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CHEST

Implication of total tumor size on the prognosis of patients with clinical stage IA lung adenocarcinomas appearing as part-solid nodules: Does only the solid portion size matter?

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Abstract

Objectives The aim was to investigate the effect of clinico-radiologic variables, including total tumor (T_{total}) size and clinical T category, on the prognosis of patients with stage IA (T1N0M0) lung adenocarcinomas appearing as part-solid nodules (PSNs).

Methods This institutional review board-approved retrospective study included 506 patients (male:female = 200:306; median age, 62 years) with PSNs of the adenocarcinoma spectrum in clinical stage IA who underwent standard lobectomy at a single tertiary medical center. Prognostic stratification of the patients in terms of disease-free survival was analyzed with variables including age, sex, T_{total} size, solid portion size, clinical T category, and tumor location using univariate and subsequent multivariate Cox regression analysis. Subgroup analysis was performed to reveal the effect of the T_{total} size at each clinical T category.

Results Multivariate Cox regression analysis demonstrated that T_{total} size*cT1b [interaction term; hazard ratio (HR) = 1.091; 95% confidence interval (CI): 1.015, 1.173; $p = 0.019$] and cT1c (HR = 68.436; 95% CI: 2.797, 1674.415; $p = 0.010$) were independent risk factors for the tumor recurrence. When patients with cT1b were dichotomized based on a T_{total} size cutoff of 3.0 cm, PSNs with $T_{total} > 3.0$ cm showed a significantly worse outcome (HR = 3.796; 95% CI: 1.006, 14.317; $p = 0.049$). No significant difference was observed in the probability of recurrence between cT1b with $T_{total} > 3.0$ cm and cT1c ($p = 0.915$).

Conclusions T_{total} size is a significant prognostic factor in adenocarcinoma patients in cT1b without lymph node or distant metastasis. PSNs in cT1b with $T_{total} > 3.0$ cm have a comparable risk of lung cancer recurrence to those in cT1c.

Key Points

- *Current T descriptor was a powerful prognostic factor in stage IA adenocarcinomas appearing as part-solid nodules.*
- *Total tumor size further stratified risk of recurrence of adenocarcinomas in cT1b.*
- *Upstaging of tumors in cT1b with total tumor size > 3.0 cm may be more appropriate.*

Keywords Lung neoplasms · Adenocarcinoma · Prognosis · Disease-free survival · Neoplasm staging

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Abbreviations

AIS	Adenocarcinoma-in-situ
CTR	Consolidation-to-tumor ratio
DFS	Disease-free survival
HU	Hounsfield unit
IQR	Interquartile range
MIA	Minimally invasive adenocarcinoma
PSN	Part-solid nodule
SSN	Subsolid nodule
T_{total}	Total tumor

Introduction

Pulmonary subsolid nodules (SSNs) represent a spectrum of adenocarcinomas including preinvasive precursors [1].

Studies to date have revealed that SSNs have distinct clinical and pathologic characteristics compared with solid lung nodules [2–4]. SSNs, particularly part-solid nodules (PSNs), have a higher likelihood of being lung cancers if they are persistent [5]. However, SSNs are typically indolent and grow slowly over serial CT surveillance [2–4].

Past studies on SSNs and solid nodules reported that solid portion size (excluding ground-glass component) was a better predictor of prognosis than total tumor (T_{total}) size [6–8]. Those studies suggested that the clinical T category of the 7th edition should be revised and be based on the solid portion size, not T_{total} size [6, 8]. Thus, the 8th edition of TNM staging specifically addressed how size should be measured for the T categorization: maximum dimension of the solid component on imaging for clinical staging and invasive component on microscopy for pathologic staging [9, 10].

The new coding proposal for T categories [10] exhibited excellent prognostic stratification of lung cancers, particularly adenocarcinomas [11]. However, there is still ambiguity regarding the clinical T categorization. The current 8th edition is based solely on the solid portion size, and T_{total} size is disregarded for the small (solid portion ≤ 3 cm) adenocarcinomas [10]. Travis et al [10] explicitly stated that a tumor > 3.0 cm could be classified as T1a, T1b, or T1c, depending on the invasive size. Nevertheless, the implication of T_{total} size has not yet been investigated thoroughly for SSNs. It is unclear whether the PSNs with the same solid portion size can be classified within the same T category regardless of the T_{total} size, and this issue particularly concerns tumors with a considerable discrepancy between the solid portion and the T_{total} size (e.g., solid portion < 1 cm and T_{total} > 3 cm).

In this study, we hypothesized that a subset of small (solid portion ≤ 3 cm) lung adenocarcinomas appearing as PSNs could be further stratified based on their T_{total} size. Therefore, we retrospectively collected surgically resected PSNs and investigated the effect of clinico-radiologic variables including clinical T category and T_{total} size on the survival outcome of patients.

Methods

This retrospective observational study was approved by the Institutional Review Board of Seoul National University Hospital, and the requirement for written informed consent was waived.

Study population

Patients with PSNs who underwent surgical resection between August 2003 and August 2015 were retrospectively identified from the SSN database of our hospital, a tertiary referral center: 727 patients with PSNs of the adenocarcinoma spectrum including adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA). Study participants were determined based on the following inclusion criteria: (1) patients in clinical stage IA without lymph node or distant metastasis and (2) those with thin-section preoperative chest CT scans (Fig. 1). Therefore, patients with tumors in cT2 or higher (n = 42), lymph node or distant metastasis (n = 26), and lack of thin-section CT scans (n = 12) were excluded. Patients with synchronous lung cancers (n = 28) and those who underwent sublobar resections (n = 113) were also excluded to eliminate potential confounders in assessing tumor recurrence. Consequently, a total of 506 patients were included in this study. There were 200 males and 306 females (median age, 62 years). Detailed patient and nodule characteristics are described in Table 1.

Part of the study population was reported in past studies [12–16]. However, none of those studies focused on the clinical T categorization or prognostic implication of T_{total} size of PSNs, and the topics were completely different from that of the present study.

Data collection

Patient demographics such as age, sex, and pathologic diagnosis of nodules were obtained from the electronic medical records. T_{total} size and solid portion size was measured as the longest diameter using the electronic caliper of picture archiving and communication system on axial CT images of lung window setting [window width, 1500 Hounsfield units (HU); level, -700 HU] by the radiologists (S.J., J.H.L., S.Y.A., R.E.Y., H.L., J.P., and W.H.L.) who were blinded to the pathologic diagnosis. Each nodule was analyzed once by one of the radiologists. The solid portion was defined as increased parenchymal attenuation that obscures the margins of vessels [17]. The solid proportion was then calculated by dividing the solid portion size by T_{total} size. Nodule location was also recorded. Clinical T category was established according to the 8th edition of the American Joint Commission on Cancer TNM staging system for lung cancer [10].

In our institution, lung cancer patients who underwent surgical resection were usually followed up with CT scans every 6-12 months for 2 years, and then they were observed with chest CT scans annually. Disease-free survival (DFS) was measured from the date of surgery until the date of pathologically or radiologically diagnosed recurrent lung cancer or death from other causes. The times of censoring were determined as the date of the last imaging study (chest CT or x-ray).

CT acquisition

CT scans were performed with eight different scanners from four manufacturers [Brilliance 64, Ingenuity, and iCT, Philips

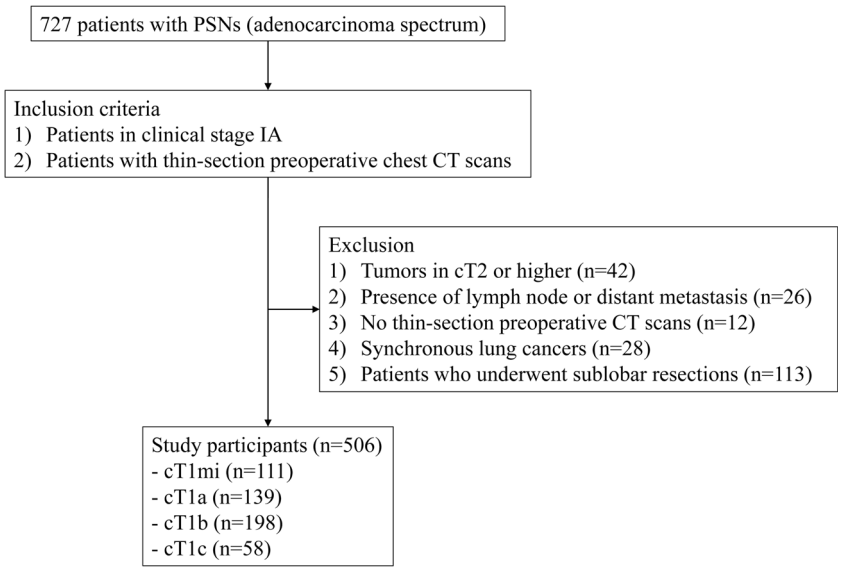

Fig. 1 Flow diagram of patient inclusion and exclusion
PSN, part-solid nodule

Healthcare; LightSpeed Ultra and Discovery CT750HD, GE Healthcare; Sensation 16 and Definition, Siemens Healthcare; Aquilion One, Toshiba Medical systems (currently Canon Medical systems)]. Our hospital is a tertiary referral center, and it operates multiple CT scanners from various vendors. Thus, heterogeneity in imaging acquisition was inevitable during the retrospective data collection. All patients underwent CT scans from the lung apex to base at suspended maximum inspiration. Scans were performed with 120 kVp and mAs ranging approximately from 20 to 200 mAs with or without automatic exposure control of each vendor. It is noteworthy that all CT scans were reconstructed with a slice thickness/interval ≤ 1.5 mm. The lung kernel or sharp kernel was used for the reconstruction.

Table 1 Patient and nodule characteristics

Variable		No. of patients (n = 506)
Sex	Male	200 (39.5)
	Female	306 (60.5)
Age (years)[a]		62 (55, 69)
T_{total} size (cm)[a]		2.0 (1.5, 2.5)
Solid portion size (cm)[a]		1.0 (0.6, 1.6)
cT category	cT1mi	111 (21.9)
	cT1a	139 (27.5)
	cT1b	198 (39.1)
	cT1c	58 (11.5)
Location	Upper lobe	309 (61.1)
	Other lobes	197 (38.9)
Pathology	AIS	19 (3.8)
	MIA	17 (3.4)
	IPA	470 (92.9)
Follow-up duration (days)[a]		1778 (1137, 2517)

Unless otherwise specified, numbers in parentheses are percentages
AIS adenocarcinoma in situ, *IPA* invasive pulmonary adenocarcinoma, *MIA* minimally invasive adenocarcinoma, $T_{total\ size}$ total tumor size
[a] Data are median (with the interquartile range in parentheses)

Pathologic diagnosis

Pathologic diagnoses were determined by the attending pathologists of our hospital according to the 2011 Lung Adenocarcinoma Classification described by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society [18]. In our institution, 10% buffered formalin was infused to inflate and fix all surgical specimens containing SSNs via the transpleural and transbronchial approach to precisely measure the invasive adenocarcinoma component [19].

Statistical analysis

To reveal the influence of clinico-radiologic variables on DFS of PSNs, univariate Cox regression analysis was initially performed. Age, sex, T_{total} size, solid portion size, clinical T category (cT1mi/cT1a, cT1b, or cT1c), and nodule location (upper lobe or other lobes) were used as input variables. T_{total} size and solid portion size were not categorized, and units of measurements were millimeters for the Cox regression. Subsequent multivariate Cox regression analysis included candidate variables with $p < 0.10$ at univariate analysis. Interaction terms between the candidate variables were also included in the Cox proportional hazard model. A backward conditional selection was used with the iterative entry of

variables on the basis of test results ($p < 0.05$). The removal of variables was based on likelihood ratio statistics with a probability of 0.10. Solid portion size and solid proportion were not included in the multivariate analysis in consideration of multicollinearity with other variables.

Then, subgroup analysis was conducted to reveal the effect of T_{total} size in each clinical T category using Cox regression. For cT1b, in which the T_{total} size had a significant association with DFS (see Results), a cutoff of 3.0 cm (T_{total} size) was applied to dichotomize PSNs into two groups (≤ 3.0 cm and > 3.0 cm). This arbitrary cutoff was chosen as 3.0 cm, a threshold that divides T1 and T2 [10, 20]. Thereafter, the pairwise log-rank test was performed between these new subgroups and other clinical T categories. Cox regression was done again to obtain the hazard ratio when the result of the log-rank test was statistically significant.

All statistical analyses were performed using the SPSS 23.0 (IBM Corp.) commercial software program. $P < 0.05$ was considered to indicate statistical significance. The p values were not adjusted for the multiple comparisons.

Results

Recurrence occurred in 1.6% (4/250) of cT1mi/cT1a, 5.6% (11/198) of cT1b, and 17.2% (10/58) of cT1c. All recurrences took place in invasive adenocarcinomas, and none were associated with pathologically diagnosed AIS or MIAs. Median T_{total} size was 1.5 cm [interquartile range (IQR): 1.2-1.9 cm] in cT1mi/cT1a, 2.2 cm (IQR: 1.9-2.7 cm) in cT1b, and 3.2 cm (IQR: 2.8-3.8 cm) in cT1c. Median solid proportion (%) was 35.0 (IQR: 23.8, 49.4) in cT1mi/cT1a, 67.0 (IQR: 57.2, 78.8) in cT1b, and 74.4 (IQR: 66.9, 84.0) in cT1c. Median follow-up duration was 1778 days (IQR: 1137–2517 days).

Univariate Cox regression analysis for disease-free survival

Clinical T category according to the solid portion size was significantly associated with DFS (Fig. 2). The hazard ratio (HR) of cT1b over cT1a was 3.585 [95% confidence interval (CI): 1.141, 11.258; $p = 0.029$] and HR of cT1c over cT1a was 12.087 (95% CI: 3.789, 38.564; $p < 0.001$). Age (HR = 1.1067; 95% CI: 1.017, 1.119; $p = 0.008$), T_{total} size (HR = 1.075; 95% CI: 1.035, 1.115; $p < 0.001$), and solid portion size (HR = 1.134; 95% CI: 1.078, 1.193; $p < 0.001$) demonstrated statistical significance. However, sex was not significantly associated with DFS ($p = 0.379$). Nodule location at the upper lobe was not a significant risk factor either ($p = 0.735$). Detailed results are described in Table 2.

Multivariate Cox regression analysis for disease-free survival

Age, clinical T category, and T_{total} size were used as input variables for the multivariate Cox regression analysis. Interaction terms between the variables were also included in the analysis. The final model revealed that T_{total} size*cT1b (interaction term; HR = 1.091; 95% CI: 1.015, 1.173; $P = 0.019$) and cT1c (HR = 68.436; 95% CI: 2.797, 1674.415; $P = 0.010$) were the independent risk factors for the recurrence (Table 3). That is, an increase in T_{total} size of 1 mm led to a 9.1% higher risk of recurrence at any time during follow-up for cT1b. cT1c had a 68 times higher risk of recurrence than cT1a.

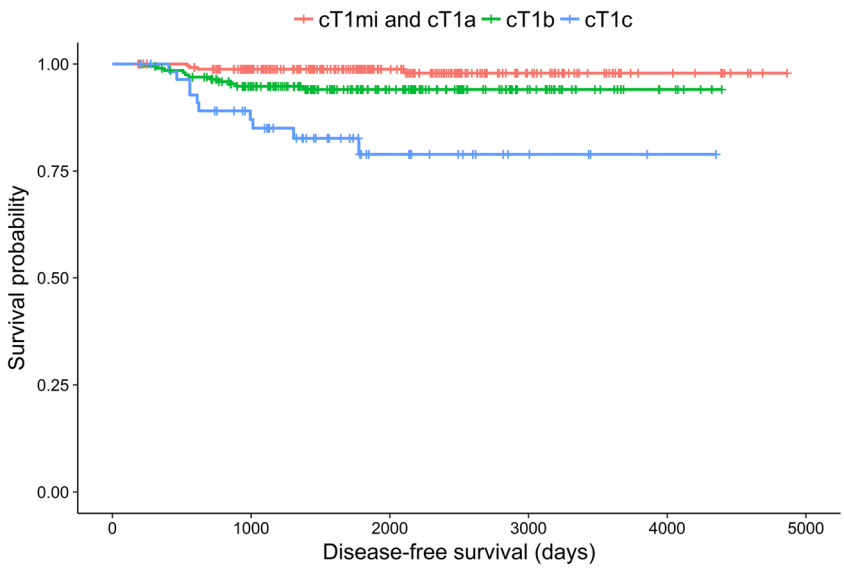

Fig. 2 Kaplan-Meier survival curves for disease-free survival of the stage IA lung adenocarcinomas appearing as part-solid nodules according to the clinical T categories

Table 2 Univariate Cox regression analysis for disease-free survival in part-solid nodules

Variable		Recurrence	Non-recurrence	HR	95% CI	*p* value
Sex	Male	12 (6.0)	188 (94.0)	-		
	Female	13 (4.2)	293 (95.8)	0.703	0.321, 1.541	0.379
Age (years)[a]		67 (60, 71)	62 (55, 68)	1.067	1.017, 1.119	0.008
T_{total} size (cm)[a]		2.8 (2.1, 3.1)	1.9 (1.5, 2.5)	1.074[c]	1.035, 1.115	< 0.001
Solid portion size (cm)[a]		1.9 (1.2, 2.3)	1.0 (0.5, 1.5)	1.134[c]	1.078, 1.193	< 0.001
cT	cT1mi/cT1a	4 (1.6)	246 (98.4)	-		
	cT1b	11 (5.6)	187 (94.4)	3.585	1.141, 11.258	0.029
	cT1c	10 (17.2)	48 (82.8)	12.087	3.789, 38.564	< 0.001
Location	Upper lobe	16 (5.2)	293 (94.8)	1.152	0.509, 2.606	0.735
	Other lobes	9 (4.6)	188 (95.4)	-		
Pathology[b]	AIS	0 (0)	19 (100)	N/A		
	MIA	0 (0)	17 (100)			
	IPA	25 (5.3)	445 (94.7)			

Unless otherwise specified, data are number of patients (with the percentage in parentheses)

AIS adenocarcinoma-in-situ, *CI* confidence interval, *cT* clinical T category, *HR* hazard ratio, *IPA* invasive pulmonary adenocarcinoma, *MIA* minimally invasive adenocarcinoma, *N/A* not applicable, *T_{total} size* total tumor size

[a] Data are median with the interquartile range in parentheses

[b] Pathologic diagnosis was not analyzed using Cox regression analysis as our study intent was to reveal prognostic variables for the clinical staging

[c] Units of measurements in Cox regression analysis were millimeters

Subgroup analysis according to clinical T category

As analyzed in the multivariate analysis, T_{total} size exhibited statistical significance in only cT1b ($p = 0.013$). In cT1a and cT1c, T_{total} size was not significantly associated with the recurrence ($p = 0.680$ and 0.224, respectively; Table 4). When patients with cT1b were dichotomized based on a T_{total} size cutoff of 3.0 cm, PSNs with T_{total} size > 3.0 cm showed a significantly worse outcome ($p = 0.034$; Fig. 3a). At Cox regression analysis, HR was 3.796 (95% CI: 1.006, 14.317; $p = 0.049$), which demonstrated that T_{total} size could further stratify the risk of recurrence in cT1b PSNs.

The pairwise log-rank test between cT1mi/cT1a and cT1b (T_{total} size ≤ 3.0 cm) showed marginal statistical significance ($p = 0.075$). There was no significant difference in the probability of recurrence between cT1b (T_{total} size > 3.0 cm) and cT1c ($p = 0.915$) (Fig. 3b).

Table 3 Multivariate Cox regression analysis for disease-free survival

Variable	HR	95% CI	*p* value
Age	1.047	0.995, 1.102	0.076
cT1b	0.377	0.039, 3.671	0.401
cT1c	68.436	2.797, 1674.415	0.010
T_{total} size*cT1b[a]	1.091	1.015, 1.173	0.019
T_{total} size*cT1c[a]	0.941	0.853, 1.038	0.222

CI confidence interval, *cT* clinical T category, *HR* hazard ratio, *T_{total} size* total tumor size

[a] Units of measurements in Cox regression analysis were millimeters

Discussion

Our study validated that the current clinical staging system (T descriptors) based on the solid portion size was a powerful prognostic determinant in adenocarcinomas appearing as PSNs. In addition, we revealed that T_{total} size had a significant prognostic implication in a subset of PSNs, which was cT1b. That is, T_{total} size was significantly associated with DFS in cT1b, while DFS in cT1a and cT1c was not affected by T_{total} size. Adenocarcinomas of cT1b with T_{total} size > 3.0 cm had a comparable probability of disease recurrence to those of cT1c.

It has been shown that the prognosis of PSNs was better than that of the solid nodules even after matching the solid portion size [6, 11, 21]. Hwang et al [6] reported that PSNs with solid portion size ≤ 2 cm had smaller HR for recurrence than the solid portion size-matched solid nodules. Aokage et al [11] reported similar findings that PSNs in clinical stages IA2 and IA3 had a more favorable outcome than radiologically solid lung cancers. These results implied that the PSNs would have a less aggressive nature than the equal-sized solid lung cancers when they are small. However, the prognostic impact of the T_{total} size or the extent of ground-glass component in PSNs has not been investigated to date. The current consensus is that PSNs can be classified solely based on the solid portion size even when T_{total} size is > 3.0 cm [10]. In fact,

Table 4 Influence of total tumor size at each clinical T category

cT category	Recurrence[a]	Non-recurrence[a]	HR[b]	95% CI	*p* value
cT1mi and cT1a	1.6 (1.0, 2.0)	1.5 (1.2, 1.9)	0.958	0.783, 1.172	0.680
cT1b	2.9 (2.3, 3.1)	2.2 (1.8, 2.6)	1.098	1.020, 1.182	0.013
cT1c	2.9 (2.4, 3.3)	3.2 (2.8, 3.8)	0.938	0.845, 1.040	0.224

CI confidence interval, *HR* hazard ratio

[a] Median total tumor size (cm) with the interquartile range in parentheses

[b] Units of measurements in Cox regression analysis were millimeters

stage IA adenocarcinomas with T_{total} size > 3.0 cm may be a minor subset in terms of incidence. However, our study demonstrated that cT1b with T_{total} size > 3.0 cm had a higher chance of recurrence than those with T_{total} size ≤ 3.0 cm. Importantly, the Kaplan-Meier survival curve of cT1b with T_{total} size > 3.0 cm was not separable from that of cT1c. Therefore, we cautiously presume that a minor adjustment may be required for the current T coding system. Clinical upstaging of the tumors in cT1b with T_{total} size > 3.0 cm may be more appropriate for the prognostication.

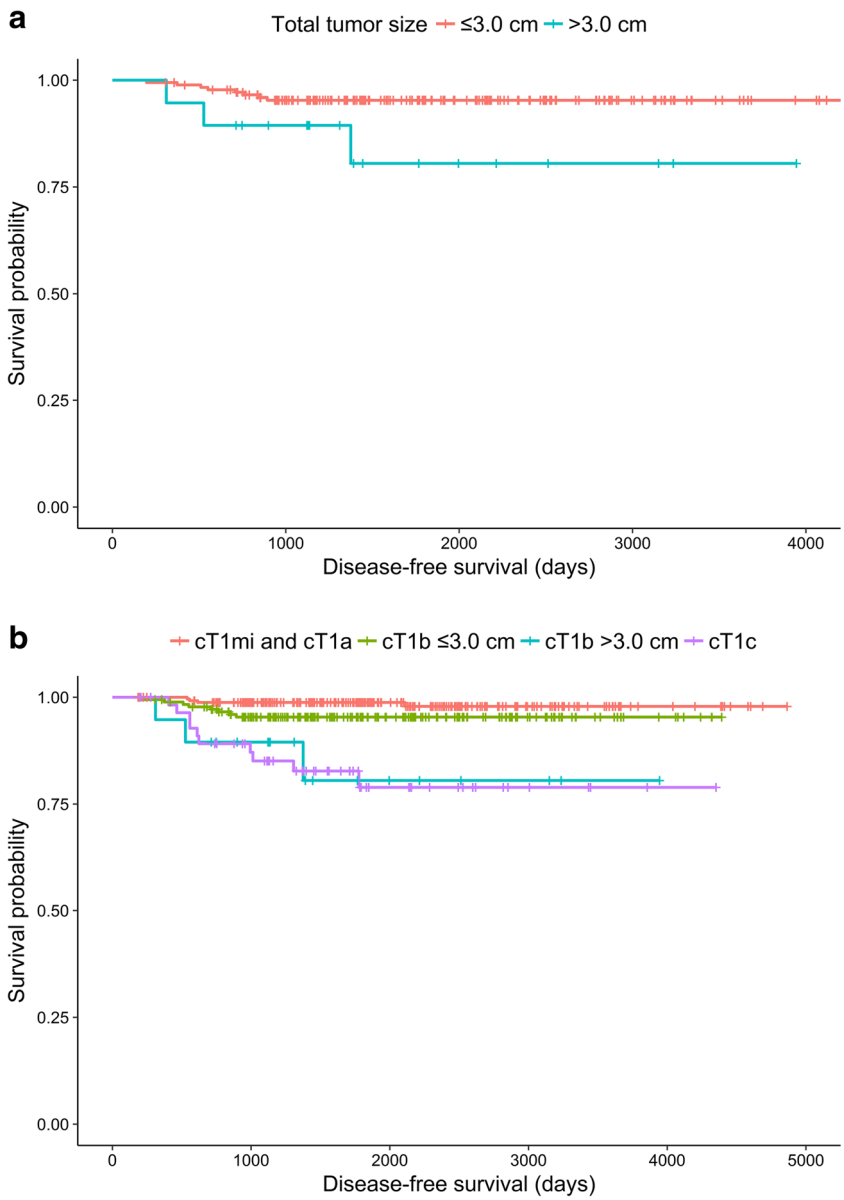

Fig. 3 Kaplan-Meier curves for disease-free survival of (**a**) cT1b lung adenocarcinomas appearing as part-solid nodules according to the total tumor size and (**b**) the stage IA lung adenocarcinomas when divided into the four groups as suggested in this study. The probabilities of recurrence between cT1b (total tumor size > 3.0 cm) and cT1c were not significantly different

Nevertheless, this issue should be scrutinized in a larger prospective cohort with a careful investigation of overall survival of the patients.

T_{total} size may gain little significance for cT1mi or cT1a as it is uncommon to encounter a PSN with solid portion ≤ 1 cm and T_{total} size > 3 cm at the same time. For PSNs of cT1c, we assume that the biologic background of this category may be identical to that of the solid nodules as reported by Hwang et al [6] Therefore, taking into account the ground-glass component or T_{total} size may not have any implication in cT1c as shown in our study. Nevertheless, a larger study population is definitely necessary to prove this assumption.

The median solid proportion was 35.0% in cT1mi/cT1a, 67.0% in cT1b, and 74.4% in cT1c. There was an increasing trend of the solid proportion according to the clinical T category. This may help understand the nature of PSNs in each T category. In cT1mi/cT1a, the predominant component was ground-glass opacity, and the prognosis was excellent regardless of T_{total} size. In cT1c, the predominant component was the solid portion, and the prognosis was expected to be similar to that of the solid nodules as described above. In cT1b, this group had an intermediate proportion of the solid component, although the major proportion was actually solid. Given the intermediate status of the solid proportion among the spectrum of stage IA adenocarcinomas, which may be translated into intermediate aggressiveness, it is partly plausible that T_{total} size or the extent of ground-glass opacity can have some prognostic effect in this category.

There are a few potential imaging features that can be helpful for predicting prognosis in lung cancer patients [22]. Particularly, the consolidation-to-tumor ratio (CTR) has been advocated by several researchers for the risk stratification of adenocarcinomas [23–26]. This feature has strength in that it may lead to a more reproducible classification of SSNs among multiple observers [27]. However, the CTR was not analyzed in our study as it is not an accepted measure for the clinical staging at the present time. Our study focused on enhancing the prognostication with respect to the clinical staging system. Nevertheless, it would be interesting to investigate whether the CTR, either quantitative or qualitative, has any association with the patients' prognosis in each cT category in the future.

Lastly, all recurrences arose in the patients with invasive adenocarcinomas in the present study. Our finding coincided with the previous reports that patients with AIS or MIA should have 100% or near-100% 5-year DFS, respectively, after a complete surgical resection [18, 28]. Kadota et al [28] stated that none of the patients with AIS or MIA experienced any recurrences in their study. As for overall survival, which was not evaluated in our study, a recent pooled analysis of the 19 studies published from 2011 to 2015 reported that the 5-year overall survival rate was 100% for AIS and 98.5% for MIA [29].

There were several limitations to this study. First, lung cancers manifesting as solid nodules were not analyzed as we aimed to focus on PSNs. However, pooled analysis of both SSNs and solid nodules is warranted in the future to assess the prognosis of lung cancer as a whole in terms of T_{total} size, presence of ground-glass opacity, and solid portion size comprehensively. Second, the number of recurrences in our study was small. For example, there were only four recurred cases in cT1mi/cT1a. However, a large retrospective cohort was included in this study, and the small number of events was inevitable given the excellent prognosis at that early stage. Third, invasive component size was not analyzed, and pathologic staging was not utilized for the prognostication in our study. These factors may be able to distinguish prognostic groups better than the clinical staging. Nevertheless, we could not obtain the pathologic staging based on the 8th edition staging system as inclusion of the study population was from 2003 to 2014, which was before the implementation of the 8th staging system. In addition, an invasive component size > 10 mm was described with an inequality sign (> 10 mm) in the pathology report until 2017 in our institution, and the units' digit was not measured. Thus, the invasive component size could not be used for analysis. Lastly, volumetric measurement was not investigated in this study. Total nodule volume, solid portion volume, or three-dimensional diameter may have greater prognostic value than the two-dimensional measurement. A recent study by Kamiya et al [30] reported the prognostic value of solid portion volume over the two-dimensional diameter measurement for the prediction of DFS in SSNs. Other researchers observed similar results [31, 32]. Nevertheless, the performance of volumetric analysis depends on the segmentation software program, and the segmentation results can be suboptimal for the juxtapleural, juxtavascular, or subsolid nodules. Thus, we assumed that the volumetric measurement could not be used for the staging as of now.

In conclusion, T_{total} size can further stratify the prognosis of adenocarcinoma patients in cT1b without lymph node or distant metastasis. PSNs in cT1b with T_{total} size > 3.0 cm have a comparable risk of lung cancer recurrence to those in cT1c.

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Compliance with Ethical Standards

Guarantor The scientific guarantor of this publication is Jin Mo Goo.

Conflict of Interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and Biometry No complex statistical methods were necessary for this paper.

Informed Consent Written informed consent was waived by the Institutional Review Board.

Ethical Approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in journal articles (Eur Radiol 2016 26:4465-4474; Eur J Radiol 2016 85:1174-1180; Eur Radiol 2017 27:3266-3274; Eur Radiol 2018 28:2124-2133; Eur Radiol 2017 27:1369-1376).

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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