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ORIGINAL ARTICLE

Verification of T descriptor with consolidation size for sub-centimeter non-small cell lung cancer

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Abstract

Purpose In the most recent (eighth) edition of the TNM classification, the clinical T descriptor has been adapted to measure the consolidation size of sub-solid lung cancer. Sub-centimeter non-small cell lung cancer (NSCLC) has thereby been subclassified into three groups: Tis, T1mi, and T1a; however, the revision has not been validated well. Thus, we investigated the clinicopathological characteristics and long-term oncological outcomes of sub-centimeter NSCLCs based on the solid size.

Methods The subjects of this retrospective review were 99 patients who underwent complete resection for NSCLC with ≤1 cm in consolidation size on computed tomography (CT). Survival was reanalyzed after reclassification according to the new TNM classification.

Results This cohort consisted of 14 patients with cTis tumors, 18 with cT1mi tumors, and 67 with cT1a tumors. Among the patients with tumors classified as cT1a, two had lymph node metastasis and two had vascular invasion. The cumulative incidences of recurrence at 5 and 10 years were 0% for cTis/cT1mi tumors, and 4.5% and 6.1% for cT1a tumors, respectively.

Conclusions There may be pathological and survival differences between cTis/cT1mi tumors and cT1a tumors, but not between cTis tumors and cT1mi tumors.

Keywords Non-small cell lung cancer · T classification · Prognosis

Introduction

The eighth edition of the TNM classification of lung cancer has now been adopted [1]. Among the revisions, the impactable change was the method of measuring tumor size. Up to the seventh edition, tumor size was measured as total tumor size, clinically and pathologically. In the eighth edition, measurement is done according to the regulation that size is measurement of the invasive component. On thin-slice computed tomography (CT), a solid component is considered invasive and adopted to clinical T factors. In the pathological findings of adenocarcinoma, invasive size is measured without the area of lepidic growth pattern (non-invasive component pathologically).

T factor according to tumor size was also revised. The 3 cm cut-point has been adopted unchanged, with tumors ≤5 cm in size classified every 1 cm, as T1a, T1b, T1c, T2a, and T2b. This classification was derived from the results of survival analysis according to the tumor size [2]. Analysis by the invasive size was not performed in that proposal of the revision. In addition, sub-centimeter non-small cell lung cancer (NSCLC) was subclassified into three groups: Tis, T1mi, and T1a. This sub-classification responded to pathological findings such as adenocarcinoma in situ and minimally invasive adenocarcinoma [3]. Although sub-centimeter NSCLCs were investigated by several researchers focusing on NSCLCs with malignant behavior, those studies were not carried out according to the new TNM classification [4–7]. The objectives of the present study were to investigate the clinicopathological characteristics and oncological outcomes of sub-centimeter NSCLCs based on the solid size with long-term follow-up.

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Materials and methods

Study population

Between January, 2004 and December, 2010, 699 consecutive patients underwent surgery for lung cancer at Nagoya University Hospital. Among the 699 patients with clinical N0 non-small cell lung cancer (NSCLC), we reviewed, retrospectively, 99 patients with a solid tumor size of ≤ 1.0 cm. This study was approved by the institutional review board of Nagoya University Hospital (2012-0162).

Radiological and pathological evaluations

Thin-slice CT images were obtained with multislice CT scanners without contrast medium. We used a 0.5–2.0 mm slice thickness and a lung algorithm. Two of the authors measured both of the total size and the solid size manually. The definition of the total size was the maximum diameter of the tumor, including ground grass opacity. The solid component was defined as any area of increased opacification that obscured the underlying vascular markings. Differences in measurement between observers were resolved by consensus. Pathologists and one author reevaluated the pathological slides to obtain pathological total size, invasive size, and predominant histologic subtype. Vascular and pleural invasion were evaluated with hematoxylin and eosin-stained slides. The tumor stages of all patients were reclassified according to the TNM classification, eighth edition. Any discrepancies between observers were resolved by consensus.

Follow-up

Routine follow-up included a physical examination, chest X-ray, and blood test, every 3–6 months for the first 3 years after surgery and every 6–12 months thereafter. Chest CT scan was performed regularly and if there were any symptoms or signs of recurrence. Magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography were also performed as necessary.

Statistical analysis

The Kruskal–Wallis test was used to compare characteristics among the three groups. The cumulative incidence of recurrence (CIR) was estimated from the time of surgery and analyzed using a competing risk approach, considering deaths of patients without recurrence as competing events. Differences in CIR between groups were assessed using Gray's method. Overall survival (OS) was defined as the time from surgery to death from any cause. OS was calculated by the Kaplan–Meier estimation method using a log-rank test. The Fine and Gray competing risk regression analysis was used to estimate the sub-hazard ratio to evaluate the association between clinicopathological variables and the risk of recurrence. Statistical analysis was considered significant when the p value was less than 0.05. All statistical analyses were performed with R 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinicopathological findings

Table 1 summarizes the clinical characteristics of the 99 patients. There were 14 patients with cTis tumors, 18 with cT1mi tumors, and 67 with cT1a tumors. The median age at the time of resection was 68 years old (range 35–87 years old). The majority of patients were never-smokers (61%) and there were significantly more smokers in the cT1a tumor group. The median tumor size was 15 mm (range 7–30 mm), and lobectomy accounted for about half of the surgical procedures. There was no significant difference in the type of surgical resection among the groups.

The median pathological total size was 13 mm (range 5–27 mm), with no significant difference among the groups. The median pathological invasive size of the cTis, cT1mi, and cT1a tumors was 0 mm, 4 mm, and 8 mm, respectively. Lymph node metastasis and vascular invasion were associated with only cT1a tumors. Concordances between the clinical and pathological T stages were seen in nine patients (64%) with Tis tumors, 4 (22%) with T1mi tumors, and 26 (39%) with T1a tumors. Lepidic predominant adenocarcinoma (adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic adenocarcinoma) were found in 13 (93%) patients with cTis tumors, 10 (55%) with cT1mi tumors, and 23 (34%) with cT1a tumors.

Prognosis

The median follow-up period was 8.0 years (range 4.2–12.7 years). Recurrence was diagnosed in four patients (4%) with tumors categorized as cT1a, three of which were resected by lobectomy, and one by segmentectomy. The types of recurrence were pulmonary metastasis in three patients and malignant pleural effusion in one (Table 2). CIR at 5 and 10 years were 0% for cTis/cT1mi tumors and 4.5% and 6.1%, respectively, for cT1a tumors, with no significant difference between the cTis/cT1mi and cT1a tumors ($p = 0.16$; Fig. 1a). The lung cancer-specific cumulative incidence of death at 5 years and 10 years for patients with cTis/cT1mi tumors were all 0%, and those for cT1a tumors were 0% and 3.8%, respectively, without any

Table 1 Clinicopathological characteristics of the patients with clinical N0 non-small cell lung cancer (sub-centimeter in solid size)

Variables	cTis $n=14$	cT1mi $n=18$	cT1a $n=67$	p value
Age, years	69 (52–77)	67 (44–74)	68 (35–87)	0.26
Gender, male	6 (43)	6 (33)	38 (57)	0.18
Current/past smoking	2 (14)	3 (17)	33 (49)	<0.01
Solid size, mm	0 (0)	5 (3–5)	8 (6–10)	<0.01
CEA, >5.0 ng/ml	3 (21)	0 (0)	10 (15)	0.15
Surgical procedure, lobectomy	9 (64)	8 (44)	44 (67)	0.21
p-Total size, mm	12.5 (5–22)	11.5 (7–20)	13 (6–27)	0.32
p-Invasive size, mm	0 (0–9)	4 (0–10)	8 (0–20)	<0.01
p-N status, positive	0 (0)	0 (0)	2 (3)	0.61
Histology				0.73
Adenocarcinoma	14 (100)	18 (100)	63 (94)	
AIS	9	7	4	
MIA	4	3	13	
LPA	0	0	6	
Other invasive adenocarcinoma	1	8	40	
Squamous cell carcinoma	0 (0)	0 (0)	1 (1)	
Other	0 (0)	0 (0)	3 (4)	
Lymphatic invasion	0 (0)	0 (0)	2 (3)	0.48
Vascular invasion	0 (0)	0 (0)	2 (3)	0.48

Values are expressed as numbers (%) or as the median (range)

CEA carcinoembryonic antigen, *AIS* adenocarcinoma in situ, *MIA* minimally invasive adenocarcinoma, *LPA* lepidic predominant invasive adenocarcinoma

Table 2 Characteristics of the patients with recurrence

Case	Age	Sex	c-SS/TS (mm/mm)	Procedure	Histology	p-IS/TS (mm/mm)	Recurrence type	DFI (months)	Status at last contact, interval (months)
1	79	M	10/10	Segmentectomy	ADSQ	11/11	Pulmonary metastasis	60	Cancer death, 64
2	69	F	10/10	Lobectomy	AD	12/12	Malignant pleural effusion	15	Alive, 81
3	81	M	10/13	Lobectomy	AD	5/13	Pulmonary metastasis	75	Non-cancer death, 86
4	64	M	10/15	Lobectomy	AD	10/13	Pulmonary metastasis	35	Alive, 111

AD Adenocarcinoma, *ADSQ* adenosquamous carcinoma, *DFI* disease free interval, *IS* invasive size, *SS* solid size, *TS* total size

significant difference between the cTis/cT1mi and cT1a tumors ($p=0.64$; Fig. 1b). OS at 5 years and 10 years were both 93.8% for patients with cTis/T1mi tumors and 94.0% and 71.9%, respectively for those with cT1a tumors (Fig. 1c). Table 3 shows the results of Fine and Gray's analysis for recurrence based on the clinical covariates. Univariate analysis revealed that consolidation size, total size, and CEA had survival associations with recurrences, whereas the radiological type of nodule did not have survival associations. Multivariate analysis revealed that consolidation size had survival associations with recurrences (sub-hazard ratio = 6.19, 95% confidence interval: 1.34–28.5, $p=0.02$).

Discussion

The eighth edition of the TNM classification of lung cancer follows the concept that the invasive component size is a criterion for the T descriptor [3]. This revision seems to follow the general rule of the TNM system. It is mentioned in the TNM supplement that when size is a criterion for the T category, it is a measurement of the invasive component [8]. There have been many reports on the non-invasiveness of the radiological and pathological findings of adenocarcinoma of the lung. A representative study was performed by the Japan Clinical Oncology Group to predict

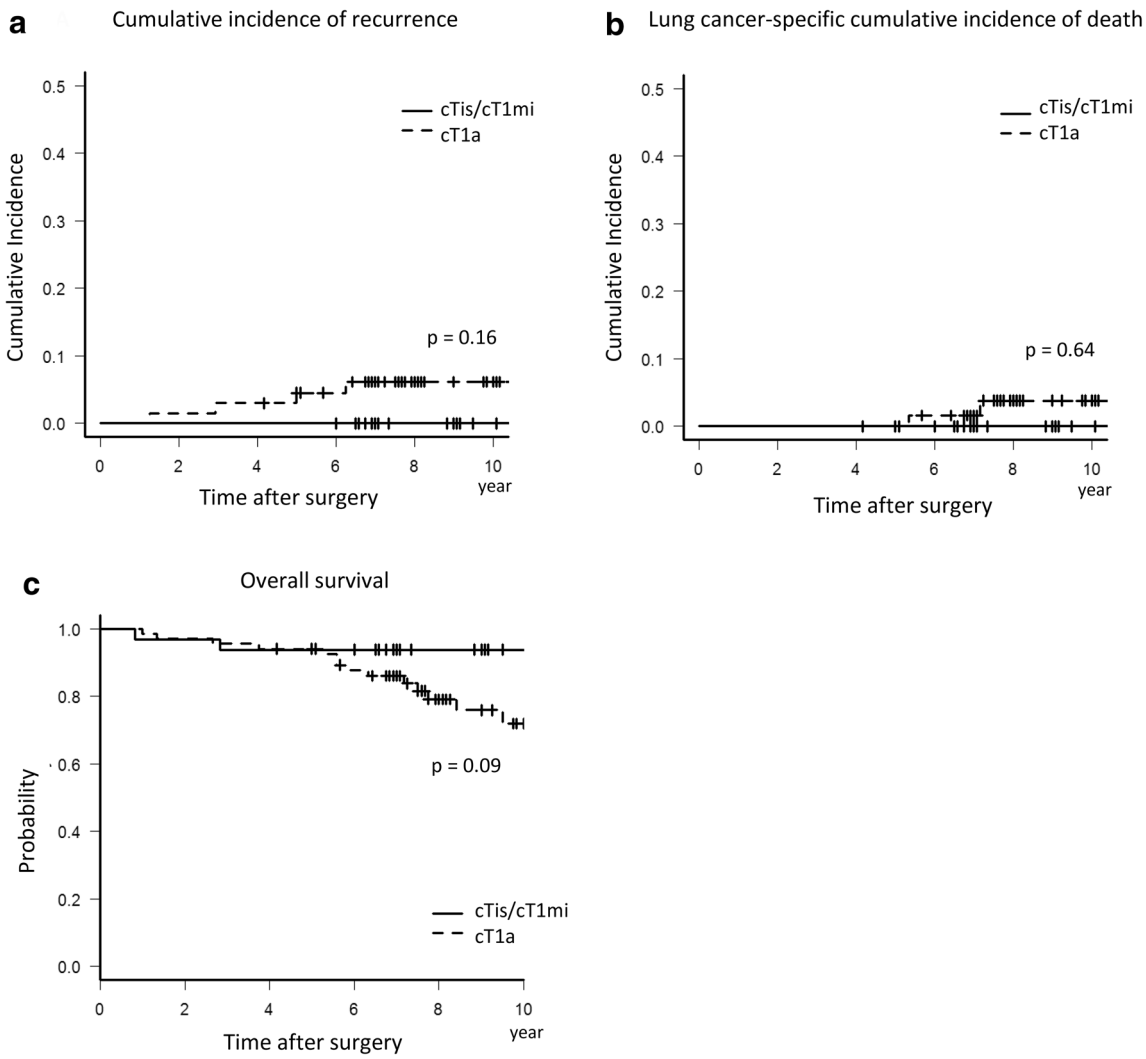

Fig. 1 Cumulative incidence of recurrence (**a**), lung cancer-specific cumulative incidence of death (**b**), and Kaplan–Meier curves of overall survival (**c**) of patients with cTis/cT1mi tumors and those with cT1a tumors. There was no incidence of recurrence or lung cancer-specific death among patients with cTis/cT1mi tumors, and no significant differences were observed

Table 3 Results of the univariable and multivariable competing risk analyses for recurrence

	Univariate		Multivariate	
	SHR (95% CI)	*p* value	SHR (95% CI)	*p* value
Age, years	1.11 (0.98–1.26)	0.10		
Gender, male	2.93 (0.30–28.0)	0.35		
Smoking history, current or past	1.57 (0.23–10.8)	0.65		
CEA level, > 5.0 ng/ml	7.38 (1.12–48.7)	0.04	2.79 (0.57–13.7)	0.21
c-Total size, mm	0.83 (0.71–0.96)	0.02	0.82 (0.70–1.00)	0.05
Consolidation size, mm	6.56 (1.63–26.4)	< 0.01	6.19 (1.34–28.5)	0.02
Radiological type of nodule, pure solid	5.22 (0.60–45.6)	0.14		
Surgical procedure, lobectomy	1.85 (0.20–17.3)	0.59		

SHR sub-hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen

radiological and pathological non-invasiveness, evaluating radiological findings such as the consolidation tumor ratio (CTR) to predict early lung cancer for the application of limited surgery [9]. Their findings were that radiological noninvasive lung adenocarcinoma could be defined as an adenocarcinoma ≤ 2.0 cm with CTR ≤ 0.25. The noninvasive nodules in their definition corresponded to cTis and cT1mi tumors of the new TNM classification and those nodules were predicted to have no pathological invasion.

Sakurai et al. reported the clinicopathological features of lung cancer sub-centimeter in size and found that nodules showing pure GGO and part-solid GGO with CTR ≤ 0.5 did not have nodal involvement or vascular invasion, whereas nodules showing pure solid and part-solid GGO with CTR > 0.5 did [5]. These findings may support that the nodules in the cTis and cT1mi category are not always pathologically invasive. Hattori et al. also investigated the radiological and clinicopathological findings of sub-centimeter NSCLC and found that patients with pure solid nodules had a poorer prognosis than those with nodules with GGO [6]. They concluded that solid nodules should be treated as invasive tumors. Although these findings are important, the cohorts of past reports were not classified according to the new TNM classification, meaning that there are no validated results on patients with sub-centimeter NSCLC using the new TNM classification. The present study shows the clinicopathological characteristics and survival outcomes of NSCLC patients with a solid component size ≤ 1 cm (sub-centimeter) tumors, following the new TNM classification, with long-term follow-up periods. Pathological invasiveness was noted in cT1a tumors, but not in cTis/cT1mi tumors in this study. This could imply that the pathological behavior of cTis/cT1mi tumors and cT1a tumors are different.

The survival analysis in this study indicated that the CIR of patients with cT1a tumors was higher than that of the other group, but the difference was not significant. Although there was no cancer-specific death among the patients with cTis/cT1mi tumors, there were four recurrences and two cancer deaths among patients with cT1a tumors. In accordance with our findings based on long-term follow-up, previous studies have reported excellent prognoses for patients with GGO-predominant small nodules [5, 6, 10]. According to the new T classification, the GGO-predominant nodules in this study were distributed in each of the three groups, with solid and solid-predominant nodules found only in the cT1a category. In other words, the cT1a tumors of this study were almost consistent with the solid-dominant nodules, excluding GGO-dominant nodules. This could result in a survival difference between patients with cTis/cT1mi tumors vs. those with cT1a tumors, but not between each group.

Single-center retrospective studies have shown the validity of measuring invasive size as the T descriptor [11–13]. The progressive degradation of survival was observed in the analysis by the new T classification in those studies, so that those results can support the classification. The multivariate analysis of our results showed that consolidation size was associated with recurrence, but total size was not. Consolidation size could be more suitable as a size for the T factor in sub-centimeter nodules, although the impact on survival was limited because of the good prognoses of these patients.

Although the size of invasion on radiological findings correlated to that in the pathological findings, the coincidence rate between the clinical T factor and the pathological T factor was low, especially in cT1mi tumors. Thus, nodules classified into the cT1mi category could easily be over- and under-diagnosed. While the area of GGO on thin-slice CT usually represents lepidic growth components pathologically, GGO sometimes represents invasive components such as acinar, papillary, and micropapillary components [14–16]. Furthermore, the consolidation area regarded as the invasive component on thin-slice CT could contain collapse without any myofibroblast or invasive component [17]. These phenomena could be more frequently associated with small consolidation, based on the present study. Making an accurate clinical diagnosis based on pathological findings may be difficult. Therefore, subdividing for sub-centimeter nodules probably leads to more mismatches in diagnosis resulting in possible inappropriate treatment, especially when underdiagnosed.

This study was limited by the fact that it was conducted retrospectively at a single center, using a small sample population. Therefore, the detective power may be insufficient and generalizing the results was difficult. Further study on a large number of patients is needed to validate our results.

In conclusion, we reported the clinicopathological characteristics and survival outcomes of NSCLC patients, focusing on a solid component size ≤ 1 cm (sub-centimeter) following the new eighth edition TNM classification, with long-term follow-up. Our findings show that there could be pathological differences between cTis/cT1mi tumors and cT1a tumors, but there was not enough impact to separate cTis and cT1mi. This might be meaningful for classifying patients with 0–5 mm consolidation size tumors into modified T1mi (Tis and T1mi) for the next revision of the TNM classification. External validation is needed and will contribute to the next revision.

Compliance with ethical standards

Conflict of interest None declared.

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