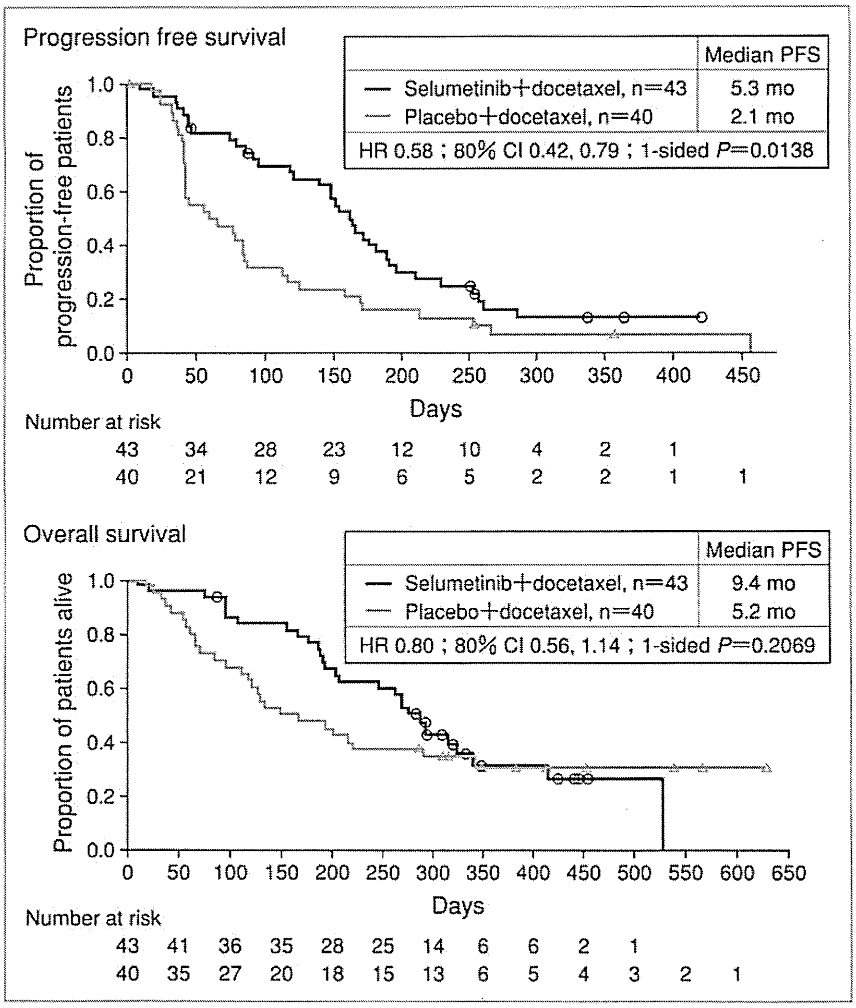
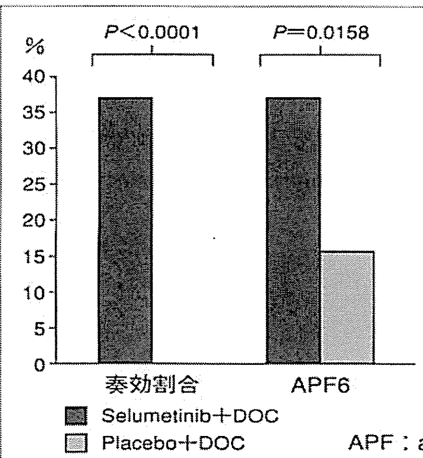


図4　ドセタキセル±selumetinib試験の生存曲線（文献[9]より引用）



	Selumetinib ＋DOC n(%)	Placebo ＋DOC n(%)
CR	0	0
PR	16(37.2)	0
SD	19(44.2)	20(50.2)
PD	8(18.6)	2(5.0)
NA	0	

APF：alive and progression-free at 6 months

図5　ドセタキセル±selumetinib試験の奏効割合とAPF6（文献[9]より引用）

である．肺がんでは*KRAS*遺伝子変異が5～10%に認められていたが[13]有効な薬剤はなかったため，今後の開発が待たれるところである．また，*RAF*遺伝子変異陽性肺がんの症例報告もあることから[14]，この対象群に対しての有用性も期待したい．

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Visceral Pleural Invasion Classification in Non–Small-Cell Lung Cancer in the 7th Edition of the Tumor, Node, Metastasis Classification for Lung Cancer: Validation Analysis Based on a Large-Scale Nationwide Database

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Objective: In the 7th tumor, node, metastasis (TNM) classification, visceral pleural invasion (VPI) is defined as invasion beyond the elastic layer, including invasion to the visceral pleural surface, and T1 tumors with VPI are upgraded to T2a. To validate this, we analyzed the survival of non–small-cell lung cancer patients from a nationwide database and evaluated the prognostic impact of VPI.

Methods: The clinicopathological characteristics and prognosis of 4995 patients who were included in the registry study of the Japanese Joint Committee of Lung Cancer Registry were retrospectively analyzed with a special interest in the prognostic impact of VPI. These patients underwent surgery in 2004 and were pathologically staged as T1a-3N0. VPI was defined as including PL1 and PL2 according to the 7th TNM Classification, but the Japanese Joint Committee of Lung Cancer Registry did not collect data regarding staining or how extensively VPI was evaluated in each participating institution.

Results: The survival differences were statistically significant between PL0 and PL1, PL1 and PL2, as well as PL2 and T3. There were no significant survival differences between T1a with VPI and T1b without VPI, or between T1a with VPI and T2a without VPI. There were no significant survival differences between T1b with VPI and T2a without VPI, or between T1b with VPI and T2b without VPI. There were no significant survival differences between T2a with VPI and T2b without VPI, or between T2b with VPI and T2b without VPI. T3 showed significantly worse prognosis than T2a with VPI and T2b with VPI.

Conclusions: In addition to the current TNM classification recommendations, in which T1 tumors with VPI are upgraded to T2a, T2a tumors with VPI should be classified as T2b.

Key Words: TNM classification, NSCLC, visceral pleural invasion

(*J Thorac Oncol.* 2013;8:606-611)

Visceral pleural invasion (VPI) of lung cancer has been known to be a poor prognostic factor.[1–10] In the 7th edition of the tumor, node, metastasis (TNM) classification for lung cancer, pleural invasion status is classified as follows: PL0, tumor within the subpleural lung parenchyma or superficial invasion into the pleural connective tissue beneath the elastic layer; PL1, tumor invasion beyond the elastic layer; PL2, tumor invasion to the pleural surface; and PL3, tumor invasion into any part of the parietal pleura.[11,12] Although the current TNM classification does not describe a survival difference between PL1 and PL2[11,12], VPI is defined to include PL1 and PL2. Tumors of 3 cm or less (T1a and T1b) with VPI (PL1 and PL2) are upgraded to T2a, whereas tumors greater than 3 and 7 cm or less (T2a and T2b) with VPI remain unchanged as T2.[13] These recommendations—to upgrade the T-classification according to VPI status—were based on the results of five retrospective studies[1–3,8,14] and not on the large-scale data accumulated by the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Project.[11]

In 2009, 253 Japanese institutions submitted information to the Japanese Joint Committee of Lung Cancer Registry (JJCLCR) regarding the outcome and clinicopathologic profiles of patients who had undergone surgical resection for primary lung cancer in the year 2004.[15] We retrospectively analyzed the survival of almost 5000 patients with pulmonary non–small-cell lung cancer (NSCLC) without node involvement from this registration to evaluate the impact of VPI on survival, and we

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propose incorporating VPI into T-status classification in the forthcoming TNM classification of the Union for International Cancer Control (UICC) staging system.

PATIENTS AND METHODS

Patient Cohort

As described previously, the JJCLCR performed a nationwide retrospective registry study in 2010 on the outcome and clinicopathologic profiles of resected primary lung neoplasms in Japan.[15] Only primary lung cancers that had been resected in 2004 at certified teaching hospitals in Japan, with a follow-up period of at least 5 years, were considered eligible for the registration. The committee received the registered data of 11,663 patients from 253 teaching hospitals. The registry questionnaire included the following items: (1) demographic background, (a) date of registry, (b) sex, (c) birth month and year, and (d) date of diagnosis; (2) preoperative status, (a) Eastern Cooperative Oncology Group performance status, (b) preoperative comorbidity, (c) smoking status, and (d) status of serum tumor markers (CEA, SCC or CYFRA, SLX and NSE, or Pro-GRP); (3) clinical T factors, (a) tumor size, (b) extent of invasion to the main bronchus, (c) pleural invasion, (d) intrapulmonary metastasis, (e) status of pleural effusion, (f) extent of atelectasis, and (g) status of invaded organ; (4) clinical N factor (status of removal of and metastasis to each lymph node); (5) clinical M factor (metastasized organ); (6) type of surgery, (a) induction therapy, (b) extent of lung resection, (c) place of tumor origin, (d) extent of lymph node removal, (e) gross curative status, (f) status of residual tumor, (g) lavage cytology findings, and (h) combined resection; (7) postoperative morbidity; (8) tumor histology; (9) adjuvant therapy; (10) pathological T factors, (a) tumor size, (b) extent of bronchial involvement, (c) pleural invasion, (d) intrapulmonary metastasis, (e) status of pleural effusion, (f) pleural dissemination, (g) status of atelectasis, and (h) status of invaded organ; (11) pathological N factor (status of removal of and metastasis to each lymph node); and (12) pathological M factor (metastasized organ). The extent of resection (exploratory, R0, R1, or R2) was also registered. Although the Japan Lung Cancer Society also recommends using not only hematoxylin and eosin (HE) staining but also elastic staining such as Victoria-blue van Gieson staining in VPI evaluation, the JJCLCR did not collect data regarding staining or how extensively VPI was evaluated in each participating institution. Diseases were staged based on the 7th edition of the UICC TNM classification.[11,12] Histopathologic classifications were described according to World Health Organization criteria.[16] Recurrent or multiple lung cancers were not included in the registration.

Of the 11,663 patients, 4995 patients (42.8%) underwent pulmonary resection (lobectomy or greater) and systematic mediastinal lymph node dissection for pathologically T1aN0, T1bN0, T2aN0, T2bN0, or T3N0 NSCLC. All these patients had curative resection, which was defined as complete removal of the ipsilateral hilar and mediastinal lymph nodes together with the complete resection of the primary tumor. Patients who had induction chemotherapy, radiotherapy, or both, and patients with evidence of residual tumor at the surgical margin, malignant effusion, interlobar invasion, or distant metastasis, verified intraoperatively or by means of postoperative pathologic examination were excluded from this study.

Statistical Analysis

Pleural invasion status was classified according to the 7th edition of the UICC TNM classification[11–13]: PL0, tumor within the subpleural lung parenchyma or superficial invasion into the pleural connective tissue beneath the elastic layer; PL1, tumor invasion beyond the elastic layer; PL2, tumor invasion to the pleural surface; and PL3, tumor invasion into any part of the parietal pleura. In the following descriptions, T-classification is determined excluding VPI status, but PL3 tumors are classified as T3.

First, we analyzed the overall survival of PL0, PL1 and PL2 or T3 patient groups. Second, defining VPI to include PL1 and PL2, we analyzed the overall survival of the pT1a patient groups with or without VPI, pT1b with or without VPI, pT2a with or without VPI, and pT2b with or without VPI or T3. The follow-up period was defined as the time from the date of surgery to the most recent follow-up examination. The survival period was defined as the number of months from the day of surgery to the day of death from any cause. Survival curves were estimated using the Kaplan-Meier method. Differences in survival were tested using the log-rank test. A p value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using software packages (SAS version 9.1.3 [SAS Institute, Inc., Cary, NC], SPSS version 19 [IBM Corp., New York, NY]).

This study was approved by the institutional review board of Osaka University Medical Hospital, where the office of JJCLCR is located, on August 13, 2009 (approval no. 09124).

RESULTS

Patient Characteristics and Visceral Pleural Invasion

Table 1 shows the patient characteristics. There were 2981 men and 2014 women, aged 15 to 90 years (median, 67 years). The extent of pulmonary resection was pneumonectomy (n = 65), bilobectomy (n = 122), and lobectomy (n = 4808). The histological types were adenocarcinoma (n = 3638), squamous cell carcinoma (n = 1028), adenosquamous carcinoma (n = 84), large-cell carcinoma (n = 149), and other histological types (n = 96).

Survival Differences

The overall 5-year survival rates for PL0 (n = 3606), PL1 (n = 727), PL2 (n = 219), and T3 (n = 443) patients were 87%, 77%, 69%, and 54%, respectively. There were significant survival differences between PL0 and PL1 (p < 0.001), between PL1 and PL2 (p = 0.023), and between PL2 and T3 (p < 0.001) patients (Fig. 1).

The survival curves stratified by T and VPI status are shown in Figure 2*A*. Figure 2*B* shows the survival impact of VPI on T1a tumors. Although T1a tumors with VPI had a

TABLE 1. Patient Characteristics

	No. of Patients (%)				
	VPI Factor of T1/T2 Cases				
Characteristics	**PL0**	**PL1**	**PL2**	**T3**	**Total**
Age, yr					
Median (range)	67 (15–89)	68 (31–90)	68 (30–85)	69 (34–83)	67 (15–90)
Sex					
Men	2034 (56)	466 (64)	142 (64)	339 (77)	2981 (60)
Women	1572 (44)	261 (36)	77 (36)	104 (23)	2014 (40)
Surgery					
Lobectomy	3477 (96)	706 (97)	215 (98)	410 (93)	4808 (96)
Bilobectomy	95 (3)	12 (2)	3 (1)	12 (3)	122 (2)
Pneumonectomy	34 (1)	9 (1)	1 (1)	21 (5)	65 (1)
Histology					
Adenocarcinoma	2743 (76)	505 (70)	168 (77)	222 (50)	3638 (73)
Squamous cell carcinoma	660 (18)	168 (23)	37 (17)	163 (37)	1028 (21)
Adenosquamous carcinoma	55 (2)	14 (2)	2 (1)	13 (3)	84 (2)
Large-cell carcinoma	81 (2)	32 (4)	7 (3)	29 (7)	149 (3)
Others	67 (2)	8 (1)	5 (2)	16 (4)	96 (2)
Tumor diameter, cm					
<2	1558 (43)	199 (27)	40 (18)	29 (7)	1826 (37)
2.1–3	1125 (31)	215 (30)	72 (33)	71 (16)	1483 (30)
3.1–5	805 (22)	252 (35)	81 (37)	130 (29)	1268 (25)
5.1–7	118 (3)	61 (8)	26 (12)	72 (16)	277 (6)
≥7.1–	–	–	–	141 (32)	141 (3)
Total	3606	727	219	443	4995

VPI status was defined according to the 7th edition of the tumor, node, metastasis classification for lung and pleural tumors.
VPI, visceral pleural invasion

significantly poorer prognosis than T1a tumors without VPI ($p < 0.001$), there were no significant survival differences between T1a tumors with VPI and T1b tumors without VPI ($p = 0.083$) or T2a tumors without VPI ($p = 0.221$).

Figure 2C shows the survival impact of VPI on T1b tumors. Although T1b tumors with VPI had a significantly poorer prognosis than T1b tumors without VPI ($p = 0.001$), there were no significant survival differences between T1b

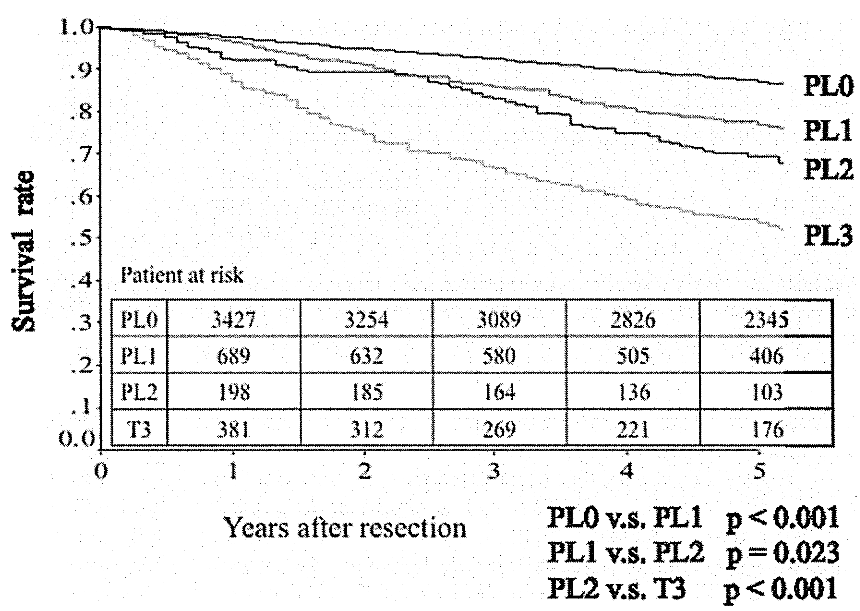

FIGURE 1. Overall survival curves of PL0, PL1, PL2, and T3 patients.

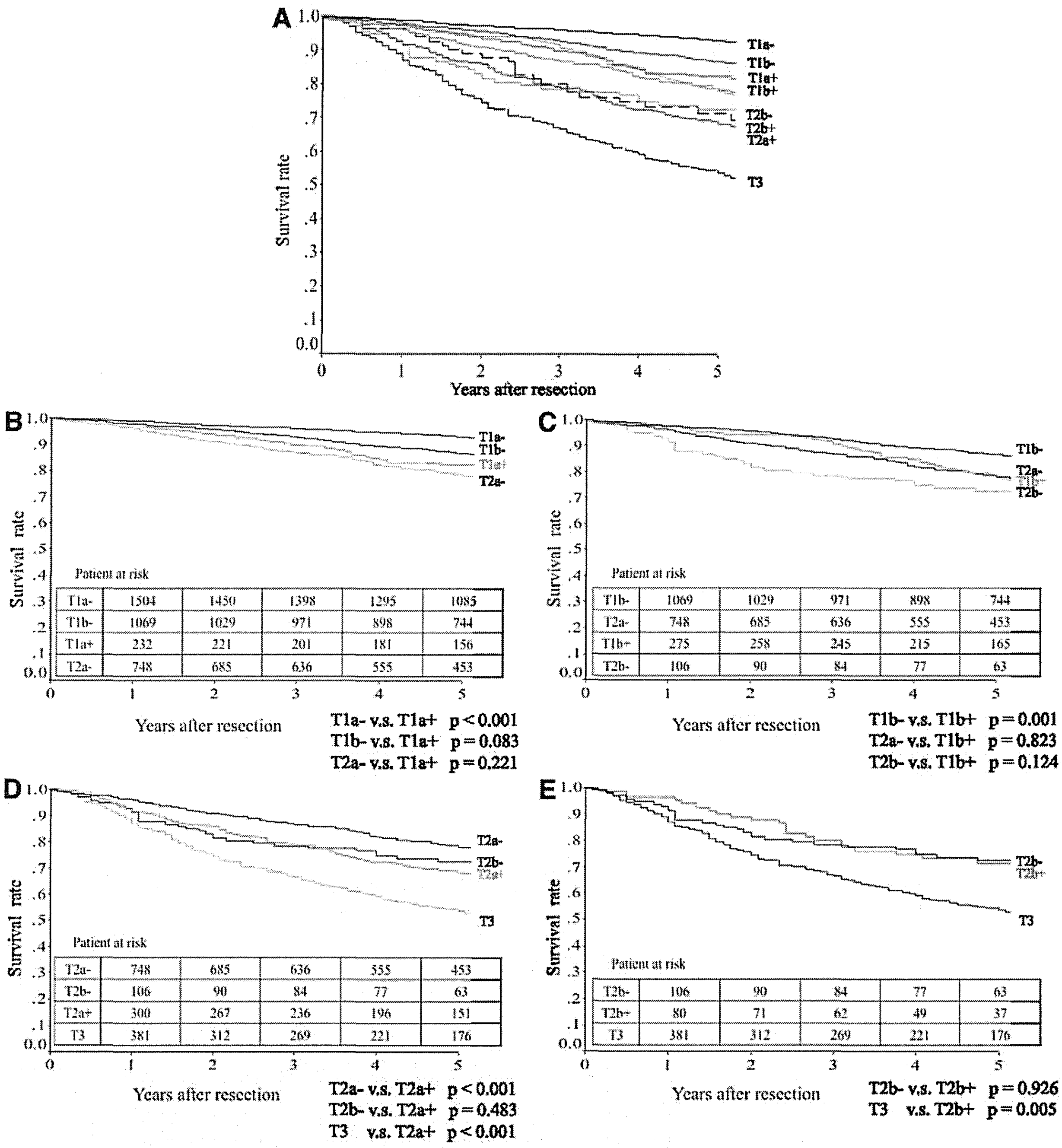

FIGURE 2. (*A*) Survival curves stratified by T stage and VPI status. (*B*) Survival curves of T1a/VPI–, T1b/VPI–, T2a/VPI–, and T1a/VPI+. (*C*) Survival curves of T1b/VPI–, T2a/VPI–, T2b/VPI–, and T1b/VPI+. (*D*) Survival curves of T2a/VPI–, T2b/VPI–, T2b/VPI–, and T2a/VPI+.(*E*) Survival curves of T2b/VPI–, T3, and T2b/VPI+.

tumors with VPI and T2a tumors without VPI ($p = 0.823$) or T2b tumors without VPI ($p = 0.124$).

Figure 2*D* shows the survival impact of VPI on T2a tumors. T2a tumors with VPI had a significantly poorer prognosis than T2a tumors without VPI ($p < 0.001$). There were no significant survival differences between T2a tumors with VPI and T2b tumors without VPI ($p = 0.483$). T2a tumors with VPI had a significantly better prognosis than T3 tumors ($p < 0.001$).

Figure 2*E* shows the survival impact of VPI on T2b tumors. There were no significant survival differences between T2b tumors with VPI and T2b tumors without VPI ($p = 0.926$). T2b tumors with VPI had a significantly better prognosis than T3 tumors ($p = 0.005$).

DISCUSSION

VPI is known to be a poor prognostic factor of NSCLC patients and is defined as a factor to upgrade T1a/T1b tumors to T2a in the 7th Edition of the TNM Classification for Lung and Pleural Tumours.[11,12,14] Travis et al.[13,17,18] recommend the use of elastic stains when invasion beyond the elastic layer is not clear on evaluation of HE sections. Although the Japan Lung Cancer Society also recommends using not only HE staining, but also elastic staining such as Victoria-blue van Gieson staining in VPI evaluation, the JJCLCR did not collect data regarding staining or how extensively VPI was evaluated in each participating institution. This is a major limitation of the present study.

In the present study, PL1 patients had a significantly poorer prognosis than PL0 patients, consistent with many previous reports.[1–10] PL2 patients had a significantly poorer prognosis than PL1 patients. The survival difference between PL1 and PL2 patients remains controversial. Kawase et al.[10] analyzed a cohort of more than 2700 patients, using the current VPI definition and elastic staining in all cases for VPI diagnosis, and reported no survival differences between PL1 and PL2 patients. Moreover, several other researchers have reported similar results.[2,6,9] In contrast, Sakakura et al.[4] reported significant differences in survival between PL1 and PL2 patients, but they did not describe whether or not they used elastic stains in diagnosing VPI status. In the data of the JJCLCR registry, it is not clear in what portion of the accumulated cases elastic staining was employed, and there remains some uncertainty regarding the determination of pleura invasion. Some PL0 patients might have been miscategorized as PL1 without the use of elastic staining, which may have led to the significant survival difference observed between PL1 and PL2 patients. To conclude whether or not a difference between PL1 and PL2 survival is valid, it is necessary to study more patients with VPI diagnoses made with the help of elastic staining.

To analyze the prognostic impact of VPI on T-status classification in the current cohort, we defined VPI to include PL1 and PL2 patients, as defined by the 7th edition of the TNM Classification for Lung and Pleural Tumours. T1a with VPI had a significantly poorer prognosis than T1a without VPI, but there were no significant survival differences between T1a with VPI and T1b without VPI, or between T1a with VPI and T2a without VPI. To summarize, T1a with VPI had prognosis similar to that of T1b/T2a without VPI, which suggests it is credible to upgrade T1a with VPI to T2a.

T1b with VPI had a significantly poorer prognosis than T1b without VPI, but there were no significant survival differences between T1b with VPI and T2a without VPI or between T1b with VPI and T2b without VPI. To summarize, T1b with VPI had a similar prognosis to T2a/T2b without VPI, which suggests it is reasonable to upgrade T1b with VPI to T2a, as described in the 7th edition of the TNM Classification for lung cancer.[11,12]

The most significant information of the present study is the outcome of T2a with VPI. T2a with VPI had a significantly poorer prognosis than T2a without VPI. There were no significant survival differences between T2a with VPI and T2b without VPI. T2a with VPI had a significantly better prognosis than T3. To summarize, T2a with VPI had a similar prognosis to T2b without VPI, which suggests T2a with VPI should be upgraded to T2b.

TABLE 2. T-Classification Comparison

Tumor Diameter, cm	VPI Ctatus	7th Edition T-Classification	Our Proposal
<2	−	T1a	T1a
<2	+	T2a	T2a (or T1b)
2.1–3	−	T1b	T1b
2.1–3	+	T2a	T2a
3.1–5	−	T2a	T2a
3.1–5	+	T2a	T2b
5.1–7	−	T2b	T2b
5.1–7	+	T2b	T2b

VPI− = PL0, VPI+ = PL1 or PL2.
VPI, visceral pleural invasion.

In the current cohort, there were no significant survival differences between T2b with VPI and T2b without VPI. T2b with VPI had a significantly better prognosis than T3. To summarize, T2b with VPI had a prognosis similar to that of T2b without VPI, which suggests there is no need to upgrade T2b with VPI. These suggestions are summarized in Table 2, and they include some differences from the conclusions of previous publications.[2,8,10]

A major limitation of the current study is that we do not know how thoroughly VPI was evaluated including elastic staining, in each participating institution. The differences observed may have been attributable to misdiagnoses of VPI status due to the lack of elastic staining use. However, the recommendation of the 7th edition of the TNM classification, that is, to upgrade T-classification according to VPI status, was determined on the basis of the results of some retrospective studies of small cohorts, in contrast to the large number cohort accumulated by the IASLC Lung Cancer Project. Moreover, the IASLC Lung Cancer Project also lacks detailed information on VPI status evaluation methodology. Therefore, we consider that a worldwide large-scale study that is limited to patients whose VPI status is diagnosed using elastic staining is necessary to determine the true impact on survival of pleural invasion and VPI.

In conclusion, in addition to the current TNM Classification recommendations—to upgrade tumors of 3 cm or less with VPI to T2a—tumors greater than 3 cm and 5 cm or less with VPI should be upgraded to T2b. However, more detailed further research is necessary for the next edition of the TNM classification for lung and pleural tumours, using a large-scale database with VPI status diagnosed using elastic staining.

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Results of T4 Surgical Cases in the Japanese Lung Cancer Registry Study

Should Mediastinal Fat Tissue Invasion Really be Included in the T4 Category?

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Introduction: T4 lung cancer is a heterogeneous group of locally advanced disease. We hypothesized that patients in whom T4 lung cancer invaded only mediastinal fat tissue would show better prognosis after surgery than patients in whom T4 disease invaded other organs. The present study aimed to investigate how different invasive features of T4 disease impacted prognosis, and what types of patients with T4 disease could benefit most from surgical treatment.

Methods: A nationwide registry study on lung cancer surgical cases during 2004 was conducted by the Japanese Joint Committee of Lung Cancer Registry, including registries of 11,663 cases within Japan. The present study analyzed 215 of these cases involving T4 structures or with ipsilateral nonprimary lobe pulmonary metastasis (PM).

Results: Reasons for T4 classification included invasion of only mediastinal tissue in 32 cases (15%), invasion of other structures in 96 cases (45%), and ipsilateral different lobe PM in 87 cases (40%); among these three groups, there were no significant differences in survival, nodal status, and patterns of first recurrence. Multivariate analysis showed an age of 70 years or above ($p = 0.022$) and nodal status ($p = 0.004$) to be significant prognostic factors. T4N0 patients less than 70 years of age showed significantly better prognosis than those who were T4N1–2 and 70 years of age or older ($p = 0.0001$; 5-year survival rate 50.3 versus 19.9%).

Conclusions: There was no significant difference in survival between T4 patients with only mediastinal fat invasion and those with other T4 organ invasion and ipsilateral different lobe PM, demonstrating appropriateness of the T4 category definition in the current tumor, node, metastasis staging system. Age and nodal status were significant independent prognostic factors in T4 patients, and the best surgical candidates were shown to be T4N0 patients who were less than 70 years of age and had a 5-year survival rate of more than 50%.

Key Words: T4 lung cancer, Mediastinal tissue, Pulmonary metastasis.

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The T4 category of lung cancer is defined by invasion of the heart, mediastinal fat tissue, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body and carina, and additional nodules in ipsilateral different lobes.[1] In T4 cases, mediastinal fat tissue invasion is considered to be the last step before involving other mediastinal organs, such as the great vessels, esophagus, or trachea (Fig. 1).

We hypothesized that patients in whom T4 lung cancer invaded only mediastinal fat tissue would show better prognosis after surgery than those in whom T4 lung cancer invaded other organs. In the present study, we analyzed the outcomes of patients enrolled in the Japanese Lung Cancer Registry Study, who had T4 disease and underwent surgery. We also investigated whether surgery conferred different survival benefits on different types of T4 lung cancer cases.

PATIENTS AND METHODS

In 2010, the Japanese Joint Committee of Lung Cancer Registry conducted a nationwide retrospective registry study on surgical cases of primary lung cancer that had occurred during 2004. The study included registries of 11,663 cases from 253 teaching hospitals in Japan; each registry contained the previously described clinicopathologic profiles and

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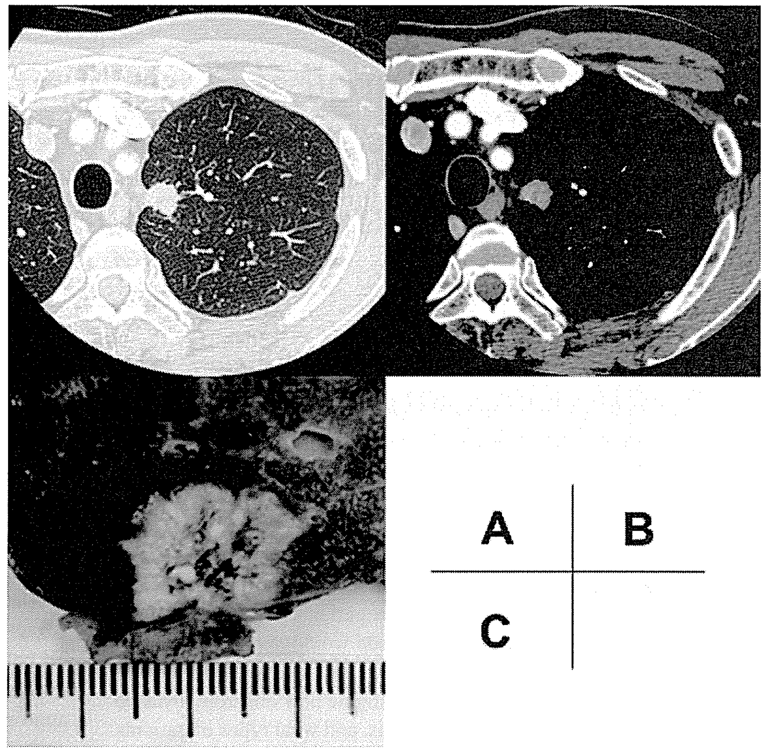

FIGURE 1. A case of pT4 disease invading the mediastinal fat tissue. *A*, CT scan (lung field window) showing a left upper lobe tumor with visceral pleura involvement. *B*, CT scan (mediastinal window) showing the tumor invading the mediastinal fat tissue. *C*, Photograph of the formalin-fixed resected specimen. CT, computed tomography.

prognoses.[2] The information collected about each tumor node metastasis (TNM) classification was used to reclassify each case according to the 7th edition of the International Union Against Cancer tumor, node, metastasis (TNM) staging system published in 2009.[1]

Of these cases, there were 218 surgical cases involving the neighboring T4 structures or ipsilateral nonprimary lobe pulmonary metastasis (PM). For the present study, three cases were excluded because the patients had both neighboring organ invasion and PM. The remaining 215 surgical cases were used in the present analysis.

Statistical Analysis

Survival was calculated by the Kaplan–Meier method, and differences in survival were determined by the log-rank test. Time zero was the date of surgery, and the terminal events were death because of cancer, noncancer, or unknown causes. Both univariate and multivariate analyses of prognostic factors were carried out using Cox proportional hazards regression models. Hazard ratios (HRs) and 95% confidence intervals were calculated. A p value less than 0.05 was considered to be statistically significant.

RESULTS

Patient Characteristics

Table 1 shows characteristics of the 215 patients enrolled in the study. The patients consisted of 166 men (77%) and 49 women (23%), with a mean age of 65.2 years and a mean tumor size of 4.5 cm. The reasons for T4 disease classification included neighboring organ invasion in 128 patients (60%) and ipsilateral different lobe PM in 87 patients (40%). Among the 128 patients with T4 disease invading neighboring organs, 32 cases (25%) invaded only mediastinal fat tissue and 96 (75%) invaded other anatomical structures. Six patients with T4 disease invading both mediastinal fat tissue and other structures were classified as other organs invasion group. The tumor cell types were adenocarcinoma in 99 (46%), squamous cell carcinoma in 77 (36%), and others in 39 patients (18%). R status was R0 in 123 (57%), R1 in 24 (11%), and R2 in 58 patients (27%). Pathologic N status was N0 in 107 (50%), N1 in 25 (12%), N2 in 79 (37%), and N3 in four patients (2%).

N and R Status Grouped by Reasons for T4 Category

Table 2 shows pathologic N status grouped by involved T4 organs. There were no significant differences in N status among the three groups ($p = 0.537$). Table 3 demonstrates R status grouped by involved T4 organs. Mediastinal fat invasion group showed significantly higher incidence of R0 than the other two groups ($p = 0.017$).

Univariate and Multivariate Analyses of Prognostic Factors

Univariate and multivariate analyses of prognostic factors were performed by means of Cox proportional hazard regression models. Univariate analysis showed age ($p = 0.02$), tumor size ($p = 0.007$), and pathologic nodal status ($p = 0.004$) to be significant prognostic factors; however, the reason for T4 disease was not a significant prognostic factor ($p = 0.949$) (Table 4). Multivariate analysis showed that ages 70 years and

TABLE 1. Patient Characteristics in Surgical Cases with Pathological T4 Disease in Japanese Lung Cancer Registry Study

No. of patients	215
Sex	
Male	166 (77%)
Female	49 (23%)
Age (yr)	
Range	32–84
Mean ± SD	65.2 ± 10.4
Tumor size (cm)	
Range	0–15
Mean ± SD	4.5 ± 2.4
Reasons for T4 disease	
Neighboring organ invasion	128 (60%)
Invading only mediastinal fat	32 (15%)
Invading other structures	96 (45%)
Great vessels	58
Heart	21
Esophagus	8
Vertebra	6
Carina	5
Trachea	3
Recurrent nerve	2
Ipsilateral different lobe PM	87 (40%)
Histological subtype	
Adenocarcinoma	99 (46%)
Squamous cell carcinoma	77 (36%)
Others	39 (18%)
R status	
R0	123 (57%)
R1	24 (11%)
R2	58 (27%)
RX (unclassified)	10 (5%)
Pathological nodal status	
N0	107 (50%)
N1	25 (12%)
N2	79 (37%)
N3	4 (2%)

PM, pulmonary metastasis; SD, standard deviation.

TABLE 2. N Status by Reasons for T4 Category

Reasons for T4	No. of Patients	N Status N0 (%)	N1 (%)	N2 (%)	*p*
Mediastinal fat invasion	31	18 (58)	4 (13)	9 (29)	0.537
Other organs invasion	95	44 (46)	14 (15)	37 (39)	—
Ipsilateral different lobe PM	85	45 (53)	7 (8)	33 (39)	—
Total	211	107 (51)	25 (12)	79 (37)	—

PM, pulmonary metastasis.

TABLE 3. R status by Reasons for T4 category

Reasons for T4	No. of Patients	R Status R0 (%)	R1 (%)	R2 (%)	*p*
Mediastinal fat invasion	32	26 (81)	2 (6)	4 (13)	0.017
Other organs invasion	94	47 (50)	16 (17)	31 (33)	
Ipsilateral different lobe PM	79	50 (63)	6 (8)	23 (29)	
Total	205	123 (60)	24 (12)	58 (28)	

PM, pulmonary metastasis

TABLE 4. Univariate Analysis of Prognostic Factors Using Cox Proportional Hazards Regression Models

Factors	Hazard Ratio	95% CI	*p*
Age (per yr increase)	1.022	1.003–1.041	0.020
Sex			
Male	1.000	—	—
Female	0.675	0.441–1.032	0.069
Tumor size (per cm increase)	1.753	1.164–2.640	0.007
Reasons for T4 disease			0.949
Mediastinal fat invasion	1.000	—	—
Other organs invasion	0.980	0.581–1.653	0.939
Ipsilateral different lobe PM	1.042	0.619–1.753	0.877
Cell type			
Non-Sq	1.000	—	—
Sq	1.138	0.792–1.636	0.484
Pathological nodal status			0.004
N0	1.000	—	—
N1	1.561	0.890–2.739	0.121
N2	1.890	1.297–2.754	0.001

CI, confidence interval; Sq, squamous cell carcinoma; PM, pulmonary metastasis.

above (p = 0.022; HR = 1.516) and pathologic nodal status (p = 0.004; HR for N0 versus N1: 1.362; HR for N0 versus N2: 1.906) were significant prognostic factors (Table 5).

Survival Analysis

Figure 2 shows the overall survival curves of the 11,663 surgical cases in the Japanese Lung Cancer Registry Study grouped by pT factors. The 3- and 5-year overall survival rates of patients with T4 disease after surgery were 48.3% and 34.5%, respectively. Figure 3 presents survival curves grouped by three reasons for T4 category (invasion of mediastinal fat, invasion of other structures, and ipsilateral different lobe PM); the 5-year survival rates in these groups were 36.1%, 36.2%, and 33.0%, respectively, with no significant between-group differences in survival. The 30-day mortality was 0.47% (1 of 215).

Table 6 describes types of first recurrence grouped by three reasons for T4 category. There was no significant difference in patterns of first recurrence among the three groups (p = 0.487).

Figure 4 shows survival curves grouped by pathologic nodal status; the 5-year survival rates in pN0, pN1, and pN2

TABLE 5. Multivariate Analysis of Prognostic Factors Using Cox Proportional Hazards Regression Models

Factors	Hazard Ratio	95% CI	p
Age (yr)			
<70	1	—	—
≥70	1.516	1.061–2.167	0.022
Tumor size (per cm increase)	1.074	0.996–1.159	0.065
pN status			0.004
pN0	1	—	—
pN1	1.362	0.767–2.420	0.291
pN2	1.906	1.306–2.781	0.001

CI, confidence interval; pN, pathologic nodal.

patients were 45.0%, 27.0, and 25.0%, respectively. Patients with pN0 disease showed significantly better prognosis than those with pN2 disease ($p = 0.0006$). Figure 5 shows survival curves grouped by R status; the 5-year survival rates in R0, R1, and R2 patients were 41.2%, 33.3%, and 18.4%, respectively. Patients with R0 disease showed significantly better prognosis than those with R2 disease ($p = 0.0002$). However, there were no significant differences in survival between patients with R0 and R1, and those with R1 and R2 (R0 versus R1; $p = 0.5536$; R1 versus R2; $p = 0.0915$).

The survival curves and 5-year survival rates of the T4 surgical cases grouped by age (< 70 years or ≥ 70 years) and pathologic nodal status (N0 or N1–2) are shown in Figure 6. Patients without nodal involvement and less than 70 years of age showed significantly better prognosis than those with nodal involvement and were 70 years of age or older ($p = 0.0001$; 5-year survival rate 50.3% versus 19.9%).

DISCUSSION

According to the 7th edition of the TNM staging system, the T4 stage includes invasion of the following adjacent organs: heart, mediastinal tissue, great vessels, trachea,

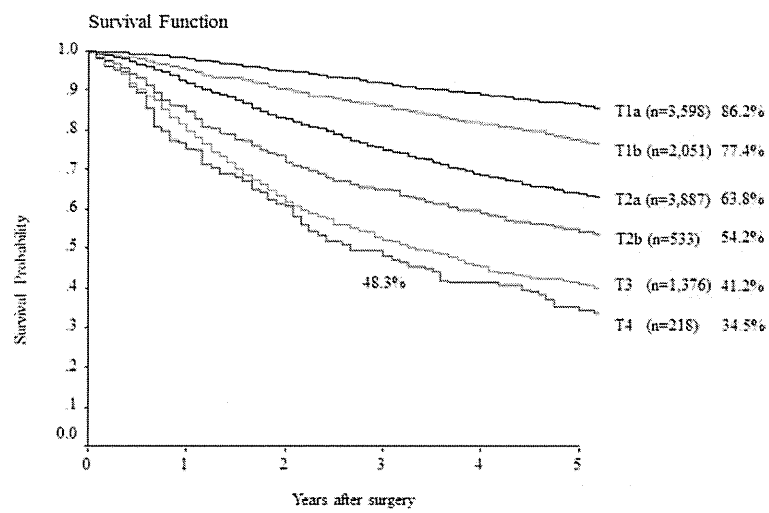

FIGURE 2. Survival curves of the 11,663 surgical cases in the Japanese Lung Cancer Registry Study grouped by pT factor International Union Against Cancer (IUCC)-Tumor Node Metastasis v. 7).

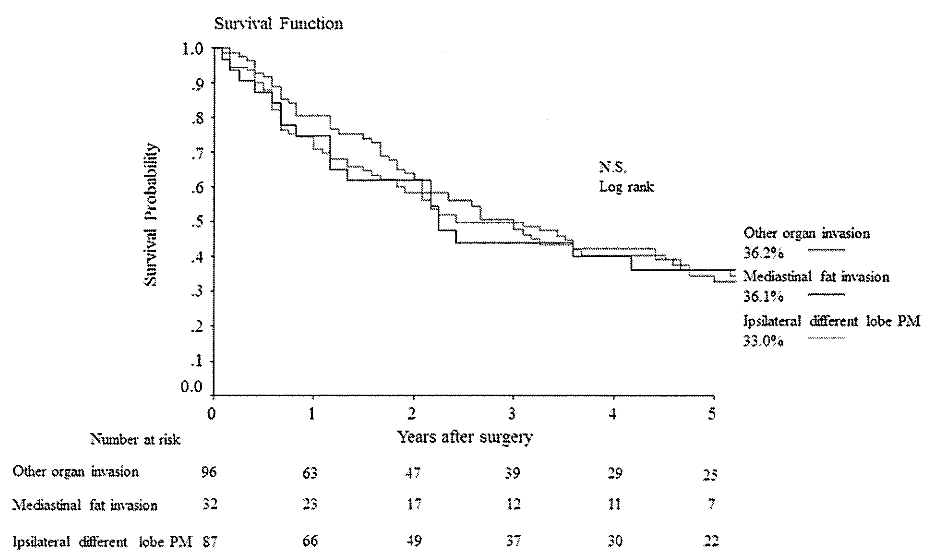

FIGURE 3. Survival curves of patients with pT4 disease grouped by reasons for being classified as T4. NS, not significant; PM, pulmonary metastasis.

TABLE 6. Types of First Recurrence by Reasons for T4 category

Reasons for T4	No. of Patients	First Recurrent Site: Local	Local + Distant	Distant	p
Mediastinal fat invasion	18	5 (28%)	4 (22%)	9 (50%)	0.487
Other organs invasion	46	8 (17%)	12 (26%)	26 (57%)	—
Ipsilateral different lobe PM	52	16 (31%)	8 (15%)	28 (54%)	—
Total	116	29 (25%)	24 (21%)	63 (54%)	—

PM, pulmonary metastasis.

recurrent laryngeal nerve, esophagus, body of vertebra, and carina.[1] Because of this great variety in neighboring organs, and the small number of resected T4 cases, there have been few review articles describing the prognosis of a substantial number of resected T4 cases.[3–6] Thus, the judgment for surgical indication is left to each institution.

Among the T4 diseases with neighboring structure invasion, mediastinal fat tissue invasion is considered to be the last step before involving other T4 organs, including mediastinal vessels, esophagus, or trachea (Fig. 1). The complete combined resection of mediastinal fat tissues adjacent to the primary tumor is technically much easier than that of other T4 organs. Therefore, we hypothesized that T4 patients with only mediastinal fat invasion might have a better prognosis than those with other T4 organ invasion or ipsilateral nonprimary lobe PM. However, the results of the present study found no significant differences in survival among these three groups with T4 disease. Although the number of patients in each T4 subset is small, these findings confirm the appropriateness of the definition of the T4 category in the current TNM staging system.

Two points constitute the prime criteria in determining the indication for resecting the neighboring organs in T4 lung cancer patients,. One is whether complete resection is possible, and the other is the length of survival that can be expected for the T4 patient even after complete resection. The presence or absence of complete resection is an absolute prognostic factor in lung cancer surgery. Although many previous reports have suggested the technical feasibility of surgery for T4 disease, fewer series have demonstrated long-term results after the extended resection.[3–6] Grunenwald et al.[7] suggested that the T4 category includes two types of disease, calling one *potentially resectable T4* and the other *definitively unresectable T4*. The potentially resectable T4 group includes cases where complete resection seems possible, based on the degree of invasion, and a better prognosis is anticipated; this group includes invasion of the carina, left atrium, superior vena cava (SVC), and mediastinal tissue. For example, in patients having tumor that directly invades the SVC, the prognosis after combined resection of the SVC is relatively good,[8–11] with a 5-year survival rate of 36%.[12] However, cases with invasion of the trachea, vertebra, and esophagus are considered to be definitively unresectable T4 because reconstruction is difficult, surgical stress is unreasonable, the operative morbidity and mortality are high, and a good prognosis cannot be expected after the resection. Grunenwald et al.[7] reported the clear identification of esophageal invasion as the worst prognostic factor,[4] and most surgeons consider invasion of the esophagus, vertebral bodies, or trachea as contraindications to surgery.

The present study was based on a nationwide registry that collected 11,663 cases during 2004 from 253 major teaching hospitals in Japan; however, only an extremely small number of surgical cases involved invasion of the esophagus, vertebra, and trachea ($n = 8$ [0.07%], $n = 6$ [0.05%], and $n = 3$

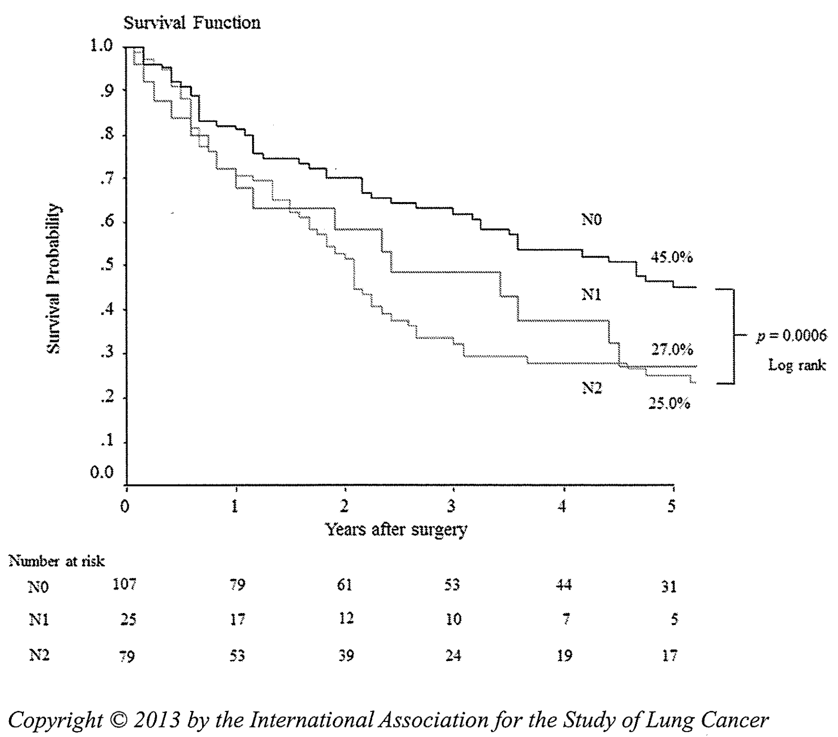

FIGURE 4. Survival curves of patients with pT4 disease grouped by pN status.

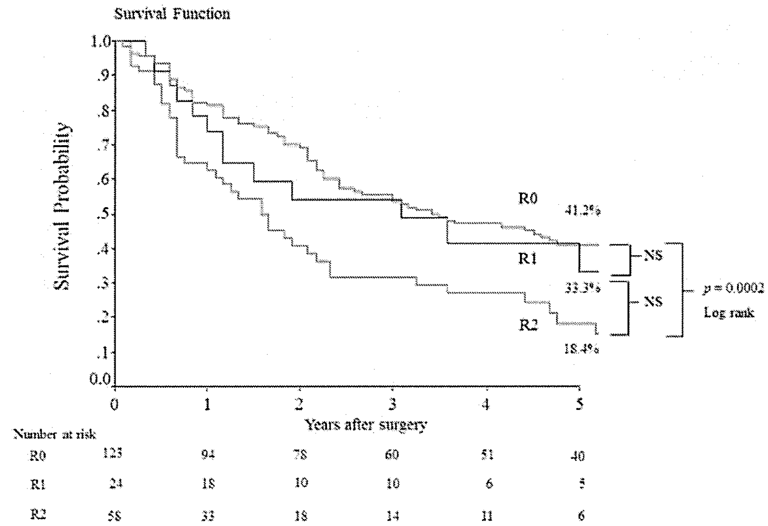

FIGURE 5. Survival curves of patients with pT4 disease grouped by R status. NS, not significant.

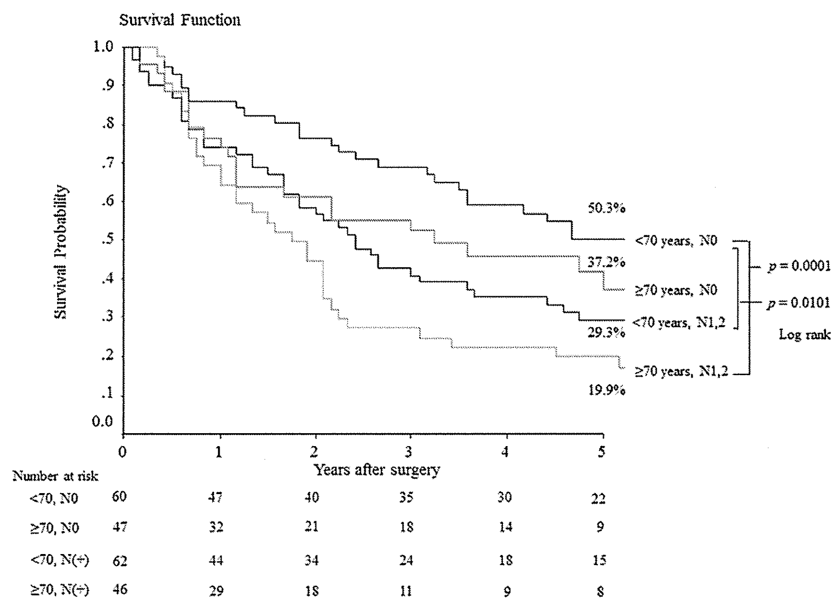

FIGURE 6. Survival curves of patients with pT4 disease grouped by age and nodal status.

[0.03%], respectively; Table 1). Overall survival of T4 surgical cases in this registration study showed better prognosis, with a 5-year survival rate of 35.4% (Fig. 2) compared with a 5-year survival rate of 22% reported in the International Association for the Study of Lung Cancer[13] staging article in 2007. These relatively good results for T4 surgical cases were probably because of the recent changes in how Japanese surgeons select T4 disease patients as surgical candidates, in accordance with the results of previous reports to determine the prognosis of resected T4 disease.[3–7] This patient selection bias may be one of the reasons why there was no significant difference in survival among the three subgroups of T4 category in our study (Fig. 3). Very low surgical mortality of these T4 patients in this registry (1 of 215; 0.47%) may support this hypothesis.

Multivariate analysis showed that nodal status was the most important prognostic factor in T4 disease (Table 5), similar to other lung cancer patients. Surgery seemed to be contraindicated in patients with mediastinal metastasis because of their poor prognosis (HR = 1.906; $p = 0.001$), as previously reported. In the TNM 7th edition, T4N0-1M0 was downstaged from stage IIIB to stage IIIA. However, the indication for N1 disease is still controversial, as some reports suggest a very poor prognosis for patients with hilar metastasis (N1). A T4N0M0 case where complete resection is possible is a good candidate for surgical treatment, as shown in Figure 4, and to perform a meticulous evaluation of the N factor through computed tomography scan, positron emission tomography scan, endobronchial ultrasound, or mediastinoscopy before any judgment is indispensable.[4–16]

In the present study, age and nodal status were revealed to be independent prognostic factors. T4 patients 70 years of age or more with any nodal involvement (N1, 2) showed poor prognosis, whereas T4 patients less than 70 years of age without nodal involvement (N0) showed good prognosis, with a 5-year survival rate of more than 50%. There was no significant difference in the distribution of involved T4 organs between the group of patients who were 70 years of age or older and that group in which patients were less than 70 years of age, in the present study (data not shown). Because the risk–benefit ratio for extended surgical resection is very high in older T4 patients,[3] special care must be taken to decide the surgical indication, especially in node-positive T4 patients who are more than 70 years old. In particular, the outcomes after resection in patients with carinal involvement reportedly show a high average operative mortality of 17% (range, 7%–29%).[17–21] According to the evidence-based clinical practice guidelines of the American College of Chest Physicians,[17] it is recommended that surgical candidates with T4 disease should be very carefully selected, and surgical resection should be carefully undertaken only at a specialized center because of the limited survival and the high mortality. It is necessary for surgeons to collectively consider the patient's nodal status, age, quality of life after resection, the presence of alternative treatment, the extent of surgery, and subsequent morbidity and mortality before performing surgery for T4 disease.

CONCLUSION

Although T4 patients with only mediastinal fat invasion showed high incidence of R0 resection, there was no significant difference in survival between T4 patients with only mediastinal fat invasion and those with other T4 organ invasion, or ipsilateral different lobe PM, which demonstrates the appropriateness of the T4 category definition in the current TNM staging system. Patients with involvement of T4 structures should be very carefully selected for surgical resection because of the limited survival. Before undergoing surgery, patients should be subjected to careful assessment of hilar and mediastinal nodal involvement, particularly for those who are 70 years of age or older. On the basis of the findings obtained to date, the best prognosis for T4 disease is found for T4N0 patients who are less than 70 years of age and have a 5-year survival rate of more than 50%.

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Comparison of Three Measurements on Computed Tomography for the Prediction of Less Invasiveness in Patients With Clinical Stage I Non–Small Cell Lung Cancer

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Background. A greater proportion of ground-glass opacity (GGO) is well known to be strongly associated with less invasive lung adenocarcinoma. Recently, the solid area diameter has also been reported to be a simple and better marker for the same purpose compared with the whole nodule diameter.

Methods. From 1997 to 2009, 383 patients with clinical T1-2N0M0 non–small cell lung cancer (NSCLC) with a solid area of 3 cm or less underwent surgical resection, and their preoperative high-resolution computed tomographic images were preserved in Digital Imaging and Communications in Medicine format. Less invasive lung cancer was defined as having no vascular, lymphatic, or pleural invasion or lymph node metastasis. We compared the solid area and whole nodule diameters and proportion of GGO, with the objective of predicting less invasive lung cancer.

Results. Among the 383 patients, 187 were men, 335 had adenocarcinoma histologic type, 242 had less invasive lung cancer, and 43 experienced recurrence. Receiver operating characteristic (ROC) analysis to predict less invasive lung cancer showed that the area under the curve of proportion of GGO was the highest (0.848; 95% confidence interval [CI], 0.810–0.886), followed by the solid area diameter (0.785; 95% CI, 0.740–0.829), and then whole nodule diameter (0.621; 95% CI, 0.565–0.677). Multiple logistic regression analyses revealed that proportion of GGO was the only significant predictor of less invasive lung cancer. The proportion of GGO was also found to be a significant prognostic factor of disease-free survival (DFS) along with solid area diameter by multivariate analysis. Regardless of the solid area diameter, no patient with a greater proportion of GGO (> 50%) experienced recurrence.

Conclusions. Proportion of GGO remains important for predicting less invasive lung cancer.

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The standard treatment for patients with stage IA non–small cell lung cancer (NSCLC) remains lobectomy. This is primarily because a randomized trial conducted by the Lung Cancer Study Group demonstrated that limited resection is significantly associated with an increase of local recurrence, measured at 3 times that of lobectomy [1]. The causes of local recurrence are thought to be an insufficient surgical margin, misdiagnosis of node negativity, and intrapulmonary lymphatic spread [2]. Currently, prospective randomized trials comparing limited resection with lobectomy in patients with clinical T1aN0M0 NSCLC are ongoing by the Japan Clinical Oncology Group and the Cancer and Leukemia Group B. Although the results of these 2 studies may change the standard treatment, these results will not be available for several years. An alternative way to carry out limited resection without an increase of local recurrence is to perform limited resection in patients with less invasive lung cancer instead of in all patients with clinical T1aN0M0 NSCLC. Several studies have reported that limited resection is an appropriate surgical procedure for nonsolid nodules observed on high-resolution computed tomography (HRCT). The majority of these nonsolid nodules were pathologically shown to be adenocarcinoma in situ [3, 4]. Other studies have also demonstrated that lung adenocarcinoma showing part-solid nodules with a greater proportion of ground-glass opacity (GGO) was less invasive lung cancer [5–9]. We have also reported the same results [10] and developed an objective method of measuring the proportion of GGO [11].

In the current TNM classification, the T descriptor refers primarily to the tumor diameter [12]. This is because several studies have demonstrated that tumor diameter is significantly associated with prognosis [13]. Recently,

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Tsutani and colleagues [14] reported that the solid area diameter is more effective in predicting high-grade malignancy and prognosis when compared with the whole nodule diameter. This means that if the nodule shows a GGO area within the tumor shadow, measuring only the solid area diameter and ignoring the GGO area is more effective than measuring the whole nodule diameter. Based on these findings, the solid area diameter should be considered as the T descriptor in future TNM classifications. We mostly agree with Tsutani's proposal; however, we question whether the solid area diameter can completely replace the proportion of GGO in predicting less invasive lung cancer. In other words, do nodules with the same solid area diameter but a different proportion of GGO show similar biological behavior, and can these nodules be treated with the same treatment strategy (Fig 1)?

The aim of this study was to compare the ability of 3 measurements—the whole nodule and solid area diameters and the proportion of GGO—to predict less invasive lung cancer, which can be a target for limited resection. In addition, we compared the 3 measurements with regard to postoperative recurrence to determine the best candidate for a new T descriptor in the next TNM classification.

Patients and Methods

Between January 1997 and December 2009, 674 patients with clinical T1-2N0M0 NSCLC underwent surgical resection of the lung at our hospital. Of these, we selected patients whose lung images on HRCT were preserved in Digital Imaging and Communications in Medicine and showed a solid area 3 cm or less in diameter. In addition, we excluded patients who had a past or current history of neoplasm other than the analyzed lung cancer within the past 5 years or those with a follow-up period less than 1 year or if we were unable to measure nodule diameter, such as a centrally located tumor. Finally, 383 cases were analyzed. Computed tomographic scanning was performed on X-Vigor, Aquilion-4, or Aquilion-64 systems (Toshiba Medical Systems, Tochigi, Japan). The scanning values were a tube voltage of 120 kV; a tube current of 250 mAs for X-Vigor, rotation speed, 0.5 second; tube voltage, 120 kV; tube current, 300 mA, 4 rows × 1-mm channels; a pitch of 0.75 for Aquilion-4, rotation speed, 0.5 second; tube voltage, 120 kV; tube current, 100 to 400 mA (Automatic Exposure Control); detector configuration, 64 rows × 0.5-mm channels; and a pitch of 0.828 for Aquilion-64. Thin-section images were reconstructed at 0.5-, 1-, or 2-mm thicknesses with 0.5-, 1-, or 2-mm reconstruction intervals. Both whole nodule and solid area diameters were measured precisely using the attached software (Fig 1). The proportion of GGO was calculated using the method we previously published [11]. We reviewed medical records, including the results of pathologic examination and recurrence status. We defined less invasive lung cancer as lung cancer showing no vascular invasion, lymphatic invasion, pleural invasion, or lymph node metastasis. Receiver operating characteristic (ROC) analysis was used to compare the ability to predict less invasive lung cancer and recurrence between the whole nodule and solid area diameters and the proportion of GGO. We also performed multiple logistic regression analyses to determine the independent variables for the prediction of pathologic, less invasive lung cancer. Disease-free survival (DFS) was measured from the date of operation until any recurrence, death from any cause, or the last date of follow-up. DFS curves were calculated using the Kaplan-Meier method, and differences in the curves were determined using the log-rank test. Multivariate analyses of DFS were performed with Cox's proportional hazard model. Statistical analyses were performed using SPSS

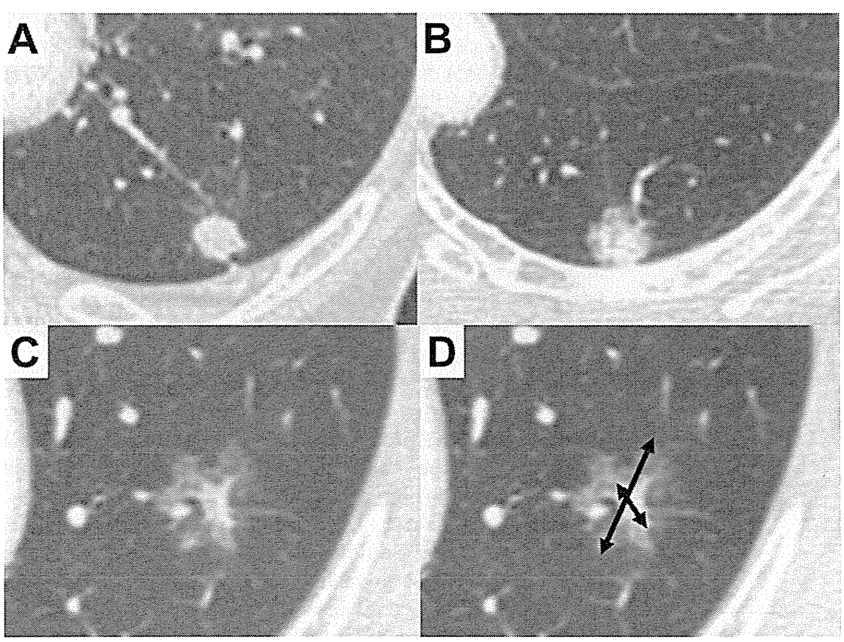

Fig 1. Lung nodules with the same solid area diameter but different proportions of ground-glass opacity (GGO). The solid area diameter of the 3 nodules was 1.2 cm. The proportions of GGO were (A) 0%, (B) 35%, and (C) 80%. (D) Longer arrow indicates whole nodule diameter and shorter arrow indicates solid area diameter.

Table 1. Patient Characteristics

Variable	Number
Sex	
Male	187
Female	196
Age (y)	
Range	34–85
Median	66
Histologic type	
Adenocarcinoma	335
Squamous cell carcinoma	31
Other histologic type	17
Clinical stage	
IA	363
IB	20
Pathologic stage	
IA	281
IB	54
IIA	19
IIB	4
IIIA	20
IIIB	0
IV	5
Whole nodule diameter	
0–10 mm	20
11–20 mm	193
21–30 mm	136
> 30 mm	34
Solid area diameter	
0 mm	20
1–10 mm	80
11–20 mm	171
21–30 mm	112
Proportion of GGO	
0–9%	119
10–49%	122
50–79%	66
80–99%	56
100%	20
Type of operation	
Pneumonectomy	5
Lobectomy	284
Segmentectomy	59
Wedge resection	35
Extent of nodal dissection	
None	65
Hilar	54
Mediastinal (selective)	91
Mediastinal (systematic)	173
Vascular invasion	
No	278
Yes	105
Lymphatic invasion	
No	312
Yes	71
Pleural invasion	
No	324
Yes	59

GGO = ground-glass opacity.

Statistics, version 17.0 (SPSS Inc, Chicago, IL). The Institutional Review Board of Tochigi Cancer Center approved this retrospective analysis and waived the need for informed consent from individual patients.

Results

Table 1 shows the patients' characteristics. Of the 383 patients, there were 187 men. The age range was 34 to 85 years, with a median of 66 years. There were 335 adenocarcinomas, 31 squamous cell carcinomas, and 17 others. Whole nodule diameters ranged from 6 to 43 mm, with a median of 20 mm. Solid area diameters ranged from 0 to 30 mm, with a median of 16 mm. Nonsolid nodules numbered 20 and part-solid nodules showing an area of GGO greater than 80% numbered 56. Lymphatic invasion was found in 71 patients, vascular invasion in 105 patients, pleural invasion in 59 patients, and lymph node metastasis in 41 patients.

The follow-up period for surviving patients ranged from 17 to 163 months, with a median of 66 months. During this follow-up period, 43 patients experienced recurrence. ROC analysis for the prediction of recurrence showed that the area under the ROC curve value of the solid area diameter was highest (0.745; 95% CI, 0.680–0.809), followed by the proportion of GGO (0.725; 95% CI, 0.677–0.783), with the lowest being the diameter of the whole nodule (0.645; 95% CI, 0.565–0.725) (Fig 2); however, the differences between the 3 values was not significant. In contrast, for the prediction of less invasive lung cancer, the ROC area under the curve value of the proportion of GGO was the highest (0.848; 95% CI, 0.810–0.886), followed by the solid area diameter (0.785; 95% CI, 0.740–0.829), and the whole nodule diameter (0.621, 95% CI, 0.565–0.677) (Fig 3). The difference between the proportion of GGO and solid area diameter was not significant. However, our data showed that the difference between these 2 ROC areas under the curve value and the whole nodule diameter was significant. Multiple logistic analyses, including the preoperatively determined variables such as age and sex, revealed that a greater proportion of GGO and female sex are independent predictive factors of less invasive lung cancer (Table 2).

Table 3 shows the number and percentages of pathologic less invasive lung cancer according to the solid area diameter and the proportion of GGO. Among each of the categories in the solid area diameter, we found that a greater proportion of GGO was associated with less invasive lung cancer. For example, among the patients with a solid area diameter measuring 10 to 15 mm, the percentage of less invasive lung cancer was 36% for nodules showing GGO less than 10%, 75% for nodules showing GGO from 10% to 50%, 92% for nodules showing

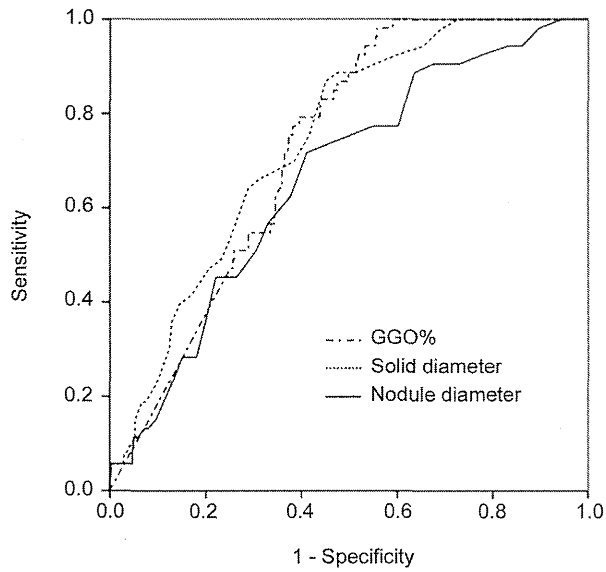

Fig 2. Receiver operating characteristic curves predicting recurrence. (GGO% = proportion of ground-glass opacity.)

GGO from 50% to 80%, and 100% when GGO was greater than 80%. In addition, in patients categorized with the same proportion of GGO, a smaller solid area diameter was associated with a higher percentage of less invasive lung cancer. We compared the number of patients in the categories consisting only of less invasive lung cancer cases. All 56 patients with a solid area diameter of 5 mm or less showed less invasive lung cancer. Conversely, all 76 patients with nodules showing GGO greater than 80% showed less invasive lung cancer (Table 3). This demonstrated that the proportion of GGO can better predict less invasive lung cancer than can the solid diameter.

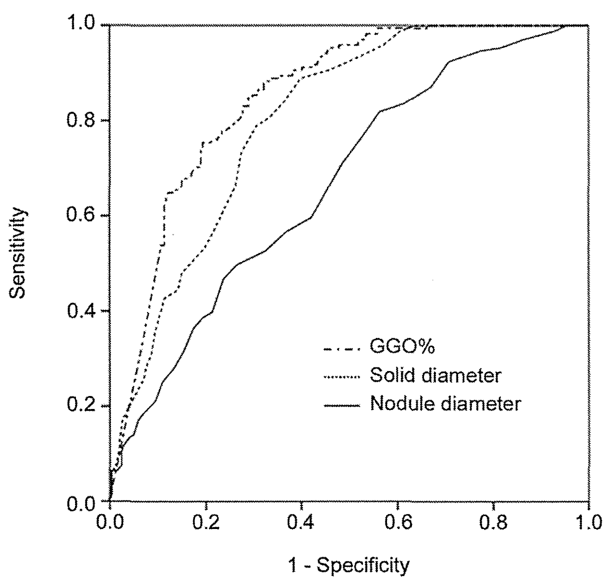

Fig 3. Receiver operating characteristic curves predicting less invasive cancer. (GGO% = proportion of ground-glass opacity.)

Table 2. Multivariate Analysis of Predicting Less Invasive Lung Cancer

Variable	Wald Statistic	Odds Ratio	95% CI	p Value
Age (y)	0.018	0.998	0.972–1.025	0.894
Sex (M/F)	6.559	2.034	1.181–3.503	0.010
Proportion of GGO	27.58	1.052	1.032–1.072	<0.001
Solid diameter	0.745	0.953	0.855–1.063	0.388
Nodule diameter	0.704	0.957	0.864–1.060	0.401

CI = confidence interval; proportion of GGO = proportion of ground–glass opacity.

Table 4 shows the numbers and percentages of cases of recurrence according to the diameter of the solid area and proportion of GGO. The number of patients who experienced recurrence was inversely distributed when compared with the number of less invasive lung cancer cases. None of the 100 patients who had nodules with a solid diameter smaller of 1 cm or less experienced recurrence. Conversely, no patients with nodules showing a GGO area greater than 50% experienced recurrence. In this case, the number of patients was 141. This number was greater than when we used the solid diameter. With regard to histologic type, all 48 tumors with histologic types other than adenocarcinoma showed GGO of less than 10% with the exception of 3 tumors showing a proportion of GGO of 10% to 50% and a solid area of 10 to 15 mm. Therefore, the data in the categories of GGO greater than 10% virtually represent adenocarcinoma cases. We compared adenocarcinoma and other histologic types in the categories with less than 10% GGO and found that there was no significant difference between the histologic features. Less invasive lung cancer was found in 24% of adenocarcinomas and 25% of the other histologic types. Recurrences occurred in 21% of adenocarcinomas and 10% of the other histologic types.

Based on the results of ROC curve analysis, we determined that the best cutoff value for predicting less invasive lung cancer was 80% for the proportion of GGO, 15 mm for the solid area nodule diameter, and 18 mm for the whole nodule diameter. Under these conditions, the sensitivities

Table 3. Number of Pathologic Less Invasive Lung Cancers According to the Solid Area Diameter and Proportion of GGO

Solid Area Diameter	Proportion of GGO <10%	10% to ≤50%	50% to ≤80%	>80%
25 to ≤ 30 mm	6/20 (30)	8/22 (36)	2/5 (40)	…
20 to ≤ 25 mm	4/27 (15)	22/34 (65)	4/4 (100)	…
15 to ≤ 20 mm	9/46 (20)	19/27 (70)	9/12 (75)	1/1 (100)
10 to ≤ 15 mm	8/22 (36)	27/36 (75)	22/24 (92)	3/3 (100)
5 to ≤ 10 mm	3/5 (60)	2/2 (100)	18/18 (100)	19/19 (100)
0 to ≤ 5 mm	…	1/1 (100)	2/2 (100)	53/53 (100)

Proportion of GGO = proportion of ground-glass opacity.

Table 4. Number of Recurrence Cases According to the Solid Area Diameter and Proportion of GGO

Solid Area Diameter	Proportion of GGO <10%	10% to ≤50%	50% to ≤80%	>80%
25 to ≤ 30 mm	5/20 (25)	7/22 (32)	0/5 (0)	–
20 to ≤ 25 mm	5/27 (19)	8/34 (24)	0/4 (0)	–
15 to ≤ 20 mm	6/46 (13)	6/27 (22)	0/12 (0)	0/1 (0)
10 to ≤ 15 mm	5/22 (23)	1/36 (3)	0/24 (0)	0/3 (0)
5 to ≤ 10 mm	0/5 (0)	0/2 (0)	0/18 (0)	0/19 (0)
0 to ≤ 5 mm	...	0/1 (0)	0/2 (0)	0/53 (0)

Proportion of GGO = proportion of ground-glass opacity.

and specificities for the prediction of less invasive lung cancer were 75% and 79% for the proportion of GGO, 87% and 62% for the diameter of the solid nodule, and 78% and 45% for the diameter of the whole nodule, respectively. Figures 4, 5, and 6 show DFS curves according to the proportion of GGO, solid area diameter, and whole nodule diameter with the preceding cutoff values, respectively. The difference in DFS curves according to the solid area diameter and proportion of GGO were larger than that of the whole nodule diameter (5-year DFS rates were 92.0% versus 79.7% in the whole nodule diameter, 96.4% versus 74.4% in the solid area diameter, and 98.7% versus 80.6% in the proportion of GGO, respectively). To assess the poten-tial independent effects of the 3 measurements, we performed multivariate analysis with Cox's proportional hazard model (Table 5). Variables analyzed included age, sex, pathologic T status, pathologic N status, histologic type (adenocarcinoma versus other histologic types), type of operation (wedge versus anatomical resection), extent of nodal dissection (with or without mediastinal nodal dissection), proportion of GGO, solid area diameter, and whole nodule diameter. Because the proportion of GGO, solid area diameter, and whole nodule diameter were strongly correlated with each other, we entered each value into the analysis individually. Multivariate analyses revealed that a smaller proportion of GGO and a larger

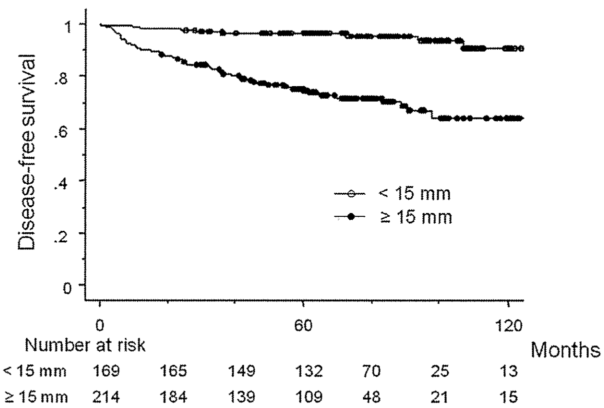

Fig 5. Disease-free survival (DFS) curves according to the diameter of the solid area. The 5-year DFS rates were 96% and 74% for solid nodule diameters of less than and greater than 15 mm, respectively.

solid area diameter were significant prognostic factors for DFS with a higher pathologic T status, higher pathologic N status, and wedge resection. However, the whole nodule diameter was not a signifi-cant factor. In addition, the Wald χ^2 statistic of the proportion of GGO was larger than that of the solid area diameter.

Comment

Several studies, including ours, have demonstrated that lung adenocarcinoma showing a greater proportion of GGO in the tumor shadow on HRCT is less invasive [5–11]. Compared with the whole nodule diameter, the solid area diameter is partly associated with the proportion of GGO because solid area diameter of a nodule with a greater proportion of GGO was smaller than that with a smaller proportion of GGO when nodules shared the same whole nodule diameter. Tsutani and colleagues [14] recently demonstrated that compared with the whole nodule diameter, the solid area diameter was more effective for predicting high-grade malignancy and prognosis and remains simple to measure. In our current

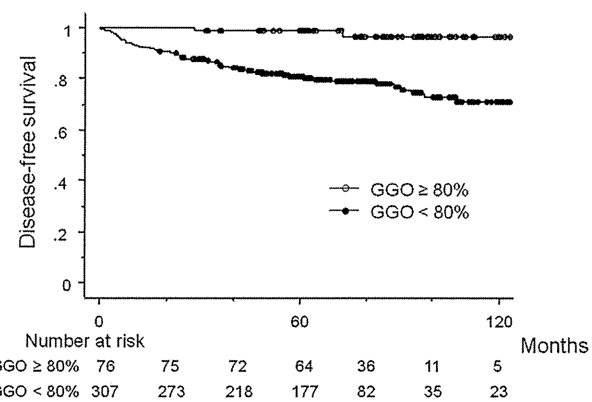

Fig 4. Disease-free survival (DFS) curves according to the proportion of ground-glass opacity (GGO). The 5-year DFS rate was 99% for GGOs 80% or greater and 81% for GGOs less than 80%.

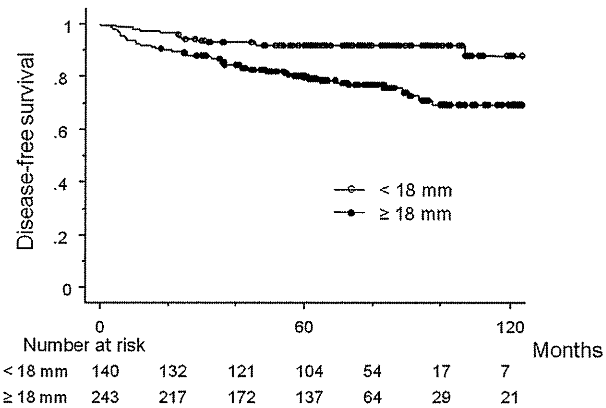

Fig 6. Disease-free survival (DFS) curves according to the whole nodule diameter. The 5-year DFS rate was 92% and 80% for whole nodule diameters of less than and greater than 18 mm, respectively.