



Consolidation-to-tumor ratio and tumor disappearance ratio are not independent prognostic factors for the patients with resected lung adenocarcinomas

Hyungjin Kim^{a,b}, Jin Mo Goo^{a,b,c}, Young Tae Kim^{c,d}, Chang Min Park^{a,b,c,*}

^a Department of Radiology, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea

^b Institute of Radiation Medicine, Seoul National University Medical Research Center, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea

^c Cancer Research Institute, Seoul National University, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea

^d Department of Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea

ARTICLE INFO

Keywords:

Adenocarcinoma
Neoplasm staging
T category
Consolidation-to-tumor ratio
Tumor disappearance ratio
Disease-free survival

ABSTRACT

Objectives: Our study aimed to investigate the independent prognostic values of consolidation-to-tumor ratio (CTR) and tumor disappearance ratio (TDR) after adjustment for the conventional prognostic factors and the eighth edition clinical T category for patients with resected lung adenocarcinomas.

Materials and Methods: This retrospective study included 691 patients (281 men and 410 women; median age, 63 years) with resected lung adenocarcinomas (clinical T1N0M0). The prognostic implications for disease-free survival (DFS) of CTR and TDR in continuous and categorical forms were analyzed using multivariable-adjusted Cox regression analysis, including multiple clinico-radiological prognostic factors and the clinical T category based on the solid portion measurement. Analysis was performed for the total study population and for two part-solid nodule subgroups (cT1mi/cT1a to cT1c and cT1mi/cT1a to cT1b, respectively).

Results: For the total study population, CTR and TDR were not selected in the multivariable Cox regression models, which indicated that these are not independent prognostic factors. Age (adjusted HR: 1.026; $P = 0.022$) and clinical T category (adjusted HR for cT1b: 3.475; $P = 0.019$; adjusted HR for cT1c: 9.938; $P < 0.001$) were independently associated with DFS. For the part-solid nodule subgroups, multivariable-adjusted HRs for CTR and TDR were not statistically significant (all $P > 0.05$).

Conclusion: CTR and TDR were not independent prognostic factors. Preoperative prognostication based on clinical T category would be sufficient without further stratification according to CTR or TDR.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. Despite advancements in diagnostic modalities and surgical techniques in recent decades, the recurrence rate of lung cancer after curative resection is still high at up to 30–55% [2].

Among various prognostic indicators for lung cancer, the most important prognostic factor would be the tumor-node-metastasis (TNM) staging system, which describes the anatomical extent of the disease [3]. For lung adenocarcinomas, recent studies have reported the prognostic value of consolidation-to-tumor ratio (CTR) [4–7] and tumor disappearance ratio (TDR) [8–11], both of which can be determined by using preoperative chest CT scans. The underlying rationale is that

these variables are strongly correlated with the pathological invasiveness of adenocarcinomas, including nodal involvement, lymphatic invasion, and vascular invasion [12]. It is reasonable to assume that the predictive performance for pathological invasiveness can be translated into useful prognostication after curative resection.

However, the prognostic values of CTR and TDR have not yet been investigated in conjunction with the eighth edition TNM staging system. The eighth T coding system has changed drastically from the previous edition. Importantly, clinical T categories are now categorized according to the size of the solid portions instead of total tumor size [13]. That is, ground-glass opacity is excluded from the measurement for the purpose of clinical staging [13]. The solid portion measured at the CT scan is a surrogate for the invasive component shown through

Abbreviations: cT, clinical T category; CTR, consolidation-to-tumor ratio; DFS, disease-free survival; HU, Hounsfield units; IQR, interquartile range; TDR, tumor disappearance ratio

* Corresponding author at: Department of Radiology, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea.

E-mail address: cmpark.morphius@gmail.com (C.M. Park).

<https://doi.org/10.1016/j.lungcan.2019.09.014>

Received 25 June 2019; Received in revised form 2 September 2019; Accepted 16 September 2019

0169-5002/ © 2019 Elsevier B.V. All rights reserved.

microscopy, which is measured to provide the pathological staging [13].

In this study, we hypothesized that the prognostic roles of the new T coding system and of CTR and TDR would overlap considerably. If patients are stratified according to their clinical T category, further stratification using CTR or TDR may not be necessary. For this reason, we investigated the independent prognostic values of CTR and TDR, after adjustment for conventional prognostic factors and the eighth edition clinical T category, in patients with resected lung adenocarcinomas.

2. Materials and methods

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

2.1. Study population

Patients with clinical T1N0M0 non-small cell lung cancers were retrospectively identified by searching the consecutive surgical cohort of Seoul National University Hospital. Between January 2009 and December 2015, 904 patients who did not have synchronous or metachronous lung cancers underwent standard lobectomy. Among these, 77 patients with pure ground-glass nodules (i.e., clinical Tis) and 136 patients with lung cancer histologies other than the adenocarcinoma spectrum were excluded. Consequently, 691 patients with lung adenocarcinomas were included in this study. The clinical T categories for the tumors ranged from cT1mi to cT1c.

2.2. Data collection

Clinical and pathological data were collected from the electronic medical records. The patients' age, sex, history of malignancy other than lung cancer, family history of lung cancer, smoking history (never smoker or ex-/current smoker), date of surgery, date of preoperative chest CT scan, and pathological diagnosis were recorded. Regarding nodule characteristics, nodule location (upper lobe or other lobes) and nodule type (part-solid or solid) were obtained from the radiology reports. Total tumor size (longest diameter) was measured using the electronic caliper of a picture archiving and communication system (INFINITT PACS, INFINITT Healthcare, Seoul, Korea) on axial CT images in the lung window setting (window width: 1500 Hounsfield units [HU]; level: -700 HU). Solid portion size (longest diameter) was measured twice: in the lung window and the mediastinal window settings, respectively (window width: 400 HU; level: 30 HU). Then, the CTR and TDR of each tumor was calculated as follows: (Fig. 1)

$$\text{CTR (\%)} = 100 \times \frac{\text{Solid portion size in the lung window}}{\text{Total tumor size in the lung window}}$$

$$\text{TDR (\%)} = 100 \times \left(1 - \frac{\text{Solid portion size in the mediastinal window}}{\text{Total tumor size in the lung window}}\right)$$

Nodule measurements were performed once by one of two trained radiology technicians (either M.L., who has seven years of research experience in chest CT, or J.Y.J., who has one year of research experience in chest CT). These measurement takers were blinded to the pathologic information and the patient outcomes. The clinical T category (from cT1mi to cT1c) of each tumor was determined using the solid portion measured in the lung window setting according to the eighth edition TNM stage classification for lung cancer of the American Joint Committee on Cancer [13].

Disease-free survival (DFS) was the primary endpoint of this study, and it was calculated from the date of surgery to the date of the first-recorded evidence of clinical (local or regional) recurrence and/or distant metastasis, as confirmed by imaging, histologic evidence, or

death by any cause. The time of censoring was determined as the date of the last chest CT scan.

2.3. CT image acquisition

CT scans were performed using nine different scanners produced by four manufacturers [Brilliance 64, Ingenuity, and iQon, Philips Healthcare, Best, Netherlands; LightSpeed Ultra and Discovery CT750HD, GE Healthcare, Waukesha, WI; Somatom Sensation 16, Definition, and Force, Siemens Healthcare, Forchheim, Germany; Aquilion One, Toshiba Medical Systems (now Canon Medical Systems), Otawara, Japan]. Our hospital is a tertiary medical center, and it operates multiple CT scanners that are purchased from various vendors. Thus, heterogeneity in imaging acquisition was inevitable during the retrospective data collection. All the patients underwent spiral CT scans from the lung apex to base at suspended maximum inspiration. The scans were performed at 120 kVp and at mAs values ranging from approximately 20 to 200 mAs with or without the automatic exposure control of each vendor. The CT scans were reconstructed with a slice thickness ≤ 5 mm. For patients with part-solid nodules, the slice thickness was less than or equal to 1.5 mm. Slice increments were equal to or less than the slice thicknesses. All CT scans included axial reconstruction and most CT scans also had coronal reformatted images. About two-thirds of the participants underwent contrast-enhanced CT scans at a scan delay of 60 s after contrast material injection.

2.4. Pathological diagnosis

In 74% of the patients (508/691), the pathological diagnosis followed the 2011 lung adenocarcinoma classification described by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society [14]. The rest of the study population, 26% (183/691), were diagnosed and treated before the 2011 classification system was introduced into our hospital.

2.5. Statistical analysis

Continuous variables were presented using the median with interquartile range (IQR), and categorical variables were described using frequency with percentage. Distribution of CTR and TDR across the clinical T categories of the total study population and in the part-solid nodule subgroup were analyzed and compared using the Kruskal-Wallis H test. CTR and TDR were then dichotomized using a single cutoff (50%), which was close to the median values for both parameters in the part-solid nodule subgroup (54.5% and 54.2%, respectively; see Results). This cutoff (50%) was used for patient selection in prospective limited resection trials [15,16]. Both continuous and categorical forms of CTR and TDR were analyzed in this study.

The prognostic significance of CTR and TDR in combination with other clinico-radiological factors was tested using the univariable Cox regression analysis followed by the multivariable analysis. Specifically, variables with P-values of less than 0.10 in the univariable Cox analysis were used as candidates for the multivariable analysis. Backward stepwise model selection was performed based on Akaike's information criterion [17,18]. Multivariable Cox models were built repeatedly, which included the clinico-radiological variables and one of the CTR and TDR variables, to investigate their independent prognostic roles after adjustment. That is, the Cox models were iterated four times (for continuous/categorical CTR and TDR).

About half of the study population had solid nodules, for which CTR and TDR may have little prognostic implication. Therefore, a subgroup analysis for the part-solid nodules was conducted. Initially, univariable and multivariable Cox regression analyses were performed for the part-solid nodules from cT1mi/cT1a to cT1c (i.e., solid portion size ≤ 3 cm). Then, cT1c was excluded, given the fact that the majority of the part-solid nodule subgroup consisted of cT1mi/cT1a and cT1b. For this

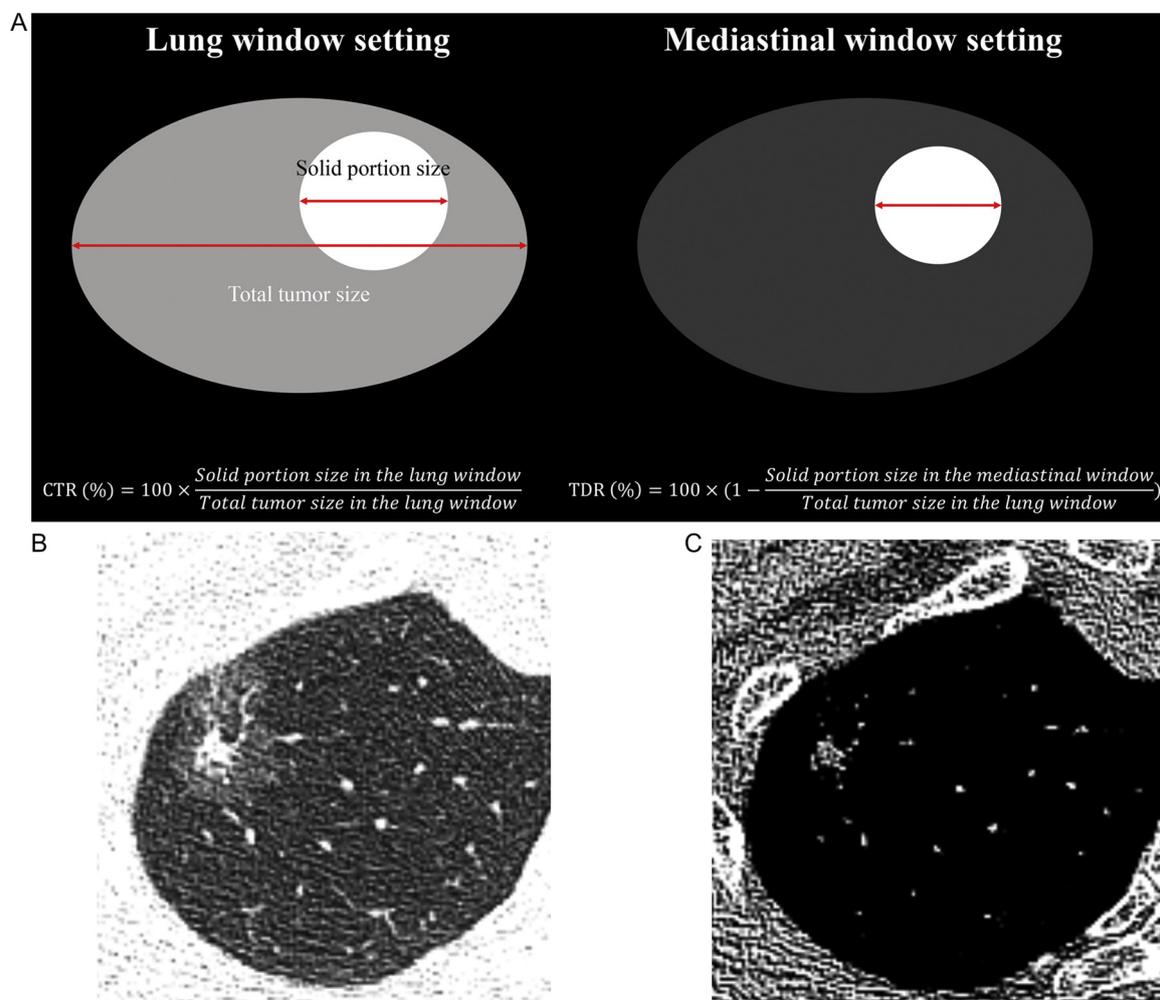


Fig. 1. Measurement of CTR and TDR. (A) A schematic representation for the measurement of CTR and TDR. (B–C) A case of a 56-year old female with a part-solid nodule in the right upper lobe. (B) Solid portion size was measured as 0.8 cm and total tumor size was measured as 2.8 cm at the lung window. CTR was calculated as 28.6%. (C) Solid portion size was 0.7 cm at the mediastinal window setting. Thus, TDR was 75%. CTR = consolidation-to-tumor ratio; TDR = tumor disappearance ratio.

secondary subgroup (i.e. solid portion size ≤ 2 cm), survival analysis was performed once again.

For the Cox regression analysis, the proportional hazard assumption was evaluated by the scaled Schoenfeld residuals using the `cox.zph` function in R package `survival`. Cox models were stratified by a variable which did not meet the proportional hazard assumption (see Results). Adjusted survival curves were drawn using a marginal approach with reweighted data. All statistical analyses were performed using R software version 3.5.1 (<http://www.R-project.org>; packages: `survival` and `survminer`). A P-value of < 0.05 was considered to indicate statistical significance. Data imputation was not performed for the missing values.

3. Results

Of the 691 patients, 281 (40.7%) were males and 410 (59.3%) were females (median age, 63 years). There were 352 (50.9%) part-solid nodules and 339 (49.1%) solid nodules. Thirty-one patients (4.5%) had cT1mi adenocarcinomas, 112 (16.2%) had cT1a adenocarcinomas, 332 (48.0%) had cT1b adenocarcinomas, and 216 (31.3%) had cT1c adenocarcinomas. Detailed patient characteristics are described in [Table 1](#).

3.1. Descriptive statistics for CTR and TDR

For the total study population, median CTR and TDR were 90.3% (IQR: 54.5, 100%) and 26.8% (IQR: 10.5, 55.8%), respectively. For the

part-solid nodule subgroup, median CTR and TDR were 54.5% (IQR: 42.0, 66.7%) and 54.2% (IQR: 38.5, 70.6%), respectively. CTR and TDR varied substantially according to the clinical T categories (all $P < 0.001$). That is, adenocarcinomas with higher clinical T categories demonstrated significantly greater CTR and smaller TDR ([Table 2](#)).

Among part-solid nodules, 213 (60.5%) exhibited CTR $> 50\%$ and 206 (58.5%) showed TDR $> 50\%$. CTR was 100% in all solid nodules by definition, but TDR $> 50\%$ was found in 10 (2.9%) of the solid nodules. The 3-year DFS rates were 86.2% (95% confidence interval [CI]: 83.1%, 89.4%) in patients with CTR $> 50\%$ and 92.4% (95% CI: 87.4%, 97.4%) in those with CTR $\leq 50\%$. The 3-year DFS rates were 93.4% (95% CI: 89.6%, 97.1%) in patients with TDR $> 50\%$ and 84.8% (95% CI: 81.3%, 88.3%) in those with TDR $\leq 50\%$.

3.2. Univariable and multivariable Cox regression analysis

With univariable analysis, CTR (hazard ratio [HR] for continuous form: 1.013; 95% CI: 1.004, 1.022; $P = 0.005$; HR for categorical form: 2.555; 95% CI: 1.286, 5.076; $P = 0.007$) and TDR (HR for continuous form: 0.983; 95% CI: 0.974, 0.991; $P < 0.001$; HR for categorical form: 0.325; 95% CI: 0.181, 0.584; $P < 0.001$) were significantly associated with DFS. Age, sex, nodule type, and clinical T category also showed P-values of less than 0.10 and were used as candidates in the subsequent multivariable analysis.

Multivariable Cox regression models demonstrated that none of the

Table 1
Patient and nodule characteristics.

Variable	No. of Patients (n = 691)
Age (years) ^a	63 (55, 70)
Sex	
Male	281 (40.7)
Female	410 (59.3)
History of malignancy other than lung cancer ^b	
Yes	116 (17.4)
No	552 (82.6)
Family history of lung cancer ^c	
Yes	42 (6.3)
No	629 (93.7)
Smoking history	
Never smoker	446 (64.5)
Ex- or current smoker	245 (35.5)
Nodule location	
Upper lobes	382 (55.3)
Other lobes	309 (44.7)
Nodule type	
Part-solid	352 (50.9)
Solid	339 (49.1)
Clinical T category ^d	
cT1mi	31 (4.5)
cT1a	112 (16.2)
cT1b	332 (48.0)
cT1c	216 (31.3)
Pathology	
Adenocarcinoma in situ	17 (2.5)
Minimally invasive adenocarcinoma	19 (2.7)
Invasive adenocarcinoma	655 (94.8)
Cancer recurrence or deaths	96 (13.9)
Follow-up interval (days) ^e	1170 (748, 1791)
CT-to-surgery interval (days) ^a	14 (2, 24)

Unless otherwise specified, numbers in parentheses are percentages.

^a Data are median with interquartile range in parentheses.

^b Data were not available for 23 patients.

^c Data were not available for 20 patients.

^d Clinical T categorization was based on the eighth edition tumor-node-metastasis classification for lung cancer.

CTR or TDR variables were chosen during the model selection procedures. The final Cox models consistently included age (adjusted HR: 1.026; 95% CI: 1.004, 1.049; P = 0.022) and clinical T category (adjusted HR for cT1b: 3.475; 95% CI: 1.233, 9.798; P = 0.019; adjusted HR for cT1c: 9.938; 95% CI: 3.591, 27.504; P < 0.001). Detailed results can be found in Table 3 and adjusted disease-free survival curves are visualized in Fig. 2.

3.3. Subgroup Cox regression analysis for the part-solid nodules

For the part-solid nodules from cT1mi/cT1a to cT1c, age, clinical T category, and history of malignancy, all of which showed P-values less than 0.10 at univariable analysis, were used to calculate the multivariable-adjusted HRs of CTR and TDR. Multivariable Cox models were stratified by the history of malignancy because the proportional hazard assumption was not met for this variable. Consequently, neither CTR nor TDR were significantly associated with DFS after adjustment for the other prognostic factors (all P > 0.05). All Cox models revealed that the patients' age and clinical T category were independent prognostic factors for DFS in the part-solid nodules (Supplementary Tables 1 and

Table 2
Median CTR and TDR according to the clinical T category.

	Clinical T category	Total population (n = 691)	P-value	Part-solid nodules (n = 352)	P-value
CTR (%)	cT1mi/cT1a	43.5 (33.3, 58.3)	< 0.001	39.6 (32.0, 54.0)	< 0.001
	cT1b	85.4 (59.3, 100)		60.0 (50.0, 68.8)	
	cT1c	100 (100, 100)		70.0 (61.0, 78.8)	
TDR (%)	cT1mi/cT1a	70.6 (54.5, 84.6)	< 0.001	72.1 (59.0, 85.0)	< 0.001
	cT1b	28.0 (12.0, 49.6)		47.5 (34.6, 59.6)	
	cT1c	11.8 (4.5, 23.5)		35.1 (22.7, 46.1)	

Data are median with interquartile range in parentheses.

cT = clinical T category; CTR = consolidation-to-tumor ratio; TDR = tumor disappearance ratio.

2). Adjusted HRs, CIs, and P-values of CTR and TDR are described in Table 4.

In the secondary subgroup (part-solid nodules from cT1mi/cT1a to cT1b), age, sex, smoking status, nodule location, clinical T category, and history of malignancy were chosen as candidates for the multivariable models, which were then investigated in relation to CTR and TDR. Again, CTR and TDR were not significantly associated with DFS after adjustment for the other prognostic factors (all P > 0.05; Table 4). Male sex and/or clinical T category were independent prognostic factors in this subgroup (Supplementary Tables 3 and 4).

4. Discussion

In this study, we showed that CTR and TDR were not independent prognostic factors for patients with resected adenocarcinomas. For the total study population, the independent prognostic factors for DFS were age and clinical T category. CTR and TDR were not included in the final prediction models. For the part-solid nodule subgroups, which had a solid portion size ≤ 3 cm or ≤ 2 cm, multivariable-adjusted HRs for CTR and TDR were not statistically significant after adjustment for the clinico-radiological factors, including the eighth edition T category.

Recent studies which included early stage lung adenocarcinomas (cT1N0M0 as based on the seventh edition) demonstrated that CTR was significantly associated with patients' survival [4,5,7]. Asamura et al. [5] reported that the five-year overall survival was 96.7% for adenocarcinomas with CTR ≤ 50% and 88.9% for adenocarcinomas with CTR > 50% (P < 0.001). However, multivariable analysis was not performed in that study. Matsunaga et al. [7] applied the same cutoff (50%) to their study population and demonstrated that the recurrence-free survival rates were significantly different for part-solid nodules with CTR < 50% and those with CTR ≥ 50% (univariable analysis; P = 0.044). In addition, Huang et al. [6] investigated clinical stage I and II adenocarcinomas and reported that for ground-glass opacity ratio, which would be the reverse of CTR, < 75% was an independent risk factor for postoperative recurrence. To be precise, a ground-glass opacity ratio ≥ 75% was associated with being female, having good tumor differentiation, being a non-smoker, and having absence of visceral pleural invasion and absence of lymphovascular invasion. These indicate that CTR is strongly correlated with multiple well-known prognostic factors, and this reminds one that a multivariable-adjusted regression analysis that includes powerful prognostic variables is necessary to confirm the true prognostic potential of CTR. According to our study results, CTR was not an independent prognostic factor for resected adenocarcinomas although it was statistically significant in the univariable analysis for both continuous and categorical forms.

TDR is similar to CTR in that it inversely reflects the ratio of the solid portion at the mediastinal window to the total tumor at the lung window. Higher TDR indicates a smaller measurable solid portion at the mediastinal window. Some studies have reported the prognostic value of TDR [8–11]. Shimizu et al. [9] reported that no relapse or death was observed with small (≤ 2 cm) peripheral lung cancers with TDR ≥ 50% after curative resection. Lee et al. [11] also reported that TDR (≥ 15%) was an independent predictor of overall survival with surgically

Table 3
Univariable and multivariable Cox regression analysis for disease-free survival.

Variable	Subcategory	Univariable analysis			Multivariable analysis		
		HR	95% CI of HR	P-value	HR	95% CI of HR	P-value
Age (year)		1.036	1.013, 1.060	0.002	1.026	1.004, 1.049	0.022
Male sex		1.402	0.939, 2.092	0.098			
History of malignancy other than lung cancer		1.376	0.836, 2.266	0.209			
Family history of lung cancer		1.494	0.690, 3.232	0.308			
Ex- or current smoker (reference: never smoker)		1.294	0.862, 1.942	0.213			
Location at upper lobes (reference: other lung lobes)		0.844	0.565, 1.259	0.405			
Solid nodule (reference: part-solid nodule)		1.596	1.060, 2.403	0.025			
cT (reference: cT1mi/cT1a)	cT1b	3.743	1.330, 10.534	0.012	3.475	1.233, 9.798	0.019
	cT1c	10.998	3.989, 30.321	< 0.001	9.938	3.591, 27.504	< 0.001
CTR (%; continuous)		1.013	1.004, 1.022	0.005			
CTR (categorical; cutoff, 50%)		2.555	1.286, 5.076	0.007			
TDR (%; continuous)		0.983	0.974, 0.991	< 0.001			
TDR (categorical; cutoff, 50%)		0.325	0.181, 0.584	< 0.001			

CI = confidence interval; cT = clinical T category; CTR = consolidation-to-tumor ratio; HR = hazard ratio; TDR = tumor disappearance ratio.

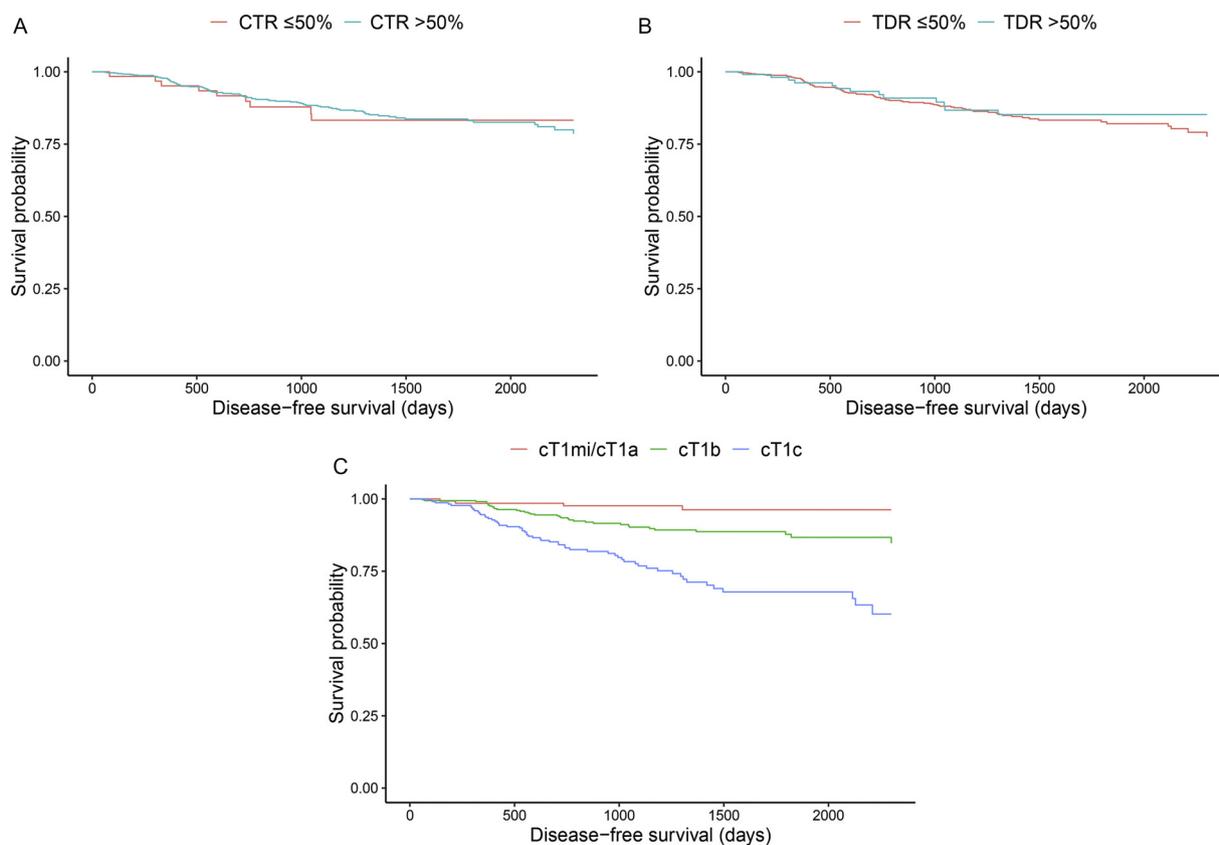


Fig. 2. Adjusted survival curves for disease-free survival of patients with resected adenocarcinomas. Patients were stratified by (A) CTR ($\leq 50\%$ and $> 50\%$) and (B) TDR ($\leq 50\%$ and $> 50\%$) and survival curves were adjusted for the patients' age and clinical T category. (C) Adjusted survival curves according to the clinical T categories of lung adenocarcinomas, which were adjusted for the patients' age and CTR. CTR = consolidation-to-tumor ratio; TDR = tumor disappearance ratio.

Table 4
Subgroup analysis for part-solid nodules.

Variable	cT1mi/cT1a to cT1c			cT1mi/cT1a to cT1b		
	Adjusted HR	95% CI of HR	P-value	Adjusted HR	95% CI of HR	P-value
CTR (%; continuous)	0.991	0.966, 1.016	0.457	0.982	0.951, 1.014	0.274
CTR (categorical; cutoff, 50%)	0.951	0.411, 2.204	0.907	1.541	0.544, 4.368	0.416
TDR (%; continuous)	1.007	0.987, 1.027	0.487	1.006	0.983, 1.030	0.600
TDR (categorical; cutoff, 50%)	1.022	0.457, 2.285	0.958	0.811	0.304, 2.166	0.676

CI = confidence interval; cT = clinical T category; CTR = consolidation-to-tumor ratio; HR = hazard ratio; TDR = tumor disappearance ratio.

resected adenocarcinomas. In that study, age, sex, pathologic T, pathologic N, history of adjuvant therapy, adenocarcinoma subtype, and maximum standardized uptake value were used for the adjustment. Interestingly, Haraguchi et al. [8] demonstrated the prognostic value of TDR in patients with advanced stage adenocarcinomas (stages III and IV). These results are all plausible considering that ground-glass opacity, which disappears at the mediastinal window, represents the lepidic component [19]. However, the prognostic information contained in the TDR was redundant in relation to the clinical T category, which resulted in a lack of statistical significance for TDR from the multi-variable regression analysis of our study.

This study had limitations. First, our study population comprised patients who had undergone at least a lobectomy to exclude a potential confounder (i.e., a surgical mode) in the survival analysis. Therefore, the prognostic value of CTR and TDR for sub-lobar resection candidates should not be evaluated solely on the basis of our study results. Nitadori et al. [20] reported that no recurrences were observed for patients with low CTR (< 25%) after limited resection (median follow-up: 37 months). Yoshida et al. [16] performed a prospective limited resection trial based on TDR ($\geq 50\%$) and reported that there were no recurrences at a median follow-up interval of 88 months. Therefore, for patients treated with limited resection, conclusions should be withheld until the outcomes of ongoing prospective trials (e.g., JCOG0804 and JCOG1211) are published. Second, *a priori* sample size estimation was not performed. Instead, we collected a large number of retrospective cohorts. Third, pathologic information, including pathologic size measurements and stage, were not analyzed as our study focused specifically on the prognostic values of CTR and TDR. Fourth, multiplanar reconstructions including both sagittal and coronal planes were not available for the entire study participants, limiting our measurements to the axial plane. This could have led to underestimation in some craniocaudal-oriented nodules. However, the relative underestimation should be similar for solid and non-solid components, with minor variations on CTR and TDR.

5. Conclusions

We conclude that CTR and TDR are not independent prognostic factors for surgically treated adenocarcinomas when the eighth edition clinical T factor is included in the survival analysis for adjustment.

Funding source

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Science, ICT & Future Planning, Republic of Korea (grant number: 2017R1A2B4008517), however, the funder had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

Activities not related to the present article: H.K., J.M.G., and C.M.P. received research grants from Lunit Inc. (Seoul, South Korea).

Declaration of Competing Interest

Activities related to the present article: none.

Activities not related to the present article: H.K., J.M.G., and C.M.P. received research grants from Lunit Inc. (Seoul, South Korea).

Acknowledgment

We sincerely express our gratitude to Myunghee Lee and Ju Young

Jeong for their help in data acquisition.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.lungcan.2019.09.014>.

References

- [1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA Cancer J. Clin.* 68 (2018) 394–424.
- [2] H. Uramoto, F. Tanaka, Recurrence after surgery in patients with NSCLC, *Transl. Lung Cancer Res.* 3 (2014) 242–249.
- [3] P. Goldstraw, K. Chansky, J. Crowley, R. Rami-Porta, H. Asamura, W.E. Eberhardt, et al., The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer, *J. Thorac. Oncol.* 11 (2016) 39–51.
- [4] K. Aokage, J. Yoshida, G. Ishii, Y. Matsumura, T. Haruki, T. Hishida, et al., Identification of early T1b lung adenocarcinoma based on thin-section computed tomography findings, *J. Thorac. Oncol.* 8 (2013) 1289–1294.
- [5] H. Asamura, T. Hishida, K. Suzuki, T. Koike, K. Nakamura, M. Kusumoto, et al., Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201, *J. Thorac. Cardiovasc. Surg.* 146 (2013) 24–30.
- [6] T.W. Huang, K.H. Lin, H.K. Huang, Y.I. Chen, K.H. Ko, C.K. Chang, et al., The role of the ground-glass opacity ratio in resected lung adenocarcinoma, *Eur. J. Cardiothorac. Surg.* 54 (2018) 229–234.
- [7] T. Matsunaga, K. Suzuki, K. Takamochi, S. Oh, What is the radiological definition of part-solid tumour in lung cancer? *Eur. J. Cardiothorac. Surg.* 51 (2017) 242–247.
- [8] N. Haraguchi, H. Satoh, N. Kikuchi, K. Kagohashi, H. Ishikawa, M. Ohtsuka, Prognostic value of tumor disappearance rate on computed tomography in advanced-stage lung adenocarcinoma, *Clin. Lung Cancer* 8 (2007) 327–330.
- [9] K. Shimizu, K. Yamada, H. Saito, K. Noda, H. Nakayama, Y. Kameda, et al., Surgically curable peripheral lung carcinoma: correlation of thin-section CT findings with histologic prognostic factors and survival, *Chest* 127 (2005) 871–878.
- [10] D. Kim, H.K. Kim, S.H. Kim, H.Y. Lee, J.H. Cho, Y.S. Choi, et al., Prognostic significance of histologic classification and tumor disappearance rate by computed tomography in lung cancer, *J. Thorac. Dis.* 10 (2018) 388–397.
- [11] H.Y. Lee, S.W. Lee, K.S. Lee, J.Y. Jeong, J.Y. Choi, O.J. Kwon, et al., Role of CT and PET imaging in predicting tumor recurrence and survival in patients with lung adenocarcinoma: a comparison with the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma, *J. Thorac. Oncol.* 10 (2015) 1785–1794.
- [12] K. Suzuki, T. Koike, T. Asakawa, M. Kusumoto, H. Asamura, K. Nagai, et al., A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201), *J. Thorac. Oncol.* 6 (2011) 751–756.
- [13] W.D. Travis, H. Asamura, A.A. Bankier, M.B. Beasley, F. Detterbeck, D.B. Flieder, et al., The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer, *J. Thorac. Oncol.* 11 (2016) 1204–1223.
- [14] W.D. Travis, E. Brambilla, M. Noguchi, A.G. Nicholson, K.R. Geisinger, Y. Yatabe, et al., International Association for the Study of Lung Cancer/American thoracic Society/European respiratory society international multidisciplinary classification of lung adenocarcinoma, *J. Thorac. Oncol.* 6 (2011) 244–285.
- [15] K. Aokage, H. Saji, K. Suzuki, T. Mizutani, H. Katayama, T. Shibata, et al., A non-randomized confirmatory trial of segmentectomy for clinical T1N0 lung cancer with dominant ground glass opacity based on thin-section computed tomography (JCOG1211), *Gen. Thorac. Cardiovasc. Surg.* 65 (2017) 267–272.
- [16] J. Yoshida, G. Ishii, T. Hishida, K. Aokage, M. Tsuboi, H. Ito, et al., Limited resection trial for pulmonary ground-glass opacity nodules: case selection based on high-resolution computed tomography-interim results, *Jpn. J. Clin. Oncol.* 45 (2015) 677–681.
- [17] F.E. Harrell, *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*, 2nd ed., Springer, New York, 2015.
- [18] K.K. Hunt, C. Karakas, M.J. Ha, A. Biernacka, M. Yi, A.A. Sahin, et al., Cytoplasmic cyclin E predicts recurrence in patients with breast cancer, *Clin. Cancer Res.* 23 (2017) 2991–3002.
- [19] J.H. Austin, K. Garg, D. Aberle, D. Yankelevitz, K. Kuriyama, H.J. Lee, et al., Radiologic implications of the 2011 classification of adenocarcinoma of the lung, *Radiology* 266 (2013) 62–71.
- [20] J. Nitadori, A.J. Bograd, E.A. Morales, N.P. Rizk, M.P. Dunphy, C.S. Sima, et al., Preoperative consolidation-to-tumor ratio and SUVmax stratify the risk of recurrence in patients undergoing limited resection for lung adenocarcinoma $\leq 2\text{ cm}$, *Ann. Surg. Oncol.* 20 (2013) 4282–4288.