A Prospective Radiological Study of Thin-Section Computed Tomography to Predict Pathological Noninvasiveness in Peripheral Clinical IA Lung Cancer (Japan Clinical Oncology Group 0201)

Kenji Suzuki, MD, Teruaki Koike, MD, Takashi Asakawa, BSc, Masahiko Kusumoto, MD, Hisao Asamura, MD, Kanji Nagai, MD, Hirohito Tada, MD, Tetsuya Mitsudomi, MD, Masahiro Tsuboi, MD, Taro Shibata, MSc, Haruhiko Fukuda, MD, and Harubumi Kato, MD, On behalf of the Japan Lung Cancer Surgical Study Group (JCOG LCSSG)

Purpose: Pathological noninvasiveness needs to be precisely predicted in preoperative radiological examinations of patients with early lung cancer for the application of limited surgery.

Patients and Methods: Patients with clinical T1N0M0 peripheral lung cancer were recruited. Radiological findings of the main tumor were evaluated as to ground-glass opacity with thin-section computed tomography. The primary end point was specificity, i.e., the proportion of patients with radiologically diagnosed invasive lung cancer to patients with pathologically diagnosed invasive lung cancer. The precision-based planned sample size was 450. We expected that the lower limit of the 95% confidence interval (CI) for specificity should be satisfied in ≥97% of patients.

Results: We enrolled 811 patients from 31 institutions between December 2002 and May 2004. The primary end point was evaluated in 545 patients. The specificity and sensitivity for the diagnosis of pathologically diagnosed invasive cancer were 96.4% (161/167, 95% CI: 92.3–98.7%) and 30.4% (115/378, 95% CI: 25.8–35.3%), respectively, i.e., a negative result. Nevertheless, the specificity for lung adenocarcinoma ≤2.0 cm with ≤0.25 consolidation to the maximum tumor diameter was 98.7% (95% CI: 93.2–100.0%), and this criterion could be used to radiologically define early adenocarcinoma of the lung.

Conclusions: Although our predetermined criterion for specificity was not statistically confirmed, radiological diagnosis of noninvasive lung cancer with a thin-section computed tomography scan corresponded well with pathological invasiveness. Radiological noninvasive peripheral lung adenocarcinoma could be defined as an adenocarcinoma ≤2.0 cm with ≤0.25 consolidation.

Key Words: Ground-glass opacity, Bronchioloalveolar carcinoma, Thin-section, Computed tomography, Limited resection.

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Lung cancer is the leading cause of cancer death worldwide.[1] Occult lymph node metastasis in hilum and mediastinum are found in approximately 15 to 20% in the literature[2,3]; however, a conventional preoperative workup cannot detect these metastases. Thus, a major lung resection with lymphadenectomy is recommended even for small-sized lung cancer.

There are two indications for the use of limited surgical resection. Some authors insist that only the size of the main tumor is an indication for limited surgical resection.[4–6] This strategy is supported by segmentectomy as the limited surgery and an intraoperative evaluation of the hilar lymph node. If there is lymph node involvement, then the surgery is converted from segmentectomy to major lung resection. Thus, diagnosis from intraoperative frozen sections of several lymph nodes is mandatory for this strategy, and a wide wedge resection, another limited surgical resection technique, is not suitable because it is impossible to evaluate the status of the hilar nodes using this approach. Conversely, a wide wedge resection can be used as a limited surgical resection for peripheral lung cancer.[7–9] This strategy should be adopted on the supposition that the lung cancer has not metastasized to the nodes. As the intraoperative nodal status cannot be estimated using a wide wedge resection, a preoperative evaluation of the primary tumor is vital. Preoperative predictors for the lack of metastasis to the lymph node are necessary for this strategy. The findings from thin-section computed tomogra-

Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo; Division of Chest Surgery, Niigata Cancer Center Hospital, Niigata; JCOG Data Center, Tokyo; Department of Thoracic Surgery, National Cancer Center Hospital East, Chiba; Department of General Thoracic Surgery, Osaka City General Hospital, Osaka; Department of Thoracic Surgery, Aichi Cancer Center, Aichi; and Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan.

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Address for correspondence: Kenji Suzuki, MD, Division of General Thoracic Surgery, Juntendo University School of Medicine, 1-3, Hongo 3 chome, Bunkyo-ku, Tokyo 113-8431, Japan. E-mail: kjsuzuki@juntendo.ac.jp

Kenji Suzuki is currently at Juntendo University School of Medicine, Tokyo, Japan.

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phy (CT) are reported to be the best predictors for the invasiveness and nodal status of lung cancers.[10–17] It has been proposed that lung cancer with a consolidation less than 50% of the maximum tumor diameter could be one of the most promising definitions to predict "early" lung cancer; however, this definition was derived from retrospective studies, and it should be confirmed in a prospective study.

Therefore, we performed a multiinstitutional prospective study for the radiological diagnosis of early lung cancer (Japan Clinical Oncology Group [JCOG] 0201) to assess these retrospective findings. If the validity of the criteria to radiologically diagnose "early" lung cancer is confirmed by this study, then a limited surgical resection could be used instead of a major lung resection.

PATIENTS AND METHODS

Patient Eligibility Criteria

The eligibility criteria were as follows: (1) a suspected or diagnosed lung cancer based on the findings from a plain x-ray and/or CT scan; (2) clinical stage IA, i.e., T1N0M0, by thoracic enhanced CT; (3) the center of the tumor was located peripherally, i.e., the outer half of the lung field on CT; (4) measurable at least in one dimension in thin section CT; (5) age range from 20 to 75 years, (6) no prior thoracotomy; (7) feasible for pulmonary lobectomy; and (8) obtained written informed consent.

The exclusion criteria included (1) synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ and (2) interstitial pneumonitis, lung fibrosis, or severe pulmonary emphysema.

All patients underwent a preoperative CT scan, and hilar or mediastinal nodes less than 1.0 cm in the shortest diameter were regarded as clinical N0. Disease stages were determined based on the tumor node metastasis classification of the International Union Against Cancer, 6th edition.[18] The study protocol was approved by the JCOG Clinical Trial Review Committee and by the institutional review board of each participating center. The JCOG Data Center conducted the central registration, data management, central monitoring, and statistical analysis.

Radiological Evaluation of the Primary Tumor

A contrast-enhanced CT scan was performed to evaluate the entire lung for preoperative staging. In addition, the main tumor was evaluated preoperatively to estimate the extent of ground-glass opacity (GGO) with thin-section helical CT scan with 1 to 3 mm collimation. Images were reconstructed with a field of view of 15 to 20 cm. The lung was photographed with a window level of −500 to −700 H and a window width of 1000 to 2000 H as a lung window setting, and with a window level of 30 to 60 H and a window width of 350 to 600 H as a mediastinal window setting. The evaluated factors on the lung window were the maximum diameters of the tumor and consolidation; the presence of a pleural tail; air bronchogram; the homogeneity of consolidation; and the sharpness of the tumor margin. The maximum tumor diameter was also evaluated from the mediastinal window. The consolidation component was defined as an area of increased opacification that completely obscured the underlying vascular markings. GGO was defined as an area of a slight, homogenous increase in density that did not obscure the underlying vascular markings.

Surgical Intervention

A preoperative needle biopsy or cytology was not required. When the diagnosis of lung adenocarcinoma was preoperatively made, a lobectomy and lymph node dissection were recommended; otherwise, an intraoperative frozen section diagnosis was performed, and if the tumor had histology other than adenocarcinoma, the protocol treatment was terminated, and the patients were excluded from the analysis. If the tumor was intraoperatively diagnosed as an adenocarcinoma, major lung resection and lymph node dissection were recommended. For some adenocarcinomas with large GGO areas, such as "pure GGO," a limited surgical resection was allowed, but this population was excluded from the primary end point analysis.

Pathological Diagnosis

The resected specimen was sectioned at intervals of 5 to 10 mm throughout the whole lung. The main tumor was sectioned into 2 to 4 mm slices, and the following pathological factors were evaluated by means of hematoxylin and eosin staining, and elastic fiber staining: histological typing; grade of differentiation; Noguchi's classification[19]; the maximum diameter of the main tumor and central fibrosis; pleural involvement; vascular invasion; lymphatic invasion; and intrapulmonary metastasis. Histological typing was determined according to the classification system of the World Health Organization.[20]

Study Design

Surgical resection was performed after the radiological evaluation of the peripherally located adenocarcinoma. The mode of surgery was basically a pulmonary lobectomy and lymph node dissection, and the postoperative pathological diagnosis was compared with the preoperative radiological diagnosis of early lung cancer. If the postoperative pathological diagnosis of "noninvasive adenocarcinoma" of the lung was predicted by the preoperative radiological diagnosis, a limited surgical resection or other nonsurgical local therapy was indicated.

Definition of Radiological Noninvasive and Invasive Lung Cancer

On the basis of retrospective findings,[10–15] radiological noninvasive lung cancer was tentatively defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter (consolidation/tumor ratio, C/T ratio) less than 0.5, indicating a tumor with a wide GGO area (Figure 1). Additionally, we adopted other criteria for radiological noninvasive lung cancer. One was the tumor shadow disappearance rate (TDR),[17] and the other was the visual estimation (VE) of the consolidation component.[11] TDR was evaluated from the maximum tumor diameter on the lung and mediastinum windows. TDR was calculated using the following formula: TDR = tumor size on mediastinal window/tumor

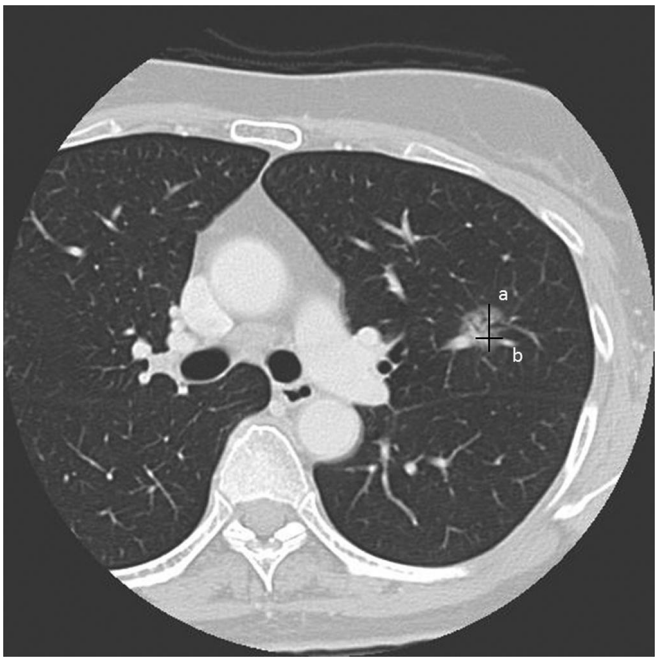

FIGURE 1. Example of radiological noninvasive lung cancer. The maximum diameter of consolidation (*B*) is less than the half of the maximum tumor diameter (*A*), which means tumor with wide area of ground glass opacity.

TABLE 1. Relationship Between Radiological and Pathological Features

	Pathological Diagnosis	
Radiological Diagnosis	**Noninvasive**	**Invasive**
Noninvasive[a]	A	C—undertreated
Invasive	B—overtreated	D

[a] Radiological noninvasive lung cancer was tentatively defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter <0.5 (see text).

Specificity = D/(C + D), sensitivity = A/(A + B), positive predictive value = A/(A + C), and negative predictive value =D/(B + D).

size on lung window. For VE, the consolidation component was defined as the proportion of the area of consolidation to that of the tumor visually estimated without measuring the diameter; a value less than 0.5 was diagnosed as noninvasive cancer. We compared the sensitivity and specificity of these three methods of radiological evaluation.

Definition of Pathological Noninvasive and Invasive Lung Cancer

The provisional pathological definition of noninvasive lung cancer was defined as a lung adenocarcinoma without nodal involvement, vascular invasion, or lymphatic invasion.

End Point and Planned Sample Size

The primary end point was the specificity based on the radiological diagnosis using the C/T ratio. The relationship between the radiological and pathological diagnoses is presented in Table 1. If limited surgical resection was performed on a patient with radiological noninvasive but pathological invasive cancer, the treatment was considered as "undertreatment" (group C, Table 1). Conversely, if major surgical resection was performed on a patient with radiological invasive but pathological noninvasive cancer, the treatment was defined as "overtreatment" (group B), and a limited surgical resection may be indicated. Patients with radiological and pathological noninvasive lung cancer belonged to group A; group D included patients with radiological and pathological invasive lung cancer. Considering that local recurrence of lung cancer results in a dismal prognosis, undertreatment should be avoided at any cost. Therefore, the number of patients belonging to "C" of Table 1 should be minimized, and the primary end point of specificity was defined as the proportion of patients with radiologically diagnosed invasive lung cancer in patients with pathologically diagnosed invasive lung cancer, i.e., D/(C + D). Conversely, patients with radiological invasive but pathological noninvasive lung cancer, who belong to category "B," may undergo overtreatment. The number of patients in the "B" category should be minimized, and sensitivity was selected as a secondary end point. Sensitivity was defined as the proportion of patients with radiologically diagnosed noninvasive cancer in patients with pathologically diagnosed noninvasive cancer, i.e., A/(A + B).

The primary end point was evaluated for the patients who were resected with a lobectomy and lymph node dissection, diagnosed with adenocarcinoma, and who were regarded as eligible in the radiological central review. We expected that the lower limit for the 95% confidence interval (CI) of specificity was satisfied in $\geq$97% of patients for an estimated sample size of 400 pathological invasive cancer cases. Assuming the sensitivity is 50% and the 95% CI range is $\leq$15%, the estimated sample size for pathological noninvasive cancer was 50 cases. The precision-based planned sample size was 450, i.e., $\geq$400 cases for pathological invasive cancers and $\geq$50 cases for pathological noninvasive cancers.

Central Review of Radiological Evaluation

To ensure the final diagnosis, radiological findings based on thin-section CT were reviewed by six reviewers. This radiological central review was indicated for patients who were preoperatively or intraoperatively diagnosed with adenocarcinoma. CT findings were evaluated coincidentally by the six reviewers, and the final results were decided in consensus.

Exploratory Analysis

We conducted additional exploratory analyses for patients with an adenocarcinoma $\leq$2.0 cm in size and evaluated the specificity and sensitivity. We also evaluated two other cutoff values for the C/T ratio on lung window, 0.25 and 0.75, to identify the optimal cutoff value to predict pathologically noninvasive adenocarcinoma of the lung.

RESULTS

Patients' Characteristics

Between December 2002 and May 2004, we enrolled 811 patients from 31 institutions. We expected that the number of pathological noninvasive and invasive cancers was 50 and 400, respectively; however, we recruited patients with

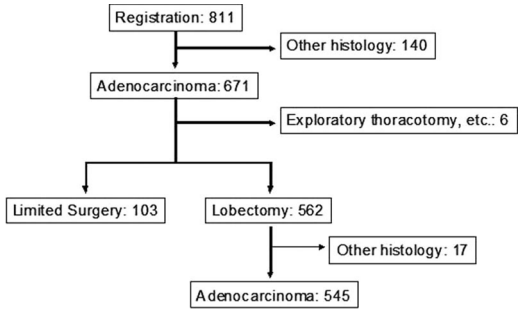

FIGURE 2. Scheme for study population. Finally, 545 patients with adenocarcinoma were the population for the primary analysis.

more pathological noninvasive and less invasive cancer than expected. Thus, we increased the total sample size to recruit more than 400 patients with pathological invasive cancer. Nevertheless, the primary end point proved to be lower than expected before sufficient numbers of pathological invasive cancer cases were recruited. Therefore, the accrual of patients was terminated before the planned period. We recruited 357 men and 454 women (age range, 27–75 years; median, 61 years). Among them, 671 (82.7%) patients were diagnosed with lung adenocarcinoma at the time of the surgical resection. The other cases included benign pathology or other type of cancers, such as pulmonary metastasis of colorectal cancer. Of the 671 patients with lung adenocarcinoma, 562 (83.8%) underwent major lung resection, 103 (15.3%) underwent limited resection, five (0.75%) underwent exploratory thoracotomy, and one underwent another procedure. Among the 562 patients, 17 (3.0%) patients were ineligible based on their postoperative pathological findings (Figure 2). Thus, the remaining 545 patients satisfied the inclusion criteria (described in the Patients and Methods section) and were taken into the primary analysis (Table 2).

TABLE 2. Characteristics of 545 Eligible Patients for the Investigation of the Primary Endpoint

Characteristics	Number of Patients
Clinical factors	
Gender	
Men	233
Women	312
Age range (median)	35–75 (62)
Maximum tumor dimension	
≤1.0cm	30
>1.0–2.0	270
>2.0–3.0	243
>3.0	2
Radiological factors	
Cons/Tumor ratio[a]	
Non-invasive (≤ 0.5)	137
The others (> 0.5)	381
TDR[b]	
Non-invasive (≤ 0.5)	234
The others (> 0.5)	311
Visual estimation of consolidation[c]	
Non-invasive (≤ 0.5)	200
The others (> 0.5)	345
Surgical factors	
Type of surgery	
Pneumonectomy	1
Lobectomy	544
Pathological factors	
Final histological diagnosis[d]	
Adenocarcinoma	529
Squamous cell carcinoma	7
Large cell carcinoma	4
Others	5
Lymph node metastasis	
Positive	47
Negative	498
Vascular invasion[e]	
Positive	100
Negative	443
Lymphatic invasion[f]	
Positive	113
Negative	428

[a] There were 27 cases of which tumors could not be evaluated the size of consolidation on lung window because of their unclear margin.
[b] TDR was calculated with the following formula: TDR = tumor size on mediastinal window/tumor size on lung window.
[c] The size of consolidation component was evaluated with visual estimation.
[d] Patients with adenocarcinoma which was diagnosed at the time of surgery were eligible and there were 16 patients with different final pathological diagnosis.
[e] There were one missing data and one unknown findings.
[f] There were one missing data and three unknown findings.
Cons, consolidation, TDR: tumor disappearance ratio.

Evaluation of the Primary End Point and Comparison among the Three Methods of Radiological Evaluation

The primary end point was evaluated among the 545 patients who met the inclusion criteria (Table 3). The specificity and sensitivity of the diagnosis for pathologically invasive cancer based on the C/T ratio from the lung window was 96.4% (161/167, 95% CI: 92.3–98.7%) and 30.4% (115/378, 95% CI: 25.8–35.3%), respectively. As a result, the lower 95% CI limit for specificity did not exceed the prespecified threshold of 97%. The specificity and sensitivity for the diagnosis of pathologically invasive cancer based on the TDR from the mediastinal window was 89.8% (150/167, 95% CI: 84.2–94.0%) and 44.4% (168/378, 95% CI: 39.4–49.6%), respectively. The most favorable specificity was obtained by the evaluation of the C/T ratio, and the lowest specificity was observed by the TDR method.

Radiological-Pathological Association in Lung Adenocarcinoma ≤2.0 cm in Size

Additional exploratory analysis was performed for lung adenocarcinoma ≤2.0 cm in size in the maximum tumor dimension to examine the appropriate tumor size for diagnosis of radiological early lung cancer. The specificity and sensitivity for the diagnosis of pathological invasive cancer based on the C/T ratio from the lung window was 97.5% (95% CI: 91.2–99.7%) and 31.0% (65/210, 95% CI: 24.8–37.7%), respectively. The point estimate of specificity was

TABLE 3. Relationship Between Radiological and Pathological Features in the 545 Eligible Cases

	Pathological Diagnosis[b]	
Radiology (Cutoff: 0.5)[a]	**Noninvasive**	**Invasive**
Consolidation/tumor ratio on lung window		
Noninvasive[a]	115	6
Invasive	263	161
Sensitivity		30.4% (95% CI: 25.8–35.3)
Specificity		96.4% (95% CI: 92.3–98.7)
TDR		
Noninvasive[a]	168	17
Invasive	210	150
Sensitivity		44.4% (95% CI: 39.4–49.6)
Specificity		89.8% (95% CI: 84.2–94.0)
Visual estimation of consolidation		
Noninvasive[a]	140	11
Invasive	238	156
Sensitivity		37.0% (95% CI: 32.2–42.1)
Specificity		93.4% (95% CI: 88.5–96.7)

[a] Radiological noninvasive lung cancer was tentatively defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter <0.5, indicating a tumor with a wide GGO area (see text).

[b] Pathological diagnosis was based on the criteria using nodal status, lymphatic invasion, and vascular invasion.

TDR, tumor disappearance ratio; CI, confidence interval; GGO, ground-glass opacity.

TABLE 4. Radiologic-Pathologic Correlation in Lung Cancer 2.0 cm or Less in Size (Cutoff: 0.25)

	Pathological Diagnosis[b]	
Radiology (Cutoff: 0.25)[a]	**Noninvasive**	**Invasive**
Consolidation/tumor ratio on lung window		
Noninvasive[a]	34	1
Invasive	176	78
Sensitivity	16.2% (95% CI: 11.5–21.9)	
Specificity	98.7% (95% CI: 93.2–100.0)	
TDR		
Noninvasive[a]	58	3
Invasive	152	76
Sensitivity	27.6% (95% CI: 21.7–34.2)	
Specificity	96.2% (95% CI: 89.3–99.2)	
Visual estimation of consolidation		
Noninvasive[a]	26	0
Invasive	184	79
Sensitivity	12.4% (95% CI: 8.3–17.6)	
Specificity	100.0% (95% CI: 95.4–100.0)	

[a] Radiological noninvasive lung cancer was tentatively defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter <0.25, indicating a tumor with a wide GGO area (see text).

[b] Pathological noninvasive is defined as adenocarcinoma with no nodal involvement, lymphatic invasion, or vascular invasion.

TDR, tumor disappearance ratio; GGO, ground-glass opacity; CI, confidence interval.

higher than observed in the primary analysis, but the lowest limit of the 95% CI for specificity was still lower than 97%.

Evaluation of the Optimal Cutoff Value for the C/T Ratio

Radiologically noninvasive lung cancer was primarily defined in this study as a C/T ratio less than 0.5 on thin-section CT; however, the specificity for this criterion was lower than expected, so we examined two other cutoff values, 0.25 and 0.75, for the C/T ratio in patients with lung adenocarcinoma ≤2.0 cm in size. As a result, the 0.25 cutoff value showed the highest specificity, although its sensitivity was relatively low (Table 4).

DISCUSSION

This is the first multiinstitutional prospective study on the definition of radiological early lung cancer. Several radiological criteria for early lung cancer have been reported, but these reports were based on retrospective and single institute analysis.[10–15] The majority of these reports supported the hypothesis that lung cancer with a consolidation less than 0.5 of the maximum tumor diameter and a wide GGO could be regarded as early lung cancer. If this hypothesis was correct, then a limited surgical resection, instead of lobectomy, should be sufficient to treat this population. Nevertheless, before generalizing the strategy, we had to confirm this hypothesis obtained from retrospective findings on a multiinstitutional basis. On the basis of our results, although the radiological findings of GGO and consolidation were well correlated with the pathologically invasive nature of the tumor, the radiological criteria for early lung cancer using the 50% cutoff value were not valid to predict pathological noninvasiveness. Thus, based on this exploratory analysis, lung carcinoma ≤2.0 cm in size and with a consolidation ≤25% of the maximum tumor diameter was considered to be radiological early lung cancer. We have just started a clinical trial to evaluate the validity of limited resection for lung cancer based on these criteria.

There has not been a general consensus formed on the optimal method to evaluate the extent of GGO. Three methods have been mainly reported: the C/T ratio from the lung window; the TDR from the mediastinal window; and the VE of the extent of GGO from the lung window. Each method has been reported as an optimal method based on a single institute retrospective analysis.[10–15] This study is the first prospective study to compare the three methods. The highest specificity was obtained from the C/T ratio and was the lowest for the TDR method. Conversely, the highest sensitivity was found with the TDR method, and the lowest was for the C/T ratio. Therefore, if the TDR method was used to determine radiological early lung cancer, more invasive cancers would be misdiagnosed as radiologically noninvasive. This situation should be avoided as much as possible because an invasive cancer would be resected using a limited resection that is ill suited for such cancers. Conversely, the C/T ratio provided clinically safe criteria to identify noninvasive cancers. On the basis of the primary analyses, the C/T ratio was the best criterion for the highest specificity. In this trial,

mode of surgery is not controlled for GGO lesions. Such GGO lesions were not included in the primary analysis because of limited surgery which was indicated for these. If these lesions were included for the analysis, sensitivity may increase with a slight decrease of specificity. The point estimate of specificity was much higher for lung cancer ≤2.0 cm in size. When the cutoff value was set as 0.25, the specificity was the highest. In short, a pathological noninvasive cancer can be predicted by a C/T ratio with a cutoff value of 0.25 and a specificity of 98.7% (95% CI: 93.2–100.0%) for lung cancer ≤2.0 cm in size. Thus, we prefer to use the criteria derived from the lung window to select candidates to undergo a limited resection.

Major lung resection has been recommended as a standard procedure, even for small-sized lung cancer, because lymph node metastasis can be found in approximately 15% of lung cancers ≤2.0 cm size.[2] Nevertheless, our radiological criteria could be used to predict pathological noninvasiveness, and such patients would be candidates to undergo a limited surgical resection. Limited pulmonary resection consists of wide wedge resection or segmentectomy. As for surgical invasiveness, a wedge resection can be performed with a smaller skin incision, reduced blood loss, and a shorter operation time. On the other hand, segmentectomy offers a sufficient surgical margin. To select the optimal limited resection, the key note is the status of lymph node metastasis. A wide wedge resection should be indicated for lung cancer without lymph node involvement.

In conclusion, although our predetermined criterion for specificity was not statistically confirmed, the radiological diagnosis of noninvasive lung cancer using a thin-section CT scan correlated well with pathological invasiveness based on the exploratory investigation. We are planning to perform a study of the efficacy of limited surgical resection for lung cancers selected by the criterion using a cutoff value of 0.25 and a maximum tumor diameter ≤2.0 cm in size. We will use a wide wedge resection as the limited surgical procedure because these cases have a limited potential for nodal involvement or lymphatic/vascular invasion. We are also planning to perform a phase III trial to compare pulmonary lobectomy and segmentectomy for lung cancer ≤2.0 cm in size, excluding patients with radiological noninvasive cancer. If we obtain positive results in these future clinical trials, it will present a good opportunity to change the standard treatment for early-stage lung cancer.

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