Radiology

Thoracic Imaging

Malignant versus Benign Nodules at CT Screening for Lung Cancer: Comparison of Thin-Section CT Findings[1]

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Abbreviations:
GGO = ground-glass opacity
PPV = positive predictive value

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PURPOSE: To evaluate thin-section computed tomographic (CT) characteristics of malignant nodules on the basis of overall appearance (pure ground-glass opacity [GGO], mixed GGO, or solid opacity) in comparison with the appearance of benign nodules.

MATERIALS AND METHODS: Institutional review board approval and patient consent were obtained. Follow-up diagnostic CT was performed in 747 suspicious pulmonary nodules detected at low-dose CT screening (17 892 examinations). Of 747 nodules, 222 were evaluated at thin-section CT (1-mm collimation), which included 59 cancers and 163 benign nodules (3–20 mm). Thin-section CT findings of malignant versus benign nodules with pure GGO (17 vs 12 lesions), mixed GGO (27 vs 29 lesions), or solid opacity (15 vs 122 lesions) were analyzed. Fisher exact test for independence was used to compare differences in shape, margin, and internal features between benign and malignant nodules. Positive predictive value (PPV) was analyzed when a category was significantly different from the others.

RESULTS: Among nodules with pure GGO, a round shape was found more frequently in malignant lesions (11 of 17, 65%) than in benign lesions (two of 12, 17%; $P = .02$; PPV, 85%); mixed GGO, a subtype with GGO in the periphery and a high-attenuation zone in the center, was seen much more often in malignant lesions (11 of 27, 41%) than in benign lesions (two of 29, 7%; $P = .004$; PPV, 85%). Among solid nodules, a polygonal shape or a smooth or somewhat smooth margin was present less frequently in malignant than in benign lesions (polygonal shape: 7% vs 38%, $P = .02$; smooth or somewhat smooth margin: 0% vs 63%, $P < .001$), and 98% (46 of 47) of polygonal nodules and 100% (77 of 77) of nodules with a smooth or somewhat smooth margin were benign.

CONCLUSION: Recognition of certain characteristics at thin-section CT can be helpful in differentiating small malignant nodules from benign nodules.

Computed tomographic (CT) screening has increased the detection rate of early peripheral lung cancer in the United States and Japan (1,2). The results of the Early Lung Cancer Action Project, or ELCAP (1), suggested that nodules with pure (nonsolid) or mixed (partially solid) ground-glass opacity (GGO) at thin-section CT are more likely to be malignant than are those with solid opacity; among 44 nodules with GGO (19% of 233 nodules identified at baseline screening), 15 (34%) were confirmed to be malignant. On the other hand, most of the benign lesions were solid at CT, although some (approximately 15%) contained elements of GGO. According to the ELCAP data, 18% of nodules (five of 28) with pure GGO were malignant and 63% of nodules (10 of 16) with mixed GGO were malignant (1). To our knowledge, there are no previous studies that specifically compare thin-section CT characteristics between malignant lesions and benign lesions with pure GGO, mixed GGO, and solid opacity.

A 3-year lung cancer screening program has recently been completed in Japan by using low-dose CT and follow-up thin-section CT. We have previously reported that among 59

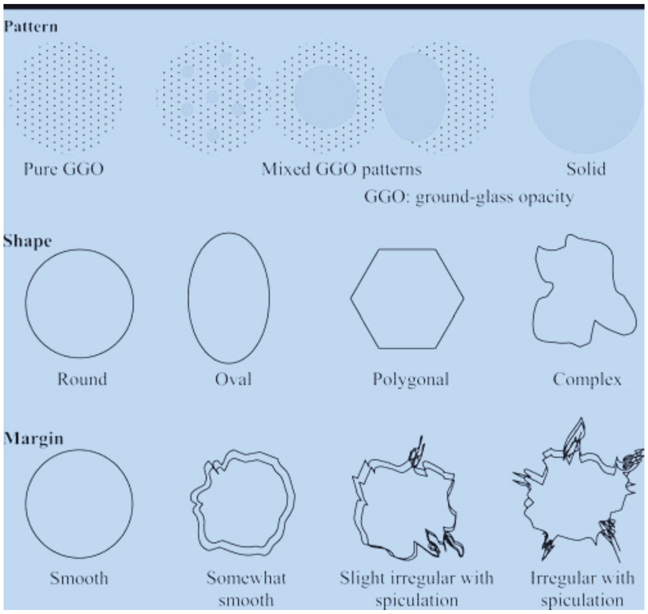

Figure 1. Typical appearance of the three patterns, four shapes, and four margins used to classify lesions in this study.

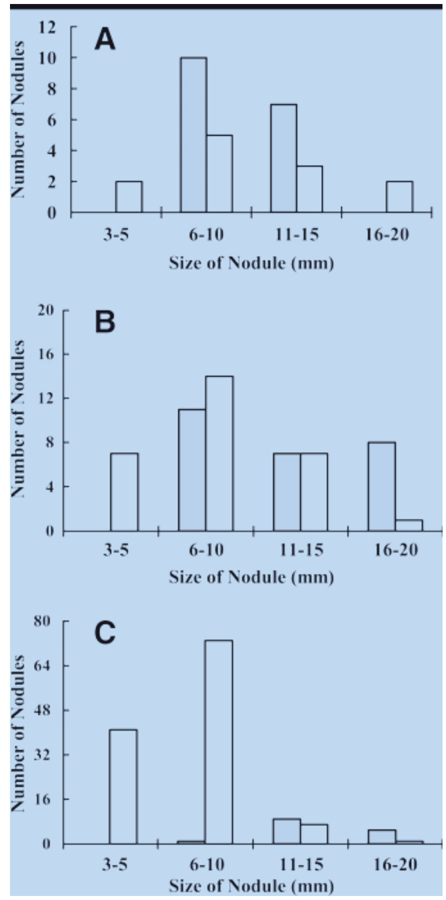

Figure 2. Graphs show distribution of sizes among, *A*, 29 nodules with pure GGO (17 malignant and 12 benign); *B*, 56 nodules with mixed GGO (27 malignant and 29 benign); and *C*, 137 nodules with solid opacity (15 malignant and 122 benign). Gray bars = malignant nodules, white bars = benign nodules. For pure and mixed GGO lesions, the size of benign nodules extensively overlaps that of malignant nodules in the 6–15-mm range.

small (6–20 mm) lung adenocarcinomas, only 16 nodules (27%) showed solid opacity and the rest (73%) showed pure or mixed GGO at thin-section CT in this screening program (2). In another study (3), thin-section CT characteristics were compared between 25 very small (≤10 mm) cancers, 24 of which were adenocarcinomas, and 40 benign lesions, most of which were solid nodules. We found that by using a single CT feature, namely polygonal shape, and a three-dimensional ratio (maximum transverse diameter to maximum z-axis dimension of a lesion, which was measured as the difference between the cephalic extent and the caudal extent of the lesion in coronal reformation) greater than 1.78, 100% specificity was shown for benign nodules (3). However, these features were not necessarily applicable to benign lesions with GGO, especially not to those larger than 10 mm. Thus, the purpose of our study was to evaluate the thin-section CT characteristics of malignant nodules on the basis of the overall appearance (pure GGO, mixed GGO, or solid opacity) compared with the appearance of benign nodules.

MATERIALS AND METHODS

Study Nodules

From May 1996 to March 1999, 17 892 examinations were performed in 7847 individuals (4288 men and 3559 women; mean age, 61 years) as part of an annual low-dose CT screening program for lung cancer in Nagano, Japan. A mobile unit equipped with a CT scanner (W950SR; Hitachi, Tokyo, Japan) was used to scan the chest with a tube current of 25 or 50 mA, a scanning time of 2 seconds per rotation of the x-ray tube (tube rotation time, 2 seconds), a table speed of 10 mm/sec (pitch of 2), 10-mm collimation, and a 10-mm reconstruction interval. The program was sponsored and supported by the Telecommunications Advancement Organization of Japan and was completed after 3 years. All subjects gave informed consent. Approval for review and research of the cases used in this study was obtained from our institutional review board at the University of Chicago.

Among those undergoing the examinations, 605 patients with 747 suspicious pulmonary nodules detected at low-dose CT underwent follow-up diagnostic CT. Diagnostic work-up CT, which included thin-section CT, was performed within 3 months of low-dose CT screening; follow-up CT examinations were performed at 3, 6, 12, 18, and 24 months, as needed. Most of the follow-up CT examinations were performed at Shinshu University Hospital, and some were performed at local hospitals. The results for follow-up work were accrued until December 1999.

The follow-up results for the 747 nodules include six categories, as follows: 76 primary lung cancers confirmed at biopsy; 11 atypical adenomatous hyperplasias confirmed at biopsy; 444 lesions, which included 167 resolved nodules, 230 nodules that were stable for 2 years or more, 38 nodules with benign-pattern calcifications (diffuse, central, popcorn, and laminar or concentric calcification), and nine nodules that were resected and confirmed as benign; 27 nodules with findings suspicious for malignancy at thin-section CT but not confirmed at biopsy; 176 nodules suspected of being benign but with insufficient follow-up; and 13 indeterminate nodules.

For this study, we used a database of thin-section CT images obtained from Shinshu University Hospital as part of the Nagano CT screening program for lung cancer. A helical scanner (HiSpeed Advantage; GE Medical Systems, Milwaukee, Wis) was used for scanning the nodules with a 200-mA tube current, 1 second per tube rotation, table speed of 1

TABLE 1
Thin-Section CT Findings in Malignant versus Benign Lesions with Pure GGO

Feature	Malignant (n = 17)	Benign (n = 12)
Shape		
Round	11	2
Oval	3	1
Polygonal	0	3
Complex	3	6
Margin		
Smooth	1	0
Somewhat smooth	9	5
Slightly irregular with spiculation	7	7
Irregular with spiculation	0	0

TABLE 2
Thin-Section CT Findings in Malignant versus Benign Lesions with Mixed GGO

Feature	Malignant (n = 27)	Benign (n = 29)
Central opacity		
Present	11	2
Absent	16	27
Air component		
Present	16	9
Absent	11	20
Shape		
Round	10	2
Oval	1	2
Polygonal	3	9
Complex	13	16
Margin		
Smooth	0	0
Somewhat smooth	4	7
Slightly irregular with spiculation	9	14
Irregular with spiculation	14	8

TABLE 3
Thin-Section CT Findings in Malignant versus Benign Solid Nodules

Feature	Malignant (n = 15)	Benign (n = 122)
Air component		
Present	7	5
Absent	8	117
Shape		
Round	7	39
Oval	0	24
Polygonal	1	46
Complex	7	13
Margin		
Smooth	0	27
Somewhat smooth	0	50
Slightly irregular with spiculation	7	37
Irregular with spiculation	8	8

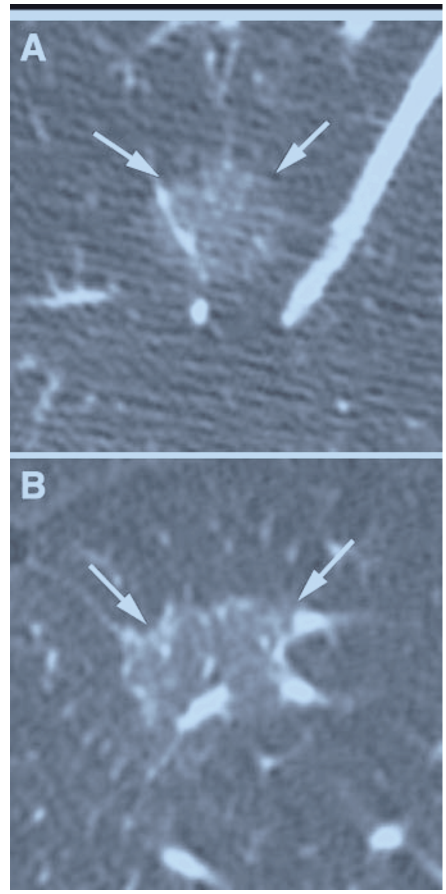

Figure 3. Transverse thin-section CT images. *A*, Image shows a malignant pure GGO lesion (adenocarcinoma) with a round shape (arrows). *B*, Image shows a benign pure GGO lesion (resolved within 3 months) with a polygonal-complex shape (arrows) that is confined to a secondary lobule.

mm/sec, 1-mm collimation, and 0.5-mm interval with a bone reconstruction algorithm. The database consisted of studies performed in 222 patients with 222 confirmed malignant or confirmed benign nodules, which were small in size (3–20 mm) on the first thin-section CT image obtained within 3 months of low-dose CT screening. Among the 222 patients, there were 14 patients with two nodules in different lung lobes, in which case the larger of the two nodules was selected for this study. Patients with two nodules in the same lung lobe and patients with more than two nodules were not included. On thin-section CT images, nonnodular lesions such as linear or scattered opacities, which had been regarded as suspicious on the original 10-mm collimation screening CT images, were excluded from the analysis. Nodules with benign-pattern calcifications were also excluded. This database contained cases of 96 pulmonary nodules that were used in two previous studies (2,3).

Among the 222 patients (mean age, 62.4 years; age range, 30–84 years), there were 119 men (mean age, 62.8 years; age range, 30–84 years) and 103 women (mean age, 61.9 years; age range, 34–75 years).

Data Analysis

Thin-section CT images for the 222 nodules were displayed and interpreted with use of “stacked” mode on a monochrome cathode ray tube monitor at a width and level of 1500 HU and −550 HU, respectively. The images of 222 nodules were randomly arranged for a reading sequence, and the final diagnosis for the nodules, which included the his-

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topathologic results, was blinded to the radiologists. Three radiologists with 20, 18, and 17 years of experience in general radiology (F.L. and H.A. included) independently viewed these images and subjectively classified the nodules as one of three patterns: pure GGO, mixed GGO, or solid opacity. They also independently determined the overall shape (round, oval, polygonal, or complex) and margin (smooth, somewhat smooth, somewhat irregular with slight spiculation, or irregular with spiculation) of the nodules, as well as the internal features. Internal features included a specific mixed GGO pattern characterized by GGO in the periphery, with a high-attenuation zone in the center and the presence or absence of air (air bronchogram, cavitation, or focal emphysema) within the nodule on thin-section CT images. The typical appearance of the three patterns, four shapes, and four margins used to classify the lesions is illustrated in Figure 1.

For pattern, shape, and margins of the nodules, the same judgment was made by all three radiologists for 75%, 40%, and 13% of cases, respectively, and the same judgment was made by any two of the radiologists for 99%, 91%, and 73% of cases, respectively. Two radiologists (F.L., H.A.) worked together to reach a consensus for the remaining 83 features in 76 nodules; these nodules were initially classified differently by each of the three radiologists. For internal features, the same judgment was made by all three radiologists in 67% of cases and by any two radiologists in 100% of cases. The final decision regarding the CT findings was based on the consensus of at least two radiologists. The mean size (average length and width) and clinical outcome for 222 nodules were recorded by one radiologist (F.L.).

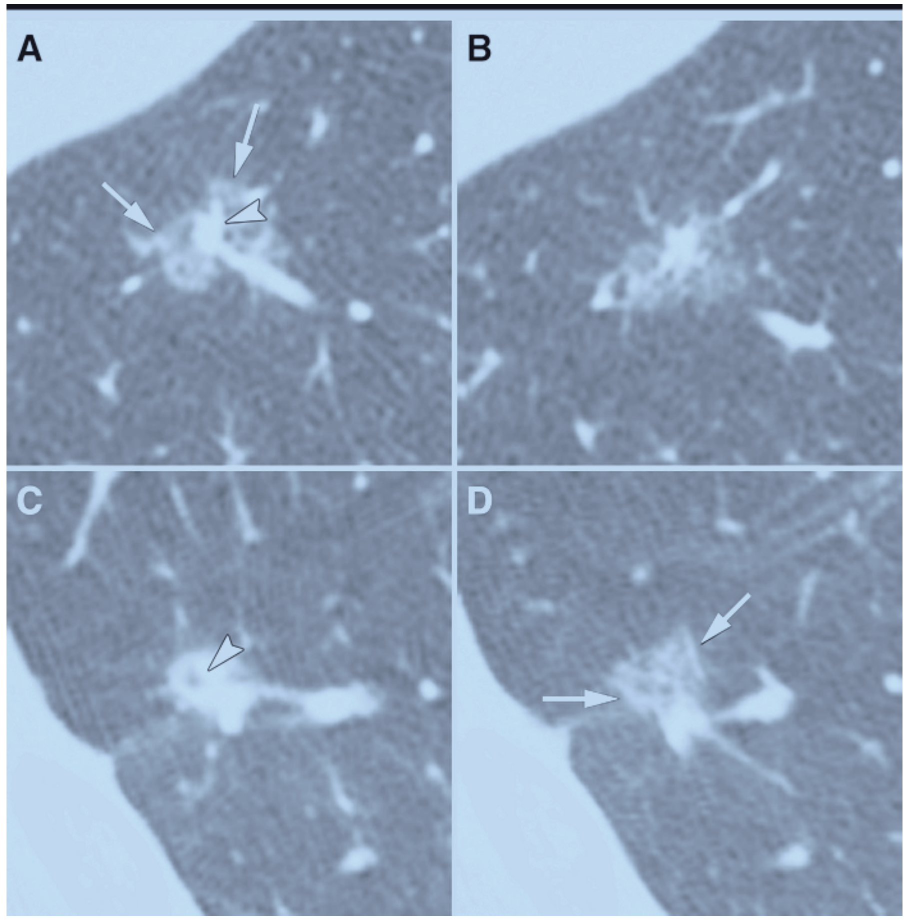

Figure 4. Transverse thin-section CT images. *A*, *B*, Images show a malignant mixed GGO lesion (adenocarcinoma) with irregular margins. The nodule shows both GGO in the periphery (arrows) and a high-attenuation zone (arrowhead) in the center. *C*, *D*, Images show a benign mixed GGO lesion (nodular fibrosis) with irregular margins. In *C*, a small air collection (arrowhead) is seen in the nodule. In *D*, the nodule (arrows) is seen on another section.

Statistical Analysis

Statistical analysis was performed by using the Student *t* test for comparison of differences in size between benign and malignant nodules. The χ^2 test for independence was used independently for comparison of the differences in patterns (nodules with and those without GGO) between the benign nodules and the malignant nodules. The data presented in Tables 1–3 were analyzed first by using the Fisher exact test for independence to determine whether there were any significant differences in the proportion of malignant lesions and benign lesions in the categories of shape, margin, and internal features. If such differences were established (the difference was significant at $P \leq .05$), additional Fisher exact tests were performed to determine which categories were significantly different from the others. Fisher exact test was used instead of χ^2 test because of the small sample size. Positive predictive value (PPV) was further analyzed when a category was significantly different from the others.

RESULTS

Of the 222 patients evaluated, 59 (27 men and 32 women; mean age, 64.6 years) had malignant nodules and 163 (92 men and 71 women; mean age, 61.6 years) had benign nodules. The mean size of the 59 malignant nodules (12.3 mm) was larger than that of the 163 benign nodules (7.2 mm, $P < .001$). Among 59 malignant nodules, there were 17 with pure GGO, 27 with mixed GGO, and 15 with solid opacity. Among 163 benign nodules, 12 showed pure GGO, 29 showed mixed GGO, and 122 showed solid opacity. The number of lesions with GGO was greater in the group of malignant nodules than in the group of benign nodules ($P < .001$).

All 17 malignant nodules with pure GGO were well-differentiated adenocarcinomas. Among 27 malignant nodules with mixed GGO, 26 were well-differentiated adenocarcinomas and one was a moderately differentiated adenocarcinoma. Of the 15 malignant nodules with solid opacity, four were well-differentiated adenocarcinomas, seven were other adenocarcinomas, two were squamous cell carcinomas, and two were small cell carcinomas. All 12 benign nodules with pure GGO had resolved at the 3-month follow-up examination. Among 29 benign nodules with mixed GGO, nodular fibrosis was confirmed at surgery in three cases, was re-

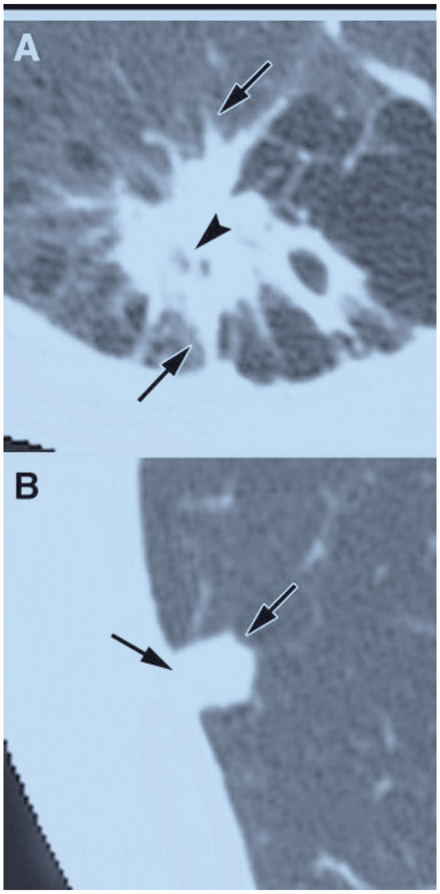

Figure 5. Transverse thin-section CT images. *A*, Image shows a malignant nodule (squamous cell carcinoma) with air components (arrowhead) and an irregular margin and gross spiculation (arrows). *B*, Image shows a small benign solid nodule (stable for more than 2 years) with a polygonal shape (arrows) and somewhat smooth margin.

solved at 3 months or more of follow-up in 17 cases, and showed no change for 2 years or more in nine cases. Among the 122 benign solid nodules, five cases (one case each of inflammatory granuloma, cryptococcoma, focal organizing pneumonia, inflammatory pseudotumor, and sclerosing hemangioma) were confirmed at surgery, 19 cases were resolved at 3 months or more of follow-up, and 98 cases showed no change for 2 years or more. All malignant nodules were confirmed at surgery.

The distribution of sizes among 29 nodules with pure GGO, 56 with mixed GGO, and 137 with solid opacity is shown in Figure 2. For GGO lesions, there was extensive overlap between the size of benign nodules and that of malignant nodules. On the other hand, for solid lesions, there was relatively limited overlap between the size of benign nodules and that of malignant nodules.

Table 1 shows the thin-section CT findings for malignant versus benign lesions with pure GGO; Figure 3 shows a malignant nodule and a benign nodule with pure GGO obtained at thin-section CT. The overall Fisher exact test indicated a significant association between lesion shape and malignancy (P = .008) but indicated no significant association between margins and malignancy (P = .826). At further examination, we found a significant association between malignancy and round nodules (P = .022); the number of round nodules was greater in the malignant group (65%, 11 of 17) than in the benign group (17%, two of 12) of pure GGO lesions. If round shape was used to discriminate between malignant lesions and benign lesions with pure GGO, the PPV (probability that a nodule is malignant, given that it is round) of such a test would be 85% (95% confidence interval: 54.55%, 98.08%) in this data set.

Table 2 lists thin-section CT findings for malignant lesions versus benign lesions with mixed GGO; Figure 4 shows a malignant nodule and a benign nodule with mixed GGO obtained at thin-section CT. The overall Fisher exact test again showed a significant association between nodule shape and malignancy (P = .020) but showed no significant association between margins and malignancy (P = .174). The association between round nodules and malignancy was found to be significant (P = .009), and the proportion of round nodules was higher among malignant lesions (37%, 10 of 27) than among benign lesions (7%, two of 29). The PPV was 83% (95% confidence interval: 51.59%, 97.91%). Furthermore, the presence of central opacity with mixed GGO was significantly associated with malignancy (P = .004), with a higher proportion of nodules with this feature in the malignant group (41%, 11 of 27) than in the benign group (7%, two of 29). The PPV of this test was 85% (95% confidence interval: 54.55%, 98.08%). However, the presence of air components within lesions was not significantly associated with malignancy (P = .059).

Table 3 lists thin-section CT findings for malignant versus benign solid nodules; Figure 5 shows malignant nodules and benign nodules obtained at thin-section CT. Fisher exact test showed a significant association between shape and malignancy ($P < .001$), as well as between margins and malignancy ($P < .001$). However, a round shape was not found to be associated with malignancy in solid nodules (P = .262), which is in contrast to the results found with pure and mixed GGO lesions. An oval shape was not significantly associated with malignancy (P = .073). The association between a complex shape and malignancy was found to be significant (P = .002)—the proportion of nodules with complex shape was higher among malignant lesions (47%, seven of 15) than among benign lesions (11%, 13 of 122). However, the PPV of this test was only 35% (95% confidence interval: 15.39%, 59.22%). The proportion of nodules with a polygonal shape was greater among benign lesions (38%, 46 of 122) than among malignant lesions (7%, one of 15; P = .019). There were 47 polygonal nodules, 46 (98%) of which were benign. When the margin classifications were dichotomized into "smooth or somewhat smooth" and "slightly irregular or irregular" categories, there was a significant difference between benign nodules and malignant nodules ($P < .001$). The proportion of smooth or somewhat smooth margins among malignant lesions was lower (0%, none of 15) than it was among benign lesions (63%, 77 of 122). There were 77 smooth or somewhat smooth nodules, and all 77 were benign. Furthermore, the presence of air components within these solid lesions was significantly associated with the malignant group (47%, seven of 15; $P < .001$) in comparison with the benign group (4%, five of 122). The PPV of this test was 58% (95% confidence interval: 27.67%, 84.83%).

DISCUSSION

Comparison of various CT features such as contour, margins, and internal characteristics of pulmonary nodules with pathologic specimens can be helpful for developing criteria to distinguish between cancers and benign lesions (1,2,4–7). In CT screening programs, however, most benign nodules are not confirmed at pathologic diagnosis. Because of this limitation, we were not able to make a detailed radiologic-pathologic comparison. Therefore, we chose to investigate two internal patterns, namely *(a)* nodules with both GGO in the periphery and a high-attenuation zone in the center and *(b)* nodules with an area of air, such as an air bronchogram, that is frequently found in small well-differentiated adenocarcinomas (2,5). Also, we classified all nodules into one of four subcategories of shape and margins on the basis of the predominant CT appearance. In our

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study, we found that differences in the CT features between benign lesions and malignant lesions were observed for each of the three patterns on thin-section CT images.

Results of previous clinical CT studies (8–10) have shown that malignant nodules commonly contain solid opacity and that benign nodules have higher attenuation, often with visible calcifications, than do malignant nodules. Siegelman et al (10) reported that 61% of 279 benign nodules (including 153 nodules with diffuse calcifications) had smooth or moderately smooth margins and 65% of 283 primary malignant tumors had irregular shapes with spiculation. Kuriyama et al (5), in a study of 20 peripheral lung cancers and 20 benign nodules less than 20 mm in diameter, reported that an air bronchogram was not observed as frequently in small benign lesions, such as hamartoma and tuberculoma, as it was in adenocarcinomas.

The number of solid benign nodules was much greater than the total number of malignant nodules in our database, which was obtained from a lung cancer CT screening program, and the frequency of some features, such as internal air bronchograms, a complex shape, and an irregular margin, was much less in common in benign lesions than in malignant lesions. However, these observations do not necessarily mean that these features are reliable for differentiating benign nodules from malignant nodules, because the absolute numbers of benign nodules with such features may be comparable to the numbers of malignant nodules with similar features. For example, the frequency of an irregular margin in solid nodules was 7% (eight of 122) for benign nodules and 53% (eight of 15) for malignant nodules. However, if a radiologist encountered such a case in a screening examination, there would be an approximately 50% (eight of 16) likelihood that the lesion was malignant, if all other factors were equal. We found that a polygonal shape or a smooth or somewhat smooth margin (98%–100% likelihood of benignity) could be more helpful for differentiating solid benign nodules from malignant nodules than would internal air bronchograms, a complex shape, or an irregular margin.

There were some limitations to this study. For instance, no malignant lesions 5 mm or smaller were found; this is probably because the database used here was compiled from images obtained with low-dose single–detector row CT at a 10-mm section thickness. Second, many of the benign GGO lesions detected at the initial screening CT had resolved before thin-section diagnostic CT was performed. In a previous study, we reported that among 108 benign nodules (54, 27, and 27 of which showed pure GGO, mixed GGO, and solid opacity, respectively, at low-dose CT), 92 (85%) resolved within 3 months (11). Also, a large variance was noted in the judgment for CT features by three radiologists, especially for margins of the nodules; this is probably because most nodules used in current study were smaller than 10 mm.

The margins and size of nodules were not useful for differentiating benign from malignant GGO lesions in this series, and benign lesions with GGO were more difficult to distinguish from malignant nodules than were those with solid opacity. However, certain features, such as a round shape or a combination of GGO in the periphery with a high-attenuation zone in the center, were observed much more frequently in malignant GGO nodules. Therefore, we believe that familiarity with the different features of benign nodules and malignant nodules can be useful to radiologists in the management of indeterminate nodules. Also, short-term follow-up imaging can be helpful for differentiating benign from malignant nodules with GGO patterns, because all 12 of the benign pure GGO lesions in this series, as well as the majority of benign mixed GGO lesions, had partially or completely resolved within 3 months.

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