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Chest 2008;133;1402-1409; Prepublished online March 13, 2008;
DOI 10.1378/chest.07-2568

ISSN:0012-3692

CHEST

Original Research

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Pulmonary Nodular Ground-Glass Opacities in Patients With Extrapulmonary Cancers*

What is Their Clinical Significance and How Can We Determine Whether They Are Malignant or Benign Lesions?

Chang Min Park, MD; Jin Mo Goo, MD; Tae Jung Kim, MD; Hyun Ju Lee, MD; Kyung Won Lee, MD; Chang Hyun Lee, MD; Young Tae Kim, MD; Kwang Gi Kim, PhD; Ho Yun Lee, MD; Eun-Ah Park, MD; and Jung-Gi Im, MD

Background: **The clinical significance of pulmonary nodular ground-glass opacities (NGGOs) in patients with extrapulmonary cancers is not known, although there is an urgent need for study on this topic. The purpose of this study, therefore, was to investigate the clinical significance of pulmonary NGGOs in these patients, and to develop a computerized scheme to distinguish malignant from benign NGGOs.**

Methods: **Fifty-nine pathologically proven pulmonary NGGOs in 34 patients with a history of extrapulmonary cancer were studied. We reviewed the CT scan characteristics of NGGOs and the clinical features of these patients. Artificial neural networks (ANNs) were constructed and tested as a classifier distinguishing malignant from benign NGGOs. The performance of ANNs was evaluated with receiver operating characteristic analysis.**

Results: **Twenty-eight patients (82.4%) were determined to have malignancies. Forty NGGOs (67.8%) were diagnosed as malignancies (adenocarcinomas, 24; bronchioloalveolar carcinomas, 16). Among the rest of the NGGOs, 14 were atypical adenomatous hyperplasias, 4 were focal fibrosis, and 1 was an inflammatory nodule. There were no cases of metastasis appearing as NGGOs. Between malignant and benign NGGOs, there were significant differences in lesion size; the presence of internal solid portion; the size and proportion of the internal solid portion; the lesion margin; and the presence of bubble lucency, air bronchogram, or pleural retraction ($p < 0.05$). Using these characteristics, ANNs showed excellent accuracy (z value, 0.973) in discriminating malignant from benign NGGOs.**

Conclusions: **Pulmonary NGGOs in patients with extrapulmonary cancers tend to have high malignancy rates and are very often primary lung cancers. ANNs might be a useful tool in distinguishing malignant from benign NGGOs.** ***(CHEST 2008; 133:1402–1409)***

Key words: computer; CT scan; lung cancer; radiology diagnostic

Abbreviations: AAH = atypical adenomatous hyperplasia; ANN = artificial neural network; Az = area under the receiver operating characteristic curve; BAC = bronchioloalveolar carcinoma; CI = confidence interval; GGO = ground-glass opacity; NGGO = nodular ground-glass opacity; ROC = receiver operating characteristic

Pulmonary nodular ground-glass opacities (NGGOs) are defined as nodules showing a hazy opacity without obscuring any underlying bronchial or vascular structures on a high-resolution CT scan.[1,2] With the popular use of CT scanning in clinical practice and the introduction of CT scan screening for lung cancer, pulmonary NGGOs that could not have been detectable on plain radiography have been discovered.[3–5] In screening situations, these lesions have been reported[3,5,6] to consist of 14.4 to 19% of

all CT scan-detected pulmonary nodules. Although several studies[2,4,7–9] have reported that pulmonary NGGOs could represent conditions such as focal fibrosis, hemorrhage, inflammation, and atypical adenomatous hyperplasia (AAH), it has been found that pulmonary NGGOs could also strongly suggest malignancies, such as bronchioloalveolar carcinoma (BAC) or pulmonary adenocarcinoma, especially when the lesions persisted during the follow-up period.[7,10–13] However, almost all of these studies have been performed without regard to whether patients with pulmonary NGGOs had previous or current malignancies. It had not been known whether those results could be directly applied to patients with previous or current extrapulmonary cancers or if we could consider NGGOs in these patients as BACs or pulmonary adenocarcinomas rather than metastasis. However, since CT scanning has become a routine tool in diagnosing malignancies and monitoring treatment response as well as disease recurrence in cancer patients, pulmonary NGGOs are not uncommonly discovered even in patients with previous or current extrapulmonary cancers. To the best of our knowledge, although there has been an urgent need for a study on the clinicopathologic significance of NGGOs in patients with extrapulmonary cancers, there have been none, aside from only a few case reports.[14,15]

Therefore, the purpose of this study was to investigate the clinicopathologic significance of NGGOs in patients with extrapulmonary cancers. We also aimed to investigate the clinical and CT scan characteristics associated with malignancy and to develop a computerized scheme to distinguish malignant from benign NGGOs in these patients.

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This study was supported by grant 10888 from the Seoul R&BD program.
The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received October 19, 2007; revision accepted February 8, 2008.

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DOI: 10.1378/chest.07-2568

Materials and Methods

This study was approved by the institutional review board of the hospitals involved; the requirement for patients' informed consent was waived in this retrospective study.

Study Subjects

Between January 2002 and March 2007, two radiologists (H.Y.L. and H.J.L.) retrospectively collected cases of pulmonary NGGOs in patients with extrapulmonary cancers from two tertiary referral hospitals (Seoul National University Hospital and Seoul National University Bundang Hospital) using electronic medical records and the radiology information systems of the hospitals. We included cases that met the following criteria: (1) pulmonary NGGOs were found in patients with previous or current malignancies other than lung cancer; (2) patients had at least one series of thin-section chest CT scans showing an NGGO; (3) the NGGO was a focal ground-glass opacity (GGO) with nodular features < 3 cm in size; and (4) the nodule was confirmed pathologically with meticulous histologic evaluation. In the end, 59 nodules in 34 patients (11 men and 23 women; mean [$\pm$ SD] age, 59.7 $\pm$ 10.7 years) met the inclusion criteria. Thirty-seven of these 59 NGGOs did not show internal solid portions, and the remaining 22 NGGOs had internal solid portions. The histologic diagnosis of the pulmonary NGGO was confirmed via wedge resection (n = 16) and lobectomy (n = 43). The median time interval between the diagnosis of primary extrapulmonary cancer and the pulmonary NGGOs was 24.6 months (range, 0 to 13 years). Table 1 shows the sites and histologies of primary extrapulmonary malignancies in the study population. One patient had synchronous breast cancer and thyroid cancer. All patients (n = 34) received appropriate treatment as recommended by the clinicians.

CT Scan Examinations

Three patients underwent initial thin-section CT scans, and the remaining 31 patients underwent initial thick-section CT scans. All patients (n = 34) underwent at least one thin-section CT scan examination during follow-up, which was performed for the further characterization of pulmonary NGGOs. The mean CT

Table 1—*Primary Extrapulmonary Malignancies Found in the Study Population*

Site of Primary Malignancy	Patients, Total No.	Histopathology of Primary Cancer (No. of Patients)	NGGOs, Total No.
Breast*	10	Ductal adenocarcinoma (9), lobular adenocarcinoma (1)	12
Thyroid*	6	Papillary carcinoma (6)	14
Stomach	4	Adenocarcinoma (4)	13
Bladder	3	Transitional cell carcinoma (3)	6
Liver	3	Hepatocellular carcinoma (3)	3
Prostate	2	Adenocarcinoma (2)	3
Thymus	2	Thymic carcinoma (2)	2
Uterine cervix	1	Squamous cell carcinoma (1)	3
Colon	1	Adenocarcinoma (1)	1
Kidney	1	Renal cell carcinoma (1)	1
Skin melanoma	1	Melanoma (1)	1
Bone	1	Chondrosarcoma (1)	1
Total	34		59

*One pulmonary NGGO was found in a patient with synchronous thyroid cancer and breast cancer.

scan follow-up period was 128.8 ± 184.6 days (range, 5 to 870 days). CT scanning was performed using various CT scanners (Light Speed Ultra; GE Medical Systems; Milwaukee, WI; Sensation-16; Siemens Medical Systems; Erlangen, Germany; and MX-8000, Brilliance-64; Phillips Medical Systems; Amsterdam, the Netherlands). CT scanning was performed at 120 kVp, 50 to 200 mA, and at a pitch of 0.875 to 1.5. Images were reconstructed using high-frequency algorithms with a slice thickness of 1 to 5 mm. Thin-section CT scan images referred to images with slice thicknesses of ≤ 1.25 mm, and thick-section CT scan images referred to images with slice thicknesses of > 1.25 mm. The mean time interval between the last thin-section CT scan and surgical resection of the NGGO was 14.6 ± 13.4 days (range, 0 to 48 days).

Evaluation of Clinical and CT Scan Characteristics of NGGOs

The clinical data for patients with NGGOs were recorded by one radiologist (E.A.P.). The following demographic and clinicopathologic data were recorded: (1) age and sex; (2) smoking history (*ie*, never-smoker or ever smoker) and smoking amount; (3) mode used for detection of the lesion (*ie*, during workup for primary cancer or during symptom evaluation); and (4) information regarding the primary extrapulmonary cancer, such as site, pathologic diagnosis, or TNM stage of the disease. If a patient had more than one primary extrapulmonary cancer, the diagnosis date of the most recently diagnosed cancer was recorded. We categorized the TNM stage of primary extrapulmonary cancers as limited disease (stage 1 or 2) or advanced disease (stage 3 or 4).

All thin-section CT scan images were reviewed by three chest radiologists (C.M.P., T.J.K., and J.M.G., with 4, 5, and 12 years, respectively, of experience in reading chest CT scans), who were blinded to the clinical information. Decisions on thin-section CT scan findings were reached through consensus. When patients had undergone more than one follow-up thin-section CT scan examination prior to surgical resection, we chose the last thin-section CT scan examination for the evaluation. Thin-section CT scan findings for each NGGO were analyzed for the following: (1) lesion location; (2) lesion size; (3) the presence of internal solid portion within the NGGO; (4) the size and proportion of internal solid lesion, if any; (5) lesion multiplicity (*eg*, solitary or multiple); (6) shape (*eg*, round or oval, and polygonal); (7) margin (*eg*, well-defined or ill-defined; smooth or lobulated); and (8) the presence of pleural retraction, air bronchogram, or bubble lucency. One radiologist (C.M.P.) recorded the average product of the height and width of a lesion to determine lesion size.

Statistical Analysis

The relationship between the final diagnosis of NGGOs and the clinical and CT scan features of NGGOs were analyzed using the Pearson χ^2 test, the Fisher exact test, or the independent sample *t* test, as appropriate. Statistical analyses were performed using a statistical software package (SPSS, version 13.0 for Windows; SPSS; Chicago, IL). A p value of < 0.05 was considered to indicate a significant difference.

Artificial neural networks (ANNs) with multilayer perceptrons were constructed and tested as a computerized scheme to predict the malignancy probability of each NGGO using commercially available software (NeuroSolution, version 5.0; NeuroDimension; Gainesville, FL).[16] The ANNs consisted of one input layer, one hidden layer, and one output layer. Statistically significant clinical features of patients and CT scan features of each NGGO were used as input data for the ANNs. All input data with numeric values were normalized to a range of 0 to 1.0, and the other input data were used as symbolic values. A nonlinear sigmoid function was used as a transfer function in the hidden layers and output layers of the networks. The hidden layer was connected to an output layer of a single neuron producing a normalized value (range, 0 to 1.0), which could be regarded as representing the malignancy probability of each NGGO (0, benign; 1, malignant). The ANNs were trained until the mean training error of the network decreased to below 0.01, meaning that if the output of the networks was not within 0.01 of the target output, it was considered to be incorrect. During the training process, the connection weights between the neurons were adjusted by using a back-propagation updating algorithm to minimize the output error. The maximum number of iterations was limited to 1,000. The ANNs were trained and tested using the leave-one-out method because of the limited data set that was available for this study. In this method, all NGGOs except one were used to train the ANNs, which in turn were applied to the independent lesion that was left out for testing. This procedure was repeated so that each NGGO was included in the testing.

The predictive performance of the ANNs was evaluated using binormal receiver operating characteristic (ROC) analysis using appropriate software (MedCalc, version 7.4; MedCalc Software; Mariakerke, Belgium).[17] The area under the ROC curve (Az) value was used as an index of the performance of ANNs in discriminating malignant from benign NGGOs. We calculated the sensitivity and specificity of the ANNs for the differentiation of malignant from benign NGGOs with an optimal ANN output level that was defined as the intersection of the ROC curve with the second bisectrix, at which point sensitivity balanced with specificity.[18]

Results

Histopathologic Diagnosis and Clinical Significance of NGGOs

The results of the histologic diagnosis of 59 NGGOs in 34 patients with extrapulmonary cancers were as follows: 24 pulmonary adenocarcinomas (Fig 1); 16 BACs (Fig 2); 14 AAHs (Fig 3); 4 focal fibroses; and 1 chronic granulomatous inflammation. None of these 59 NGGOs constituted metastasis from primary cancers, although eight solid nodules in our study were pathologically confirmed as metastasis in three patients. Table 2 summarizes the diagnostic results for the NGGOs based on primary extrapulmonary cancers. Twenty-eight of 34 patients (82.4%; 95% confidence interval [CI], 69.6 to 95.2%) were determined to have malignancies, and 6 patients (17.6%; 95% CI, 4.8 to 30.4%) had benign NGGOs. Forty lesions (67.8%; 95% CI, 55.9 to 79.7%) were diagnosed as malignancies.

Clinical and CT Scan Characteristics of NGGOs

Regarding the clinical characteristics of the 34 patients (Table 3), there was no significant difference between patients with malignant NGGOs and those with benign lesions. Although the frequency of malignancy was higher in women or never-smokers than in men or smokers, statistical significance was not found between malignant and benign NGGOs

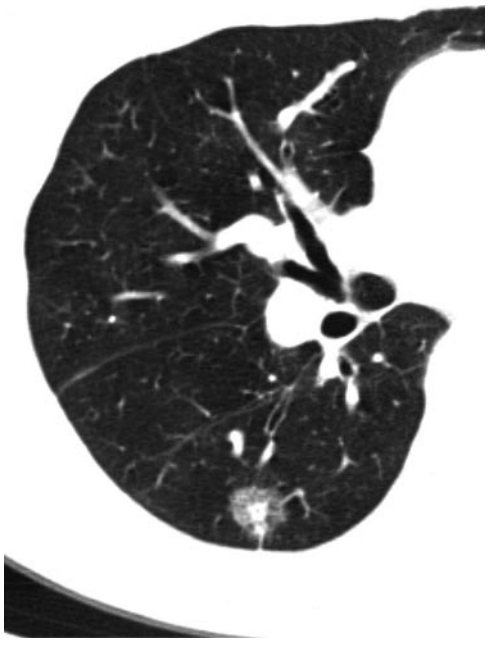

FIGURE 1. Adenocarcinoma in a 51-year-old asymptomatic woman with previous breast cancer. The transverse thin-section CT scan shows a 14-mm GGO nodule with internal solid part in the right lower lobe. This lesion was confirmed as pulmonary adenocarcinoma with a mixed BAC pattern.

with regard to patient sex ($p = 0.178$) or smoking history ($p = 0.315$). There was no significant difference in the other clinical characteristics such as smoking amount, mode used for detection of the lesion, and stage of primary extrapulmonary cancer.

Thin-section CT scan features of NGGOs are summarized in Table 4. The right upper lobe was the most common location of NGGOs; however, the difference was not significant ($p = 0.951$). The mean size of NGGOs in the present study was 11.2 ± 6.9 mm (range, 3 to 30 mm), and the sizes of the malignant NGGOs (mean, 13.18 ± 7.28 mm) were significantly larger than those of the benign lesions (mean, 6.86 ± 3.26 mm; $p < 0.01$). Most benign NGGOs were < 10 mm in diameter. However, of all NGGOs < 10 mm in size in our study, 50% (16 of 32 NGGOs) were malignancies. With respect to the presence of an internal solid portion within the NGGO, there was significant difference between malignant and benign NGGOs ($p < 0.05$). The mean size and proportion of the internal solid components in the case of malignant NGGOs (4.38 ± 5.92 mm and $26.0 \pm 30.76\%$, respectively) were greater than those of benign lesions (0.37 ± 1.61 mm and $3.7 \pm 16\%$, respectively; $p < 0.01$). The morphologic characteristics of nodules such as lesion margin, and the presence of bubble lucency, air bronchogram, or pleural retraction were significantly different between malignant and benign NGGOs ($p < 0.05$) [Table 4].

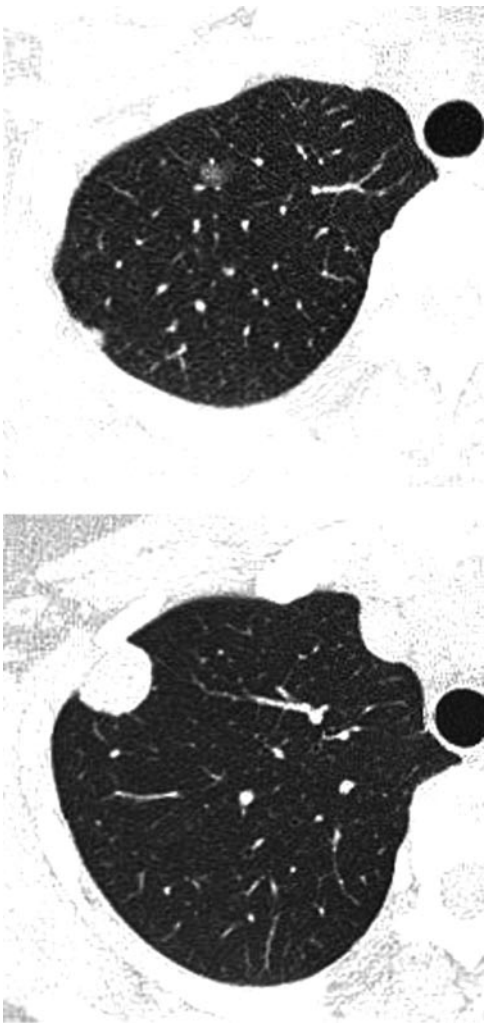

FIGURE 2. BAC in a 45-year-old woman with current hepatocelluar carcinoma in the liver. *Top*: transverse thin-section CT scan shows a 6-mm GGO nodule without an internal solid part in the right upper lobe. This lesion was confirmed as BAC of the lung. *Bottom*: a well-defined solid nodule is seen in the right upper lobe at the 2-cm caudal to the *top* image. This lesion was confirmed as metastatic hepatocellular carcinoma.

Performance of ANNs in Discriminating Malignant From Benign NGGOs

Lesion size, the presence of internal solid portion, the size of internal solid portion, the lesion margin, and the presence of bubble lucency, air bronchogram, or pleural retraction, which were significantly different between malignant and benign NGGOs in the univariate analysis, were used as input parameters for the ANNs. The ROC curve of ANNs for distinguishing malignant from benign NGGOs is illustrated in Figure 4. The performance of the ANNs occurred with multilayer perceptrons in our study, and the Az value was 0.973 (95% CI, 0.903 to 0.996). With an ANN output level of 0.57, the sensitivity and specificity of the ANNs for the differ-

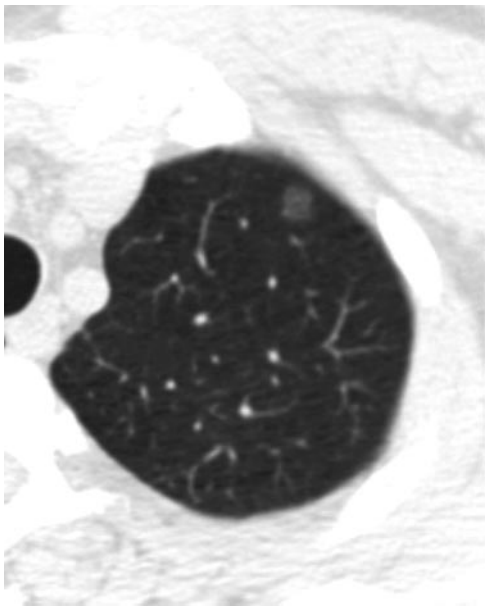

FIGURE 3. AAH in a 64-year-old asymptomatic woman with previous thyroid cancer. Transverse thin-section CT scan shows a 7-mm GGO nodule without an internal solid part in the left upper lobe.

entiation of malignant from benign NGGOs were 97.5% (95% CI, 86.8 to 99.6%) and 93.5% (95% CI, 78.5 to 99.0%), respectively.

DISCUSSION

To our knowledge, this is the first study to document the clinical significance of pulmonary NGGOs in patients with extrapulmonary cancers. The major findings of this study were as follows: (1) the malignancy rate for NGGOs in patients with extrapulmonary cancers was high (patients, 82.4%; nodules, 67.8%); (2) all malignant NGGOs were primary lung cancers; (3) the CT scan characteristics of NGGOs were useful in discriminating malignant NGGOs from benign NGGOs, and CT scan findings showed that there was a significant difference in lesion size, the presence of an internal solid portion within the NGGO, the size and proportion of the internal solid component, the lesion margin, and the presence of bubble lucency, air bronchogram, or pleural retraction; and (4) ANNs showed excellent accuracy in the discrimination of malignant NGGOs from benign NGGOs.

The malignancy rate of NGGOs in patients with extrapulmonary cancers in our study was 82.4% for patients and 67.8% for nodules. According to several more recent studies[19–21] that have been conducted in the CT scan era, the malignancy rates of noncalcified solid nodules in patients with extrapulmonary cancers ranged from approximately 42 to 80.7%, and the rates of lung cancers ranged from 21.2 to 50.3%. Considering that none of the NGGOs in our study were metastases, the malignancy rate of the NGGOs was very high. The high malignancy rate of the NGGOs, particularly NGGOs with internal solid components, has already been reported in several other studies.[1,7,22] In one study, Henschke et al[1] reported a higher malignancy rate for the NGGOs than for solid nodules, even though the study was performed in the screening setting. In another study, Nakata et al[7] reported that all of their persistent NGGOs were neoplasms and the malignancy rate of NGGOs was 79.1%. Kim et al[22] also reported that in their study 75% of the persistent NGGOs were malignancies. These results were consistent with those of our study, although their study populations were composed

Table 2—*Diagnostic Results of NGGOs Based on Primary Extrapulmonary Malignancies**

Site of Primary Malignancy	Patients, Total No.	Patients With Benignity	Patients With Lung Cancer	NGGOs, %	Nodule Diagnosed as Benign	Nodule Diagnosed as Lung Cancer
Breast†	10	3 (30)	7 (70)	12	4 (33.3)	8 (66.7)
Thyroid†	6	1 (16.7)	5 (83.3)	14	8 (57.1)	6 (42.9)
Stomach	4	1 (25)	3 (75)	13	5 (38.5)	8 (61.5)
Bladder	3	0	3 (100)	6	0	6 (100)
Liver	3	1 (33.3)	2 (66.7)	3	1 (33.3)	2 (66.7)
Prostate	2	0	2 (100)	3	0	3 (100)
Thymus	2	2 (100)	0	2	2 (100)	0
Uterine cervix	1	0	1 (100)	3	1 (33.3)	2 (66.7)
Colon	1	0	1 (100)	1	0	1 (100)
Kidney	1	0	1 (100)	1	0	1 (100)
Skin melanoma	1	0	1 (100)	1	0	1 (100)
Bone	1	0	1 (100)	1	0	1 (100)
Total	34	7	27	59	20	39

*Values are given as No. (%), unless otherwise indicated.
†One benign NGGO was found in patient with synchronous thyroid cancer and breast cancer.

Table 3—*Clinical Features of Patients With NGGOs and Extrapulmonary Cancers

Characteristics	Patients With Benign Lesion (n = 7)	Patients With Malignant Lesion (n = 27)	p Value
Age, yr†	63.0 ± 10.39	58.78 ± 10.74	0.358†
Sex			
Male	4 (57.14)	7 (25.93)	0.178‡
Female	3 (42.86)	20 (74.07)	
Smoking history			
Never-smoker	4 (57.14)	22 (81.48)	0.315‡
Ever smoker	3 (42.86)	5 (18.52)	
Smoking amount,† pack-yr	14.57 ± 22.05	8.15 ± 19.22	0.450†
Mode of detection			
During workup for primary cancer	7 (100)	26 (96.29)	1.00‡
During symptom evaluation	0	1 (3.71)	
Stage of primary cancer			
Limited disease (I or II)	7 (100)	20 (74.07)	0.300‡
Advanced disease (III or IV)	0	7 (25.93)	

*Values are given as the mean ± SD or No. (%), unless otherwise indicated.
†Independent sample *t* test.
‡Fisher exact test.

of asymptomatic screening individuals and patients with other diseases.[7,22]

In the present study, all malignant NGGOs were primary lung cancers. It has been reported in several studies[1,4,7,10,11] that NGGOs have a high probability of being BACs or pulmonary adenocarcinomas. However, those studies have been performed without regard to whether patients had previous or concurrent cancers. This result in our study might be helpful in determining whether an NGGO is benign, a primary lung cancer, or metastasis. Indeed, some cases of metastatic tumors showing NGGOs have been reported;[15,23] however, NGGOs representing metastasis seem to be very rare. Gaeta et al[24] reported that 2 of 65 patients in their study with proven lung metastasis from adenocarcinoma of the GI tract showed NGGOs. However, the frequency of metastasis showing NGGOs may have been overestimated in their study because they excluded pathologically unproven round pulmonary nodules. Metastasis from malignant melanoma could also manifest as NGGOs in the lung.[15] The metastatic lesions from malignant melanomas were presumed to come to the alveoli via the bloodstream and spread beneath the alveolar epithelium.[15] However, even though it might be possible that metastatic tumors manifest as NGGOs in the lung, it is not common for us to encounter such metastatic nodules showing NGGOs. In this context, Fraser et al[25] recommended that we should consider the possibility of early pulmonary adenocarcinoma or BAC when we come across persistent NGGOs in the lung.

There was a significant difference in lesion size, the presence of an internal solid portion within the NGGO, the size and proportion of the internal solid component, the lesion margin, and the presence of bubble lucency, air bronchogram, or pleural retraction between malignant and benign NGGOs. In our study, malignant NGGOs were significantly larger than benign NGGOs. This result might be explained by the fact that the majority of benign NGGOs were AAHs, and all malignancies were BACs or pulmonary adenocarcinomas in our study. A couple of studies[7,11] have also reported that AAH was smaller than BAC or pulmonary adenocarcinoma and was not > 1 cm in size. In that context, 1 cm in diameter has been suggested as a criterion for discriminating BAC from AAH.[7] It has also been reported that NGGOs containing solid components had higher malignancy rates than those without solid components.[1,4,7,13]

ANNs showed excellent performance in distinguishing between malignant and benign NGGOs. This computerized scheme might be a useful tool for that purpose, in that, according to one study,[26] the diagnostic yield of CT scan-guided aspiration biopsy was not so good in NGGOs, even when the sizes of the NGGOs were between 10 and 15 mm in diameter. However, the performance of the ANNs in discriminating malignant from benign NGGOs should be tested and confirmed in an independent group of subjects before the ANNs are applied to the general population.

Our study has several limitations. First, due to the retrospective nature of our study, CT scan examinations were not carried out using the same protocol. It is possible that some NGGOs could have been undetected since patients underwent only initial thick-section CT scans. Second, the number of pa-

Table 4—*CT Scan Features of NGGOs in Patients With Extrapulmonary Cancers

Characteristics	Benign Lesion (n = 20)	Malignant Lesion (n = 39)	p Value
Lesion location			
RUL (n = 24)	8 (40)	16 (41)	0.951†
RML (n = 11)	3 (15)	8 (20.5)	
RLL (n = 14)	5 (25)	9 (23.1)	
LUL (n = 6)	2 (10)	4 (10.3)	
LLL (n = 4)	2 (10)	2 (5.1)	
Lesion size, mm	6.86 ± 3.26	13.18 ± 7.28	< 0.01‡
Presence of internal solid portion			
Yes (n = 22)	3 (15)	19 (48.7)	< 0.05†
No (n = 37)	17 (85)	20 (51.3)	
Internal solid component			
mm	0.37 ± 1.61	4.38 ± 5.92	< 0.01‡
%	3.7 ± 16	26.0 ± 30.76	< 0.01‡
Lesion multiplicity			
Solitary (n = 22)	6 (30)	16 (41)	0.407†
Multiple (n = 37)	14 (70)	23 (59)	
Shape of lesion			
Round or oval (n = 23)	20 (100)	33 (84.6)	0.087§
Polygonal (n = 6)	0	6 (15.4)	
Border of lesion			
Well defined (n = 58)	19 (95)	39 (100)	0.339§
Ill-defined (n = 1)	1 (5)	0	
Margin of lesion			
Smooth (n = 51)	20 (100)	31 (79.5)	< 0.05§
Lobulated (n = 8)	0	8 (20.5)	
Bubble lucency, air bronchogram, pleural retraction			
Yes (n = 18)	1 (5)	17 (43.6)	< 0.01§
No (n = 41)	19 (95)	22 (56.4)	

*Values are given as No. of nodules (%) or mean ± SD, unless otherwise indicated. RUL = right upper lobe; RML = right middle lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe.
†Pearson χ^2 test.
‡Independent sample *t* test.
§Fisher exact test.

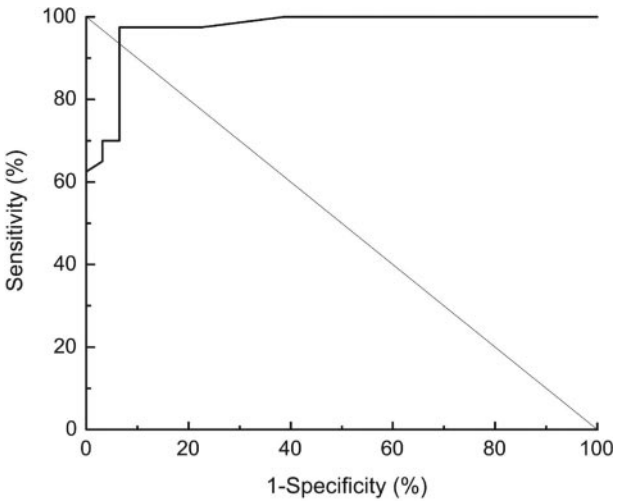

FIGURE 4. A ROC curve of ANNs with multilayer perceptrons for distinguishing malignancy from benignity is shown. In the performance of the ANNs, the Az value was 0.973. The intersection of the curve with the second bisectrix at which sensitivity balanced specificity was used to determine the optimal threshold to discriminate malignant NGGOs from benign NGGOs.

tients in our study was small; therefore, it could be difficult to state confidently a malignancy rate or a rate of metastasis that manifests as NGGOs. Third, we only included cases that were confirmed with a pathologic specimen; therefore, we may have omitted many malignancies that were not resected and may have only included lesions with a high probability of malignancy. In addition, many cancer patients did not undergo lung nodule resection if the risk of the procedure exceeded the benefits of the procedure, possibly leading to bias. Thus, further study is necessary in a larger number of patients with a prospective study design. Despite these limitations, however, we are confident that this study will be helpful in clinical practice and in the decision making of clinicians and radiologists when NGGOs are encountered in patients with extrapulmonary cancers.

In summary, NGGOs in patients with extrapulmonary cancers tend to have a high malignancy rate and are very often primary lung cancers. ANNs with

multilayer perceptrons may be a useful tool in distinguishing malignancies from benign lesions.

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Chest 2008;133; 1402-1409; Prepublished online March 13, 2008;
DOI 10.1378/chest.07-2568