Correlation of the Solid Part on High-resolution Computed Tomography with Pathological Scar in Small Lung Adenocarcinomas

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Objective: To predict the grade of invasion in small (≤3 cm in diameter) lung adenocarcinomas from preoperative high-resolution computed tomography (HRCT), we measured CT numbers of the solid part and compared these with pathological features.

Methods: We reviewed 131 cases of lung adenocarcinoma (≤3 cm in diameter) surgically resected between January 1999 and December 2000, which had >10% ground glass opacity (GGO) area on HRCT. The CT numbers of solid parts were measured on HRCT in each tumor. According to our criteria of histopathological grade of stromal invasion, all tumors were classified into four grades: no evidence of stromal invasion (Grade 0), stromal invasion in the area of bronchioloalveolar growth (Grade 1), stromal invasion localized on the periphery of a fibrotic focus (Grade 2), and stromal invasion into the center of a fibrotic focus (Grade 3).

Results: Nineteen cases that had pure GGOs were excluded. In 112 cases that showed a mixed type of both GGO and solid part, the mean CT number of the overt-invasion group was significantly higher than the no invasion and micro-invasion groups. We adopted −40 as a threshold CT number to determine the degree of invasion. Tumors with values <−40 included no case of overt invasion.

Conclusions: Small lung adenocarcinomas with a solid part CT number under −40 in on HRCT usually show no invasion or micro-invasion. Limited surgery may be indicated for such cases because of their good prognosis.

Key words: Lung neoplasm — adenocarcinomas — high-resolution computed tomography — invasion — scar

INTRODUCTION

With the increase of smaller lung adenocarcinomas being detected by low-dose computed tomography screening, occasional non-invasive or micro-invasive cancers have been observed. Several recent studies have compared the images of high-resolution computed tomography (HRCT) with the histology of lung adenocarcinoma. Most studies investigated the property of ground glass opacity (GGO) part or the ratio of GGO area on HRCT (1–8). Matsuguma et al. (1) revealed the correlation between smaller GGO area measured on HRCT and higher tumor aggressiveness. Okada et al. (2) reported a method to analyse the solid component by measuring the maximum dimension of the tumor on the lung (IDmax) and mediastinal (mDmax) windows and found that the mDmax was a significant predictive factor for lymph node metastasis in clinical-T1 adenocarcinoma, whereas IDmax was not significantly predictive.

Conventional lung adenocarcinomas have both of the non-invasive components (bronchioloalveolar growth pattern) at the peripheral area and invasive fibrotic focus at the central area. With respect to the central fibrotic scar, Shimosato...
et al. (11) indicated that the quality of fibrosis was related to the prognosis, and Suzuki et al. (12) found that the size of central scar was an independent prognostic factor. Because it was thought that the solid part closely corresponded to the central fibrous area in lung adenocarcinoma, we considered that an investigation about the quality of the solid part on HRCT was important.

In this study, we used our proposed grading system of stromal invasion (13) for pathological evaluation of the solid part. We intended to apply the concept of the grade of stromal invasion to evaluation of the solid part on HRCT.

MATERIALS AND METHODS

Patients

Among surgically resected lung adenocarcinoma from January 1999 to December 2000 at our hospital, 131 patients were identified to have tumors, which were small (<3 cm in the longest diameter) and had >10% of ground-glass opacity (GGO) on HRCT. The patients consisted of 64 males and 67 females, and mean age was 62.8 years old (range 23–89 years old). On HRCT imaging, these lesions were categorized as 19 pure GGO cases, 112 mixed GGO, and solid component cases.

The definition of GGO is a hazy increase in lung attenuation without obscuring the underlying vascular markings. Pure GGO consists of only a homogenous translucent density, and mixed GGO consists of a heterogeneous attenuation with both GGO and solid components. To analyse the characteristics of the solid component, the cases that have pure GGOs were excluded.

HRCT FINDINGS

Chest CT scans were performed with an X-Vigor Scanner (Toshiba Medical, Tokyo, Japan) or TCT 900S units (Toshiba Medical). The scans were obtained using lung window settings (width 2000 HU, level -600 HU). HRCT scans were performed with a 2-mm collimation and at interval of 2 mm. The observers selected the slice with the largest tumor size, visually quantified area, and the percentage of solid component. The visual area was divided by percentages in 10 steps from 5 to 90% (minimum area is 5% and above 10% divided into 10% intervals). In the tumor, we identified the solid part by excluding the obvious GGO part on the CT images. Optional regions of interest (ROI) of 1 cm in diameter were made and measured at three different places in the solid part of a nodule. The CT number of one ROI was defined by taking the average in the ROI area. Then we calculated the mean of three CT numbers and determined it as the CT number of the solid part of the tumor. When the solid part of a tumor was <1 cm, the greatest circular ROI in the solid part was set and the mean CT number of the ROI was used. Iopamidol 300 mg iodine/ml (Iopamiron; Nihon Schering K.K., Osaka, Japan) was administered at an injection rate 2.0 ml/s with a 50 s delay.

Histopathologic Examination

The resected specimens were routinely fixed with 10% formalin after lung inflation by intubation from the bronchus. Tumors were sliced at regular intervals into 5-mm-thick sections and embedded in paraffin. Both routine hematoxylin–eosin and elastica-stained slides from representative parts of the tumor specimens including the largest cut surface were used for histological examination.

Histopathological grade of stromal invasion according to our criteria (13) was used in this study. We defined the degree of invasion in lung adenocarcinoma as follows: no evidence of stromal invasion (Grade 0), stromal invasion in the area of bronchioalveolar growth (Grade 1), stromal invasion localized on the periphery of a fibrotic focus (Grade 2), and stromal invasion into the center of a fibrotic focus (Grade 3). All cases were classified into one of the four grades of stromal invasion and we categorized Grade 0 with the no invasion group, Grades 1 and 2 with the micro-invasion group, and Grade 3 with the overt-invasion group.

Statistics

All of the statistical analyses were performed using Stat View J 5.0 (SAS Institute Inc., Cary, NC, USA). Scheffe’s F test was used and significance was defined as P < 0.01.

RESULTS

Mean tumor size was 1.7 cm (range 0.7–3.0 cm). The mean CT numbers of each group are shown in Table 1. The mean CT number of the overt invasion group was significantly higher than the no invasion and micro-invasion group respectively, whereas the mean CT number was not significantly different between the no invasion and micro-invasion groups.

The distribution of CT numbers of the solid component in each group is presented in Fig. 1. CT numbers of the no invasion and micro-invasion groups scattered between −500 and 200, whereas many cases of the overt-invasion group were >0 and the lowest number was −31. Therefore, we adopted −40 as a cut-off point and categorized the CT numbers (Table 2). The category of <−40 included 14 cases (42%) of the no invasion group, 12 cases (30%) of the micro-invasion group, and no case (0%) of the overt-invasion group. Representative CT images and histopathological sections are shown in Figs. 2–4.

DISCUSSION

The CT number of primary pulmonary adenocarcinoma is influenced by various factors. Factors that increase the CT
number are: (i) thickening of alveolar septa, (ii) diminished alveolar sac by scar formation or intra-alveolar organization, and (iii) decrease of intra-alveolar air due to repletion of tumor cells or necrotic tissue, mucus, or inflammatory cells. Factors that decrease the CT number are: (i) remnant alveolar structure, (ii) existent dilated bronchioles in the scar, and (iii) cavitation caused by elimination or excretion of necrotic elements inside the tumor. Interaction of these factors determines the CT number. To clarify the relationship between the CT image and the invasive degree of primary pulmonary adenocarcinoma, we compared pathological features with the CT number of the solid component of the tumor.

Lung adenocarcinomas usually have both a bronchioloalveolar growth part and a central scar area, and it has already been known that pathological quality of the central scar is one of the most important factors to affect prognosis. Shimosato et al. (11) proposed that the central scar of lung adenocarcinoma was made by the process of tumor growth and the collagenous fibrosis was correlated with prognosis. Several studies indicated that the tumors with a large and destructive central scar had a poor prognosis (12,14–16). From these results, we hypothesized that the preservation of elastic fibers and bronchovascular structure in the central scar correlated with the aggressiveness of the invasion. On the basis of these observations, we proposed a grading system of stromal invasion (13). We defined a tumor of

![Figure 1](image1.png)

**Figure 1.** Distribution of computed tomography numbers of the solid component in each group. Many cases of the overt-invasion group were >0 and the lowest number was −31.

![Figure 2](image2.png)

**Figure 2.** Lung adenocarcinoma in no invasion group. (a) High-resolution computed tomography scan shows a 24-mm nodule with solid part at the periphery. The computed tomography number of this solid part is 18. (b) The upper photograph is from ground glass opacity part of the tumor, and the lower one is from solid part. Histologic specimens reveal only replacement growth pattern and macrophages in the alveoli. Although elastic fiber networks seem to be destroyed, this may occur in benign lesions such as emphysema and therefore is not necessarily a sign of tumor invasiveness. (Hematoxylin–eosin stain ×100.)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Computed tomography number (mean ± SD)</th>
<th>NS</th>
<th>P &lt; 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>No invasion</td>
<td>33</td>
<td>−61 ± 41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro-invasion</td>
<td>40</td>
<td>−18 ± 113</td>
<td>NS</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Overt invasion</td>
<td>39</td>
<td>62 ± 46</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean CT number of the overt-invasion group was significantly higher than the other two groups.

SD, standard deviation, NS, not significant.

<table>
<thead>
<tr>
<th>Group</th>
<th>Computed tomography number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Under −40</td>
</tr>
<tr>
<td>No invasion</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>Micro-invasion</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Overt invasion</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

The computed tomography number −40 was set as a cut-off point and as a result no case of overt-invasion group was included in the category < −40.
Grade 2 invasion (stromal invasion localized on the periphery of a fibrotic focus) as micro-invasive adenocarcinoma because of its excellent prognosis. Because the tumor with Grade 3 invasion (stromal invasion into the center of a fibrotic focus) showed marked destruction of elastic and bronchovascular structure in the central fibrotic focus, it was important to standardize the level of tumor invasion to evaluate the properties of a solid part.

The solid component on CT imaging represents fibrosis, collapse of alveoli, mass of tumor cells or macrophages which fill alveolar sacs, intra-alveolar hemorrhage, etc. The CT numbers of solid component of non-invasive and micro-invasive cancer were significantly lower than that of overtly invasive carcinoma, and all cases with a CT number $<-40$ were non-invasive or micro-invasive tumors. We identify that inclusion of the air in the bronchiole or remnant alveoli reduces the CT number to under $-40$ in the solid part of a non-invasive and micro-invasive cancer, whereas destruction or organization of bronchial and alveolar structures increase it to over $-40$ in overtly invasive cancer. There may be qualitative differences among these groups even if CT findings are similar.

Furthermore, we feel that the analysis of the solid component on preoperative HRCT is one of the important factors that affects prognosis. In this study, we also measured the area and CT number of the GGO component (data not shown). The area of the GGO part is larger in the no and micro-invasion groups than in the overt-invasion group, but the difference in CT number is not significant between the micro- and overt-invasion groups. This result suggests that the CT number of the GGO part is ineffective in excluding overtly invasive cancer.

Our results indicate that less invasive surgery such as segmentectomy or partial resection can be performed in the cases whose CT number of solid part is under $-40$. In support of our hypothesis, Nomori et al. (17) investigated the peak CT number on histogram and classified them into three patterns: (i) one peak at a high CT number, (ii) 1 peak at a low CT number, (iii) two peaks. The low peak is from $-680$ to $-240$ HU and the high peak is from $-100$ to $80$ HU. They described that the one peak at a low CT number group has a large area of bronchioloalveolar carcinoma-like spread and the one peak at a high CT number tumor showed a large area of solid growth or central fibrosis, and they concluded that limited surgery might be indicated for the one peak at a low CT number group. Their study supports our results although the objective CT numbers are different.

An advantage of this study is that our method is simple. It is easy to make optional size of ROI on CT images and calculate the average CT numbers without complex arithmetic. We can recognize the solid part visually, not by using mediastinal window setting. In fact, measuring the precise area of the solid part is very difficult because the solid part is unsteady shape and the separation between the GGO part and solid part is obscure.

Our study has some limitations. First, our study cohort is small. Secondly, this method has some problems in reproducibility and objectivity. As we mentioned, the CT numbers were measured at three different areas, ROI of 1 cm because of reproducibility and accuracy. As a result, the large dispersion of measured CT numbers was not observed. Thirdly, the group with CT number over $-40$ contains not only overtly invasive cancer but also more than half of the cases of non-invasive and micro-invasive cancers. It is difficult to make a clear distinction between overt invasion and non- or...
micro-invasion only with the CT number of the solid component. We propose that the combination of CT number and other parameters, such as the area of GGO or serum carcinoembryonic antigen (CEA) level (a critical risk factor of lymph node metastasis) (4,18) will increase the accuracy of preoperative diagnosis.

In this study, we did not present the survival rates and patient outcomes. It has been already reported that the prognosis of no invasion group and micro-invasion group was excellent and the 5-year disease free survival rates were 100% by the study of our institute. This shows the excellent prognosis of cases with micro-invasion (13).

There are arguments against limited surgery for micro-invasive adenocarcinomas, although its excellent prognosis is reported in cases operated by lobectomy. Further investigations are needed to clarify the correlation between CT numbers and prognosis.

In conclusion, small adenocarcinomas with a CT number under 40 in the solid part on HRCT usually show no or micro-invasion. Limited surgery such as segmentectomy or partial resection may be indicated even for micro-invasive tumors because of their good prognosis. Estimating the malignant potential of small adenocarcinomas before surgery is important in order to select the operative procedure, and findings on HRCT have been researched to predict it.

Conflict of interest statement
None declared.

References