

# Clinical Outcomes of Proton Beam Therapy for Ground-Glass Opacity-Type Lung Cancer

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**Purpose:** Surgery is the standard treatment for early-stage non-small cell lung cancer (NSCLC), including ground-glass opacity (GGO)-type lung cancer. However, some patients are inoperable or refuse to undergo surgery. To explore whether proton beam therapy (PBT) can be an alternative to surgical resection in these patients, this study aimed to examine the retrospective treatment outcomes of patients with GGO-type lung cancer who underwent PBT.

**Patients and Methods:** Patients with stage I NSCLC and GGOs who underwent PBT at the Medipolis Proton Therapy and Research Center (Kagoshima, Japan) between April 2011 and September 2015 were included. Patients were treated with a total dose of 66 GyE delivered in 10 fractions. Survival curves were calculated using the Kaplan–Meier method, and treatment-related adverse events (AEs) were assessed.

**Results:** A total of 48 patients (median age: 70.9 ± 9.2 years; men: 54.2%) were analyzed, among whom 53 tumors were observed. The 3-year overall survival rate after PBT was 91.7% (95% confidence interval [CI], 79.3–96.8%), the 3-year disease-free survival rate was 85.4% (95% CI: 71.8–92.8%), and the 3-year local control rate among 53 tumors was 92.5% (95% CI: 81.1–97.1%). During the 3-year follow-up period, 4 patients died, and 3 survived despite recurrence or metastasis. Common AEs were radiation pneumonitis (89.6%), rib fracture (27.1%), and cough (27.1%). None of the patients developed grade ≥3 treatment-related AEs.

**Conclusion:** The results of this study suggest that PBT may be a promising alternative for patients with GGO-type lung cancer when surgical resection is not feasible, with excellent survival outcomes and tolerable treatment-related AEs.

**Keywords:** proton therapy, carcinoma, non-small-cell lung, ground-glass opacity, adenocarcinoma, Japan

## Introduction

Lung cancer is the leading cause of cancer-related deaths in Japan. In 2017, 74,120 people died of lung cancer, which accounted for 19.9% of all cancer deaths in Japan.<sup>1</sup> Surgical resection is the standard treatment for stage I non-small cell lung cancer (NSCLC) including ground-glass opacity (GGO)-type lung cancer.<sup>2</sup> However, some patients are medically inoperable due to presence of comorbidities or advanced age, and even operable patients may refuse to undergo surgery. For these patients, stereotactic body radiation therapy (SBRT), a technique used to deliver a high dose of radiation to the target, is a good alternative. However, the use of X-rays still involves the risk of radiation-induced complications, such as radiation pneumonitis, because X-rays require irradiation from multiple directions, thereby increasing the risk of radiation injury to normal tissues.

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Unlike photon beams such as X-rays, proton beams have a very rapid energy loss immediately before they stop within the body, resulting in a sharply localized peak of dose (Bragg peak).<sup>3</sup> As the depth of the Bragg peak is determined based on the energy of protons, varying the amount of energy enables the delivery of a desired dose over the target tumor volume, with minimal damage to normal tissues. With this characteristic, proton beam therapy (PBT) has the potential to improve the clinical outcomes of lung cancer patients with decreased toxicity, compared with photon radiation therapy.<sup>4</sup> In recent years, studies have demonstrated the efficacy and safety of PBT for early-stage NSCLC, some of which have supported PBT as a promising alternative for medically inoperable patients.<sup>5–8</sup>

The characteristics of GGOs on computed tomography (CT) scans can be defined as “hazy increased opacity of the lung, with preservation of the bronchial and vascular margins”<sup>9</sup> and observed in various pathologic entities from benign to malignant, including inflammation, organizing pneumonia, focal fibrosis, and lung adenocarcinoma.<sup>10,11</sup> Because most benign conditions usually resolve within 3 months<sup>10,12</sup> and even growing GGOs typically show an indolent course,<sup>13</sup> the current treatment strategies basically consider that GGOs <5 mm do not require treatment.<sup>13</sup> However, a portion of GGOs increase, although usually slowly, in size or density,<sup>13</sup> and persistent GGOs are highly suggestive of neoplastic conditions, including atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA).<sup>10</sup> As these lesions can develop into invasive adenocarcinoma, early treatment of these adenocarcinomas (GGO-type lung cancer) is important to achieve a better prognosis.<sup>12</sup>

Although the data on PBT for early-stage NSCLC are accumulating, no studies have specifically examined the efficacy and safety of PBT in patients with GGO-type lung cancer among early-stage NSCLCs. Additionally, a study published by Japan Clinical Oncology Group 0201 demonstrated that the lower a consolidation/tumor ratio, the better in prognosis.<sup>14</sup> Therefore, in this study, we aimed to retrospectively explore the treatment outcomes of patients with GGO-type lung cancer who underwent PBT at our center to generate new knowledge in order to determine whether PBT may be a good alternative for these patients when surgical resection is not feasible.

## Patients and Methods

### Patients

This retrospective observational study included all patients with GGO-type lung cancer who underwent PBT at the Medipolis Proton Therapy and Research Center (Kagoshima, Japan) between April 2011 and September 2015. Patients who had 1) histologically or clinically diagnosed stage I (T1a–c or T2a N0 M0) NSCLC through biopsy or high-resolution CT scans, and 2) GGOs identified on high-resolution CT scans were eligible for the study. All patients were diagnosed with GGO-type lung cancer at the time of referral to the facility. Additionally, the treatment decisions of these patients were confirmed at the cancer board conference held within the facility.

Information about this study, such as purposes, methods, and contact details, was posted at the study site, providing patients with an opportunity to opt out of the study. Thus, the study was exempted from taking individual agreement from each patient. This study was approved by the ethics committee of the Medipolis Proton Therapy and Research Center and was conducted in accordance with the Declaration of Helsinki (R2018-1).

### Proton Beam Therapy

The treatment plan was developed using a CT-based three-dimensional treatment planning system (XiO-M; Elekta, Stockholm, Sweden). Patients were immobilized in the supine position with a thermoplastic cast, and 2-mm-thick CT images were obtained during the exhalation phase using a respiratory gating system. The gross tumor volume (GTV) was identified from the images in the pulmonary window setting. The clinical target volume (CTV) was defined as the GTV plus a 5-mm margin in all directions. The planning target volume (PTV) was defined as the CTV plus a set-up margin of 5 mm and an internal margin, which was determined depending on the respiratory movements. The relative biological effectiveness (RBE) of the proton beam was determined to be 1.1, according to a previous study that compared the RBE of proton beam and photon (GyE = Proton Gy × 1.1).<sup>15</sup> In all patients, a total dose of 66 GyE in 10 fractions, which is a Japanese standard for proton beam therapy for Stage I lung cancer,<sup>16</sup> was delivered to the PTV. The patients were treated equal doses every time over 10 days (5 days a week). Patients were treated with proton beams produced by a PBT system employing the beam-wobbling method with a ridge filter to spread the

Bragg peak (Mitsubishi Electric Corporation, Tokyo, Japan). Patients were treated with 2-portal irradiation. The dose–volume constraint was set as lung V20 (lung volume receiving more than 20 Gy)  $\leq 30\%$ . Although this rule follows the Japanese standard, V20 is usually much lower in the actual treatments in both SBRT and proton beam therapy. Moreover, a study that compares dose volume of proton beam therapy and SBRT demonstrated that proton has less dose distributions for all OAR including V20 for lung.<sup>17</sup> Treatment was administered during the end-expiration phase using a respiratory gating system with two or four portals of proton beams arranged in a way that would minimize dose exposure to the normal tissue. The wobler method was used to produce the spread out Bragg Peak with 150 MeV proton beams.

After PBT, patients underwent follow-up examinations every 3 months for the first year and every 6 months thereafter. Regular follow-up examinations included chest CT and blood tests to identify the tumor markers.

## Outcomes and Analyses

Data on patient characteristics, tumor characteristics, PBT, and follow-up evaluations (eg, survival, tumor control, and adverse events [AEs]) were retrospectively collected. The efficacy outcomes were 3-year overall survival (OS), disease-free survival (DFS), and local control (LC) rates. The OS, DFS, and LC were calculated from the date of PBT using the Kaplan–Meier method. For safety, treatment-related AEs reported at any time during the follow-up were assessed and graded according to the Common Terminology Criteria for Adverse Events v4.0. All analyses were performed using SAS Release 9.4 (SAS Institute, Cary, NC, USA).

## Results

### Patient and Tumor Characteristics

Of the 49 patients included, 1 who was lost to follow-up was excluded from the analysis. Thus, 48 patients were analyzed. The median  $\pm$  standard deviation (SD) age of these 48 patients was  $70.9 \pm 9.2$  years, and 54.2% were men (Table 1). The median follow-up period was 49 months. Of these, 11 (22.9%) patients had a past history of lung cancer, among whom 9 had surgery, 1 had chemoradiation therapy, and 1 had chemoradiation therapy and radiofrequency ablation. Patients for whom PBT was chosen over surgery for clinical reasons (ie, complication, high age, and clinical preference) accounted for 20.8% of

**Table 1** Patient Characteristics

	Total	
	(n = 48)	
Age (years)		
Median (SD)	70.9	(9.2)
Sex		
Male	26	(54.2)
Brinkman Index (cigarettes/day $\times$ years)		
0 (non-smoker)	25	(52.1)
1–1,000	13	(27.1)
1,001–2,000	10	(20.8)
Past history of cancer		
Lung cancer	11	(22.9)
Other cancer	14	(29.2)
None	23	(47.9)
Reasons for PBT		
Complications	5	(10.4)
Elderly	4	(8.3)
Clinically preferred	1	(2.1)
Patient preference	29	(60.4)
Refusal of surgery	9	(18.8)
ECOG performance status		
0	43	(89.6)
1	3	(6.3)
2	1	(2.1)
3	1	(2.1)

**Note:** Data are presented as numbers and percentages unless otherwise indicated.  
**Abbreviations:** SD, standard deviation; PBT, proton beam therapy; ECOG, Eastern Cooperative Oncology Group.

the study population, while those for whom PBT was chosen as their preferred treatment or as they refused to undergo surgery accounted for 79.2% of the population.

Among the 48 patients, 53 tumors were observed. The characteristics of these tumors are summarized in Table 2. Of these, 44 (83.0%) were stage IA1–3, while 9 (17.0%) were stage IB. According to the radiological diagnosis, the most frequent subtypes of GGO adenocarcinomas were lepidic-predominant adenocarcinoma (LPA, 52.8%), followed by AIS (28.3%), MIA (17.0%), and AAH (1.9%). Only 16 of 53 tumors were diagnosed through biopsy, whose histological types were adenocarcinomas (10/16), alveolar cell carcinoma (1/16), and unknown despite biopsy (5/16).

### Survival and Local Control

The 3-year OS rate after PBT among 48 patients was 91.7% (95% confidence interval [CI], 79.3–96.8%)

**Table 2** Tumor Characteristics

Clinical Stage (UICC 8th Edition)	Total: 53 Tumors	
IA1	2	(3.8)
IA2	26	(49.1)
IA3	16	(30.2)
IB	9	(17.0)
Subtype of GGO adenocarcinoma		
AAH	1	(1.9)
AIS	15	(28.3)
MIA	9	(17.0)
LPA	28	(52.8)
Biopsy for diagnosis		
TBLB/TBB	12	(22.6)
CT-guided biopsy	3	(5.7)
BAL	1	(1.9)
Not performed	37	(69.8)

**Abbreviations:** UICC, Union for International Cancer Control; GGO, ground-glass opacity; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; LPA, lepidic-predominant adenocarcinoma; TBLB, transbronchial lung biopsy; TBB, transbronchial biopsy; CT, computed tomography; BAL, bronchoalveolar lavage.

(Figure 1). The 3-year DFS rate among 48 patients was 85.4% (95% CI: 71.8–92.8%). The 3-year LC rate among 53 tumors was 92.5% (95% CI: 81.1–97.1%).

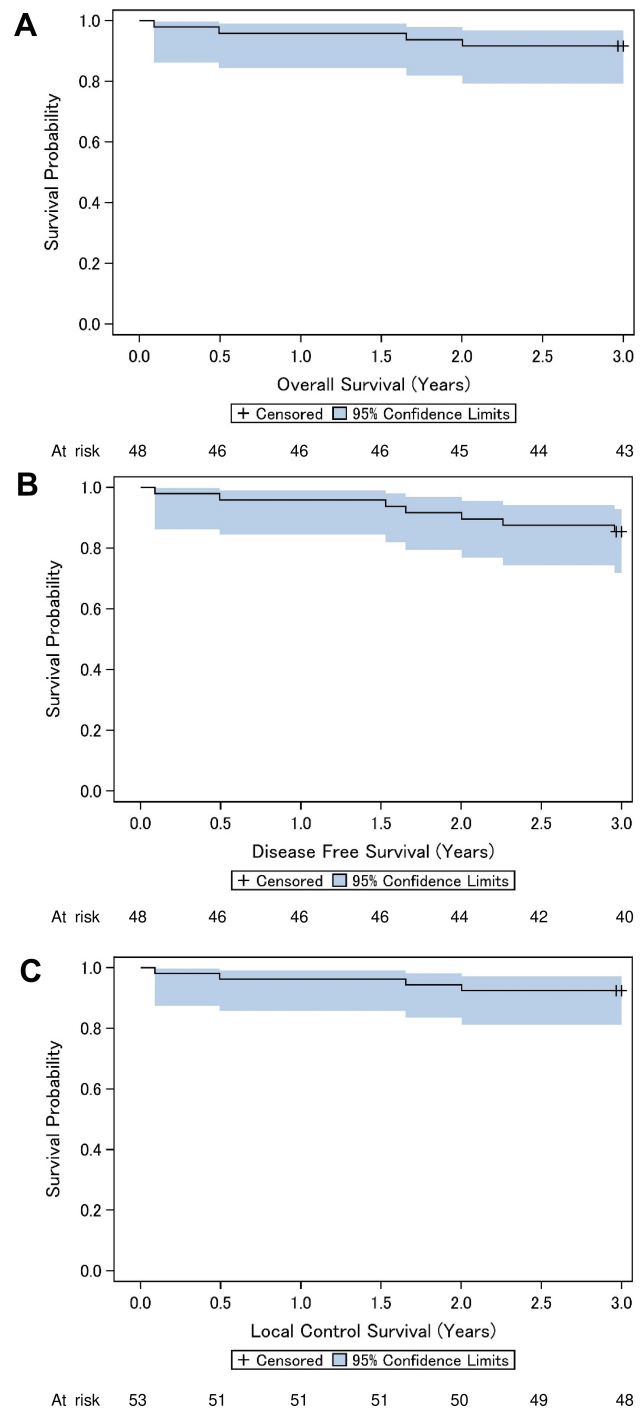
During the 3-year follow-up, 4 patients died (patient #1, 2, 5, and 6), and 3 survived despite recurrence or metastasis (patient #3, 4, and 7). Data of these 7 patients with death or recurrence during the 3-year follow-up are summarized in Table 3.

### Adverse Events

Overall, none of the patients developed grade ≥3 treatment-related AEs (Table 4). The most common AE was radiation pneumonitis: 37 (77.1%) developed grade 1, while 6 (12.5%) developed grade 2 radiation pneumonitis. Of the 48 patients, 13 (27.1%) had rib fractures, all of which were grade 1. Cough was reported in 13 (27.1%) patients, among which 11 (22.9%) had grade 1 and 2 (4.2%) had grade 2 cough. Other reported AEs were grade 1 pleural effusion (n = 1), grade 1 pleurisy (n = 1), and grade 1 chest pain (n = 8). None of the patients reported dermatitis.

### Discussion

In this study, to generate new knowledge on the potential of PBT as an alternative to surgical resection, particularly in patients with GGO-type lung cancer among early-stage



**Figure 1** Overall survival, disease-free survival, and local control rates. (A) Overall survival curve for 48 patients. (B) Disease-free survival curve for 48 patients. (C) Local control curve for 53 tumors.

NSCLC, we retrospectively examined the treatment outcomes of 48 patients with GGO-type lung cancer who received PBT at our center. Although some AEs such as radiation pneumonitis, rib fracture, and cough occurred at a relatively high rate, these patients had excellent survival with no grade ≥3 treatment-related AEs, and a high local control rate was achieved.

**Table 3** Summary of Patients Who Died or Experienced Recurrence Following PBT (n = 7)

#	Age, y	Sex	PS	Stage	TNM	Tumor Type	History of Cancer	Recurrence/ Metastasis	AE	Complications
1	87	M	1	IA3	T1c N0 M0	MIA	Chemoradiotherapy for left upper lobe lung cancer	Dead	Gr.I RP (3 months)	None
2	79	F	2	IA3	T1c N0 M0	AIS	Surgery for primary lung cancer (lymph node dissection)	Metastasis to the pancreas or primary pancreatic cancer	Gr.I RP (6 months)	None
3	76	M	0	IA2	T1b N0 M0	AIS	Surgery for left lung cancer (pT2N0M0; stage IB)	CR for treated site, three GGOs at left lower lobe	Gr.I RP (8 months)	None
4	63	M	0	IA2	T1b N0 M0	MIA	Surgery for bladder cancer	CR for treated site, GGO at left S1 + S2	Gr.I RP	None
5	85	M	1	IA3	T1c N0 M0	LPA	Surgery for right lung cancer	Dead	Unknown	Cardiac aortic aneurysm (received stent grafting)
6	80	M	0	IB	T2a N0 M0	LPA	None	Dead	None	Hypertension, unruptured cerebral aneurysm, thoracic aneurysm, hemorrhagic duodenal ulcer
7	66	M	0	IB	T2a N0 M0	LPA	None	CR for treated site, #4R lymph node showed slight growth	Gr.I RP (3 months)	bronchial asthma, diabetes, prostatitis

**Abbreviations:** PBT, proton beam therapy; PS, performance status; MIA, minimally invasive adenocarcinoma; AIS, adenocarcinoma in situ; LPA, lepidic-predominant adenocarcinoma; AE, adverse event; CR, complete response; RP, radiation pneumonitis.

The 3-year OS rate after PBT in patients with GGO-type lung cancer was 91.7%. Although direct comparison is not appropriate, our results were similar to or better than those reported in previous retrospective studies of PBT for stage I NSCLC in Japan (3-year OS = 61–90%),<sup>5–7</sup> and even higher than the 3-year OS after SBRT for early-stage NSCLC (55.8–76.5%),<sup>18–20</sup> The standard treatment option for GGO-type lung cancer is still surgical resection. However, our results suggest that the prognosis after PBT may not be far inferior to that after lobectomy or segmentectomy for stage I lung adenocarcinomas (3-year OS = 94.1–96.9%<sup>21,22</sup>), which would support PBT as a positive alternative, especially when surgical resection is not feasible.

In addition to the survival rate, the 3-year LC rate after PBT was also high (92.5%). Although direct comparison is

not appropriate due to the differences in study designs and methods, the LC rate observed in this study was high, similar to those achieved by SBRT for stage I lung cancer (80–97%).<sup>23</sup> However, one study previously reported that the 3-year LC after SBRT for biopsy-proven or radiographically diagnosed bronchioloalveolar carcinoma (ie, MIA and AIS) was 100%, although the sample size was small (n=18).<sup>24</sup> The efficacy of PBT versus SBRT specifically for GGO-type lung cancer may be worthy of further study.

Of the 48 patients included in this study, 3 patients survived despite recurrence or metastasis, and 4 patients died in the 3-year follow-up period. The number of patients in this study with worse prognosis was relatively small, and other techniques also share these risks. For example, one study previously reported that 5 of 97 (5.1%) patients with GGOs

**Table 4** Adverse Events Reported During the Follow-Up Period (n = 48)

	No Event <sup>a</sup>	Status Unknown <sup>b</sup>	Grade	
			1	2
Radiation pneumonitis	3	2	37 (77.1)	6 (12.5)
Rib fracture	32	3	13 (27.1)	–
Cough	27	8	11 (22.9)	2 (4.2)
Pleural effusion	45	2	1 (2.1)	–
Pleurisy	45	2	1 (2.1)	–
Chest pain	32	8	8 (16.7)	–

**Notes:** Data are presented as n or n (%); The proportions were calculated using the total number of patients (n = 48) as a denominator; <sup>a</sup>The number of patients in whom AE was confirmed absent; <sup>b</sup>The number of patients for whom the presence or absence of each AE was unknown due to lack of data.

experienced recurrence after wedge resection (4 had local recurrence and 1 had distant metastasis).<sup>25</sup> Another study reported that 9 of 18 patients with biopsy-proven or radiographically diagnosed bronchioalveolar carcinoma developed metastases after SBRT, although none had local failure.<sup>24</sup> Considering these, the recurrence or metastasis rates may not be high for PBT; nevertheless, it is important to acknowledge the existence of these risks.

Although a large proportion of patients (89.6%) developed radiation pneumonitis, most of them (37/43) were grade 1 and none were grade  $\geq 3$ . A meta-analysis previously reported that early-stage NSCLC patients who received particle beam therapy, including PBT, had a lower incidence of grade  $\geq 3$  radiation pneumonitis than those with photon SBRT (0.9% vs 3.4%,  $p < 0.001$ ).<sup>26</sup> As the reduced dose to the normal lung is one advantage of PBT over photon SBRT,<sup>27</sup> PBT may be associated with a lower risk of severe radiation pneumonitis, which is worth investigating in further research. Another noticeable AE was rib fracture (27.1%), which was consistent with previous reports on PBT for stage I NSCLC (26.3–35.7%).<sup>5–7</sup> Although the proportion was relatively high, all cases were grade 1, indicating that they were asymptomatic or required no treatment. Cough was also relatively common (27.1%) among our study population, which may be the clinical manifestation of radiation pneumonitis. Although dermatitis has been frequently reported in previous studies,<sup>5–7</sup> no dermatitis was reported in our study population. Overall, as no grade  $\geq 3$  AEs were reported in this study, PBT may be considered a relatively tolerable treatment.

For the first time, this study suggested that PBT may be a good alternative for patients with GGO-type lung cancer. However, because this study had no control group,

conclusions could not be drawn on whether PBT was indeed comparable or superior to existing techniques such as photon SBRT, which needs to be confirmed in future research. One limitation inherent in its retrospective design was the lack of available data, such as the operability of patients. Because PBT was chosen due to patient preference rather than clinical reasons for the majority of patients, most of our study population may have been operable, which may have contributed to the better survival outcomes. Second, because of the relatively short follow-up period (median: 49 months), the survival analysis was limited to 3 years. Long-term efficacy and safety should be examined in a future study. Third, because 37 out of 53 tumors were diagnosed clinically through high-resolution CT scan, malignancy of these tumors was uncertain compared with those diagnosed histologically. This uncertainty could influence the outcome. Furthermore, while radiation pneumonia and rib fractures were detected using imaging modalities, other AEs basically depended on patients' self-reports, which may have resulted in underestimation of these AEs. In addition, data of AEs were unavailable for some patients, which implies a potential for underreporting of some important AEs. Thus, our results need to be interpreted with caution.

## Conclusion

The results of this study suggest that PBT may be a promising alternative for patients with GGO-type lung cancer when surgical resection is not feasible, with excellent survival outcomes and tolerable treatment-related AEs. Future prospective, confirmatory studies are warranted to elucidate the advantages of PBT over other treatment options for the treatment of these patients.

## Disclosure

The authors declare that they have neither conflict of interest nor financial support.

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