Nodular ground glass opacities on thin-section CT: differentiation among adenocarcinoma in situ, minimally invasive adenocarcinoma and lepidic predominant invasive adenocarcinoma

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Aims and objectives

The purpose of our study was to retrospectively investigate the differentiating computed tomographic features (CT) among adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and lepidic predominant invasive adenocarcinoma (LPA) appearing as nodular ground glass opacity (GGN).
Methods and materials

This retrospective study was approved by the institutional review board of Gangneung Asan hospital, which waived the requirement for patients' informed consent.

Patients

Between November 2006 and April 2013, AIS was pathologically confirmed in 19 patients at our institution. 18 patients had video-assisted thoracic surgery (VATS) performed on them. One patient had lobectomy without biopsy due to central location of nodule in the lung. MIA was pathologically proved in 4 patients with wedge resection by VATS (n=3) and lobectomy (n=1). LPA was pathologically proved in 9 patients with direct lobectomy (n=5) and lobectomy after wedge resection by VATS (n=4).

Clinical Features of the Patients

We reviewed the medical records using medical chart of our hospital. The following clinical features of patients were recorded: gender, age, smoking history, the presence of symptom, a past history of diseases including any kind of malignancies or respiratory disease, and the presence and histologic type of synchronous malignancy.

CT scanning

In all individuals, a thin-section CT (GE Medical System, Milwaukee, WI) was performed at one times during the follow-up. The scanning parameters were 120 kVp and 400 mAs, a pitch of 0.87, and collimation of 1.25 mm. Images were reconstructed with 1-2.5mm thickness. Each patient underwent chest CT examination for an average of 3.47 times of AIS, an average of 3.50 times of MIA and an average of 2.33 times of LPA before surgery and in all patients except 5 LPA patients, follow up chest CT performed. The interval between the initial scan and the last CT scan before surgery was an average of 548 days (AIS), 507 days (MIA), and 488 days (LPA). When several CT scans were available for CT morphologic analysis, we selected the last CT scan prior to surgery or biopsy. The mean interval between CT and surgery or biopsy was 19.0 days (range, 1-87 days; median 12 days).

Analysis of CT features and pathology

One radiologist (D.S.R) and two residents of the radiology (D.Y.K, M.H.L) analyzed all CT images using the lung setting (a window level of -700 HU and a width of 1,500 HU). Any discrepancies were resolved by consensus. The CT findings of each lesion were recorded as follows: 1. location of the lesion (central VS subpleural), 2. Involved lobe,
3. shape (round, polygonal, and complex), 4. size 5. CT morphology: (a) Pure GGO Vs part solid, (b) margin (smooth, VS irregularity), (c) pleural tag, (d) internal air density, (e) any change of the lesion on the follow-up CT scans.

A subpleural location of the lesion was defined as a lesion that located at outer third in the lung. Pure GGO was defined as a hazy opacity that did not obscure the underlying pulmonary vessels (6). A pleural tag was defined as a linear strand that originated at the nodule surface and terminated at the pleural surface. Internal air density included pseudocavitation, bubble lucency, and air bronchogram.

We measured size of solid portion in part solid GGOs as the maximum dimension of the solid component of the lung windows excluding GGO. We grade the area of the solid portion in part-solid nodule on thin section CT scans with two point scale; Grade 1 as a solid portion < 50%, and Grade 2 as a solid portion > 50%.

CT findings between Group A (AIS and MIA) suitable for sublobar resection and Group B (LPA) suitable for lobectomy were analyzed. CT findings between AIS and MIA were analyzed.

The lesions were microscopically evaluated by conventional hematoxylin-eosin (H-E) staining. The cases were diagnosed according to an International Association for the study of lung cancer, American Thoracic Society, and European Respiratory Society (IASLE/ATS/ERS) classification in 2011. Pathologic sections of the each resected lesion were compared to the corresponding CT images. These comparisons were performed via a consensus between a pathologist (J.H.J) and a radiologist (D.S.R).

**Statistical Analysis**

Statistical analyses were performed with SAS software (version 9.13; SAS Institute, Cary, NC). Patient demographics (the ratio of men to women, GGO nodule multiplicity, the presence of respiratory symptoms, smoking history, and prior history of other malignancy) were compared with AIS, MIA and LPA by using the Fisher exact test. Ages were compared by using the Kruskal-Wallis test.

Morphologic features regarding nodule size were compared with Group A and B by using the Kruskal-Wallis test. Shape, marginal characteristics, pleural tag, internal air density, and part solid were compared with Group A and B by using the fisher exact test. A P value of less than .05 was considered to indicate a significant difference.
Results

Clinical Features of Patients

The clinical background of 32 patients is shown in Table 1. 32 patients consisted 18 men and 14 women, and their ages ranged from 36 to 81 years (mean age: 63.7 years), and 13 patients were never-smokers. 13 patients had history of previous cancer (40.6%). Two patients had multiple lesions: One patient with breast cancer showed AIS in the right middle lobe with another similar lesion in the left lower lobe on CT scans. One patient with colon cancer showed LPA in the right upper lobe with two similar lesions in the left upper lobe and left lower lobe on CT scans.

<table>
<thead>
<tr>
<th>Character of 32 patients (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex ratio (M:F)</td>
</tr>
<tr>
<td>age (years)*</td>
</tr>
<tr>
<td>multiplicity</td>
</tr>
<tr>
<td>smoking Hx.</td>
</tr>
<tr>
<td>cancer Hx.</td>
</tr>
<tr>
<td>F-up period (days)*</td>
</tr>
<tr>
<td>F-up numbers*</td>
</tr>
</tbody>
</table>

Table 1: Patient demographics

Note.- Except where indicated, data are numbers of nodules, and numbers in parentheses are percentages.

* Data are mean ± standard deviation.

† Kruskal-Wallis test.

CT findings of Patients

The nodule location of all patients are listed in Table 2. The location of the lesion was characteristically a subpleural portion of the lung (n=28, 90.3%) in 32 patients. The upper lobes (51.6%) were characteristically involved in 17 patients, especially in RUL (43.8%).
<table>
<thead>
<tr>
<th>Location</th>
<th>Characteristics of nodules (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLL</td>
<td>7/32 (21.9)</td>
</tr>
<tr>
<td>LUL</td>
<td>3/32 (9.4)</td>
</tr>
<tr>
<td>RLL</td>
<td>5/32 (15.6)</td>
</tr>
<tr>
<td>RML</td>
<td>3/32 (9.4)</td>
</tr>
<tr>
<td>RUL</td>
<td>14/32 (43.8)</td>
</tr>
<tr>
<td>Subpleural location</td>
<td>28/32 (90.3)</td>
</tr>
<tr>
<td>Wedge resection : lobectomy</td>
<td>25:7</td>
</tr>
</tbody>
</table>

**Table 2: Nodule location and surgery method**

CT morphology is listed in Table 3.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=23)</th>
<th>Group B (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>shape</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>round</td>
<td>13/23 (56.5)</td>
<td>0/9 (0.0)</td>
<td>0.002‡</td>
</tr>
<tr>
<td>polygonal</td>
<td>3/23 (13.0)</td>
<td>0/9 (0.0)</td>
<td></td>
</tr>
<tr>
<td>complex</td>
<td>7/23 (30.4)</td>
<td>9/9 (100.0)</td>
<td></td>
</tr>
<tr>
<td>characteristics marginal irregularity</td>
<td>8/23 (34.8)</td>
<td>9/9 (100.0)</td>
<td>0.001‡</td>
</tr>
</tbody>
</table>

**Table 3: Comparison of CT morphology between group A and B**

Note.-Except where indicated, data are numbers of nodules, and numbers in parentheses are percentages.

* Data are mean ± standard deviation.

† Kruskal-Wallis test.

‡ Fisher exact test.
CT features comparisons between Group A and Group B

The CT features comparisons between Group A and Group B are listed in Table 4. A significant linear trend was seen for lesion size, complex shape, marginal irregularity, internal air density, solid portion (<0.005) except pleural tag from AIS to LPA.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (n=23)</th>
<th>Group B (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nodule size(mm)*</td>
<td>11.39±3.87</td>
<td>18.56±4.28</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>part-solid</td>
<td>5/23(21.7)</td>
<td>8/9(89.9)</td>
<td>0.001‡</td>
</tr>
<tr>
<td>internal air</td>
<td>3/23(13.0)</td>
<td>6/9(66.7)</td>
<td>0.006‡</td>
</tr>
<tr>
<td>density</td>
<td>8/23(34.8)</td>
<td>9/9(100.0)</td>
<td>0.001‡</td>
</tr>
<tr>
<td>marginal</td>
<td>7/23(30.4)</td>
<td>6/9(66.7)</td>
<td>0.109‡</td>
</tr>
<tr>
<td>irregularity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pleural tag</td>
<td>7/23(30.4)</td>
<td>4/9(44.4)</td>
<td>0.681‡</td>
</tr>
</tbody>
</table>

Table 4: Comparison of CT morphology between group A and B

Note.- Except where indicated, data are numbers of nodules, and numbers in parentheses are percentages.

* Data are mean ± standard deviation.

† Kruskal-Wallis test.

‡ Fisher exact test.

Round or polygonal shape was significantly associated with Group A (p=0.002) (Fig.1) and finding of marginal irregularity and complex shape was associated with Group B (p=0.001) (Fig.2 and 3).
**Fig. 1**: Slow growing pure GGN with round shape and smooth margin as a MIA.  
A. Initial CT shows 9 mm pure GGN with round shape and smooth margin in the right upper lobe.  
B. Thin-section CT after 29 months shows persistent GGN with an increase in lesion size.  
C. Photomicrograph (H-E stain; magnification, x1) demonstrates MIA, non-mucinous type with a round homogeneous nodule (dashed line).

**References**: Radiology, University of Ulsan College of Medicine, GangNeung Asan Hospital - Gangneung/KR

**Fig. 2**: Slow growing part-solid GGN with complex shape and marginal irregularity as a LPA.  
A. Initial CT shows 12 mm pure GGN with polygonal shape and smooth margin in the right middle lobe.  
B. Thin-section CT after 23 months shows GGN with an increase in size. The lesion shows from polygonal shape to complex shape with pleural tag and increased attenuation suggesting part solid...
nodule (dashed line). C. Photomicrograph (H-E stain; magnification, x1) demonstrates LPA non-mucinous type with complex shape and marginal irregularity.

**References:** Radiology, University of Ulsan College of Medicine, GangNeung Asan Hospital - Gangneung/KR

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**Fig. 3:** No growing pure GGN with complex shape and marginal irregularity as a LPA. A. Initial CT shows 14 mm pure GGN with complex shape and marginal irregularity in the left lower lobe with no interval change after 12 months. B. Photomicrograph (H-E stain; magnification, x1) demonstrates LPA, non-mucinous type with complex shaped nodule (dashed line) with 7 mm stromal invasion (ovoid-dashed line)

**References:** Radiology, University of Ulsan College of Medicine, GangNeung Asan Hospital - Gangneung/KR

There was a significant differences in nodule size, solid nodule, and internal air density between Group A and Group B (p<0.005) except pleural tag. Part-solid nodule of Group A was 21.7%. In Group A with part-solid GGNs, except mucinous AIS (Fig.4), maximum diameter of solid component excluding GGO were less than 5 mm in size and classified as grade 1.
Fig. 4: Slow growing part-solid GGN with polygonal shape & smooth margin as a mucinous AIS (solid portion 7mm in size and grade 2). A. Initial CT shows 7 mm pure GGN in the right upper lobe. B. Thin-section CT after 25 months shows persistent GGN with 90% solid portion and an increase in lesion size. C. Photomicrograph (H-E stain; magnification, x1) shows polygonal shape tumor (dashed line) composed of uniform cuboid cell proliferation involving alveolar walls.

References: Radiology, University of Ulsan College of Medicine, GangNeung Asan Hospital - Gangneung/KR

Part-solid nodule of Group B was 89.9%. In Group B with part-solid GGNs was over than 5mm in size and classified as grade 2 in all cases.

CT features comparisons of part-solid GGNs between Group A and Group B.

The CT features comparisons of part-solid GGNs between Group A and Group B are listed in Table 5.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>5/23 (21.7%)</td>
<td>8/9 (89.9%)</td>
</tr>
<tr>
<td>Solid Size (mm)</td>
<td>3.8 mm</td>
<td>11.37 mm</td>
</tr>
<tr>
<td>Range (mm)</td>
<td>2 mm (non-mucinous) ~</td>
<td>6 mm ~ 16 mm</td>
</tr>
<tr>
<td></td>
<td>7 mm (mucinous AIS)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>4*/5 (80.0%)</td>
<td>3/8 (37.5%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1†/5 (20.0%)</td>
<td>5/8 (62.5%)</td>
</tr>
</tbody>
</table>
Table 5: comparisons of part-solid GGNs between Group A and Group B

Note.-Except where indicated, data are numbers of nodules.

* Non-mucinous
† Mucinous

Grade 1 as a solid portion < 50%, and Grade 2 as a solid portion > 50%.

CT features comparisons between AIS and MIA.

There was no significant difference between AIS and MIA for shape, marginal irregularity, pleural tag, internal air density, lesion size and solid portion.
Fig. 1: Slow growing pure GGN with round shape and smooth margin as a MIA. A. Initial CT shows 9 mm pure GGN with round shape and smooth margin in the right upper lobe. B. Thin-section CT after 29 months shows persistent GGN with an increase in lesion size. C. Photomicrograph (H-E stain; magnification, x1) demonstrates MIA, non-mucinous type with a round homogeneous nodule (dashed line).

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Fig. 2: Slow growing part-solid GGN with complex shape and marginal irregularity as a LPA. (solid portion 8 mm in size, and grade 1). A. Initial CT shows 12 mm pure GGN with polygonal shape and smooth margin in the right middle lobe. B. Thin-section CT after 29 months shows persistent GGN with an increase in lesion size. C. Photomicrograph (H-E stain; magnification, x1) demonstrates LPA, non-mucinous type with a complex structure (dashed line).
months shows GGN with a increase in size. The lesion shows from polygonal shape to complex shape with pleural tag and increased attenuation suggesting part solid nodule (dashed line). C. Photomicrograph (H-E stain; magnification, x1) demonstrates LPA non-mucinous type with complex shape and marginal irregularity.

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**Fig. 3:** No growing pure GGN with complex shape and marginal irregularity as a LPA. A. Initial CT shows 14 mm pure GGN with complex shape and marginal irregularity in the left lower lobe with no interval change after 12 months. B. Photomicrograph (H-E stain; magnification, x1) demonstrates LPA, non-mucinous type with complex shaped nodule (dashed line) with 7 mm stromal invasion (ovoid-dashed line)

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**Fig. 4:** Slow growing part-solid GGN with polygonal shape & smooth margin as a mucinous AIS (solid portion 7mm in size and grade 2). A. Initial CT shows 7 mm pure GGN in the right upper lobe. B. Thin-section CT after 25 months shows persistent GGN with 90% solid portion and an increase in lesion size. C. Photomicrograph (H-E stain; magnification, x1) shows polygonal shape tumor (dashed line) composed of uniform cuboid cell proliferation involving alveolar walls.

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Conclusion

Round shape or polygonal shape indicates Group A. There was no significant difference between AIS and MIA. In Group A with part-solid GGNs, except mucinous AIS, maximum diameter of solid component excluding GGO were less than 5 mm in size. Group A can be distinguished from Group B by the smaller lesion size, smaller solid proportion, round or oval shape and smooth margin.
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