PET regarding the identification of malignancy has been reported as being approximately 95% and 82%, respectively [24]. It has also been reported that pulmonary nodules which are <1 cm in size or show GGO images on CT cannot be evaluated accurately using PET-CT [25]. In our study, approximately one-third of lesions in the IPN group had a pure or part-solid GGO appearance on CT scans. Some of these lesions may have included benign disease, such as hamartoma, granulomatous infections and non-specific granulomas. Further development of imaging modalities would probably increase the sensitivity and specificity regarding the detection of early lung cancer; however, it would be difficult to completely distinguish malignant from benign disease. As the ACCP guidelines recommend, clinicians should discuss the benefits and risks of alternative management strategies and elicit patient preference for management [6].

Our study had certain limitations. First, it was a retrospective analysis involving a single institution, using a patient population that was heterogeneous with regard to tumor opacity, operability, radiation dose, beam type and other factors. For this reason, the statistical power was low, and no firm conclusions regarding treatment recommendations for the IPNs can be drawn. A prospective study of SBRT for small lung lesions clinically diagnosed as primary lung cancer without pathologic confirmation has been initiated in Japan. In the near future, the results of this study will help clinicians make appropriate therapeutic decisions for this patient population. Second, IPNs may include benign disease as described above, and it is difficult to anticipate how this may have influenced our data, as benign lesions would have artificially improved treatment outcomes.

In conclusion, particle therapy for IPNs clinically diagnosed as stage I NSCLC achieved favorable outcomes with minimal toxicity in the current study. Therefore, this therapy could be one of the alternative treatments for IPNs. Although our retrospective study showed no statistical difference in outcomes between the IPN and PPLC groups, the management of IPNs should be carefully examined while considering patient preferences, co-morbidities and the risk of tumor growth under watch-and-wait. Further studies will be needed to clarify the optimal management of IPN patients.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer. Radiother Oncol 2010;94:1–11.

[2] Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–6.

[3] Liao Z, Lin SH, Cox JD. Status of particle therapy for lung cancer. Acta Oncol 2011;50:745–56.

[4] Iwata H, Murakami M, Demizu Y, Miyawaki D, Terashima K, Niwa Y, et al. High-dose proton therapy and carbon-ion therapy for stage I non-small cell lung cancer. Cancer 2010;116:2476–85.

[5] Fujii O, Demizu Y, Hashimoto N, Araya M, Takagi M, Terashima K, et al. A retrospective comparison of proton therapy and carbon ion therapy for stage I non-small cell lung cancer. Radiother Oncol 2013;109:32–7.

[6] Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? ACCP evidence-based clinical practice guidelines, 3rd ed. Chest 2013;143:93s–120s.

[7] Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: An analysis of discharge records. Ann Intern Med 2011;155:137–44.

[8] Boffa DJ, Allen MS, Grab JD, Gaissert HA, Harpole DH, Wright CD. Data from the Society of Thoracic Surgeons General Thoracic Surgery database: The surgical management of primary lung tumors. J Thorac Cardiovasc Surg 2008;135:247–54.

[9] Inoue T, Shimizu S, Onimaru R, Takeda A, Onishi H, Nagata Y, et al. Clinical outcomes of stereotactic radiotherapy for small lung lesions clinically diagnosed as primary lung cancer on radiologic examination. Int J Radiat Oncol Biol Phys 2009;75:683–7.

[10] Takeda A, Kunieda E, Sanuki N, Aoki Y, Oku Y, Handa H. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: Comparison with non-small-cell lung cancer. Lung Cancer 2012;77:77–82.

[11] Verstegen NE, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: Comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol 2011;101:250–4.

[12] Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007; 2:706–14.

[13] Douglas BG, Fowler JF. The effect of multiple small doses of X-rays on skin reactions in the mouse and a basic interpretaion. Radiat Res 1976;66:401–26.

[14] Matsuo Y, Shibuya K, Nagata Y, Takayama K, Norihisa Y, Mizowaki T, et al. Prognostic factors in stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011;79:1104–11.

[15] Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy for stage I non-small cell lung cancer: Update results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94–100.

[16] Suit H, DeLaney T, Goldberg S, Paganetti H, Clasie B, Gerweck L. Proton vs carbon ion beams in the definitive radiation treatment of cancer patients. Radiother Oncol 2010;95:3–22.

[17] Kadoya N, Obata Y, Kato T, Kagiya M, Nakamura T, Tomoda T, et al. Dose-volume comparison of proton radiotherapy and stereotactic body radiotherapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2011;79: 1225–31.

[18] Iwata H, Demizu Y, Fujii O, Terashima K, Mima M, Niwa Y, et al. Long-term outcome of proton therapy and carbon-ion therapy for large (T2a-T2bN0M0) non-small-cell lung cancer. J Thorac Oncol 2013;8:726–35.

[19] Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685–92.

[20] Baumann P, Nyman J, Hoyer M, Gagliardi G, Lax I, Wennberg B, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer – a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. Radiother Oncol 2008;88:359–67.

[21] van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: The PLUS multicentre randomized trial. Lancet 2002;359: 1388–93.

[22] Herder GJ, Kramer H, Hoekstra OS, Smit EF, Pruim J, van Tinteren H, et al. Traditional versus up-front (^{18}F)fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: A Dutch cooperative randomized study. J Clin Oncol 2006;24:1800–6.

[23] Belgers EH, Siebenga J, Bosch AM, van Haren EH, Bollen EC. Complete video-associated thoracoscopic surgery lobectomy and its learning curve. A single center study introducing the technique in The Netherlands. Interact Cardiovasc Thorac Surg 2010;10:176–80.

[24] Cronin P, Dwamena BA, Kelly AM, Carlos RC. Solitary pulmonary nodules: Meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. Radiology 2008;246:772–82.

[25] Nomori H, Watanabe K, Ohtsuka, Naruke T, Suemasu K, Uno K. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules. Lung Cancer 2004;45: 19–27.

Supplementary material available online

Supplementary Table I available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.974828.