Objective definition and measurement method of ground-glass opacity for planning limited resection in patients with clinical stage IA adenocarcinoma of the lung

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Abstract

Objective: The standard operation for patients with stage IA lung adenocarcinoma is considered to be a lobectomy. Recently, some researchers have reported that patients with tumors showing greater proportions of ground-glass opacity (GGO) at computed tomography (CT) could be candidates for limited resection, because of its less aggressive nature. However, the lack of a precise definition or standard measuring method of GGO prevents its general use as an index for planning limited resection. Therefore, we attempted to define GGO based on CT number and measured it more objectively.

Methods: Between 1998 and 2001, 90 patients with clinical stage IA adenocarcinoma, who underwent standard or intentional limited resection and whose images of chest high-resolution CT were preserved in Digital Imaging and Communications in Medicine (DICOM) format, constituted the study population. The tumor shadow seen on the solid window (WL, −160 HU; WW, 2 HU) was regarded as the central solid area of the tumor seen on the lung window, and GGO was defined as the whole tumor area with the exception of the central solid area. Each area was measured using Scion Image (Scion Corp., Frederick, MD). We analyzed the relationship between the proportion of GGO and both of pathologic findings and recurrence.

Results: Among the 90 tumors, 31 (34.4%) were calculated to have a GGO area greater than or equal to 50%. Of these, 27 (87%) tumors were bronchioloalveolar carcinoma. Lymphatic and vascular invasions, or nodal involvement were found only in patients with a smaller proportion of GGO (<50%) (P < 0.05). During the follow-up period (median 36 months), recurrences occurred in eight patients who were diagnosed as having tumors showing smaller proportion of GGO (<50%).

Conclusions: Tumors with a greater proportion of GGO measured by our method are thought to have a less invasive nature. Our objective measuring method of GGO could be useful for future multicenter trials to elucidate the value of limited resection for clinical stage IA adenocarcinoma based on the proportion of GGO.

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1. Introduction

The standard operation for patients with T1N0M0 stage IA non-small cell lung cancer is still lobectomy with systematic nodal dissection, because limited resection for such patients was reported to increase local recurrence and decrease the survival rate compared to lobectomy in a randomized control trial conducted by the Lung Cancer Study Group [1]. Candidates for limited resection, therefore, are thought to be rather a group of patients that have less invasive tumors and a better prognosis than the whole group of stage IA non-small cell lung cancer patients [2]. Much research has been conducted to identify the group of patients with less invasive tumors preoperatively based on the tumor size. However, the tumor size turned out to be less useful, because the incidence of lymph node metastasis in patients with tumors smaller than 2 cm in diameter were reported to be 10–20% [3,4].

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Jang et al. reported that the focal area of ground-glass opacity (GGO) on high-resolution computed tomography (HRCT) could be an early sign of localized bronchioalveolar carcinoma (BAC) [5]. We demonstrated that in patients with clinical T1N0M0 adenocarcinoma the patients with a higher proportion of GGO area (≥ 50%) on HRCT by visual estimation had neither lymph node metastasis nor lymphatic invasion and were alive without recurrence [6]. From these results, it is considered that such patients may be candidates for limited resection.

However, the lack of a precise definition or standard measuring method of GGO prevents its general use as an index for planning limited resection. To resolve the problems, we characterized the GGO using CT number, and developed more objective measurement methods using Scion Image to quantitate the proportion of GGO area. Then, we tested whether or not this method was useful in predicting less invasive tumors in clinical stage IA adenocarcinoma patients.

2. Materials and methods

Between January 1998 and December 2001, 284 patients with primary lung cancer underwent surgical resection of the lung at our hospital. Of these, 103 patients were given a diagnosis of clinical stage IA lung adenocarcinoma. Among the patients, 90 underwent standard surgical resection or intentional limited resection and their lung images of HRCT were preserved in Digital Imaging and Communications in Medicine (DICOM) format. These patients constituted the study population. For four patients with multiple lung cancer, we investigated the most advanced tumor. Fifty-one patients were men, and the average age was 60.3 years (range 36–78 years). CT scanning was performed on X-Vigor or Aquilion (Toshiba Medical Systems, Tokyo, Japan). HRCT scans were performed over a range of 50 mm, covering the entire lesion. The scanning parameters were a tube voltage of 120 kV, a tube current of 250 mAs for X-Vigor and 150 mAs for Aquilion, 1 or 2 mm collimation, and a reconstruction interval of 1 or 2 mm by using a bone algorithm. The field of view was focused at about 20 cm. GGO was defined as a hazy increase in lung attenuation without obscuring the underlying vascular marking. We tried to define the GGO based on CT number (Hounsfield unit (HU)). When we fixed the window width of CT at 2 HU, the tumor shadow represented the area where the CT value was greater than that of the window level. We changed the window level from 40 to −320 HU to select the best window level at which the tumor shadow was visually almost identical to the central solid area on the lung window. As a result, we decided the best window level was −160 HU, and referred to the window setting as ‘solid window’ (window level −160 HU; window width 2 HU). The tumor shadow seen on the solid window was thought to represent the central solid area seen on the lung window. Therefore, the GGO area was defined as the tumor shadow on solid window subtracted from tumor shadow on lung window. The areas of the tumor shadows were measured with Scion Image (Scion Corp., Frederic, MD, USA) on one level of each tumor shadow equator on each window settings. Scion Image is an image processing and analysis program for windows computer that is based on the popular NIH Image (NIH, Bethesda, MD, USA) for Macintosh computer. These are freely available for download from their respective website. We used the ‘Density slice’ command to segment the target area. The details of how to use the Scion Image are also referable to the manual in the website.

Vessels or bronchi in the tumor shadow were erased if the areas were larger than 5% of the tumor shadow. The proportion of GGO was calculated as follows: [(Area on lung window − Area on solid window)/Area on lung window] × 100. A representative case is shown in Fig. 1.

Fig. 1. Seventy-seven-year-old woman with a pulmonary nodule detected by annual screening using chest X-ray examination. Her HRCT images showed a GGO nodule dotted with small solid areas (a). The proportion of GGO was calculated at 86% (b). Pathologic examination revealed that the tumor was BAC. She was alive without any sign of recurrence at 42 months after operation (c).
Four-micrometer sections, including the largest piece cut from the surface of the tumor in each case, were stained with hematoxilin and eosin and elastica van Gieson and examined by means of light microscopy. Intra-tumoral vascular invasion was determined by means of the identification of tumor cells in blood vessels. Lymphatic invasion was also morphologically distinguished from vascular invasion. Pleural invasion was judged as positive if tumor cells invaded across the visceral pleural elastic layer. The tumors were classified into two histologic subtypes according to the classification determined by the World Health Organization (WHO), BAC and other subtypes including acinar, papillary, solid carcinoma with mucin, and adenocarcinoma with mixed subtype [7]. Pathologic stages were classified according to the International System for Staging Lung Cancer criteria [8].

All patients were followed up until death, or the last date of the follow-up (December 31, 2002). The average length of follow-up was 36 months. We investigated the relationship between the proportion of GGO area calculated using our method compared with the pathologic findings and recurrence. The $\chi^2$-test or Fisher's exact test was used to compare several clinical or pathological factors.

### 3. Results

The distribution of pathologic BAC, nodal status, lymphatic, vascular and pleural invasions, and recurrence by proportion of GGO were shown in Table 1. Among the 90 tumors, 31 (34.4%) were calculated to have a GGO area greater than or equal to 50%. Among the 31 tumors showing a greater GGO proportion ($\geq 50\%$), 27 (87%) tumors were BACs, and no tumors accompanied vessel invasion, pleural invasion, or lymph node metastasis. On the other hand, among the 34 tumors with a GGO area smaller than 20%, 12 (35%) had lymphatic invasion and 11 (32%) accompanied lymph node metastasis. Lymphatic and vascular invasions, or nodal involvement was found more frequently in patients with a smaller proportion of GGO ($<50\%$) than patients with a greater proportion of GGO ($\geq 50\%$) ($P < 0.05$). During the follow-up period, eight patients had tumor recurrences. Of the patients, six were diagnosed as having mediastinal nodal involvement after surgery. There were three local recurrence cases, three distant recurrence cases, and two both local and distant recurrence cases. Seven patients had tumors showing less than 20% of GGO, and one patient had a tumor showing 33% of GGO.

### 4. Discussion

Detections of nodules showing greater proportion of GGO had increased strikingly since lung cancer screening with low dose CT began [9]. Higashiyama and colleagues investigated the relation between the proportion of BAC component and prognosis. They documented that the greater degree of BAC involvement might reflect the less frequent nodal involvement and good prognosis [10]. We reported the relation between the proportion of GGO and both clinicopathologic characteristics and recurrence in patients with clinical T1N0M0 adenocarcinoma [6]. In this study,

### Table 1

<table>
<thead>
<tr>
<th>% GGO</th>
<th>Number of patients</th>
<th>Number of BAC patients</th>
<th>Lymphatic invasion</th>
<th>Vascular invasion</th>
<th>Pleural invasion</th>
<th>Nodal involvement</th>
<th>Recurrence</th>
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<td>30–39</td>
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<td>2</td>
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<td>1</td>
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<tr>
<td>0–19</td>
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<td>12</td>
<td>9</td>
<td>5</td>
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### Table 2

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<th>Slice</th>
<th>Method</th>
<th>Parameter</th>
<th>Window setting</th>
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<td>One</td>
<td>Visual</td>
<td>Area</td>
<td>Lung window</td>
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<tr>
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<td>One</td>
<td>Visual</td>
<td>Area</td>
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<td>Kodama et al.</td>
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<td>One</td>
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<td>Aoki et al.</td>
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<td>Diameter</td>
<td>Lung window</td>
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<td>One</td>
<td>Visual</td>
<td>Area</td>
<td>Lung window/mediastinal window</td>
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<tr>
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<td>All</td>
<td>Visual</td>
<td>Area</td>
<td>Lung window</td>
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<tr>
<td>Takashima et al.</td>
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<td>One</td>
<td>Measure</td>
<td>Area</td>
<td>Lung window</td>
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the GGO was estimated using visual estimation on all slices in which the tumor appeared. The patients with a higher proportion of GGO area (≈50%) on HRCT had neither lymph node metastasis nor lymphatic invasion and were alive without recurrence. Besides our study, several studies focusing on GGO have been reported to date (Table 2) [11–16]. In many studies including ours, proportions of GGO were semiquantitated by visual estimation. In one study, diameters of nodules and central solid portions were measured instead of area [14]. And in only one study, GGO area was measured using transparent overlay with crossing points of vertical and transverse lines [16]. We think that calculating the area is better than focusing on dimensions because the shape of the central solid portions are often irregular, and sometimes separate as can be seen in our case in Fig. 1.

Standardization for dealing with GGO in selecting candidates for limited resection is urgently needed so that the data from many studies can be compared. Below, we have listed some problems regarding our former published method of measuring GGO. First, visual estimation is somewhat vague and less reproducible. Second, the definition of GGO itself is determined by visual judgment and can result in inter-observer difference. Third, there is a question as to whether the cut-off value of 50% of GGO is or is not the most valuable point in identifying a candidate for limited resection. This is because the cut-off value of 50% was fixed in order to simplify visual judgment. To resolve these problems, we characterized GGO with a CT number, and the proportion of GGO is quantitated more objectively using software. As a result, we obtained almost the same results as our previous study. Furthermore, it has become much clearer that the tumor shows more invasiveness as its proportion of GGO decreases. From our results, the most useful cut-off value for area of GGO may be around 50%, even when using our method. However, future prospective studies are needed to evaluate the effectiveness of limited resection for patients in the early stages of lung cancer based on the objective measurement of GGO. As mentioned above, NIH Image and Scion Image are now freely available. If the images are saved only on the hard-copy film, not as digital data as we have done, you only have to save a few additional images on solid window on hard copy film in addition to the standard lung and mediastinal window images, and transform them into digital data using a scanner. We believe that our methods could be useful and easily available throughout the world.

References


Appendix A. Conference discussion

Dr Hyun-Sung Lee (South Korea): Regarding the proportion of GGO, you measured only the area of tumor and GGO, in other words, a two-dimensional evaluation, but I think the proportions of GGO should be
evaluated by the volume, not the area. With the hypothesis that the shape of tumor and GGO is a sphere, the area is proportional to the square of the diameter, but volume is proportional to the square of the diameter. By its volume or three-dimensional evaluation, the proportion of GGO will lead to different results. I think this is more reliable. What do you think?

**Dr Matsuguma:** In our previous study we measured the GGO on all slices and in this study we measured on one slice. One slice is two-dimensional and all slices is three-dimensional, so I cannot directly compare these results. We measured the GGO proportion using the software, so we precisely measured GGO. GGO is not equally distributed around the central solid portion, but we measured on both slices of the maximum shadow of the nodule and maximum shadow of the central solid portion. I thought it might almost represent the nature of the GGO tumor.

**Dr P. De Leyn** (*Leuven, Belgium*): This entity will gain importance also in West Europe when we will have screening programs. We will see more of these patients than we see now.

When you talk about limited resection, do you mean for nodal dissection, or would you also perform wedge resections for these types of lesions?

**Dr Matsuguma:** In this study?

**Dr De Leyn:** Not only in this study, but in your country you see more of these patients and you have a lot of experience. Would you perform wedge resections for these kinds of lesions instead of lobectomy?

**Dr Matsuguma:** Our limited resection included segmentectomy and wedge resection. In this study there were 10 patients who underwent wedge resection and 7 patients who underwent segmentectomy, that were based on the GGO proportion. Usually we carried out the standard operation for a solid nodule.

**Dr F. Rea** (*Padova, Italy*): I don’t understand. Do you know the histology before planning your operation? Do you do frozen section? Do you decide, using a frozen section?

**Dr Matsuguma:** Preoperatively?

**Dr Rea:** Yes, preoperatively. Do you know preoperatively the diagnosis?

**Dr Matsuguma:** In many cases we diagnosed preoperatively, but in some cases, such as pure GGO or small nodule, were not diagnosed preoperatively.

**Dr Rea:** And then you decide with the frozen section!

**Dr Matsuguma:** Yes.