Radiologic Criteria in Predicting Pathologic Less Invasive Lung Cancer According to TNM 8th Edition

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Abstract

The optimal radiologic criteria of selecting a candidate for sublobar resection is still unclear. Our study indicated that tumors of clinical T1a or less and consolidation-to-tumor ratio, calculated with the maximum solid component diameter divided by the maximum tumor diameter, of 0.5 or less can predict pathologic less invasive (with no nodal involvement and no vessel invasion) lung cancer (specificity, 30.7%). Lung cancers with these radiologic criteria will be appropriate candidates for limited resection.

Purpose: The Japan Clinical Oncology Group Study 0201 has proposed radiologic criteria on thin-slice computed tomography to diagnose pathologic less invasive lung adenocarcinoma that could be a candidate for sublobar resection based on the previous tumor, node, metastasis classification system (TNM). The aim of this study was to propose the new radiologic criteria for predicting pathologic less invasive cancer according to the 8th edition TNM. **Patients and Methods:** We analyzed 744 patients who had peripheral clinical Tis-T1cN0M0 non–small-cell lung cancer of 3 cm or less and underwent complete resection by lobectomy from 2003 to 2011. We defined lung cancer with no nodal involvement and no vessel invasion pathologically as a pathologic less invasive cancer and investigated the radiologic criteria on the basis of the solid component size and by the consolidation-to-tumor (C/T) ratio (calculated with the maximum solid component diameter divided by the maximum tumor diameter) by using preoperative thin-slice computed tomography to predict them with a specificity of 97% or more, and evaluated overall survival. **Results:** Patients with clinical Tis/T1mi/T1a disease had no pathologic invasive cancer except for one patient (specificity, 99%). From the investigation with the C/T ratio, only the criterion of C/T ratio 0.5 or less met the standard (specificity, 100%). The final specificity after combining these criteria was 99.6%, and they showed excellent prognosis (5-year overall survival rate, 96.2%). **Conclusion:** Lung cancer with clinical Tis/T1mi/T1a or a C/T ratio of 0.5 or less can be completely cured by sublobar resection with sufficient margin because of its less invasive nature pathologically.

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Introduction

The standard procedure for operable lung cancers since 1960 remains lobectomy.[1] The only randomized controlled trial comparing lobectomy and limited resection indicated that limited resection should not be used even in patients with stage IA non–small-cell lung cancer (NSCLC).[2] However, as radiologic diagnostic modalities such as thin-slice computed tomography (TSCT) or positron emission tomography (PET) advance rapidly, the number of small lung cancers detected at early stages has been increasing in recent years. The Lung Cancer Surgical Study Group

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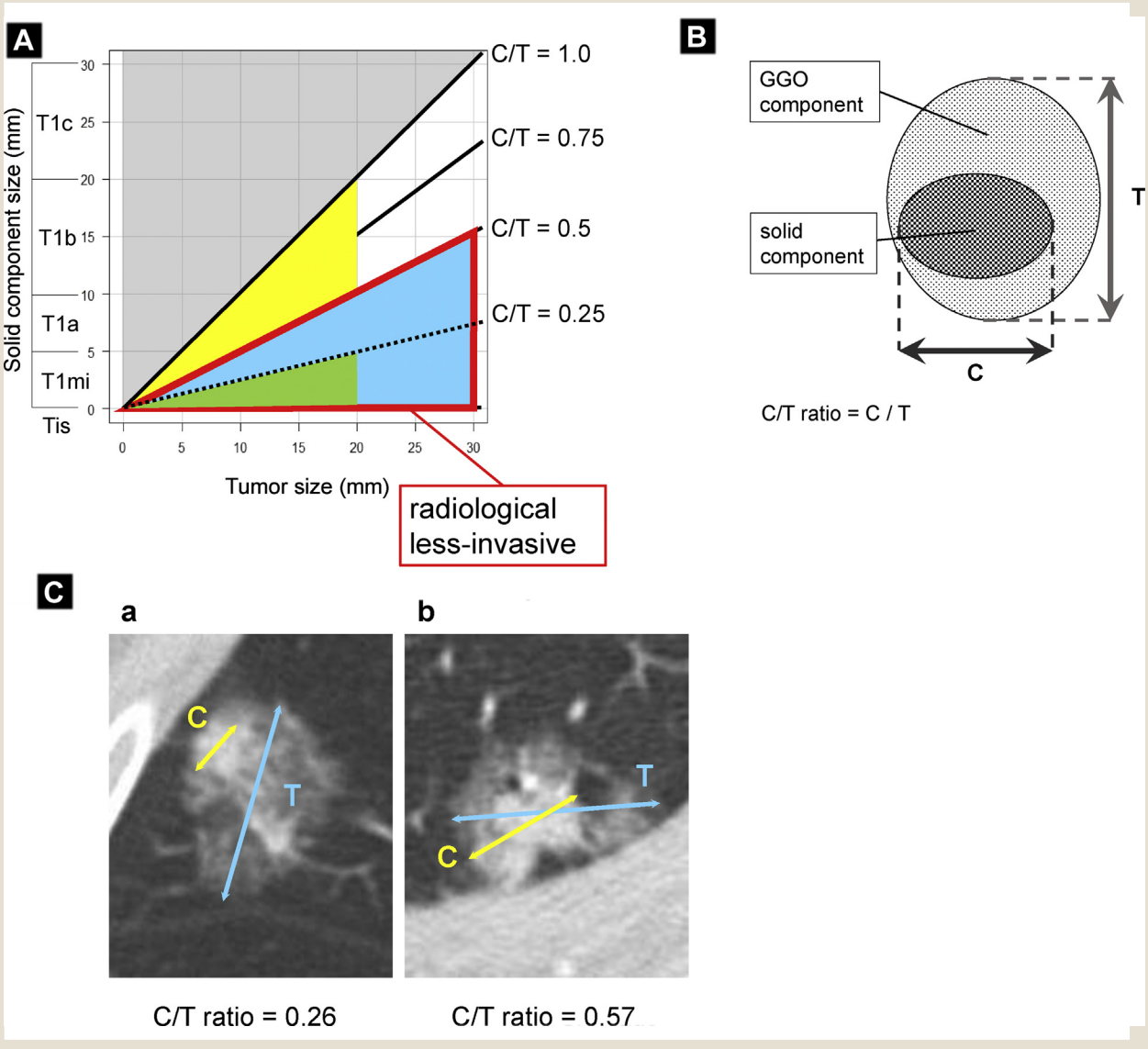
of the Japan Clinical Oncology Group (JCOG) has conducted a prospective study to propose the radiologic criteria predicting pathologic less invasive lung adenocarcinoma with no lymph node metastasis or vessel invasion (JCOG 0201 trial); radiologic less invasive lung tumor was defined as a lung tumor of 2 cm or less with a consolidation-to-tumor (C/T) ratio of 0.25 or less.[3] Subsequently, Asamura et al[4] reported that lung tumors of 3 cm or less with C/T ratio 0.5 or less also show extremely good prognosis. Because these tumors could also be leading candidates for limited resection, segmentectomy, or wide-wedge resection, 2 prospective trials targeting these tumors as well as another prospective trial related to limited resection have been ongoing in Japan (JCOG 0804, 1211, and 0802 trials) (Figure 1A).[5,6] However, the tumor, node, metastasis classification system (TNM) was drastically revised in 2016 and solid component size, except for the ground-glass opacity (GGO) component, was newly adopted as an important parameter by which to categorize T classification.[7-9] In this study, we reconsidered the optimal radiologic criteria by which to predict pathologic less invasive lung cancer based on solid component size.

Figure 1 **Prospective Trials Related to Limited Resection. (A) Distribution Map of Radiologic Less Invasive Tumors Defined by JCOG 0201 Trial, and Tumors Being Subject to Ongoing Phase 3 JCOG Clinical Trials Investigating Feasibility, Safety, or Noninferiority of Sublobar Resection. (B) Scheme of Measurement for Lung Cancer in Radiologic Findings on TSCT. (C) Solid Component Size (Without GGO Component) for (a) 8th and (b) 9th TNM. C/T Ratio Calculated as Maximum Diameter of Solid Component (Consolidation, C) Divided by Maximum Tumor Diameter (Tumor, T). C Indicates Solid Component Size (Without GGO Component) and T, Tumor Size With GGO Component**



Abbreviations: C/T ratio = consolidation-to-tumor ratio; GGO = ground-glass opacity; JCOG = Japan Clinical Oncology Group; TNM = tumor, node, metastasis classification system; TSCT = thin-slice computed tomography.

The aim of this study was to propose the new radiologic criteria by considering solid component size to predict pathologic less invasive lung cancer (with no lymph node metastasis or vessel invasion), which can be applied for limited resection.

Patients and Methods

Patients

We retrospectively evaluated patients who had peripheral clinical Tis-T1cN0M0 NSCLC with total tumor size of 3.0 cm or less and who underwent complete R0 resection by lobectomy or greater between January 2003 and December 2011 at our institution. A tumor whose center is located in the outer third of the lung field on TSCT is defined as a peripheral tumor. Patients receiving preoperative therapy or who had insufficient data were excluded from this cohort. In total, we analyzed the results of 744 patients in this study.

This retrospective study was conducted under the waiver of authorization approved by the National Cancer Center East institutional review board (no. 2016-399).

Radiologic Evaluation

We routinely performed preoperative TSCT within 60 days before surgery. The findings of preoperative TSCT images at 1 to 2 mm collimation were reviewed by 2 authors (S.K. and K.A.) to evaluate tumor size, solid component size, presence of GGO, C/T ratio, and other findings. C/T ratio was calculated with the maximum diameter of the solid component (consolidation, C) divided by the maximum tumor diameter (tumor, T) (Figure 1B, C). These findings were evaluated on a monitor display with a lung window, a window level of −600 Hounsfield units, and a window width of 1800 Hounsfield units. Measurement errors between the 2 observers were corrected by consensus. On the TSCT, the GGO area was defined as an increased hazy density area without obscuring the underlying vascular structure, and in contrast, the solid area was defined as an increased density area completely obscuring the underlying vascular structure. The C/T ratio was defined as the ratio of maximum solid component size to maximum tumor size on TSCT. Clinical lymph node staging was determined by contrast computed tomography, PET, or both. Mediastinal lymph node of greater than 1.0 cm in the shortest dimension on TSCT, and/or showing abnormal taking of ^{18}F-fluoro-2-deoxy-D-glucose, was defined as a node-positive tumor. As necessary, we performed endobronchial, ultrasound-guided, transbronchial needle aspiration cytology for clinical staging. Then we determined tumor stage according to the 8th edition of the TNM.

Pathologic Evaluation

All resected specimens were fixed in 10% formalin and embedded in paraffin. Serial 4 μm sections were stained with hematoxylin and eosin. Invasion of vascular or lymphatic vessels and pleural invasion were identified by hematoxylin and eosin and Victoria blue−van Gieson staining for visualizing elastic fibers. Histologic type and pathologic tumor size or invasive component size were reviewed by S.K. and G.I. according to the 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus and Heart. Staging of the tumor was based on the TNM of the International Association for the Study of Lung Cancer, 8th edition.

Sensitivity and Specificity Related to Radiologic Evaluation to Predict Pathologic Less Invasive Lung Cancer

Table 1 shows 2 × 2 tables of sensitivity and specificity related to radiologic evaluation to predict pathologic less invasive lung cancer. Patients in group C in Table 1 represented a radiologic less invasive tumor but showed invasive cancer pathologically. To perform limited resection for patients in this cohort is considered an undertreatment, causing an increasing local recurrence rate or unfavorable prognosis. It is necessary to decrease the number of patients in group C to avoid undertreatment, so that the specificity calculated by D/(C + D) must be as high as possible. Therefore, we set keeping high specificity as a primary object. On the other hand, the number of patients in group B who had radiologically invasive but pathologically less invasive cancers should have been minimized too. They risked overtreatment and the possibility of losing a chance to undergo limited resection, a function-preserving surgery. However, overtreatment may not cause a critical result, so we decided to keep a high level of sensitivity as a secondary object. Following a previous study,[3] we set the standard for specificity at 97% or more to minimize the number of cancers undertreated by limited resection and investigated the new radiologic criteria that could meet the standards with the highest sensitivity.

Survival Analysis

All patients were followed up for at least 5 years after surgery and up to 10 years. Survival information was obtained as much as possible by follow-up letters for up to 10 years when patients could not make regular clinic visits. The length of overall survival was defined as the period between the date of surgery and the last follow-up date or death by any cause. Observations were censored at the last follow-up at which the patient was alive or lost to follow-up. The data cutoff date was May 2016 at our institution.

The probability of overall survival by univariate analysis was evaluated by the Kaplan-Meier method, and the log-rank test was used to determine the differences in survival. Two-sided $P < .05$ was considered statistically significant. All data were analyzed by EZR 1.32 (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).[10]

Results

Patient Characteristics

The median follow-up period was 80.0 months (range, 0.6-150.6 months). Patient clinicopathologic characteristics are shown in

Table 1 Relationships of Clinical and Pathologic Findings

Clinical (Radiologic)[a]	Pathologic	
	Less Invasive	Invasive
Less invasive	A	C[b]
Invasive	B	D

Specificity = D/(C + D); sensitivity: A/(A + B).
[a]We investigated optimal criteria of clinical findings satisfying specificity of 97% or more.
[b]Number of tumors belonging to group C, having possibility of being undertreated, should be minimized.

Table 2 Characteristics of 744 Patients

Characteristic	N	%
Age, y		
<65	335	45
≥65	409	55
Sex		
Female	333	45
Male	411	55
Smoking History		
Never smoker	301	40
Current/former smoker	443	60
Preoperative Serum CEA Level		
≤5.0 ng/mL	568	76
>5.0 ng/mL	176	24
Clinical T Stage		
Tis	19	3
T1mi/T1a/T1b/T1c	38/92/333/262	5/12/45/35
C/T Ratio		
≤0.5	130	17
≤0.75	82	11
<1.0	52	7
=1.0	480	65
Presence of GGO		
Absent	455	61
Present	289	39
Pathological T Stage		
Tis	20	3
T1mi/T1a/T1b/T1c	84/124/245/121	11/17/33/16
T2a/T2b	137/2	18/0
T3	10	1
T4	1	0
Pathological N Stage		
N0	664	89
N1	31	4
N2	49	7
Histologic Type		
Adenocarcinoma	619	83
Squamous-cell carcinoma	84	11
Large-cell carcinoma	12	2
LCNEC	12	2
Adenosquamous-cell carcinoma	7	1
Pleomorphic carcinoma	10	1
Visceral Pleural Invasion		
Absent	595	80
Present	149	20
Pulmonary Metastasis		
Absent	737	99
Present	7	1
Lymphatic Permeation		
Absent	666	90
Present	78	10
Vascular Invasion		
Absent	547	74
Present	197	26
***EGFR* Mutation**		
Absent	177	24
Present	113	15
Not examined	454	61

Abbreviations: CEA = carcinoembryonic antigen; C/T ratio = consolidation tumor ratio; EGFR = epidermal growth factor receptor; GGO = ground glass opacity; LCNEC = large cell neuroendocrine carcinoma.

Table 2. About 55% of the patients were men, and 40% had never smoked. GGO presence was found in about 40% of patients, and all of them were adenocarcinoma pathologically. Pathologic lymph node metastasis was detected in 80 patients (11%), and lymphatic permeation and vascular invasion were detected in 78 (10%) and 197 (26%) patients, respectively. A total of 290 patients were examined for epidermal growth factor receptor (*EGFR*) mutation, and 113 had positive *EGFR* mutation.

Radiologic Characteristics of Pathologic Invasive or Less Invasive Tumors

Figure 2 shows radiologic characteristics of all 744 tumors, according to the preoperative radiologic findings. Black dots show the pathologic invasive tumors (239 cases), and empty dots represent pathologic less invasive tumors (505 cases). Tumors are marked in adequate position on the map on the basis of their radiologic findings. Most pathologic invasive tumors were distributed on a line of C/T ratio 1.0. There were a few pathologic invasive tumors in the clinical T1a (cT1a) or less category.

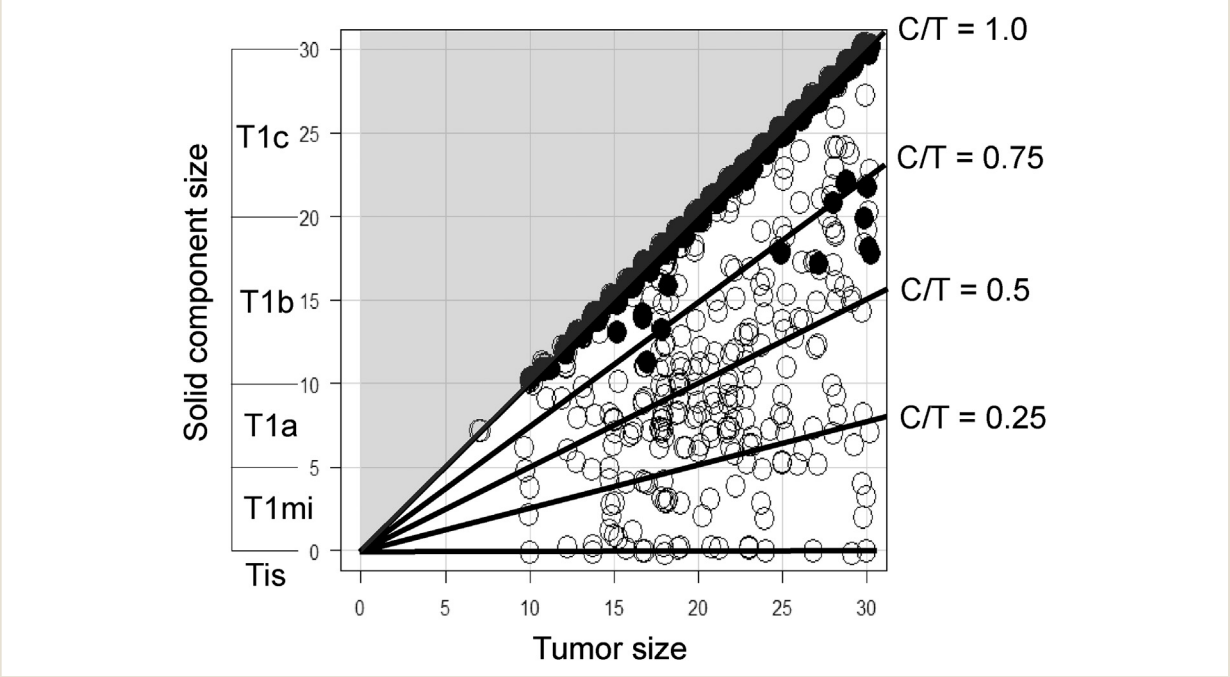
Solid Component Size for Predicting Pathologic Less Invasive Tumors

We investigated 3 radiologic criteria that were based on solid component size. These solid component size criteria included 10 mm or less (equivalent to cT1a or less), 15 mm or less, and 20 mm or less (equivalent to cT1b or less). The results with these criteria are shown in Table 3. For the criteria with a solid component size of 10 mm or less, only one tumor was pathologic invasive, so the specificity and sensitivity were 99.6% (238/239; 95% confidence interval [CI], 97.7-100.0) and 29.3% (148/505; 95% CI, 25.4-33.5), respectively. With the size of 15 mm or less, the specificity was 84.5% (202/239; 95% CI, 79.3-88.9), and with the size of 20 mm or less, specificity was 54.4% (109/239; 95% CI, 47.8-60.8). Only the specificity of the criterion with solid component size of 10 mm or less (equivalent to clinical T1a or less) met the prespecified threshold value of 97% or more.

C/T Ratio or GGO Presence for Predicting Pathologic Less Invasive Tumors

We investigated 3 radiologic criteria that were based on C/T ratio and the presence of GGO. These criteria included a C/T ratio of 0.5

Figure 2 Distribution Map of All Tumors (744 Cases). Black Colored Dots Indicate Pathologic Less Invasive Tumors; Hollow Dots, Pathologic Invasive Tumors. Vertical Axis Indicates Solid Component Size; Horizontal Axis, Tumor Size Including GGO Component; and Slope of Line, C/T ratio. Tumors Are Marked in Adequate Position on Map Based on Radiologic Findings. To Prevent Marks From Being Indistinct by Overlapping With Each Other, We Used a Jitter Function to Add a Small Amount of Noise to a Numeric Vector of Tumor Size and Solid Component Size



Abbreviations: C/T ratio = consolidation-to-tumor ratio; GGO = ground-glass opacity.

Table 3 Radiologic-Pathologic Correlation for Solid Component Size Criteria

Radiologic Feature (Solid Component Size)	Pathologic Diagnosis	
	Less Invasive	Invasive
Total	505	239
≤10 mm (≤Clinical T1a)		
Less invasive	148	1
Invasive	357	238
Specificity: 99.6% (95% CI, 97.7-100.0)		
Sensitivity: 29.3% (95% CI, 25.4-33.5)		
≤15 mm		
Less invasive	249	37
Invasive	256	202
Specificity: 84.5% (95% CI, 79.3-88.9)		
Sensitivity: 49.3% (95% CI, 44.9-53.8)		
≤20 mm (≤Clinical T1b)		
Less invasive	373	109
Invasive	132	130
Specificity: 54.4% (95% CI, 47.8-60.8)		
Sensitivity: 73.9% (95% CI, 69.8-77.6)		

Abbreviation: CI = confidence interval.

or less or of 0.75 or less, and tumors with a GGO component. The results are summarized in Table 4. For the criterion of C/T ratio 0.5 or less, the specificity and sensitivity were 100.0% (239/239; 95% CI, 97.7-100.0) and 25.7% (130/505; 95% CI, 22.0-29.8), respectively. In the case of C/T ratio 0.75 or less, the specificity and sensitivity were 96.2% (230/239; 95% CI, 93.0-98.3) and 40.2% (203/505; 95% CI, 35.9-44.6), respectively. For the criterion of the tumors with GGO, the specificity was 91.2% (218/239; 95% CI, 86.9-94.5). As a result, only the criterion of C/T ratio 0.5 or less exceeded the prespecified threshold value.

Survival Outcome With New Radiologic Criteria

We investigated the correlation of radiologic and pathologic findings and detected the new criteria that met the prespecified threshold value. Those were cT1a or less and C/T ratio 0.5 or less, and tumors meeting these criteria were considered less invasive tumors in this study (Figure 3A). The final specificity and sensitivity after combining these criteria were 99.6% (238/239; 95% CI, 97.7-100.0) and 30.7% (155/505; 95% CI, 26.7-34.9), respectively (data not shown). Finally, we investigated the prognostic value of the new criteria. Comparison of radiologic less invasive tumors and invasive tumors for overall survival is shown in Figure 3B. Overall survival was significantly better in radiologic less invasive tumors than in invasive tumors ($P < .01$). Therefore, these radiologic criteria were also reasonable from the prognostic standpoint.

Table 4 Radiologic-Pathologic Correlation for C/T Ratio or Presence of GGO

Radiologic Feature	Pathologic Diagnosis	
	Less Invasive	Invasive
Total	505	239
C/T Ratio ≤ 0.5		
Less invasive	130	0
Invasive	375	239
Specificity: 100.0% (95% CI, 97.7-100.0)		
Sensitivity: 25.7% (95% CI, 22.0-29.8)		
C/T Ratio ≤ 0.75		
Less invasive	203	9
Invasive	302	230
Specificity: 96.2% (95% CI, 93.0-98.3)		
Sensitivity: 40.2% (95% CI, 35.9-44.6)		
Tumors With GGO Component		
Less invasive	268	21
Invasive	237	218
Specificity: 91.2% (95% CI, 86.9-94.5)		
Sensitivity: 53.1% (95% CI, 48.6-57.5)		

Abbreviations: CI = confidence interval; C/T ratio = consolidation tumor ratio; GGO = ground glass opacity.

Discussion

To select the optimal patient for limited resection, including wide-wedge resection, absence of lymph node metastasis is a key factor.[11] In addition, many researchers reported that lymphatic permeation or blood vessel invasion affected the survival of patients even with pathologic N0 disease.[12-15] The JCOG 0201 trial was conducted on the basis of this idea, and from its result, prospective trials related to limited resection have been ongoing in Japan (Figure 1A). Therefore, following the previous study, we defined NSCLC with no nodal involvement and no vessel invasion (both lymphatic and blood) pathologically as a pathologic less invasive cancer. In this study, we took the solid component size into consideration and reassessed the criteria of less invasive cancer. It was clear at a glance that most pathologic invasive tumors were distributed on a line of C/T ratio 1.0 (Figure 2, black dots), and almost all of the pathologic invasive tumors were in the cT1b or cT1c area. These findings are consistent with previous reports; Hattori et al[16] reported that pure-solid tumors had a small number of lepidic predominant adenocarcinoma and were associated with more presence of nodal involvement, lymphovascular invasion, or pathologically advanced-stage disease. Table 2 shows that tumors classified as T1a or less were considered radiologically less invasive. Particularly, as for the patients with subcentimeter tumors, no one experienced cause-specific death (data not shown). These results again indicated that invasive component size was associated with tumor malignancy and had a great impact on patient prognosis.

In the evaluation of C/T ratio or presence of GGO, C/T ratio 0.5 or less met the prespecified threshold value. This result was consistent with many previous reports,[17,18] but it is little different from the results of the JCOG 0201 trial. In that trial, they investigated only adenocarcinomas, and the same criteria (C/T ratio 0.5 or less) did not meet the prespecified threshold value of 97%. In contrast, we included nonadenocarcinoma tumors located peripherally as well. Because many of the early-stage small tumors located peripherally cannot be examined histologically before surgery, we think including nonadenocarcinoma tumors in this investigation is important. Moreover, some previous studies reported a strong correlation between the sizes of the solid component determined by TSCT and the pathologically invasive component.[19,20] Kadota et al[21] reported that patients with > 50% lepidic pattern tumors had no recurrences, and Lee et al[22] reported similar results. These findings also support our results.

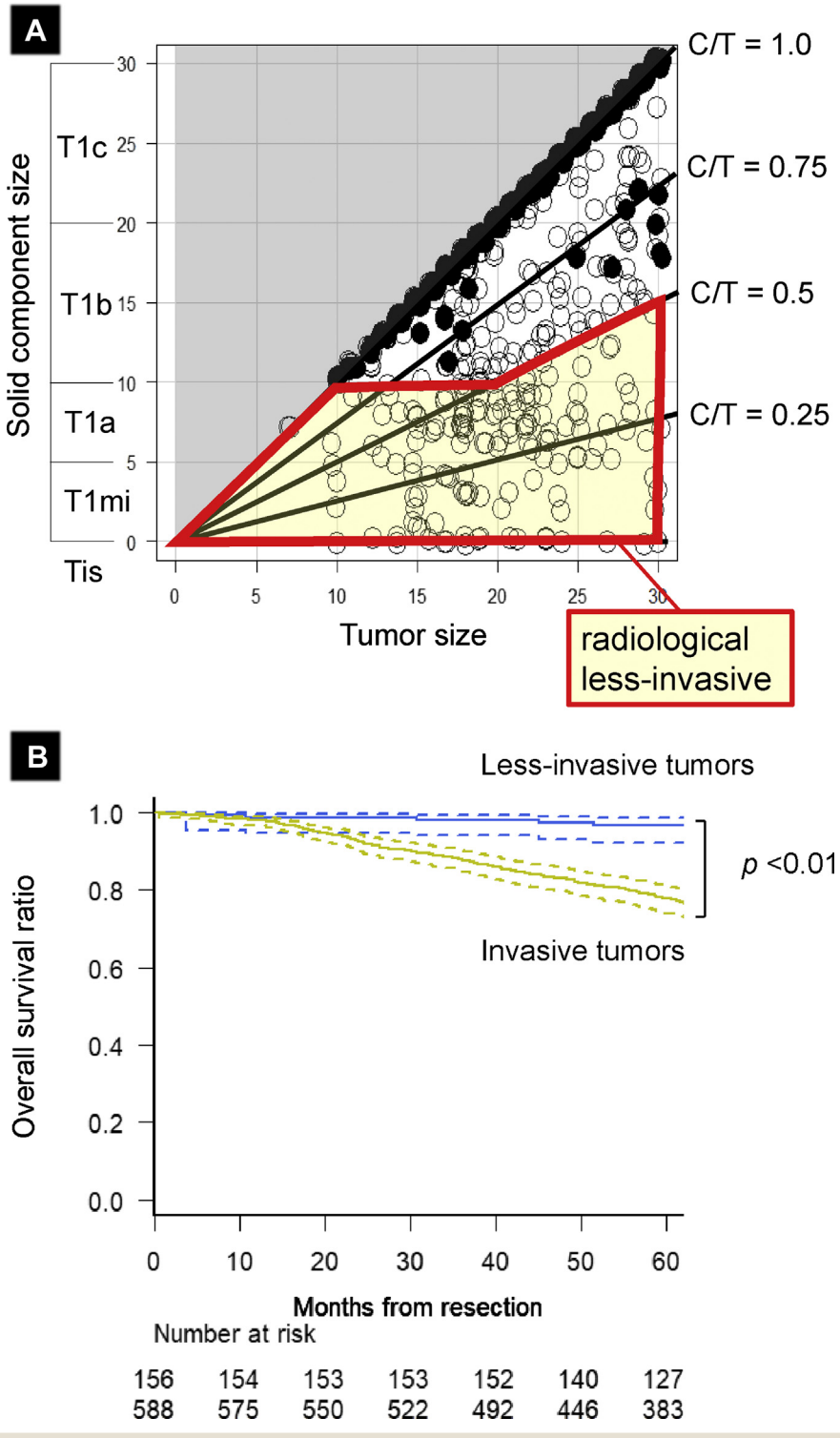
From the pathologic standpoint, we previously reported that adenocarcinomas containing lepidic component are less invasive with less metastatic potential.[23] But tumors with GGO presence could not meet the criteria in the current study. It is difficult to explain these findings; however, Aokage et al[20] reported that there was still a little difference between clinical and pathologic invasive size. Possibly lepidic-negative adenocarcinomas were included in GGO-positive tumors.

In the current study, the new criteria of radiologic less invasive tumors showed an excellent prognosis for overall survival. From the prognostic standpoint, the new criteria can be considered a reasonable standard.

The scope of the radiologic less invasive tumors in our study was similar to the previous study; however, it was different on a few points (Figure 1A and Figure 3A).[3,24] First, cT1a tumors with C/T ratio greater than 0.5 were considered radiologic less invasive tumors in our study. This result might depend on a relatively small invasive component. We think we can perform limited resection for this group with new prospective studies in the future. Second, among the tumors with total tumor size of 2 cm or less, we detected many pathologic invasive tumors in cT1b with C/T ratio > 0.5 tumors. We must be careful when performing limited resection for those tumors because of their invasive nature, but the prognosis of the tumors with total tumor size of 2 cm or less was reported to be good,[25,26] so we should assess this in prospective studies. Those tumors were included in the ongoing study of the JCOG 0802 trial for noninferiority of segmentectomy in Japan and in a randomized control trial, launched in an attempt to compare limited resection (segmentectomy or wedge resection) and lobectomy (CALGB-140503, NCT00499330; ClinicalTrials.gov) in the United States. Those results are yet to be published.

There are several limitations to this study. First, this was a retrospective study of a single institution's database. Second, a precise measurement of the solid component in TSCT is controversial worldwide because evaluation of the GGO component often differs between observers. Given that, it was reported that the agreement between observers for subclassification in adenocarcinoma is difficult.[27,28] To minimize the influence, we evaluated all patients with preoperative TSCT images; these were reviewed by 2 authors independently, and the discrepancies of measuring results between observers were then corrected by consensus. However, we did not assess the concordance rate between observers, so improving the agreement of the observers is a challenge for future investigation. Third, we investigated a small number of pure-solid, subcentimeter tumors, so even for a cT1a status, whether a pure-solid tumor is less invasive was

Figure 3 New Criteria Meeting Prespecified Threshold Value. (A) Distribution Map of Radiologic Less Invasive Tumors Selected With New Criteria Indicated by Our Study. New Criteria of Radiologic Less Invasive Tumors Are Tumors of cT1a or Less, or C/T Ratio of 0.5 or Less. (B) Overall Survival Curves Based on Radiologic Findings Indicated by Our Study. Blue Line Indicates Radiologic Less Invasive Tumors; Yellow Line, Radiologic Invasive Tumors; and Dotted Line, Range of 95% CI. Five-year Overall Survival Rates Are 96.2% in Radiologic Less Invasive Tumors and 75.7% in Invasive Tumors



Abbreviations: CI = confidence interval; C/T ratio = consolidation-to-tumor ratio.

unclear. Sakurai et al[29] reported that subcentimeter tumors without a GGO component had pathologic nodal involvement at the rate of 10%. Hattori et al[30] also reported that standardized maximum uptake value on PET had a prognostic impact for subcentimeter NSCLC, especially in a pure-solid tumor. Including standardized maximum uptake value on PET in preoperative criteria may contribute to predicting less invasive tumors more precisely.[31]

Conclusion

We determined new criteria of radiologically less invasive cancer in patients who could be appropriate candidates for limited resection. cT1a or less and C/T ratio of 0.5 or less tumors were radiologically less invasive and had excellent prognosis. Further prospective study is required to confirm our hypothesis.

Clinical Practice Points

- As radiologic diagnostic modalities advance rapidly, the number of early-stage lung cancers has been increasing in recent years.
- Limited resection for early-stage NSCLC located peripherally has been suggested as function-preserving surgery.
- On the basis of the 7th TNM, JCOG 0201 has proposed radiologic criteria on TSCT to diagnose pathologic less invasive lung adenocarcinoma. However, TNM was revised into the 8th edition, and solid component size was newly adopted as an important parameter by which to categorize T classification. Many early-stage NSCLC located peripherally cannot be examined histologically before surgery.
- The optimal radiologic criteria of selecting a candidate for limited resection is still unclear.
- By retrospectively analyzing 744 patients who had peripheral clinical Tis-T1cN0M0 NSCLC of 3 cm or less in size, our study indicated that clinical T1a or less and C/T ratio 0.5 or less tumors can predict pathologic less invasive (with no nodal involvement and no vessel invasion) lung cancer (specificity, 30.7%). They also showed excellent prognosis (5-year overall survival rate, 96.2%).
- To our knowledge, this is the first study to propose the preoperative radiologic criteria by considering solid component size to predict pathologic less invasive lung cancer.
- Solid component size and C/T ratio on preoperative TSCT had a great potential to predict invasiveness of lung cancer, which will help the surgeon to plan limited resection for less invasive tumors with a good outcome.

Disclosure

The authors have stated that they have no conflict of interest.

References

1. Cahan WG. Radical lobectomy. *J Thorac Cardiovasc Surg* 1960; 39:555-72.
2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non—small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995; 60:615-22.
3. Suzuki K, Koike T, Asakawa T, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). *J Thorac Oncol* 2011; 6:751-6.
4. Asamura H, Hishida T, Suzuki K, et al. Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201. *J Thorac Cardiovasc Surg* 2013; 146:24-30.
5. Nakamura K, Saji H, Nakajima R, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non—small cell lung cancer (JCOG0802/WJOG4607L). *Jpn J Clin Oncol* 2010; 40:271-4.
6. Aokage K, Yoshida J, Hishida T, et al. Limited resection for early-stage non—small cell lung cancer as function-preserving radical surgery: a review. *Jpn J Clin Oncol* 2017; 47:7-11.
7. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015; 10:990-1003.
8. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2016; 11:1204-23.
9. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11:39-51.
10. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013; 48:452-8.
11. Speicher PJ, Gu L, Gulack BC, et al. Sublobar resection for clinical stage Ia non—small-cell lung cancer in the United States. *Clin Lung Cancer* 2016; 17:47-55.
12. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Prognostic impact of intratumoral vascular invasion in non—small cell lung cancer patients. *Thorax* 2010; 65:1092-8.
13. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Risk factors for tumor recurrence in patients with early-stage (stage I and II) non—small cell lung cancer: patient selection criteria for adjuvant chemotherapy according to the seventh edition TNM classification. *Chest* 2011; 140:1494-502.
14. Tsuchiya T, Akamine S, Muraoka M, et al. Stage IA non—small cell lung cancer: vessel invasion is a poor prognostic factor and a new target of adjuvant chemotherapy. *Lung Cancer* 2007; 56:341-8.
15. Tao H, Hayashi T, Sano F, et al. Prognostic impact of lymphovascular invasion compared with that of visceral pleural invasion in patients with pN0 non—small-cell lung cancer and a tumor diameter of 2 cm or smaller. *J Surg Res* 2013; 185:250-4.
16. Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Oncological characteristics of radiological invasive adenocarcinoma with additional ground-glass nodules on initial thin-section computed tomography: comparison with solitary invasive adenocarcinoma. *J Thorac Oncol* 2016; 11:729-36.
17. Ohde Y, Nagai K, Yoshida J, et al. The proportion of consolidation to ground-glass opacity on high resolution CT is a good predictor for distinguishing the population of non-invasive peripheral adenocarcinoma. *Lung Cancer* 2003; 42:303-10.
18. Kodama K, Higashiyama M, Yokouchi H, et al. Prognostic value of ground-glass opacity found in small lung adenocarcinoma on high-resolution CT scanning. *Lung Cancer* 2001; 33:17-25.
19. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011; 6:244-85.
20. Aokage K, Miyoshi T, Ishii G, et al. Clinical and pathological staging validation in the eighth edition of the TNM classification for lung cancer: correlation between solid size on thin-section computed tomography and invasive size in pathological findings in the new T classification. *J Thorac Oncol* 2017; 12:1403-12.
21. Kadota K, Villena-Vargas J, Yoshizawa A, et al. Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. *Am J Surg Pathol* 2014; 38:448-60.
22. Lee HY, Han J, Lee KS, et al. Lung adenocarcinoma as a solitary pulmonary nodule: prognostic determinants of CT, PET, and histopathologic findings. *Lung Cancer* 2009; 66:379-85.
23. Katsumata S, Aokage K, Miyoshi T, et al. Differences of tumor microenvironment between stage I lepidic-positive and lepidic-negative lung adenocarcinomas. *J Thorac Cardiovasc Surg* 2018; 156:1679-88.e1672.
24. Nakagawa K, Watanabe SI, Kunitoh H, Asamura H. The Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group: past activities, current status and future direction. *Jpn J Clin Oncol* 2017; 47:194-9.
25. Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. *J Thorac Cardiovasc Surg* 2014; 147:754-62.
26. Su H, Dai C, Xie H, et al. Risk factors of recurrence in patients with clinical stage IA adenocarcinoma presented as ground-glass nodule. *Clin Lung Cancer* 2018; 19:e609-17.
27. Noguchi M, Minami Y, Iijima T, Matsuno Y. Reproducibility of the diagnosis of small adenocarcinoma of the lung and usefulness of an educational program for the diagnostic criteria. *Pathol Int* 2005; 55:8-13.
28. Thunnissen E, Beasley MB, Borczuk AC, et al. Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. *Mod Pathol* 2012; 25:1574-83.
29. Sakurai H, Nakagawa K, Watanabe S, Asamura H. Clinicopathologic features of resected subcentimeter lung cancer. *Ann Thorac Surg* 2015; 99:1731-8.
30. Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Clinical significance of positron emission tomography in subcentimeter non—small cell lung cancer. *Ann Thorac Surg* 2017; 103:1614-20.
31. Fu L, Alam MS, Ren Y, et al. Utility of maximum standard uptake value as a predictor for differentiating the invasiveness of T1 stage pulmonary adenocarcinoma. *Clin Lung Cancer* 2018; 19:221-9.