

*research article*

# High dose hypofractionated proton beam therapy is a safe and feasible treatment for central lung cancer

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**Background.** There have been few reports about high total dose hypofractionated proton beam therapy for central lung cancer. The aim of this study was to examine retrospectively the safety and efficacy of high total dose hypofractionated proton beam therapy for central lung cancer.

**Patients and methods.** Patients treated by proton beam therapy for central lung cancer located less than 2 cm from the trachea, mainstem bronchus, or lobe bronchus were included in this study. All patients received 80 Gy of relative biological dose effectiveness (RBE) in 25 fractions with proton beam therapy over 5 weeks between January 2009 and February 2015. The toxicities were evaluated using the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer criteria.

**Results.** Twenty patients, including 14 clinically inoperable patients (70%), received proton beam therapy for central lung cancer. The median patient age was 75 years (range: 63–90 years), the median follow up time was 27.5 months (range: 12–72 months), and the median tumor diameter was 39.5 mm (range: 24–81 mm). All patients were followed for at least 20 months or until death. The 2-year overall survival rate was 73.8% (100% in operable patients, and 62.5% in inoperable patients), and the 2-year local control rate was 78.5%. There was no Grade 3 or higher toxicities, including bronchial stricture, obstruction, and fistula.

**Conclusions.** The present study suggests that a high total dose hypofractionated proton beam therapy for central lung cancer was safe and feasible.

Key words: central; lung cancer; hypofractionated; proton beam therapy

## Introduction

Lung cancer accounted for approximately 13% of total cancer diagnoses and was the most frequently diagnosed cancer worldwide in 2012.<sup>1</sup> In 2013, the number of lung cancer deaths was estimated to be 1.6 million, while 34.7 million disability-adjusted life-years were also caused. Specifically, it was the most common cause of cancer death globally, including both developing and developed countries.<sup>2</sup>

Early-stage lung cancer is treated via lung resection. However, an increasing number of people are now receiving radiotherapy, including stereotactic body radiotherapy (SBRT).<sup>3-5</sup> SBRT can also be used for inoperable patients, and several studies have also demonstrated that SBRT is as effective for stage I lung cancer as lung resection.<sup>5,6</sup> However, SBRT for centrally located lung cancer has been reported to cause more toxicity than for peripheral lung cancer.<sup>7</sup>

An increasing number of patients with lung cancer, including those with locally advanced lung cancer, have been treated using proton beam therapy (PBT) with or without chemotherapy.<sup>8-12</sup> The advantage of PBT is that it can shape the dose more conformally to the target volume than conventional radiotherapy or SBRT using X-ray irradiation, thus reducing the dose distributed to surrounding healthy structures.<sup>13-15</sup> However, few reports have been published regarding the use of PBT in the treatment of patients with central lung cancer.

The purpose of the present study was to evaluate retrospectively the efficacy and safety of PBT for central lung cancer.

## Patients and methods

### Ethics statement

The treatment methods and procedures were approved by the Ethics committee of our institution. The study was conducted in accordance with the Declaration of Helsinki. Patients signed informed consent.

### Patients

The present study enrolled patients who were diagnosed with central lung cancer and were treated with PBT between January 2009 and February 2015 at the Southern Tohoku Proton Therapy Center. Central lung cancer was defined as tumors located less than 2 cm from the trachea, mainstem bronchus, or lobe bronchus.<sup>7</sup> Patients were retrospectively recruited from our database.

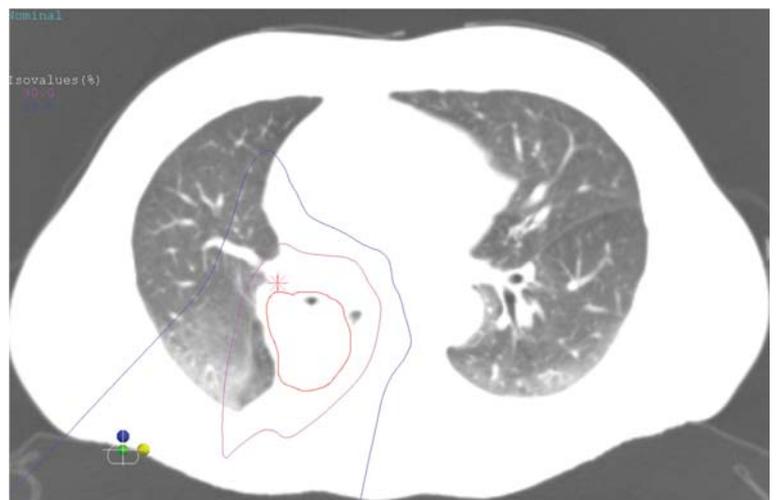
Whether or not the pathology of the lung tumor was histologically confirmed did not matter. If the pathology was not confirmed, an increase in the size of the lung tumor or high positron emission tomography (PET) uptake was regarded as a clinical malignancy. The clinical stage of the lung cancer was determined using computed tomography (CT) and PET-CT. Written informed consent was obtained from all of patients.

The inclusion criteria were as follows: (1) a solitary lung tumor without any previous treatment for it, (2) a World Health Organization performance status of 0–2, (3) no lymph node metastasis, and (4) the absence of distant other-organ metastasis or other sites of uncontrolled cancer. Patients with interstitial pneumonia were excluded from this study.

### Proton beam therapy

Treatment planning for PBT was based on 3-dimensional CT images taken at 2 mm intervals in the

exhalation phase while using a respiratory gating system (Anzai Medical, Tokyo, Japan). A custom-indexed vacuum-lock bag (Engineering System Co, Nagano, Japan) was used to immobilize the patients. A Xio-M treatment planning system (CMS Japan, Tokyo, Japan; and Mitsubishi Electric) was used to calculate the dose distributions for PBT. The gross tumor volume (GTV) included the lung tumor, the clinical target volume (CTV) was defined as the GTV plus 0.5 cm, and the planning target volume (PTV) was the CTV plus a 0.5 cm margin. The proton energy levels of 150 MeV and 210 MeV for 1–3 portals and a spread-out Bragg peak were tuned as much as possible until the PTV was exposed to a 90% isodose of the prescribed dose, and was not exposed to 110% isodose (upper limit) (Figure 1). The PBT system at our institute (Proton Beam System; Mitsubishi, Tokyo, Japan) uses a synchrotron and a passive scattering method in which a proton beam passes a bar ridge filter, a range shifter, and a customized compensator before entering the patient. The treatment was administered during the exhalation phase using a respiratory gating system. A multileaf collimator, which consisted of 40 iron plates with a width of 3.75 mm, and could be formed into an irregular shape, was used. Daily front and lateral X-ray imaging was used for positioning. The PBT for central lung tumors was set at 80 Gy of relative biological dose effectiveness (RBE) in 25 fractions over 5 weeks in our institution (isocenter prescription); the biological equivalent dose was 105.6 Gy when tumor alpha/beta ratio was regarded 10. The dose constraints were set for the esophagus ( $\leq 55$  Gy [RBE]), spinal cord ( $\leq 40$



**FIGURE 1.** Dose distribution map of proton beam therapy for central lung cancer. The red line represents the gross tumor volume and the purple line around the tumor represents the 90% dose line. The region outside the outermost blue line is allocated to < 10% radiation.

TABLE 1. The patient characteristics (n = 20)

Characteristics	Patients
Age (years)	
Median (range)	75 (63–90)
Gender	
Male	17 (85%)
Female	3 (15%)
Performance status	
0	8 (40%)
1	8 (40%)
2	4 (20%)
Charlson Index	
0	5 (25%)
1	6 (30%)
2	7 (35%)
3	2 (10%)
Follow-up time (months)	
Median (range)	27.5 (12–72)
Chronic obstructive pulmonary disease	
Yes	9 (45%)
No	11 (55%)
T category*	
T1	4 (20%)
T2	11 (55%)
T3	4 (20%)
T4	1 (5%)
Stage*	
I	15 (75%)
II	4 (20%)
III	1 (5%)
Tumor location	
Right upper lobe	7 (35%)
Right middle lobe	2 (10%)
Right lower lobe	6 (30%)
Left upper lobe	3 (15%)
Left lower lobe	2 (10%)
Histopathology	
Squamous cell carcinoma	8 (40%)
Adenocarcinoma	5 (25%)
Clinical malignancy	7 (35%)
Diameter of lung tumor (mm)	
Median (range)	39.5 (24–81)

\* Numbers correspond to the tumor-node-metastasis system of classification (International Union Against Cancer criteria)

Gy [RBE]), and heart ( $\leq 40$  Gy [RBE]) in principle. However, we did not reduce prescribed dose and irradiated over 40 Gy (RBE) to the heart when the lung tumor was too close to it.

## Evaluation and follow-up

All patients underwent either CT or PET-CT to evaluate the initial tumor response within 3 months after the completion of treatment. The initial treatment response was evaluated based on the Response Evaluation Criteria in Solid Tumors version 1.1.<sup>16</sup> A complete response was defined as the complete disappearance of all detectable tumors. In this study, a complete metabolic response (extinction of PET uptake) was also defined as a complete response.<sup>17</sup> A partial response was defined as  $\geq 30\%$  reduction in the maximal diameter of the tumor. Stable disease was defined as neither a partial response nor progressive disease. Progressive disease was defined as  $\geq 20\%$  enlargement of the primary tumor or the appearance of new lesions, including lymph node metastases and distant metastases. The evaluation of comorbidities was performed in accordance with Charlson *et al.* previously reported.<sup>18</sup> The follow-up interval was every 1–3 months for the first year and every 3–6 months thereafter. Imaging performed every 3–6 months after evaluating the initial tumor response. The cause of death was determined as lung cancer when patients had local recurrence or metastases and no other causes of death except for cancer, were presented. Toxicities were evaluated using the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer criteria.<sup>19</sup> The following dosimetric factors were examined with the use of a dose volume histogram of the lung minus the GTV and heart: mean lung dose, lung V5 (lung irradiated 5 Gy [RBE]), lung V10, lung V15, lung V20, and mean heart dose.

## Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics software program (version 22; SPSS Inc., Chicago, IL, USA). The overall survival (OS) time was defined as the time between the start of PBT and the time of the last follow-up examination or death. The Kaplan-Meier method and a log rank test were used to estimate the survival probability and compare the survival, respectively. The relationships between the occurrence of lung or heart toxicities and the dose volume histogram

factors were examined using the Mann-Whitney *U* test. All *p*-values were two-sided, and *p*-values of < 0.05 were considered to indicate statistical significance.

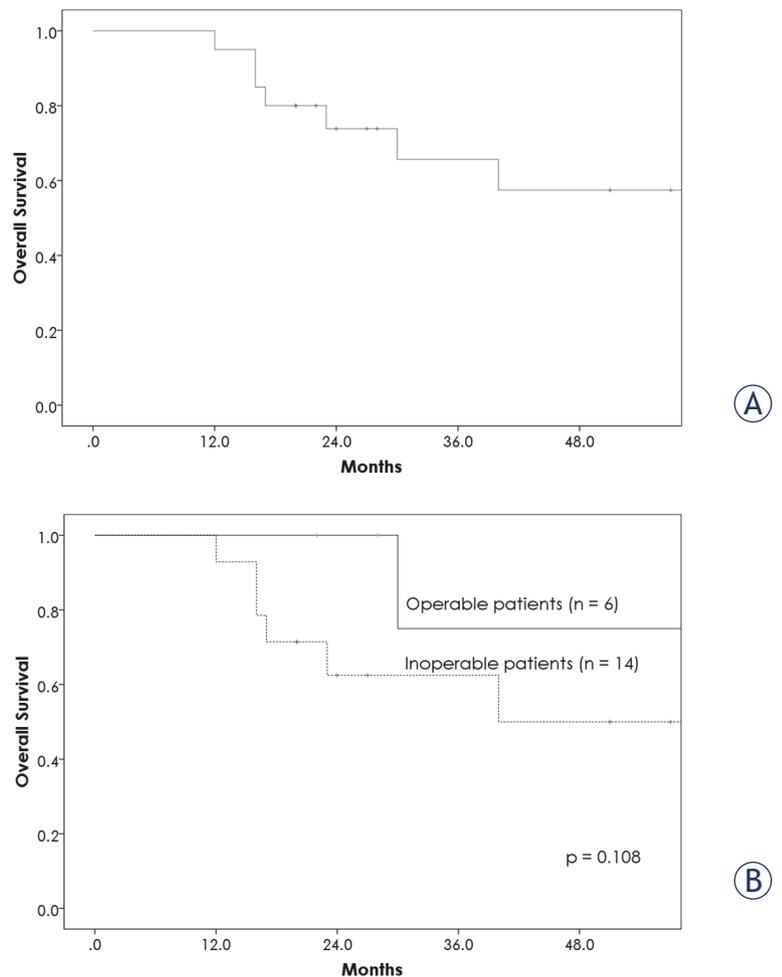
## Results

### Patients

The initial study population included 86 patients who received 80 Gy (RBE) for lung cancer. Patients were excluded from the analysis for the following reasons: lymph node metastasis, *n* = 13; distant other-organ metastasis, *n* = 13; treatment for lung cancer before PBT *n* = 7; other sites of uncontrolled cancer *n* = 5; interstitial pneumonia *n* = 9; and failure to satisfy the criteria of central lung cancer, *n* = 19. Thus, the characteristics of 20 patients, including 14 (70%) with clinically inoperable cancer due to poor respiratory function (*n* = 9), elderly (90 years old, *n* = 1), comorbidities (*n* = 4), as well as 9 (45%) with chronic obstructive pulmonary disease, were analyzed (Table 1). The median age was 75 years (range: 63–90 years), the median follow up time was 27.5 months (range: 12–72 months), the median tumor diameter was 39.5 mm (range: 24–81 mm), the median tumor volume 35.7 cc (range: 6.1–151.2 cc), and the median dose of mean PTV coverage was 79.5 Gy (RBE) (range: 75–81 Gy [RBE]).

### Survival and local control

All patients were followed for at least 20 months (living patients) or until death. The 1- and 2-year overall survival (OS) rates were 95.0% (95% confidence interval [CI]: 87.7–100%), and 73.8% (95% CI: 53.9–93.7%), respectively (Figure 2A). The 2-year OS rates of stage I and II/III were 80% and 53.3%, respectively. Six patients died of lung cancer, due to local recurrence (*n* = 3) and distant failure (*n* = 3) and 2 of other disease, due to heart failure (*n* = 1) and sepsis (*n* = 1). The 2-year OS rates for operable and inoperable patients were 100%, and 62.5%, respectively (Figure 2B), although the 2-year OS between the two groups was not significantly different (*p* = 0.109). Thirteen patients (65%) achieved a complete response, 5 (25%) achieved a partial response, and 2 (10%) achieved stable disease. The 2-year local control rate was 78.5% (95% CI: 59.5–97.5%); all local recurrences were in-field recurrence) (Figure 3A). The 2-year local control rates of lung cancers with diameters of ≤ 39.5 mm and > 39.5 mm (39.5 mm was the median tumor diameter) were 90% and 68.6%, respectively (Figure 3B), although the 2-year



**FIGURE 2. (A)** The overall survival rate of the patients treated for central lung cancer. The 1- and 2-year overall survival rates were 95.0% and 73.8%, respectively. **(B)** The 2-year overall survival rates of operable and inoperable patients were 100% and 62.5%, respectively.

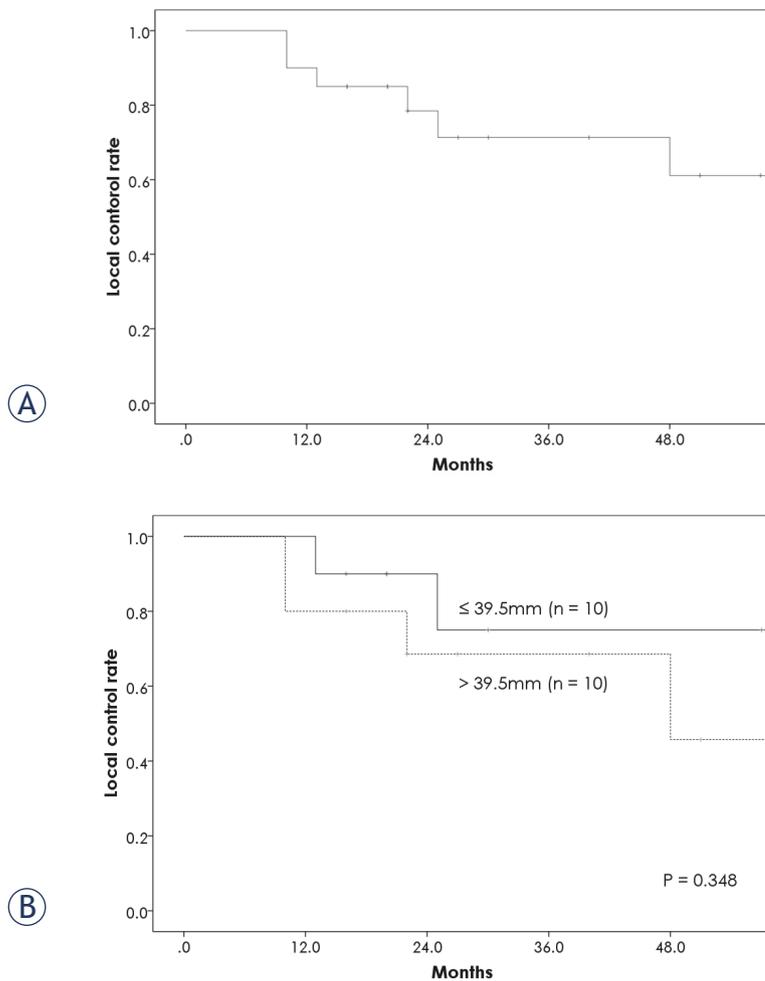
**TABLE 2.** Toxicities

Toxicities	Grade 0	Grade 1	Grade 2	Grade 3 - 5
Lung	0	18 (90%)	2 (10%)	0
Esophagus	20 (100%)	0	0	0
Heart	16 (80%)	4 (20%)	0	0
Bone	15 (75%)	3 (15%)	2 (10%)	0

local control rate between the two groups was not significantly different (*p* = 0.348).

### Toxicities

Table 2 shows the toxicities after PBT. The median dose of mean lung dose and mean heart dose were



**FIGURE 3.** (A) The local control rate for patients with central lung cancer after proton beam therapy. The 2-year local control rate was 78.5%. (B) The 2-year local control rates of lung cancers with a diameter  $\leq 39.5$  mm and  $> 39.5$  mm were 90% and 68.6%, respectively ( $p = 0.348$ ).

7.2 Gy (RBE) and 0.5 Gy (RBE), respectively. There were 2 patients (10%) with Grade 2 lung toxicities (both pneumonitis) and no patients with Grade 3

or higher lung toxicities, including bronchial stricture, obstruction, and fistula. Moreover, there were 2 patients (10%) with Grade 2 bone toxicities (both rib fracture). No Grade 2 or higher heart toxicities were observed, although 4 patients had Grade 1 toxicities (all of them pericardial effusion). Lastly, there were no esophageal toxicities, as no tumor included in the study was close enough to the esophagus. There were no statistically significant differences with regard to the dosimetric factors of mean lung dose (7.4 Gy [RBE] vs 7.0 Gy [RBE],  $p = 0.830$ ), lung V5 (18.2% vs 16.6%,  $p = 0.677$ ), lung V10 (16.1% vs 14.5%,  $p = 0.647$ ), lung V15 (14.8% vs 13.1%,  $p = 0.625$ ), and lung V20 (13.5% vs 12.0%,  $p = 0.629$ ) between patients with Grade 2 pneumonitis and those without it. Furthermore the dosimetric factors of mean heart dose (1.3 Gy [RBE] vs 1.9 Gy [RBE],  $p = 0.667$ ) between patients with Grade 1 pericardial effusion and those without it demonstrated no statistically significant differences.

## Discussion

Table 3 shows the OS of the present study and previous reports.<sup>20-23</sup> According to that, the 2-year OS of the present study was not inferior to that in previous studies. At our institution, PBT for central lung cancer delivered 3.2 Gy (RBE) per fraction, because a high dose per fraction using SBRT for central lung cancer was reported to be associated with a high risk of morbidity.<sup>7</sup> However, by comparing the outcomes between the present and previous studies, it was demonstrated that a high OS was achieved in our patients with high total dose, comparable with other series that used SBRT with a higher dose per fraction, although the ratio of T1 stage in the present study (20%) was less than that reported in previous studies (35–63%).<sup>20-23</sup> Nagata *et al.* reported on the outcomes of SBRT for opera-

**TABLE 3.** Overall survival of central lung cancer

	Number of patients	Median follow up time	treatment	Overall survival rate	All grade 3-5 toxicities
Song et al. (20)	9	26.5 months	SBRT	50% (2-year)	33%
Modh et al. (21)	125	17.4 months	SBRT	64% (2-year)	8%
Chaudhuri et al. (22)	34	18.4 months	SBRT	63.2% (2-year)	3%
Tekatli et al. (23)	80	47 months	SBRT	53% (3-year)	6.4%
Bush et al. (8)	33	48 months	PBT	Not applicable	0
present study	20	27.5 months	PBT	73.8% (2-year)	0

Abbreviations: SBRT = stereotactic body radiotherapy

ble and inoperable patients with lung cancer.<sup>5</sup> They reported that the 3-year OS of operable patients was superior to that of inoperable patients (76.5% vs 59.9%). In the present study, the OS of operable patients was also superior to that of inoperable patients, but not to a significant degree. Therefore, a better OS may be achieved if PBT for central lung cancer is only administered in medically operable patients who refused surgery.

Grade 3 or higher lung toxicities of SBRT for central lung tumor were reported at rates of 1.5–4.8%.<sup>21,22,24,25</sup> However, Bush *et al.* reported no Grade 3 or higher toxicities including lung toxicities after PBT for central lung cancer (table 3).<sup>8</sup> These results were consistent with the results the present study, even though the tumors irradiated were larger than those subjected to SBRT. These findings suggest that high total dose PBT may result in lower rates of lung toxicities than SBRT, although the relatively low dose per fraction may also have been involved. This finding may be because PBT can reduce the irradiated lung dose compared with SBRT.<sup>13</sup> Indeed, there have been some reports suggesting that reducing the lung dose leads to a low rate of lung toxicities. Matsuo *et al.* reported that the lung volume, which was irradiated with 25 Gy, was significantly associated with radiation pneumonitis.<sup>26</sup> Barriger *et al.* also reported that the mean lung dose and lung volume irradiated with 20 Gy was significantly associated with Grade 2–4 radiation pneumonitis.<sup>27</sup> PBT has the advantage of a dose fall-off associated with particle beams and as such offers the possibility of sparing healthy lung tissue, and the low rate of toxicities makes it an attractive potential treatment choice.

Regarding the impact of the total dose for the treatment lung cancer, Bush *et al.* reported that a high dose level PBT for lung cancer, including central lung cancer, significantly improved the 4-year OS compared with lower doses.<sup>8</sup> Nakayama *et al.* also reported good OS with high total dose for stage I peripheral and central lung cancer; specifically, patients with central lung cancer received 72.6 Gy (RBE) in 22 fractions.<sup>28</sup> These suggest that a higher total dose for lung cancer can improve the OS of patients with lung cancer. Paul *et al.* reported that SBRT resulted in an equivalent OS to surgery in patients with tumors sized  $\leq 2$  cm, but in an inferior OS in patients with tumors sized  $\leq 5$  cm.<sup>29</sup> Indeed, larger lung tumor resulted in a lower local control rate in the present study, but no statistically significance difference was observed. Therefore, a high dose may be needed to control the disease and prolong the OS in patients with lung tumors,

especially large tumors. PBT can increase the dose to tumors without increasing the lung dose compared with SBRT. PBT may therefore be useful for increasing the dose to lung tumors in order to achieve better control and prolong the OS.

Several limitations associated with the present study warrant mention. First, the number of patients was small. However, there have been few reports about PBT for central lung cancer, so we feel that the present study is still meaningful. Second, the present study was retrospective. Third, we did not examine the trachea with endoscopy, mainstem bronchus, or main bronchi. Therefore, bronchial stenosis and obstruction might have been more prevalent than we assumed. However, there were no problems clinically, as there was no Grade 3 or higher lung toxicities in the present study.

The present study suggests that high-dose hypofractionated PBT for central lung cancer is safe and feasible.

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