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Implications of the Eighth Edition of the TNM Proposal: Invasive vs. Total Tumor Size for the T Descriptor in Pathologic Stage I-IIA Lung Adenocarcinoma

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Abstract

Introduction: The eighth edition of the tumor, node, and metastasis (TNM) staging system included the proposal that the T descriptor be determined according to the invasive component, excluding lepidic component, for nonmucinous lung adenocarcinomas. We sought to conduct a clinicopathologic comparative analysis of the newly proposed classification using invasive size versus total tumor size.

Methods: Patients who underwent lung resection for primary lung adenocarcinoma with pathologic stage (p-Stage) I-IIA (based on total size [t]) were reviewed (n=1704). Pathologic

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invasive size was measured, and tumors were reclassified using invasive size (i). Cumulative incidence of recurrence (CIR) and lung cancer–specific cumulative incidence of death (LC-CID) were analyzed using a competing-risks approach. Prognostic discrimination by p-Stage(t) and p-Stage(i) was evaluated using a concordance index (C-index).

Results: The use of invasive size resulted in downstaging in 377 of 1704 patients (22%), with twice as many patients with p-Stage IA1 (IA1[i] vs. IA1[t]: 389 [23%] vs. 195 [11%]). However, outcomes were similar between the two groups (IA1[i] vs. IA1[t]: 5-year-CIR, 11% vs. 13%; 5-year LC-CID, 5% vs. 7%). Prognostic discrimination by p-Stage(i) was better than by p-Stage(t) (C-index for p-Stage[i] vs. p-Stage[t]: recurrence, 0.614 vs. 0.593; lung cancer–specific death, 0.634 vs. 0.621).

Conclusions: When invasive size, rather than total size, was used for the T descriptor, a larger number of patients were classified with a favorable prognosis (p-Stage IA1) and better prognostic discrimination of p-Stage I-IIA nonmucinous lung adenocarcinomas was achieved.

Keywords

Lung adenocarcinoma; invasive tumor size; consolidation tumor size; lung cancer-specific death; recurrence

Introduction

Following the results of the National Lung Screening Trial, which showed that screening with low-dose computed tomography (CT) reduces mortality from lung cancer, the detection of early-stage lung cancer has been expected to increase.[1] In 2016, using survival data from a multinational cohort of patients with non-small cell lung cancer (NSCLC), the International Association for the Study of Lung Cancer (IASLC) refined their classification of early-stage node-negative lung cancers ≤5 cm as follows: IA (≤3 cm) and IB (>3 to ≤5 cm) in the seventh edition of the tumor, node, and metastasis (TNM) classification became IA1 (≤1 cm), IA2 (>1 to ≤2 cm), IA3 (>2 to ≤3 cm), IB (>3 to ≤4 cm), and IIA (>4 to ≤5 cm) in the eighth edition.[2] Furthermore, the eighth edition addressed the correlation between radiologic part-solid nodules and the histologic components of nonmucinous lung adenocarcinomas (ADCs) and proposed the use of invasive size, rather than total size, for the T descriptor for nonmucinous lung ADCs with a lepidic component.[3]

These changes follow previous efforts to achieve better prognostic stratification in lung ADC, the most common histologic subtype of NSCLC. In 2011, a multidisciplinary group of experts from the IASLC, American Thoracic Society (ATS), and European Respiratory Society (ERS) proposed a new classification of lung ADC that included two new subtypes: ADC in situ (AIS) and minimally invasive ADC (MIA).[4] The authors proposed that histologic patterns should be recorded in 5% increments and, on this basis, the predominant histologic pattern (lepidic, acinar, papillary, micropapillary, or solid) determined. In 2013, the Fleischner Society largely based their recommendations for the management of subsolid pulmonary nodules detected by CT scan on this histologic classification system.[5] In 2015, the World Health Organization (WHO) adopted the histologic classification system following validation of independent cohorts.[6–9]

The TNM staging system remains the most useful tool for determining treatment options for patients with lung cancer.[2] Tumor size is a key element of TNM staging,[10] and the available evidence suggests that, for lung ADC tumors, invasive size is a better predictor of outcomes than total size.[6, 11, 12] Recently, Aokage and colleagues analyzed a cohort of patients with resected stage I-IV NSCLC using both the seventh and eighth editions of the TNM classification.[13] For staging of nonmucinous lung ADCs with a lepidic component, the T descriptor was determined by total size when the seventh edition was used and invasive size when the eighth was used; comparison revealed good correlation between solid size on CT and invasive size on pathologic assessment. In addition, concordance probability estimates and Akaike's information criterion values for overall survival were higher for the eighth edition than the seventh edition.

To date, no study has investigated the impact of the changes to the definitions of T1 (a, b, and c) and T2 nonmucinous lung ADCs or compared the effect on prognosis of using invasive versus total size for the T descriptor. In this study, we performed a clinicopathologic comparative analysis of total versus invasive size in nonmucinous lung ADCs, with the goal of determining whether the use of invasive size improves prognostic discrimination when using the eighth edition of the TNM classification.

Methods

Patient Cohort

This retrospective study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSK). All patients diagnosed with solitary lung ADC who had undergone surgical resection at MSK between January 2000 and December 2014 were reviewed. Patients who had undergone lung resection for primary lung ADC with pathologic stage (p-Stage) I-IIA (based on total tumor size) were included. Patients who had received induction therapy, had multiple nodules, had lung cancer within the preceding two years, had positive surgical margins, or had concurrent disease progression were excluded from analysis, as were patients with a histologic diagnosis of AIS, MIA, invasive mucinous ADC, or colloid predominant ADC (Supplementary Figure S1). Patient demographic information was obtained from the MSK Thoracic Surgery Service's prospectively maintained lung cancer database. Data on clinical variables and follow-up information were obtained by reviewing patient medical records.

Recurrence and Lung Cancer–Specific Death as Endpoints

Postoperative lung cancer surveillance was performed in accordance with National Comprehensive Cancer Network (NCCN) guidelines.[14] During the first 2 years after surgery, each patient received a physical examination, interval history review, and chest/upper abdomen CT scan, with or without contrast, every 6 to 12 months. Follow-up visits and surveillance CT scans were performed yearly after the first 2 years.

The study endpoints were recurrence and lung cancer–specific death. All recurrences were confirmed by clinical, radiologic, and pathologic assessment.[15] In cases where a new tumor developed in the lung or pleura and a biopsy specimen was available, the histologic profile

was reviewed to determine whether the new tumor was a metachronous primary tumor, a recurrence, or a metastasis; this was completed in accordance with the method developed by our group.[16] Lung cancer–specific death was defined as death due to recurrent disease associated with resected lung cancer.[17]

Histologic Evaluation

All available hematoxylin and eosin–stained tumor slides were reviewed by at least two pathologists (S.L., K.K., and W.D.T.), who were blinded to patient clinical outcomes, using an Olympus BX51 microscope (Olympus, Tokyo, Japan) with a standard 22-mm diameter eyepiece. Any discrepancies between the pathologists during assignment of predominant subtypes were later resolved via consensus using a multihead microscope. The percentage of each histologic pattern was recorded in 5% increments. Tumors were classified in accordance with the 2011 IASLC/ATS/ERS classification and the 2015 WHO classification.[4, 8] Tumors were grouped by histologic grading as low (lepidic), intermediate (papillary or acinar), or high (micropapillary or solid).[18] Visceral pleural invasion (VPI), lymphovascular invasion (LVI), necrosis, and tumor spread through air spaces[19] were also investigated.

Pathologic Assessment of Total and Invasive Tumor Size

Pathologic total tumor size was defined as the maximum diameter of the tumor. Pathologic tumor size was initially assessed by gross measurement using a ruler placed along the tumor in the gross specimen before or after cross-section of the tumor. The initial gross measurement was then reevaluated by microscopic evaluation to ultimately determine pathologic total tumor size.

Pathologic invasive tumor size was defined as the size of invasive components, excluding lepidic component, on microscopic examination. Although in some cases invasive size could be measured with a ruler in a single focus, in most cases this was not possible, owing to multiple foci of invasion or the presence of invasive areas on multiple slides. Therefore, as proposed by our group in 2014[20] and included in the 2015 WHO classification,[8] for all cases in this study pathologic invasive tumor size was estimated using the following equation: pathologic invasive size = pathologic total size × percentage of invasive components/100. p-Stages for all tumors based on total size (t) were reclassified on the basis of invasive size (i).

Statistical Analysis

The outcomes of interest—recurrence and lung cancer–specific death—were analyzed in a competing-risk framework. For recurrence, death from any cause without recurrence was considered a competing event. For lung cancer–specific death, death from causes other than lung cancer or from unknown causes was considered a competing event. The cumulative incidence of recurrence (CIR) and the lung cancer–specific cumulative incidence of death (LC-CID) were used to estimate the probability of recurrence or lung cancer–specific death following surgical resection with curative intent.[21] Patients who did not experience recurrence or die during the study period were censored at the time of the last available follow-up (assessed in April 2017). Differences in CIR or LC-CID between groups were tested using the Gray method.[22] The concordance index (C-index) was assessed to evaluate prognostic discrimination by TNM classification. Statistical analyses were performed using

R 3.1.1 (R Development Core Team, Vienna, Austria); the “survival” and “cmprsk” software packages were used in the analyses. All *P* values were two-sided, and significance was set at 5%.

Results

Number and Proportion of Patients with Each p-Stage

The use of invasive size resulted in downstaging in 377 patients (22%). In particular, twice as many patients were classified as the lowest stage (p-Stage IA1) when invasive size was used (IA1[i] vs. IA1[t]: 389 [23%] vs. 195 [11%]), secondary to downstaging in 194 patients (downstaged from: IA2[t], 164 [42%]; IA-3[t], 26 [7%]; IB[t] 4 [1%]). The proportion and number of patients who were classified with the same stage or downstaged when invasive size was used for staging are shown in Figure 1. Of the 195 patients with p-Stage IA1(t) according to the eighth edition of the TNM classification by total size, all were classified with the same stage according to the eighth edition TNM classification by invasive size (p-Stage IA1[i]). Of the 685 patients with p-Stage IA2(t), 164 (24%) were downstaged to IA1(i). Of the 336 patients with p-Stage IA3(t), 134 (40%) were downstaged to IA2(i) (n=108 [32%]) or IA1(i) (n=26 [8%]). Of the 133 patients with p-Stage IB(t) without VPI, 49 (37%) were downstaged to IA3(i) (n=32 [24%]), IA2(i) (n=13 [10%]), or IA1(i) (n=4 [3%]). All 260 patients with p-Stage IB(t) with VPI were classified with the same stage (p-Stage IB[i]) because of the presence of VPI, regardless of differences between total and invasive sizes. Of the 95 patients with p-Stage IIA(t), 30 (32%) were downstaged to IB(i) (n=23 [24%]), IA3(i) (n=5 [5%]), or IA2(i) (n=2 [2%]).

Clinicopathologic Characteristics by p-Stage(t) and p-Stage(i)

Table 1 lists clinicopathologic characteristics stratified by p-Stage(t) and p-Stage(i). Figure 2 shows the incidence of prognostic pathological factors by p-Stage(t) and p-Stage(i). When invasive size was used, better stepwise stratification of all factors, except low histologic grade, was achieved (lower incidence among the lowest stage [IA1] and higher incidence among the highest stage [IIA]). On the other hand, the use of invasive size resulted in a larger distribution of low-grade tumors in the p-Stage IA1 group (% of low-grade histologic subtype in p-Stage IA[i] vs. IA[t], 34% vs. 5%).

CIR by Same Stage or Downstaged

Figure 3 shows a comparison of CIR between patients who were classified as the same stage and those who were downstaged when invasive size was used. As shown in the figure, for all stages, patients who were downstaged had a lower risk of recurrence than those whose stage remained the same.

CIR and LC-CID by p-Stage(t) and p-Stage(i)

Figure 4 shows CIR and LC-CID curves stratified by p-Stage(t) and p-Stage(i). Although the p-Stage IA1(i) group (n=389) included 194 patients (50%) who were downstaged, risk of recurrence and lung cancer–specific death were slightly better in this group than in the p-Stage IA1(t) group (n=195) (IA1[i] vs. IA1[t]: 5-year CIR, 11% vs. 13%; 5-year LC-CID, 5% vs. 7%). On the other hand, 30 of 95 patients with p-Stage IIA(t) were downstaged,

resulting in the higher risk of recurrence and lung cancer–specific death in the p-Stage IIA(i) group (n=65) (IIA[i] vs. IIA[t]: 5-year CIR, 41% vs. 32%; 5-year LC-CID, 25% vs. 20%). To ensure that patients who underwent sublobar resection did not skew the results, in Supplementary Figure S2, we show the results of only patients who underwent lobectomy—the results are similar and did not affect the statistical analysis.

Prognostic Discrimination (C-index) by p-Stage(t) and p-Stage(i)

Competing-risk regression models and C-indices for recurrence and lung cancer–specific death by p-Stage(t) and p-Stage(i) are summarized in Table 2. A higher C-index indicates better prognostic discrimination. Prognostic discrimination for predicting recurrence was better by p-Stage(i) than p-Stage(t); for predicting lung cancer–specific death, p-Stage(i) was better than p-Stage(t).

Discussion

Our findings in this study validate the use of invasive size, rather than total size, for the T descriptor in nonmucinous lung ADCs with a lepidic component. The strengths of our study are as follows: (1) this is the first study to validate the use of invasive tumor size in a large, uniform cohort of patients with p-Stage I-IIA lung ADC; (2) our investigation revealed that the use of invasive size with the newly proposed staging system provides better stratification of lung cancer–specific outcomes (recurrence and lung cancer–specific death) and prognostic pathologic factors (such as presence of LVI and high-grade subtypes) according to increasing stage; and (3) our prognostic analysis used a competing-risks approach to address the large number of competing events among patients with early-stage lung cancer.[17]

When invasive size was used for the T descriptor, >20% of patients were downstaged to the most favorable stage (p-Stage IA1); furthermore, the IA1(i) group (n=389) had a slightly better prognosis than the IA1(t) group (n=195) (5-year CIR, 11% vs. 13%; 5-year LC-CID, 5% vs. 7%). Another important finding of our study was the better prognostic stratification when invasive size was used—that is, patients who were downstaged when invasive size was used had fewer recurrences than patients who were not downstaged—especially among patients with p-Stage IIA tumors. In p-Stage I-IIA lung ADCs following margin-negative (R0) resection, the recent NCCN guidelines do not recommend adjuvant chemotherapy, except for those with stage IB (T2aN0) or IIA (T2bN0) tumors with high-risk factors such as >4 cm tumor size, vascular or pleural involvement, wedge resection, or no lymph node evaluation.[14] On the basis of the findings of the present study, we suspect that invasive size may be the important factor for consideration of adjuvant chemotherapy, owing to the significant prognostic difference between tumors >4 cm and 3–4 cm in invasive size. However, this requires further investigation in large clinical studies.

Previous studies investigated radiologic-pathologic correlation in lung nodules.[23–26] Lee and colleagues investigated 58 lung ADCs using ≤1.25-mm-section CT images with three-dimensional (3-D) and two-dimensional (2-D) assessment. The authors observed a strong correlation between radiologic consolidation size and pathologic invasive size (correlation coefficient: 3-D, 0.82–0.87; 2-D, 0.72–0.88), with excellent interobserver reproducibility for

radiologic consolidation size assessment (intraclass correlation coefficient, 0.92–0.98).[26] A recent study investigated radiologic and pathologic correlation in 1792 patients with resected stage I-IV NSCLC and found a strong correlation between consolidation size on thin-section CT and pathologic invasive size (correlation coefficient, 0.83).[13] Consolidation size on preoperative CT may be used to predict pathologic invasive size in clinical practice; however, further investigation (such as a prospective study) is warranted.

One of the potential challenges of using invasive size for staging is reproducibility of the distinction between lepidic and invasive patterns, the kappa value of which was reported to be 0.55 in typical cases and 0.08 in difficult cases.[27] Specifically, it has been reported that it is difficult to differentiate lepidic pattern from papillary or acinar patterns.[28] However, in another study, agreement in the distinction between AIS/MIA and invasive ADC was good, with a kappa of 0.65.[29] In another study, the concordance (using intraclass correlation coefficients) between lepidic predominant subtype and other subtypes was 0.94.[30] In addition, training may increase concordance in histologic subtyping.[28, 31] Although these previous studies that distinguished lepidic “predominant” subtypes (or AIS/MIA) from other invasive morphologic pattern- predominant subtypes showed good results, the reproducibility of determining percentage of lepidic pattern might be more challenging.

It is recommended that mucinous ADCs be measured using total size, regardless of the extent of lepidic component, owing to the lack of validated data supporting the use of invasive size for these tumors[3]; therefore, we did not include patients diagnosed with invasive mucinous ADC or colloid tumors. In addition, mucinous ADCs usually display a consolidation area on CT scan, and radiologic-pathologic correlations between ground-glass and solid patterns on CT and lepidic and invasive patterns on histologic analysis have not been established[4]—although specific radiologic characteristics of mucinous ADC on thin-section CT were reported to be prognostic.[32] More investigation of these tumors is needed.

For pathologic analysis in the present study, we estimated invasive size by multiplying the total tumor size by the percentage of the invasive component. Since, for many tumors, it is impossible to find a single focus of invasion on a single histologic slide, it is essential to have an alternative method. Our results suggest that the approach used in this study is significantly aligned with prognosis. Further investigation is warranted to compare the two methods for determining invasive size—(1) multiplying the total size by the percentage of the invasive component and (2) measuring the greatest diameter of the largest invasive focus using a ruler—especially in cases with multiple areas of invasion.

In conclusion, as proposed in the eighth edition of the TNM staging system, using invasive size, rather than total size, for the T descriptor achieves better prognostic discrimination by identifying a larger number of patients with a favorable prognosis (p-Stage IA1)—patients who were overstaged using total size. The use of invasive size also provides better stratification of prognoses, which may be useful for determining the most appropriate treatment for patients with early-stage nonmucinous lung ADCs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

2-D	two-dimensional
3-D	three-dimensional
ADC	adenocarcinoma
AIS	adenocarcinoma in situ
ATS	American Thoracic Society
C-index	concordance index
CIR	cumulative incidence of recurrence
CT	computed tomography
ETS	European Respiratory Society
i	invasive size
IASLC	International Association for the Study of Lung Cancer
LC-CID	lung cancer–specific cumulative incidence of death
LVI	lymphovascular invasion
MIA	minimally invasive adenocarcinoma
MSK	Memorial Sloan Kettering Cancer Center
NSCLC	non-small cell lung cancer
p-Stage	pathologic stage
t	total size
TNM	tumor, node, and metastasis
WHO	World Health Organization

VPI	visceral pleural invasion

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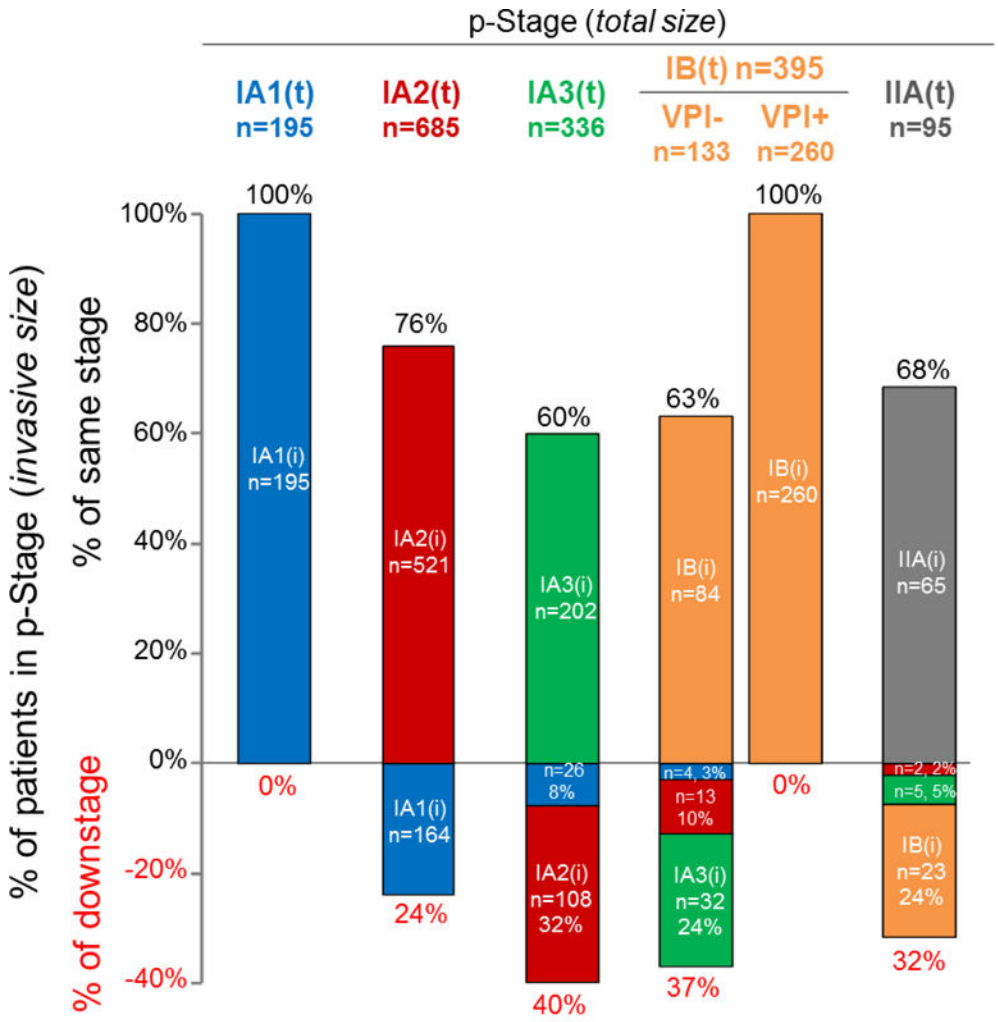

The number of patients

	Total size					
Invasive size	IA1(t) (n=195)	IA2(t) (n=685)	IA3(t) (n=336)	IB(t)VPI- (n=133)	IB(t)VPI+ (n=260)	IIA(t) (n=95)
IA1(i) (n=389)	195	164	26	4	0	0
IA2(i) (n=644)	0	521	108	13	0	2
IA3(i) (n=239)	0	0	202	32	0	5
IB(i) (n=367)	0	0	0	84	260	23
IIA(i) (n=65)	0	0	0	0	0	65

Red color represents the number of patients who were downstaged in p-Stage (*invasive size*)

Figure 1.

Proportion and number of patients who were classified as the same stage or downstaged when invasive size (i) was used, rather than total size (t), for each pathologic stage (p-Stage). VPI, visceral pleural invasion.

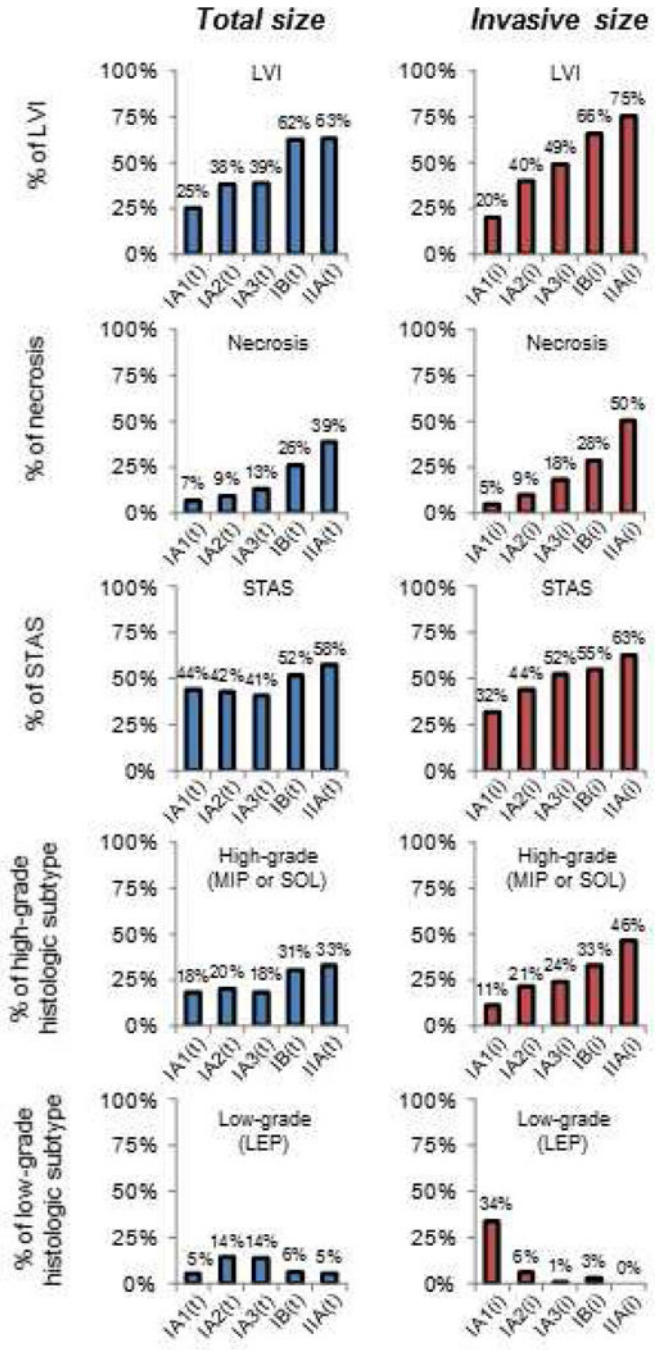

Figure 2.

Incidence of prognostic pathologic factors stratified by pathologic stage based on invasive (i) size and pathologic stage based on total (t) size. LEP, lepidic; LVI, lymphovascular invasion; MIP, micropapillary; SOL, solid; STAS, spread through air spaces.

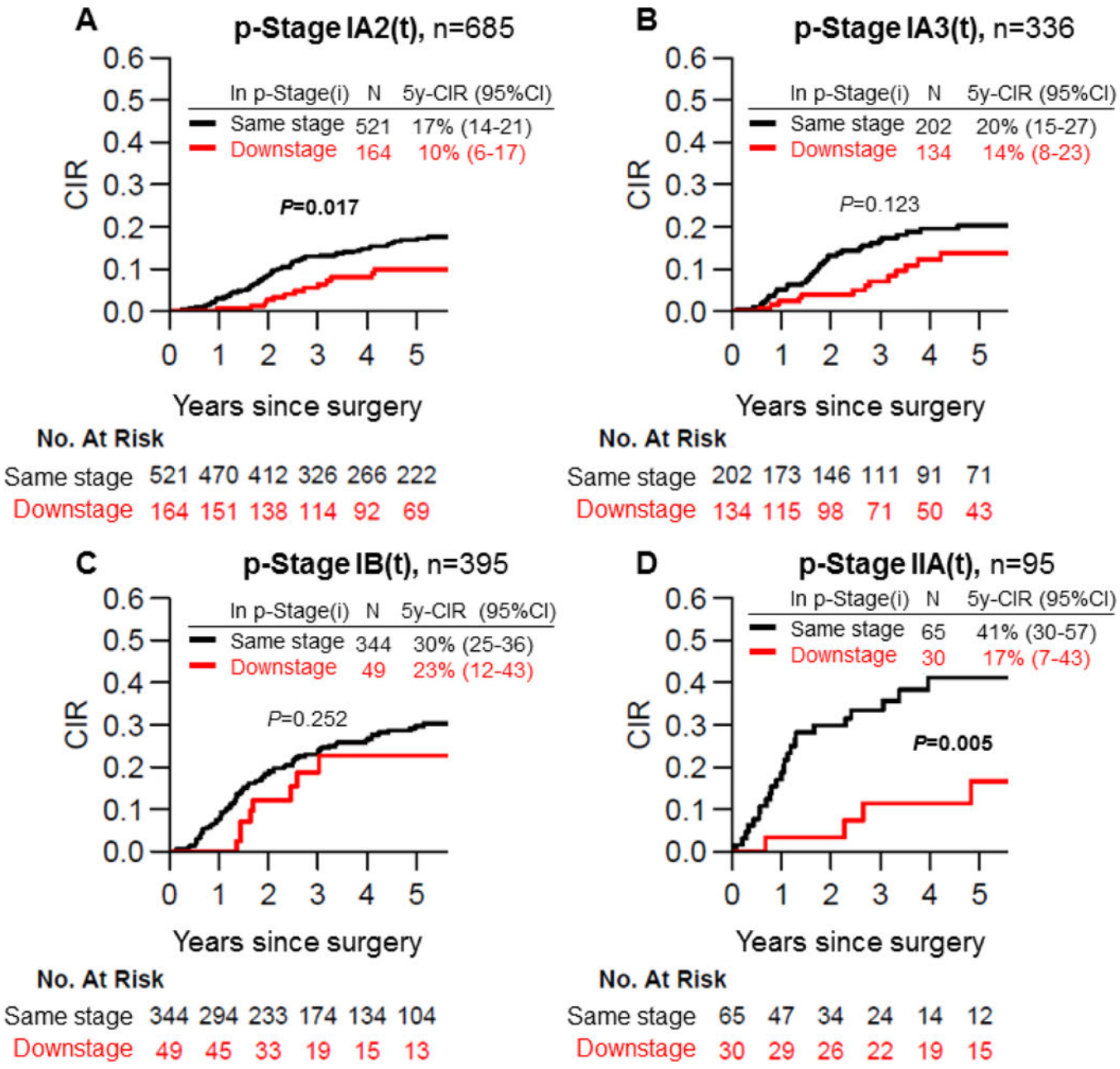

Figure 3.

Cumulative incidence of recurrence between patients who were classified as the same stage and those who were downstaged when invasive size (i) was used, rather than total size (t), for the T descriptor. CIR, cumulative incidence of recurrence; p-Stage, pathologic stage.

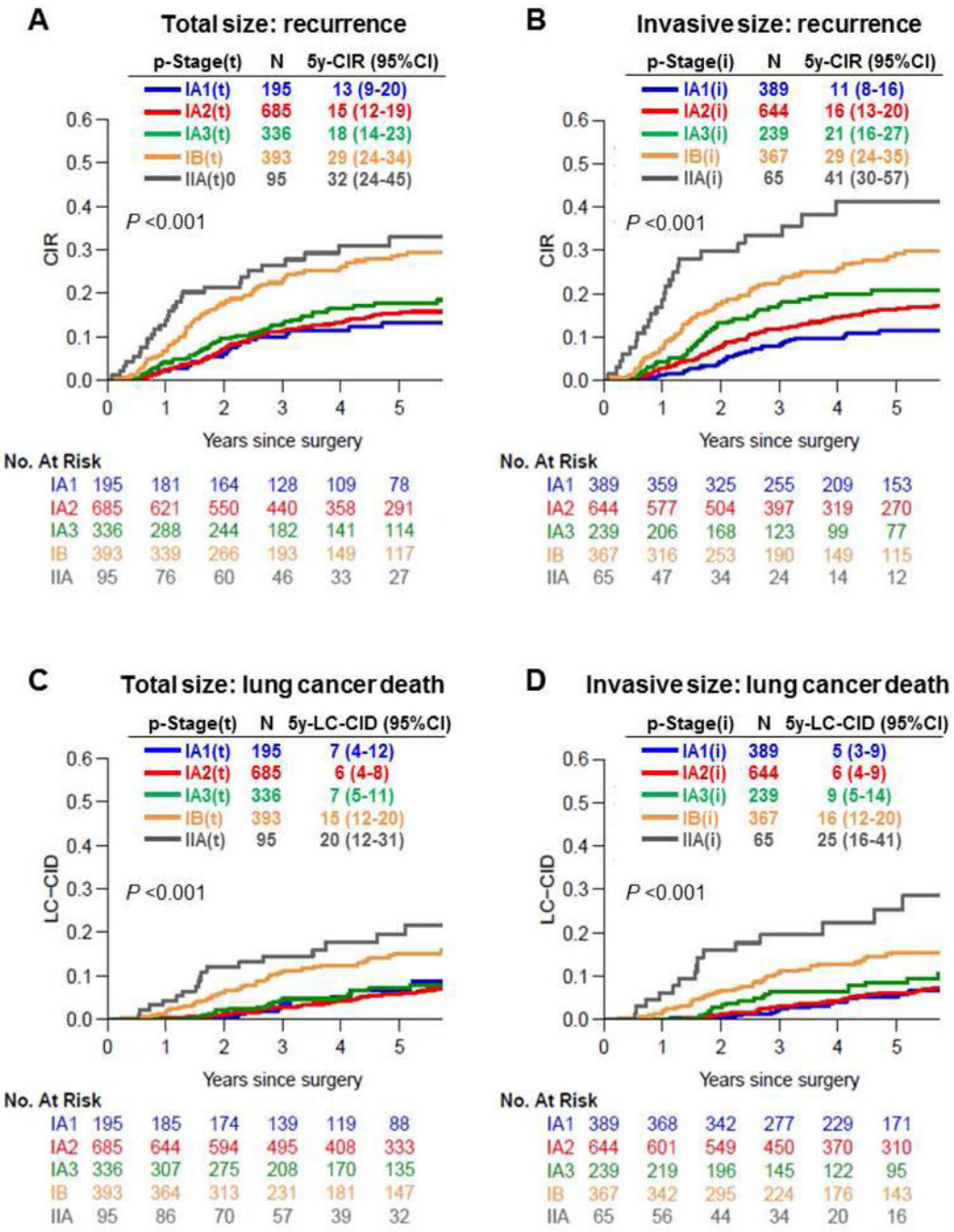

Figure 4.

Cumulative incidence of recurrence and lung cancer–specific death by pathologic stage based on invasive size (p-Stage[i]) and pathologic stage based on total size (p-Stage[t]). CI, confidence interval; CIR, cumulative incidence of recurrence; LC-CID, lung cancer-specific cumulative incidence of death; p-Stage, pathologic stage; p-Stage based on invasive size; p-Stage(t), p-Stage based on total size.

Table 1.

Clinicopathologic Characteristics and Outcomes by p-Stage(t) and p-Stage(i)

	p-Stage(t)					p-Stage(i)				
	IA1(t) n=195	**IA2(t) n=685**	**IA3(t) n=336**	**IB(t) n=393**	**IIA(t) n=95**	**IA1(i) n=389**	**IA2(i) n=644**	**IA3(i) n=239**	**IB(i) n=367**	**IIA(i) n=65**
Age, years, median (25th–75th percentile)	67 (61–72)	69 (62–75)	71 (65–77)	70 (62–76)	71(63–76)	68 (62–74)	70 (62–76)	71 (63–78)	69 (62–76)	72 (63–78)
Sex										
Female	134 (69)	428 (62)	210 (63)	235 (59)	54 (57)	261 (67)	398 (62)	152 (64)	214 (58)	36 (55)
Male	61 (31)	257 (38)	126 (38)	158 (40)	41 (43)	128 (33)	246 (38)	87 (36)	153 (42)	29 (45)
Smoking status										
Never	28 (14)	123 (18)	72 (21)	69 (17)	17 (18)	71 (18)	115 (18)	49 (21)	67 (18)	7 (11)
Former	138 (71)	472 (69)	235 (70)	272 (69)	69 (73)	268 (69)	454 (70)	166 (69)	249 (68)	49 (75)
Current	29 (15)	90 (13)	29 (9)	52 (13)	9 (9)	50 (13)	75 (12)	24 (10)	51 (14)	9 (14)
Type of resection										
Lobectomy[a]	87 (45)	436 (64)	278 (83)	289 (73)	90 (95)	199 (51)	437 (68)	213 (89)	269 (73)	62 (95)
Sublobar	108 (55)	249 (36)	58 (17)	104 (26)	5 (5)	190 (49)	207 (32)	26 (11)	98 (27)	3 (5)
LVI										
Absent	146 (75)	424 (62)	206 (61)	148 (37)	35 (37)	310 (80)	386 (60)	122 (51)	125 (34)	16 (25)
Present	49 (25)	261 (38)	130 (39)	245 (62)	60 (63)	79 (20)	258 (40)	117 (49)	242 (66)	49 (75)
VPI										
Absent	195 (100)	685 (100)	336 (100)	133 (34)	70 (74)	389 (100)	644 (100)	239 (100)	101 (28)	46 (71)
Present	0 (0)	0 (0)	0 (0)	260 (66)	25 (26)	0 (0)	0 (0)	0 (0)	266 (72)	19 (29)
Necrosis (n=1519)										
Absent	165 (93)	568 (91)	261 (87)	246 (74)	52 (61)	332 (95)	535 (91)	170 (82)	227 (72)	28 (50)
Present	12 (7)	57 (9)	39 (13)	86 (26)	33 (39)	16 (5)	56 (9)	38 (18)	89 (28)	28 (50)
STAS (n=1461)										
Absent	102 (56)	363 (58)	164 (59)	149 (48)	28 (42)	239 (68)	331 (56)	90 (48)	130 (45)	16 (37)
Present	79 (44)	267 (42)	112 (41)	159 (52)	38 (58)	111 (32)	261 (44)	97 (52)	159 (55)	27 (63)
Predominant subtype										
Lepidic	10 (5)	97 (14)	46 (14)	24 (6)	5 (5)	131 (34)	38 (6)	2 (1)	11 (3)	0 (0)
Acinar	114 (58)	326 (48)	145 (43)	185 (47)	37 (39)	162 (42)	336 (52)	115 (48)	173 (47)	21 (32)
Papillary	36 (18)	123 (18)	83 (25)	64 (16)	22 (23)	54 (14)	133 (21)	64 (27)	63 (17)	14 (22)

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	p-Stage(t)					p-Stage(i)				
	IA1(t) n=195	**IA2(t) n=685**	**IA3(t) n=336**	**IB(t) n=393**	**IIA(t) n=95**	**IA1(i) n=389**	**IA2(i) n=644**	**IA3(i) n=239**	**IB(i) n=367**	**IIA(i) n=65**
Micropapillary	8 (4)	39 (6)	22 (7)	21 (5)	5 (5)	10 (3)	40 (6)	19 (8)	22 (6)	4 (6)
Solid	27 (14)	100 (15)	40 (12)	99 (25)	26 (27)	32 (8)	97 (15)	39 (16)	98 (27)	26 (40)
Histologic grade										
Low	10 (5)	97 (14)	46 (14)	24 (6)	5 (5)	131 (34)	38 (6)	2 (1)	11 (3)	0 (0)
Intermediate	150 (77)	449 (66)	228 (68)	249 (63)	59 (62)	216 (56)	469 (73)	179 (75)	236 (64)	35 (54)
High	35 (18)	139 (20)	62 (18)	120 (30)	31 (33)	42 (11)	137 (21)	58 (24)	120 (33)	30 (46)
Mutation (n=1385)										
Wild type	78 (50)	289 (52)	163 (53)	166 (56)	36 (56)	162 (51)	272 (51)	113 (53)	159 (57)	26 (63)
EGFR	25 (16)	116 (21)	64 (21)	61 (21)	11 (17)	61 (19)	116 (22)	41 (19)	55 (20)	4 (10)
KRAS	54 (34)	155 (28)	83 (27)	67 (23)	17 (27)	95 (30)	148 (28)	58 (27)	64 (23)	11 (27)
Outcomes, % (95% confidence interval; lower, upper)										
5-year CIR	13 (9, 20)	15 (13,19)	18 (14, 23)	29 (24, 34)	33 (24, 45)	11 (8, 16)	16 (13, 19)	21 (16, 27)	29 (24, 35)	41 (30, 57)
5-year LC–CID	7(4, 12)	6 (4, 8)	7 (5, 11)	15 (12, 20)	20 (12, 31)	5 (3, 9)	6 (4, 9)	9 (5, 14)	16 (12, 20)	25 (16, 41)
5-year OS	86 (80, 92)	82 (79, 86)	78(73, 83)	72 (67, 77)	63 (53, 76)	84 (80, 89)	81 (78, 85)	79 (73, 85)	71 (66, 77)	51 (38, 68)

Data are shown as no. (%), unless otherwise noted. CIR, cumulative incidence of recurrence; LC-CID, lung cancer-specific cumulative incidence of death; LVI, lymphovascular invasion; OS, overall survival; p-Stage(i), pathologic stage based on invasive size; p-Stage(t), pathologic stage based on total size; STAS, spread through air spaces; SUVmax, maximum standardized uptake value; VPI, visceral pleural invasion.

[a]Included pneumonectomy or bilobectomy.

Table 2.

Competing-Risk Regression Model and Concordance Index for Recurrence and Lung Cancer-Specific Death

	Recurrence				Lung cancer-specific death			
	Total Size		Invasive Size		Total Size		Invasive Size	
p-Stage	SHR (95% CI)	*P*	SHR (95% CI)	*P*	SHR (95% CI)	*P*	SHR (95% CI)	*P*
IA1	ref.		ref.		ref.		ref.	
IA2	1.14 (0.73–1.80)	0.6	1.53 (1.05–2.22)	**0.026**	0.85 (0.47–1.54)	0.6	1.18 (0.71–1.98)	0.5
IA3	1.39 (0.85–2.27)	0.19	2.02 (1.31–3.12)	**0.002**	0.98 (0.50–1.89)	0.9	1.69 (0.93–3.08)	0.088
IB	2.44 (1.55–3.83)	<**0.001**	2.97 (2.04–4.32)	<**0.001**	2.14 (1.19–3.82)	**0.011**	2.87 (1.74–4.74)	<**0.001**
IIA	3.15 (1.82–5.46)	<**0.001**	5.43 (3.26–9.06)	<**0.001**	3.25 (1.64–6.43)	**0.001**	5.84 (3.06–11.13)	<**0.001**
C-index (95% CI)	0.593 (0.579–0.642)		0.614 (0.598–0.662)		0.621 (0.603–0.687)		0.634 (0.608–0.695)	

CI, confidence interval; C-index, concordance index; p-Stage, pathologic stage; SHR, subhazard ratio.