Long-Term Outcomes of Wedge Resection for Pulmonary Ground-Glass Opacity Nodules

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Background. We aimed to characterize ground-glass opacity (GGO) nodules and evaluate the prognosis of clinical stage IA lung adenocarcinoma with GGO nodules after wedge resection.

Methods. Patients who underwent wedge resection for early stage lung cancer and proven adenocarcinoma on postoperative pathologic report were enrolled in the study between 2004 and 2010. Radiologic findings of the main tumor were evaluated for ground-glass opacities with chest computed tomography (CT). We divided patients into two groups based on the consolidation-to-tumor ratio (C/T ratio ≤0.25, pure GGO group; C/T ratio >0.25, mixed GGO group). Overall survival and recurrence-free survival were analyzed for all patients.

Results. A total of 97 patients were included in our study. Among these, 71 patients were categorized into the pure GGO group and 26 patients into the mixed GGO group. The 5-year overall survival rate was 98.6% in the pure GGO group and 95.5% in the mixed GGO group (p = 0.663). Five patients (5.1%) experienced recurrences; only 1 patient (1/71, 1.4%) in the pure GGO group and 4 patients (4/26, 15.3%) in the mixed GGO group had recurrence.

Conclusions. GGO-dominant clinical stage IA lung adenocarcinoma (pure GGO group) showed an excellent prognosis. Wedge resection should be carefully considered for patients with mixed GGO nodules (C/T ratio >0.25) because of the high recurrence rate. Radiologic noninvasiveness (C/T ratio ≤0.25) might be a good indicator for candidates for sublobar resection in cases of early stage lung adenocarcinoma.

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according to the seventh edition of the TNM classification. The patients’ medical records were reviewed to determine the clinical rationale for limited resection. The inclusion criteria were as follows: tumors less than 3 cm in diameter that were diagnosed as or suspected to be a clinical T1N0M0 ADC on chest CT scan suggesting early stage lung ADC. We excluded patients who had a past or current history of neoplasm other than the analyzed lung cancer within the previous 5 years or those who received neoadjuvant therapy for current lung cancer. To determine whether radiologic tumor density could serve as a predictor of tumor aggressiveness, we investigated the C/T ratio, which was defined as the proportion of the maximum consolidation (C) diameter divided by the maximum tumor (T) diameter. The maximum tumor diameter, the consolidation diameter, and the presence and extent of consolidation or GGO components in the tumor were determined digitally on the basis of the findings of the lung window on CT scan. The consolidation component was defined as an area of increased opacification that completely obscured the underlying vascular markings. The GGO was defined as an area of slight homogeneous increase in density that did not obscure the underlying vascular markings. In statistical analyses using the C/T ratio, a cutoff value of 25% was used for analysis of postoperative recurrence and survival in our study cohort on the basis of results obtained by the Japan Clinical Oncology Group 0201 investigation. According to the radiologic criteria for noninvasive ADC mainly represented by the C/T ratio 0.25, patients were divided into two groups: (1) pure GGO group (C/T ratio ≤0.25) and (2) mixed GGO group (C/T ratio >0.25).

We performed wedge resections as appropriate and attempted to obtain a resection margin greater than 1 cm or the diameter of the tumor. Postoperatively, patients were routinely evaluated by CT every 3 to 4 months for the first 2 years after operation and then every 6 months thereafter. The patients were annually evaluated by positron emission tomography/CT. Locoregional recurrence was defined as that occurring within the ipsilateral hemithorax, including the pleura and mediastinal lymph nodes. Distant recurrence was defined as that developing within the contralateral hemithorax or a distant solid organ. Whenever recurrence was suspected, we tried to obtain histologic or unequivocal radiologic proof.

Statistical Analysis
Descriptive statistics were used to assess the patient demographic characteristics and outcomes. Normally distributed continuous data were expressed as mean ± standard deviation. Categoric data were expressed as counts and proportions. Student’s t tests or the Wilcoxon rank-sum test, depending on the normality of distribution, and the χ² test or Fisher’s exact test were used to compare continuous and categoric variables, respectively. Overall survival (OS) was defined as the time from the date of operation until the last date of follow-up for patients who remained alive or until death. Recurrence-free survival (RFS) was defined as the time from the date of operation to recurrence or death. Survival curves were prepared by use of the Kaplan-Meier method and were compared univariately with the log-rank test. All statistical tests were two-sided, with a significance level set at 0.05, and were performed with JMP 10.1 software (SAS Institute Inc, Cary, NC).

Results
Patient Demographics
Of 159 candidates, 97 patients were enrolled in this study. These patients were classified into two groups by a C/T ratio of 0.25 as suggested: pure GGO (C/T ratio ≤0.25, n = 71) and mixed GGO (C/T ratio >0.25, n = 26). Of those, 43 (44.3%) were men and 54 (55.7%) were women. The median age was 62 years (range, 36 to 81 years). The mean follow-up period was 44.7 months (range, 5 to 93 months). No 30-day postoperative mortality was observed for this population. The patient characteristics are summarized in Table 1. Statistically significant differences were detected in age and tumor size between the two groups.

Characteristics of the Tumors
The tumors had a mean maximal diameter of 1.2 cm (range, 0.4 to 2.3 cm). The pathology of the tumors fell into one of five categories: 54 patients (55.7%) patients had ADC with bronchoalveolar features, 14 (14.4%) had invasive ADC, 17 (17.5%) had nonmucinous bronchoalveolar carcinoma (BAC), 10 (10.3%) had mucinous BAC, and 2 (2.0%) had minimally invasive adenocarcinoma. None of the operations resulted in pathologically positive resection margins; however, the resection margin distance was reported for only 8 patients (range, 0.5 to 2.0 cm) with the others reported as negative.

The OS and RFS of these groups are shown in Figures 1 and 2. The 5-year OS rates of the pure GGO and mixed GGO groups were 98.6% and 95.5%, respectively. There was no significant difference between the two groups in terms of OS (log-rank, p = 0.663). The 5-year RFS of the pure GGO and mixed GGO groups were 100% and 85.0%, respectively. There was a statistically significant difference between the two groups in terms of RFS (log-rank, p = 0.003).

Patterns of Recurrence
Five patients (5.1%) experienced recurrence during the follow-up period (Table 2). One patient (1/71, 1.4%) in the pure GGO group had recurrence; local recurrence developed around the stapling site 82 months after operation. Histopathologic examination of this patient revealed that the tumor was very close to the stapling margin at the time of initial operation. Four patients in the mixed GGO group (4/26, 15.3%) experienced recurrence. Of those, 3 patients had local recurrence; all 3 showed soft tissue mass around the stapling site by wedge resection. Among those, 2 patients underwent reoperation (completion lobectomy), and 1 patient refused treatment. One patient had distant metastasis, which metastasized to the contralateral lung and an
extrathoracic lymph node, and he received chemotherapy for treatment of recurrence.

Comment

The results of our study revealed that patients with GGO clinical stage IA lung ADC had an excellent prognosis, even though all patients underwent wedge resection. Our study indicated that the 5-year OS and RFS after wedge resection were similar to or better than previously reported outcomes after lobectomy for stage I lung cancer [11, 12]. In addition, our findings were consistent with previous reports showing that GGO-dominant lung ADC had low malignant potential and good prognosis [10, 13]. However, during the follow-up of patients who underwent wedge resection for primary lung ADC, 5 patients experienced recurrence after operation. In 4 patients, this occurred in the areas around the initial wedge resection site, which suggests they were recurrences rather than metachronous primary cancer; however, lung-to-lung metastasis and lymph node recurrence developed in 1 patient. The resection margin of this procedure may not be sufficient to remove cancer. On the basis of the current evidence, the standard surgical treatment for primary lung cancer is still lobectomy, even though several trials have explored sublobar resection for lung cancer [9, 14, 15]. There are two situations in which we consider sublobar resection for primary lung cancer. Sublobar resection can be performed either inevitably for compromised patients who cannot be offered lobectomy or intentionally for patients who have very early stage lung cancer. Moreover, it is unclear whether wedge resection or segmentectomy would be as appropriate as sublobar resection when sublobar resection might be indicated. El-Sherif and colleagues [16] showed that segmentectomy improved deep margins and that wedge resection was associated with a high risk for locoregional recurrence. A recent study reported that increasing the margin distance to 15 mm or less significantly decreased the local recurrence risk with no evidence of additional benefit beyond 15 mm in wedge resections for non-small cell

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 97)</th>
<th>Pure GGO (n = 71)</th>
<th>Mixed GGO (n = 26)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>60.3 (31–81)</td>
<td>58.8 (36–81)</td>
<td>64.2 (37–77)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>43/54</td>
<td>29/42</td>
<td>14/12</td>
<td>0.109</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.177</td>
</tr>
<tr>
<td>Adenocarcinoma with BAC features</td>
<td>54 (55.7%)</td>
<td>39 (54.9%)</td>
<td>15 (57.7%)</td>
<td></td>
</tr>
<tr>
<td>Nonmucinous BAC</td>
<td>17 (17.5%)</td>
<td>15 (21.1%)</td>
<td>2 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Invasive adenocarcinoma</td>
<td>14 (14.4%)</td>
<td>11 (15.5%)</td>
<td>3 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Mucinous BAC</td>
<td>10 (10.3%)</td>
<td>6 (8.4%)</td>
<td>4 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (2.0%)</td>
<td>0 (0%)</td>
<td>2 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Preoperative FEV1, L/sec (range)</td>
<td>2.4 (1.2–4.4)</td>
<td>2.4 (1.2–4.4)</td>
<td>2.5 (1.5–4.2)</td>
<td>0.273</td>
</tr>
<tr>
<td>SUV max, PET-CT (range)</td>
<td>1.0 (0–12.6)</td>
<td>1.0 (0–1.9)</td>
<td>1.7 (0–12.6)</td>
<td>0.074</td>
</tr>
<tr>
<td>Tumor size, cm (range)</td>
<td>1.2 (0.4–2.3)</td>
<td>1.1 (0.4–2.3)</td>
<td>1.3 (0.6–2.5)</td>
<td>0.014</td>
</tr>
<tr>
<td>Consolidation/tumor ratio (range)</td>
<td>0.1 (0–0.9)</td>
<td>0.03 (0–0.2)</td>
<td>0.40 (0.26–0.9)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

BAC = bronchoalveolar carcinoma; CT = computed tomography; FEV1 = forced expiratory volume in 1 second; GGO = ground-glass opacity; PET = positron emission tomography; SUV = standardized uptake value.
lung cancer [17]. However, these reports included patients who underwent sublobar resection because of impaired cardiopulmonary reserve or for small tumors less than 2 cm. Sawabata and colleagues [18] suggested that the optimal margin distance should be greater than the maximum tumor diameter for prevention of margin relapse. These three results might be different from our results because their inclusion criteria for wedge resection of primary lung cancer were related to poor cardiopulmonary function rather than to early stage lung cancer. Moreover, it is difficult to identify margin distance on a frozen-section specimen when we perform wedge resection for GGO-dominant ADC. However, great concern still exists regarding local recurrence, especially given that the LCSG has suggested a diminished survival rate among patients who undergo resection rather than lobectomy [5]. Available published information is scarce on the association between margin distance and the risk of local recurrence and what, if any, distance constitutes the optimal margin distance in pulmonary wedge resection. No clear guidelines are available in the current data regarding the margin distance. Finally, we could not show comparative results between wedge resection and segmentectomy.

In conclusion, GGO-dominant clinical stage IA lung ADC had an excellent prognosis. Radiologic invasiveness (C/T ratio <0.25) might be a good indicator for candidates for sublobar resection in cases with early stage lung ADC.

### References


INVITED COMMENTARY

I read with interest the article by Cho and colleagues [1]. Ground glass opacity (GGO) is a roentgenologic term that describes a localized, nodular lesion characterized by a low to moderate increase in computed tomography (CT) density that does not obscure lung structures such as the pulmonary artery or vein and bronchus. Such an appearance can be recognized only on thin-sectioned or high-resolution CT images with 1-mm to 2-mm scanning thickness. The nodules are more or less accompanied by a solid consolidated part in the center with a variety of sizes.

Many clinicopathologic studies have already been done to understand the pathobiologic nature of these nodules. Especially, the microscopic morphology of GGOs and its prognostic significance have been extensively examined [2]. The correlation between the CT appearance and their histologic findings has also been analyzed, with a great interest [3].

We have already realized that the size of the solid consolidation part, not the GGO part, in the nodule determines the prognosis of patients who undergo resection [4]. For this purpose, the actual diameter of consolidation part, or the consolidation/tumor ratio was used to categorize the invasive nature of the GGO nodules. These results have made it possible for us to speculate on the natural history of adenocarcinomas arising in the lung, and based on these, a new classification for lung adenocarcinoma was proposed [5]. In this multidisciplinary classification, the early forms of adenocarcinoma were newly defined as AAH (atypical adenomatous hyperplasia), AIS (adenocarcinoma in situ), or MIA (minimally invasive adenocarcinoma). Invasive adenocarcinomas are classified according to the predominant pattern of growth as lepidic, acinar, papillary, micropapillary, or solid.

When we look at the patient with a GGO nodule, what should our strategy be? Should all of GGO nodules be resected? If they should be resected, how are they resected, by lobectomy or by segmentectomy or by wedge resection? After they are resected, what is the prognosis? How much should we speculate on the local recurrence rate? In the surgical oncologic community, we need to answer these questions in a scientific way.

 Needless to say, the present-day gold standard for the curative resection of lung cancer has remained unchanged as at least lobectomy with lymph node sampling and dissection. This has been strongly supported by the results from only one randomized clinical trial performed by the North American Lung Cancer Study Group in the late 1980s, in which the lobectomy and sublobar resection (wedge resection and segmentectomy) were compared with a primary end point of survival at 5 years after resection [6]. More than 20 years have passed since the results of this trial became available. Are these results still valid? Maybe partly yes and partly no. As of now, the important prospective trials, Japan Clinical Oncology Group 0802/West Japan Oncology Group 4607L and Cancer and Leukemia Group B 140503, are underway to obtain a definitive answer to the question, whether sublobar resection could be indicated for the small nodules with or without GGO appearance. We should realize that the results of the former Lung Cancer Study Group trial cannot be simply applied for these early adenocarcinomas.

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References