Association of Computed Tomography-detected Pulmonary Interstitial Changes with Severe Radiation Pneumonitis for Patients Treated with Thoracic Radiotherapy

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Interstitial lung disease/Interstitial pulmonary fibrosis/Lung cancer/Radiation pneumonitis/Radiotherapy.

We evaluated associations of interstitial changes with radiation pneumonitis (RP) for patients treated with thoracic radiotherapy. Between 2005 and 2009, patients who received thoracic radiotherapy of 40 Gy or more for lung cancer or thymic tumors and were followed-up for more than 6 months were eligible for this study. Possible risk factors for RP included the presence of interstitial changes on computed tomography before radiotherapy, and elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels; these were compared with the incidences of severe RP. A total of 106 patients were included. The incidences of RP were 4 (4%), 0 (0%), and 5 (5%) for grades 3, 4, and 5, respectively. For those with interstitial changes, the incidence of RP ≥ grade 3 was significantly increased from 3% (2/79) to 26% (7/27) (p < 0.001). CRP and LDH levels were also associated with increased RP, as were pulmonary emphysema and performance status ≥ 2. Among 91 patients with RP ≥ grade 1, RP grade ≥ 3 occurred significantly earlier than grades 1 and 2. In conclusion, pulmonary interstitial changes, LDH and CRP levels, pulmonary emphysema, and performance status ≥ 2 were significantly associated with RP ≥ grade 3. The early appearance of interstitial changes requires careful management due to the possibility of severe RP.

INTRODUCTION

The incidence of lung cancer associated with interstitial pneumonias (IP) is higher than in the general population.1–5) Treatment of this cancer is extremely limited owing to concerns for various adverse sequelae, including acute IP exacerbations. The main treatments for lung cancer, such as chemotherapy, surgery, and radiation therapy, are all thought to be risks for acute IP exacerbations.6,7) Therefore, it is important to make a decision regarding the presence or absence of IP during the treatment of thoracic malignancies. However, pulmonary interstitial changes that are detected only on computed tomography (CT) are often seen in daily practice, particularly in elderly lung cancer patients who have not been definitively diagnosed with IP. The significance of such pre-existing interstitial changes for acute interstitial lung disease (ILD) is recognized in chemotherapy, although the sparse amount of data that is available has come primarily from retrospective trial analyses, predominantly for Japanese patients treated with gefitinib.8–10)

Regarding radiation therapy, some acute ILD exacerbations may partially appear as a form of severe radiation pneumonitis (RP) that is the major toxicity in thoracic radiotherapy, which progresses from sharply demarcated to diffuse or discrete consolidation. Indeed, some radiation oncologists have noted a relationship between ILD and an increased incidence of RP.11–13) However, there have been no reports regarding whether there is an increased risk for or severity of RP in patients who have non-specific interstitial changes detected only on CT.

This study was a retrospective analysis that evaluated the associations of pre-existing interstitial changes with RP for
patients with pulmonary malignancies who were treated with radiation therapy.

MATERIALS AND METHODS

Patients and treatments

From September 2005 to September 2009, 183 consecutive patients with lung cancer or thymic tumors were treated with thoracic radiotherapy of 40 Gy or more at our institution. All of the patients provided written informed consents. Survivors who were followed-up shorter than for 6 months were excluded from this study.

Radiation therapy was delivered with conventional fractions using a linear accelerator (Clinac 21EX, Varian Medical Systems, USA) with a 10 MV photon beam. All patients underwent CT-based treatment planning using Eclipse software, version 7.3 (Varian Medical Systems, Palo Alto, California, USA). Target volumes were defined according to treatment intent of cure or palliation. In a typical definitive thoracic radiotherapy, a gross tumor volume (GTV) was defined as the volume of a primary tumor demonstrated by a CT scan, as well as metastatic lymph nodes that measured ≥ 1 cm in the short axis. A clinical target volume (CTV) for the primary tumor was created to add a 0.5–1 cm margin to GTV and to include elective regional lymph nodes, while a CTV margin for metastatic lymph nodes was not added. A planning target volume (PTV) was defined by adding margins at the discretion of radiation oncologists (typically 0.5–1 cm for lateral margins and 1–2 cm for crano-caudal margins, depending on respiratory motion and patient fixation). A typical radiotherapy field consisted of two opposing fields for 40 Gy in 20 fractions, 1.8 to 2.0 Gy per a fraction, 5 fractions per week, followed by off-cord oblique fields as a boost of 20 to 30 Gy to the target volume. The presence of pre-treatment interstitial changes on CT did not affect prescribed dose. Each dose was delivered to an isocenter. Tissue heterogeneity correction was used for monitor unit calculation. If chemotherapy was given, it was administered concurrently or sequentially with radiation therapy.

Interstitial changes and RP on CT

A routine CT examination was performed throughout the entire thorax with a 64 channel-detector row helical CT scanner (Aquilion 64, Toshiba, Tokyo, Japan) with a reconstructed slice width of 5 mm and a slice interval of 5 mm. Scanning parameters were 120 kV, 100–200 mA, 1.0-mm section thickness, 27.0 helical pitch (CT pitch factor 0.844), and 0.75 second rotation speed. For CT evaluation, the window level and width were set to –650 and 1350 Hounsfield units (HU), respectively.

The presence of interstitial changes on CT before radiation therapy, pulmonary emphysema, and RP were judged by 4 domestically board-certified radiologists (A.O., N.K., E.K., and T.M.) without knowledge of clinical or physiological parameters. Three criteria for the indications of interstitial changes on CT included sub-pleural reticular opacities, macrocystic honeycombing, and traction bronchiectasis, as well as an apico-balast gradient as a supplemental finding, according to ATS-ERS criteria for the diagnosis of IPF in the absence of surgical lung biopsy.\(^5\) CT findings of RP were described as a homogeneous slight increase in attenuation at the beginning, then patchy consolidation conforming to the outline of the sharply demarcated irradiated area, or non-uniform discrete consolidation. Pulmonary infection was excluded by a blood test, response to antibiotics, or an extensive spread of infiltrates beyond the boundary of the anatomical structure of the lung.

Patient follow-up and RP risk factors

Patients were followed-up each month for up to 3–6 months, then every 3 months thereafter. At regular follow-up visits, patients underwent a plain chest X-ray, and a CT scan was requested if they were suspected to have RP. Otherwise, a CT scan was basically planned at 1 month after radiotherapy and every 3 months thereafter. RP grading was based on the Common Terminology Criteria for Adverse Events, version 3, of the National Cancer Institute.\(^14\) For this study, the onset of RP was recorded by radiologists based on CT findings taken either by plan or by request.

Possible risks for RP included age, sex, pre-treatment performance status, smoking history, interstitial opacity before radiation, pulmonary emphysema, elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels over normal limits which were measured before treatment, use of chemotherapy (concomitantly or sequentially), total radiation dose, chemotherapy regimen (platinum-based agents, taxanes, vinorelbine, and irinotecan), and thoracic surgery within 6 months before radiotherapy.

Statistical analysis

Comparisons of the proportions of patients in various subgroups were performed using two-sided Chi-squared tests and F-tests. A p-value of < 0.05 was considered significant. Dr. SPSS II 11 for Windows software (SPSS Japan Inc., Tokyo, Japan) was used for the analyses.

RESULTS

Patient characteristics

Of 183 lung cancer patients who received thoracic radiotherapy in our institution from September 2005 to September 2009, 77 patients were excluded from this study because of short follow-up time: 47 were lost to follow-up or were unavailable for post-treatment evaluation; 28 had incomplete treatments due to toxicity or early lung cancer progression; and 8 received total doses of less than 40 Gy. The remaining 106 patients were included in this study. Their median follow-up time was 12.5 months (range: 0.2–54 months).
These patients’ characteristics are shown in Table 1. There were no histologically confirmed cases of IP.

**RP incidence**

The incidences of RP were 4 (4%), 0 (0%), and 5 (5%) for grades 3, 4, and 5, respectively. Among patients classified as grade 5, the clinical presentations of 2 cases appeared too rapidly to identify the causes of pneumonitis; however, these cases were included as grade 5 for the purpose of this study to investigate the incidence of treatment-related pulmonary injury. Overall, 27 (25%) patients were judged to have had at least 1 characteristic among the criteria for pulmonary interstitial changes.

For those with pre-existing interstitial changes, the incidence of RP ≥ grade 3 was significantly increased to 26% (7/27), while it was 3% (2/79) for those without these changes (p < 0.001). Statistical significance was consistent regardless of the number of items that were met among the criteria for interstitial changes.

Figure 1 shows a case with typical pulmonary interstitial changes which developed RP after RT. An 81-year-old male with lung adenocarcinoma had undergone video-assisted left lower lobectomy plus mediastinal lymphadenectomy. Eight months after surgery, he presented with another pulmonary tumor in the right lower lobe with right hilar lymphadenopathy that was diagnosed as a second primary lung cancer. He chose to receive RT, and 60 Gy in 30 fractions was delivered to the lesion. Initially, pulmonary interstitial changes were noted, such as sub-pleural reticular opacities with traction bronchiectasis. Three weeks after the completion of RT, he began to have a low grade fever, which gradually increased, and he also developed a dry cough and dyspnea. A plain chest X-ray revealed confluent consolidation confined to the radiation portal, which was considered to be grade 3 RP. He was admitted to the hospital and received steroid-pulse therapy (methylprednisolone at 500 mg daily for 3 days). After the initial therapy relieved his symptoms, the prescription was switched to daily prednisolone at 30 mg, which was gradually tapered.

Table 2 shows the characteristics of 5 patients who presented with grade 5 pneumonitis due to any causes. Three cases had interstitial changes on CT and all of their presentations started with focal consolidation corresponding to the radiation fields, but they rapidly expanded bilaterally beyond radiation portals, which made it difficult to distinguish RP from acute exacerbation of possibly unrecognized IPF-related disease. The other two cases without pulmonary interstitial changes presented with acute pneumonitis before completing radiotherapy; the causes of pneumonitis were not clearly identified because they did not respond to steroids and antibiotics. No apparent trend was found among the characteristics of these 5 cases, except that their events occurred during or within 1 month after radiation.

**Factors associated with RP of grade 3 or higher**

Table 3 shows possible risk factors for RP grade ≥ 3. The presence of pre-existing pulmonary interstitial changes was the strongest risk factor for RP, regardless of the number of items that met the criteria for interstitial changes. Elevated CRP and LDH levels also increased the risk of RP, as did pulmonary emphysema and performance status of ≥ 2. If a patient had at least 1 of the factors with a p value less than 0.05, the incidence of RP was 7 of 75 (19%), while none of the patients without any of these risk factors developed RP (p < 0.038). The use of chemotherapy did not increase the risk of RP. No correlation was observed between the chemotherapy regimen and RP. Surgery within 6 months before radiotherapy also did not influence the development of RP. There was no correlation between the incidence of RP and the total radiation dose when patients were divided into two categories: < 55 Gy and ≥ 55 Gy.

### Time to develop RP

Among 91 patients with RP ≥ grade 1, RP grade ≥ 3 occurred significantly earlier than grades 1 and 2. Figure 2 shows the mean time to develop RP by grades after completing radiotherapy. On average, RP grades 3–5 occurred within 1 month, while RP grades 2 and 1 occurred within 2.3 and 4.6 months, respectively.

Of those with RP (n = 91), the number of patients who presented with RP grade ≥ 3 within 1 month was 9/14 (64%), while the number after 1 month was 0/77 (0%) (p < 0.001). Among 14 patients who had RP within 1 month after...
Fig. 1. An 81-year-old male with lung adenocarcinoma with pulmonary interstitial changes who developed RP after RT. (a) Before RT, he initially had pulmonary interstitial changes, including sub-pleural reticular opacities (arrow) with traction bronchiectasis (arrowhead). (b) 60 Gy in 30 fractions was delivered to a pulmonary tumor in the right lower lobe with right hilar lymphadenopathy. (c) (Left) Three weeks after completing RT. A homogeneous increase in attenuation was seen conforming to the outline of the sharply demarcated irradiated area. (Right) Fibrosis developed within the irradiated area leading to a reduction in lung volume.

Table 2. Characteristics of patients with grade 5 acute pneumonitis

<table>
<thead>
<tr>
<th>Primary tumor age/sex</th>
<th>PS</th>
<th>Interstitial changes on CT</th>
<th>Elevated CRP/LDH</th>
<th>Smoking</th>
<th>Chemotherapy</th>
<th>Surgery</th>
<th>Dose (Gy)</th>
<th>Latent period* (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer 54/female</td>
<td>3</td>
<td>No</td>
<td>No/Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>60</td>
<td>0/During RT</td>
</tr>
<tr>
<td>Lung cancer 75/male</td>
<td>3</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>50.4</td>
<td>0/During RT</td>
</tr>
<tr>
<td>Lung cancer 76/male</td>
<td>1</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>66</td>
<td>0.3</td>
</tr>
<tr>
<td>Lung cancer 77/male</td>
<td>2</td>
<td>No</td>
<td>Yes/No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>60</td>
<td>0.7</td>
</tr>
<tr>
<td>Lung cancer 68/male</td>
<td>1</td>
<td>Yes</td>
<td>Yes/No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>60</td>
<td>1</td>
</tr>
</tbody>
</table>

*Time to develop radiation pneumonitis after completion of radiotherapy

Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase; PS, performance status; RT, radiotherapy
DISCUSSION

Pulmonary interstitial changes in patients without clinically recognizable IPF

This study demonstrated that the presence of non-specific interstitial lung changes was significantly associated with severe RP. However, the etiology of pre-existing, focal “IP-like interstitial changes” is not clear. There are several clinico-pathological studies by examining resected lung tissues regarding relationship between focal sub-pleural fibrosis and clinically unrecognizable IPF, however, reports in English literatures are extremely limited. Differential diagnosis of sub-pleural fibrosis includes smoking-related ILDs.\textsuperscript{15–17} Honeycombing, reticular opacities, and traction bronchiectasis in the lower lungs are the most frequent findings, while the upper lungs exhibit paraseptal and centrilobular emphysema.\textsuperscript{18} The features of focal IPF and smoking-related ILDs have much in common with our criteria for the presence of pulmonary interstitial changes. However, mixed patterns of disease frequently coexist in the same patients involving a variety of backgrounds. One of the limitations of our study is relevant to such variety. Besides, our objectives included patients with different primary tumors and locations which could affect the probability of RP. Furthermore, it was impossible to distinguish acute ILD exacerbation from severe RP. However, to identify the type of ILD by invasive procedures is not always practical in the treatment of lung cancer patients who have non-specific interstitial changes. In light of this, our findings are useful because interstitial changes can be evaluated on pre-treatment CT.

Acute IPF exacerbations in cancer treatment

It has recently been recognized that an acute IPF exacerbation involves a rapid progression of the disease, which often results in respiratory failure and death. The reported 2-year incidence of acute exacerbation is 9.6% and the mortality rate is 78%.\textsuperscript{24} Proposed diagnostic criteria include subjective worsening over 30 or fewer days, new bilateral radiographic opacities, and the absence of infection or another identifiable etiology.\textsuperscript{7} These considerations led us to focus on acute post-radiotherapy pneumonitis that occurred within 1 month.

Minegishi \textit{et al.}\textsuperscript{16} reported that the overall incidence of acute exacerbation that was related to cancer treatment was 22.7%. A similar incidence of 17–21% has been reported with regard to chemotherapy and surgery.\textsuperscript{8,19–23} In the current study, lung cancer patients with pulmonary interstitial changes on pre-treatment CT had an increased risk of severe RP (26%), as compared to 3% for those with normal lungs. Although our subjects were not diagnosed with IP, the percentage is close to the known incidence of acute exacerbation following radiotherapy that is as high as 25%.\textsuperscript{6} These considerations led us to focus on acute post-radiotherapy pneumonitis that occurred within 1 month.

Table 3. Possible risk factors for developing pneumonitis ≥ grade_3

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Without risk factors</th>
<th>With risk factors</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial changes on CT</td>
<td>2/79 (3%)</td>
<td>7/27 (26%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Elevated CRP</td>
<td>5/93 (5%)</td>
<td>4/13 (31%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>4/79 (5%)</td>
<td>5/27 (19%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Pulmonary emphysema</td>
<td>1/51 (2%)</td>
<td>8/55 (15%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Performance status ≥2</td>
<td>6/95 (6%)</td>
<td>3/11 (27%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Smoking</td>
<td>1/22 (5%)</td>
<td>8/84 (10%)</td>
<td>0.404</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1/19 (5%)</td>
<td>8/87 (9%)</td>
<td>0.494</td>
</tr>
<tr>
<td>Age ≥ 70 years old</td>
<td>3/47 (6%)</td>
<td>6/59 (10%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Total radiation dose (≥ 55 Gy)</td>
<td>6/74 (8%)</td>
<td>3/32 (9%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Surgery within 6 months before radiation</td>
<td>7/92 (8%)</td>
<td>2/14 (14%)</td>
<td>0.338</td>
</tr>
<tr>
<td>Chemotherapy use</td>
<td>6/43 (14%)</td>
<td>3/63 (5%)</td>
<td>0.095</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; CRP, C-reactive protein; LDH, lactate dehydrogenase. p-values from group comparisons by Chi-squared tests.

Fig. 2. Mean time to develop radiation pneumonitis after completion of radiotherapy. Results shown are means and error bars are ranges between a minimum and a maximum.

 Completing radiotherapy, 10 patients (71%) had interstitial changes on CT, and all but 1 patient had at least one of the risk factors.

<table>
<thead>
<tr>
<th>RP grade</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>5</td>
</tr>
<tr>
<td>0.3</td>
<td>3</td>
</tr>
<tr>
<td>2.3</td>
<td>2</td>
</tr>
<tr>
<td>4.6</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; CRP, C-reactive protein; LDH, lactate dehydrogenase. p-values from group comparisons by Chi-squared tests.
Regarding the mechanisms and etiology of acute IPF exacerbations, no consensus opinion has yet been reached.\(^{28}\) Minegishi \textit{et al.} reported that patients with elevated CRP levels had a significantly higher risk of developing acute exacerbations (odds ratio = 5.60, \(p = 0.028\)).\(^{6}\) CRP levels or white blood cells counts are also reported to be elevated during acute exacerbation of IPF.\(^{28}\) These factors correspond with the results of our study in which elevated CRP and LDH levels increased the risk of severe RP, as did pulmonary interstitial changes.

Kudoh \textit{et al.} identified the risk factors for acute ILD in 3166 Japanese patients with non-small cell lung cancer during treatment with gefitinib or chemotherapy.\(^{8}\) The risk factors identified in that study for acute ILD included reduced areas of normal lung tissue on CT, pre-existing chronic ILD, age, performance status, and smoking; these are somewhat similar to risk factors for IPF exacerbation. In terms of the significance of pre-existing ILD in radiotherapy, Onishi \textit{et al.} reviewed the characteristics of patients who developed grade 5 RP after stereotactic body radiation therapy and found that 14 of 24 (58\%) with grade 5 RP had pulmonary fibrosis in IPF pattern on CT.\(^{11}\) Although the grade 5 RP in our series included cases without clearly identified causes, it was also revealed that grade 3–4 RP did not occur in patients without pre-treatment interstitial changes. These findings suggest that there may be a common etiology that makes some patients with pre-existing ILD more susceptible to acute lung injury after various treatments.

Since dosimetric factors such as mean lung dose or V20 (a normal lung volume receiving 20 Gy or more) are well known to correlate with RP, the lack of dose-volume histogram analysis in this study requires a further investigation to evaluate its influence on severe RP in relation to pre-existing ILD.

**Time to presentation of RP after radiotherapy**

Time to develop RP after radiotherapy seems to correlate with its severity. In our series, grades 3–5 RP occurred within 1 month, while RP grades 2 and 1 occurred relatively later. Although the onset of RP grade \(\geq 3\) could be recorded as early as at the time of developing symptoms, grade 1 RP not associated with symptoms could only be detected on planned CT scans. This may possibly attribute to the difference in time to develop RP by grade categories.

Takeda \textit{et al.} reported that only a latent period of 1–2 months after stereotactic body radiation therapy until the graphical appearance of RP was a significant risk factor for RP grade \(\geq 3\) among 128 patients who were treated: 40\% for a latent period of 1–2 months vs. 1.3\% for a latent period \(\geq 3\) months.\(^{10}\) Four of 7 patients with Grade 3 RP had severe pulmonary co-morbidities, such as IPF or chronic obstructive pulmonary disease. Sekine \textit{et al.} also found a correlation between the latent period and RP severity after analyzing 385 lung cancer patients who developed radiation-induced lung injuries after radiotherapy.\(^{29}\) They divided their patients into 3 groups: Group 1 included 307 stable patients without corticosteroids; Group 2 included 64 patients with corticosteroids; and Group 3 included 14 patients who died in spite of corticosteroid administration. The median numbers of weeks between the end of radiotherapy and the first graphical changes were 9.9, 6.7, and 2.4 for Groups 1, 2, and 3, respectively (\(p < 0.001\)).

Considering these findings, some cases of early and severe RP in patients with pre-existing interstitial changes may have certain etiological features that are common with acute IPF exacerbations. Although acute IPF exacerbations are strictly limited to those situations with unknown causes and cannot be clearly correlated with RP, radiotherapy may trigger a pre-existing underlying disease process in patients without clinically recognizable IPF or related ILD. In the situation where a patient has “non-specific interstitial changes,” but a definitive diagnosis is not yet feasible, it is important to be aware of the possibility of increased risk for severe RP.

In conclusion, the presence of pulmonary interstitial changes on CT, elevated LDH and CRP levels, pulmonary emphysema, and performance status \(\geq 2\) were significantly associated with increased risk of RP \(\geq\) grade 3. If a patient has any one of these risk factors, special consideration is needed when applying radiotherapy. The early appearance of interstitial changes requires careful management based on the possibility of severe post-radiotherapy pneumonitis.

**REFERENCES**


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