Clinicopathological Characteristics of Lung Cancer Mimicking Organizing Pneumonia on Computed Tomography – A Novel Radiological Entity of Pulmonary Malignancy

Running title: Lung Cancer mimicking Organizing Pneumonia

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ABSTRACT

OBJECTIVES

Lung cancer could be misdiagnosed as benign due to its atypical radiological findings, or difficulty in the histological diagnosis. We intended to elucidate the clinicopathological features of such lung cancers.

METHODS

Between 2008 and 2011, we performed surgical resection for 564 consecutive patients with lung adenocarcinoma. Findings on thin-section CT were reviewed for all patients, 13 of whom were found to have lung cancer mimicking organizing pneumonia (LCOP). The radiological and clinicopathological features of LCOP and other adenocarcinomas were evaluated.

RESULTS

Among 13 LCOP patients, four were men. The median age was 70 years (range 62-81 years). Six patients were followed up for more than one year (range 1-108 months) as their lesions were misdiagnosed as organizing pneumonia. Preoperative carcinoembryonic antigen was significantly high (p=0.025), and maximum tumor dimension was significantly large for LCOP (30mm vs. 23.6mm, p=0.001). Pathologically, there was no vascular invasion (p=0.012) and only one lymphatic invasion (p=0.064). One case of lymph node metastasis to the N2 node was found and due to misdiagnosis as organizing pneumonia for 9 years.

CONCLUSION

Basically, LCOP was less invasive and showed slow growth. However, nodal metastasis could be found. Thus, radiological diagnosis based on the findings of thin-section CT is valuable to avoid delay in diagnosis.

Mini-abstract

Lung cancer could be misdiagnosed as benign due to its radiological findings. We defined these lesions as lung cancer mimicking organizing pneumonia (LCOP). LCOP has less
invasiveness

Key words: lung cancer, computed tomography, diagnosis
Introduction

Due to the recent introduction of computed tomography (CT) for the screening of lung cancer and advances in thin-section CT scan, the clinicopathological and radiological correlations for early-stage non-small cell lung cancer (NSCLC) have been evaluated [1]. The clinicopathological characteristics of ground glass opacity (GGO) dominant lesions are considered to be relatively indolent, and the long-term course after surgical resections is excellent due to their less invasive nature [1-5]. Furthermore, in addition to the frequently observed radiological features presenting GGO, part-solid, and solid appearances on thin-section CT scan that correlate well with the pathological invasiveness based on the measurement of the size of the solid component of the tumor, we sometimes encounter some lung cancers with air bronchogram or a scattered consolidation [6, 7], which are often difficult to diagnose as malignant due to their atypical radiological features. In addition, a new radiological entity was noticed in this study, namely, lung cancer mimicking organizing pneumonia (LCOP) on thin-section CT, which had been misdiagnosed as inflammatory lesions for a long time. The clinicopathological features of the LCOP have not been clarified and never reported in association with this new radiological category to date. Hence, in the current study, we investigated the clinicopathological and radiological features of LCOP and to provide some insight into the appropriate management of patients with LCOP.

Patients and Methods

Study population

Between April 2009 and July 2012, a total of 862 consecutive patients underwent surgery for lung cancer at Juntendo Hospital, Tokyo, Japan. Of the patients, 564 who were diagnosed as lung adenocarcinoma were enrolled in this study. Medical records of each patient were reviewed with regard to sex, age, smoking status (pack-year smoking), maximum tumor dimension (mm),
consolidation tumor ratio (CTR), serum carcinoembryonic antigen level (CEA, cutoff value at
normal upper limit of 3.0 ng/ml in our institution), operative modes, histology, lymphatic
invasion (Ly), vascular invasion (V), pathological nodal status (N0, N1, or N2), pathological
stages (p-stage IA to p-stage IV), and information regarding postoperative adjuvant
chemotherapy. This retrospective study was performed under a waiver of authorization
approved by the institutional review board of Juntendo University School of Medicine, Tokyo,
Japan.

**Thin-section CT and evaluation**

For all patients, the findings of preoperative thin-section CT scan were reviewed in detail
by the authors (TI, MT, KT, and KS). Tumor size or other radiological findings were determined
preoperatively based on the findings of thin-section CT scan. In addition, all tumors were
subsequently evaluated to estimate the extent of GGO using thin-section CT with a collimation
of 1-2 mm (X-vision/SP, Aquilion 16, Aquilion 64, Toshiba, Tokyo, Japan). The lung was
photographed with a window level of -500 to -700 Hounsfield units (HU) and a window width
of 1500-2000 HU as a lung window. The solid component was defined as an area of increased
opacification that completely obscured the underlying vascular markings. GGO was defined as
an area of slight, homogeneous increase in density that did not obscure the underlying vascular
markings [1, 8].

Among the several radiological features of the resected lung adenocarcinomas, we found
a rare entity of lung adenocarcinoma which looked like inflammatory lesions and could be
misdiagnosed as organizing pneumonia. In this study, we defined these lesions as LCOP. The
first step of diagnosis of LCOP is to rule out organizing pneumonia. Interval change of size of
the tumor would be useful for the differential diagnosis, although it is very difficult or almost
impossible. Radiological description is not easy, but we use the following criteria on
thin-section CT: (a) irregular extension along the broncho-vascular tree toward the hilum, (b)
irregular shaped opacity adjacent to thickened bronchial wall or dilated bronchus, and
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(c) reticular opacity with surrounding GGO. The diagnosis of LCOP was made based on the evaluation of at least two radiologists or thoracic surgeons in this study. GGO was present in the periphery in the tumor, as somewhat denser GGO than typical pure GGO. We excluded adenocarcinomas with emphysematous or scarring of the lung because some of these areas of consolidation seem to be discontinuous. (Figure 1)

Pathological Examinations

All specimens were fixed after infusion of formalin through bronchial tree. All sections of lesion were stained with hematoxylin-eosin and elastica-van Gieson. All of the slides were reviewed by experienced lung pathologists. All tumors were staged pathologically using the 7th edition of the TNM classification of lung cancer published by the International Association for the Study of Lung Cancer (IASLC) [9]. In addition, pathological lymphatic and vascular invasions were determined by identification of tumor cells in the lymphatic lumen or vein vessel lumen. Tissue sample for EGFR mutation was prepared as fresh frozen sample just after resection of the tumor intraoperatively.

Operation policy

As for the operative modes, if a tumor is GGO dominant or pure GGO, the patient would be a candidate for limited surgical resection, whereas a major lung dissection with systematic or selective lymph node dissection is warranted for a part-solid or solid tumor at our institution [10]. Intentional segmentectomy with systematic or selective lymph node dissection is now indicated for part-solid or solid lung cancers 2cm or smaller in size according to a prospective randomized trial in Japan [11]. Non-anatomic wedge resection was performed for a few patients who were elderly or cardio-pulmonary high risk cases.

Follow-up policy

The postoperative follow-up was decided by each surgeon based on the pathological stage and pathological features of the tumors. The routine follow-up evaluation included physical examination, chest radiography, and blood examination including measurements of tumor
markers every 6 to 12 months. A chest CT scan was performed periodically after surgical resection. If any symptom or sign of recurrence was observed, further evaluation was performed, including CT, brain magnetic resonance imaging, and positron emission tomography (PET). Locoregional recurrence was defined if it occurred within the same lobe, or in the ipsilateral thoracic cavity, and hilum or mediastinal lymph nodes.

**Statistical analyses**

Several clinicopathological factors were evaluated to elucidate the clinicopathological and radiological correlations of the LCOP in this study. Unpaired t-test or chi-square test was used to compare each factor using SPSS Statistics 21 (SPSS Inc.). Values for OS were calculated by Kaplan-Meier estimation methods using log-rank test. The date of surgical resection was set as the starting point and the date of death or last date of follow-up as the end point. Reported continuous data are presented as means and standard deviation (SD) for normality. Statistical analysis was considered significant when the probability value was less than 0.05.

**Result**

**Characteristics of LCOP**

Characteristics of LCOP are presented in Table 1. Of the 564 patients, LCOP was observed in 13 (2.3%), comprising of 4 men and 9 women. The median age at the time of the operation was 70 years (range 62-81 years). Ten patients (76.9%) were never smokers. Six patients were misdiagnosed as organizing pneumonia for more than one year (range 1-108 months), and they received only follow-up managements without any treatment until enlargement of the tumor was discovered. The tumor doubling time (TDT) could be calculated using the Schwartz formula in 7 cases. Mean tumor doubling time was 1955 days. Synchronous multifocal adenocarcinomas were found in 3 patients (23.1%) and the metachronous type was noted in one patient (7.7%). With regard to the operative modes for LCOP, lobectomy or segmentectomy with systemic lymph node dissection was performed for the main tumor
because such tumors showed a relatively large diameter. The number of the patients according to the pathological stage was 5 with IA, 5 with IB, 1 with IIA, 1 with IIB, and 1 with IIIA. LCOP was located in the upper lobe in 10 patients (77%), and epidermal growth factor receptor (EGFR) mutation was found in 9 patients (69%).

Lymph node metastasis was noted in only one patient. She was a 66 year-old woman. In 2003, a medical check revealed a tumor in the left upper lobe. She had been diagnosed as old inflammation and the follow-ups had ended. In 2012, a tumor was again indicated in a medical check. She was introduced to our hospital, and underwent left upper lobectomy. Although her lymph nodes were not swollen and PET showed clinical N0, one lymph node metastasis to N2 node was found without N1 infiltration (skip N2).

**Pathological findings of LCOP**

General pathological findings of the LCOP are shown in Fig. 2. Most of the tumor was composed of collapsed lung and collagenous fibers (zone A). Few cancer cells were involved in the fibrosis (yellow arrow). Most cancer cells were in the peripheral area of the tumor (zone B). The number of tumor cells gradually decreased in the central area of the tumor. External layer was composed by adenocarcinoma with lepidic growth pattern (zone C).

**Relationship between LCOP and other adenocarcinomas**

Table 2 showed the result of relationship between LCOP and other adenocarcinomas. Median tumor size of the LCOP cases was 30 mm (range 14–75 mm). Compared with other adenocarcinomas, maximum tumor dimension was significantly large for the LCOP cases (P=0.001), and preoperative carcinoembryonic antigen (CEA) was significantly high (P=0.025). LCOPs tended to have favorable pathologic features and to be related to negative lymph node metastasis, vascular invasion (p=0.012), and lymphatic invasion (p=0.064). Of the patients in this study, 396 were treated with standard thoracotomy by lobectomy while the rest of the patients were treated with segmentectomy (n=94), wedge resection (n=66), and pneumonectomy (n=7).
Oncological outcome of LCOP

Oncological outcomes of LCOP are presented in Fig 3. The 5-year OS and recurrence-free survival (RFS) of the 564 patients with adenocarcinoma of the lung was 79.1% and 76.7%, respectively, with 45.1 months of median follow-up time. The 5-year OS and RFS of the LCOP patients were 91.7 and 100%, respectively, while those of the other adenocarcinoma patients were 78.9 (P=0.441) and 76.3% (P=0.084), respectively (OS: Figure 3A, RFS: Figure 3B).

Discussion

Among the wide variety of radiological findings on lung adenocarcinomas, we have focused on the new radiological entity of pulmonary malignancy, namely, LCOP. On the whole, LCOP showed a less invasive nature similar to other GGO dominant lesions, but is extremely difficult to diagnose as lung cancer due to its atypical radiological characteristics. LCOP tends to have tumors with significantly large maximum dimension regardless of its less invasive nature, presumably due to its long standing history. However, one patient who received follow-up examination for 9 years had N2 lymph node metastasis. An accurate diagnosis cannot be reached by bronchoscopy for most cases of LCOP due to the scattered distribution and small amount of tumor cells. Therefore, when LCOP is suspected on thin-section CT, an aggressive pathological diagnosis by surgical intervention is necessary.

Many authors have reported that some radiological features such as air-bronchogram, bubble-like appearance or scattered consolidation are predictors of good prognosis [12-15]. In this study, we found that LCOP itself could be one of the radiological factors of excellent prognosis. As to change in radiologic findings during follow-up, for cases with two- or three-year follow-up the size was almost the same. For case with more than 9 year follow-up, previous CT was not good enough to be evaluated. Thus changes in radiological findings were not conclusive in the study. However, special attention is required for their diagnosis as they are
often detected in tumors with large diameters compared to other non-invasive peripheral adenocarcinomas of the lung due to their abnormal radiological patterns.

Furthermore, LCOP has unique pathological findings. Most of the tumor is composed of collapsed lung, collagenous fibers, and the number of cancer cells in the tumor is quite few. In 1980, Shimosato et al reported that central fibrosis in adenocarcinoma occurred along with tumor development and characteristics of the central fibrosis were important for estimating the prognosis of patients [16]. Suzuki et al reported that the size of the fibritic focus within the tumor was shown to be a significant prognostic factor [17]. In a recent study, Borczuk et al demonstrated that invasive size or size of fibrosis as a surrogate for invasion was associated with prognosis in all stages [18]. The findings for LCOP were consistent with these prior studies. Relationship between scar and cancer in LCOP remains unclear. It is impossible to answer this question. However we consider this tumor developed in the lung parenchyma without any inflammatory change. Reasons for it are as follows: 1) tumor cells are existing mainly in the periphery, which suggest the tumor develop with gradual disappearance of tumor cells in the central area, such as central fibrosis of typical adenocarcinoma such as Noguchi type C, or collapse in adenocarcinoma such as Noguchi type B; 2) tumor cells tends to exist in the surrounding area of the tumor. The size of invasion has been one of the most important prognostic factors. On the other hand, few reports have mentioned the quality of invasion as a prognostic factor. Several authors stated that invasive adenocarcinoma with central fibrotic consists of two different types: one is invasive tumor cells in the periphery of the central fibrotic focus, which is considered less invasive; the other is invasive tumor cells in the center of the central fibrotic focus which is considered as true invasion [19, 20]. However, these reports did not mention the degree of stromal invasion in the central fibrotic focus, and thus needs to be investigated further. In addition, the pathological rationale for the small number of cancer cells in LCOP is not well understood. LCOP consists mainly of collapsed lung and collagenous fibers which are probably derived from tumor shrinkage and tumor apoptosis, respectively. We noted
that LCOP had a slow growth rate; the mean TDT was 1955 days. Tumor shrinkage and apoptosis appear to be the cause of a longer TDT and decreased number of the cancer cells.

In principal, we would like to suggest that major lung resection with mediastinal lymph node dissection should be performed for LCOP because of its large diameter. However, segmentectomy with thorough lymph node dissection might be a feasible option, because LCOP tends to be less invasive pathologically. The indication of limited resection has been extended to very early lung cancers that are located peripherally and show a GGO appearance on thin-section CT [21-24]. On the other hand, we investigated the indication of limited resection for lung cancer with solid appearance in thin-section CT, i.e., invasive lung cancer [6, 8]. LCOP did not show nodal metastasis with the exception of one patient with mediastinal nodal metastasis. Surgery was performed for this case nine years later since the presence of a tumor was indicated in the medical check, and the patient did not have hilar lymph node metastasis. In this cohort, we performed segmentectomy for two patients with LCOP because of multiple lung cancers. Both patients are alive and without recurrence. Synchronous or metachronous lung cancer was found in four of thirteen patients, so limited resection is indicated for some populations of LCOP.

This study was limited in that it was a retrospective study in a single institute and the sample size of LCOP was small. Our results are not helpful to diagnosis LCOP because we analyzed only cases of adenocarcinoma for LCOP in this period. Further investigation is warranted in the future.

In conclusion, we investigated a novel radiological entity of pulmonary malignancy, LCOP. LCOP has a less invasive nature regardless of its large tumor diameter, however, it is quite difficult to diagnose as lung adenocarcinoma due to its radiological characteristics. As a result, there is the possibility that LCOP is diagnosed as an inflammatory lesion resulting in proper treatment not being rendered as a lung adenocarcinoma. To avoid misdiagnosing this rare radiological entity, aggressive pathological diagnosis by surgical intervention should be
performed for cases of suspected LCOP seen on thin-section CT.

Conclusion

We investigated novel radiological entity of pulmonary malignancy, lung cancer mimicking organizing pneumonia (LCOP). LCOP has less invasiveness regardless of its large tumor diameter. However, nodal involvement would be observed and histological diagnosis is mandatory.
REFERENCES


Figure 1
The criteria of lung cancer mimicking organizing pneumonia. (a) Irregular shape, (b) reticular pattern, and (c) extension along broncho-vascular tree toward hilum.

Figure 2
Pathological findings of lung cancer mimicking organizing pneumonia - tumor size was 40 × 29 mm. The tumor was composed mainly of collapsed lung and collagenous fibers. (Zone A, H-E stain, mid power view). Few cancer cells were involved in the fibrosis. (Yellow arrow) More cancer cells exist in the peripheral area of the collapsed tumor. (Zone B, H-E stain, high power view) The number of tumor cells gradually decreased in the central area of tumor. External layer composed of adenocarcinoma with a lepidic growth pattern. (Zone C, H-E stain, high power view)

Figure 3
The 5-year overall survival rate (OS: Figure 3A) and relapse-free survival rate (RFS: Figure 3B) in patients with lung cancer mimicking organizing pneumonia were 91.7 and 100 %, respectively, whereas those of the other adenocarcinoma patients were 78.9 and 76.3 %, respectively.
Figure 1
The criteria of lung cancer like organizing pneumonia (LCOP).
(a) irregular extension along the broncho-vascular tree toward the hilum (red arrow),
(b) irregular shaped opacity adjacent to thickened bronchial wall or dilated bronchus (yellow arrow),
and (c) reticular opacity with surrounding GGO (yellow arrow head).
Figure 2
Pathological findings of LCOP - The tumor size were 40 × 29 mm.
Most of tumor was composed by collapsed lung and elastic fibers. (zone A, H -E stain, mid power view)
Few cancer cells were involved in the fibrosis. (yellow arrow)
More cancer cells exist peripheral of collapsed tumor. (zone B, H -E stain, high power view)
As closing with the center, the number of cancer diminishes gradually.
External layer was composed by adenocarcinoma with lepidic growth pattern. (zone C, H -E stain, high power view)
Figure 3
The 5-year overall survival rate (OSR: A) and relapse-free survival rate (RFS: B) of the LCOP patients were 91.7 and 100 %, respectively, whereas those of the other adenocarcinoma patients were 78.9 and 76.3 %, respectively.
<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Pack-year</th>
<th>CEA (ng/ml)</th>
<th>Follow up period (month)*</th>
<th>Location of tumor</th>
<th>Tumor diameter (mm)</th>
<th>Type of operation</th>
<th>p-stage</th>
<th>EGFR mutation subtype</th>
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<td>1.8</td>
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<td>25</td>
<td>Segmentectomy</td>
<td>IA</td>
<td>Wt</td>
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<td>18</td>
<td>RUL</td>
<td>32</td>
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<td>IB</td>
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<td>6.5</td>
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<td>23</td>
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<td>0</td>
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<td>41</td>
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<td>Lobectomy+WWR</td>
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<td>5.9</td>
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<td>RUL</td>
<td>29</td>
<td>Lobectomy</td>
<td>IA</td>
<td>Exon 21</td>
</tr>
<tr>
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<td>Exon 21</td>
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<td>9.8</td>
<td>5</td>
<td>RLL</td>
<td>22</td>
<td>Segmentectomy</td>
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<td>75</td>
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<td>IIB</td>
<td>Exon 21</td>
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<td>2.4</td>
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<td>RLL</td>
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<td>Lobectomy</td>
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<td>LUL</td>
<td>40</td>
<td>Lobectomy</td>
<td>IIIA</td>
<td>Exon 19</td>
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CEA, carcinoembryonic antigen; RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; WWR, wide wedge resection; Wt, wild type; Exon 21, exon 21 L858R point mutation; Exon 18, exon 18 deletion; Exon 19, exon 19 deletion;

* The period between detection of abnormal shadow by diagnostic imaging and surgery
Table 2. The relationship between lung cancer mimicking organizing pneumonia and other adenocarcinomas

<table>
<thead>
<tr>
<th>Variables</th>
<th>LCOP (n=13)</th>
<th>Adenocarcinoma (n=551)</th>
<th>p-value</th>
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<td>Age, range (median)</td>
<td>62-81 (70)</td>
<td>24-89 (65.6)</td>
<td>0.777</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>4 (30.8%)</td>
<td>271 (49.2%)</td>
<td>0.263</td>
</tr>
<tr>
<td>Female</td>
<td>9 (69.2%)</td>
<td>280 (50.8%)</td>
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</tr>
<tr>
<td>Smoking status</td>
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<tr>
<td>pack year ≥ 40</td>
<td>2 (15.4%)</td>
<td>121 (24.2%)</td>
<td>0.743</td>
</tr>
<tr>
<td>pack year &lt; 40</td>
<td>11 (84.6%)</td>
<td>377 (76.8%)</td>
<td></td>
</tr>
<tr>
<td>CEA (ng/ml)</td>
<td></td>
<td></td>
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<tr>
<td>≥ 3.0</td>
<td>10 (76.9%)</td>
<td>208 (44.6%)</td>
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<tr>
<td>&lt; 3.0</td>
<td>3 (23.1%)</td>
<td>258 (55.4%)</td>
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<td>Maximum tumor dimension (range)</td>
<td>30mm (14-75)</td>
<td>23.6mm (2-115)</td>
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<td>≤ 20mm</td>
<td>1 (7.7%)</td>
<td>278 (52.6%)</td>
<td>0.001</td>
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<td>&gt;20mm</td>
<td>12 (92.3%)</td>
<td>251 (48.4%)</td>
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<td>Type of operation</td>
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<td>Lobectomy</td>
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<td>Pathologic stage</td>
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<td>IA</td>
<td>5 (38.4%)</td>
<td>330 (59.9%)</td>
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<td>IB</td>
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<td>104 (18.9%)</td>
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<td>Lymphatic invasion</td>
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<td>Vascular invasion</td>
<td>1 (7.7%)</td>
<td>175 (31.8%)</td>
<td>0.064</td>
</tr>
</tbody>
</table>

LCOP, lung cancer mimicking organizing pneumonia; CEA, carcinoembryonic antigen