Identification of Early T1b Lung Adenocarcinoma Based on Thin-Section Computed Tomography Findings

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Introduction: The aim of this study was to radiologically identify early lung adenocarcinoma in clinical T1bN0M0 lung cancer, based on pathological findings and long-term prognosis.

Methods: In this study, we reviewed lung nodules findings on thin-section computed tomography in 173 patients with clinical T1bN0M0 lung adenocarcinoma who underwent surgery between 2003 and 2007. The ratio of the size of solid attenuation to the maximum tumor dimension (consolidation/tumor [C/T] ratio) was calculated. We defined two groups of patients by C/T ratio cutoff levels of 0.00, 0.25, 0.50, 0.75, and 1.00 and compared the rates of pathological nonaggressive lung adenocarcinoma, overall survival, and recurrence rates between the groups. The percentages of predominant histological subtypes were compared between two groups divided by the optimal cutoff level. Various clinical factors were analyzed by univariate and multivariate analyses to predict pathological lymph node involvement.

Results: The median follow-up period was 62 months. All patients with C/T ratios of 0.5 or less were diagnosed as having pathological nonaggressive adenocarcinomas, and there was no recurrence; their 5-year overall survival rate was 97.4%, which was significantly better than that for patients with C/T ratios of greater than 0.5 (76.2%). None of the ground-glass opacity–predominant tumors were predominantly solid adenocarcinoma with mucin. The C/T ratio of 0.5 or more was an independent predictor of lymph node involvement.

Conclusion: In patients with clinical T1bN0M0 disease, the C/T ratio of 0.5 or less identified early lung adenocarcinoma. In patients with the identified early disease, a feasibility study of limited surgery may be warranted.

Key Words: Early lung cancer, Ground-glass opacity, Non–small-cell lung cancer, Limited surgery.

(*J Thorac Oncol*. 2013;8: 1289–1294)

Remarkable improvement in spatial resolution of computed tomography (CT) has provided new tools for lung cancer diagnosis. Thin-section CT (TSCT) findings of lung cancer have been extensively analyzed. Various measures to predict less-invasive lung cancers have been reported, for example, classically used tumor size, tumor shadow disappearance rate,[1,2] visual estimation of the consolidation component,[3–5] size of the solid component, maximum standardized uptake value by ^{18}F-fluorodeoxyglucose positron emission tomography/CT,[6] and the ratio of the size of solid attenuation to the maximum tumor dimension (consolidation/tumor [C/T] ratio).[7] Suzuki et al.[8] reported a multi-institutional prospective radiological study for early lung cancer (Japan Clinical Oncology Group: JCOG trial 0201) in 2011 and concluded that the C/T ratio was the most reliable measure for identification of nonaggressive lung cancer on TSCT, compared with the visual estimation and tumor shadow disappearance rate methods. On the basis of these results, two pivotal prospective studies on limited resection for small peripheral lung cancer assessed by C/T ratios were initiated in Japan (JCOG trial 0802/West Japan Oncology Group trial 4607L and JCOG trial 0804).[9] In addition, there is an ongoing, prospective, randomized controlled trial (lobectomy versus sublobar resection) for small (≤2 cm) peripheral stage IA non–small-cell lung cancer in the United States of America and Canada (Cancer and Leukemia Group B trial 14053). However, there are no prospective, limited resection trials for clinical T1b (cT1b) early lung cancer. The aim of this study was to radiologically identify early lung adenocarcinoma in patients with cT1bN0M0 lung cancer, based on pathological findings and long-term outcomes.

PATIENTS AND METHODS

Patient Selection

Between January 2003 and December 2007, 1000 non-small cell lung cancer patients underwent complete resection by lobectomy or pneumonectomy with systematic lymph node dissection. Basically, regional lymph nodes were dissected in our hospital according to the previous article by Naruke et al.[10] Of these, 210 patients (21.0%) had lung adenocarcinoma of cT1bN0M0 according to the 7th edition of the tumor–node–metastasis (TNM) classification.[11] We excluded patients with multiple primary lung cancers, extensive cavity formation, or massive occlusive pneumonia on preoperative TSCT as well as those who underwent induction therapy or whose clinical course records were incomplete. Thus, we included 173 patients (17.3%) whose preoperative TSCT data

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/13/0810-1289

were available for review in this study. Data collection and analyses were approved, and the need to obtain informed consent from each patient was waived by the institutional review board in February 2013.

Radiological Evaluation by TSCT

Contrast-enhanced CT scans at 5 to 10 mm collimation of the chest and upper abdomen were used to assess the clinical staging of all patients with cT1N0M0 lung cancer. In addition, TSCT images at 1 to 2 mm collimation were used to evaluate primary lesions. The X-vigor CT system (Toshiba Medical Systems, Tokyo, Japan) was used to perform the CT scans. CT images were evaluated on a monitor display with a window level of −600 HU and a window width of 1800 HU. Two observers (KA and TH), who were unaware of the pathological findings and prognosis, reviewed each lung nodule on preoperative TSCT scans. Tumor diameter was measured at the longest dimension of a tumor. The C/T ratio was calculated in one dimension on TSCT (Supplemental Figure). The consolidation component was defined as an area of increased opacification that completely obscured the underlying vascular structures. Ground-glass opacity (GGO) was defined as increased hazy density in an area without obscuring the underlying vascular structure.[8] Discrepancies in interpretation between observers were resolved by consensus. We set C/T ratio cutoff levels at 0.0, 0.25, 0.5, 0.75, and 1.0. A C/T ratio of 0.0 represented pure GGO nodules, and the C/T ratio of 1.0 represented solid nodules without GGO components. Disease stage during the study period was determined according to the 6th edition of the TNM classification,[12] but for this report we reclassified this study population according to the 7th edition of the TNM classification.[11]

Pathological Evaluation

Surgical specimens were fixed with 10% formalin and embedded in paraffin. Serial 4-μm sections were stained with hematoxylin and eosin and by the Alcian blue–periodic acid–Schiff method for cytoplasmic mucin production. We used elastica van Gieson or Victoria blue–van Gieson staining to visualize elastic fibers and evaluate vascular and pleural invasion. Lymphatic permeation was diagnosed with the help of D2-40 staining. Histological type was determined according to the World Health Organization classification of cell types.[13]

Patient Follow-Up

Patients were evaluated at 3-month intervals for the first 2 years and typically at 6-month intervals thereafter on an outpatient basis. The follow-up evaluation included physical examination, chest radiography, and blood examination including pertinent tumor markers. Whenever any symptoms or signs of recurrence were detected, further evaluations were conducted, including CT scan of the chest and abdomen, brain magnetic resonance imaging, and bone scintigraphy. After 2004, integrated positron emission tomography/CT was also performed when appropriate. Annual follow-up CT examination was also used for lung cancer patients who had undergone complete resection in the absence of some symptoms or abnormal examination findings. Recurrence was diagnosed on the basis of compatible physical examination and diagnostic imaging findings, and the diagnosis was histologically confirmed when clinically feasible. The length of overall survival was defined as the interval in months between the date of surgical intervention and the last follow-up date or death resulting from any cause. Observations were censored at the last follow-up when the patient was alive or lost to follow-up. The date of recurrence was defined as the date of histological proof or, in cases diagnosed on the basis of clinicoradiological findings, the date of identification by a physician.

Pathological and Prognostic Analyses

We defined pathological nonaggressive lung adenocarcinoma as lung adenocarcinoma without nodal involvement, vascular invasion, lymphatic permeation, and pleural invasion, and its rates, overall survival, and recurrence rates were compared between each group defined by the C/T ratio cutoff levels. On the basis of the pathological findings and prognoses, we determined the optimal cutoff C/T ratio that best discriminated early lung adenocarcinoma. The predominant histological subtype (bronchioloalveolar carcinoma [BAC], papillary adenocarcinoma, acinar adenocarcinoma, and solid adenocarcinoma with mucin) of each tumor was determined, and the percentages of these subtypes were calculated for the groups divided by the optimal C/T ratio cutoff level. Various clinical factors (C/T ratio, sex, age, smoking history, preoperative serum carcinoembryonic antigen level, laterality, tumor origin lobe, and maximum tumor diameter) were used for univariate and multivariate analyses to predict pathological lymph node involvement.

Statistical Analysis

All cumulative overall survival rates were estimated by the Kaplan–Meier method. Comparisons between groups were calculated by the log-rank test. We used Fisher's exact test for univariate analysis as well as multivariate logistic regression analysis to identify pathological lymph node involvement predictors. All statistical analyses were performed using JMP 10 statistical software (Version 10.0.2. 64-bit edition; SAS Institute Inc., Cary, NC) and GraphPad Prism (Prism for Windows, Version 5.02; GraphPad Software, Inc., La Jolla, CA).

RESULTS

Patient clinical and pathological characteristics are summarized in Table 1. The median follow-up period was 62 months (range, 3–108 months). The average ± SD of the tumor diameter was 25 ± 2.8 mm. There were only five patients (2.9%) with pure GGO tumor (C/T ratio = 0.0) and 69 patients (39.9%) with completely solid tumor (C/T ratio = 1.0). There were no significant correlations between the maximum tumor diameter and C/T ratio ($r = 0.16$, Spearman's rank correlation coefficient). Lymph node metastasis was pathologically confirmed in 19 patients (10.9%).

There were 109 patients (63.0%) with pathological nonaggressive lung adenocarcinoma (defined as lung adenocarcinoma without nodal involvement, vascular invasion, lymphatic permeation, and pleural invasion). All patients with C/T ratios

TABLE 1. Patients Clinicopathological Characteristics

Patient Characteristics	No. of Patients (%) (*N* = 173)
Age (yr)	
<70	111 (64.2)
≥70	62 (35.8)
Sex	
Male	75 (43.4)
Female	98 (56.6)
Smoking history	
Never smoker	85 (49.4)
Current/former smoker	88 (50.6)
Preoperative serum CEA level[a]	
≤5.0 ng/ml	137 (79.2)
>5.0 ng/ml	35 (20.2)
Tumor location	
Right upper lobe	62 (35.8)
Right middle lobe	13 (7.5)
Right lower lobe	32 (18.5)
Left upper lobe	41 (23.7)
Left lower lobe	25 (14.5)
Maximum tumor size (mm)	
Average ± SD	25 ± 2.8
C/T ratio	
0 (pure GGO)	5 (2.9)
>0, ≤0.25	8 (4.6)
>0.25, ≤0.5	26 (15.0)
>0.5, ≤0.75	33 (19.1)
>0.75, <1.0	32 (18.5)
1 (solid tumor)	69 (39.9)
Pathological lymph node metastasis	
pN0	154 (89.0)
pN1	9 (5.2)
pN2	10 (5.7)
Lymphatic permeation	
Absent	147 (85.0)
Present	26 (15.0)
Vascular invasion	
Absent	123 (71.1)
Present	50 (28.9)
Pleural invasion	
Absent	138 (80.2)
Present	34 (19.8)

[a]One patient with missing value.
CEA, carcinoembryonic antigen; C/T ratio, consolidation/tumor ratio; GGO, ground-glass opacity.

of 0.5 or less had pathological nonaggressive cancers (Table 2). Of the 69 pure solid tumors (C/T ratio = 1.0), 38 (55%) were pathologically diagnosed as invasive adenocarcinoma (having any of the following pathological findings: nodal involvement, vascular invasion, lymphatic permeation, or pleural invasion). When C/T ratio cutoff levels were set at 0.50, 0.75, and 1.00, overall survival was significantly better in the lower C/T ratio group than that in the higher C/T ratio group (Fig. 1). The

TABLE 2. Relationship between C/T Ratio and Pathological Invasiveness

C/T Ratio	Total No. of Patients	Pathological Nonaggressive Cancer[a]	Pathological Invasive Cancer[a]
0 (Pure GGO)	5	5 (100)	0 (0)
0 < C/T ratio ≤ 0.25	8	8 (100)	0 (0)
0.25 < C/T ratio ≤ 0.5	26	26 (100)	0 (0)
0.5 < C/T ratio ≤ 0.75	33	24 (73)	9 (27)
0.75 < C/T ratio < 1.0	32	15 (47)	17 (53)
1 (Pure solid)	69	31 (45)	38 (55)

Numbers in parentheses are percentages.
[a]Defined as absence of nodal involvement, pleural invasion, lymphatic permeation, and vascular invasion. If one or more of these findings were positive, tumors were classified as invasive cancer.
C/T ratio, consolidation/tumor ratio; GGO, ground-glass opacity.

5-year survival rate of patients with C/T ratios of 0.5 or less was 97.4%, which was significantly better compared with that of the patients with C/T ratios 0.5 or more (76.2%; Fig. 1*C*). During the follow-up period, 42 recurrences (22 locoregional only and 20 including distant sites) were observed (Table 3). Patients with C/T ratios of 0.5 or less did not develop recurrence, but one patient died of another cancer. In contrast, 31% patients (42 of 134) with C/T ratios 0.5 or more developed recurrences. On the basis of these results, we determined that a C/T ratio cutoff level of 0.5 was optimal for discrimination of early lung adenocarcinoma. Otherwise, seven patients (6%) among 109 patients who revealed pathological nonaggressive lung adenocarcinoma developed recurrence and 31 patients (48%) among 64 patients who revealed pathological invasive lung adenocarcinoma developed recurrence.

In more than half of the GGO-predominant tumors (C/T ratio ≤0.5), the predominant histological subtype was BAC (62%) followed by papillary adenocarcinoma (33%), whereas there were no tumors of predominantly solid adenocarcinoma with mucin. In contrast, of all consolidation-predominant tumors (C/T ratio >0.5), solid adenocarcinomas accounted for 11% (16 of 152) and BAC for only 22% (33 of 152; Table 4). There was a significant difference in the distribution of predominant subtypes between GGO-predominant and consolidation-predominant tumors ($p < 0.01$; Fisher's exact test).

On the univariate analysis, the C/T ratio cutoff levels of 0.0, 0.25, and 1.0 were not significantly associated with pathological lymph node metastasis. On multivariate analysis, the C/T ratio cutoff level of 0.75 was an independent predictor of node metastasis (odds ratio for C/T ratio >0.75, 3.4); however, a C/T ratio cutoff level of 0.5 was by far a stronger independent predictor (odds ratio for C/T ratio >0.5, >100; Table 5) than C/T ratio of 0.75.

DISCUSSION

Since 1995, lobectomy and lymph node dissection have been the standard therapy for stage IA lung cancer, because of the only randomized controlled trial reported by the Lung Cancer Study Group.[14] However, the development of CT technology and the widespread use of TSCT have enabled earlier

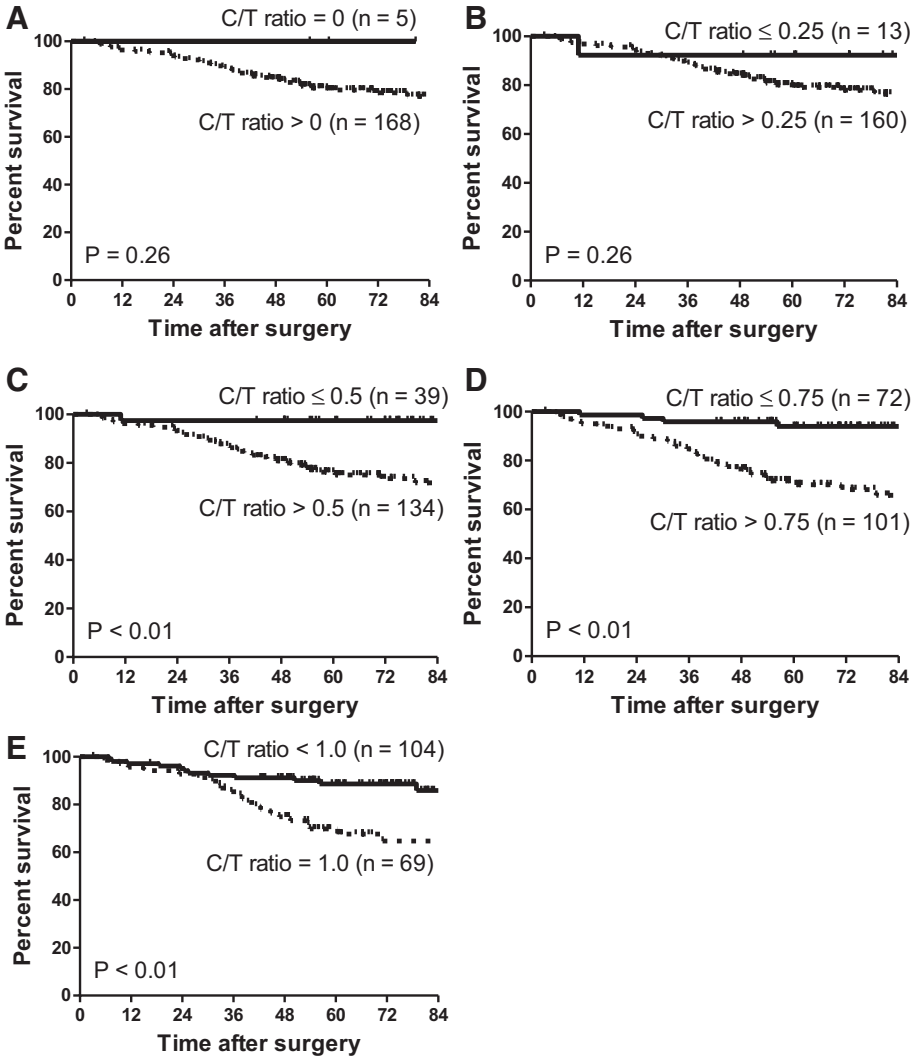

FIGURE 1. Overall survival comparison between two groups divided by C/T ratio. *A*, Cut-off level of C/T ratio at 0, (*B*) at 0.25, (*C*) at 0.5, (*D*) at 0.75, and (*E*) at 1.0. *p* was determined by the log-rank test. C/T, consolidation/tumor.

detection of primary lung cancers, particularly tumors with GGO components. Many retrospective studies[3–5,7,15–18] have focused on identifying less-invasive lung cancers on the basis of preoperative TSCT findings along with the recognition of BAC and Noguchi's classification.[16,19] On the basis of the findings from these retrospective studies, two trials of limited resection for small peripheral lung cancer according to C/T ratios determined on preoperative TSCT were initiated for patients with T1a lung cancer in Japan.[7,8,15,17] The results from these studies may change future surgical strategies for lung adenocarcinomas that are less than 2 cm in diameter.

In 2009, the TNM classification for primary lung cancer was revised, and T1 tumors were subcategorized as T1a (≤2.0 cm) and T1b (>2.0 cm and ≤3.0 cm) in the current 7th

TABLE 3. Relationship between Relapse Site and C/T Ratio

C/T Ratio	Total No. of Patients	No Recurrence	Locoregional Site Only	Including Distant Site
0 (Pure GGO)	5	5 (100)	0 (0)	0 (0)
0 < C/T ratio ≤ 0.25	8	8 (100)	0 (0)	0 (0)
0.25 < C/T ratio ≤ 0.5	26	26 (100)	0 (0)	0 (0)
0.5 < C/T ratio ≤ 0.75	33	27 (82)	4 (12)	2 (6)
0.75 < C/T ratio < 1.0	32	21 (66)	7 (22)	4 (13)
1 (Pure solid)	69	44 (64)	11 (16)	14 (20)

Numbers in parentheses are percentages.
C/T ratio, consolidation/tumor ratio; GGO, ground-glass opacity.

TABLE 4. Predominant Histological Subtype

C/T Ratio	C/T ≤0.5 (%) *n* = 39	0.5 < C/T < 1.0 (%) *n* = 83	C/T = 1.0 (%) *n* = 69
Bronchioloalveolar carcinoma	21 (62)	16 (19)	17 (25)
Papillary adenocarcinoma	13 (33)	38 (46)	32 (46)
Acinar adenocarcinoma	2 (5)	22 (27)	11 (16)
Solid adenocarcinoma with mucin	0 (0)	7 (8)	9 (13)

C/T ratio, consolidation/tumor ratio.

TABLE 5. Predictive Factor for Pathologic Lymph Node Metastasis

Variables	Univariate Analysis[a] *p* Value	Multivariate Analysis[b] Odds Ratio	95% CI	*p* Value
Sex (man)	0.46	3.53	0.72–18.77	0.12
Age (≥70)	1.00	1.07	0.38–3.26	0.90
Smoking history (smoker)	0.47	4.39	0.92–24.09	0.06
Preoperative serum CEA level (>5.0 ng/ml)	0.03	2.98	1.00–8.74	0.05
Tumor laterality (right/left)	0.80	NA	NA	NA
Tumor location (RUL/RML/RLL/LUL/LLL)	0.78	NA	NA	NA
Larger maximum tumor size (mm)	0.79	NA	NA	NA
C/T ratio (>0.5)	<0.01	>100	2.86-	<0.01

[a]Fisher's exact test or logistic analysis.
[b]Logistic regression analysis.
CI, confidence interval; CEA, carcinoembryonic antigen; NA, not applicable; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; C/T ratio, consolidation/tumor ratio.

TNM classification. Because most researchers have targeted peripheral early lung adenocarcinomas of 2 cm or less in diameter, we focused on T1b tumors and examined the possibility of limited resection for this population.

Aoki et al.[15] reported that patients who had tumors composed of less than 50% GGO showed significantly better outcomes than patients who had tumors composed of less than 50% GGO. They also pointed out that 17 patients with adenocarcinomas (<2 cm) that were composed of less than 50% GGO had no lymph node metastases or vessel invasion and developed no recurrence. However, the median follow-up period in that study was relatively short at 31 months, and the study did not separately examine cT1b patients.[15]

The present study showed that GGO-predominant tumors (C/T ratio ≤0.5) in patients with cT1b lung adenocarcinoma were nonaggressive adenocarcinomas, and no locoregional or distant metastases developed after lobectomy and lymph node dissection. Patients were observed for a minimum of 5 years. The result that no distant or lymph node metastases were observed in the GGO-predominant tumors strongly suggests that these tumors are localized. These results are compatible with those from a recent report on a prospective CT finding study in Japan to define nonaggressive adenocarcinoma of the lung.[20] These GGO-predominant tumors can most likely be cured by limited lung resection alone without lymph node dissection when an adequate margin is secured.

GGO components of lung tumors on TSCT histologically correspond to lepidic growth patterns of cancer cells, and central consolidation typically corresponds to alveolar collapse and/or fibrotic foci.[16,21] Kuriyama et al. reported that the measurement of the GGO area in a lung tumor was useful in differentiating localized BAC from invasive adenocarcinoma.[21] It may be difficult to clearly determine histological subtypes of adenocarcinoma on the basis of TSCT findings, but we found that no cT1b GGO-predominant (C/T ratio ≤0.5) lung adenocarcinomas were solid adenocarcinoma predominant. Solid adenocarcinoma with mucin is known to be highly aggressive, with frequent vessel invasion and lymph node metastases, and their surgical outcome is significantly poorer than that for other subtypes.[22] In consolidation-predominant (C/T ratio >0.5) tumors, solid adenocarcinomas with mucin were histologically predominant in approximately 10% cases. Patients with these tumors must be carefully evaluated before deciding whether limited resection or omission of lymph node dissection is indicated.

A limitation of this study is its retrospective nature. Because the C/T ratio is a subjective parameter, more objective and quantitative parameters of these nodules are sought. Further research is necessary to achieve good inter- and intraobserver reproducibility of C/T ratio. de Hoop et al.[23] reported mass value, which was calculated by multiplying nodule volume by mean nodule density on TSCT as an objective measurement. In the future, innovative developments in imaging technology may enable accurate diagnosis of less-invasive lung cancer comparable with pathological evaluation.

In conclusion, the C/T ratio of 0.5 or less identified early lung adenocarcinoma in patients with clinical T1bN0M0 disease. None of these tumors were solid adenocarcinoma predominant. The patients with these tumors had no lymph node involvement and developed no recurrence. These findings warrant a feasibility study of sublobar resection or reduction of the extent of mediastinal lymph node dissection for this population.

ACKNOWLEDGMENT

This study was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan.

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