Focal area of ground-glass opacity and ground-glass opacity predominance on thin-section CT: Discrimination between neoplastic and non-neoplastic lesions

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AIM: To reveal differences in thin-section computed tomography (CT) findings between lung neoplastic lesions and non-neoplastic lesions, which showed a focal area of ground-glass opacity or ground-glass opacity predominance.

MATERIALS AND METHODS: A total of 82 focal areas of ground-glass opacity and ground-glass opacity predominance, consisting of 38 neoplastic and 44 non-neoplastic lesions, were assessed retrospectively regarding their thin-section CT findings.

RESULTS: The frequency of wholly well-defined margin (p=0.001), spiculation (p=0.019), pleural indentation (p=0.016), air bronchograms (p=0.027), air-containing space (p=0.004) was significantly higher in neoplastic lesions than in non-neoplastic lesions. Thirty-four of 38 (89%) neoplastic lesions were well-defined in more than 50% of the circumference, of which nine had an air-containing space other than air bronchogram, whereas only one non-neoplastic lesion had these features.

CONCLUSION: A focal area of ground-glass opacity or ground-glass opacity predominance with a well-defined margin and air-containing space is more likely to be a neoplasm.

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Introduction

Recently lung cancer screening using computed tomography (CT) has been introduced in Japan and has become gradually more prevalent. A preliminary study reported that lung carcinoma was more easily detected using CT compared with plain radiographs, and thus the potential to reduce the death rate from lung cancer was greater using CT. Many of the lung cancers solely detected using CT manifest as focal ground-glass opacity (GGO) or GGO-dominant lesions. Thus, radiologists have come to encounter focal areas of GGO or GGO-dominant lesions more frequently.

In our institution, focal GGO or GGO predominance was previously managed using a follow-up CT examination with an interval of several months, unless non-neoplastic infiltrates were apparent. Lesions that disappeared or were reduced in size on the follow-up CT examination were judged to be...
non-neoplastic. Conversely, lesions that had increased in size were investigated further, for example using video-assisted thoracic surgery (VATS). However, this approach led to a considerable number of unnecessary CT examinations in patients with non-neoplastic lesions and delayed treatment in those patients with lung carcinomas. Furthermore, patients felt anxious during the long follow-up period. Therefore, we tried to refine the management of these lesions by improving the diagnostic accuracy on thin-section CT.

Materials and methods

Patients

Our institutional review board does not require its approval for a retrospective study of routine clinical data. Patient informed consent was not required.

The study group were patients with a focal area of GGO- and GGO-dominant lesions. A focal GGO was defined as a patchy or nodular area of mildly increased attenuation, which appeared lower than that of pulmonary vasculature. GGO-dominant lesions were defined as lesions of mixed solid and GGO components where the GGO component contributed more than 50% of the area of the lesion on any axial section. An area of over 50% GGO was set as the cut-off value to exclude solid lesions. Although solid nodules frequently had minimal GGO at their margin, possibly representing surrounding oedema or merely poor aeration of the surrounding lung tissue due to compression or retraction by the nodule, these lesions have already been sufficiently well defined using CT and were not examined by the present study.

We excluded those lesions with apparent non-neoplastic features, including association with adjacent extensive consolidation, centrilobular nodules or GGO, segmental opacity, mild heterogeneity of the lung parenchyma, and focal increased opacity at the paravertebral area due to lung parenchymal compression by spondylotic spine osteophytes. Patients with lung disease, possibly representing focal GGO, such as sarcoidosis or pulmonary haemorrhage were also excluded.

However, because lung adenocarcinoma is occasionally multicentric, multiple focal areas of GGO were included unless they assumed a centrilobular distribution. In addition, the size of the GGO was not considered to be a criterion for exclusion, because relatively large adenocarcinomas with almost pure GGO measuring several centimetres in maximum diameter were found in the first period of this study.

Atypical adenomatous hyperplasia (AAH) is a benign neoplasm, which can appear as a focal GGO although it is considered to be a precursor of adenocarcinoma. AAH has been reported to have a similar appearance to early lung carcinomas on high-resolution (HR) CT. In addition, AAH is sometimes difficult to distinguish from early lung carcinoma even on pathology. Therefore, for practical purposes we grouped AAH and lung adenocarcinomas together.

Between May 1999 and October 2002, there were 123 lesions from 112 patients which matched the criteria. Of these, by November 2002, a diagnosis had been obtained in 82 lesions from 78 patients, who were selected as the subjects of this study (Table 1). Fifteen patients were lost to follow-up, and the remaining 26 lesions are still under clinical surveillance. The diagnosis was made during surgery or clinically based on follow-up examinations. If the GGO markedly shrunk or disappeared, it was judged a non-neoplastic lesion (NNL). Although most were considered to be acute to sub-acute inflammatory infiltrates, the term “NNL” was used because their pathological diagnoses were unknown. Conversely, if the GGO was unchanged in size during the follow-up period, it could not be determined whether the lesion was neoplastic or non-neoplastic based solely on follow-up examinations, as lung carcinoma presenting with GGO is known to grow very slowly. Although partial resection by VATS to confirm the diagnosis was often employed with such lesions, a number of cases are still being followed up in our institution, and were not included in the present study.

Thin-section CT technique

Thin-section CT was carried out using a HiSpeed Advantage LX/i or SG (GE Medical Systems, Milwaukee, WI, USA), a single section helical machine in all cases. The routine chest CT examination consisted of a helical scan of the whole lung with 7 mm collimation and 7 mm table motion per one rotation of the X-ray tube (i.e. pitch 1:1) in two or three breath holds. A chest radiologist (A.N.) prospectively checked over the conventional helical CT images that provided clinical information of suspected pulmonary nodule or abnormal opacity. When a focal GGO was found, thin-section CT was additionally obtained. Experienced technologists also obtained thin-section CT whenever they found a focal GGO on routine helical CT. The thin-section CT was generally a contiguous helical scan.
in one breath hold with 1 mm collimation and a high spatial frequency algorithm using a voltage of 120–140 kV peak and current of 180–230 mA in 0.8 or 1.0 s per section. In larger lesions, which were difficult to image with contiguous thin-section helical CT, a non-contiguous axial scan with 1 mm collimation and 2–3 mm inter-section gap was performed. Contrast medium was generally not administered. The hardcopy films were displayed with a window level of \(-700\) HU and a window width of 1500 HU.

**Evaluation of thin-section CT findings**

For each lesion, margin characteristics, radiological shape, presence of a solid portion, spiculation, pleural indentation, convergence of vessels, linear margin and internal air density were retrospectively and independently evaluated by two chest radiologists (A.N., Y.T.), who were blinded to the histological diagnoses, with hardcopy films.

The extent of a well-defined margin in the whole circumference of a lesion was evaluated as a percentage and was then divided into four categories according to: Wholly well-defined; partially well-defined in more than 50% of the circumference; partially well-defined in less than 50% of the circumference; and wholly ill-defined. As the number of scanned sections was different between lesions, we selected a section showing the maximum diameter as a representative for margin evaluation.

A linear margin was defined as a well-defined, straight or slightly concaved border between the lesion and normal lung parenchyma with or without a marginal pulmonary vein, indicating demarcation by an interlobular septum. Although a linear margin was included in well-defined margins, the incidence of linear margins was evaluated separately because it could have indicated other pathologies.

Spiculation was defined as at least one linear opacity radiating from the lesion, excluding vessels that were suggested by branching shape or continuity to the proximal vasculature. Pleural indentation had similar opacity to spiculation, but had an attachment to the pleural surface associated with a subpleural triangular opacity.

Vascular convergence was considered to be present if crowding of internal vasculature or vessels abnormally angled toward the lesion were seen in comparison with the normal lung parenchyma. Air density was divided into air bronchograms, which were evidenced by branching or tubular air density, and other air-containing space such as cavities, including equivocal air densities. The presence of underlying emphysema was also assessed, which could be easily defined on HRCT.10

The shape of each lesion was also recorded, dividing it into three types: Round to ovoid, polygonal or irregular. A polygonal shape indicated that a lesion had linear margins in every direction. An irregular shape included all shapes other than round to ovoid and polygonal.

**Pathological-radiological correlation**

Of the 42 surgically proved lesions, 28 lesions were available for pathological-radiological correlation, including 25 adenocarcinomas, one AAHs and two NNLs. Pathological-radiological correlation was made by an experienced pathologist (K.M.) and chest radiologist (A.N.) with special attention given to the margin characteristics and internal airspace of the lesions.

**Statistical analysis**

The final decision for each finding was made by consensus between the radiologists. Kappa values between the readers were calculated for each finding. The frequency of each finding was compared between NLs including AAH and NNLs using the chi-square test or Fisher’s exact test with SPSS version 11 software. A \(p\)-value of less than 0.05 was considered to be statistically significant.

In addition, multiple logistic regression analysis was performed to draw a regression equation to estimate the likelihood of NLs using these findings.
The backward method was employed for variable selection.

Results (Tables 2 and 3)

Lesion characteristics

In the 78 patients, there were 50 women and 28 men, age range 28–88 years, with a median of 64 years. The maximum diameters of the lesions were 8–50 mm with a median of 21 mm in NNLs, and 7–43 mm with a median of 20 mm, in NLs, respectively. Of the 82 lesions, the diagnosis was made by surgery in 42 cases, including four NNLs, four atypical adenomatous hyperplasias (AAH, synonym for bronchioloalveolar adenoma) and 34 well-differentiated adenocarcinomas, while 40 cases were diagnosed clinically as NNLs based on follow-up CT examinations. The follow-up period required for the resolution of these lesions ranged from 6 days to 2 years, usually 2–3 months.

Thin-section CT findings

Kappa values were 0.505-0.656, indicating moderate to good inter-reader agreement. A wholly well-defined margin was seen in 21 of 38 NLs (55%) and in nine of 44 NNLs (20%; Figs. 1 and 2). The difference was statistically significant ($p = 0.001$). Conversely, a wholly ill-defined margin was significantly less common in NLs (5%) than in NNLs (25%; $p = 0.015$). In addition, most NLs ($n = 34, 89\%$) had a margin which was well-defined in more than 50% of the circumference. A statistically significant difference was also observed in the frequency of spiculation (50% in NLs versus 25% in NNLs, $p = 0.019$), pleural indentation (39% in NLs versus 16% in NNLs, $p = 0.016$), air bronchograms (63% in NLs versus 39% in NNLs, $p = 0.027$), and air-containing space (32% in NLs versus 7% in NNLs, $p = 0.004$; Fig. 3). Also noted was the fact that 17 of 19 (89%) lesions with spiculation and 14 of 15 (93%) lesions with pleural indentation were seen in GGOs with solid components. The air-containing spaces appeared as relatively large cystic air densities in four adenocarcinomas; equivocal aggregated tiny air densities in six adenocarcinomas; and multiple scattered spots of air density associated with pulmonary emphysema in two adenocarcinomas and three NNLs. Pulmonary emphysema was seen in five (11%) of NNLs and three (8%) of NLs. Conversely, there was no significant difference in the incidence of solid portions, linear margins or vascular convergence between the two entities. The pattern of GGO shape was also not significantly different. No NLs had a polygonal shape (Fig. 4). All four AAHs had a well-defined margin, of which two had linear margins. No AAH in the present series demonstrated a solid portion, spiculation, pleural indentation, or vascular convergence. Nine of 38 NLs were well-defined in more than 50% of the circumference and had air-containing space other than air bronchogram, whereas only one of 44 NNLs had these features.

<table>
<thead>
<tr>
<th>Number of the subjects</th>
<th>Neoplastic lesions ($n = 38$)</th>
<th>Non-neoplastic lesions ($n = 44$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wholly well-defined</td>
<td>21 (55)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Partially well-defined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wholly ill-defined</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Extent of well-defined margins in the 82 lesions

Table 3: Other thin-section computed tomography findings of the 82 lesions

<table>
<thead>
<tr>
<th>Number of the subjects</th>
<th>Neoplastic lesions ($n = 38$)</th>
<th>Non-neoplastic lesions ($n = 44$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid portion</td>
<td>22 (58)</td>
<td>20 (45)</td>
</tr>
<tr>
<td>Linear margin</td>
<td>19 (50)</td>
<td>20 (45)</td>
</tr>
<tr>
<td>Spiculation</td>
<td>19 (50)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Pleural indentation</td>
<td>15 (39)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Vascular convergence</td>
<td>13 (34)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Internal air density</td>
<td>28 (74)</td>
<td>19 (43)</td>
</tr>
<tr>
<td>Air bronchograms</td>
<td>24 (63)</td>
<td>17 (39)</td>
</tr>
<tr>
<td>Other air-containing space</td>
<td>12 (32)</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Shape of the lesions</th>
<th>Round to ovoid</th>
<th>Polygonal</th>
<th>Irregular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 (21)</td>
<td>0 (0)</td>
<td>30 (79)</td>
</tr>
</tbody>
</table>
| Numbers in parentheses are percentages.
Figure 1  An 81-year-old woman with a well-differentiated adenocarcinoma (localized bronchioloalveolar carcinoma) with a well-defined margin. (a) HRCT shows a well-defined GGO at the subpleural region of right S5. A linear margin is noted at the right side of the lesion (arrow). However, there is a focal protrusion disrupting the linear margin at its posterior portion. In addition, the left side of lesion shows a mildly bulging contour. These findings do not meet the criteria for a polygonal shape, which is suggestive of benignity. (b) On a photomicrograph (haematoxylin–eosin stain; original magnification, ×1.5), the well-defined margin corresponds to the forefront of the tumour, which is abruptly cut-off. The linear margin is consistent with demarcation by an interlobular septum (arrow).
Multiple logistic regression analysis (Table 4)

We obtained the following regression equation by multiple regression analysis:

\[
2.06 - 0.027 \times \text{extent of well–defined margin (\%)} - 0.550 \times \text{internal air density (1 if present or 1 if absent)} = \log(1 - p)/p
\]

where \( p \) is the probability of a NL.

We regarded NLs and NNLs as induced variables and extent of well-defined margin, vascular convergence, internal air density, spiculation pleural indentation, and linear margin as independent variables in this analysis. The shape of each lesion was excluded from the independent variables because there were too few numbers in each category—except for "irregular"—to be significant.

The probability of a NL was calculated for each lesion with this regression equation. When the probability of a NL was \( \geq 0.5 \), the lesion was expected to be a NL. The others were categorized into NNLs. Table 4 lists the numbers of expected diagnoses by this regression equation (rows) and final pathological diagnoses (columns) of NLs and NNLs. Sensitivity, specificity and accuracy with this regression equation are calculated to be 79, 64 and 71%, respectively.

Pathological–radiological correlation

Margin characteristics

A total 17 of 28 lesions had a wholly well-defined margin, including two NNLs (Fig. 5) and 15 adenocarcinomas. A well-defined margin corresponded to the forefront of the lesion, which also appeared to be well-defined on pathology, in all cases. There were two adenocarcinomas with ill-defined margins on HRCT. In one adenocarcinoma with mucin production, heterogeneous spillage of mucin into the alveolar spaces was considered to be responsible for the ill-defined margin (Fig. 6). The other case showed gradual thinning of the alveolar wall toward the periphery, merging into the surrounding alveoli, probably causing the ill-defined margin. For partly well-defined lesions, a confident pathological interpretation for their margins could not be provided as the pathological sections were not consistent with the CT sections.

Linear margins were observed in 15 of 28 lesions, and were confirmed to be consistent with interlobular septa as the boundary between the lesions and lung parenchyma in all lesions. Although tumour extension beyond the interlobular septa was not uncommon, part of the circumference of the tumour was often demarcated linearly by interlobular septa (Fig. 7).

Internal air-containing space

Air-containing spaces were seen on thin-section CT in 10 of 28 adenocarcinomas, including four with cystic air densities, five with equivocal tiny aggregated air densities and one with multiple scattered spots of air density associated with pulmonary emphysema. The four cystic air densities corresponded to relatively large cystic airspaces lined by cancer cells. Of the five equivocal tiny air densities, one equivocal air-containing space was revealed to be an air bronchogram on pathological examination, whereas the other four were consistent with tiny airspaces within the tumour. In the case of multiple spots of air density with pulmonary emphysema, there were spotty airspaces within the alveolar-replacing type tumour similar to those in the surrounding emphysematous lung parenchyma. They were considered to be a representation of the underlying emphysema.

Discussion

Lung adenocarcinoma and AAH are known to frequently present as focal GGO, mainly due to their growth patterns replacing the alveolar lining cells without destroying the underlying lung architecture, leaving air in the lesion. Although several reports have documented CT findings of lung adenocarcinomas to date, including those representing GGO or GGO predominance, the differences between NLs and NNLs have still not been clarified.
A well-defined margin was a common finding and was more frequently seen in NLs than in NNLs. About 90% of NLs were well-defined in more than 50% of the circumference. In NLs, the periphery of the tumour was abruptly cut off in many cases on pathology. We believe that an abrupt change in the alveolar wall thickness at the margin of adenocarcinoma or AAH creates a well-defined margin. Conversely, NNLs causing focal GGO are usually of cellular infiltrates, which, gradually diminish toward the margin resulting in an indistinct margin, and in many cases, have microscopically irregular margins. We think that margin characteristics are one of the most valuable indicators to differentiate NLs from NNLs: A well-defined margin is more suggestive of NLs, whereas GGO with ill-defined margin is more likely to be a NNL. However, there were exceptions to this rule regarding margin characteristics in both NLs and NNLs. First, two of three cases of purely non-neoplastic focal fibrosis in the present series had well-defined margins mimicking NLs; they had thickened alveolar walls with fibrosis diffusely preserving the intra-alveolar air, as seen in adenocarcinomas. Focal fibrosis has recently been recognized in the surgical management of a focal GGO.\textsuperscript{17,20} Its aetiology is still unknown. Definitive discriminators between NLs and such focal fibrosis were not found in the present study. Although this is a relatively uncommon disease, the possibility that focal fibrosis could masquerade as a NL should be borne in mind when considering invasive management of the focal area of GGO.

The second exception was a mucin-producing tumour, which was malignant but resembled an area of focal inflammation on HRCT because it had a wholly ill-defined margin. The presence of mucin in the surrounding alveolar spaces could result in an ill-defined margin. Diffuse bronchioloalveolar carcinoma, which is characterized pathologically by abundant mucin production, sometimes shows ill-defined nodules on HRCT.\textsuperscript{21}

There was no statistically significant difference in the shape of lesions between NLs and NNLs. However, no NL showed a polygonal shape, indicating demarcation by linear margins in all directions. This finding might be specific for NNLs. The present authors speculate that blockage of disease extension in focal inflammation by interlobular septa leads to a polygonal

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{image}
\caption{A 46-year-old woman with a NNL with an ill-defined margin. HRCT shows a focal GGO at the left S4, of which the margin is almost ill-defined (arrow). This opacity disappeared over a follow-up period of 1 month.}
\end{figure}
shape. It should be noted, however, that both NLs and NNLs had an almost equal frequency of linear margin, and therefore, a single linear margin does not exclude the possibility of NL. Therefore the interlobular septa, could possibly act as a barrier to disease extension in the same way as the alveolar-replacing type of adenocarcinoma appearing as GGO.

Air bronchograms were often seen in both entities, probably reflecting the preservation of

Figure 3 A 58-year-old woman with well-differentiated adenocarcinoma (LBAC) with cystic changes. HRCT demonstrates a patchy area of GGO with a wholly well-defined margin at the left S1 + 2, in which a cyst with internal septa is seen. Pleural indentation is also seen (arrow head). Note the linear margin demarcated by a pulmonary vessel with partial disruption (arrow).

Figure 4 A 28-year-old woman with a NNL with a polygonal shape. HRCT reveals a polygonal GGO at the right apex, which is demarcated by peripheral vessels, probably consistent with pulmonary veins, in every direction. This opacity disappeared over 2 months.
Figure 5  A 46-year-old woman with focal fibrosis with a well-defined margin. (a) HRCT shows a wholly well-defined GGO at the right S1. (b) A low-power photomicrograph (haematoxylin-eosin stain; original magnification, $\times 1.5$) reveals alveolar wall thickening preserving alveolar airspaces, as seen in LBAC or AAH. (c) A high-power photomicrograph (haematoxylin-eosin stain; original magnification, $\times 40$), however, shows only fibrosis of alveolar walls, but no cell atypia or hobnail pattern of the lining cells suggestive of LBAC.
underlying pulmonary architecture in a lesion, but were more prevalent in NLs. The difference in the prevalence could be partly explained because most NNLs were infiltrative and therefore more easily opacified the pulmonary airspaces, including bronchi, than NLs, in which cellular infiltrates were less common.

Other air-containing spaces were also more prevalent in NLs than NNLs and were uncommonly seen in NNLs. They appeared as tiny or relatively large smooth cystic areas within the lesions on thin-section CT. This finding is not frequent in NLs, but may be a specific finding in NLs appearing as GGO and GGO predominance.

The frequency of spiculation and pleural indentation was also higher in NLs. However, these findings were mostly seen in lung adenocarcinomas with solid components. These features have been previously shown to be caused by a desmoplastic reaction of the solid portion, rather than occurring as features of lung carcinomas with GGO predominance.

The multiple regression analyses revealed that the extent of a well-defined margin and presence of

![Figure 6](image_url)

**Figure 6** A 59-year-old man with a well-differentiated, mucin-producing adenocarcinoma. (a) HRCT shows an ill-defined focal GGO with an internal solid component at the right lower lobe. (b) Photomicrograph (haematoxylin-eosin stain; original magnification, ×20) reveals cuboidal cells lining the alveolar walls and mucin spilling out into the surrounding alveolar spaces (asterisk), which probably accounts for the ill-defined margin of the GGO.
air density were the most notable discriminators between the NLs and NNLs. Spiculation or pleural indentation are also likely to be incorporated into the regression equation as the frequency of occurrence of each finding was significantly different between NLs and NNLs. However, these findings are associated with the extent of the well-defined margin and the presence of air density, and therefore, if they are analysed together, their impact on the discrimination between NLs and NNLs becomes small. Using this equation, a focal GGO can be diagnosed with relatively high sensitivity. Although this regression equation could be also applied in other institutions, it should be noted that "extent of well-defined margin" as an independent variable is a relatively subjective finding.

Using these results, the management of a focal GGO may be altered as follows; surgical approach or biopsy without follow-up would be justified to a well-defined lesion with an air-containing space other than air density.
bronchogram or in a patient with pulmonary emphysema. Unfortunately, we could not find definitive features of benignity to obviate follow-up examinations. Although a polygonal shape might be specific for a benign lesion, further study will be required to conclude that NLS can have a linear margin.

There are several limitations to the present study. First, although we included NNLs diagnosed clinically by interval shrinkage or disappearance, NNLs may be unchanged in size even over a long follow-up period. Such lesions might have distinctive features but were not incorporated into the present study. Therefore, the discriminating CT findings of such lesions from NLS were not revealed by the present study. Second, thin-section CT slices were spaced in about half of the lesions, so some lesion characteristics may have been missed for them. Third, although we excluded focal GGOs where a histological diagnosis was not available and clinical findings were equivocal, the exclusion criteria were somewhat subjective and could vary as the radiologists became experienced in the evaluation of GGO, possibly resulting in a significant bias of case selection.

In conclusion, a well-defined focal area of GGO or GGO predominance associated with internal air density other than an air bronchogram in a patient without pulmonary emphysema is more likely to be a neoplasm. These findings would warrant further investigation without follow-up examination.

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