context (Figure 1). Here are only some of the topics that are under investigation in early stages: the extent of parenchymal resection, the role of robotic surgery, a better definition of the role of SBRT, the role of IMRT as adjuvant treatment, and an update of the PORT meta-analyses, which will include last-generation radiation techniques. In the area of systemic treatment, the impact of pharmacogenomic factors, definition of prognostic and predictive factors, and the role of targeted drugs and immunotherapy are only some of the main themes worth of investigation.

The IASLC is the only international association grouping together all the specialists involved in the early disease approach and, consequently, the only scientific association potentially able to promote and support initiatives devoted to implement knowledge in this field.

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Review Article

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Correlation between whole tumor size and solid component size on high-resolution computed tomography in the prediction of the degree of pathologic malignancy and the prognostic outcome in primary lung adenocarcinoma

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Abstract

Background: The presence of ground glass opacity (GGO) on high-resolution computed tomography (HRCT) is well known to be pathologically closely associated with adenocarcinoma in situ.

Purpose: To determine whether it is more useful to evaluate the whole tumor size or only the solid component size to predict the pathologic high-grade malignancy and the prognostic outcome in lung adenocarcinoma.

Material and Methods: Using HRCT data of 232 patients with adenocarcinoma who underwent curative resection, we retrospectively measured the whole tumor and solid component sizes with lung window setting (WTLW and SCLW) and whole tumor sizes with a mediastinal window setting (WTMW).

Results: There was significant correlation between the WTLW and the measurements of pathological whole tumor (pWT) ($r = 0.792$, $P < 0.0001$). The SCLW and WTLW values significantly correlated with the area of pathological invasive component (pIVS) ($r = 0.762$, $P < 0.0001$ and $r = 0.771$, $P < 0.0001$, respectively). The receiver operating characteristics area under the curve for WTLW, SCLW, and WTMW used to identify lymph node metastasis or lymphatic or vascular invasion were 0.693, 0.817, and 0.824, respectively. Kaplan-Meier curves of disease-free survival (DFS) and overall survival (OS) were better divided according to SCLW and WTMW, compared with WTLW. Multivariate analysis of DFS and OS revealed that WTMW was an independent prognostic factor (HR = 0.72, 95% confidence interval [CI] = 0.58–0.90, $P = 0.004$ and HR = 0.74, 95% CI = 0.57–0.96, $P = 0.022$, respectively).

Conclusion: The predictive values of the solid tumor size visualized on HRCT especially in the mediastinal window for pathologic high-grade malignancy and prognosis in lung adenocarcinoma were greater than those of whole tumor size.

Keywords
Lung adenocarcinoma, prognosis, solid component, ground glass nodule, high-resolution computed tomography

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Introduction

The National Lung Screening Trial demonstrated a significant reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% confidence interval [CI], 6.8–26.7; $P = 0.004$) (1). Recent advances in

high-resolution computed tomography (HRCT) and the widespread application of CT screening due to the positive results of screening CT trial have enhanced the discovery of small lung cancers, particularly adenocarcinoma (1). These often contain a non-solid component that presents as ground glass opacity (GGO) features on HRCT. Several investigators have reported that GGO is closely associated with bronchioloalveolar carcinoma (BAC) (2).

Recently, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society proposed a new classification of lung adenocarcinoma. The terms BAC and mixed subtype adenocarcinoma are no longer used. For resected specimens, new concepts have been introduced such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) for small solitary adenocarcinomas with either pure lepidic growth: AIS or predominantly lepidic growth with 5 mm invasion and MIA to define patients who, if they undergo complete resection, will have 100% or near 100% disease-specific survival rates, respectively (3,4). We therefore hypothesized that the GGO component is not related to malignancy or prognosis, implying that only the solid component of the tumor on HRCT (solid tumor size) is indicative of malignancy and prognosis in lung adenocarcinoma.

In this study, we first compared the whole tumor and solid component size, excluding areas of GGO, on preoperative HRCT with a lung window setting and whole tumor size with a mediastinal window setting with pathological whole tumor size and the area of pathologically confirmed invasion. We then determined whether it is more useful to evaluate the whole tumor size or that of only the solid component size to predict the degree of malignancy including lymph node involvement, lymphatic invasion, or vascular invasion of tumors in lung adenocarcinoma.

Material and Methods

Patients

Using preoperative HRCT data of 277 consecutive patients with adenocarcinoma who underwent curative surgical resection from January 2005 to December 2007, we retrospectively measured the whole tumor size and solid component size as follows: the whole tumor and solid component size was measured with lung window setting (WTLW and SCLW) and whole tumor size, with a mediastinal window setting (WTMW) on HRCT. Staging was determined according to the 7th edition of the TNM staging system (5). The histological tumor type was determined according to the World Health Organization (WHO) classification, 3rd edition. In addition, we measured the maximum size of the area pathologically confirmed invasion for this study. We excluded 21 patients with adenocarcinoma with scattered invasive components for this analysis, due to difficulty in measuring not only the pathological invasive area but also the size of the solid component radiologically. Twenty-four patients with inappropriate tissue samples were also excluded following induction therapy or divided tumor resection due to intraoperative frozen diagnosis. Ultimately, 232 consecutive patients with adenocarcinomas were enrolled in this study. Radiological and pathological findings were conducted by SA and JP, and JM and TN, respectively, who were blinded from any clinical information.

Patients were examined at 3-month intervals for the first 2 years and at 6-month intervals for the next 3 years and thereafter on an outpatient basis. The follow-up evaluation involved the following procedures: physical examination, chest radiography, CT of the chest and abdomen, and blood examination, including that of pertinent tumor markers. Further evaluations, including brain magnetic resonance imaging or CT, bone scintigraphy and integrated positron emission tomography, were performed on the first appearance of any symptom or sign of recurrence. The median follow-up time of this series was 4.4 years.

HRCT scanning

Chest images were obtained using 64-detector row CT scanners (LightSpeed VCT: GE Healthcare, Milwaukee, WI, USA and SOMATOM Sensation Cardiac 64: Siemens Medical Systems, Erlangen, Germany) and a 16-detector row CT scanner (BrightSpeed Elite: GE Healthcare, Milwaukee, WI, USA). High-resolution images of the tumors were acquired using the following parameters: 120 kV and auto exposure control; collimation, 0.6–1.25 mm; pitch, 0.9–0.984; 0.4–0.5 s per rotation; reconstructed interval, 1.25–1.5 mm; pixel resolution, 512 × 512; field of view, 20 cm; and a lung window settings (level = −500/width = 1500 HU) with high spatial frequency algorithm and mediastinal window settings (level = 40/width = 320 HU) with soft-tissue algorithm. GGO was defined as an increase in lung attenuation that did not obscure the underlying vascular markings. We defined the solid tumor size as the maximum dimension of the solid component of the lung windows excluding GGO (SCLW) or the maximum dimension of the whole tumor size of mediastinal setting (WTMW) (Fig. 1a and b).

Pathological findings

Histopathological studies were performed according to WHO criteria, 3rd edition (6). All resected

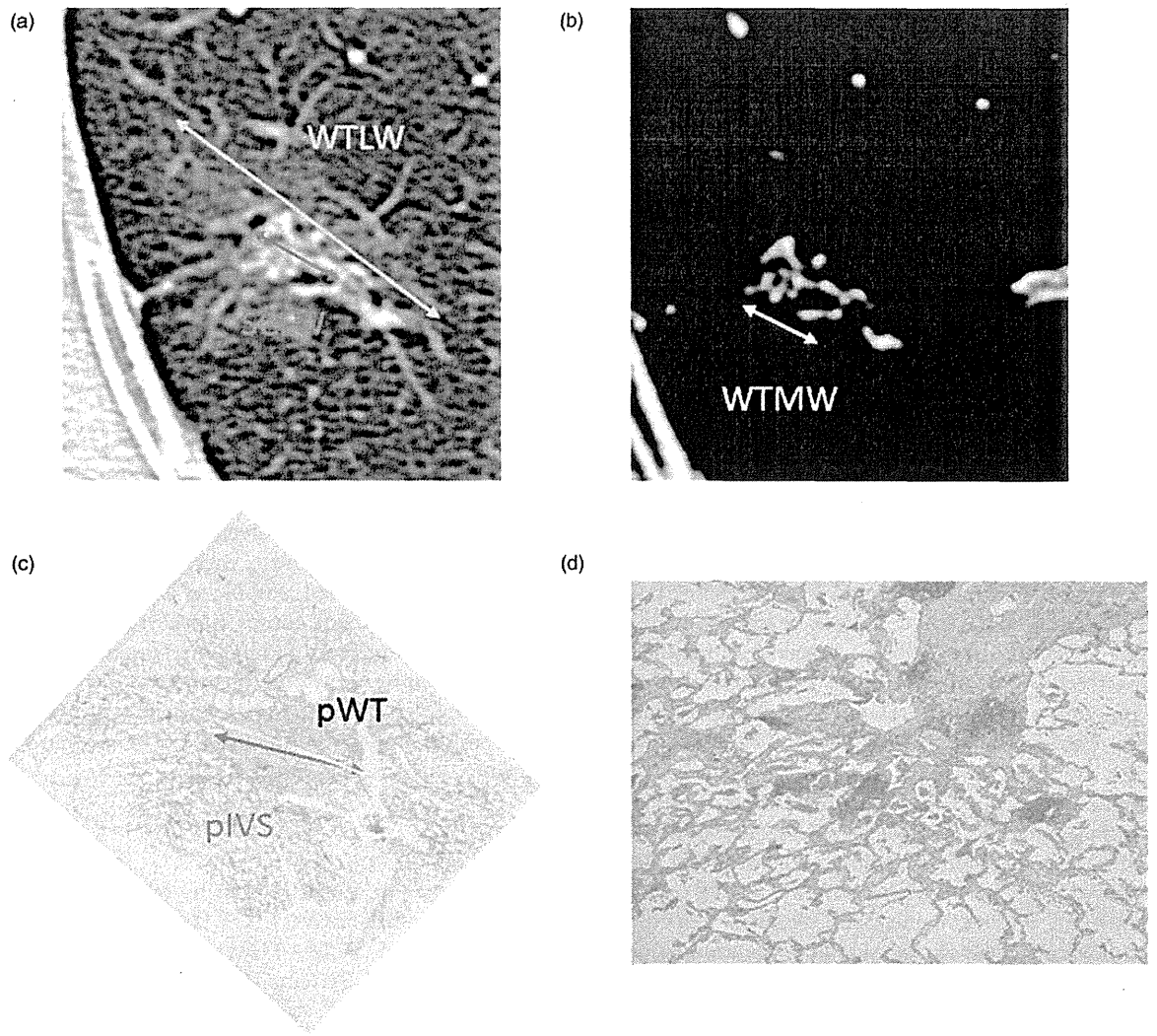

Fig. 1. Correlation between radiological and pathological findings in one typical case. WTLW and SCLW (a), WTMW (b), pWT and pIVS (c), pathological invasive area with high magnification (d). pIVS, pathologically confirmed invasion size; pWT, pathologically confirmed whole tumor size; SCLW, solid component size of lung windows setting; WTLW, whole tumor size of lung windows setting; WTMW, whole tumor size of mediastinal setting.

specimens were formalin-fixed and stained with hematoxylin and eosin in the routine manner. For detailed examinations of lymphatic or vascular invasion or pleural invasion, Elastica van Gieson stain was used to evaluate histological structure and tumor invasion. We also assessed several histological factors: (i) pathological nodal status (pN); (ii) vascular (v) or lymphatic (ly) invasion; and (iii) degree of tumor differentiation (well [G1], moderate [G2], poor [G3]). The maximum size of the pathological whole tumor (pWT) and of the pathological invasive component were measured (pIVS). The maximum size of pWT was assessed by standard gross measurement or histological reconstruction, as necessary. The maximum size of the invasive component was measured microscopically. If the tumor was large, the maximum size of the invasive area was calculated by reconstruction of the tumor slides and measured (Fig. 1c and d). Pathologic high-grade malignancy was defined as lymph node involvement, lymphatic invasion, or vascular invasion.

Statistical analysis

The data are presented as numbers and percentages or mean ± standard deviation, unless otherwise stated. The receiver operating characteristic curves of the whole and solid tumor sizes were used for the

Table 1. Radiological and pathological findings of 232 patients with lung adenocarcinoma.

Variables	*n* (% or range)	
Radiological findings		
WTLW: mean ± SD (cm)	2.59 ± 1.09 (0.73–6.84)	
SCLW: mean ± SD (cm)	2.01 ± 1.18 (0.00–5.78)	
WTMW: mean ± SD (cm)	1.87 ± 1.18 (0.00–5.71)	
Pathological findings		
pT status: pT1a / pT1b / pT2a / pT2b / pT3	86 (37.2) / 68 (29.2) / 61 (26.2) / 6 (2.7) / 11 (4.7)	
pN status: pN0 / pN1 / pN2	195 (83.7) / 20 (8.6) / 17 (7.7)	
pStage: pIA / pIB / pIIA / pIIB / pIIIA	141 (60.5) / 48 (20.6) / 8(3.4) / 8 (3.4) / 27 (12.1)	
pWT: mean ± SD, cm	2.61 ± 1.11 (0.90–7.20)	
pIVS: mean ± SD, cm	2.26 ± 1.27 (0.00–7.2)	
Differentiated: well or poorly	118 (50.6) / 107 (45.9)	ND: 8
Ly: positive / negative	127 (54.5) / 102 (43.8)	ND: 3
V: positive / negative	82 (35.2) / 150 (64.8)	

Ly, lymphatic invasion; ND, no data; pIVS, pathological invasion size; pN, pathological nodal status; pT, pathological T status; pWT, pathological whole tumor size; SCLW, solid component size of lung windows setting; V, vascular invasion; WTLW, whole tumor size of lung windows setting; WTMW, whole tumor size of mediastinal setting.

prediction of lymph node involvement, lymphatic invasion, or vascular invasion or well differentiation. We also performed multiple logistic regression analysis to determine the independent variables related to the whole tumor size and the solid tumor size for the prediction of the pathologic finding of high-grade malignancy. Overall survival (OS) was calculated from the date of surgery to the time of death. Observations were censored at final follow-up if the patient was living. Disease-free survival (DFS) was defined as the interval from the date of surgery until the first event (relapse or death from any cause) or the last follow-up visit. The duration of DFS was analyzed using the Kaplan-Meier method. Differences in OS or DFS were assessed using the log-rank test. To assess the potential independent and valuable prognostic effects of clinical tumor size on OS or DFS, we performed multivariate analysis with the Cox proportional hazards model using variables with $P < 0.05$. The data were statistically analyzed using the Statistical Package for Social Sciences software, version 10.5 (SPSS Inc., Chicago, IL, USA).

Ethical considerations

The approval of the Institutional Review Board of Tokyo Medical University was obtained (project approval No. 1665), but as this was a retrospective study the need to obtain written informed consent from either the patients or their representatives was waived, in accordance with the American Medical Association Manual of Style (10th edition).

Results

Patient characteristics

There were 118 (51.0%) women and 114 (49.0%) men aged 35–86 years (mean, 65.0 years). The several radiological and pathological findings of 232 patients are summarized in Table 1.

Correlation between radiological and pathological findings

Fig. 2 shows several correlations between radiological findings including WTLW, SCLW, or WTMW, and pathological findings including pWT or pIVS. There were significant correlations between SCLW and pIVS ($R = 0.762$, 95% CI = 0.702–0.811, $P < 0.0001$), WTMW and pIVS ($R = 0.771$, 95% CI = 0.713–0.819, $P < 0.0001$), and WTLW and pIVS ($R = 0.792$, 95% CI = 0.735–0.835, $P < 0.0001$), respectively.

Receiver operating characteristic curve

The receiver operating characteristic area under the curve values of WTLW, SCLW, WTMW, and pIVS used for predicting lymph node involvement, lymphatic invasion, vascular invasion, degree of differentiation, and pathologic high-grade malignancy (lymph node involvement or lymphatic or vascular invasion) are given in Table 2 and Fig. 3. The predictability of all outcomes on the basis of solid tumor size such as SCLW and WTMW was better than that using the

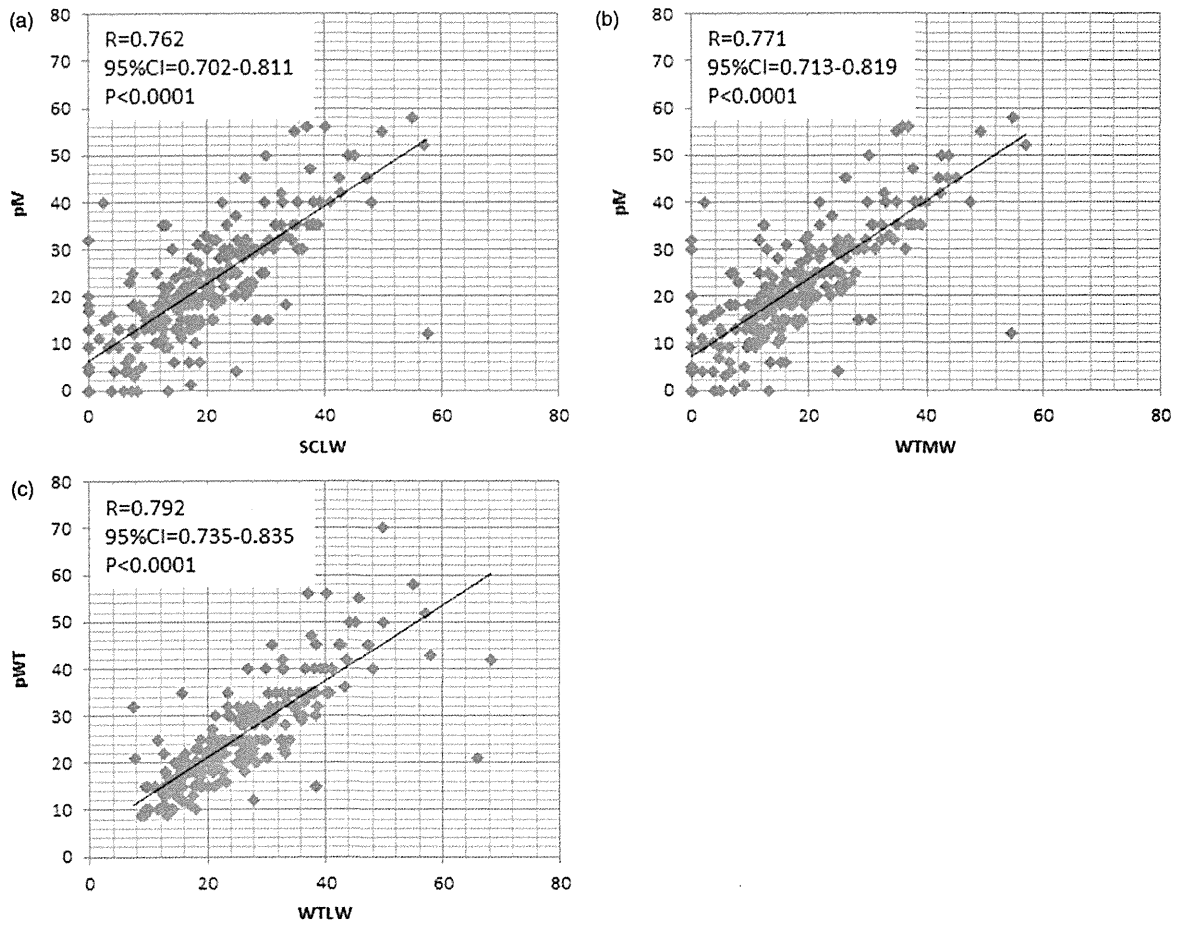

Fig. 2. Correlative graphs between radiological and pathological findings. There were significant correlations between SCLW and pIVS (R = 0.762, 95% CI = 0.702–0.811, $P < 0.0001$) (a), WTMW and pIVS (R = 0.771, 95% CI = 0.713–0.819, $P < 0.0001$) (b), and WTLW and pIVS (R = 0.792, 95% CI = 0.735–0.835, $P < 0.0001$) (c), respectively. pIVS, pathologically confirmed invasion size; pWT, pathologically confirmed whole tumor size; SCLW, solid component size of lung windows setting; WTLW, whole tumor size of lung windows setting; WTMW, whole tumor size of mediastinal setting.

Table 2. Receiver operative characteristic area under the curve values of WTLW, SCLW, WTMW, and pIVS used to predict pathologic findings.

	WTLW		SCLW		WTMW		pIVS	
Variable	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value
pN	0.711 (0.625–0.797)	<0.0001	0.796 (0.723–0.870)	<0.0001	0.809 (0.737–0.880)	<0.0001	0.788 (0.717–0.859)	<0.0001
Ly	0.685 (0.616–0.754)	<0.0001	0.793 (0.735–0.852)	<0.0001	0.801 (0.744–0.859)	<0.0001	0.772 (0.711–0.833)	<0.0001
V	0.646 (0.593–0.719)	<0.0001	0.766 (0.704–0.828)	<0.0001	0.769 (0.706–0.831)	<0.0001	0.777 (0.717–0.837)	<0.0001
pN or Ly or V	0.693 (0.623–0.762)	<0.0001	0.817 (0.761–0.873)	<0.0001	0.824 (0.769–0.879)	<0.0001	0.796 (0.733–0.855)	<0.0001
Well diff.	0.623 (0.551–0.695)	0.001	0.770 (0.710–0.830)	<0.0001	0.771 (0.711–0.832)	<0.0001	0.770 (0.709–0.830)	<0.0001

Ly, lymphatic invasion; pIVS, pathological invasion size; pN, pathological lymph node status; SCLW, solid component size of lung windows setting; V, vascular invasion; Well diff., well differentiated; WTLW, whole tumor size of lung windows setting; WTMW, whole tumor size of mediastinal setting.

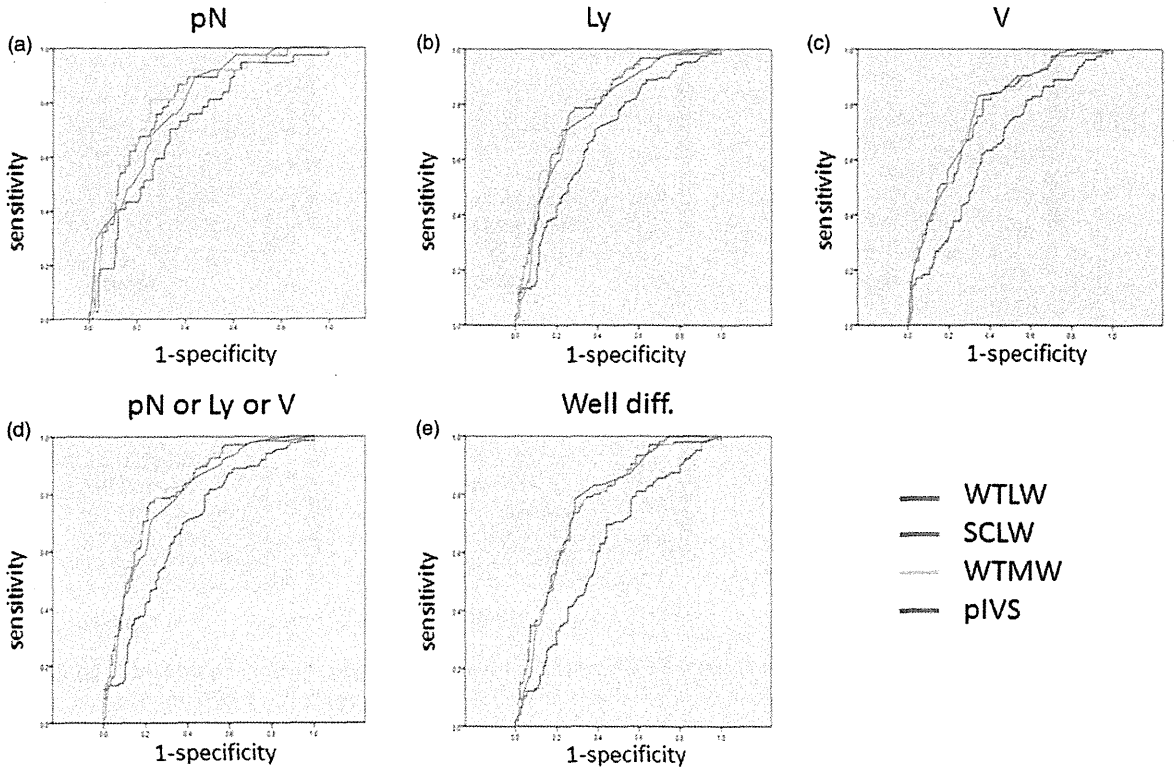

Fig. 3. Receiver operating characteristic area under the curve for detecting (a) pathological lymph node metastasis (pN), (b) lymphatic invasion (Ly), (c) vascular invasion (V), (d) high-grade malignancy (pN, VI, or PI), and (e) degree of differentiation for radiological whole and solid tumor sizes including WTLW, SCLW, and WTMW and pathological invasion area, pIVS. SCLW, solid component size of lung windows setting; WTLW, whole tumor size of lung windows setting; WTMW, whole tumor size of mediastinal setting.

whole tumor size that is WTLW for all subjects. The receiver operating characteristic curves of SCLW and WTMW were similar to that of pIVS that is pathological confirmed invasion area.

Survival significance

We assessed survival significance of preoperative radiological findings including WTLW, SCLW, and WTMW. Patients were categorized into radiological measurement of tumor size greater than 2 cm or those 2 cm or less according to WTLW, SCLW, and WTMW. There were significant differences in both the DFS and OS of this series according to SCLW ($P=0.0001$ and $P=0.023$) and WTMW ($P<0.0001$ and $P=0.008$), respectively (Fig. 4). Moreover, to find the most valuable and independent radiological prognostic factor including WTLW, SCLW, and WTMW as a candidate of next T factor, we performed multivariate analysis of DFS and OS. Table 3 revealed that WTMW (HR = 0.72, 95% CI = 0.58–0.90, $P=0.004$ and HR = 0.74, 95% CI = 0.57–0.96, $P=0.022$, respectively) was the independent prognostic factor among preoperative variables among age, sex, WTLW, and SCLW in this series.

Discussion

The frequency of identification of small lung cancers has increased since CT and enhanced scanning have become routine procedures. Small tumors, especially in lung adenocarcinomas, often contain GGO components as visualized on HRCT (2,7–9). Noguchi et al. first reported that type A and B small peripheral adenocarcinomas (localized bronchioloalveolar carcinoma without foci of active fibroblastic proliferation) showed no lymph node metastasis and a favorable prognosis (100% 5-year survival rate) (10). In 2011, new concepts were introduced including AIS and MIA. Because some of these cancers did not show growth for a long period, controversy remains as to how to manage subsolid nodules (11–14). Furthermore, both subsolid nodules and AIS have been discussed in relation to over diagnosis, which is defined as a diagnosis of lung cancer that would not lead to an individual's death because of the slow

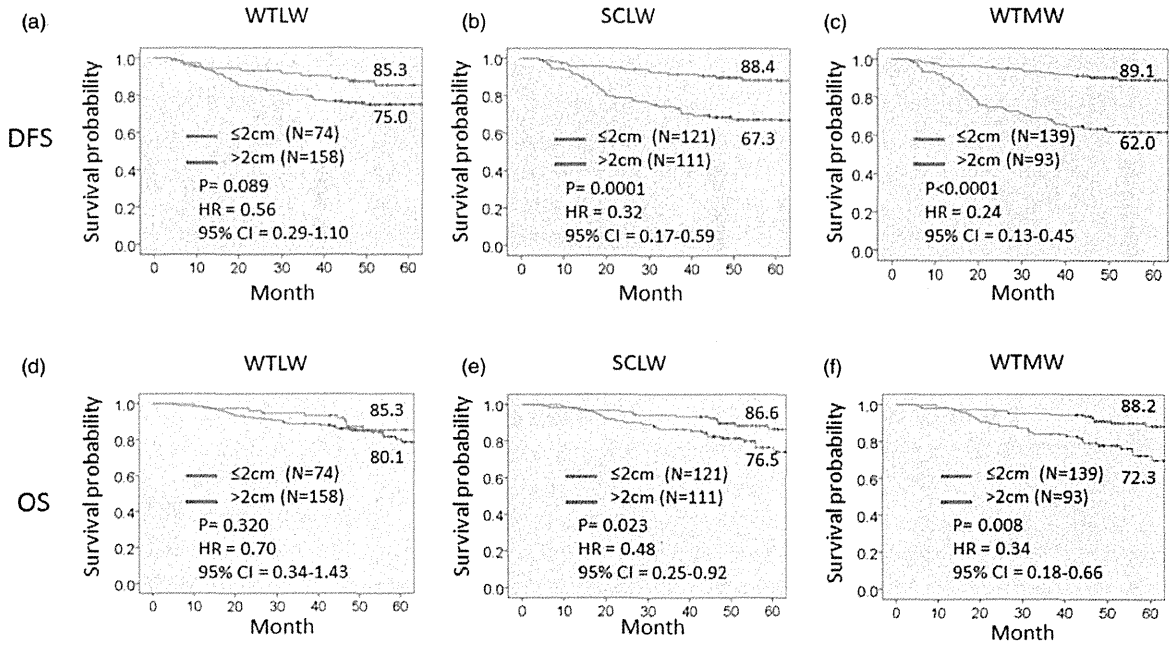

Fig. 4. Disease-free survival (DFS) and overall survival (OS) curves of patients according to tumor size on HRCT. (a) five-year DFS rate of 85.3% and 75.0% for a WTLW of 2.0 cm or less and greater than 2.0 cm, respectively ($P = 0.089$). (b) five-year DFS rate of 88.4% and 67.3% for a SCLW of 2.0 cm or less and greater than 2.0 cm, respectively ($P = 0.0001$). (c) five-year DFS rate of 89.1% and 62.0% for a WTMW of 2.0 cm or less and greater than 2.0 cm, respectively ($P < 0.0001$). (d) five-year OS rate of 85.2% and 80.1% for a WTLW of 2.0 cm or less and greater than 2.0 cm, respectively ($P = 0.320$). (e) five-year OS rate of 86.6% and 76.5% for a SCLW of 2.0 cm or less and greater than 2.0 cm, respectively ($P = 0.023$). (f) five-year OS rate of 88.2% and 72.3% for a WTLW of 2.0 cm or less and greater than 2.0 cm, respectively ($P = 0.008$). SCLW, solid component size of lung windows setting; WTLW, whole tumor size of lung windows setting; WTMW, whole tumor size of mediastinal setting.

Table 3. Multivariate analysis of DFS and OS.

		DFS			OS		
Variable	Category	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)	<70						
	≥70	1.57	0.82–3.01	0.177	1.14	0.57–2.26	0.715
Sex	Men						
	Women	0.97	0.54–1.74	0.911	0.603	0.30–1.20	0.148
WTLW		0.94	0.89–1.00	0.040*	0.97	0.92–1.03	0.345
SCLW		0.82	0.66–1.01	0.067	0.80	0.62–1.03	0.078
WTMW		0.72	0.58–0.90	0.004 *	0.74	0.57–0.96	0.022*

*Statistically significant.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; SCLW, solid component size of lung windows setting; WTLW, whole tumor size of lung windows setting; WTMW, whole tumor size of mediastinal setting.

growth rate and competing age-related risks for death (15–18).

The general concept of TNM classification by UICC is that "For consistency, in the TNM system, carcinoma in situ is categorized as Stage 0", according to the 7^{th} edition of the TNM Classification of Malignant Tumours (19), which means AIS itself should not be used for staging grouping. However, clinical physicians specializing in lung cancer measure the tumor size by including the GGO components visualized on HRCT. On the basis of our hypothesis that the solid components, not the GGO components, of tumors as

visualized on HRCT, indicate malignancy and prognosis, we evaluated the role of solid tumor size (the size without the GGO component) in cases of lung adenocarcinoma.

First, we demonstrated that correlations between radiological findings including WTLW, SCLW, or WTMW, and pathological findings including pWT or pIVS. There were significant correlations between pIVS and SCLW or WTMW and between pWT and WTLW. Next we analyzed sensitivity and specificity of these radiological factors for predicting pathological malignant factors including lymph node involvement, lymphatic invasion, vascular invasion, and differentiation of the tumor. All receiver operating characteristic areas under the curves for predicting pN, Ly, V, high-grade malignancy (pN or Ly or V) and well differentiation were greater in the solid components size which is SCLW and WTMW than those for the whole tumor size which is WTLW. Because the range of mean radiological measurement of WTLW, SCLW and WTMW were from 1.87 to 2.59 cm in size and the cutoff point of 2 cm is also used as T factor. Finally, we analyzed each DFS and OS according to the cutoff point of 2 cm using whole and solid tumor sizes. Kaplan-Meier curves of both DFS and OS showed better division according to the solid components size, SCLW and WTMW, compared with the whole tumor size, WTLW. Moreover, multivariate analysis revealed that WTMW were identified as independent predictive factors for both DFS and OS. These results indicate that solid tumor size, not whole tumor size, more closely reflects the pathologic findings and those related to clinical tumor malignancy.

Several investigators have reported that the prognosis of patients with lung adenocarcinoma and a large GGO component visualized on HRCT was much better than that of patients with other adenocarcinoma types, irrespective of the maximal tumor dimension (20–23). In addition, JCOG0201, a multicenter prospective radiological study has examined the specificity, sensitivity, and accuracy of the radiologic diagnoses of lymphatic/vessel invasion and nodal involvement of clinical T1N0M0 adenocarcinoma made according to the HRCT findings (24). Recently, a multicenter registration study demonstrated that solid tumor size on HRCT and maximum standardized uptake values on PET/CT has greater predictive value for high-grade malignancy and prognosis in clinical stage IA lung adenocarcinoma than that of whole tumor size (25). This final result indicated that using the solid tumor size is much simpler than using the GGO ratio; furthermore, the solid tumor size can be applied to the T descriptor in the TNM classification.

In this study, patients with lung adenocarcinoma were eligible for assessment and approximately one-third of the patients with whole tumors greater than 3 cm were included in final analysis. This confirmation of the significance of using the solid component for prognosis is consistent with previous studies using small-sized lung adenocarcinoma. Therefore, this result suggested that this concept of using solid tumor size can be applied to the T descriptor of TNM classification for larger tumors.

To the best of our knowledge, this is the first study demonstrating the correlation between radiological and pathological findings and the prognostic significance of solid tumor size in lung adenocarcinoma including tumors larger than 3 cm. However, there are several limitations in this study. First, this was a medium-size retrospective, single-institution analysis. Second, to clarify and simplify measuring the radiological and pathological size, we excluded lung adenocarcinoma with scattered invasive components which were slightly less than 10% of the population. It remains unclear whether we should count the largest scattered invasive components or the sum total of them. Third, we used two radiological measurements, SCLW and WTMW, in this analysis. Our results suggested that using WTMW counting for solid invasive components might be a better mediator for prognostic outcome of lung adenocarcinoma compared with SCLW, which is consistent with some of the previous. It remains unclear whether WTMW or SCLW should be a better predictor. Therefore, larger and multicenter studies using identical protocols are needed.

In conclusion, the predictive values of solid tumor size visualized on HRCT especially in mediastinal windows for pathologic high-grade malignancy and prognosis in patients with lung adenocarcinoma were greater than those of the whole tumor size. We recommend that the solid tumor size be used to determine the T descriptor in the TNM classification of lung tumor and be defined as the true tumor size in cases of lung adenocarcinoma with a GGO component visualized on HRCT.

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Conflict of interest

None declared.

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Propensity score–matched analysis of adjuvant chemotherapy for stage I non–small cell lung cancer

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Objective: The aim of this study was to reevaluate the role of adjuvant chemotherapy for patients with stage I non–small cell lung cancer (NSCLC).

Methods: Data from 800 patients with completely resected pathologic stage I NSCLC who received adjuvant chemotherapy (n = 191) and those who did not (n = 609) were analyzed retrospectively and propensity score–matched pairs were determined.

Results: Although recurrence-free survival (RFS) and overall survival (OS) were not significantly different between patients who received adjuvant chemotherapy and those who did not in the univariate analyses, multivariate Cox analyses demonstrated that adjuvant chemotherapy was an independent prognostic factor for RFS and OS ($P = .008$ and $P = .009$, respectively). In 159 propensity score–matched pairs, including variables such as age, gender, smoking history, comorbidity, postoperative complication, histology, size of the invasive component of the tumor, and status of lymphatic, vascular, and pleural invasion, RFS and OS were considerably better in patients who received adjuvant chemotherapy (5-year RFS rate, 79.8%; 5-year OS rate, 89.3%) than in those who did not (5-year RFS rate, 60.2%; 5-year OS rate, 75.2%). Patients who received adjuvant chemotherapy showed significantly better RFS than those who did not in the group with an invasive component larger than 2 cm (5-year RFS rate, 74.4% vs 55.2%; $P = .015$) or in those with positive lymphatic invasion (5-year RFS rate, 63.3% vs 44.8%; $P = .05$).

Conclusions: Adjuvant chemotherapy is effective for patients with stage I NSCLC, particularly those with an invasive component larger than 2 cm or those with lymphatic invasion. (J Thorac Cardiovasc Surg 2014;148:1179-85)

Platinum-based adjuvant chemotherapy after surgical resection in patients with stage II to IIIA non–small cell lung cancer (NSCLC) is recognized as a standard treatment and is currently used.[1-3] However, for patients with stage I NSCLC, the use of adjuvant chemotherapy remains controversial. From the subgroup analysis in a clinical trial for stage IB NSCLC, platinum-based adjuvant chemotherapy was suggested to benefit patients with tumors of 4 cm or greater.[4] In addition, tegafur-uracil (UFT) significantly improves survival in patients with stage I NSCLC, particularly those with lung adenocarcinomas greater than 2 cm, as revealed by randomized phase 3 trials and meta-analysis.[5-7] These reports suggest that a subgroup of selected patients with stage I NSCLC will benefit from adjuvant chemotherapy.

The aim of this retrospective study was to reevaluate the role of adjuvant chemotherapy for patients with stage I NSCLC and define the type of patients who would benefit from this chemotherapy.

PATIENTS AND METHODS

Patients

A retrospective review of 914 consecutive cases of completely resected pathologic stage I NSCLC between July 1, 2002, and December 31, 2011, was conducted. All patients who were staged according to the *TNM Classification of Malignant Tumours, 7th Edition*, underwent curative R0 resections.[8] The inclusion criteria included curative surgery without neoadjuvant chemotherapy or radiotherapy and a definitive histopathologic diagnosis of NSCLC. Patients with incompletely resected tumors (R1 or R2), multiple tumors, or previous lung surgery were excluded from the analysis. After excluding 114 ineligible patients, 800 patients were included in this study (Figure 1). Comorbidities were defined as low pulmonary function, diabetes mellitus, ischemic heart disease, hypertension, or other severe comorbidities. Segmentectomy with systematic lymph node dissection was considered in patients with a clinical stage IA tumor with ample surgical margins for complete removal. Wedge resection for tumors that consisted primarily of a ground-glass opacity component on high-resolution computed tomography (CT) was performed. During lobectomy or segmentectomy, more than 6 lymph nodes, including the hilar and mediastinal lymph nodes, were sampled. Lobectomy or segmentectomy was performed using the same approach: hybrid video-assisted thoracoscopy.[9,10]

Adjuvant chemotherapy was considered for patients who underwent a standard operation and whose postoperative Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 and in whom the total tumor size exceeded 2 cm. Performance status was determined by a physician.

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Abbreviations and Acronyms

CI = confidence interval
CT = computed tomography
CTCAE = Common Terminology Criteria for Adverse Events
ECOG = Eastern Cooperative Oncology Group
EVG = Elastic-Van Gieson
HR = hazard ratio
NSCLC = non–small cell lung cancer
OS = overall survival
RFS = recurrence-free survival
UFT = tegafur-uracil

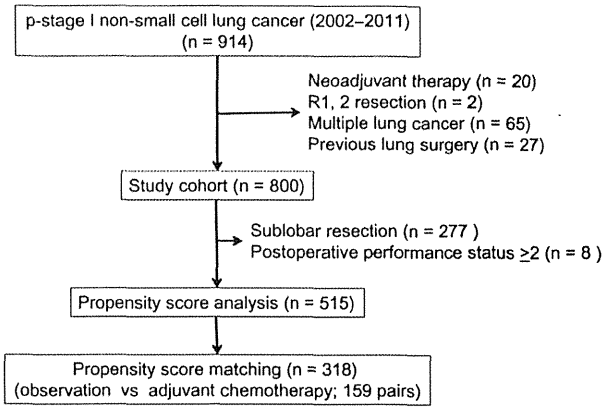

FIGURE 1. Flow chart for selection of patients for this study.

The recommendation for adjuvant chemotherapy was made at a cancer board meeting where the pathologic findings were reported. Of the 800 patients, 191 received adjuvant chemotherapy and 609 did not. The chemotherapy regimen included cisplatin plus vinorelbine in 10 patients, carboplatin plus paclitaxel in 12, carboplatin plus VP-16 in 1, gemcitabine plus tegafur-gimeracil-oteracil potassium (TS-1) in 5, gemcitabine in 1, UFT in 129, and TS-1 in 33 patients. This multicenter study was approved by the institutional review board; the requirement for informed consent from individual patients was waived for this retrospective analysis of a prospective database.

All patients who underwent lung resection were followed up from the day of surgery. Postoperative complications were defined as grade 2 or higher by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Postoperative follow-up procedures including physical examination, chest roentgenogram every 3 months, and chest and abdominal CT examinations every 6 months were performed for the first 2 years; thereafter, a physical examination and chest roentgenogram were performed every 6 months and a CT examination was performed annually.

Pathologic Examination

The size of the invasive component was defined as the maximum dimension of the invasive tumor component, excluding the lepidic growth component described previously.[11] Lymphatic and vascular invasion was assessed by immunohistochemistry for D2-40, which stains the lymphatic ducts, and elastic Van Gieson (EVG) staining of the elastic fiber of the vessels. Lymphatic and vascular invasion was determined to be positive when the process of spreading through or penetration was detected as an extension of a malignant neoplasm. To evaluate pleural invasion, elastic tissue fibers were subjected to EVG staining. Pleural invasion was defined as positive if cancer had invaded beyond the elastic layer, including invasion into the visceral pleural surface or neighboring organs. Histologic examinations were determined by pathologists from each institution for the purpose of this study.

Statistical Analysis

Data are presented as the number (%) or the mean ± standard deviation unless otherwise stated. The χ^2 test for categorical variables was used to compare frequencies, and the Fisher exact test was applied to small samples in all cohorts. McNemar tests were used to analyze the propensity score–matched pairs; *t* tests and Mann-Whitney *U* tests were used to compare continuous variables in all cohorts. Wilcoxon tests were used to analyze propensity score–matched pairs. Recurrence-free survival (RFS) was defined as the time from the day of surgery until the first event (relapse or death from any cause) or last follow-up. Overall survival (OS) was defined as the time from the day of surgery until death from any cause or the last follow-up. The Kaplan-Meier method was used to analyze the duration of RFS and OS, and differences were assessed using the log-rank test. Multivariate analyses using the Cox proportional hazards models was used to assess the potential independent effects of adjuvant chemotherapy on RFS or OS. The following variables were included: age, gender, smoking history, comorbidity, procedure, performance status, postoperative complication, histology, size of the invasive component, status of lymphatic, vascular, and pleural invasion, and the use of adjuvant chemotherapy.

After excluding patients who had poor ECOG performance status (≥2), and who underwent sublobar resection, propensity score matching was applied to balance the assignment of the patients and to correct for the presence of adjuvant chemotherapy, which confounded the survival calculations. The variables were age (continuous), gender, smoking history, comorbidity, postoperative complication, histology, size of the invasive component size (continuous), and status of lymphatic, vascular, and pleural invasion. Each variable was multiplied by a coefficient that was calculated using logistic regression analysis, and the sum of these values was taken as the propensity score for individual patients. The C statistic of the variables was 0.688 (95% confidence interval [CI], 0.641-0.735, $P < .0001$). For matching, adjuvant chemotherapy and observation pairs with an equivalent propensity score were selected by a 1-to-1 match with a caliper width of 0.2 of standard deviation. Statistical Package for the Social Sciences (SPSS) software (version 10.5; SPSS Inc, Chicago, Ill) was used to statistically analyze the data.

RESULTS

The characteristics of the 800 patients in the study are summarized in Table 1. The median follow-up period after surgery was 48.7 months, during which the tumor recurred in 128 patients. Of the 800 patients, 191 received adjuvant chemotherapy and 609 did not. Adjuvant chemotherapy was given significantly more often to male patients undergoing lobectomy, with a smoking history, without a postoperative complication, with a larger tumor size, larger invasive component, and lymphatic, vascular, and pleural invasion.

Taking all patients into account, there was no significant difference in the RFS and OS rates between patients who received adjuvant chemotherapy (5-year RFS rate, 78.1%; 5-year OS rate, 88.1%) and those who did not (5-year RFS rate, 71.5%; $P = .69$; 5-year OS rate, 81.5%;

TABLE 1. Patient characteristics

	Observation (n = 609)	Adjuvant chemotherapy (n = 191)	*P* value
Age, y ± SD	67.3 ± 9.9	66.3 ± 9.5	.26
Gender, n (%)			
Male	343 (56.3)	126 (66.0)	.019
Smoking history, n (%)			
Yes	322 (52.9)	119 (62.3)	.024
Comorbidity, n (%)			
Yes	87 (14.3)	36 (18.8)	.14
Procedure, n (%)			<.001
Lobectomy	344 (56.5)	179 (93.7)	
Segmentectomy	173 (28.4)	10 (5.2)	
Wedge resection	92 (15.1)	2 (1.0)	
Performance status (ECOG), n (%)			
≥2	12 (2.0)	2 (1.0)	.54
Postoperative complication, n (%)			
Yes	105 (17.2)	20 (10.5)	.029
Histology, n (%)			.99
Adenocarcinoma	451 (74.1)	141 (73.8)	
Squamous cell carcinoma	99 (16.3)	31 (16.2)	
Others	59 (9.7)	19 (10.0)	
Total tumor size, cm ± SD	2.2 ± 0.9	3.2 ± 0.9	<.001
Invasive tumor component size, cm ± SD	1.7 ± 1.2	2.6 ± 1.3	<.001
Lymphatic invasion, n (%)			
Positive	126 (20.7)	65 (34.0)	<.001
Vascular invasion, n (%)			
Positive	118 (19.4)	75 (39.3)	<.001
Pleural invasion, n (%)			
Positive	90 (14.8)	60 (31.4)	<.001

SD, Standard deviation; *ECOG*, Eastern Cooperative Oncology Group.

P = .17; Figure 2). However, multivariate Cox analyses demonstrated that adjuvant chemotherapy was an independent prognostic factor of RFS (hazard ratio [HR], 0.58; 95% CI, 0.39-0.87; P = .008) and OS (HR, 0.47; 95% CI, 0.27-0.83; P = .009) as were age, gender, comorbidity, performance status, histology, size of the invasive component, and lymphatic and vascular invasion (Table 2).

When propensity score matching was used and variables such as age, gender, smoking history, comorbidity, postoperative complication, histology, size of the invasive component, and lymphatic, vascular, and pleural invasion were included, adjuvant chemotherapy and observation pairs were well matched (159 patients each), without significant differences in clinical and pathologic factors (Table 3). Among propensity score–matched pairs, patients who received adjuvant chemotherapy showed better RFS and OS rates (5-year RFS rate, 79.8%, 5-year OS rate, 89.3%) than those who did not (5-year RFS rate, 62.0%; 5-year OS rate, 75.2%; Figure 3).

Among all patients, those who received adjuvant chemotherapy showed significantly better RFS rates than those who did not in the group with an invasive component size greater than 2 cm (5-year RFS rate, 74.4% vs 55.2%; P = .015) or in those with positive lymphatic invasion (5-year RFS rate, 63.3% vs 44.8%; P = .05); no difference was observed in the group with invasive component size of 2 cm or less (5-year RFS rate, 78.9% vs 81.4%; P = .90) or in those with negative lymphatic invasion (5-year RFS rate, 85.4% vs 79.5%; P = .78; Figure 4). The 5-year RFS rates of patients who received adjuvant chemotherapy and those who did not were 78.6% and 57.7%, P = .023, in the subgroup with an invasive component size of 2 to 3 cm, and 71.3% and 51.3%, P = .15, in the subgroup with an invasive component size of 3 to 5 cm, respectively. There was no difference in the RFS rates between patients who received adjuvant chemotherapy and those who did not in the groups divided by age, gender, smoking history, comorbidity, performance status, postoperative complication, histology, vascular, and pleural invasion. Among patients

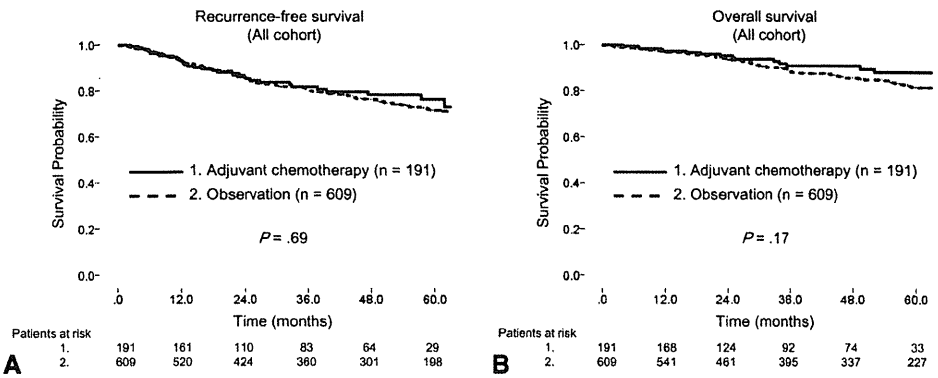

FIGURE 2. A, In all patients, there was no significant difference in the recurrence-free survival (RFS) rates between patients who received adjuvant chemotherapy (5-year RFS rate, 76.3%; mean RFS rate, 78.1 months; 95% confidence interval [CI], 70.5-85.8 months) and those who did not (5-year RFS rate, 71.5%; mean RFS rate, 80.8 months; 95% CI, 77.5-84.0 months; P = .69). B, In all patients, there was no significant difference in the overall survival (OS) rates between patients who received adjuvant chemotherapy (5-year OS rate, 88.1%; mean OS rate, 89.6 months; 95% CI, 83.6-95.5 months) and those who did not (5-year OS rate, 71.5%; mean OS rate, 81.5 months; 95% CI, 88.0-90.8 months; P = .17).

TABLE 2. Multivariate Cox analyses for recurrence-free survival and overall survival

	HR	95% CI	*P* value
Multivariate analysis of recurrence-free survival			
Age	1.04	1.02-1.05	<.001
Gender			
Male (vs female)	1.73	1.10-2.73	.018
Smoking history			
Yes	0.88	0.57-1.36	.58
Comorbidity			
Yes	1.49	0.99-2.24	.056
Procedure			
Lobectomy (vs sublobar resection)	0.92	0.64-1.32	.65
Performance status			
≥2	15.8	7.87-31.5	<.001
Postoperative complication			
Yes	1.26	0.86-1.83	.23
Histology			
Adenocarcinoma (vs nonadenocarcinoma)	0.96	0.68-1.35	.80
Invasive tumor component size	1.29	1.22-1.49	.001
Lymphatic invasion			
Positive	2.23	1.57-3.16	<.001
Vascular invasion			
Positive	1.80	1.23-2.64	.003
Pleural invasion			
Positive	1.07	0.74-1.55	.71
Adjuvant chemotherapy			
Yes	0.58	0.39-0.87	.008
Multivariate analysis of overall survival			
Age	1.06	1.03-1.08	<.001
Gender			
Male (vs female)	1.85	1.04-3.31	.037
Smoking history			
Yes	1.06	0.62-1.79	.84
Comorbidity			
Yes	1.86	1.15-3.03	.012
Procedure			
Lobectomy (vs sublobar resection)	1.07	0.68-1.67	.78
Performance status			
≥2	12.4	5.81-26.5	<.001
Postoperative complication			
Yes	1.21	0.77-1.89	.42
Histology			
Adenocarcinoma (vs nonadenocarcinoma)	0.99	0.66-1.51	.98
Invasive tumor component size	1.23	1.02-1.57	.031
Lymphatic invasion			
Positive	1.86	1.29-2.91	.006
Vascular invasion			
Positive	1.99	1.23-3.20	.005
Pleural invasion			
Positive	0.88	0.55-1.39	.58
Adjuvant chemotherapy			
Yes	0.47	0.27-0.83	.009

HR, Hazard ratio; *CI*, confidence interval.

TABLE 3. Propensity score–matched comparison of clinical and pathologic factors between patients who received adjuvant chemotherapy and those who did not

	Observation (n = 159)	Adjuvant chemotherapy (n = 159)	*P* value
Age, y ± SD	67.2 ± 9.8	66.4 ± 9.2	.44
Gender, n (%)			
Male	100 (62.9)	102 (64.2)	.91
Performance status (ECOG), n (%)			
0 or 1	159 (100)	159 (100)	1.0
Smoking history, n (%)			
Yes	91 (57.2)	96 (60.4)	.65
Comorbidity, n (%)			
Yes	29 (18.2)	26 (16.4)	.77
Procedure, n (%)			
Lobectomy	159 (100)	159 (100)	1.0
Postoperative complication, n (%)			
Yes	18 (11.3)	18 (11.3)	1.0
Histology, n (%)			.60
Adenocarcinoma	118 (74.2)	113 (71.1)	
Squamous cell carcinoma	25 (15.7)	29 (18.2)	
Others	16 (10.1)	17 (10.7)	
Tumor size, cm ± SD*	2.5 ± 1.2	2.6 ± 1.3	.63
Lymphatic invasion, n (%)			
Positive	51 (32.1)	48 (30.2)	.78
Vascular invasion, n (%)			
Positive	54 (34.0)	55 (34.6)	1.0
Pleural invasion, n (%)			
Positive	40 (25.2)	40 (25.2)	1.0

SD, Standard deviation; *ECOG*, Eastern Cooperative Oncology Group. *Size of the invasive component of the tumor.

who underwent sublobar resection, those who received adjuvant chemotherapy had significantly worse RFS (Table 4).

In the multivariate Cox analyses, adjuvant chemotherapy was identified as an independent favorable prognostic factor for RFS among patients with invasive component size greater than 2 cm or positive lymphatic invasion, but not among those with invasive component size of 2 cm or less and negative lymphatic invasion (Table 5).

DISCUSSION

Although there was no difference in the RFS and OS rates between patients who received adjuvant chemotherapy and those who did not in the univariate analyses, multivariate analyses demonstrated that adjuvant chemotherapy was an independent favorable prognostic factor for patients with stage I NSCLC. This discrepancy may be a result of differences in the background characteristics of patients who received adjuvant chemotherapy and those who did not.

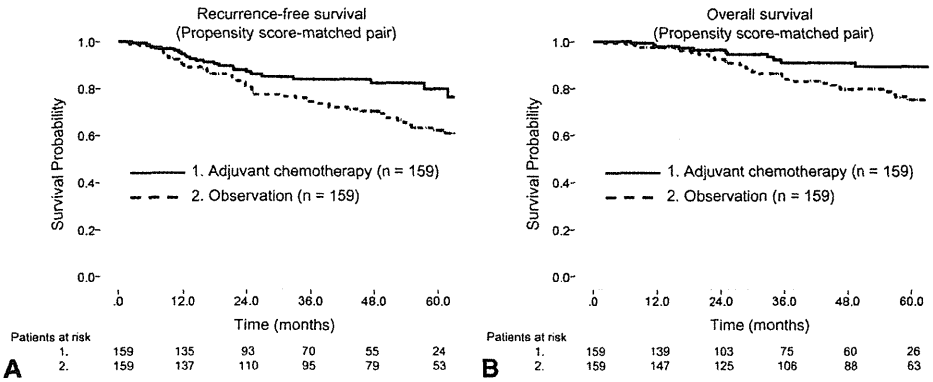

FIGURE 3. A, In propensity score–matched pairs, 5-year recurrence-free survival (RFS) rates of 79.8% (mean RFS rate, 80.8 months; 95% confidence interval [CI], 72.8-88.7 months) and 62.0% (mean RFS rate, 68.9 months; 95% CI, 62.7-75.0 months) were identified for patients who received adjuvant chemotherapy and those who did not, respectively. B, In propensity score–matched pairs, 5-year overall survival (OS) rates of 89.3% (mean OS rate, 89.8 months; 95% CI, 82.9-96.7 months) and 75.2% (mean OS rate, 82.2 months; 95% CI, 76.4-88.1 months) were identified for patients who received adjuvant chemotherapy and those who did not, respectively.

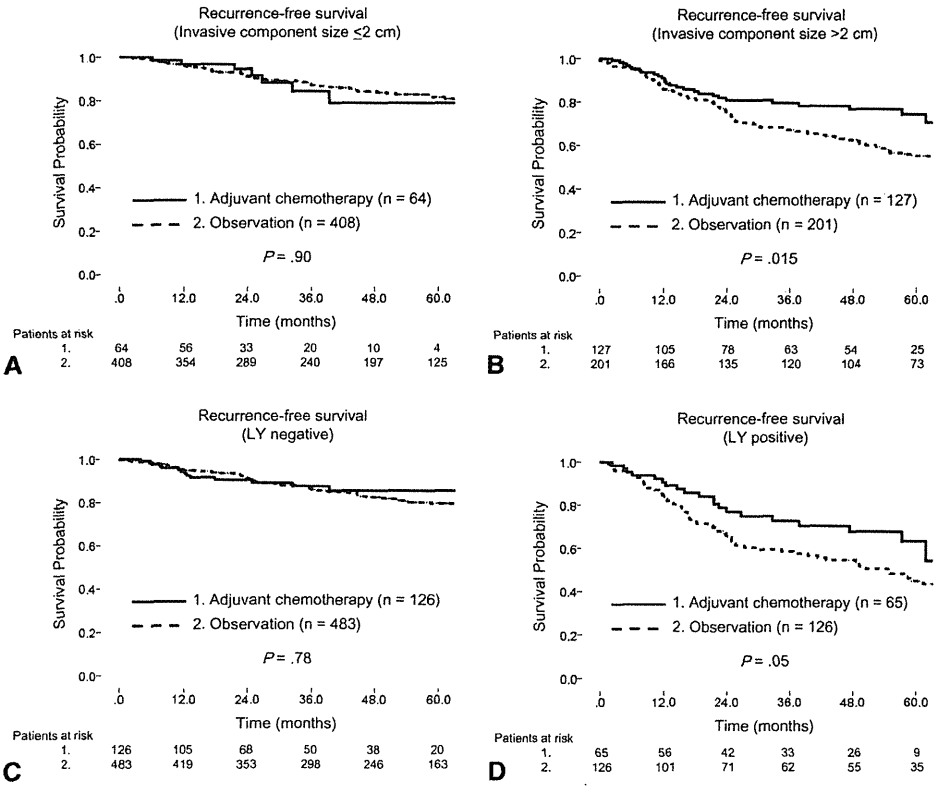

FIGURE 4. A, There was no difference in the recurrence-free survival (RFS) rate between patients who received adjuvant chemotherapy and those who did not in the group with an invasive component size ≤2 cm: 5-year RFS rate, 78.9% (mean RFS rate, 85.1 months; 95% confidence interval [CI], 74.3-95.8 months) versus 81.4% (mean RFS rate, 89.2 months; 95% CI, 85.7-92.7 months; $P = .90$). B, There was a significant difference in the RFS rate between patients who received adjuvant chemotherapy and those who did not in the group with an invasive component size >2.0 cm: 5-year RFS rate, 74.4% (mean RFS rate, 74.0 months; 95% CI, 65.6-82.3 months) versus 55.2% (mean RFS rate, 64.0 months; 95% CI, 58.5-69.5 months; $P = .015$). C, There was no difference in the RFS rate between patients who received adjuvant chemotherapy and those who did not in the group without lymphatic invasion: 5-year RFS rate, 85.4% (mean RFS rate, 83.9 months; 95% CI, 74.1-93.7 months) versus 79.5% (mean RFS rate, 87.5 months; 95% CI, 84.2-90.7 months; $P = .78$). D, There was a significant difference in the RFS rate between patients who received adjuvant chemotherapy and those who did not in the group with lymphatic invasion: 5-year RFS rate, 63.3% (mean RFS rate, 62.7 months; 95% CI, 53.5-71.8 months) versus 44.8% (mean RFS rate, 57.4 months; 95% CI, 49.8-65.0 months; $P = .05$). *LY*, Positive lymphatic invasion.

TABLE 4. Comparison of recurrence-free survival between patients who received adjuvant chemotherapy and those who did not in each subgroup based on the clinicopathologic factors

	5-y recurrence-free survival (%)		
	Observation	Adjuvant chemotherapy	*P* value
Age			
≤68 y	78.1	83.3	.38
>68 y	64.6	69.4	.84
Gender			
Male	62.5	73.2	.16
Female	83.4	85.0	.64
Smoking history			
No	82.0	80.9	.25
Yes	62.2	75.3	.08
Comorbidity			
No	72.1	77.7	.61
Yes	68.8	76.2	.82
Procedure			
Sublobar resection	74.3	47.1	.036
Lobectomy	69.5	79.0	.16
Performance status			
<2	72.9	76.6	.94
≥2	8.3	50.0	.31
Postoperative complication			
No	73.9	78.5	.84
Yes	60.7	59.2	.78
Histology			
Adenocarcinoma	75.5	80.4	.62
Nonadenocarcinoma	60.6	65.1	.92
Invasive component tumor size			
≤2 cm	81.4	78.9	.90
>2 cm	55.2	74.4	.015
Lymphatic invasion			
Negative	79.5	85.4	.78
Positive	44.8	63.3	.05
Vascular invasion			
Negative	77.7	89.0	.13
Positive	47.1	60.5	.19
Pleural invasion			
Negative	74.8	86.6	.09
Positive	53.6	57.8	.93

Propensity score–matching analysis allowed us to compare survival among patients with similar background characteristics. Because the pathologic size of the invasive component reflects the malignancy grade and prognosis considerably better than the total tumor size in patients with early lung adenocarcinoma,[11,12] we included the size of the invasive component instead of the total size of the tumor in the propensity score analysis. When potentially confounding variables such as age, gender, smoking history, comorbidity, postoperative complication, histology, size of the invasive component, and status of lymphatic, vascular, and pleural invasion were matched, patients who received adjuvant chemotherapy had considerably better RFS and OS rates than those who did not. These results strongly suggest that adjuvant chemotherapy is effective for selected patients with stage I NSCLC.

Although there is no definite consensus on the use of adjuvant chemotherapy for stage I NSCLC, platinum-based adjuvant chemotherapy was effective in patients with larger tumor size, poorly differentiated cancer, and good performance status.[4,13] In Japanese patients, oral UFT was effective for patients with stage I NSCLC, particularly when the tumor was 2 cm or larger.[5-7] Because of the heterogeneity of stage I NSCLC, selecting optimal candidates for adjuvant chemotherapy would be the appropriate strategy. In this study, we defined patients who would benefit from adjuvant chemotherapy. In patients with a tumor in which the size of the invasive component is more than 2 cm or with accompanying lymphatic invasion, adjuvant chemotherapy provides significantly better RFS rates than observation alone. In contrast, there is no significant difference in the RFS rates between patients who received adjuvant chemotherapy and those who did not among patients with an invasive component of 2 cm or less or without lymphatic invasion. In the subgroups stratified by age, gender, smoking history, histology, vascular, or pleural invasion, we could not identify patients who benefited from adjuvant chemotherapy. Therefore, the size of the invasive component and lymphatic invasion are predictive factors for the outcome of adjuvant chemotherapy as well as prognostic factors for RFS and OS in patients with stage I NSCLC. These findings were also supported by multivariate Cox analyses based on the subgroups for invasive component size and lymphatic invasion status.

This study has some limitations. Because this was a retrospective study, patients who received adjuvant chemotherapy were possibly selected; therefore, we performed multivariate analyses and propensity score–matched analysis to eliminate the selection bias as much as possible. In addition, because the adjuvant chemotherapy regimens were not consistent in this study, we could not conclude which regimen had a benefit for patients with stage I NSCLC, although there was no significant difference in the RFS rates between patients who received platinum-based chemotherapy and those who received other chemotherapies (data not shown). Prospective studies comparing observation versus adjuvant chemotherapy or UFT versus platinum-based chemotherapy for patients with stage I NSCLC with a larger invasive component or lymphatic invasion are warranted.

In conclusion, adjuvant chemotherapy is effective for patients with stage I NSCLC. Patients with a tumor with an invasive component greater than 2 cm or lymphatic invasion may particularly benefit from adjuvant chemotherapy.

TABLE 5. Multivariate Cox analysis for recurrence-free survival based on invasive tumor size or lymphatic invasion

	Invasive tumor size <2 cm		Invasive tumor size >2 cm		Lymphatic invasion negative		Lymphatic invasion positive	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.05 (1.02-1.08)	.004	1.04 (1.01-1.07)	.002	1.05 (1.02-1.08)	.001	1.23 (0.99-1.06)	.060
Gender								
Male	2.73 (1.25-5.94)	.012	1.25 (0.72-2.18)	.43	1.23 (0.67-2.24)	.51	2.58 (1.30-5.10)	.007
Smoking history								
Yes	1.15 (0.55-2.40)	.71	0.79 (0.46-1.35)	.39	1.59 (0.88-2.86)	.13	0.46 (0.24-0.87)	.016
Comorbidity								
Yes	0.89 (0.41-1.92)	.76	1.87 (1.13-3.08)	.014	1.54 (0.87-2.74)	.14	1.56 (0.85-2.87)	.16
Procedure								
Lobectomy	0.74 (0.44-1.25)	.26	1.04 (0.60-1.82)	.88	1.12 (0.68-1.85)	.66	0.82 (0.47-1.43)	.47
Performance status (ECOG)								
≥2	6.45 (1.75-23.8)	.005	21.3 (9.09-49.8)	<.001	16.0 (7.20-35.5)	<.001	379.4 (28.8-4992.5)	<.001
Postoperative complication								
Yes	1.35 (0.71-2.54)	.36	1.18 (0.74-1.90)	.49	1.49 (0.92-2.41)	.11	1.15 (0.61-2.14)	.67
Histology								
Adenocarcinoma	0.89 (0.47-1.69)	.72	0.88 (0.59-1.31)	.52	0.73 (0.46-1.18)	.20	1.36 (0.82-2.25)	.24
Size of invasive component	N/A	N/A	N/A	N/A	1.30 (1.07-1.58)	.010	1.24 (0.97-1.57)	.080
Lymphatic invasion								
Positive	5.03 (2.63-9.64)	<.001	1.72 (1.14-2.61)	.010	N/A	N/A	N/A	N/A
Vascular invasion								
Positive	1.14 (0.57-2.29)	.71	2.23 (1.40-3.56)	.001	2.49 (1.52-4.08)	<.001	1.52 (0.90-2.58)	.12
Pleural invasion								
Positive	0.96 (0.46-1.98)	.91	1.03 (0.66-1.59)	.91	0.83 (0.45-1.50)	.53	1.08 (0.67-1.76)	.75
Adjuvant chemotherapy								
Yes	0.97 (0.42-2.27)	.95	0.62 (0.39-0.98)	.040	0.66 (0.36-1.21)	.18	0.55 (0.32-0.95)	.033

HR, Hazard ratio; *CI*, confidence interval; *ECOG*, Eastern Cooperative Oncology Group; *N/A*, not available.

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Surgical and nonsurgical approaches to small-size nonsmall cell lung cancer

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ABSTRACT Lobectomy and systematic nodal dissection are still the standard for small-size (<3 cm) nonsmall cell lung cancer. There is growing interest in more parenchyma-sparing surgery, so-called sublobar resections (wedge resection or segmentectomy). Indeed, nonrandomised trials suggest that a segmentectomy may result in local control rates that are similar to lobectomy. Nonsurgical approaches, such as stereotactic ablative radiotherapy, consistently result in local control rates of ~90% and survival rates that are comparable to lobectomy. Therefore, we are moving towards an era in which several therapeutic possibilities are available, that are probably equivalent from an oncological point of view. Further trials are needed to define the optimal therapy for individual patients.

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