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ORIGINAL REPORT

Impact of Increasing Age on Cause-Specific Mortality and Morbidity in Patients With Stage I Non–Small-Cell Lung Cancer: A Competing Risks Analysis

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ABSTRACT

Purpose
To perform competing risks analysis and determine short- and long-term cancer- and noncancer-specific mortality and morbidity in patients who had undergone resection for stage I non–small-cell lung cancer (NSCLC).

Patients and Methods
Of 5,371 consecutive patients who had undergone curative-intent resection of primary lung cancer at our institution (2000 to 2011), 2,186 with pathologic stage I NSCLC were included in the analysis. All preoperative clinical variables known to affect outcomes were included in the analysis, specifically, Charlson comorbidity index, predicted postoperative (ppo) diffusing capacity of the lung for carbon monoxide, and ppo forced expiratory volume in 1 second. Cause-specific mortality analysis was performed with competing risks analysis.

Results
Of 2,186 patients, 1,532 (70.1%) were ≥ 65 years of age, including 638 (29.2%) ≥ 75 years of age. In patients < 65, 65 to 74, and ≥ 75 years of age, 5-year lung cancer–specific cumulative incidence of death (CID) was 7.5%, 10.7%, and 13.2%, respectively (overall, 10.4%); noncancer-specific CID was 1.8%, 4.9%, and 9.0%, respectively (overall, 5.3%). In patients ≥ 65 years of age, for up to 2.5 years after resection, noncancer-specific CID was higher than lung cancer–specific CID; the higher noncancer-specific, early-phase mortality was enhanced in patients ≥ 75 years of age than in those 65 to 74 years of age. Multivariable analysis showed that low ppo diffusing capacity of lung for carbon monoxide was an independent predictor of severe morbidity ($P < .001$), 1-year mortality ($P < .001$), and noncancer-specific mortality ($P < .001$), whereas low ppo forced expiratory volume in 1 second was an independent predictor of lung cancer–specific mortality ($P = .002$).

Conclusion
In patients who undergo curative-intent resection of stage I NSCLC, noncancer-specific mortality is a significant competing event, with an increasing impact as patient age increases.

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INTRODUCTION

Among solid tumors, lung cancer carries a relatively high risk of competing cancer and noncancer events because more than two thirds of patients with lung cancer are ≥ 65 years of age at the time of diagnosis,[1] and one half of those patients are ≥ 75 years of age with associated high comorbidities.[2] As age increases, the risk of competing events increases, such as death from noncancer diseases.[3] In this era of personalized cancer therapy, important to the stratification of individualized treatments is the determination of how both cancer and noncancer risk factors—specifically, comorbidities associated with increasing age—contribute to the risk of death.

After the publication of the National Lung Screening Trial results, which demonstrated the efficacy of low-dose computed tomography screening for lung cancer, detection of early-stage lung cancer, for which curative-intent resection is the standard treatment,[4] is expected to increase.[5-7] The data from the International Association for the Study of Lung Cancer, which were derived from a multinational cohort, are

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Data Supplement

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considered the reference standard for overall survival (OS) in patients with non–small-cell lung cancer (NSCLC). According to these data, the estimated 5-year overall mortality from stage IA and IB NSCLC is 17% and 29%, respectively, after curative-intent R0 resection.[8] Smoking status, chronic obstructive pulmonary disease (COPD) history, and pulmonary function have been reported to be predictive of OS or lung cancer–related survival after resection of NSCLC.[9-20] Noncancer risk factors, such as Charlson comorbidity index (CCI), cardiovascular disease (CVD) history, body mass index, and serum creatinine level, have been reported to influence outcomes.[18,21-23] However, a comprehensive analysis of all variables known to affect outcomes has not been published and, to our knowledge, no study has included a cause-specific analysis with an evaluation of competing risks. The goal of this study, therefore, was to perform a competing risks analysis to determine short- and long-term cancer- and noncancer-specific mortality and morbidity in patients who had undergone resection for stage I NSCLC.

By using a large, uniform cohort of patients with stage I NSCLC, we analyzed short- and long-term cause-specific outcomes through competing risks analysis. This comprehensive prognostic analysis included all preoperative variables known to contribute individually to outcomes, including lung-related (forced expiratory volume in 1 second [FEV1]; diffusing capacity of lung for carbon monoxide [DLCO]); age-related (cardiorespiratory comorbidities, renal function, CCI); and cancer-related (tumor size on computed tomography scan) parameters. In light of the ongoing debate about the appropriate type of surgical resection for small NSCLC—lobectomy versus sublobar resection (wedge resection or segmentectomy)—the identification of predictive factors for cancer- and noncancer-specific morbidity and mortality will be of substantial value for stratifying therapy.[24,25] The establishment of such factors is even more important for older patients, who comprise the majority of patients with stage I NSCLC.

Our investigation yielded novel and previously unreported observations on outcomes in patients who undergo resection of stage I NSCLC: Noncancer-specific mortality is a prominent competing event, with an increasing impact as age increases; noncancer-specific mortality is higher than lung cancer–specific mortality for up to 1.5 years after resection, particularly in older patients (≥ 65 years of age); and low predicted postoperative (ppo) DLCO is an independent predictor of noncancer-specific mortality, whereas low ppo FEV1 is an independent predictor of lung cancer–specific mortality.

PATIENTS AND METHODS

Study Cohort

This retrospective study (WA0269-08, WA0219-09, and WA0280-12) was approved by the institutional review board at Memorial Sloan Kettering Cancer Center. Medical records of 5,371 patients with primary lung cancer who had undergone lung resection at our center between 2000 and 2011 were reviewed. Patient exclusion criteria; preoperative, surgical, pathologic data variables; and the surveillance protocol are provided in detail in the Data Supplement. A total of 2,186 patients were included in the study (Fig 1).

End Points and Cause of Death

The end points of this study were severe morbidity, 1-year mortality, lung cancer–specific mortality, noncancer-specific mortality, and OS. Severe morbidities were defined as grade 3 and higher, occurring within 30 days after surgery, in accordance with Common Terminology Criteria for Adverse Events (version 4.03).[26] The classification of severe morbidities and corresponding incidence rates are shown in the Data Supplement.

The cause of death was classified as lung cancer specific, noncancer specific, other cancer specific, or unknown. Lung cancer–specific mortality was defined as death as a result of recurrent disease associated with resected lung cancer. Patients who had progressive recurrent disease at the last follow-up and death without a documented specific reason were included in the lung cancer–specific group. Noncancer-specific mortality was defined as death as a result of specific causes other than malignant disease, including death without a documented specific reason within 6 months of the last follow-up in the absence of lung cancer recurrence or progressive malignant disease. Death as a result of second primary lung cancer or other malignancies was regarded as other cancer specific.

Statistical Analyses

Patient demographic and clinical characteristics were summarized with descriptive statistics. Associations between variables were analyzed with Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables by age-group (< 65, 65 to 74, ≥ 75 years) and surgical procedure (lobectomy *v* sublobar resection).

To evaluate age-related changes in preoperative variables (cardiopulmonary function and CCI), patients were divided into the seven increasing age-groups (≤ 55, 56 to 60, 61 to 65, 66 to 70, 71 to 75, 76 to 80, > 80 years) that were explored graphically. The mean for each variable of the seven groups was summarized and fitted by using cubic B-splines for graphical representation.[27] Differences in age-related change between the lobectomy and sublobar resection groups were evaluated by multivariable logistic regression for COPD and CVD history and linear regression for continuous variables. Model covariates included surgical procedure,

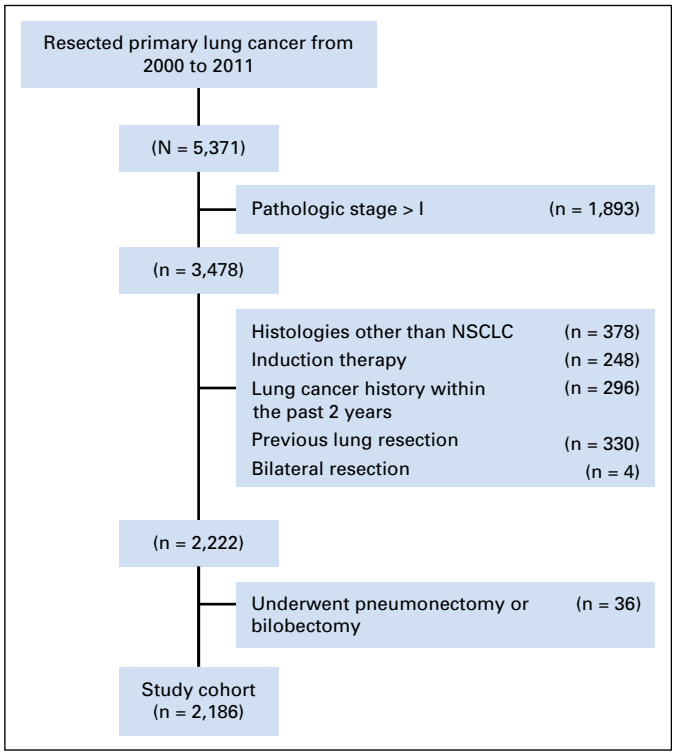

Fig 1. CONSORT diagram. The study cohort included all consecutive patients who underwent R0 resection for pathologic stage I non–small-cell lung cancer (NSCLC). R0, microscopically margin-negative resection.

Table 1. Patient Characteristics by Age Group and Surgical Procedure

		Age Group, No. (%)				Surgical Procedure, No. (%)		
	Total (N = 2,186)	< 65 Years (n = 654)	65-74 Years (n = 894)	≥ 75 Years (n = 638)	*P*	Lobectomy (n = 1,612)	Sublobar (n = 574)	*P*
Preoperative variables								
Age at diagnosis, years	70.3 (63.2-76.2)					69.7 (62.4-75.6)	71.9 (65.2-77.0)	**< .001**
Age group, years								
< 65	654 (29.9)					514 (31.9)	140 (24.4)	**.002**
65-74	894 (40.9)					651 (40.4)	243 (42.3)	
≥ 75	638 (29.2)					447 (27.7)	191 (33.3)	
Sex								
Female	1,293 (59.1)	431 (65.9)	496 (55.5)	366 (57.4)	**< .001**	953 (59.1)	340 (59.2)	1
Male	893 (40.9)	223 (34.1)	398 (44.5)	272 (42.6)		659 (40.9)	234 (40.8)	
Smoking history								
Never	346 (15.8)	127 (19.4)	103 (11.5)	116 (18.2)	**< .001**	257 (15.9)	89 (15.5)	.5
Former	1,523 (69.7)	391 (59.8)	669 (74.8)	463 (72.6)		1,113 (69.0)	410 (71.4)	
Current	317 (14.5)	136 (20.8)	122 (13.6)	59 (9.2)		242 (15.0)	75 (13.1)	
COPD history	539 (24.7)	112 (17.1)	248 (27.7)	179 (28.1)	**< .001**	346 (21.5)	193 (33.6)	**< .001**
CVD history	416 (19.0)	75 (11.5)	179 (20.0)	162 (25.4)	**< .001**	274 (17.0)	142 (24.7)	**< .001**
CCI								
0	895 (40.9)	318 (48.6)	338 (37.8)	239 (37.5)	**< .001**	730 (45.3)	165 (28.7)	**< .001**
1	589 (26.9)	144 (22.0)	251 (28.1)	194 (30.4)		429 (26.6)	160 (27.9)	
2	398 (18.2)	112 (17.1)	171 (19.1)	115 (18.0)		274 (17.0)	124 (21.6)	
3	214 (9.8)	50 (7.6)	94 (10.5)	70 (11.0)		133 (8.3)	81 (14.1)	
≥ 4	90 (4.1)	30 (4.6)	40 (4.5)	20 (3.1)		46 (2.9)	44 (7.7)	
BMI (n = 2,116), kg/m^2*	26.5 (23.5-30.1)	26.2 (22.9-29.9)	26.8 (24.0-30.7)	26.5 (23.5-29.5)	**.005**	26.4 (23.4-29.9)	27.0 (23.7-31.1)	**.029**
Serum Cr, mg/dL*	1.0 (0.9-1.2)	1.0 (0.9-1.1)	1.0 (0.9-1.2)	1.1 (0.9-1.3)	**< .001**	1.0 (0.9-1.2)	1.0 (0.9-1.2)	**.02**
FEV1 (n = 2,108), %*	89.0 (74.0-102.0)	90.0 (77.0-101.0)	87.0 (71.0-101.0)	89.0 (75.0-105.0)	**.002**	90.0 (77.0-103.0)	83.0 (65.0-99.0)	**< .001**
ppo FEV1 (n = 2,108), %*	72.2 (59.7-84.3)	72.5 (61.6-83.2)	69.9 (57.8-82.9)	73.7 (61.5-87.6)	**< .001**	70.7 (59.7-81.7)	77.2 (59.9-92.6)	**< .001**
DLCO (n = 2,001), %*	80.0 (65.0-95.0)	87.0 (71.0-101.0)	79.0 (65.0-93.0)	75.0 (61.0-90.0)	**< .001**	82.0 (67.0-96.0)	73.0 (60.0-89.0)	**< .001**
ppo DLCO (n = 2,001), %*	65.3 (53.1-77.8)	69.9 (57.5-83.3)	63.5 (52.2-76.6)	62.9 (51.1-74.9)	**< .001**	64.1 (52.9-76.6)	68.9 (54.0-82.4)	**< .001**
Tumor size on CT scan, cm*	2.0 (1.5-2.8)	2.0 (1.4-2.6)	2.0 (1.5-2.8)	2.2 (1.6-3.0)	**< .001**	2.2 (1.6-3.0)	1.6 (1.2-2.2)	**< .001**
Surgical procedure								
Lobectomy	1,612 (73.7)	514 (78.6)	651 (72.8)	447 (70.1)	**.002**			
Sublobar	574 (26.3)	140 (21.4)	243 (27.2)	191 (29.9)				
Pathologic finding								
Subtype								
Adenocarcinoma	1,744 (79.8)	566 (86.5)	697 (78.0)	481 (75.4)	**< .001**	1,287 (79.8)	457 (79.6)	1
Squamous	340 (15.6)	61 (9.3)	157 (17.6)	122 (19.1)		250 (15.5)	90 (15.7)	
Adenosquamous	28 (1.3)	3 (0.5)	12 (1.3)	13 (2.0)		21 (1.3)	7 (1.2)	
Large	60 (2.7)	22 (3.4)	21 (2.3)	17 (2.7)		43 (2.7)	17 (3.0)	
Pleomorphic	14 (0.6)	2 (0.3)	7 (0.8)	5 (0.8)		11 (0.7)	3 (0.5)	
Pathologic stage								
IA	1,551 (71.0)	478 (73.1)	637 (71.3)	436 (68.3)	.2	1,098 (68.1)	453 (78.9)	**< .001**
IB	635 (29.0)	176 (26.9)	257 (28.7)	202 (31.7)		514 (31.9)	121 (21.1)	

(continued on following page)

Table 1. Patient Characteristics by Age Group and Surgical Procedure (continued)

		Age Group, No. (%)				Surgical Procedure, No. (%)		
	Total (N = 2,186)	< 65 Years (n = 654)	65-74 Years (n = 894)	≥ 75 Years (n = 638)	*P*	Lobectomy (n = 1,612)	Sublobar (n = 574)	*P*
Outcome								
Severe morbidity (CTCAE grade ≥ 3)	167 (7.6)	50 (7.6)	71 (7.9)	46 (7.2)	.9	136 (8.4)	31 (5.4)	**.017**
Mortality								
30 day	15 (0.7)	1 (0.2)	6 (0.7)	8 (1.3)	.05	10 (0.6)	5 (0.9)	.6
90 day	27 (1.2)	4 (0.6)	9 (1.0)	14 (2.2)	**.034**	17 (1.1)	10 (1.7)	.2
1 year	90 (4.1)	12 (1.8)	37 (4.1)	41 (6.4)	**< .001**	56 (3.5)	34 (5.9)	**.014**
5-year lung cancer-specific CID, %†	10.4 (8.9 to 11.8)	7.5 (5.3 to 9.8)	10.7 (8.3 to 13.0)	13.2 (10.1 to 16.2)	.117	9.3 (7.7 to 10.8)	14.0 (10.6 to 17.4)	**.002**
5-year noncancer-specific CID, %†	5.3 (3.4 to 6.8)	1.8 (0.7 to 2.8)	4.9 (3.4 to 6.4)	9.0 (6.6 to 11.5)	**< .001**	4.1 (3.0 to 5.1)	8.3 (5.8 to 10.8)	**.006**
5-year OS, %†	75.1 (73.1 to 77.3)	85.0 (82.0 to 88.1)	75.8 (72.6 to 79.1)	63.6 (59.3 to 68.1)	**< .001**	78.0 (75.7 to 80.3)	66.6 (62.1 to 71.3)	**< .001**

NOTE. Statistically significant *P* values are indicated by boldface.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CID, cumulative incidence of death; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); CVD, cardiovascular disease; DLCO, diffusing capacity of lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; ppo, predicted postoperative.

*Data are shown as median (25th-75th percentile).

†Data are shown as estimated CID or survival probability (95% CI).

continuous age, and interaction of both, where applicable. A significant interaction indicates that the pattern of age-related change is significantly different between surgical procedures.

Univariable and multivariable logistic models were constructed to identify factors associated with severe morbidity and 1-year mortality. We elected to use ppo FEV1 and ppo DLCO instead of FEV1 and DLCO in our regression models because risk of postoperative morbidity has been linked to ppo lung function.[11,28]

The associations between factors and the risk of each cause of death were evaluated with competing risks analysis. Patients were censored if they were alive at the time of the last follow-up. Cumulative incidence functions for each competing event were calculated by competing risks methodology.[29] Without loss of generality, analyses of the cumulative incidence of lung cancer–specific mortality considered noncancer-specific and all-other-cause mortality as two separate competing risks, and Fine and Gray's[30] competing risks regressions were used to estimate the subhazard ratio to evaluate the association between preoperative variables and risk of each cause of death. Multivariable regression models included all variables with $P < .1$ on univariable analysis. Competing risks analyses were conducted with the R project's Subdistribution Analysis of Competing Risks (cmprsk) package (version 2.13.1) and the Stata 13 Competing Risks Regressions (stcrreg) command (StataCorp, College Station, TX). Estimation of 5-year cumulative incidence of death (CID) by using ppo DLCO, ppo FEV1, and CCI was explored graphically; the estimated 5-year CID by groups (ppo FEV1, ≤ 50%, 51% to 60%, 61% to 70%, 71% to 80%, 81% to 90%, > 90%; ppo DLCO, ≤ 45%, 46% to 55%, 56% to 65%, 66% to 75%, 76% to 85%, > 85%; CCI, 0, 1, 2, 3, ≥ 4) was summarized and fitted by using cubic B-splines for graphical representation. OS was estimated by the Kaplan-Meier method and compared between groups by log-rank test. Hazard ratios were estimated from Cox univariable and multivariable models. As a representation of the performance of multivariable models in terms of discrimination, the concordance index (C-index) was reported for logistic,[31] survival,[32] and competing risks models.[33] Analysis for cumulative incidence of recurrence was performed (Data Supplement). All statistical tests were two sided, and $P < .05$ was considered significant.

RESULTS

Patient Characteristics

Of the 2,186 patients evaluated, the majority were women (59.1%), were former or current smokers (84.2%), had no history of COPD (75.3%) or CVD (81.0%), had a CCI ≥ 1 (59.1%), were diagnosed with adenocarcinoma (79.8%), and had stage IA disease (71.0%). Patient characteristics are listed in Table 1.

Comparison by Age Groups and Surgical Procedures

Among the cohort, 1,532 (70.1%) of patients were ≥ 65 years of age, including 638 (29.2%) ≥ 75 years of age. The majority of patients underwent lobectomy (73.7%). All preoperative variables were statistically different among the three age-groups (< 65, 65 to 74, and ≥ 75 years). All preoperative variables, except sex and smoking status, were statistically different between the lobectomy and sublobar resection groups (Table 1).

The Data Supplement shows preoperative variables stratified by surgical procedure for each age-group. Serum creatinine level, COPD history, CVD history, and CCI increased as age increased; in contrast, DLCO decreased as age increased. For most age-groups, COPD history, CVD history, and CCI were higher in the sublobar resection group than in the lobectomy group. In contrast, DLCO and FEV1 were lower in the sublobar resection group than in the lobectomy group.

Postoperative Severe Morbidities

Of the 2,186 patients evaluated, postoperative severe morbidities developed in 167 (7.6%). Among them, 114 (68.3%) and 31 (18.6%) had respiratory and cardiovascular morbidities, respectively. Overall severe morbidity and respiratory morbidity were significantly more common in the lobectomy group than in the sublobar resection group ($P = .017$ and .002, respectively) and in patients who underwent right-side lower lobectomy ($P = .025$ and .029, respectively; Data Supplement).

Causes of Short- and Long-Term Mortality

The median follow-up was 4.2 years (range, 0.01 to 14.4 years). The 30-day, 90-day, 1-year, and 5-year mortality rates were 0.7% (n = 15), 1.2% (n = 27), 4.1% (n = 90), and 19.9% (n = 436), respectively. Cardiorespiratory disease was the most frequent specific cause of death at 30 and 90 days. At 1 year, the leading cause of death was noncancer specific (45 of 90 [50.0%]) followed by lung cancer specific (25 of 90 [27.8%]) and other cancer specific (12 of 90 [13.3%]). At 5 years, the leading cause of death was lung cancer specific (181 of 436 [41.5%]) followed by noncancer specific (97 of 436 [22.2%]) and other cancer specific (63 of 436 [14.4%]; Table 2).

Univariable and Multivariable Analyses for Short- and Long-Term Outcomes

Univariable analyses are outlined in the Data Supplement. Multivariable analyses revealed the following independent predictors of each outcome: COPD history, lower ppo DLCO, higher serum creatinine level, and lobectomy for severe morbidity (C-index, 0.686); older age, male sex, lower ppo DLCO, larger tumor size, and sublobar resection for 1-year mortality (C-index, 0.771); former and current smoker, lower ppo FEV1, larger tumor size, and sublobar resection for lung cancer–specific mortality (C-index, 0.668); older age, male sex, CVD history, lower ppo

Table 2. Causes of Mortality (N = 2,186)

Cause of Mortality	Mortality, No. (%)			
	30 Day	90 Day	1 Year	5 Year
Any cause	15 (0.7)	27 (1.2)	90 (4.1)	436 (19.9)
Cause specific				
Lung cancer specific	0 (0.0)	3 (0.1)	25 (1.1)	181 (8.3)
Noncancer specific	15 (0.7)	24 (1.1)	45 (2.1)	97 (4.4)
Respiratory	5 (0.2)	11 (0.5)	15 (0.7)	33 (1.5)
Cardiovascular	7 (0.3)	7 (0.3)	9 (0.4)	15 (0.7)
Nervous system	0 (0.0)	1 (0.0)	2 (0.1)	5 (0.2)
Renal/urinary tract	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GI	1 (0.0)	1 (0.0)	2 (0.1)	5 (0.2)
Other*	2 (0.1)	4 (0.2)	17 (0.8)	39 (1.8)
Other cancer specific	0 (0.0)	0 (0.0)	12 (0.5)	63 (2.9)
Unknown	0 (0.0)	0 (0.0)	8 (0.4)	95 (4.3)

*Includes unknown death within 6 months after the last follow-up in the absence of recurrence or other malignant disease.

DLCO, and sublobar resection for noncancer-specific mortality (C-index, 0.769); and older age, male sex, current smoker, higher CCI, lower ppo FEV1, lower ppo DLCO, larger tumor size, and sublobar resection for OS (C-index, 0.709; Table 3).

Longitudinal Patterns of Lung Cancer–Specific and Noncancer-Specific CID by Age Group

Lung cancer–specific and noncancer-specific CID curves are shown in Fig 2. In patients < 65, 65 to 74, and ≥ 75 years of age, 5-year lung cancer–specific CID was 7.5%, 10.7%, and 13.2%, respectively (overall, 10.4%), and noncancer-specific CID was 1.8%, 4.9%, and 9.0%, respectively (overall, 5.3%). Noncancer-specific CID was higher than lung cancer–specific CID for up to 1.5 years after resection. After 1.5 years, lung cancer–specific CID surpassed noncancer-specific CID. The difference between curves in the early phase after resection was enhanced in the cohort of patients ≥ 75 years of age in which noncancer-specific mortality was higher until approximately 2.5 years postsurgery. In the cohort of patients 65 to 74 years of age, the shapes of both curves were similar to that for the overall cohort. However, in the cohort of patients < 65 years of age, the early-phase increase in noncancer-specific mortality was not observed, and lung cancer–specific mortality was higher than noncancer-specific mortality during most of the postoperative period.

Estimation of 5-Year Lung Cancer–Specific and Noncancer-Specific CID by Using PPO FEV1, PPO DLCO, and CCI

Figure 3A demonstrates that lung cancer–specific CID was the highest (approximately 15%) with the lowest ppo FEV1 and that it decreased linearly as ppo FEV1 increased. Noncancer-specific CID plateaued when ppo FEV1 was ≥ 65% (61% to 70%) but increased as ppo FEV1 decreased below that point. Figure 3B shows that lung cancer–specific CID gradually decreased as ppo DLCO increased, but the gradient was more gradual than it was for ppo FEV1. In contrast, as ppo DLCO increased, noncancer-specific CID decreased linearly, from approximately 11% to 1%. Figure 3C demonstrates an increase of noncancer-specific and lung cancer–specific CID as CCI increased from 0 to 1; however, it plateaued when CCI increased to > 1.

DISCUSSION

This study differentiates the influence of cancer-related and noncancer-related risk factors by age-group and further identifies factors that are predictive of short- and long-term cause-specific mortality in patients with stage I NSCLC. We have shown that in

Table 3. Multivariable Analysis for Short- and Long-Term Outcomes

	Short-Term Outcome						Long-Term Outcome								
	Severe Morbidity			1-Year Mortality			Lung Cancer–Specific Mortality			Noncancer-Specific Mortality			Overall Survival		
Variable	OR	95% CI	*P*	OR	95% CI	*P*	SHR	95% CI	*P*	SHR	95% CI	*P*	HR	95% CI	*P*
Age at diagnosis (per 1-year increase)				1.04	1.01 to 1.07	**.015**				1.05	1.03 to 1.08	**< .001**	1.05	1.04 to 1.06	**< .001**
Male sex (*v* female)				1.76	1.10 to 2.79	**.017**				1.92	1.31 to 2.83	**.001**	1.38	1.17 to 1.63	**< .001**
Former smoker (*v* never)							1.7	1.07 to 2.70	**.026**				1.17	0.89 to 1.54	.3
Current smoker (*v* never)							1.82	1.04 to 3.19	**.037**				1.59	1.14 to 2.22	**.007**
COPD history (*v* no history)	1.61	1.12 to 2.31	**.01**												
CVD history (*v* no history)										1.68	1.12 to 2.52	**.012**			
BMI (per 1-index increase)															
CCI (per 1-index increase)													1.14	1.07 to 1.21	**< .001**
ppo FEV1 (per 1% increase)							0.99	0.98 to 1.00	**.002**				0.99	0.99 to 1.00	**.019**
ppo DLCO (per 1% increase)	0.97	0.96 to 0.98	**< .001**	0.96	0.95 to 0.98	**< .001**				0.96	0.95 to 0.98	**< .001**	0.99	0.98 to 0.99	**< .001**
Serum Cr (per 1 mg/dL increase)	1.48	1.03 to 2.12	**.032**												
Tumor size on CT scan (per 1-cm increase)				1.63	1.30 to 2.03	**< .001**	1.44	1.27 to 1.64	**<.001**				1.27	1.17 to 1.38	**< .001**
Sublobar resection (*v* lobectomy)	0.58	0.37 to 0.90	**.014**	2.54	1.51 to 4.26	**< .001**	2.06	1.53 to 2.79	**<.001**	1.53	1.03 to 2.28	**.034**	1.74	1.45 to 2.10	**< .001**
C-index (95% CI)	0.686 (0.641 to 0.732)			0.771 (0.729 to 0.813)			0.668 (0.631 to 0.706)			0.769 (0.731 to 0.813)			0.709 (0.688 to 0.731)		

NOTE. Statistically significant *P* values are indicated by boldface.
Abbreviations: BMI, body mass index; C-index, concordance index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CT, computed tomography; CVD, cardiovascular disease; DLCO, diffusion capacity of lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; HR, hazard ratio; OR, odds ratio; ppo, predicted postoperative; SHR, subhazard ratio.

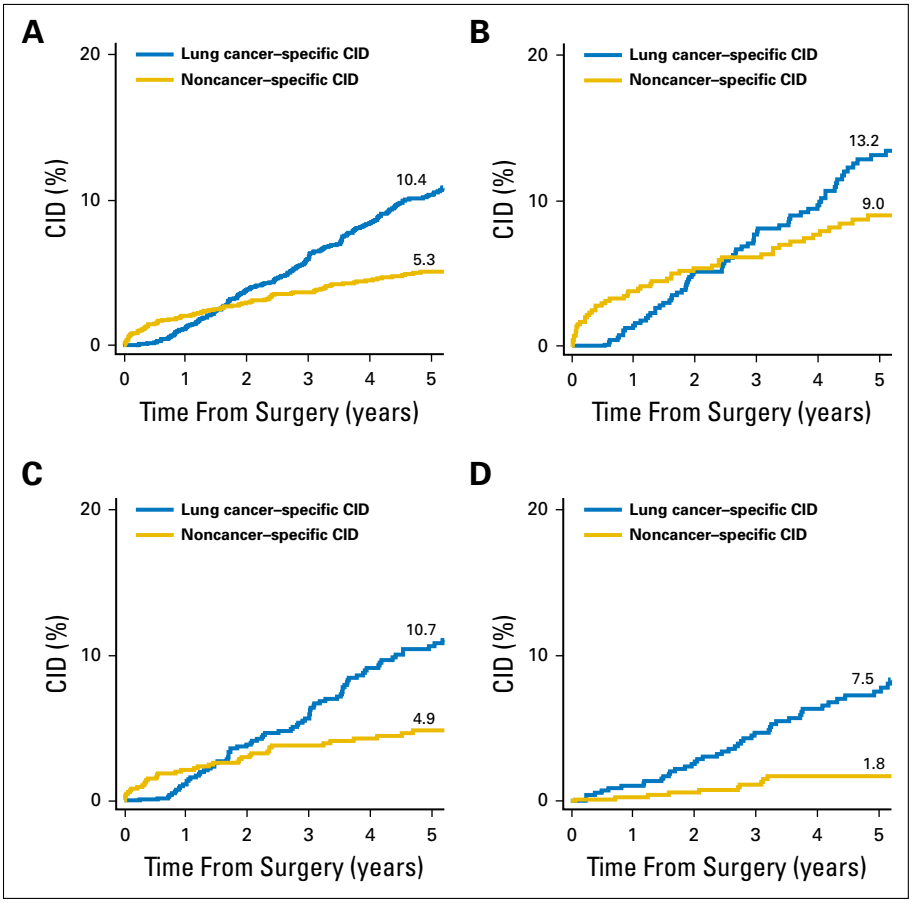

Fig 2. Lung cancer–specific and noncancer-specific 5-year cumulative incidence of death (CID) by age-group. (A) Up to approximately 1.5 years after surgery, noncancer-specific CID was higher than lung cancer–specific CID. After 1.5 years, lung cancer–specific CID surpassed noncancer-specific CID (N = 2,186). (B) The higher noncancer-specific CID observed in the early postoperative phase increased in patients ≥ 75 years of age, in whom noncancer-specific mortality was higher than lung cancer–specific mortality until approximately 2.5 years postsurgery (n = 638). (C) In patients 65 to 74 years of age, the difference between curves was similar to that for the total cohort (n = 894). (D) In patients < 65 years of age, lung cancer–specific mortality was higher than noncancer-specific mortality during most of the postoperative period (n = 654).

patients with stage I NSCLC, the majority of postoperative severe morbidity, 1-year mortality, and 5-year noncancer-specific mortality were attributable to cardiorespiratory diseases. We have also shown that short-term mortality is primarily attributable to noncancer-specific diseases. More importantly, the higher incidence of short-term noncancer-specific mortality was enhanced in the older cohort (≥ 75 years of age) and diminished in the younger cohort (< 65 years of age), which underscores the clinical significance of assessing noncancer-specific mortality as a competing event in older patients (Data Supplement).

Multivariable analyses revealed that ppo DLCO was a strong predictor of severe morbidity, 1-year mortality, and noncancer-specific mortality. Low DLCO has been associated with obstructive,[34] restrictive,[35] and pulmonary vascular diseases[36] as well as with chronic heart failure.[37] In previous studies, ppo DLCO represents an independent risk factor for postoperative morbidity and operative mortality.[11,13,38] Tumor size, ppo FEV1, and smoking status were found to be independent predictors of lung cancer–specific mortality. In addition, smoking-induced COPD and associated CVD are linked to severe morbidity and CVD to noncancer-specific death; CCI, which includes a history of cancer (other than lung cancer), in addition to noncancer conditions, predicts OS. Because the current study spans a long period, we performed subanalyses of early (2000 to 2005) and later (2006 to 2011) cohorts. Conclusions were similar among all multivariable models of outcomes (Data Supplement).

A review of the prior literature found 11 studies that investigated the prognostic value of preoperative pulmonary function tests or comorbidities in patients with resected NSCLC[11,14,15,17-20,39-42]; six of these explored national databases[14,15,17,39,40,42] (Data Supplement). Only two studies included FEV1, DLCO, and comorbidities as prognostic variables in the multivariable model.[14,18] Of the two studies that focused on stage I NSCLC,[20,42] only one evaluated both FEV1 and DLCO with OS as an end point.[20] None of the studies evaluated cause-specific mortality with competing risks analysis, and only one study investigated both short- and long-term outcomes.[40] The strengths of the current study include its comprehensive exploration of short- and long-term cause-specific outcomes, with competing risks analysis, in a large, uniform cohort of patients with stage I NSCLC; a multivariable analysis that included all preoperative variables known to contribute individually to outcomes; and the identification of independent predictors of each outcome, which showed that ppo DLCO and comorbidities are predictors of noncancer-specific mortality and postoperative morbidity and that ppo FEV1 is a predictor of lung cancer–specific mortality.

The study cohort reasonably reflects that of the SEER database, with the representation of patients 65 to 74 years of age approximately 10% higher in our cohort and those > 84 years of age 6% lower (Data Supplement). A possible explanation for these differences is that the SEER database includes patients with more–advanced stage cancer and/or patients treated with nonsurgical intervention. Because one third of patients with stage I

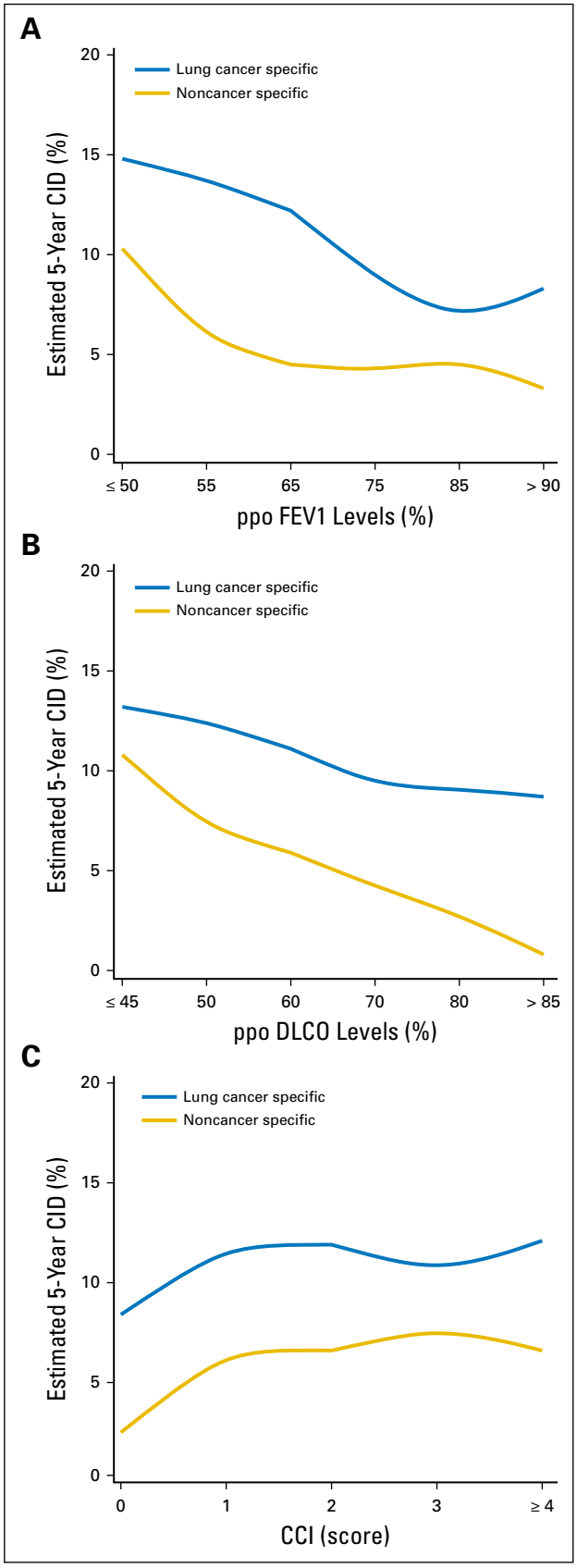

Fig 3. Estimated 5-year lung cancer–specific and noncancer-specific Charlson Comorbidity index (CCI). The mean for each variable was summarized and fitted by using cubic B-splines for graphic representation. Along the x-axis, each group interval was represented as the middle number, such as 55 for 51-60 in panel A. (A) Lung cancer–specific cumulative incidence of death (CID) is highest (approximately 15%) at the lowest predicted postoperative (ppo) forced expiratory volume in 1 second (FEV1) and decreases linearly as ppo FEV1 increases. Noncancer-specific CID plateaus when ppo FEV1 is ≥ 65% (61%-70%) but increases precipitously as ppo FEV1 decreases below that point. (B) Lung cancer–specific CID gradually decreases as ppo diffusing capacity of lung for carbon monoxide (DLCO) increases, but the gradient is more gradual than that for ppo FEV1. By contrast, noncancer-specific CID decreases linearly from approximately 11%-1% as ppo DLCO increases. (C) Noncancer-specific and lung cancer–specific CID increase as CCI increases from 0 to 1 but essentially plateaus when CCI increases to > 1.

NSCLC are ≥ 75 years of age at the time of diagnosis, the significant competing risks outlined in the current study have broad implications for disease management in these patients. These observations can inform conversations with patients and can be used when deciding on aggressive treatments, particularly for high-risk patients. For clinicians who manage patients with stage I NSCLC, the study provides clinically applicable information on the time-related change in mortality risk, including higher noncancer-specific mortality than lung cancer–specific mortality in the early postoperative period; the importance of predicting noncancer-specific mortality in older patients; an estimation of the 5-year CID for each cause-specific mortality; and the importance of cardiorespiratory diseases for postoperative severe morbidity and short-term mortality.

In this study, sublobar resection was associated with a lower incidence of severe morbidity, particularly respiratory events, as well as worse 1-year mortality, lung cancer–specific mortality, noncancer-specific mortality, and OS. Previous studies reported an association between sublobar resection and locoregional recurrence,[43-46] which suggests worse lung cancer–specific mortality. Lower pulmonary function test and higher comorbidity status seen in the sublobar resection group indicate selection bias on the basis of cardiorespiratory condition and explains the worse noncancer-specific outcomes (Data Supplement). These observations should be taken into consideration during analysis in ongoing randomized clinical trials (CALGB140503 and JCOG0802) in the assessment of outcomes of sublobar versus lobar resection.

One limitation of this study is the number of patients with an unknown cause of death. Of the 436 deaths within 5 years of surgery, 95 were of unknown causes. Among these patients, 83 experienced no recurrence at the last visit (median follow-up, 0.8 years); the other 12 experienced recurrence but had stable disease at the last visit (median follow-up, 1.6 years). Of these 95 patients, eight died within 1 year. These deaths may have affected our results (Data Supplement). Another limitation is that we did not evaluate patient family and/or social support, which may have affected the analyses, especially that of the long-term, noncancer-specific outcomes in elderly patients.

In conclusion, we have shown that compared with the common approach of OS or event-free survival, cause-specific outcome analysis better stratifies patients with stage I NSCLC according to their risk of cancer mortality relative to noncancer competing causes of death. Noncancer-specific mortality represents a significant competing event for lung cancer–specific mortality, with an increasing impact as age increases. These findings can provide patients with more accurate information on survivorship on the basis of their individual preoperative status and help determine patients' optimal treatment options.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of Increasing Age on Cause-Specific Mortality and Morbidity in Patients With Stage I Non–Small-Cell Lung Cancer: A Competing Risks Analysis

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