Computed tomographic image comparison between mediastinal and lung windows provides possible prognostic information in patients with small peripheral lung adenocarcinoma

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Objectives: The purpose of this study was to determine whether the ratio of the area of the mediastinal computed tomographic image to that of the lung computed tomographic image can be a prognostic factor of small peripheral lung adenocarcinoma.

Methods: We studied the computed tomographic images of 143 patients with primary peripheral lung adenocarcinoma of 30 mm or less in maximum diameter. Two groups were categorized according to the tumor's ratio of the area of the mediastinal computed tomographic image to that of the lung computed tomographic image (tumor's area in the mediastinal computed tomographic image/tumor's area in lung computed tomographic image $\times$ 100%), both faint density-type (<50%) and solid-type images ($\geq$ 50%). Clinical factors and prognoses of the 2 groups were analyzed.

Results: There were 58 patients with the solid-type tumor image and 85 patients with the faint density-type tumor image. The number of patients with tumor size of less than 20 mm in the faint density-type tumor group ($n = 30$) was significantly higher than that in the solid-type tumor group ($n = 8$, $P = .008$). The 5-year survival of patients with faint density-type tumors was 74.1%, whereas that in patients with solid-type tumors was 54.2% ($P = .013$). Furthermore, the survival curve of patients with the solid-type computed tomographic image combined with ground-glass opacity was similar to that of patients with the faint density-type image. Multivariate analysis revealed the prognostic influence of the ratio of the area of the mediastinal computed tomographic image to that of the lung computed tomographic image on survival ($P = .029$, relative risk = 0.48) and showed to be of second highest influence after the N factor.

Conclusions: It is suggested that the ratio of the area of the mediastinal computed tomographic image to that of the lung computed tomographic image can be a prognostic factor in patients with small peripheral lung adenocarcinoma.

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Received for publication Nov 5, 2001; revisions requested Feb 5, 2002; revisions received Feb 13, 2002; accepted for publication April 16, 2002.

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J Thorac Cardiovasc Surg 2002;124:1014-20

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0022-5223/2002 \$35.00+0 12/1/125647

doi:10.1067/mtc.2002.125647

Recently, the number of patients with small peripheral lung cancer detected by means of computed tomographic (CT) scanning has been increasing. In Japan, CT mass screening has been started in many local municipalities. Most cancers detected by this method are small stage IA lung cancers in peripheral locations. In the United States the National Cancer Institute launched lung cancer screening with spiral CT scanning. Despite the small size of these tumors, some patients die of cancer recurrence, and thus it is important for us to know the biologic behavior of this type of cancer. Although many reports on the radiologic-pathologic correlation of small

lung adenocarcinoma have been published, little clinical information on prognostic factors during the pretreatment state is available.¹⁻⁵ Thus, new information relevant to prognosis is highly desired.

Patients and Methods

From January 1990 to December 1993, surgical resections were performed in 143 patients with primary peripheral lung adenocarcinoma with a maximum diameter of 30 mm or less. Of the 143 patients, 136 (95.1%) underwent lobectomies, 5 (3.5%) underwent pneumonectomies, and 2 (1.4%) underwent segmental resections combined with systematic hilar and mediastinal node dissection. Informed consent was obtained from each patient before the op-

Figure 1. CT images of a patient with a solid-type tumor with GGO. The patient was a 70-year-old woman who underwent a right upper lobectomy combined with systematic nodal dissection. She remained alive for 7.6 years after the operation. The CT M/L ratio was 60.5%, and GGO was found around the solid-type tumor image. The tumor was proved to be a well-differentiated stage IIA (T1 N1 M0) papillary adenocarcinoma with a maximum tumor diameter of 25 mm.

Figure 2. CT images of a patient with a faint density-type tumor with GGO. The patient was a 72-year-old man who underwent a right upper lobectomy combined with systematic nodal dissection. He was still alive as of the last follow-up (9.5 years). The CT M/L ratio was 3.9%, and GGO was observed. The tumor was proved to be moderately differentiated stage IA (T1 N0 M0) papillary adenocarcinoma with a maximum tumor diameter of 20 mm.

Figure 3. Survival curves of patients with completely resected tumors. The survival of patients with faint density-type CT images was significantly higher than that of patients with solid-type CT images ($P = .013$, log-rank test).

eration. Tumors were completely removed in 137 patients, but 6 had residual tumors: 3 patients had malignant pleural effusion; 1 patient had pleural dissemination; 1 patient had malignant pericardial effusion; and 1 patient had residual tumor at the bronchial stump. CT images were photographed with a window level of -600 H and window width of 2000 H for lung windows and a level of 10 H and width of 300 H for mediastinal windows. Each image was analyzed with National Institutes of Health imaging software. The areas in the lung and mediastinal windows of the tumors were both measured 3 times. Mean values were used to calculate the tumor's ratio of the area of the mediastinal computed tomographic image to that of the lung computed tomographic image (CT M/L ratio; CT M/L ratio = tumor's area in the mediastinal CT image/tumor's area in the lung CT image $\times 100\%$). All patients were classified into one of two groups: the solid-type tumor group (CT M/L ratio $\geq 50\%$) and the faint density-type tumor group (CT M/L ratio $< 50\%$).⁶ Examples of CT images of the two groups are shown in Figures 1 and 2. Tumors with ground-glass opacity (GGO)⁷ in lung CT images were defined as GGO positive. The medical records of all patients were reviewed for clinical and pathologic characteristics, including age, sex, tumor size, lymph node involvement, pathologic stage, and histologic grade. The length of survival was defined as the period from the day of the operation to the last day of follow-up or the date of death from any cause. The survivals were calculated by means of the Kaplan-Meier method, and statistical analysis was performed by means of the log-rank test. The χ^2 test or Fisher exact test was used to compare several clinical or pathologic factors. The Cox

proportional hazards model was applied for multivariate analysis by using version 5.0 of the StatView software package (SAS Institute Inc, Cary, NC).

Results

Patient characteristics are summarized in Table 1. There were 58 patients with solid-type tumors and 85 patients with faint density-type tumors. There was no significant difference in age distribution and sex between the two groups. Of 58 patients with solid-type tumors, only 8 had tumors with maximum diameters of 20 mm or less, whereas there were 30 patients in the total of 85 with faint density-type tumors ($P = .008$). Thirty-seven patients with solid-type tumors proved to have no nodal involvement, 2 patients had N1 disease, and 19 had N2 disease pathologically. In the faint density group the numbers of patients with no nodal involvement, N1 disease, and N2 disease were 68, 6, and 11, respectively. The number of patients with nodal involvement was significantly higher in the solid-type tumor group than that among the patients with faint density-type tumors ($P = .032$). We also compared histologic grade between the two groups but found no statistical difference ($P = .056$). In the lung CT images of patients with faint density-type tumors, 45 were proved to have GGO, and 40 were proved not to have GGO. In the solid-type tumor group, on the

other hand, only 7 patients had GGO, and 41 did not ($P < .0001$).

The 5-year survival of patients with faint density-type images whose tumors were completely resected was 74.1%, which was significantly higher than that of patients with solid-type CT images (5-year survival, 54.2%; $P = .013$; Figure 3). To exclude the influence of lymph node metastasis, we also compared the survivals of the patients with stage IA disease between the two groups. The 5-year survival of patients with stage IA disease with faint density-type images was 86.1%, whereas it was 74.5% in the other group, which showed a significant difference ($P = .047$, Figure 4). The curve of patients with solid-type images without GGO showed the worst survival. However, there was no significant difference among patients with faint density-type tumors with GGO, faint density-type tumors without GGO, and solid-type tumors with GGO (Figure 5). A significant difference existed between the prognosis of the solid-type tumor group without GGO and that of the group consisting of faint density-type and solid-type tumors with GGO ($P = .005$, Figure 6).

The multivariate analysis (Table 2) showed the CT M/L ratio to be a significant prognostic factor ($P = .03$; hazard ratio, 0.48; 95% confidence interval, 0.24-0.95). The P value of the CT M/L ratio was the second highest after that of the N factor and was the same as that of tumor size.

Discussion

Several factors, such as lymph node metastasis, histologic subtype (as proposed by Noguchi and colleagues⁸), and size of central fibrosis, have been proved to be of prognostic importance, but few of them can be evaluated preoperatively.^{1-5,9} In this study we found that the 5-year survivals of patients with faint density-type CT images were significantly better than those of patients with solid-type CT images (Figure 3). There was also a significant difference between the two groups, even if the cases were limited to stage IA disease (Figure 4). Furthermore, patients with solid-type CT images who had no GGO component had the worst 5-year survival (Figures 5 and 6). The multivariate analysis revealed the prognostic influence of the CT M/L ratio on survival ($P = .029$; relative risk, 0.48; Table 2), with its effect being the second highest after that of the N factor. All these findings strongly suggest that the CT M/L ratio might be a possible prognostic factor of peripheral lung adenocarcinomas 30 mm or less in size that can be evaluated preoperatively.

The reason why patients with small peripheral lung adenocarcinomas with solid-type CT images have a poor prognosis is still unclear. Isobe and coworkers¹⁰ reported that small peripheral lung lesions that have high CT M/L ratios (the solid type) often appear as poorly differentiated adenocarcinomas. On the other hand, tumors with 0% CT M/L ratios often appear as well-differentiated adenocarci-

TABLE 1. Characteristics and CT images of patients with adenocarcinoma of the lung (tumor diameter ≤ 30 mm, $n = 143$)

	No. of patients	CT findings	
		Solid type*	Faint density type†
Total	143	58	85
Sex			
Male	65	28	37
Female	78	30	48
Age (y)	62.6 $\pm$ 9.9	62.5 $\pm$ 9.9	62.8 $\pm$ 9.9
Tumor size			
≤ 20 mm	38	8	30
> 20 mm	105	50	55
Nodal involvement			
N0	105	37	68
N1	8	2	6
N2	30	19	11
p Stage			
Stage I	101	35	66
Stage II	8	2	6
Stage III	33	20	13
Stage IV	1	1	0
Histologic grade			
Well	52	18	34
Moderate	73	36	37
Poor	18	4	14
GGO			
+	52	7	45
-	91	51	40

*Solid type: tumor's area in mediastinal window/tumor's area in lung window $\geq 50\%$.

†Faint density type: tumor's area in mediastinal window/tumor's area in lung window $< 50\%$.

nomas. Andoh and associates⁶ studied the roentgenopathologic correlation of 12 patients with small peripheral adenocarcinomas measuring 15 mm or less in greatest dimension and found that all patients ($n = 4$) who had a faint density type of thin-section CT images were classified as having histologic subtypes A and B (Noguchi classification).⁸ Among the 8 patients of the solid-type tumor group, there were also 3 patients classified as having subtypes A and B in whom the alveolar spaces were filled with mucus. Therefore, it cannot be demonstrated that the change of the tumor's area in the thin-section CT image correlates with the histologic subtype of Noguchi's classification. However, our study demonstrated that CT image comparison between the mediastinal and lung CT images is possibly of prognostic value in patients with peripheral lung adenocarcinoma. Because our study included patients whose tumors were larger than 15 mm, the biologic behavior and clinical values of the CT images are different from those in the previous studies, which dealt with only small nodules.

It is generally thought that most adenocarcinomas develop either de novo or through the stage of atypical adeno-

Figure 4. Survival curves of patients with stage IA disease. The survival of patients with faint density-type CT images was significantly higher than that of patients with solid-type CT images ($P = .047$, log-rank test).

TABLE 2. Multivariate analyses of prognostic factors

Variables	Estimated coefficient	SE	P value	Relative risk (95% CI)
Nodal involvement (N0 vs N1+2)	−2.27	0.35	<.0001	0.10 (0.05-0.20)
CT M/L ratio* (<50% vs ≥50%)	−0.73	0.34	.03	0.48 (0.24-0.95)
Tumor size (≤20 mm vs >20 mm)	−0.64	0.39	.03	0.43 (0.20-0.93)
Sex (male vs female)	−0.55	0.35	.12	0.58 (0.29-1.16)
Histologic grade (well vs moderate + poor)	−0.44	0.43	.30	0.64 (0.28-1.49)
Age (<60 y vs ≥60y)	−0.04	0.34	.91	0.96 (0.49-1.89)

CI, Confidence interval.

*CT M/L ratio: tumor’s area in the mediastinal CT image/tumor’s area in the lung CT image × 100%.

matous hyperplasia.¹¹ Several investigators have reported that GGO demonstrated by means of high-resolution computed tomography might be due to bronchioloalveolar adenoma of the lung or bronchioloalveolar carcinoma.^{7,12,13} In the study by Jang and associates,¹⁴ follow-up CT scans in 3 of 4 patients with bronchioloalveolar carcinoma showed replacement of the GGO by means of consolidation, leading to speculation that the areas of GGO might represent an early stage of bronchioloalveolar carcinoma. Kodama and coworkers¹⁵ proved that the bronchioloalveolar carcinoma area was well correlated with the GGO area on high-resolution computed tomography. He also showed that the 3-year relapse-free survivals of patients with GGO of

greater than 50% were significantly better than those of patients with GGO of less than 50%. All of these findings suggest that GGO is well correlated with the development and malignant progression of some adenocarcinomas of the lung. It was also supported by our finding that tumors of the solid-type CT image group without GGO had the worst prognosis (Figures 5 and 6).

In conclusion, our results suggest that the CT M/L ratio is a possible prognostic factor of small peripheral lung adenocarcinoma of 30 mm or less, which can be evaluated preoperatively. The multivariate analysis showed the prognostic influence of the CT M/L ratio on survival to be the second highest after that of the N factor. We believe that

Figure 5. Survival curves on the basis of CT images (with or without GGO in both types). There were no significant differences among patients with faint density-type tumors with GGO, solid-type tumors with GGO, and faint density-type tumors without GGO ($P^1 = .89$, $P^2 = .99$, $P^3 = .88$).

Figure 6. Survival curves of patients with solid-type tumors without GGO and of patients with other types of CT images. There was a significant difference between the two groups (solid-type tumors without GGO vs faint density-type tumors and solid-type tumors with GGO: $P = .005$).

these findings hold promise for a new prognostic factor in the pretreatment period.

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