**TABLE 4. Clinicopathologic findings in patients with clinical stage IA but pathologic lymph node positive lung adenocarcinoma, according to lymphatic invasion status**

| Finding | Lymph node metastasis positive: Lymphatic invasion negative (n = 13) | Lymph node metastasis positive: Lymphatic invasion positive (n = 28) | *P* value |
|---|---|---|---|
| Age | | | |
| Median | 64 | 66 | .96 |
| Interquartile range | 56-72 | 55.25-73.25 | |
| Sex | | | |
| Female | 4 | 15 | .20 |
| Male | 9 | 13 | |
| CEA | | | |
| Median | 3.7 | 3.4 | .81 |
| Interquartile range | 2.5-4.075 | 2.65-4.25 | |
| Size* | | | |
| Median | 2 | 2.2 | .62 |
| Interquartile range | 1.6-2.6 | 1.775-2.5 | |
| GGO† ratio | | | |
| Median | 0 | 0 | .75 |
| Interquartile range | 0-10 | 0-2.5 | |
| SUV max | | | |
| Median | 3.4 | 3.7 | .87 |
| Interquartile range | 2.7-4.0 | 2.175-4.925 | |
| LC ratio | | | |
| Median | 10 | 10 | .16 |
| Interquartile range | 10-20 | 0-12.5 | |
| Blood vessel invasion | | | |
| Negative | 7 | 10 | .32 |
| Positive | 6 | 18 | |
| Pleural invasion | | | |
| Negative | 11 | 18 | .28 |
| Positive | 2 | 10 | |
| Lymph node metastasis | | | |
| N1 | 9 | 11 | .18 |
| Single station N2 or single station N2 + N1 | 2 | 11 | |
| Multistation N2 | 2 | 6 | |

*CEA*, Carcinoembryonic antigen; *GGO*, ground-glass opacity; *SUV*, standardized uptake value; *LC*, lepidic component. *Tumor size on the high-resolution computed tomography scan. †GGO ratio on the high-resolution computed tomography scan.

for OS,[20] to evaluate RFS may effectively be equivalent to assessing OS in identifying prognostic factors.

## CONCLUSIONS

LI was not always present in pN+ adenocarcinoma patients. In addition, pN(+)LI(−) patients had a better prognosis than pN(+)LI(+) patients, whereas there was no significant difference in RFS between pN(+)LI(−) and pN(−)LI(+) patients with clinical stage IA lung adenocarcinoma. LI status was indicated to classify clinical T1 N0 M0 lung adenocarcinoma patients with and without lymph node involvement into good and poor prognosis groups, the preoperative staging of which conducted using high-resolution CT and FDG-PET/CT. LI status may affect the selection of patients who have to receive adjuvant therapy.

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# Prophylaxis for acute exacerbation of interstitial pneumonia after lung resection

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# Prophylaxis for acute exacerbation of interstitial pneumonia after lung resection

**Hiroyuki Ito[1], Haruhiko Nakayama[1], Tomoyuki Yokose[2] and Kouzo Yamada[3]**

## Abstract

**Background and purpose:** Acute exacerbation of interstitial pneumonia is a life-threatening complication after lung cancer surgery. Dorsal subpleural fibrotic changes occupying 3 or more segments of both lower lobes on high-resolution computed tomography indicate a very high risk. We conducted a prospective phase II study to assess the efficacy of prophylactic treatment.

**Methods:** Patients with lung cancer underwent high-resolution computed tomography preoperatively to assess the risk of acute exacerbations of interstitial pneumonia. Before induction of general anesthesia, high-risk patients received 125 mg of methylprednisolone as an intravenous bolus and sivelestat sodium hydrate 300 mg·day$^{-1}$ as a continuous intravenous infusion. From January 2010 through August 2011, a total of 327 patients underwent surgery for lung cancer, and 31 (9.5%) were enrolled.

**Results:** There was no case of acute exacerbation. No adverse events were associated with prophylaxis. Usual interstitial pneumonia was confirmed histopathologically in 25 (80.6%) patients. Four (12.9%) patients had major complications. Usual interstitial pneumonia was diagnosed postoperatively in 4 (1.4%) of 327 patients who did not meet the inclusion criteria, and 1 of these patients died due to acute exacerbation of occult interstitial pneumonia.

**Conclusion:** Perioperative use of sivelestat sodium hydrate and low-dose methylprednisolone may be useful as prophylaxis for acute exacerbation of interstitial pneumonia.

## Keywords

Interstitiall lung diseases, lung neoplasms, pulmonary fibrosis, postoperative complications

Surgery remains the standard treatment for early stage primary lung cancer. Recent improvements in patient selection criteria, operative techniques, and postoperative management have contributed to lower mortality. In 1999, an analysis of data from a Japanese lung cancer registry estimated that mortality had decreased to 0.9%.[1] Respiratory complications are very common, and approximately half of all postoperative deaths are attributed to interstitial pneumonia (IP).[2] Apparent IP, as represented by idiopathic pulmonary fibrosis (IPF), is an important risk factor for postoperative mortality; postoperative acute exacerbation of interstitial pneumonia (AE-IP) is a life-threatening complication after lung cancer surgery.[3,4] We previously reported that dorsal subpleural fibrotic changes occupying 3 or more segments in both lower lobes (honeycombing) on high-resolution computed tomography (HRCT) and operative time are clinically significant risks factor for AE-IP in patients with lung cancer;[5] the incidence of postoperative AE-IP among patients with CT honeycombing was 10.9% (5/46), 80% of whom died of AE-IP. The onset of AE-IP in patients with occult IPF leads to poor outcomes despite medical therapy. At present, effective treatments for AE-IP remain to be established.[6–10] We conducted a prospective phase II study to assess the efficacy of prophylactic treatment

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against postoperative AE-IP in patients with CT honeycombing who were treated in a single center.

## Patients and methods

Our institutional internal review board approved this prospective study (institutional acceptance number Ken-24, 2009), and written informed consent was obtained from all patients. From January 2010 through August 2011, 327 patients underwent surgical treatment for lung cancer at our hospital. Tumors were staged according to the 7th UICC TNM staging system.

All patients had resectable non-small-cell lung cancer. Patients at high risk of postoperative AE-IP were identified on the basis of HRCT findings. Both lungs were examined within 1 month before surgery. The conditions of HRCT were a slice thickness of 3 mm or thinner, and use of the same window settings. HRCT scans were double-checked by a pulmonologist and a surgeon. The criteria for CT honeycombing in this study were dorsal and focal or diffuse subpleural honeycomb formation with or without fibrotic changes, occupying 3 or more segments of both lower lobes (Figure 1). Curvilinear shadows and dependent densities indicating gravitational effects were excluded. We excluded patients with currently treated IP, a treatment history of IP within the past 5 years, and a history of induction therapy, chemotherapy, or radiotherapy for any type of thoracic malignancy. Patients with unstable ischemic heart disease, a history of acute myocardial infarction within the past 3 months, heart failure, unstable arrhythmias, poorly controlled diabetes mellitus, or uncontrolled infectious disease, and pregnant women were also excluded. All patients underwent a preoperative functional cardiologic evaluation and pulmonary function testing. Lobectomy with systematic mediastinal lymph node dissection was the standard procedure. In patients with complications, wide wedge resection or segmentectomy was performed to achieve complete resection with definite surgical margins.

Most cases of AE-IP develop within several weeks after the operation,[5–7] a time associated with high levels of cytokines. During surgery and in the early postoperative period, a number of cytokines are released. These mediators of the host defense response of mesenchymal cells induce deposition of extracellular matrix products and collagen, resulting in fibrosis. This might the one of the causes of postoperative acute exacerbation of interstitial lung disease. The postoperative host defense response is most likely a major contributing factor to AE-IP. We hypothesized that suppressing the postoperative inflammatory response during operation and in the early postoperative period was the key to reducing the risk of postoperative AE-IP. Sivelestat sodium hydrate (sodium N-{2-[4-(2, 2-dimethylpropionyloxy) phenylsulfonylamino] benzoyl} aminoacetate tetra hydrate (Elaspol, ONO-5046-Na [C20H21N2NaO7S-Na-4H2O, molecular weight, 528.51]; Ono Pharmaceutical Co., Osaka, Japan) was developed as a specific inhibitor of neutrophil elastase, an extremely cytotoxic enzyme in plasma and interstitial fluid.[11] Sivelestat competitively inhibits the activity of neutrophil elastase in humans, but it does not affect other proteases.[12,13] Sivelestat has been approved in Japan for the indications of acute lung injury (ALI) and acute respiratory distress syndrome ARDS).[14] Although there have been conflicting results regarding its benefits,[15] a Japanese phase III trial demonstrated that sivelestat was effective in patients with ALI/ARDS

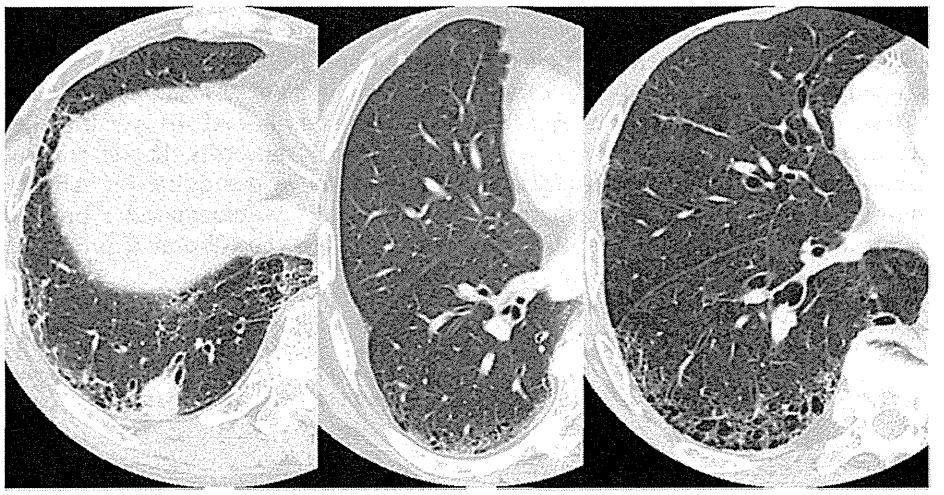

**Figure 1.** Preoperative high-resolution computed tomography in 3 patients with computed tomography honeycombing. Diffuse subpleural dorsal honeycombing with focal fibrotic changes can be seen.

associated with systemic inflammatory response syndrome. The benefits of sivelestat include improved pulmonary oxygenation, a reduced duration of mechanical ventilation, and a shorter stay in the intensive care unit (ICU).[14] These results suggest that sivelestat could potentially suppress the severe inflammatory response after highly invasive operations such as thoracotomy. In addition, serum levels of inflammatory cytokines such as interleukin-1b and neutrophil elastase are suppressed by treatment with sivelestat.[13] Serious adverse events associated with sivelestat include dyspnea (0.2%), leukopenia (0.2%), thrombocytopenia (0.2%), and severely impaired liver function (0.2%). Corticosteroids inhibit the host defense response at many levels, and suppress fibrogenesis and the expression of adhesion molecules.[16] Treatment with corticosteroids did not reduce mortality in patients with ARDS,[17,18] but low-dose corticosteroids in the early stage of ARDS was found to lead to complete maintenance of respiratory mechanics in mild ALI, as well as minimal changes in tissue impedance and extracellular matrix components in severe lesions.[19] The use of low-dose methylprednisolone in early postoperative ARDS has produced favorite outcomes by significantly reducing postoperative mortality and promoting recovery without mechanical ventilation.[9]

We studied whether the perioperative combined use of sivelestat and low-dose methylprednisolone reduced postoperative levels of inflammatory cytokines in patients with lung cancer who were preoperatively identified to be at high risk of acute exacerbations of interstitial lung disease. Immediately before induction of general anesthesia, 125 mg of methylprednisolone was given as an intravenous bolus and 300 mg·day$^{-1}$ of sivelestat was administered as a continuous intravenous infusion. Sivelestat was continued for 48 h; this period is associated with high levels of postoperative cytokines.

Preoperative assessments, surgery, anesthesia, and postoperative management were performed by the same anesthesia and surgical team in all patients. Postoperatively, patients were admitted to the ICU for that day only. Transfusion was performed at a rate of 1.25 mL·kg$^{-1}$·h$^{-1}$, and the patient wore an oxygen (40%) mask until the next morning. As routinely performed for postoperative patients, percutaneous oxygen saturation ($SpO_2$) and chest radiography were performed on postoperative days 0, 1, 4, and 7. Laboratory values were checked on postoperative days 1, 4, and 7. Discharge was scheduled for postoperative day 7. Chest CT was performed immediately if the $SpO_2$ was <93% while breathing room air or an infiltrating shadow was noted on chest radiography. Sputum cultures were examined or bronchofibroscopy was performed to exclude the possibility of aspiration and bacterial infection. Cardiac ultrasonography was performed to rule out acute heart failure. Patients were closely monitored postoperatively, and adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0. Any grade 2 or higher complications were recorded as postoperative complications. In addition to routine histological examinations and staging, lung specimens from all patients were histopathologically examined for evidence suggesting IP, especially usual interstitial pneumonia (UIP), a typical histological finding of IPF. If honeycomb lesions seen on CT were not included in the specimens resected at lung cancer surgery, an additional partial resection, such as biopsy of a lower lobe, was performed to confirm the presence of IP.

The primary endpoint was the incidence of AE-IP within 30 days after surgery. Secondary endpoints were the diagnostic accuracy of UIP on HRCT, postoperative morbidity, and mortality. The expected incidence of AE-IP within 30 days after operation was assumed to be less than 1%, with a threshold value of 10% or higher. A sample size of 30 patients was calculated to be necessary, with an alpha error of 0.05 and a beta error of 0.2. Postoperative AE-IP was diagnosed on the basis of acute hypoxia-like ALI/ARDS; a $PaO_2$-to-fraction of inspired $O_2$ ratio <300 with bilateral infiltrations on chest radiography; and the involvement of both lungs. AE-IP caused by aspiration, bacterial infection, or acute heart failure was excluded. We also studied patients' clinical characteristics (age, sex, smoking history, $PaO_2$, % of predicted forced vital capacity, % of predicted forced expiratory volume in 1 s, coexisting heart disease, TNM stage), preoperative laboratory data, and surgical records (operation time, blood loss, extent of surgery, blood transfusion). Postoperative morbidity and mortality were defined as events occurring within 30 days after operation. Each variable was tested by the chi-square test, Fisher's exact test, or Student's $t$ test. Logistic-regression analysis was used for multivariate analysis and performed with StatView for Windows version 5.0 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was defined as a $p$ value of less than 0.05.

## Results

During the study period, 31 (9.5%) patients were enrolled. Table 1 shows the clinical characteristics of these patients. All were smokers, and many had several cardiopulmonary comorbidities; only 4 were free of comorbidities. On spirography, 23 (74.2%) patients showed normal function, but the mean diffusing capacity for carbon monoxide was decreased to 75.3% ±22.5%, which tended to be lower than that in other

**Table 1.** Characteristics of 31 patients at high risk of acute exacerbation of interstitial pneumonia.

| Variable | No. of patients | Mean [range] |
|---|---|---|
| Sex (male/female) | 30/1 | |
| Age (years) | | 72.3 ± 6.49 [61–86] |
| Smoker | 31 (100%) | |
| Smoking index | | 1087 ± 597 [210–2700] |
| %FVC | | 99.0% ±17.2% [62.4%–129%] |
| $\%FEV_1$ | | 76.4% ±6.2% [64.0%–94.9%] |
| %DLCO | | 75.3% ±22.5% [34.8%–140%] |
| Spirogram pattern | | |
| Normal | 23 | |
| Obstructive | 2 | |
| Restrictive | 5 | |
| Combined | 1 | |
| Clinical stage | | |
| IA | 10 | |
| IB | 7 | |
| IIA | 8 | |
| IIB | 3 | |
| IIIA | 3 | |
| Elevated WBC | 0 | |
| Elevated CRP ($mg \cdot dL^{-1}$) | 13 | 1.27 [0.33–4.87] |
| Elevated LDH ($U \cdot L^{-1}$) | 3 | 275.3 [260–290] |
| Elevated KL-6 ($U \cdot mL^{-1}$) | 17 | 788 [504–1360] |
| Comorbidities* | | |
| Emphysema | 18 | |
| Hypertension | 9 | |
| Diabetes | 5 | |
| Ischemic heart disease | 4 | |
| Bronchial asthma | 3 | |
| Tuberculosis | 3 | |
| Arrhythmia | 3 | |
| Ischemic cerebral disease | 2 | |
| Hepatitis | 2 | |
| Rheumatoid arthritis | 1 | |
| Abdominal aortic aneurysm | 1 | |
| Extent of surgery | | |
| Lobectomy | 22 | |
| Segmentectomy | 3 | |
| Wide wedge resection | 6 | |

*There was some overlap. CRP: C-reactive protein; %DLCO: % of predicted diffusing capacity of the lung for carbon monoxide; %FVC: % of predicted forced vital capacity; $\%FEV_1$: % of predicted forced expiratory volume in 1 s; LDH: lactate dehydrogenase; KL-6: sialylated carbohydrate antigen KL-6; WBC: white blood cells.

patients with lung cancer. Wide wedge resection was performed in 6 patients, and segmentectomy was performed in 3 because of lower cardiopulmonary reserve and comorbidities. The mean operation time was 144 ± 62.0 min (range 36–280 min), the mean blood loss was 35.0 ± 34.0 g (range 5–130 g), and no patient received a blood transfusion. There was no case of postoperative AE-IP. Major morbidity occurred in 4 (12.9%) patients. One (3.2%) patient had a myocardial infarction (grade 5) on postoperative day 29 and died within 30 days after operation. Another patient had a bronchopleural fistula (grade 5) after a right lower

lobectomy; bacterial pneumonia developed, and the patient died 43 days after the operation. Other major morbidities were cerebral infarction (cerebrovascular ischemia grade 2) in one patient, and prolonged air leakage requiring pleurodesis (pulmonary fistula grade 2) in another. The Data and Safety Monitoring Committee concluded that these complications were not clearly but possibly related to prophylaxis. These two patients were originally thought to be at high risk for lung cancer surgery. They had several comorbidities: one had ischemic heart disease with past history of acute myocardial infarction, emphysema, and diabetes mellitus; and the other had history of heavy smoking and hypertension, and the operative procedure was a right lower lobectomy which carries a risk of bronchopleural fistula. None of the variables we tested showed statistical significance regarding the incidence of postoperative death. Besides these morbidities, there was no other grade 2 or higher adverse effect. UIP was histopathologically confirmed in 25 (80.6%) patients. Three patients were confirmed to have nonspecific interstitial pneumonia, and 3 had smoking-related interstitial fibrosis of the lung. The overall diagnostic accuracy of IP on HRCT was 90.3% (28/31). The mean postoperative hospital stay was $8.2 \pm 5.2$ days (range 4–30 days), and the ICU stay was 1.1 days (range 1–2 days). Four of 327 (1.4%) patients who did not meet the HRCT criteria were postoperatively given a diagnosis of UIP on histopathological examination; one of these had postoperative acute exacerbation of UIP and died of respiratory failure on postoperative day 42. During this period, 2 patients with currently treated apparent IPF were excluded from this study. A lobectomy and a partial resection were performed; AE-IP did not develop in either of these patients. The overall operative mortality was 0.9%.

## Discussion

The incidence of postoperative mortality related to AE-IP remains high; this is a major problem that needs to be overcome in thoracic surgery. Once postoperative AE-IP develops, even in the presence of occult or apparent IPF, mortality is extremely high.[5–7] Perioperative use of sivelestat and low-dose methylprednisolone may be useful as prophylaxis against AE-IP in high-risk patients. Retrospective studies have reported that the postoperative administration of sivelestat increases oxygenation, reduces the duration of mechanical ventilation, and shortens the ICU stay in patients who undergo thoracic surgery.[13,20] However, in our previous study, patients with UIP who had ALI/ARDS postoperatively received sivelestat and steroids, but mortality was high,[5] consistent with the results of the STRIVE study.[15] This finding implies that starting treatment with sivelestat after the onset of AE-IP is too late. To our knowledge, the value of prophylactic therapy in patients with occult IPF who undergo lung cancer surgery has not been evaluated previously. In this sense, the results of our trial are very promising.

The mechanism of AE-IP remains unclear, but several factors appear to be involved. Representative factors include highly invasive procedures and treatment such as pneumonectomy, induction therapy, prolonged operations, and high blood loss.[6,21] Besides countermeasures against postoperative AE-IP in patients with occult IPF, careful postoperative management should be implemented. Avoiding excessive perioperative fluid administration also has an important role in reducing the risk of AE-IP.[22] In this study, a single integrated surgical team performed postoperative fluid management by controlling the infusion rate and checking the body weight of all patients.

The detailed images obtained on HRCT were very useful for detecting IPF. In a previous study, we showed that focal dorsal subpleural honeycombing occupying 3 or more segments of both lower lobes on HRCT suggests the presence of occult IPF. CT honeycombing on HRCT is a simple and useful predictor of the risk of postoperative AE-IP. Measures to prevent postoperative AE-IP in patients with occult IPF are essential to improve the safety of lung cancer surgery. In the present study, the presence or absence of UIP was confirmed histopathologically in all patients with evidence of UIP on HRCT, and UIP was accurately detected in 80% of patients. Three patients were given a diagnosis of smoking-related interstitial fibrosis, which is a distinct form of chronic interstitial fibrosis that is common in smokers.[23,24] This is not a critical disease nor related to AE-IP, but smoking-related interstitial fibrosis may rarely present with radiologic findings similar to those associated with UIP; it is therefore difficult to distinguish smoking-related interstitial fibrosis from occult IPF in some patients. Nearly all of our patients were men and heavy smokers who had several comorbidities, including vascular disease, cardiopulmonary disease, and diabetes. The Data and Safety Monitoring Committee concluded that these were possibly related to prophylaxis because of the high incidence of postoperative death; we thought the subjects of our study were a group of very high-risk patients for lung cancer surgery. The high mortality and major morbidity rates in this study can thus probably be attributed to the need for prophylaxis against AE-IP combined with other high-risk factors. When such patients are scheduled to undergo lung cancer surgery, it is essential to obtain fully informed consent and to

perform thorough preoperative evaluation and careful postoperative management.

Our study had several important limitations. Although this trial was prospective and achieved our main objectives, the sample size was small, the study was performed at a single center, and the accuracy of our data is considered inadequate. We performed this trial as a pilot study, given the small number of target patients. Our findings should be confirmed in larger prospective multicenter clinical trials involving sufficient numbers of patients. Nevertheless, we concluded that perioperative administration of sivelestat sodium hydrate and low-dose methylprednisolone may be useful as prophylaxis against AE-IP in high-risk patients who undergo lung cancer surgery. The patients who could be enrolled for this prophylaxis were thought to be at very high risk of postoperative mortality, thus physicians should pay much attention to preoperative evaluation and postoperative management.

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## Conflicts of interest statement

None declared.

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# Sublobar Resection for Lung Adenocarcinoma Meeting Node-Negative Criteria on Preoperative Imaging

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*Background.* This study evaluated the usefulness of sublobar resection for patients with clinical stage IA lung adenocarcinoma that met our proposed node-negative criteria: solid tumor size of less than 0.8 cm on high-resolution computed tomography or maximum standardized uptake value of less than 1.5 on [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography.

*Methods.* A multicenter database of 618 patients with completely resected clinical stage IA lung adenocarcinoma who underwent preoperative high-resolution computed tomography and [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography was used to evaluate the surgical results of sublobar resection for patients who met our node-negative criteria.

*Results.* No patient who met the node-negative criteria had any pathological lymph node metastasis. Recurrence-free survival (RFS) and overall survival (OS) rates at 5 years were significantly higher for patients who met the node-negative criteria (RFS: 96.6%; OS: 95.9%) than for patients who did not (RFS: 75.5%, $p < 0.0001$; OS: 83.1%, $p < 0.0001$). Among patients who met the node-negative criteria, RFS and OS rates at 5 years were not significantly different between those who underwent lobectomy (RFS: 96.0%; OS: 95.9%) and those who underwent sublobar resection (RFS: 97.2%, $p = 0.94$; OS: 95.9%, $p = 0.98$). Of 264 patients with T1b (2-cm to 3-cm) tumors, 106 (40.2%) met the node-negative criteria.

*Conclusions.* Sublobar resection without systematic nodal dissection is feasible for clinical stage IA lung adenocarcinoma that meets the above-mentioned node-negative criteria. Even a T1b tumor, which is generally unsuitable for intentional sublobar resection, can be a candidate for sublobar resection if it meets these node-negative criteria.

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Early-stage lung cancer, particularly lung adenocarcinoma, is now frequently being detected because of advanced radiographic techniques, such as high-resolution computed tomography (HRCT), and the widespread use of low-dose helical CT for tumor screening [1–3]. In a prospective randomized controlled study, the Lung Cancer Study Group reported that the outcomes of limited resections, such as segmentectomy and wedge resection, were inferior to those of standard lobectomy in patients with clinical T1 node-negative (N0) M0 non-small cell lung cancer (NSCLC) [4]. However, several studies have demonstrated the usefulness of sublobar resection for peripheral small-sized NSCLC [3, 5–10].

Theoretically, true N0 lung cancer can be treated by sublobar resection without nodal dissection when surgical margins are adequate. We previously reported that preoperative HRCT and [18F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) were useful for predicting N0 clinical stage IA lung adenocarcinoma [11].

The objective of this study was to evaluate the usefulness of sublobar resection for clinical stage IA lung adenocarcinoma that met our previously proposed N0 criteria: solid tumor size of less than 0.8 cm on HRCT or a maximum standardized uptake value (SUVmax) of less than 1.5 on FDG-PET/CT [11].

## Patients and Methods

### *Patients*

Between August 1, 2005, and June 30, 2010, we enrolled 618 patients with clinical T1 N0 M0 stage IA lung adenocarcinoma from 4 institutions in Japan (Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center). For this study, we retrospectively analyzed the data for all 618 patients in

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Abbreviations and Acronyms

| | |
|---|---|
| CI | = confidence interval |
| CT | = computed tomography |
| F | = female |
| FDG | = [18F]-fluoro-2-deoxy-D-glucose |
| HR | = hazard ratio |
| HRCT | = high-resolution computed tomography |
| IRB | = Institutional Review Board |
| LI | = lymphatic invasion |
| LN | = lymph node |
| LNM | = lymph node metastasis |
| M | = male |
| N0 | = node-negative |
| NSCLC | = non-small cell lung cancer |
| OS | = overall survival |
| PET | = positron emission tomography |
| PI | = pleural invasion |
| Pt | = patient |
| RFS | = recurrence-free survival |
| SUVmax | = maximum standardized uptake value |
| VI | = vascular invasion |

this multicenter database. The database included patients who underwent preoperative staging using HRCT and FDG-PET/CT, followed by curative resection without neoadjuvant chemotherapy or radiotherapy, with a definitive histopathologic diagnosis of lung adenocarcinoma. Excluded were those with incompletely resected tumors (R1 or R2) and those with synchronous multiple tumors or previous lung operations. This database has been prospectively collected and maintained.

HRCT and FDG-PET/CT, followed by curative R0 resection, had been performed for all patients who were staged according to the TNM Classification of Malignant Tumours, 7th Edition [12]. Mediastinoscopy and endobronchial ultrasonography were not routinely performed because all patients had undergone preoperative HRCT and FDG-PET/CT. HRCT revealed less than 1-cm enlargement of mediastinal or hilar lymph nodes and FDG-PET revealed a SUVmax of less than 1.5 in these lymph nodes.

Segmentectomy was considered for patients with clinical stage IA tumors that could be completely resected with ample surgical margins. No lymph node metastasis was intraoperatively confirmed on rapid frozen sections for enlarged lymph nodes or lymph nodes that were suspected with disease in the thoracic cavity. In cases of apparent or suspected nodal metastasis, lobectomy was chosen. Systematic lymphadenectomy, including hilar and mediastinal node dissection, was performed during segmentectomy but not during wedge resection. Therefore, wedge resection was performed for tumors, of which a ground glass opacity component accounted for great majority on HRCT. All patients who had pathologically diagnosed lymph node metastases received four cycles of platinum-based chemotherapy after the operation. None of the study patients received adjuvant radiotherapy.

Patients were divided into two groups. One group included patients who met the N0 criteria of solid tumor size of less than 0.8 cm on HRCT or a SUVmax of less than 1.5 on FDG-PET/CT [11]. The other group included patients who did not meet these N0 criteria.

This multicenter study was approved by the Institutional Review Boards (IRBs) of Hiroshima University Hospital (IRB No. EKI-644), Kanagawa Cancer Center (IRB No. KEN-31), Cancer Institute Hospital (IRB No. 2008-1018), and Hyogo Cancer Center (IRB No. H20-RK-15). All IRBs waived the requirement for informed consent from individual patients for this retrospective review of a prospective database.

### *HRCT Acquisition*

Chest images were acquired with 16-row multidetector CT independently of subsequent FDG-PET/CT examinations. For high-resolution tumor images, the following parameters were used: 120 kVp; 200 mA; 1- to 2-mm section thickness; 512- × 512-pixel resolution; 0.5- to 1.0-second scanning time; a high-spatial reconstruction algorithm with a 20-cm field of view; and mediastinal (level: 40 HU; width: 400 HU) and lung (level: −600 HU; width: 1,600 HU) window settings. Ground glass opacity was defined as a misty increase in lung attenuation that did not obscure underlying vascular markings. We defined solid tumor size as the maximum dimension of the solid component in the lung windows, excluding the ground glass opacity [13]. Radiologists from each participating institution reviewed the CT scans and determined the tumor sizes.

### *FDG-PET/CT Acquisition*

Patients were instructed to fast for more than 4 hours before intravenous injection of 74 to 370 MBq of FDG, which was followed by a relaxation period of at least 1 hour before FDG-PET/CT scanning. Blood glucose levels were determined before the tracer injection to confirm a level of less than 150 mg/dL. Patients with blood glucose levels of 150 mg/dL or more were excluded from PET/CT imaging. For imaging, we used a Discovery ST (GE Healthcare, Little Chalfont, UK), Aquiduo (Toshiba Medical Systems Corp, Tochigi, Japan), or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated 3-dimensional PET/CT scanner.

Following a standard protocol, low-dose, nonenhanced CT images (2- to 4-mm section thickness) for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient. Immediately after CT, PET covered the same axial field of view for 2 to 4 minutes per table position, depending on the condition of the patient and scanner performance.

An iterative algorithm with CT-derived attenuation correction was used to reconstruct all PET images with a 50-cm field of view. An anthropomorphic body phantom (NEMA NU2-2001; Data Spectrum Corp, Hillsborough, NC) was used to minimize variations in SUVs among the institutions. A calibration factor was evaluated by dividing the actual SUV by the gauged mean SUV in the

phantom background to decrease interinstitutional SUV inconsistencies. The final SUV used here is referred to as the revised maximum SUVmax. Radiologists from each institution determined the original SUVmax values.

### *Follow-Up Evaluations*

All patients who underwent lung resection were followed up from the day of the operation. Postoperative follow-up procedures for the first 2 years included physical examination and chest roentgenography every 3 months and chest and abdominal CT examinations every 6 months. Subsequently, physical examination and chest roentgenography were performed every 6 months and chest CT examination was performed every year.

### *Statistical Analysis*

Results are given as numbers (%) or medians, unless otherwise stated. A $\chi^2$ test was used to compare frequencies for categoric variables. The Fisher exact test was used when sample sizes were small. Recurrence-free survival (RFS) was defined as the time from the date of the operation until the first event (relapse or death from any cause) or the last follow-up. Overall survival (OS) was defined as the time from the date of the operation until death from any cause or the last follow-up. The Kaplan-Meier method was used to analyze RFS and OS durations, and a log-rank test was used to compare differences in RFS and OS. We performed a Cox proportional hazards model to determine whether age (continuous), sex, solid tumor size (continuous), SUVmax (continuous), or surgical procedure influenced RFS. We only used preoperative potential confounding factors as variables because postoperative factors would never influence the decision for surgical procedure. SPSS 10.5 software (SPSS Inc, Chicago, IL) was used for statistical analysis. The level of statistical significance was set at a $p$ value of less than 0.05.

*Table 1. Clinicopathologic Features of Patients Who Did and Did Not Meet the Node-Negative Criteria*

| Variables[a] | Solid Tumor Size ≥0.8 cm and SUVmax ≥1.5 (n = 293) | Solid Tumor Size <0.8 cm or SUVmax <1.5 (n = 325) | $p$ Value |
|---|---|---|---|
| Age, y | 67.0 (37–84) | 65 (31–89) | 0.04 |
| Male sex | 137 (46.8) | 135 (41.5) | |
| Whole tumor size (cm) | 2.2 (0.8–3.0) | 1.8 (0.6–3.0) | <0.001 |
| Solid tumor size (cm) | 1.8 (1.0–3.0) | 0.4 (0–3.0) | <0.001 |
| Clinical T | | | <0.001 |
| T1a | 135 (46.1) | 219 (67.4) | |
| T1b | 158 (53.9) | 106 (32.6) | |
| SUVmax | 3.0 (1.5–17.0) | 0.9 (0–9.8) | <0.001 |
| Adenocarcinoma in situ | 5 (1.7) | 92 (28.3) | <0.001 |
| Procedure | | | <0.001 |
| Lobectomy | 246 (84.0) | 137 (42.2) | |
| Sublobar resection | 47 (16.0) | 188 (57.8) | |
| Segmentectomy[b] | 23 (7.8) | 75 (23.1) | |
| Wedge resection | 24 (8.2) | 113 (34.8) | |
| Lymphatic invasion | 87 (29.7) | 5 (1.5) | <0.001 |
| Vascular invasion | 101 (34.5) | 5 (1.5) | <0.001 |
| Pleural invasion | 62 (21.2) | 5 (1.5) | <0.001 |
| Lymph node metastasis | 45 (15.4) | 0 (0) | <0.001 |
| N1 | 24 (8.2) | 0 (0) | |
| N2 | 21 (7.2) | 0 (0) | |
| Recurrence | 57 (19.5) | 2 (0.6) | <0.001 |

[a] Categoric data are shown as number (%) and continuous data as median (range). [b] Details of segmentectomy were right S1 in 4, S2 in 12, S3 in 3, S6 in 23, S8 in 5, S7 + 8 in 1, S8 + 9 in 3, S7 + 8 + 9 + 10 in 1, left S1 + 2 in 7, S3 in 3, S1 + 2 + 3 in 10, S1 + 2 + 3c in 1, S4 in 2, S5 in 1, S4 + 5 in 7, S6 in 10, S8 in 1, S9 in 3, and S6 + 8 + 9 + 10 in 1.

SUVmax = maximum standardized uptake value.

## Results

The characteristics of the 325 patients who met our N0 criteria and the 293 patients who did not are summarized in Table 1. There were no 30-day postoperative deaths in this study population. The median follow-up period of censored patients after the operation was 42.9 months. The mean follow-up period after lobectomy and segmentectomy were 43.3 months ± 15.6 and 40.4 ± 14.7 months in the N0 criteria group ($p = 0.10$) and 43.8 ± 16.8 months and 40.1 ± 19.3 months in the non-N0 criteria group ($p = 0.39$), respectively. There were significant differences between the two groups with regard to age, whole tumor size, solid tumor size, clinical T factor, SUVmax, surgical procedure, pathologic invasiveness (lymphatic, vascular, and pleural invasion), lymph node metastasis, and recurrence.

Patients who met the N0 criteria had significantly fewer pathologically invasive tumors and underwent sublobar resection. Lymph node metastases were found in 45 of the 293 patients (15.4%) who did not meet the N0 criteria. Of 45 patients with lymph node metastasis, 1 was N2 after sublobar resection (S6 segmentectomy), 24 were N1 after lobectomy, and 20 were N2 after lobectomy. Two patients who met the N0 criteria had tumor recurrences (Table 2). One was a 57-year-old woman with a solid tumor size of 1.3 cm and an SUVmax of 1.2. Although she had undergone standard lobectomy and had no lymph node metastasis, mediastinal lymph node recurrence subsequently developed. The other patient was a 59-year-old man with a solid tumor size of 1.8 cm and an SUVmax of 1.4. He had undergone wedge resection without lymph node dissection, and multiple lung metastases without lymph node recurrence subsequently developed.

The 5-year RFS rate (96.6%) was significantly better for patients who met the N0 criteria than for patients who did not (75.5%, $p < 0.0001$; Fig 1A). The 5-year OS rate (95.9%) was also significantly better for patients who met the N0 criteria than for patients who did not (83.1%, $p < 0.0001$; Fig 1B).

Among the patients who met the N0 criteria, no significant difference was noted in the 5-year RFS rate

*Table 2. Patients Who Met the Node-Negative Criteria and Developed Recurrences*

| Pt | Age | Sex | Whole Tumor Size | Solid Tumor Size | SUVmax | Procedure | LI | VI | PI | LNM | Recurrence Site | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 57 | F | 1.4 cm | 1.3 cm | 1.2 | Lobectomy | 1 | 0 | 0 | 0 | Mediastinal LN | 24 m, dead |
| 2 | 59 | M | 1.8 cm | 1.8 cm | 1.4 | Wedge resection | 0 | 0 | 0 | 0 | Multiple lung | 48.8 m, dead |

F = female; LN = lymph node; LI = lymphatic invasion; LNM = lymph node metastasis; M = male; PI = pleural invasion; Pt = patient; SUVmax = maximum standardized uptake value; VI = vascular invasion.

between those who underwent lobectomy (96.0%) and those who underwent sublobar resection (97.2%, $p = 0.94$; Fig 2A). Similarly, the 5-year OS rate was not significantly different between patients who underwent lobectomy (95.9%) and those who underwent sublobar resection (95.9%, $p = 0.98$; Fig 2B). Of 164 patients with T1b tumors, 106 (40.2%) met the N0 criteria (Table 3). These patients rarely had pathologic invasiveness, and no recurrences developed.

In patients who did not meet the N0 criteria, the 5-year RFS rate was 63.9% for those who underwent segmentectomy and 77.7% for those who underwent lobectomy; this difference was not statistically significant ($p = 0.058$; Fig 2C). The 5-year OS rate for patients who underwent lobectomy (82.8%) and those who underwent sublobar resection (85.2%) was also not significantly different ($p = 0.69$; Fig 2D).

Multivariate Cox analysis including the preoperative factors and surgical procedures revealed that solid tumor size and SUVmax were independent prognostic factors for RFS, whereas age, sex, and surgical procedure were not (Table 4). In clinical T1b patients, SUVmax was an independent prognostic factor for RFS, whereas surgical procedure was not (Table 5).

## Comment

The purpose of the current study was to assess the usefulness of sublobar resection for clinical stage IA lung adenocarcinoma that met our proposed N0 criteria. Patients who met our N0 criteria had fewer pathologically invasive tumors and fewer recurrences compared with those who did not meet these criteria. These results were consistent with those of our previous report [11].

Recurrences developed in 2 patients in this study who met the N0 criteria. Mediastinal lymph node recurrence developed in 1 patient after standard lobectomy, whereas multiple lung metastases without lymph node involvement after wedge resection without lymph node dissection were found in the other patient. We assumed that these patients would have had recurrences even if they had undergone standard surgical procedures.

Patients who met our N0 criteria had significantly better prognoses compared with those who did not. Therefore, clinical stage IA lung adenocarcinoma could be divided into two groups with different malignant behaviors and prognoses using solid tumor size on HRCT and SUVmax on FDG-PET/CT. These findings support our previous results that solid tumor size on HRCT and SUVmax on FDG-PET/CT were predictors of pathologic tumor invasiveness, lymph node metastasis, and prognosis [11, 13].

Among the patients who met the N0 criteria, we compared 5-year RFS and OS rates between those who underwent lobectomy and those who underwent sublobar resection. Patients who underwent sublobar resection had excellent prognoses, without any significant differences in RFS and OS rates compared with those

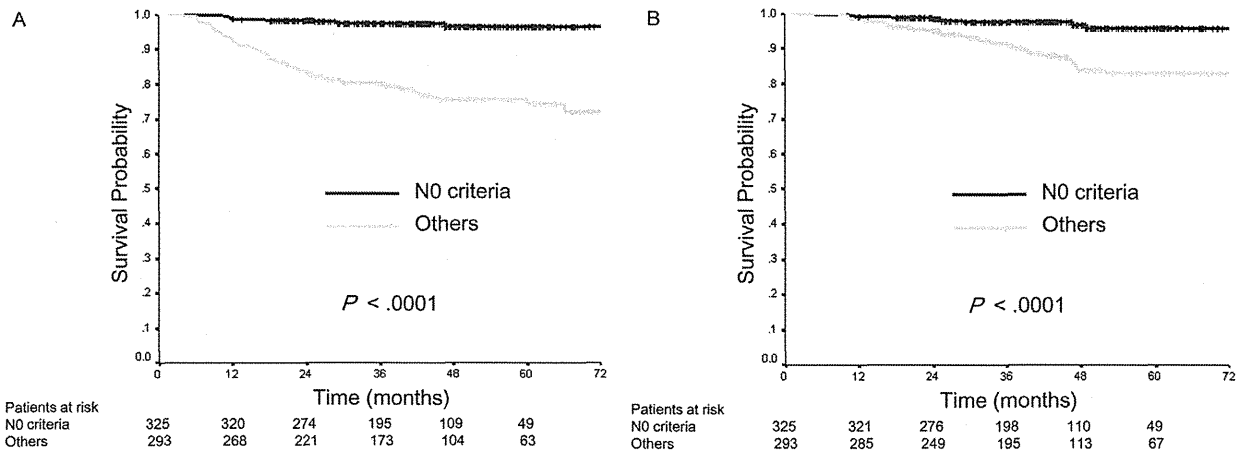


*Fig 1. Recurrence-free survival (RFS) and overall survival (OS) curves are shown for patients who met the node-negative (N0) criteria (blue lines) and those who did not (yellow lines). (A) RFS at 5 years was significantly different between patients who met the N0 criteria (96.6%) and those who did not (75.5%, $p < 0.0001$). (B) OS at 5 years was significantly different between patients who met the N0 criteria (95.9%) and those who did not (83.1%, $p < 0.0001$).*

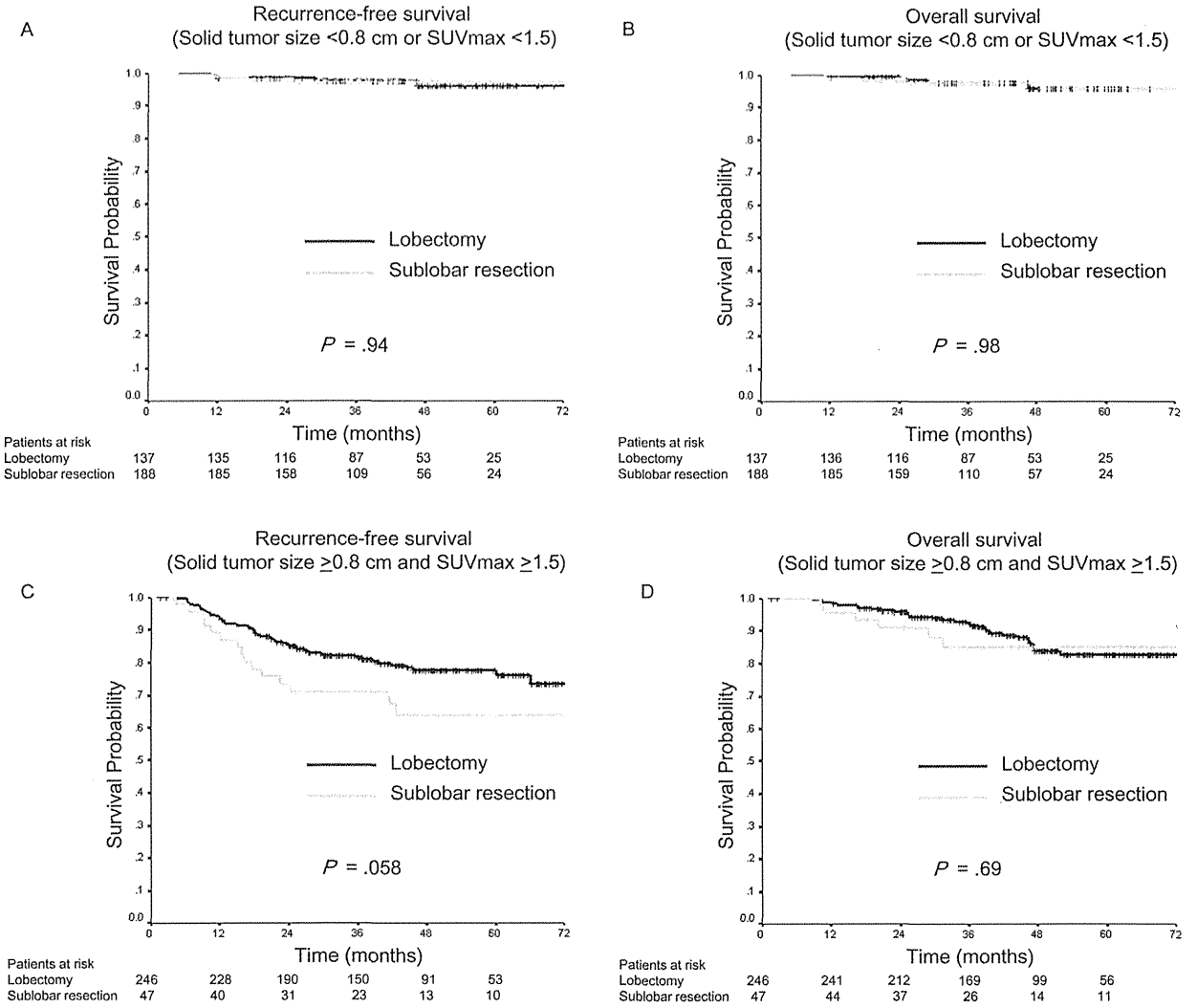


*Fig 2. Recurrence-free survival (RFS) and overall survival (OS) curves are shown for patients who underwent lobectomy (blue line) or sublobar resection (yellow line) on the basis of the node-negative (N0) criteria. (A) For the group that met the N0 criteria, the RFS rate at 5 years was not significantly different between patients who underwent lobectomy (96.0%) and those who underwent sublobar resection (97.2%, p = 0.94). (B) For the group that met the N0 criteria, the OS rate at 5 years was not significantly different between patients who underwent lobectomy (95.9%) and those who underwent sublobar resection (95.9%, p = 0.98). (C) For the group that did not meet the N0 criteria, patients who underwent sublobar resection tended to have a worse RFS rate at 5 years (63.9%) than patients who underwent lobectomy (77.7%, p = 0.058). (D) For the group that did not meet the N0 criteria, there was no significant difference in the OS rate at 5 years between patients who underwent lobectomy (82.8%) and those who underwent sublobar resection (85.2%, p = 0.69). (SUVmax = maximum standard uptake value.)*

who underwent lobectomy. For this study, we included segmentectomy and wedge resection as sublobar resections.

Actually, segmentectomy and wedge resection are considerably different procedures. The former can be used to approach hilar lymph nodes, whereas the latter cannot. However, patients who met our N0 criteria were considered not to have lymph node metastasis; therefore, systematic lymph node dissection did not appear to be necessary. Both procedures can be used for patients with solid tumor size of less than 0.8 cm on HRCT or a SUVmax of less than 1.5 on FDG-PET/CT. We should consider the surgical margin, and not lymph node dissection, when selecting the surgical procedure for patients with clinical stage IA lung adenocarcinomas that meet these N0 criteria.

Interestingly, approximately 40% of clinical T1b (2 to 3 cm) tumors in this study met the N0 criteria. Most research done in this area has generally not included patients with tumor sizes exceeding 2 cm for sublobar resection [3, 5–8]. However, these patients had T1b tumors with considerably low malignant potentials, and no recurrence developed. Therefore, even patients with T1b tumors that meet these N0 criteria can be candidates for

*Table 3. Characteristics of Patients With Clinical T1b Tumors That Met the Node-Negative Criteria*

| Variables[a] | Solid Tumor Size <0.8 cm or SUVmax <1.5 (n = 106) |
|---|---|
| Age, y | 67.5 (33–89) |
| Male sex | 48 (45.3) |
| Whole tumor size, cm | 2.4 (2.1–3.0) |
| Solid tumor size, cm | 0.6 (0–2.5) |
| SUVmax | 1.0 (0–4.1) |
| Adenocarcinoma in situ | 19 (17.9) |
| Procedure | |
| Lobectomy | 67 (63.2) |
| Sublobar resection | 39 (36.8) |
| Segmentectomy | 22 (20.8) |
| Wedge resection | 17 (16.0) |
| Lymphatic invasion | 2 (1.9) |
| Vascular invasion | 2 (1.9) |
| Pleural invasion | 2 (1.9) |
| Lymph node metastasis | 0 (0) |
| Recurrence | 0 (0) |

[a] Categoric data are shown as number (%) and continuous data as median (range).

SUVmax = maximum standardized uptake value.

sublobar resection if there are sufficient surgical margins. Cox proportional hazards model in this subpopulation also supported the use of sublobar resection. To achieve complete resection with adequate margins, we recommend segmentectomy, but not wedge resection, for T1b tumors meeting these N0 criteria, because providing an adequate margin for T1b tumors by wedge resection is difficult. The extent of resection should be chosen according to tumor size and location, and procedures that can lead to local recurrence must be avoided.

A benefit of sublobar resection is preservation of lung function [3, 14, 15]. In addition, sublobar resection provides outcomes that are equivalent to those of lobectomy for patients selected on the basis of HRCT and FDG-PET/CT findings; therefore, this can be a suitable procedure for these patients. However, 47 of 293 patients who did not meet the N0 criteria and could have possibly had lymph node metastasis underwent sublobar resection. The RFS rate for patients who underwent sublobar resection appeared to be worse than that for patients who underwent lobectomy, although the results were not significantly different ($p = 0.058$). Among 47 patients in the sublobar resection group, 24 (51%) underwent wedge resection. Therefore, patients who do not meet the N0 criteria (solid tumor size >0.8 cm and SUVmax >1.5) should be treated with segmentectomy or lobectomy with systematic hilar and mediastinal lymph node dissection, not wedge resection, because they may have LN metastasis. If segmentectomy is applied to patients who do not meet the N0 criteria, intraoperative lymph node examinations using frozen sections are mandatory. When lymph node metastasis is detected intraoperatively, the procedure should be converted to a lobectomy.

*Table 4. Multivariate Cox Analysis for Recurrence-Free Survival (All Patients)*

| Variables | HR (95% CI) | *p* Value |
|---|---|---|
| Age | 1.02 (0.99–1.04) | 0.24 |
| Sex (male) | 1.06 (0.67–1.68) | 0.80 |
| Solid tumor size (cm) | 2.04 (1.47–2.81) | <0.001 |
| SUVmax | 1.15 (1.07–1.24) | <0.001 |
| Procedure (lobectomy) | 0.64 (0.35–1.18) | 0.15 |

CI = confidence interval; HR = hazard ratio; SUVmax = maximum standardized uptake value.

*Table 5. Multivariate Cox Analysis for Recurrence-Free Survival (Clinical T1b Patients)*

| Variables | HR (95% CI) | *p* Value |
|---|---|---|
| Age | 1.02 (0.98–1.06) | 0.40 |
| Sex (male) | 1.43 (0.75–2.73) | 0.28 |
| Solid tumor size (cm) | 1.44 (0.88–2.36) | 0.14 |
| SUVmax | 1.25 (1.12–1.39) | <0.001 |
| Procedure (lobectomy) | 0.83 (0.29–2.34) | 0.72 |

CI = confidence interval; HR = hazard ratio; SUVmax = maximum standardized uptake value.

A strength of this study was that HRCT and FDG-PET/CT were performed for all patients and could be used to analyze the details of tumor morphology and glucose metabolism. In addition, SUVmax on FDG-PET/CT is a known prognostic factor for NSCLC, particularly adenocarcinoma [11, 13, 16–22]. Furthermore, we used an anthropomorphic body phantom to minimize interinstitutional SUV variability, which is a major limitation of multicenter PET studies.

Although this was a retrospective study, our updated database included a large number of patients with moderate follow-up periods. This allowed us to validate our N0 criteria and conclude that sublobar resection was useful for patients who met these criteria. Longer follow-up periods will be needed to ensure that these results are reliable.

This study had several limitations. Because this was a retrospective study, patients who underwent sublobar resection were possibly highly selected. In addition, preoperatively verifying the histologic origin of a tumor, particularly small tumors, is sometimes difficult. The lack of data on comorbid conditions and lung function also limited the definitive conclusion that sublobar resection is not less effective than lobectomy for clinical stage IA lung adenocarcinoma. A prospective study to assess the prognostic significance of sublobar resection for patients who meet our proposed N0 criteria is warranted.

In conclusion, we demonstrated that sublobar resection was feasible for patients with clinical stage IA lung adenocarcinomas that met our proposed N0 criteria of solid tumor size of less than 0.8 cm on HRCT or a SUVmax of less than 1.5 on FDG-PET/CT, with a survival rate equivalent to that associated with standard lobectomy. Even a T1b tumor, which is generally unsuitable for

intentional sublobar resection, can be a candidate for sublobar resection if it meets these N0 criteria and has adequate surgical margins.

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ORIGINAL ARTICLE

THORACIC

# Segmentectomy for clinical stage IA lung adenocarcinoma showing solid dominance on radiology

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## Abstract

**OBJECTIVES**: This study aimed to compare prognosis after segmentectomy and after lobectomy for radiologically determined solid-dominant clinical stage IA lung adenocarcinoma.

**METHODS**: From a multicentre database of 610 consecutive patients with clinical stage IA lung adenocarcinoma who underwent complete resection after preoperative high-resolution computed tomography (HRCT) and F-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), 327 patients with a radiologically determined solid-dominant tumour (solid component on HRCT ≥50%) who underwent lobectomy ($n = 286$) or segmentectomy ($n = 41$) were included.

**RESULTS**: No significant difference existed in recurrence-free survival (RFS) between the lobectomy and segmentectomy groups (3-year RFS, 84.4 vs 84.8%, respectively; $P = 0.69$). There was no significant difference in recurrence pattern between these two groups (local, 5.6 vs 7.3%, $P = 0.72$; distant, 9.1 vs 4.9%, $P = 0.55$, respectively). Even in patients with pure solid tumours, no significant difference was observed in RFS between lobectomy and segmentectomy groups (3-year RFS, 76.8 vs 84.7%, respectively; $P = 0.48$), as well as in those with a mixed ground-glass opacity tumour (3-year RFS, 91.0 vs 85.0%, respectively; $P = 0.60$). Multivariate Cox analysis demonstrated that solid tumour size on HRCT ($P = 0.048$) and maximum standardized uptake value (SUVmax) on FDG-PET/CT ($P < 0.001$), not the surgical procedure ($P = 0.40$), were independent prognostic factors for RFS.

**CONCLUSIONS**: RFS depends on solid tumour size on HRCT and SUVmax on FDG-PET/CT, rather than on the surgical procedure, in patients with radiologically detected solid-dominant clinical stage IA lung adenocarcinoma. Patient prognosis is similar after lobectomy and after segmentectomy for solid-dominant tumour.

**Keywords:** Lung cancer surgery • Positron emission tomography • Computed tomography

## INTRODUCTION

Sublobar resection for small-sized non-small-cell lung cancer (NSCLC) has been a topic of debate for a long time [1–6]. Ground-glass opacity (GGO)-dominant early lung adenocarcinomas are thought to be relatively benign [7–9] and can be treated with sublobar resection, including segmentectomy or wedge resection, because these tumours seldom lead to lymph node metastasis [9]. On the other hand, radiologically determined solid-dominant NSCLCs show a more malignant potential, such as pathological invasiveness and lymph node metastasis, than GGO-dominant tumours [8]. Wedge resection, which cannot be used to approach hilar lymph nodes, is inappropriate as a radical procedure for a solid-dominant tumour because such a tumour might have metastasized to lymph nodes. On the other hand, segmentectomy can be used to approach hilar lymph nodes and may be applied to a solid-dominant tumour with ample surgical margin. At present, segmentectomy for a solid-dominant tumour as a radical procedure is controversial. The purpose of this study is to evaluate and compare the prognosis after segmentectomy with that after lobectomy in patients with radiologically assessed solid-dominant clinical stage IA lung adenocarcinoma.

## PATIENTS AND METHODS

### Patients

We enrolled 610 patients with clinical T1N0M0 stage IA lung adenocarcinoma from four institutions (Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo

Cancer Center, Japan) between 1 August 2005, and 30 June 2010. Patients with incompletely resected tumours (R1 or R2) and those with multiple tumours or previous lung surgeries were not included in the database. The database has been maintained prospectively. The patient data obtained from this multicentre database were retrospectively analysed in the present study. High-resolution computed tomography (HRCT) and F-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) followed by curative R0 resection were performed for all patients staged according to the tumour, node, metastasis (TNM) Classification of Malignant Tumours, 7th Edition [10]. Neither Mediastinoscopy nor endobronchial ultrasonography was routinely performed because all patients received preoperative HRCT and FDG-PET/CT. HRCT and FDG-PET revealed an absence of >1-cm enlargement in mediastinal or hilar lymph nodes and an absence of >1.5 accumulation for maximum standardized uptake values (SUVmax's) in these lymph nodes, respectively. Sublobar resection was allowed as an optional procedure for peripheral clinical T1N0M0 tumours that were intraoperatively assessed as N0 by frozen section evaluation of enlarged lymph nodes or by ensuring that there was no obvious lymph node enlargement in the thoracic cavity. Systematic lymph node dissection, such as that of hilar and mediastinal nodes, was performed during segmentectomy but not during wedge resection. All segmentectomies were performed exclusively in the patients who could tolerate lobectomy. All patients showing pathological lymph node metastasis received four cycles of platinum-based chemotherapy after surgery.

The inclusion criteria were preoperative staging determined using HRCT and FDG-PET/CT, curative surgery without neoadjuvant chemotherapy or radiotherapy and a definitive histopathological diagnosis of lung adenocarcinoma. This study was approved by the Institutional Review Boards (IRB) of the participating institutions (Hiroshima University Hospital IRB, No. EKI-644; Kanagawa Cancer Center IRB, No. KEN-31; Cancer Institute Hospital IRB, No. 2008-1018; Hyogo Cancer Center IRB, No. H20-RK-15). The requirement of informed consent from individual patients was waived because this study was a retrospective review of a patient database.

## High-resolution computed tomography

Sixteen-row multidetector CT was used to obtain chest images, independent of subsequent FDG-PET/CT examinations. For high-resolution images of the tumours, the following parameters were used: 120 kVp, 200 mA, 1–2 mm section thickness, 512 × 512 pixel resolution, 0.5–1.0 s scanning time, a high-spatial reconstruction algorithm with a 20-cm field of view (FOV), and mediastinal (level, 40 HU; width, 400 HU) and lung (level, −600 HU; width, 1600 HU) window settings. GGO was defined as a misty increase in lung attenuation without obscuring the underlying vascular markings. Radiologically determined solid-dominant tumour was defined as a tumour with ≥50% solid component. Solid tumour size was defined as the maximum dimension of the solid component measured on lung window settings, excluding GGO [11]. Mixed GGO tumour was defined as a tumour that had both GGO and solid component. CT scans were reviewed and tumour sizes were determined by radiologists from each institution.

## F-18-fluorodeoxyglucose positron emission tomography/computed tomography

The patients were instructed to fast for at least 4 h before intravenous injection of 74–370 MBq of FDG and were then advised to rest for at least 1 h before FDG-PET/CT scanning. Blood glucose levels were calculated before the tracer injection to confirm a level of <150 mg/dl [12]. Patients with blood glucose levels ≥150 mg/dl were excluded from the PET/CT imaging. For imaging, Discovery ST (GE Healthcare, Little Chalfont, UK), Aquiduo (Toshiba Medical Systems Corporation, Tochigi, Japan) or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated three-dimensional PET/CT scanner were used. Low-dose non-enhanced CT images of 2–4 mm section thickness for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient according to a standard protocol.

Immediately after CT, PET was performed with the identical axial FOV for 2–4 min/table position, depending on the condition of the patient and the scanner performance. An iterative algorithm with CT-derived attenuation correction was used to reconstruct all PET images with a 50-cm FOV. An anthropomorphic body phantom (NEMA NU2-2001, Data Spectrum Corp, Hillsborough, NC, USA) was used to minimize the variations in SUVs among the institutions [13]. A calibration factor was derived by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease interinstitutional SUV inconsistencies. The final SUV used in this study is referred to as the revised SUVmax [14]. The original SUVmax values were determined by radiologists from each institution.

## Follow-up evaluation

All patients who underwent lung resection were followed up from the day of surgery. Postoperative follow-up procedures, including a physical examination, chest roentgenogram every 3 months and chest and abdominal CT examinations every 6 months, were performed for the first 2 years. Subsequently, a physical examination and chest roentgenogram were performed every 6 months, and a chest CT examination was performed every year.

## Statistical analysis

Results are given as numbers (%) or medians, unless stated otherwise. A $\chi^2$ test was used to compare categorical variable frequencies. Fisher's exact test was used when sample sizes were small. Mann–Whitney *U*-test was used to compare continuous variables. Recurrence-free survival (RFS) was defined as the time from the date of surgery until the first event (relapse or death due to any cause) or the last follow-up. The Kaplan–Meier method was used to assess RFS durations and these were compared using log-rank tests. To assess the potential independent effects of the surgical procedure on RFS, we used multivariate analyses with a Cox proportional hazards model. The SPSS software (version 10.5; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Level of significance was set at a *P*-value of <0.05.

# RESULTS

Of the 610 patients, 371 had radiologically determined solid-dominant tumours that had ≥50% solid component on HRCT analysis. Of these, 327 patients underwent lobectomy or segmentectomy and were analysed in this study (Fig. 1). No 30-day postoperative mortality was observed for the study subjects. The mean follow-up period after lobectomy and segmentectomy were 42.2 ± 16.4 months and 42.0 ± 19.2 months, respectively ($P = 0.79$).

The characteristics of the 327 patients are given in Table 1. Of these, 286 patients underwent lobectomy and 41 patients underwent segmentectomy. Lobectomy was performed significantly more often for patients with large whole and solid tumour size and high SUVmax tumours of clinical factors, and as a result, for those with vascular invasion and higher pathological stage. Details of procedures in segmentectomy are given in Table 2. One patient who underwent right S6 segmentectomy had lymph node involvement in Station 7. He developed multiple lung metastases 19.2 months after the operation. He has been receiving gefitinib and is alive and well without disease 43.3 months after the operation.

When comparing mixed GGO tumours with pure solid tumours, preoperative solid tumour size and SUVmax were significantly larger and carcinoembryonic antigen (CEA) was significantly higher in pure solid tumours. Regarding pathological factors, lymphatic invasion, vascular invasion, pleural invasion and lymph node metastasis were significantly more frequent in pure solid tumours (Table 3).

There was no significant difference in RFS between patients with a solid-dominant tumour who underwent lobectomy and those who underwent segmentectomy (3-year RFS, 84.4 vs 84.8%, respectively; $P = 0.69$, Fig. 2A). In patients with a mixed GGO tumour, there was no difference in RFS between patients who underwent lobectomy and those who underwent segmentectomy (3-year RFS, 91.0 vs 85.0%, respectively; $P = 0.60$, Fig. 2B). Even in patients with pure solid tumours, no significant difference in RFS was observed between the lobectomy and segmentectomy groups (3-year RFS, 76.8 vs 84.7%, respectively; $P = 0.48$, Fig. 2C). Univariate and multivariate analyses of RFS are given in Table 4. Multivariate analysis, including variables such as age, gender, solid tumour size on HRCT, SUVmax on FDG-PET/CT, tumour type, CEA and the surgical procedure, revealed that solid tumour size and SUVmax were independent prognostic factors for RFS ($P = 0.048$ and $P < 0.001$, respectively, Table 4).

Table 5 shows postoperative recurrence patterns between the patients who underwent lobectomy and those who underwent segmentectomy. No significant difference in local and distant recurrence rate was observed between the lobectomy and the segmentectomy groups (local, 5.6 vs 7.3%, $P = 0.72$; distant, 9.1 vs 4.9%, $P = 0.55$, respectively).

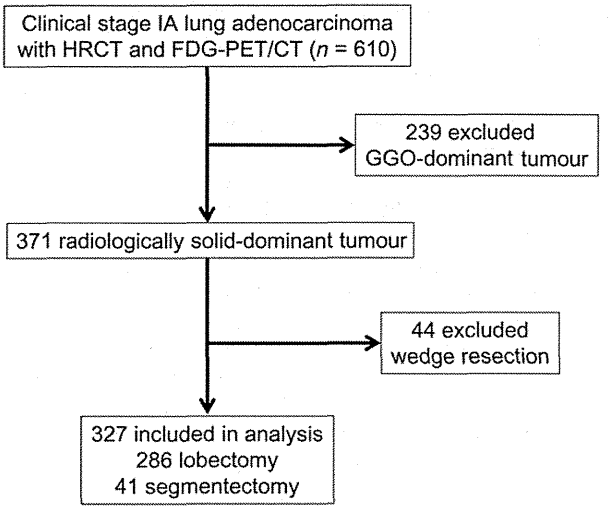


**Figure 1:** Flow chart of patients in the study.

## DISCUSSION

In previous studies, GGO-dominant tumours were reported to be relatively benign tumours, which rarely have pathological invasiveness and lymph node metastasis, and are therefore suitable for sublobar resection such as wedge resection and segmentectomy [9]. On the other hand, radiologically determined solid-dominant tumours have a higher chance to exhibit pathological invasion such as lymphatic, vascular or pleural invasion and lymph node metastasis [8]. Indeed, about 20% of solid-dominant tumours had lymph node metastasis in this study. The prognostic significance of segmentectomy in such more malignant tumours is currently not well known. In the current study, the RFS of patients with solid-dominant tumour who underwent segmentectomy was similar to (no significant difference) that of those who underwent lobectomy.

Among radiologically determined solid-dominant tumours, pure solid tumours had a higher malignant potential than mixed tumours with GGO [15–17]. The present study also showed that pure solid tumours, which had a larger solid tumour size and

**Table 1:** Clinicopathological features of patients with solid-dominant tumours

| | Solid-dominant tumours ($n = 327$) | Lobectomy ($n = 286$) | Segmentectomy ($n = 41$) | $P$-value[a] |
|---|---|---|---|---|
| Age | 66 (33–86) | 66 (33–84) | 68 (45–86) | 0.21 |
| Gender, male | 148 (45.2%) | 126 (44.5%) | 22 (53.7%) | 0.31 |
| Whole tumour size (cm) | 2.1 (0.6–3.0) | 2.2 (0.8–3.0) | 1.6 (0.6–3.0) | <0.001 |
| Solid tumour size (cm) | 1.7 (0.5–3.0) | 1.8 (0.6–3.0) | 1.2 (0.5–3.0) | <0.001 |
| SUVmax | 2.3 (0–16.9) | 2.5 (0–16.9) | 1.6 (0–4.6) | <0.001 |
| CEA (ng/ml) | 2.6 (0–114) | 2.6 (1.0–114) | 2.4 (0–17) | 0.28 |
| Lymphatic invasion, positive | 77 (23.5%) | 71 (24.8%) | 6 (14.6%) | 0.17 |
| Vascular invasion, positive | 92 (28.1%) | 86 (30.1%) | 6 (16.8%) | 0.042 |
| Pleural invasion, positive | 53 (16.2%) | 49 (17.1%) | 4 (9.8%) | 0.36 |
| Pathological stage | | | | |
| IA | 126 (38.5%) | 98 (34.3%) | 28 (68.3%) | <0.001 |
| IB | 162 (49.5%) | 150 (52.4%) | 12 (29.3%) | |
| IIA (N1) | 18 (5.5%) | 18 (6.3%) | 0 (0%) | |
| IIIA (N2) | 21 (6.4%) | 20 (7.0%) | 1 (2.4%) | |

[a]Lobectomy vs segmentectomy.
GGO: ground-glass opacity; SUVmax: maximum standardized uptake value; CEA: carcinoembryonic antigen.

SUVmax, exhibited more pathological invasiveness and lymph node metastasis than mixed tumours. However, in pure solid tumours as well as mixed tumours, there was no significant difference in RFS between patients who underwent lobectomy and those who underwent segmentectomy. Interestingly, multivariate Cox proportional hazard model revealed that only solid tumour size on HRCT and SUVmax on FDG-PET/CT, and not tumour type (pure solid or mixed tumour) and the surgical procedure, were independent prognostic factors for RFS. In early lung adenocarcinoma, tumour types on HRCT are often classified as pure GGO, mixed GGO and pure solid tumour according to the GGO ratio, and these classifications represent their pathological malignancies well [16–18]. Actually, we reported that GGO-dominant lung adenocarcinoma rarely exhibited pathological invasiveness or lymph node metastasis regardless of solid tumour size and SUVmax [9]. However, in solid-dominant lung adenocarcinoma, solid tumour size on HRCT and SUVmax on FDG-PET/CT, rather than the presence of a GGO component, represent pathological malignancies. Solid tumour size on HRCT and SUVmax on FDG-PET/CT are important preoperative factors for early lung adenocarcinoma to predict pathological invasiveness, lymph node status and prognosis [11, 19–21]. In addition, the present study suggests that the RFS of segmentectomy is similar to that of lobectomy, even in more malignant populations such as those with large solid tumour sizes and high SUVmax.

When we apply segmentectomy to early lung cancers, we must avoid any recurrence in the residual pulmonary segments as much as possible. Although the recurrence patterns between lobectomy and segmentectomy groups were not significantly different, we experienced two recurrences in the residual segments after segmentectomy. Fortunately, those patients were treated with completion lobectomy and are alive and well without disease for 31 and 72 months after the initial operation. Because solid tumour size on HRCT and SUVmax on FDG-PET/CT were reported as independent prognostic factors for local RFS [6], patients with tumours with a large solid tumour size or a high SUVmax should carefully be chosen for segmentectomy. Taking wide surgical margins and intraoperative lymph node examinations using frozen sections are mandatory for such risky cases. When taking wide margins is difficult or lymph node metastasis is detected intraoperatively, the procedure should be converted to a lobectomy.

Because this was a retrospective study, patient selection for segmentectomy may have been very strict. Far degree of selection bias might lead to the results of this study, shown in baseline characteristics of patients (Table 1) between the lobectomy and segmentectomy groups. Also, to definitely conclude that segmentectomy does not worsen the prognosis when compared with lobectomy is difficult since the follow-up period is relatively short. We are eagerly awaiting the results of the large phase III trials, CALGB140503 in the USA and JCOG0802/WJOG4607L in Japan [22].

In conclusion, segmentectomy for solid-dominant clinical stage IA lung adenocarcinoma showed RFS equivalent to that of standard lobectomy in our selected patients. Segmentectomy can be performed even for a pure solid tumour under strict intraoperative lymph node examination. The prognosis of patients with a solid-dominant tumour depends on the solid tumour size on HRCT and SUVmax on FDG-PET/CT, rather than the surgical procedure.

**Table 2:** Details of procedures in segmentectomy

| Site | *n* |
|---|---|
| Right | |
| S1 | 1 |
| S2 | 8 |
| S3 | 1 |
| S6 | 9 |
| S8 + 9 | 1 |
| Left | |
| S1 + 2 | 4 |
| S3 | 1 |
| S1 + 2 + 3c | 1 |
| S1 + 2 + 3 | 4 |
| S4 | 2 |
| S5 | 1 |
| S4 + 5 | 3 |
| S6 | 2 |
| S8 | 1 |
| S9 | 2 |

**Table 3:** Comparison of clinicopathological factors between patients with mixed GGO tumours and those with pure solid tumours

| | Mixed GGO tumours (*n* = 182) | Pure solid tumours (*n* = 145) | *P*-value |
|---|---|---|---|
| Age | 66 (37–86) | 66 (33–84) | 0.70 |
| Gender, male | 74 (40.7%) | 74 (51.0%) | 0.06 |
| Whole tumour size (cm) | 2.1 (0.6–3.0) | 2.0 (0.8–3.0) | 0.50 |
| Solid tumour size (cm) | 1.5 (0.5–2.9) | 2.0 (0.8–3.0) | <0.001 |
| SUVmax | 1.9 (0–12.4) | 3.5 (0.4–16.9) | <0.001 |
| CEA (ng/ml) | 2.3 (1.0–25) | 2.9 (0–114) | 0.024 |
| Procedure | | | |
| Lobectomy | 154 (84.6%) | 132 (91.0%) | 0.08 |
| Segmentectomy | 28 (15.4%) | 13 (9.0%) | |
| Lymphatic invasion, positive | 26 (14.3%) | 51 (35.2%) | <0.001 |
| Vascular invasion, positive | 34 (18.7%) | 58 (40.0%) | <0.001 |
| Pleural invasion, positive | 18 (9.9%) | 35 (24.1%) | <0.001 |
| Lymph node metastasis, positive | 11 (6.0%) | 28 (19.3%) | <0.001 |

GGO: ground-glass opacity; SUVmax: maximum standardized uptake value; CEA: carcinoembryonic antigen.