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A decrease in the size of ground glass nodules may indicate the optimal timing for curative surgery

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ABSTRACT

Objectives: Although ground glass nodules (GGNs) are generally considered to grow slowly to a large size, their natural progression remains unclear, and a decrease in tumor size has been reported in a few previous studies. The study aimed to retrospectively review the radiologic and pathological characteristics of resected ground glass nodules (GGNs) followed with chest computed tomography (CT) for at least a year before surgery to clarify the natural progression of GGNs.

Patients and methods: The chest CT cans and clinical charts of 32 GGNs in 31 patients who underwent pulmonary resection between January 2006 and March 2013 were retrospectively reviewed. The definitions of pure GGNs and part-solid nodules were based on the tumor shadow disappearance rate. The tumor size was measured twice, and the mean size was used for evaluation.

Results: The mean GGN size before surgery was 15.2 mm, and the median follow-up period before surgery was 21 months. In the follow-up period, 15 (58%) of 26 pure GGNs at the initial CT remained pure GGNs at the last CT. However, a solid component appeared in the remaining 11 tumors (42%) of the 26 initial pure GGNs. Furthermore, 1 GGN of the 15 GGNs that remained pure and 10 of the 11 GGNs with solid component also showed a size decrease. In addition, 6 part-solid nodules were observed at the initial CT. Of these, 3 showed a decrease in size during follow-up. Overall, 47% of the GGNs showed a size reduction on follow-up chest CT.

Conclusions: A size reduction was observed in nearly half of the GGNs and suggested the progression to an invasive adenocarcinoma. When a mild collapse of the GGNs is observed, a careful follow-up is necessary to identify a solid component. Tumor size decreases may represent the optimal timing of pulmonary resection for curative treatment.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide, and non-small cell lung cancer (NSCLC) represents the majority of lung cancer [1]. Traditionally, lung adenocarcinoma were treated as NSCLCs. However, molecular-biological evaluations and the characterization of histological differences by pathologic findings have improved the diagnosis of lung adenocarcinoma and enabled their differential treatment [2,3]. Coupled with recent improvements in treatment, the ability to a accurately identify the adenocarcinomas has resulted in a positive clinical impact. In lung adenocarcinoma, as observed in colon carcinogenesis, a multi-step tumor progression from atypical adenomatous hyperplasia (AAH) to invasive adenocarcinoma has been supported by a number of recent reports [4,5]. Moreover, a growing body of evidence based on pathologic–radiologic correlations has revealed that most cases of AAH, adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and lepidic predominant adenocarcinoma can be detected by ground glass nodules (GGNs) – the radiographic appearance of a hazy lung opacity not associated with the obscuration of underlying vessels. As computed tomography (CT) screening for lung cancer has become more widely available, focally pure GGNs have become a major focus, not only in the field of diagnostic imaging, but also in the field of surgery.

Although GGNs are generally considered to grow slowly to a large size [6], their natural progression remains unclear. Moreover,

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a decrease in tumor size has been reported in a very few previous studies [7–9]. In this study, we retrospectively reviewed the radiologic and pathological characteristics of resected GGNs followed with chest CT for at least a year before surgery (1) to clarify the natural progression of GGNs and (2) to evaluate the changes in GGN size in relation to tumor progression.

2. Patients and methods

We retrospectively reviewed clinical charts and chest CT in patients who underwent pulmonary resection between January 2006 and March 2013 at the Kansai Medical University Hirakata Hospital. Patients with GGNs that were followed for more than 12 months before surgery were included. Patients were excluded if the GGNs were not evaluated with surgery or did not represent the primary lung cancer. Some patients who had curative surgery for primary lung cancer and had been followed were included in this study, if the GGNs represented the second or third primary lung cancer. The study was approved by the Institutional Review Board of Kansai Medical University. The requirement for informed consent was waived because of the retrospective nature of the study.

2.1. Radiologic evaluation

For enrolled patients, all available chest CT scans were evaluated and the changes in the size and characteristics of the GGNs were recorded. Evaluated CT scans were obtained with a 32-detector row scanner at the end of inspiration in one breath hold. Image data were reconstructed with a pitch of 0.828, a thickness of 7 mm, and an intervals of 7 mm. Both mediastinal window images [width, 350 Hounsfield units (HU); level, 40 HU] and lung window image [width, 1400 HU; level, −600 HU] were viewed. The use of the terms "pure GGN", "part-solid nodules", and "solid nodules, were based on the new international classification of pulmonary adenocarcinoma [10]. The definitions of pure GGNs and part-solid nodules were based on the tumor shadow disappearance rate (TDR), which was graded as follows; solid nodule (TDR = 1), part-solid nodule (0 < TDR < 1), and pure GGN (TDR = 0). Tumor size was measured twice and the mean size was used for the evaluation. A decreased in the size of the GGNs was defined as a decrease of ≥1 mm since the previous CT scan. For comparison with pathologic findings, the solid component and tumor size decrease were analyzed. For the analysis, at least one observation of reduction in size was considered to classify them as reduced nodules.

2.2. Histopathologic findings

The histopathologic evaluation followed the adenocarcinoma classification of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma [10]. For the comparison of radiologic observations, we classified the 32 tumors into the following two groups based on pathological findings: (1) more invasive group: papillary and acinar predominant adenocarcinoma, and (2) less or non invasive group: AIS, MIA, and lepidic predominant adenocarcinoma. An additional grouping was subsequently performed: (1) more invasive group: lymphatic involvement or vessel invasion, and (2) less invasive group: no lymphatic involvement and no vessel invasion.

2.3. Statistical analysis

The data are presented as the number (%) or median (range) unless otherwise stated. The duration of nodule follow-up was defined as the period from the available initial CT scan to the date of the surgery. Student *t*-tests and chi-squared tests were used for continuous and categorical data, respectively. *P* values of <0.05 were considered statistically significant. All statistical tests were performed with JMP software version 7.0.2 (SAS Institute, Inc., Cary, NC, USA).

Table 1
Clinical characteristics of the patients and the radiological and pathological findings of the 32 GGNs.

No. of patients/no. of GGNs	31/32
Mean age (years, range)	69 (51–88)
Sex (male/female)	14/17
Follow-up period of GGNs before surgery (months: median, range)	26 (12–72)
Surgical procedures	
Wedge resection	17 (53)
Segmentectomy	4 (13)
Lobectomy	11 (34)
Radiological observations	
Pure GGNs/Part-solid nodules, at initial CT	26/6
Pure GGNs/Part-solid nodules, at last CT	15/17
Mean tumor size at initial CT (mm, range)	14 (5.8–26.1)
Mean tumor size at last CT (mm, range)	20 (10.0–33.3)
Size down during the follow-up period	15 (47)
Pathological findings	
AIS	6 (19)
MIA	4 (13)
Invasive adenocarcinoma	
Lepidic predominant	8 (25)
Papillary predominant	13 (41)
Acinar predominant	1 (3)
Lymphatic involvement	17 (53)
Vascular invasion	10 (31)
Pleural invasion	3 (9)
Lymph node metastasis	3 (9)

3. Results

A total of 568 patients underwent pulmonary resection during the study periods. Of these, 404 patients had adenocarcinoma, which included 207 tumors with a lepidic growth pattern. A total of 32 GGNs in 31 patients were observed by chest CT at least 12 months before surgery. The mean GGN size before surgery was 15.2 mm and the median follow-up period before the surgery was 21 months. The characteristics, radiologic observations, and pathological findings of the 31 patients with the GGNs are shown in Table 1. Three GGNs showed lymph node metastasis, and one patient had recurrence.

In the follow-up periods, 15 (58%) of 26 pure GGNs on the available initial CT remained pure GGNs on the last CT before surgery. Meanwhile, a solid component appeared in the remaining 11 tumors (42%) of the 26 initial pure GGNs. Moreover, one GGN (7%) of the 15 GGNs that remained pure and 10 (91%) of 11 GGNs with a solid component also showed a decreased size As well, 6 part-solid nodules were observed on the initial CT. Of these, 3 (50%) showed a decrease in the tumor size during the follow-up. Overall, 47% of the GGNs showed a size reduction on follow-up chest CT.

Table 2 shows the results of a statistical analysis conducted to examine the correlation between the radiologic observations and pathological findings. For statistical analysis, we classified 32 GGNs into 2 groups based on the pathological findings. In the first analysis, more invasive group that was defined by papillary and acinar predominant adenocarcinoma showed statistically more solid component and decrease in tumor size (*P* value: <0.001 and 0.0015 respectively). In the second analysis, group with lymphatic involvement or vessel invasion showed more solid component and decrease in tumor size (*P* value: 0.0048 and 0.0042 respectively).

As shown in Fig. 1, GGNs generally grew slowly to a large size. However, as noted above, a decrease in size was also observed and usually coincided with the appearance of a solid component. Fig. 2 shows the size progression of 10 GGNs that decreased in size at least