Late radiological changes after passive scattering proton beam therapy for Stage I lung cancer

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ABSTRACT

This study aimed to examine late radiological changes after proton beam therapy (PBT) for early-stage non–small cell lung cancer (NSCLC) and to clarify correlations between mass-like radiological changes and patient characteristics. CT scans of patients who underwent passive scattering PBT for T1–2N0M0 NSCLC were analyzed retrospectively. Patients were considered eligible if follow-up CT was performed for at least 2 years, with no definite evidence of local recurrence. The following five periods were defined: (i) 6–12 months, (ii) 12–24 months, (iii) 24–36 months, (iv) 36–48 months and (v) 48–60 months after PBT. Late (≥6 months) radiological changes were scored by consensus of three radiation oncologists according to classifications set forth by Koenig (Radiation injury of the lung after three-dimensional conformal radiation therapy. AJR Am J Roentgenol 2002;178:1383–8.). CT scans of 113 patients (median follow-up, 36 months; range, 24–137 months) were evaluated. Late radiological changes during Periods (i), (ii), (iii), (iv) and (v) included modified conventional pattern (80%, 79%, 72%, 58% and 56%, respectively), mass-like changes (8%, 9%, 14%, 22% and 18%, respectively), scar-like changes (4%, 9%, 11%, 17% and 24%, respectively) and no increased density (8%, 3%, 3%, 2% and 2%, respectively). Mass-like changes were observed in 23 patients (20%). Among patients who developed mass-like changes, the median interval between the initiation of PBT and the onset of mass-like changes was 19 months (range, 6–62 months). In multivariate analysis, a peripheral location was found to be a significant factor (P = 0.035; odds ratio: 4.44; 95% confidence interval: 1.12–21.28). In conclusion, mass-like changes were observed in 20% of patients who underwent PBT. Patients with peripheral tumors showed a higher incidence of mass-like changes.

Keywords: lung cancer; radiation therapy; proton beam therapy; radiological change

INTRODUCTION

Recent studies have shown that surgery and high-dose radiotherapy for early-stage non–small cell lung cancer (NSCLC) have similar outcomes [1, 2], and high-dose radiotherapy has been performed increasingly as a curative treatment option, even for operable patients [3, 4]. Proton beam therapy (PBT) can provide an inherently 3D conformal dose distribution without exposing surrounding normal tissue to extra radiation. PBT has been performed clinically for the treatment of NSCLC in selected patients at National Cancer Center Hospital East since 1999 [5]. Routine CT surveillance following radiotherapy may promote early detection of local recurrences. However, it is often difficult to distinguish benign post-treatment mass-like radiological changes, which usually appear 6 months or more after the initiation of radiotherapy from persistent or recurrent tumors [6]. Difficulties surrounding early diagnosis of local recurrences may reduce the chance of successful salvage surgery. Therefore, information such as when and how often benign mass-like radiological changes occur as a consequence of lung radiotherapy is important. Several studies have examined the features of
radiological lung changes following stereotactic body radiotherapy (SBRT) [6–12]. However, to the best of our knowledge, no study has focused on radiological lung changes following PBT. This study aimed to examine late radiological changes after PBT for early-stage NSCLC, and to clarify correlations between mass-like radiological changes and patient characteristics.

**MATERIALS AND METHODS**

**Patient characteristics**
CT scans of patients who underwent PBT for T1-2N0M0 [Union for International Cancer Control (UICC), 7th edition] NSCLC at National Cancer Center Hospital East between 2003 and 2013 were retrospectively analyzed. Patients were considered eligible if follow-up CT was performed for ≥2 years, with no definite evidence of local recurrence. This study was performed with the approval of our Institutional Review Board.

**Treatment planning**
Initial staging procedures were encouraged to include bronchoscopy and CT. Positron emission tomography (PET)-CT was performed for patients without histologic confirmation of cancer. Patients with increasing lung nodules showing abnormal fluorodeoxyglucose (FDG) uptake, as typically characterized by a maximum standardized uptake value (SUV) >2.5, were also considered eligible for PBT. Thoracic CT images were obtained in the exhalation phase with a respiratory gating system. The primary tumor was delineated on a lung window as the gross tumor volume (GTV). The clinical target volume (CTV) was defined as the GTV with an 8-mm margin in all directions of subclinical tumor extension. The planning target volume (PTV) was defined as the CTV with a set-up margin of 5 mm and an internal margin to account for uncertainty of respiratory motion. From April 2011, we added a 4-mm proximal and distal margin to the PTV, considering the uncertainty of the range of proton beams. Passive scattering PBT with one to three ports was used with respiratory gating systems.

**Follow-up procedures**
Typically, follow-up CT examinations were performed every 6 months after PBT. If local recurrence was suspected, bronchoscopy or PET-CT was performed to confirm it.

**Scoring of radiological changes**
Lung changes after 6 months from the initiation of PBT were defined as late radiological changes. To characterize late radiological changes over time, the following five periods were defined: (i) 6–12 months, (ii) 12–24 months, (iii) 24–36 months, (iv) 36–48 months and (v) 48–60 months after PBT. CT changes during Periods (i)–(v) were classified into the following four categories according to Koenig’s classification [11, 13]: (1) modified conventional pattern (consolidation, volume loss, and bronchiectasis); (2) mass-like pattern; (3) scar-like pattern; and (4) no evidence of increased density (Fig. 1). Scoring of radiological changes was performed by the consensus of three radiation oncologists.

**Statistical analysis**
The Statistical Package of Social Sciences (SPSS version 21.0, Chicago, USA) was used for statistical analysis. Time to onset of mass-like changes from the initiation of PBT was estimated using the Kaplan–Meier method.

A tumor within 2 cm of the proximal bronchial tree (the distal 2 cm of the trachea, carina, and main bronchi, or adjacent to the esophagus and major vessels) was defined as a centrally located tumor. Otherwise, a tumor was defined as a peripherally located tumor.

![Fig. 1. Classification of late radiological changes after proton beam therapy.](image-url)
Univariate and multivariate analyses were performed to examine potential associations between the incidence of mass-like changes and baseline factors (age, sex, forced expiratory volume in 1 s [FEV 1.0], smoking history, chronic obstructive pulmonary disease [COPD], pathology, T stage, lobe, location, PTV, dose fractionation, and radiation pneumonitis). The irradiated lung volumes (V5, V10, V20, V50 and V100) were also included in uni- and multivariate analyses. Vx indicates the percentage of the lung volume without gross tumor volume that received x Gy or more. The doses were calculated as an equivalent dose in 2-Gy fractions (EQD2) according to the linear–quadratic model with an α/β ratio of 4.0 Gy.

In univariate analysis, Pearson’s chi-square test was used to determine the significance of intergroup differences for discontinuous variables, and the independent t-test was used for continuous variables. Multivariate logistic regression analysis was performed for factors with P-values of <0.25 in univariate analysis. P < 0.05 (two-tailed) was considered statistically significant.

### RESULTS

Four patients developed local recurrences during the study period. CT scans of 113 patients with no definite evidence of local recurrences were evaluated. The median follow-up was 36 months

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### Table 1. Patient characteristics

| Factor               | Number of patients |
|----------------------|--------------------|
| Age (range)          | 75 years (48–94)   |
| Sex                  |                    |
| Female               | 36 (32%)           |
| Male                 | 77 (68%)           |
| FEV 1.0 (range)      | 1.6 L (0.7–3.5)    |
| Smoking history      |                    |
| Yes                  | 79 (70%)           |
| No                   | 34 (30%)           |
| COPD                 |                    |
| Yes                  | 30 (27%)           |
| No                   | 83 (73%)           |
| Pathology            |                    |
| Adenocarcinoma       | 38 (34%)           |
| Squamous cell carcinoma | 13 (12%)       |
| Other                | 4 (4%)             |
| Not proven           | 58 (51%)           |
| Lobe                 |                    |
| Right upper          | 34 (30%)           |
| Right middle         | 5 (4%)             |
| Right lower          | 26 (23%)           |
| Left upper           | 31 (27%)           |
| Left lower           | 17 (15%)           |
| Location             |                    |
| Central              | 42 (37%)           |
| Peripheral           | 71 (63%)           |
| T stage (UICC 7th)   |                    |
| T1                   | 82 (73%)           |
| T2                   | 31 (27%)           |
| Gross tumor volume   | 9.2 mL (0.8–58.0)  |
| Clinical target volume | 33.1 mL (4.0–124.1)|
| Planning target volume | 59.0 mL (12.1–187.0)|
| Dose fractionation   |                    |
| 80 Gy (RBE) in 20    | 73 (65%)           |

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### Table 1. Continued

| Factor               | Number of patients |
|----------------------|--------------------|
| FEV 1.0 = forced expiratory volume in 1 s, COPD = chronic obstructive pulmonary disease, UICC = Union for International Cancer Control, RBE = relative biological effectiveness, Vx = the percentage of the lung volume without gross tumor volume that received x Gy or more. The doses were calculated as an equivalent dose in 2-Gy fractions (EQD2) according to a linear–quadratic model with an α/β ratio of 4.0 Gy. |
| Number of ports      |                    |
| 1                    | 1 (1%)             |
| 2                    | 109 (96%)          |
| 3                    | 3 (3%)             |
| Irradiated lung volumes (mean ± SD) |          |
| V5                   | 11.4 ± 4.4%        |
| V10                  | 10.4 ± 3.9%        |
| V20                  | 9.0 ± 3.5%         |
| V50                  | 4.4 ± 2.6%         |
| V100                 | 2.1 ± 1.7%         |
| Radiation pneumonitis|                    |
| ≤ Grade 1            | 105 (93%)          |
| ≥ Grade 2            | 8 (7%)             |

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(range, 24–137 months). The numbers of evaluated CT scans for Periods (i), (ii), (iii), (iv) and (v) were 143, 235, 193, 88 and 62, respectively. Patient characteristics are summarized in Table 1.

Patterns of late radiological changes are shown in Fig. 2. Mass-like radiological changes were observed in 23 patients (20%). The cumulative incidence of mass-like changes is shown in Fig. 3. The 3-year cumulative incidence of mass-like changes was 16.4%. Among patients who developed mass-like changes, the median interval between the initiation of PBT and the onset of mass-like changes was 19 months (range, 6–62 months).

Univariate analysis revealed that $V_{5}$ ($P = 0.043$) and $V_{10}$ ($P = 0.023$) were significantly correlated with the incidence of mass-like changes. Female sex ($P = 0.081$), peripheral location ($P = 0.070$), $V_{10}$ ($P = 0.097$) and $V_{100}$ ($P = 0.059$) showed a trend for a higher incidence (Table 2). In multivariate analysis, peripheral location was found to be a significant factor ($P = 0.035$; odds ratio: 4.44, 95% confidence interval: 1.12–21.28) (Table 3).
Continued

Table 2

| Factor                      | Patients with mass-like changes (n = 23) | Patients without mass-like changes (n = 90) | P-value |
|-----------------------------|----------------------------------------|--------------------------------------------|---------|
|                             |                                        |                                            | 0.293   |
| Dose fractionation          |                                        |                                            |         |
| 80 Gy (RBE) in 20           | 18 (78%)                               | 55 (61%)                                   |         |
| 66 Gy (RBE) in 10           | 5 (22%)                                | 34 (38%)                                   |         |
| 60 Gy (RBE) in 20           | 0 (0%)                                 | 1 (1%)                                     |         |
| V5 (mean ± SD)              | 9.8 ± 3.5%                             | 11.8 ± 4.4%                                | 0.043   |
| V10 (mean ± SD)             | 9.0 ± 3.2%                             | 10.6 ± 4.4%                                | 0.097   |
| V20 (mean ± SD)             | 7.9 ± 2.9%                             | 9.3 ± 3.6%                                 | 0.100   |
| V50 (mean ± SD)             | 3.7 ± 1.2%                             | 4.5 ± 2.4%                                 | 0.023   |
| V100 (mean ± SD)            | 1.8 ± 0.8%                             | 2.2 ± 1.6%                                 | 0.059   |
| Radiation pneumonitis       |                                        |                                            | 0.567   |
| ≤ Grade 1                   | 22 (96%)                               | 83 (92%)                                   |         |
| ≥ Grade 2                   | 1 (4%)                                 | 7 (8%)                                     |         |

SD = standard deviation, FEV1.0 = forced expiratory volume in 1 s, COPD = chronic obstructive pulmonary disease, RBE = relative biological effectiveness, Vx indicates the percentage of the lung volume without gross tumor volume that received x Gy or more. The doses were calculated as an equivalent dose in 2-Gy fractions (EQD2) according to a linear–quadratic model with an α/β ratio of 4.0 Gy. Values in boldface type indicate statistically significant difference.

DISCUSSION

To the best of our knowledge, this is the first report focusing on radiological lung changes following PBT. The incidence of mass-like changes was similar to that following SBRT, as previously reported [7, 8, 10–12]. It is difficult to distinguish between benign mass-like changes and local recurrences. Dunlap et al. reported that all patients with local recurrences experienced consecutive rises in the volume of mass-like consolidation on serial CT imaging at 3-month intervals [8]. Fluorodeoxyglucose positron emission tomography (FDG-PET) is commonly performed when local recurrence is suspected on CT. However, the usefulness of FDG-PET in distinguishing between benign post-treatment radiological changes and local recurrences is controversial [14]. Huang et al. reported that a maximum standardized uptake value threshold of 5 at 3–6 months post-SBRT may serve as a useful cut-off value for identifying lesions at high risk of subsequent local failure [6].

We found a higher incidence of mass-like changes in patients with peripheral tumors than in those with central tumors. Furthermore, patients with mass-like changes had smaller irradiated lung volumes throughout low to high doses than those without mass-like changes, although some factors were not statistically significant. These facts suggest that larger irradiated lung volumes have a negative impact on the incidence of mass-like changes. Larger irradiated lung volumes may frequently cause diffuse lung changes, such as a modified conventional pattern. On PBT, patients with peripheral tumors can spare larger lung volumes without radiation exposure than those with central tumors. This may lead to the lower incidence of mass-like changes.

Senthin et al. reported that mass-like changes were observed much less frequently after arc SBRT compared with after fixed-beam SBRT [7]. This is compatible with our hypothesis that larger irradiated lung volumes have a negative impact on the incidence of mass-like changes. To examine the occurrence of mass-like changes, CT scans with short intervals, FDG-PET, and/or biopsy need to be performed in order to rule out local recurrences, despite their low incidence. If SBRT or PBT procedures affect the incidence of mass-like changes, techniques should be developed to minimize the possibility of causing these changes. The development of treatment techniques with a similar local control rate, similar toxicity, and lower incidence of mass-like changes will be beneficial for patients.

The present study has some limitations. First, patients who were diagnosed with local recurrence were excluded from our analyses. However, some patients who had local recurrence might also have been included in this analysis because it was difficult to precisely differentiate between local recurrences and benign post-treatment mass-like radiological changes, even though most patients with suspected local recurrence underwent additional examinations like bronchoscopy or PET-CT. Moreover, scoring of radiological changes was subjective, although scores were determined by consensus of three radiation oncologists, as was done in the study of Dahele et al. [11], which was focused on radiological changes after SBRT.

In conclusion, mass-like radiological changes were observed in 20% of patients who underwent PBT. Patients with peripheral tumors showed a higher incidence of mass-like changes.

Table 3. Multivariate analysis on the incidence of mass-like radiological changes and patient characteristics

| Factor                      | P-value | Odds ratio (95% confidence interval) |
|-----------------------------|---------|-------------------------------------|
| Location                    | 0.035   | 4.44 (1.12–21.28)                   |
| Planning target volume      | 0.121   |                                     |
| V5                          | 0.133   |                                     |
| V20                         | 0.176   |                                     |
| Sex                         | 0.204   |                                     |
| V100                        | 0.551   |                                     |
| V10                         | 0.648   |                                     |
| V50                         | 0.894   |                                     |

Vx indicates the percentage of the lung volume without gross tumor volume that received x Gy or more. The doses were calculated as an equivalent dose in 2-Gy fractions (EQD2) according to a linear–quadratic model with an α/β ratio of 4.0 Gy. Values in boldface type indicate statistically significant difference.
CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest.

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