Similar radiopathological features, but different postoperative recurrence rates, between Stage I lung cancers arising in emphysematous lungs and those arising in nonemphysematous lungs

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Abstract

OBJECTIVES: The aim of the present study was to clarify the differences between lung cancer arising in emphysematous lungs and that arising in nonemphysematous lungs with regard to radiopathological features and the postoperative recurrence rate.

METHODS: We retrospectively reviewed a prospective database of 212 patients who underwent major lung resection for clinically diagnosed Stage I primary lung cancer. Emphysematous lungs were identified on the basis of quantitative computed tomography (CT). The biological features of the primary tumour were diagnosed according to the presence or absence of a ground-glass component on high-resolution CT and the maximum standardized uptake value in [18F]-fluorodeoxyglucose positron emission tomography, in addition to conventional characteristic factors.

RESULTS: The risk factors for postoperative recurrence were underlying emphysema, a high maximum standardized uptake value, the absence of a ground-glass component, the pathological grade and lymph node metastasis, whereas the risk factors for lymph node metastasis were a high maximum standardized uptake value, the absence of a ground-glass component and the pathological grade. Surprisingly, these risk factors were entirely matched between patients with and without emphysematous lungs, regardless of the fact that patients with emphysematous lungs had a higher recurrence rate.

CONCLUSIONS: Similar clinicopathological features, but different postoperative recurrence rates, were found between Stage I lung cancers arising in emphysematous lungs and those arising in nonemphysematous lungs. It may be valuable to search for underlying molecular mechanisms that promote metastasis from primary tumours arising in emphysema, such as paracrine effects between the tumour and pulmonary emphysema.

Keywords: Pulmonary emphysema • PET • Chronic obstructive pulmonary disease • Maximum standardized uptake value • Lung cancer

INTRODUCTION

It has been recognized that smoking-related lung cancer exhibits aggressive biological features via the accumulation of genomic alterations induced by chronic inflammatory stimulation, which affect the airway epithelial cells [1–3]. In addition, chronic obstructive pulmonary disease (COPD) is known to be the strongest risk factor for the development of lung cancer [4, 5], probably because the patients with COPD have a higher susceptibility to epithelial injury by smoking than do patients without COPD. However, the clinical aggressiveness of lung cancers arising in COPD patients is not remarkably different from that arising in non-COPD patients.

We preliminarily reported that both the overall survival and disease-specific survival were not significantly different between patients with resected Stage I lung cancer arising in COPD and those with Stage I cancer arising in non-COPD lungs [6]. Nevertheless, when patients were divided according to the presence or absence of emphysema, as defined by quantitative computed tomography (CT), both the overall survival and disease-specific survival were significantly lower in the patients with emphysema than in patients without [6]. Therefore, we believe that COPD and pulmonary emphysema may play different roles in the development and progression of lung cancer. However, it remains unknown whether the aggressive clinical features of lung cancers arising in emphysema are attributable to the biological aggressiveness of the primary tumours or not.

With the increasing incidence rate of peripheral-type lung adenocarcinoma, particularly that showing a lepidic growth...
pattern, the biological aggressiveness of lung cancer can be estimated using radiological techniques. Namely, tumours with ground-glass attenuation on high-resolution CT are associated with a favourable prognosis [7], while tumours with a high uptake value in $[{\text{18F}}]$-fluorodeoxyglucose positron emission tomography ($[{\text{18F}}]$-FDG-PET) are associated with frequent lymph node metastasis and a poor prognosis [7–10]. The aim of the present study was to validate the significance and a poor prognosis [7] of the presence or absence of emphysema on the prognosis after the resection of clinical stage I lung cancer in current lung cancer patients, and to clarify the differences between lung cancer arising in emphysematous lungs and that arising in nonemphysematous lungs with regard to the radiologically defined biological features.

**PATIENTS AND METHODS**

**Patients**

We retrospectively reviewed a prospective database of 212 patients who underwent major lung resection and lymphadenectomy for clinically diagnosed Stage I primary lung cancer. This study was approved by our institutional review board. We performed a lobectomy in 163 patients and an anatomical segmentectomy in the remaining 49 patients. Although we generally selected lung lobectomy for patients with tumours larger than 2 cm in diameter, we optionally selected lung segmentectomy in patients with tumours smaller than 2 cm in diameter, after they gave their informed consent, if the tumours were at least 2 cm from the intersegmental plane. Operability was determined according to the existing guidelines for pulmonary resection [11]. Preoperative patient data included age, sex, performance status, presence or absence of breathlessness, smoking habit, spirometric variables, tumour size and the extent of emphysema. Smoking data were based on the pack-years smoked, with the smoking index calculated by the average number of packs of cigarettes smoked per day multiplied by the number of years the person had smoked. Pulmonary emphysema was diagnosed by quantitative CT, as described later. The spirometric variables were obtained within a month preoperatively, and included the forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). The percent FVC was expressed as the percentage of the predicted value based on age, sex and height. FDG-PET/CT scanning was performed within 1 month preoperatively to assess the biological activity of the primary lung lesions, as expressed by the maximum standardized uptake value ($\text{SUV}_{\text{max}}$).

The primary lung lesions were classified into two subtypes: solid lesions and non-solid lesions, according to the presence or absence of a ground-glass component within the lesions on high-resolution CT. The pathological data obtained after surgery included the histological subtype, histological grade, vascular invasion, lymphatic vessel invasion and pathological TNM status. The tumours were classified histologically as adenocarcinoma or nonadenocarcinoma, and were graded as G1, G2 or G3 according to the World Health Organization classification. Likewise, vascular invasion and lymphatic vessel invasion were diagnosed histologically using hematoxylin and eosin and Elastica van Gieson staining. Positive lymphovascular invasion was considered to be present if there was any vascular invasion and/or lymphatic vessel invasion.

The patients’ clinicopathological characteristics are summarized in Table 1. The mean smoking index was 31.5 pack-years (median, 27.3 pack-years). Preoperatively, 19 patients complained of slight breathlessness, defined as the inability to keep up with healthy persons of equivalent age on hills or stairs [12], and 35 patients had restricted physically strenuous activity, defined as Eastern Cooperative Oncology Group-performance status Grade 1 [13].

<table>
<thead>
<tr>
<th>Table 1: Characteristic variables according to the presence or absence of emphysema</th>
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<tr>
<td>Variables</td>
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<td>Upper lobe/other</td>
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<td>Clinical T-factor</td>
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<td>T1a/T1b/T2a</td>
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<td>Solid/non-solid</td>
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<td>SUVmax Value &lt;2.0/≥2.0</td>
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<td>Surgical procedure</td>
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FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; CT: computed tomography; SUVmax: maximum standardized uptake value in $[{\text{18F}}]$-fluorodeoxyglucose positron emission tomography.
Computed tomography scanning

Helical CT scans were obtained using 4-detector (Somatom plus4 or Somatom volume zoom; Siemens Medical Solutions, Erlangen, Germany) and 64-detector (Somatom Definition or Sensation 64; Siemens) row CT scanners. With the patient in the supine position, we obtained 2-mm high-resolution CT images of the entire lungs during a deep inspiratory breathhold. We used a 512 × 512 matrix, 2-mm collimation and a scan time of 1.0 s, at 120–130 kVp and 220–230 mA. This was a routine examination and, thus, the patients were not exposed to additional radiation for the purpose of measuring the radiological parameters in this study. Three-dimensional (3D) volume-rendering lung images were created using a commercially available, user-friendly, imaging software package (AZE, Virtual Place Raijin, Tokyo). Threshold limits of −600 to −1024 Hounsfield units (HU) were applied to segment the lung parenchyma and to exclude the soft tissue surrounding the lung and the large vessels within the lung. The total number of voxels with any selected specific attenuation number (in HU) in the lung model was counted automatically by the computer. The percentage of voxels with attenuation values lower than −910 HU among the total number of voxels in the entire lung was considered to be the low-attenuation area [14–16]. Emphysema was defined as being present if low-attenuation areas occupied more than 20% of the lung.

[18F]-Fluorodeoxyglucose positron emission tomography/computed tomography scanning

FDG-PET/CT scanning was performed on a PET/CT scanner (Gemini GXL16, Philips Medical Systems, Cleveland, OH, USA). At the time of 18F-FDG injection, all patients had fasted for at least 5 h and had blood sugar levels less than 128 mg/dl. The whole-body scan was performed 60 min (range 56–65 min) after the intravenous injection of 4.4 MBq/kg of 18F-FDG. The scan started at the head and included the thorax, abdomen and pelvis, and consisted of six or seven emission frames 25.6 cm in length. Emission PET images were reconstructed with non-contrast CT, using the three-dimensional row-action maximum likelihood algorithm (slice thickness = 3.2 mm). Attenuation-corrected PET/CT fusion images on three orthogonal (transaxial, coronal and sagittal) planes were reviewed on a workstation.

The presence or absence of FDG uptake in the primary lung lesions in individual patients was consensually interpreted by two experienced radiologists. Regions of interest (ROIs) were overlaid over the primary lung lesions on the attenuation-corrected PET/CT fusion images, and the SUVmax [the maximum ROI activity (MBq/g)/[injected dose (MBq)/body weight (g)] was measured.

Postoperative follow-up

The patients were followed up in our outpatient clinic at 6-month intervals by chest CT, peripheral blood examinations and, if necessary, head and abdominal CT and FDG-PET.

Statistical analysis

The values are expressed as the means ± SD. We compared continuous variables by the unpaired Student’s t-test, and categorical variables by the χ² test. The dependence between two continuous variables was tested by a linear regression analysis. The survival curves were drawn by the Kaplan–Meier method, and the differences between the curves were determined by the generalized Wilcoxon test. All tests were two-tailed, with significance defined as 0.05, and were performed using the STATA 12 software program (Stata Corp., College Station, TX, USA).

RESULTS

A total of 111 and 91 patients were diagnosed as having emphysematous lungs (%LAA ≥20%) and airflow obstruction (FEV₁/FVC <70%), respectively. Figure 1 shows the linear dependence between the FEV₁/FVC and %LAA (Fig. 1). Slight dependence was noted between the parameters (r = 0.354, P < 0.0001). Airflow obstruction was observed in 58 of the 111 (52%) patients with emphysematous lungs, while it was observed in 33 of the 101 (33%) patients without emphysematous lungs.

The characteristic variables in patients with and without emphysematous lungs are shown in Table 1. Patients with emphysematous lungs had a higher incidence rate of a smoking history and airflow obstruction than those without. In contrast, no significant differences were observed between patients with and without emphysematous lungs with respect to tumour-related characteristics, such as the primary site, tumour diameter, clinical T factor, CT-based subtype (solid or non-solid) and SUVmax (Table 1). In addition, no significant differences were observed in the pathological status, such as the histological type, histological grade, lymphovascular invasion, T status and N status (Table 2).

During the median postoperative follow-up of 25.3 months, recurrence developed in 19 patients. The 3-year and 5-year postoperative recurrence-free survival rates were 90.3 and 86.8%, respectively. The preoperative factors that were significantly associated with postoperative recurrence were the CT-based tumour
subtype and SUVmax, and the pathological factors significantly associated with postoperative recurrence were the tumour histological grade, lymphovascular invasion and N status. A higher recurrence rate was observed in patients with solid tumours ($P = 0.0497$) (Fig. 2A), patients with tumours with an SUVmax $\geq 2.0$ ($P = 0.0014$) (Fig. 2B), patients with G2 or G3 disease ($P = 0.0052$), patients with lymphovascular invasion ($P < 0.0001$) and patients with positive (N1 or N2) lymph nodes ($P < 0.0001$). Importantly, patients with emphysematous lungs experienced a higher rate of postoperative recurrence than those without (Fig. 2C). Fifteen patients with emphysematous lungs developed recurrence (distant metastasis in 8 patients, lymph node metastasis in 2, both metastases in 3, pleural dissemination in 1 and cut-end recurrence in 1), while 4 patients without emphysematous lung developed

![Table 2: Pathological findings according to the presence or absence of emphysema](image)

Figure 2: Recurrence-free survival curves according to the computed tomography-based tumour subtype (solid line, non-solid type; dashed line, solid type) (A); maximum standardized uptake value (SUVmax) on [18F]-fluorodeoxyglucose positron emission tomography (solid line, SUVmax < 2.0; dashed line, SUVmax $\geq 2.0$) (B); presence or absence of emphysema (solid line, non-emphysema; dashed line, emphysema) (C) and presence or absence of airflow obstruction (solid line, forced expiratory volume in s/forced vital capacity (FEV1/FVC) < 70%; dashed line, FEV1/FVC $\geq$ 70%) (D).
recurrence (distant metastasis in 1 patient and pleural dissemination in 3). No other preoperative or pathological factors, including surgical procedures, were significantly associated with the postoperative recurrence rate (all, \( P > 0.1 \)).

Table 3 shows the characteristic variables according to the presence or absence of lymph node metastasis. The significant risk factors for lymph node metastasis were the CT-based subtype, \( \text{SUV}_{\text{max}} \), tumour grade and lymphovascular invasion. Notably, the grade of LAA was not associated with lymph node metastasis. None of the patients with an \( \text{SUV}_{\text{max}} <2.0 \) had lymph node metastasis.

An exploratory evaluation revealed that patients with airflow obstruction had a higher age, higher rate of male gender, higher rate
of a smoking history, higher level of smoking exposure, higher rate of the solid subtype on high-resolution CT and a higher tumour SUVmax on FDG-PET when compared with patients without airflow obstruction (Table 4). Nevertheless, the postoperative recurrence rate of patients with airflow obstruction was not significantly different from that of patients without airflow obstruction (Fig. 2D).

**DISCUSSION**

We previously reported that primary lung cancer arising in emphysematous lungs was associated with a poorer overall survival due to the high recurrence rate compared with that arising in non-emphysematous lungs [6]. In the current study, we re-evaluated this possibility in a new cohort of patients and obtained supportive results. Importantly, the current study revealed that the differences in the postoperative recurrence rates between patients with and without emphysematous lungs were not attributable to the differences in the tumour characteristics, and that the clinicopathological features, including the CT- and PET-based features, of the primary lesions were not significantly different between the two groups. Therefore, it may be valuable to search for the underlying mechanisms that promote metastasis from primary tumours arising in patients with emphysema.

Female gender and never smoker were more predominant in patients without emphysematous lungs. Although gender and smoking history were not significant factors associated with postoperative recurrence rate in univariate analysis, such demographic differences could affect the postoperative recurrence rate. Nevertheless, according to a multivariate Cox regression analysis, patients with emphysematous lung had significant risk of postoperative recurrence, versus patients without emphysematous lung (RR 3.73, 95% confidence interval (CI) 1.19–11.628), while female gender and never smoker did not have significant risk of postoperative recurrence compared with male gender (RR 0.681, 95% CI 0.178–2.602) and smoker (RR 1.610, 95% CI 0.435–5.961), respectively.

It is widely known that cigarette smoking and COPD are risk factors for developing lung cancer [4, 5]. Many investigators have attempted to compare the clinical and biological characteristics of lung cancers between patients with and without a smoking history, as well as between patients with and without COPD. According to these studies, although smoking-related lung cancer tended to possess aggressive biological features, the results of the prognostic analysis regarding the overall and disease-specific survival were inconsistent. For example Kavaguchi et al. reported that never smokers with lung cancer had a favourable prognosis [17], while Subramanian et al. reported that the prognostic advantage of never smokers over smokers disappeared after adjustment for characteristic variations between the groups [18].

In the current series, patients with airflow obstruction had more aggressive biological features, as shown by the higher rate of the solid tumour subtype on high-resolution CT and higher SUVmax on FDG-PET. However, the presence or absence of a smoking history, as well as the presence or absence of airflow obstruction, was not associated with high recurrence rate. These results may suggest that neither smoking nor airflow obstruction are directly linked to the progression of lung cancer, regardless of their critical role in the development of lung cancer. Future studies are needed to clarify whether pulmonary emphysema can contribute to tumour progression via paracrine effects. Some experimental and clinical studies support a paracrine effect between lung cancer cells and the surrounding stromal cells on tumour progression [19].

The pathogenesis of pulmonary emphysema is not fully understood. Yokohori et al. reported that enhanced turnover of the alveolar wall cells was found in patients with emphysema, suggesting that emphysema was not a simple consequence of alveolar tissue degradation due to an elastase/antielastase imbalance. They showed the percentage of TUNEL-positive cells, representing apoptotic cells, to be positively correlated with the percentage of proliferating cell nuclear antigen-positive cells, representing proliferating cells, in the alveolar wall [20]. This result is supported by the fact that the hyperplasia of alveolar type II cells has been noted in emphysematous lungs. Because emphysema is a dynamic disease process, some growth-related signalling pathways may affect the maintenance of alveolar wall tissue, which can also promote the progression of tumours arising in emphysematous lungs.

The apoptosis of alveolar epithelial wall cells may be induced by not only cigarette smoking, but also some proteases, such as matrix metalloproteinases (MMPs) [6, 21, 22]. Various types of MMPs are up-regulated in emphysematous lungs, and the levels of MMPs are not necessarily associated with the severity of emphysema [23]. In addition, some types of MMPs, especially MMP-2 and -9, are also strongly linked to tumour metastasis in various types of human cancer [24]. Interestingly, Ishikawa et al. reported that when MMP-2 was overexpressed in stromal cells, but not in tumour cells, it was associated with a poor prognosis in patients with resected Stage I non-small-cell lung cancer [25]. This suggested the possibility that there is an interaction between the tumour cells and the surrounding environment. Because tumour invasion and migration via the degradation of the extracellular matrix are essential events in the process of metastasis, pulmonary emphysema, with its abundant proteases, may thus provide a tumour-friendly microenvironment.

To our knowledge, there have been no previously published studies comparing the prognosis of lung cancer patients according to the presence or absence of pulmonary emphysema, probably because the low-attenuation area is not routinely measured in lung cancer patients, despite the fact that whole-lung CT scans are routinely taken in these patients preoperatively. However, because of the user-friendly computer software program that we used, the low-attenuation area can be measured readily, within 3 min per patient. Because the assessment of emphysema on the quantitative CT does not require additional cost or labour, a multi-institute study with a large number of patients should be conducted to verify our results.

In the present study, there was a relatively small number of events, which could limit the robustness of the results. The statistically significant difference between 111 patients with emphysematous lungs and 101 patients without emphysematous lungs with regard to the recurrence-free survival rate was based on 15 recurrences and four recurrences in the respective groups. Therefore, a larger scale study is needed before confirmation of our results.

In conclusion, similar clinicopathological features, but different postoperative recurrence rates, were found between Stage I lung cancers arising in emphysematous lungs and those arising in nonemphysematous lungs. It may be valuable to search for the underlying molecular mechanisms that promote metastasis from primary tumours arising in emphysematous lungs, specifically
focusing on the paracrine effects between the tumour and pulmonary emphysema.

Conflict of interest: none declared.

REFERENCES


