pISSN 1598-2998, eISSN 2005-9256

https://doi.org/10.4143/crt.2020.1308

Cancer Res Treat. 2021;53(4):1057-1071

Original Article

Conditional Survival of Surgically Treated Patients with Lung Cancer: A Comprehensive Analyses of Overall, Recurrence-Free, and Relative Survival

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Purpose Survival probability changes over time in cancer survivors. This study examined conditional survival in patients undergoing curative resection for non-small cell lung cancer (NSCLC).

Materials and Methods Five-year conditional recurrence-free survival (CRFS), conditional overall survival (COS), and conditional relative survival (CRS) up to 10 years after surgery were calculated in patients who underwent NSCLC resection from 1994 to 2016. These rates were stratified according to age, sex, year of diagnosis, pathological stage, tumor histology, smoking status, comorbidity, and lung function.

Results Five-year CRFS increased from 65.6% at baseline to 90.9% at 10 years after surgery. Early differences in 5-year CRFS according to stratified patient characteristics disappeared, except for age: older patients exhibited persistently lower 5-year CRFS. Five-year COS increased from 72.7% to 78.3% at 8 years and then decreased to 75.4% at 10 years. Five-year CRS increased from 79.0% at baseline to 86.8% at 10 years. Older age and higher pathologic stage were associated with lower 5-year COS and CRS up to 10 years after surgery. Female patients, those with adenocarcinoma histology, non-smokers, patient without comorbidities and had good lung function showed higher COS and CRS.

Conclusion CRFS improved over time, but significant risk remained after 5 years. CRS slightly improved over time but did not reach 90%, suggesting significant excess mortality compared to the general population. Age and stage remained significant predictors of conditional survival several years after surgery. Our conditional survival estimates should help clinicians and patients make informed treatment and personal life decisions based on survivorship status.

Key words Conditional survival, Lung neoplasms, Cancer survivor, Prognosis, Korea

Introduction

Lung cancer is the most common cancer worldwide, with 2.1 million new incident cases as of 2018 [1]. While the survival of lung cancer is still low, there is increasing numbers of lung cancer survivors due to the early detection and advancement of treatments. Therefore, survivorship management of them becomes more important than ever.

Survival probability is critical information for the clinicians to guide cancer patients and their families for balanced healthcare decisions. Currently, 5-year (5Y) recurrence-free survival (RFS) and overall survivor (OS) rates, which mean cumulative survival probability of being alive or disease-free from the time of diagnosis (or treatment) to 5 years respectively, are most commonly used survival estimates available from the literature or consumer information source. In addition, relative survival (RS) is calculated as the ratio of observed survival to that of the expected survival of a general population with same period, age, and sex [2]. RS is an approximation of disease-specific survival, and could overcome the limitation of inaccuracy of cause of death data on death certificates [3].

However, these survival probabilities could be misleading or become less meaningful for survivors who have survived for some time. In this respect, conditional recurrence-free survival (CRFS) and conditional overall survival (COS), which

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Received December 14, 2020 **Accepted** March 6, 2021 **Published Online** March 9, 2021
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describes the probability of a patient remaining disease free and surviving a given additional time at different time points after cancer diagnosis respectively, reflects the updated cancer prognosis and would be more relevant indicator [4]. Also, RS is calculated as the ratio of observed survival to that of the expected survival of a general population with same period, age, and sex [2]. RS is an approximation of disease-specific survival, and could overcome the limitation of inaccuracy of cause of death data on death certificates [3]. Conditional relative survival (CRS) rates, which takes into account changes in prognosis over time, therefore offer more useful estimates for the survivors and clinicians for their medical and personal life decisions, such as duration of disease surveillance [5].

Several studies reported COS and CRS in non-small cell lung cancer (NSCLC) cancer patients using the population-based multi-cancer registry in the United States [3,6] and Europe [7]. However, these studies are limited by absence of CRFS estimates due to lack of clinical data and stratification by only a few characteristics such as age, sex, and stage. In addition, they are outdated and included all NSCLC patients regardless of treatment, and are therefore limited for clinical use. Other studies involving U.S. Surveillance, Epidemiology, and End Results data reported conditional cancer-specific survival, which is limited by the inaccuracy of cause of death data [8,9].

There are a few study which investigated conditional survival of lung cancer who underwent surgery for NSCLC: one Japanese study involving 859 patients showed COS by age, sex, stage, histology, and smoking, but they had only 50 months of follow-up [10]; one Korean study involving 723 patients with only adenocarcinoma showed 3-year CRFS and COS according to stage and performance status, but had only 3.8 years of follow-up (max 9.8 years) [11]. These institution-based studies are limited by its patients' number, limited follow-up information, and short follow-up period [10,11]. Recently, a nationwide Korean study using insurance claims data reported CRS, but was limited by absence of cancer stage data [12].

Thus, this study aims to estimate 5-year CRFS, COS, and CRS of NSCLC patients receiving surgery with curative intent using a comprehensive cancer center registry.

Materials and Methods

1. Study population

Patients with NSCLC who received pulmonary resection for curative purpose between September 1994 and December 2016 were included in this study (n=10,852). Among these, those who were < age of 20 (n=10), had synchronous double primary cancer (n=677), who received chemo- or radiotherapy before surgery (n=1,090), who had stage IV disease (n=145), and who did not have R0 resection (n=132) were excluded resulting in 8,798 patients in the final analyses.

2. Data collection and follow-up

Data was obtained from the lung cancer registry which is based on electronic medical records. Information on age, sex, tumor histologic type, pathologic stage (TNM classification and American Joint Committee on Cancer [AJCC] stage), smoking history, comorbidities, preoperative pulmonary function, surgical procedure and other treatment were obtained.

The postoperative patients in our institution were scheduled for routine follow-up every 3 months for the first 2 years and every 6 months during the next 3 years or even longer for higher risk patients at surgeon's discretion. Most patients were transferred back to regional hospital usually after 5 years, but those who wanted to stay in our center were followed up once per year. Routine follow-up tests to detect recurrence include chest computed tomography scan, serum carcinoembryonic antigen levels. When recurrence was suspected, additional imaging evaluation were performed mostly by bone scan, positron emission tomography/computed tomography, and brain magnetic resonance imaging.

Recurrence or death status of patients were regularly updated through electronic medical records and linkage to mortality data from the Korean National Statistical Office, respectively up to December 31, 2017. Specifically, recurrence was defined by any clinical or pathologic evidence of local or distant recurrence documented in the hospital record. We distinguished recurrence from a second primary lung cancer using the criteria established by Martini and Melamed [13], which was revised by Antakli et al. [14], and a second primary lung cancer was not considered a recurrence. Vital status was ascertained by linkage to death registration database of Korean National Statistical Office.

3. Statistical analysis

Study outcomes of this study are CRFS, COS, and CRS which are conditional on years already survived. RFS was defined as the time from the date of surgery to the time of recurrence. Patient records were censored at the time of death or last follow-up, at which time they were known to be recurrence-free, as used in previous studies [10,15]. Although RFS was also defined as the time to recurrence or death in some literature, our primary interest was to report the probability of "recurrence" after a certain period of survival.

For conditional survival, only those who survived a certain amount of time are included in the analysis. The survival time is defined as the already survived time to the occurrence of recurrence or death. Therefore, conditional survival for

Table 1. Characteristics of study population at the time of surgery

Characteristic	No. (%)
Age (yr)	
Mean±SD	61.7±9.8
20-49	918 (10.4)
50-59	2,428 (27.6)
60-64	1,718 (19.5)
65-69	1,673 (19.0)
≥ 70	2,061 (23.4)
Sex	
Male	5,732 (65.2)
Female	3,066 (34.8)
Year of diagnosis	
1994-1999	497 (5.6)
2000-2009	2,815 (32.0)
2010-2016	5,486 (62.4)
Smoking[a]	
Never smoker	2,975 (40.8)
Ex-smoker	2,249 (30.9)
Current smoker	2,064 (28.3)
Comorbidities	
Hypertension	2,905 (33.0)
Diabetes mellitus	1,282 (14.6)
Cardiovascular disease	809 (9.2)
Lung disease	623 (7.1)
Histology (ICD-O-3)	
Adenocarcinoma	5,536 (62.9)
Squamous cell carcinoma	2,475 (28.1)
Large cell carcinoma	210 (2.4)
Others/Mixed	577 (6.6)
Pathologic stage	
I	5,617 (63.8)
II	1,943 (22.1)
III	1,238 (14.1)
Surgical approach	
VATS	4,202 (47.8)
Open	4,596 (52.2)
Surgical procedure	
Pneumonectomy	471 (5.4)
Bilobectomy	448 (5.1)
Lobectomy	6,856 (77.9)
Segmentectomy	406 (4.6)
Wedge resection	617 (7.0)
Preoperative pulmonary function[a]	
FEV_1 (%), mean±SD	94.4±18.5
FEV_1 < 80% of predicted	1,652 (19.2)
DLCO (%), mean±SD	90.9±18.7
DLCO < 80% of predicted	1,609 (26.1)

Cardiovascular disease includes a history of ischemic heart disease, heart failure, and cerebrovascular disease. Lung disease includes a history of chronic pulmonary obstructive disease, asthma, and diffuse interstitial lung disease. Numbers of each category might not sum up to the total number due to missing information: n=7,288 for smoking, n=8,592 for FEV_1, n=6,173 for DLCO. DLCO, single-breath carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; SD, standard deviation.

another y years is calculated by dividing the survival at (x+y) years by the survival at x years:

$$CS(y \mid x) = \frac{S(x+y)}{S(x)}$$

For example, 5Y CS conditional on surviving 3 years are calculated by dividing 8-year survival by 3-year survival. In our study, we presented the 5Y CSs from baseline to 10 years by 1-year interval. 95% confidence intervals was also calculated assuming that conditional survival follows a normal distribution.

To calculate RS of our NSLCL patients in comparison to survival of general population, expected mortality rate in the general population was obtained from the population from the National Statistics Korea. CRS for another y years was calculated by dividing the RS at (x+y) years by the RS at x years.

For the stratified analyses, patients were categorized into five groups by age at cancer diagnosis: 20-39, 40-49, 50-59, 60-69, and ≥ 70 years. Stages at diagnosis were classified as I, II, and III using the AJCC VII staging scheme. Histology of NSCLC was categorized as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and others or mixed. Smoking status at the time of diagnosis was categorized as non-smoker, past smoker, and current smoker (defined by current smoking or quitting within 1 month at the time of survey administration) and the latter was further classified by amount of smoking (< 10, 10-19, and 20 cigarettes). The years of diagnosis were classified as three groups: 1994-1999, 2000-2010, and 2011-2016. Stratified analyses were also made based on the presence of major comorbidities (hypertension, diabetes mellitus, cardiovascular disease, and lung disease) and preoperative pulmonary function (forced expiratory volume in 1 second [FEV_1] and single-breath carbon monoxide diffusion capacity [DLCO], dichotomized at 80% of predictive value).

All analyses were conducted using Stata ver. 15.0 (Stata-

Table 2. Five- and 10-year recurrence-free, overall, and overall relative survival of lung cancer patients

	Recurrence-free survival (%)[a]		Overall survival (%)		Overall relative survival (%)	
	5 Years (95% CI)	10 Years (95% CI)	5 Years (95% CI)	10 Years (95% CI)	5 Years (95% CI)	10 Years (95% CI)
Total	65.5 (64.3-66.8)	58.8 (57.0-60.5)	72.7 (71.6-73.7)	56.7 (55.2-58.1)	79 (78.8-79.1)	67.8 (67.6-68.0)
Age (yr)						
20-49	70.1 (66.5-73.5)	68.6 (64.8-72.1)	85.7 (83.0-88.0)	76.5 (72.8-79.9)	88.3 (88.2-88.4)	81.4 (81.2-81.5)
50-59	69.3 (67.0-71.5)	63.2 (60.1-66.2)	82.4 (80.6-84.0)	70.6 (67.9-73.1)	84.4 (84.3-84.4)	75.4 (75.4-75.5)
60-64	68.5 (65.7-71.2)	61.9 (58.0-65.6)	75.1 (72.7-77.3)	61.5 (58.2-64.7)	80.3 (80.2-80.3)	69.5 (69.4-69.6)
65-69	63.4 (60.5-66.2)	53.6 (49.0-57.9)	66.6 (64.0-69.0)	46.1 (42.7-49.5)	74.3 (74.2-74.3)	61.1 (60.9-61.2)
≥ 70	56.0 (52.8-59.0)	42.0 (35.1-48.7)	57.9 (55.5-60.4)	33.2 (29.8-36.7)	71.2 (71.1-71.3)	56.9 (56.8-57.1)
Sex						
Male	63.3 (61.8-64.9)	57.3 (55.2-59.3)	66.1 (64.8-67.4)	50.1 (48.3-51.8)	78.3 (78.2-78.5)	66.9 (66.7-67.1)
Female	69.3 (67.1-71.5)	61.1 (57.7-64.3)	85.6 (84.1-87.0)	70.6 (68.0-73.1)	80.2 (80.0-80.4)	69.6 (69.3-69.9)
Histology (ICD-O-3)						
Adenocarcinoma	66.4 (64.8-68.0)	58.2 (55.6-60.7)	80.0 (78.7-81.2)	63.7 (61.6-65.7)	79.7 (79.5-79.9)	68.9 (68.7-69.1)
Squamous cell carcinoma	62.6 (60.2-64.9)	56.8 (53.7-59.7)	59.1 (57.0-61.1)	43.3 (40.9-45.7)	76.9 (76.7-77.2)	64.9 (64.6-65.3)
Large cell carcinoma	49.3 (41.7-56.5)	43.6 (35.0-51.9)	47.8 (40.6-54.6)	36.8 (29.6-44.0)	77.9 (77.1-78.7)	66.3 (65.1-67.4)
Others/Mixed	70.5 (66.1-74.5)	67.3 (62.4-71.7)	74.4 (70.5-78.0)	63.5 (58.7-68.0)	80.9 (80.3-81.5)	70.7 (69.8-71.5)
Stage at diagnosis						
I	78.2 (76.7-79.6)	71.2 (69.0-73.4)	84.5 (83.4-85.6)	69.6 (67.8-71.4)	79.3 (79.1-79.4)	68.3 (68.0-68.5)
II	50.6 (47.8-53.2)	43.9 (40.4-47.4)	58.0 (55.6-60.4)	41.7 (38.8-44.5)	78.3 (78.0-78.5)	66.8 (66.4-67.2)
III	31.3 (28.0-34.5)	26.5 (23.0-30.1)	45.0 (41.8-47.9)	27.4 (24.1-30.8)	78.7 (78.3-79.1)	67.5 (67.0-68.0)
Year of diagnosis						
1994-1999	51.5 (46.7-56.1)	46.7 (41.8-51.5)	53.5 (49.0-57.8)	39.03 (34.7-43.3)	80.0 (79.5-80.5)	69.3 (68.6-70.1)
2000-2009	63.3 (61.4-65.2)	56.6 (54.3-58.3)	68.1 (66.4-69.8)	53.7 (51.8-55.6)	79.1 (78.9-79.3)	68.0 (67.7-68.4)
2010-2016	68.5 (66.6-70.3)		78.0 (76.6-79.3)		78.8 (78.6-79.0)	67.6 (67.4-67.8)
Smoking status						
Never smoker	69.3 (67.2-71.3)	60.9 (57.6-63.9)	84.6 (83.1-86.0)	70.3 (67.8-72.7)	88.9 (88.8-88.9)	77.9 (77.8-80.0)
Ex-smoker	62.9 (60.4-65.2)	57.5 (54.0-60.8)	66.2 (64.0-68.3)	49.6 (46.6-52.5)	74.6 (74.3-75.0)	62.7 (62.2-63.2)
Current smoker	64.2 (61.7-66.7)	58.5 (55.1-61.8)	67.8 (65.6-69.9)	50.8 (47.7-53.7)	73.7 (73.3-74.0)	61.5 (61.0-62.0)
Comorbidities						
Hypertension						
No	65.3 (63.8-66.8)	58.5 (56.4-60.5)	72.5 (71.2-73.8)	57.8 (56.0-59.5)	78.0 (77.8-78.2)	67.5 (67.3-67.8)
Yes	66.0 (63.7-68.2)	59.5 (56.2-62.7)	73.1 (71.2-74.9)	53.8 (51.0-56.6)	80.6 (80.5-80.8)	68.1 (67.9-68.4)
Diabetes mellitus						
No	65.8 (64.4-67.1)	58.8 (56.9-60.6)	73.9 (72.7-75.0)	57.9 (56.3-59.5)	79.9 (79.8-80.0)	69.3 (69.1-69.4)
Yes	64.1 (60.5-67.4)	59.2 (54.5-63.6)	65.7 (62.6-68.6)	48.9 (44.8-52.9)	73.9 (73.4-74.3)	59.8 (59.2-60.5)

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Table 2. Continued

	Recurrence-free survival (%)[a]		Overall survival (%)		Overall relative survival (%)	
	5 Years (95% CI)	10 Years (95% CI)	5 Years (95% CI)	10 Years (95% CI)	5 Years (95% CI)	10 Years (95% CI)
CVD						
No	65.6 (64.3-66.9)	58.9 (57.1-60.7)	73.4 (72.3-74.4)	57.6 (56.0-59.1)	79.5 (79.3-79.6)	68.5 (68.3-68.7)
Yes	64.3 (59.5-68.8)	56.7 (48.2-64.2)	65.7 (61.7-69.3)	45.2 (39.1-51.1)	74.4 (74.1-74.7)	61.6 (61.2-62.0)
Lung disease						
No	65.9 (64.6-67.2)	59.1 (57.2-60.8)	74.0 (72.9-75.0)	58.0 (56.5-59.5)	80.2 (80.1-80.3)	69.4 (69.2-69.6)
Yes	59.4 (54.0-64.4)	55.9 (49.3-62.0)	55.1 (50.4-59.5)	36.1 (30.0-42.2)	63.7 (62.9-64.5)	45.8 (44.8-46.9)
Preoperative pulmonary function						
FEV_1 < 80% of predicted						
No	66.2 (64.8-67.6)	59.6 (57.7-61.5)	74.9 (73.8-76.1)	59.5 (57.9-61.1)	81.1 (80.9-81.2)	70.6 (70.4-70.8)
Yes	61.3 (58.2-64.4)	53.8 (49.0-58.3)	62.3 (59.5-64.9)	80.3 (78.9-81.6)	69.3 (69.1-69.6)	54.2 (53.8-54.6)
DLCO < 80% of predicted						
No	69.5 (67.7-71.3)	60.9 (56.8-64.7)	80.3 (78.9-81.6)	62.3 (59.2-65.2)	86.5 (86.4-86.7)	74.5 (74.2-74.7)
Yes	58.7 (54.2-62.9)	54.8 (48.5-60.6)	41.1 (34.1-48.0)	41.1 (34.1-48.0)	67.9 (67.3-68.5)	53.5 (52.7-54.3)

CI, confidence interval; CVD, cardiovascular disease; DLCO, single-breath carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition. [a]Events for RFS included recurrence only and deaths were censored.

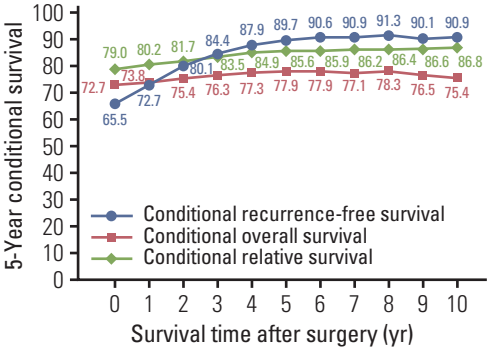


Fig. 1. Conditional survival estimates in all patients who underwent curative surgery for non-small cell lung cancer. Events for recurrence-free survival included recurrence only and deaths were censored.

Corp LP, College Station, TX). All statistical tests were two-sided, and p-values < 0.05 were considered significant.

Results

1. Baseline characteristics

The mean age (standard deviation) of the study population was 61.7 (9.8) and two-thirds were male. About 28.2% and 25.9% of the patients were ex-smokers and current smokers at diagnosis, respectively. Adenocarcinoma was most common histologic type (63%), followed by squamous cell carcinoma (28%). Of total, 63.8% and 22.1% were pathologic stage I and II cancer. Around half of the patients received video-assisted thoracoscopic surgery, and 78% received lobectomy (Table 1).

2. Traditional RFS, OS, and RS from baseline

Median follow-up durations (interquartile range) for RFS and OS were 2.0 (1.0-4.7) and 4.1 (2.1-7.3) years, respectively. 5Y RFS, OS, and RS calculated from were 65.6, 72.7, and 79.0%, respectively. Ten-year estimates were 58.5, 56.7, and 67.8% for each (Table 2).

3. Conditional RFS, OS, and RS

In total study population, 5Y CRFS increase from 65.6% at baseline to 90.9% after 10 years after surgery. 5Y COS increased from 72.7 to 78.3% at 8 years, but then decreased to 75.4% at 10 years. 5Y CRS increased from 79.0% at baseline to 86.8% at 10 years (Fig. 1).

5Y CRFS was lower in older patients at baseline and the gap remained significantly even after 5 years. There was no significant difference between sex. Patients who received surgery in 1990s showed lower CRFS at baseline, but the gap

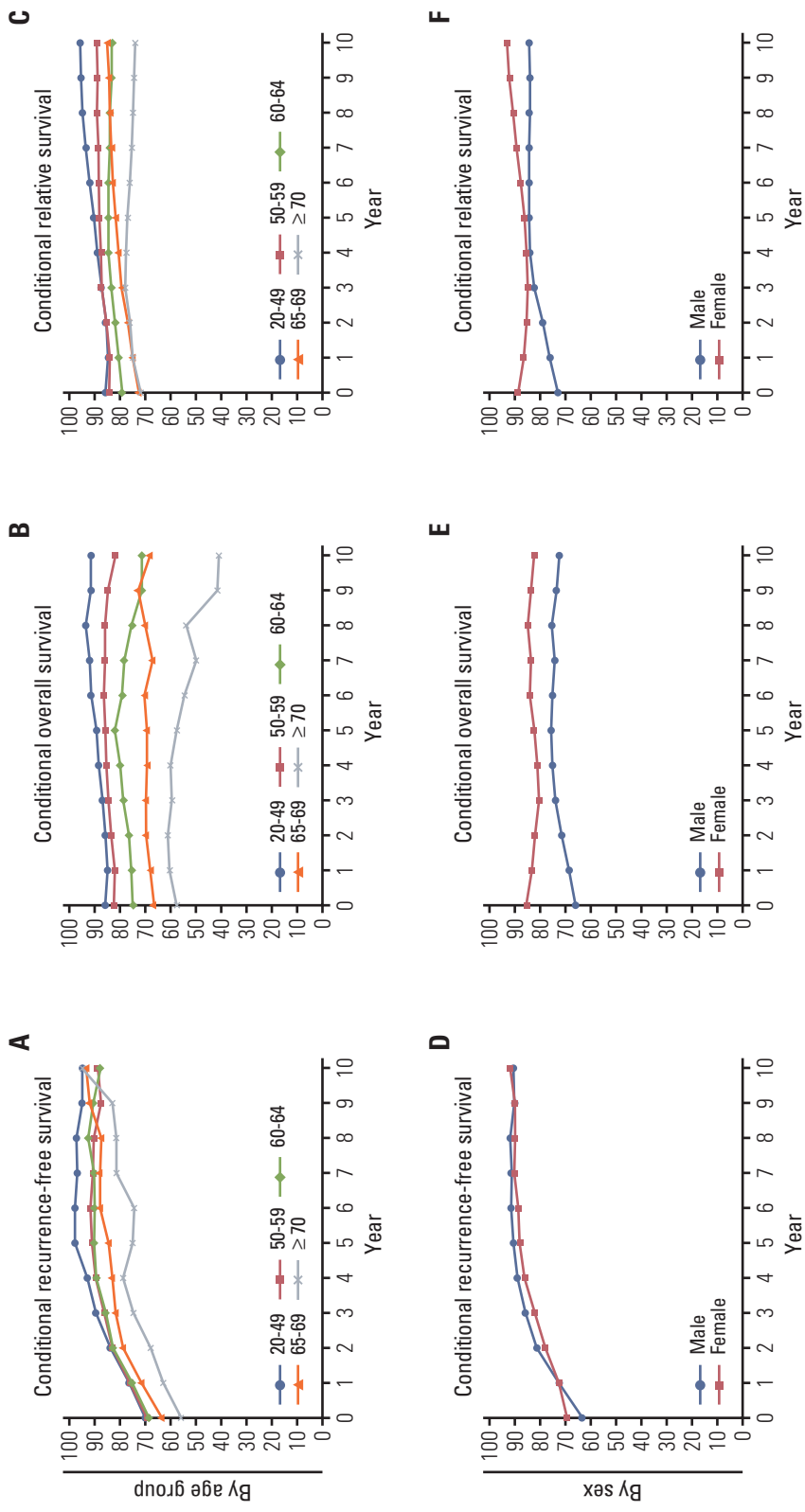
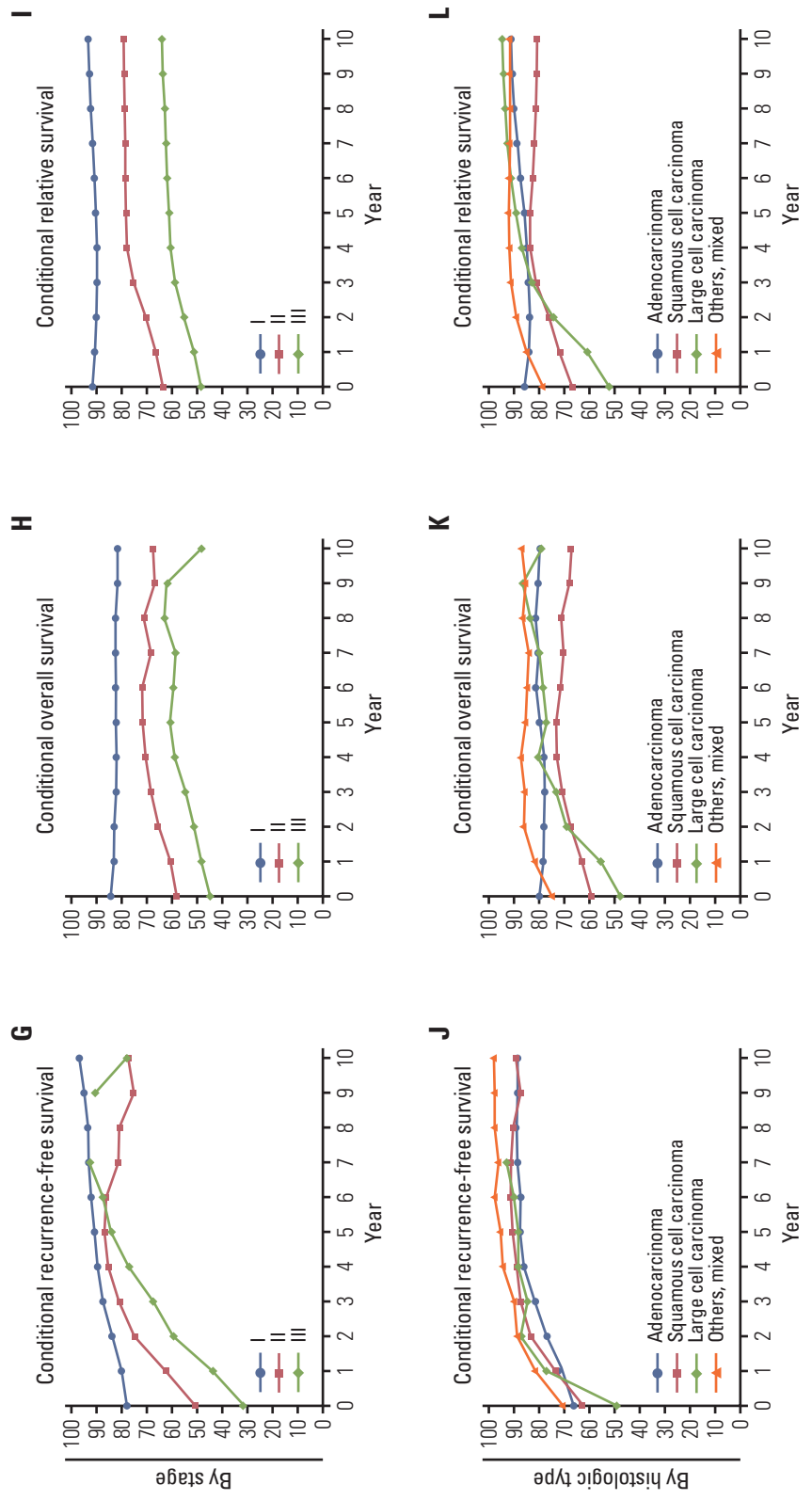


Fig. 2. Conditional survival estimates in all patients who underwent curative surgery for non-small cell lung cancer stratified by patient characteristics: conditional recurrence-free survival (A, D, G, J, M, P), conditional overall survival (B, E, H, K, N, Q), and conditional relative survival (C, F, I, L, O, R). Events for recurrence-free survival included recurrence only and deaths were censored. *(Continued to the next page)*



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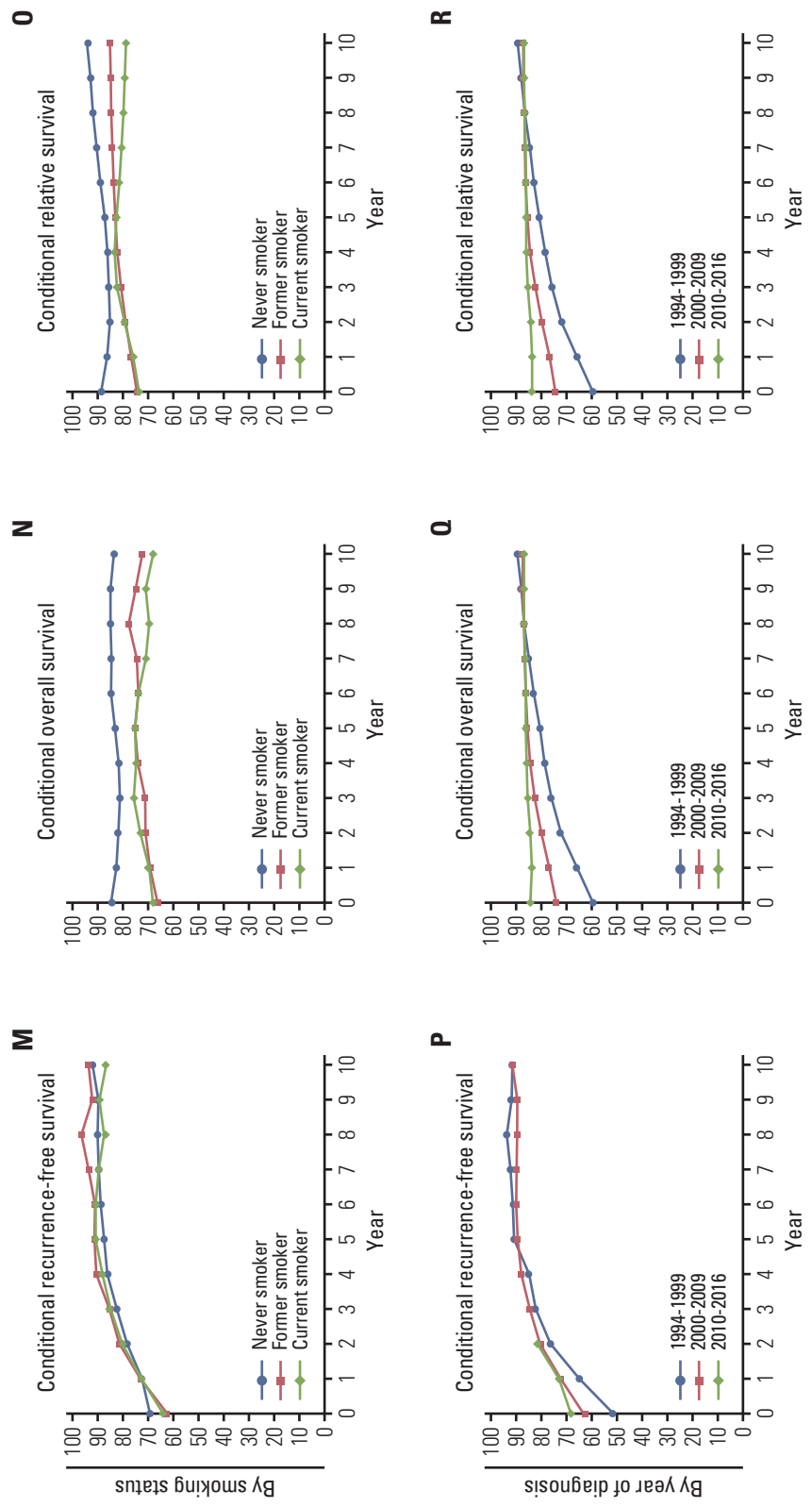

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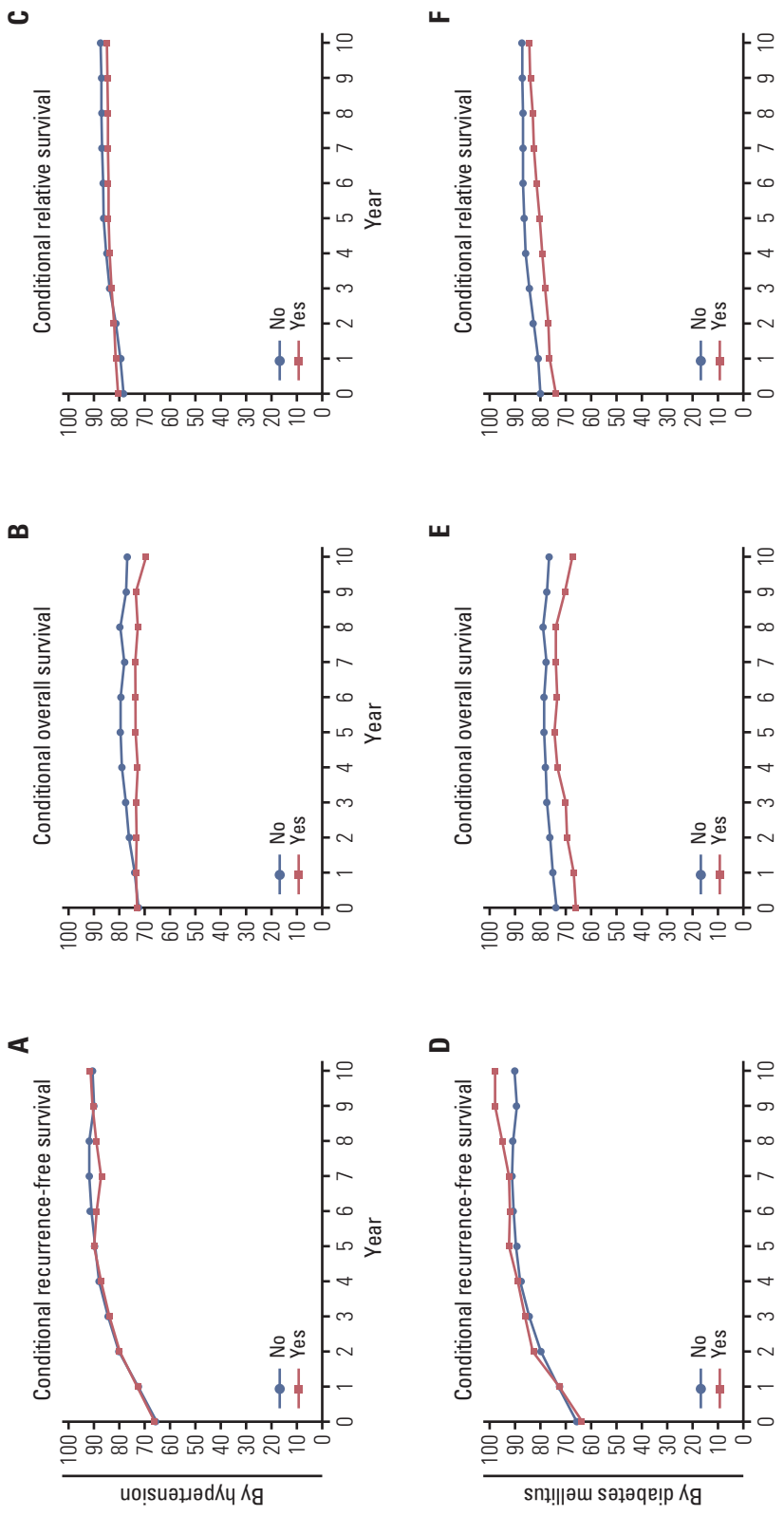
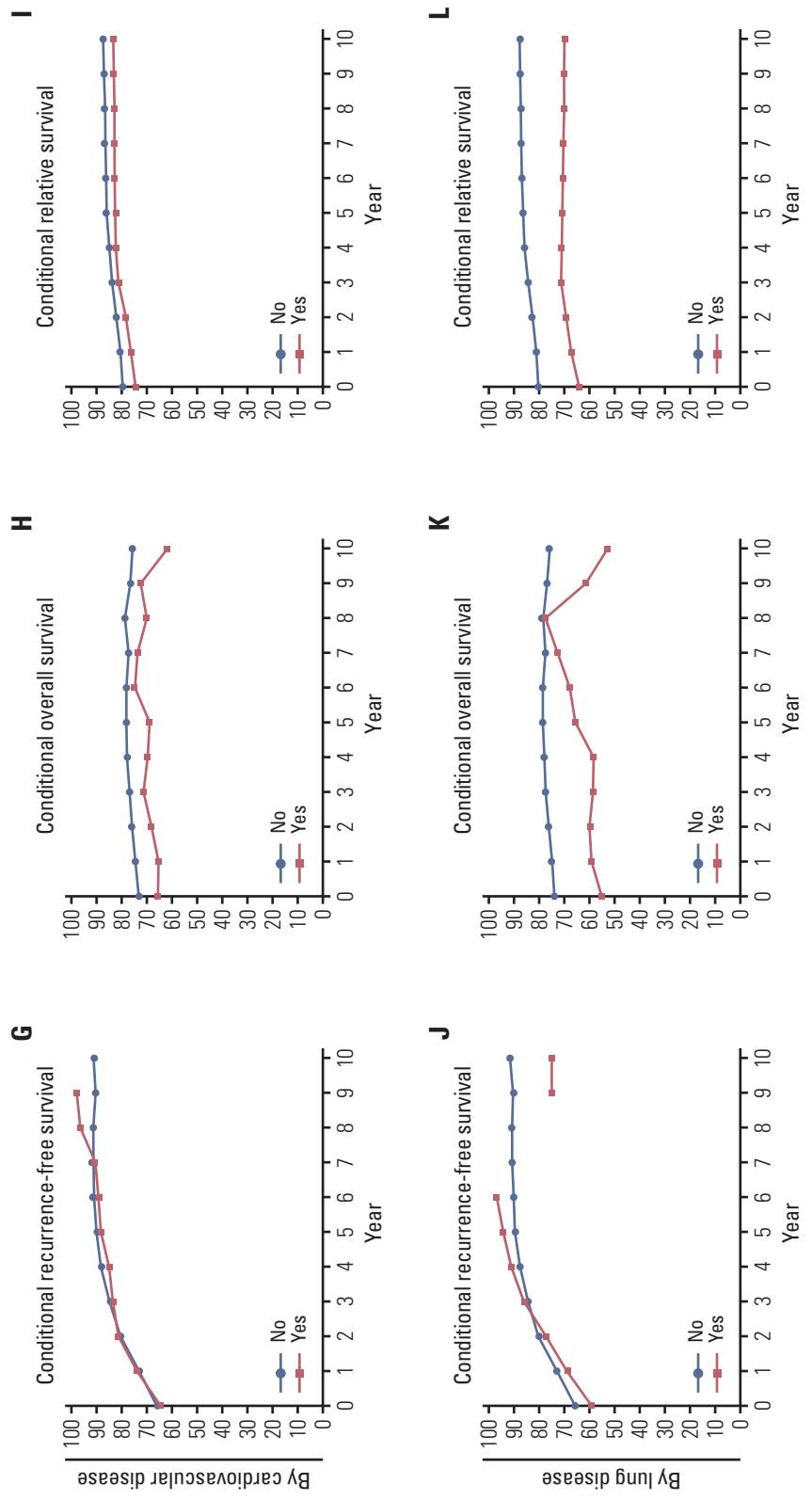


Fig. 3. Conditional survival estimates in all patients who underwent curative surgery for non-small cell lung cancer stratified by comorbidities and preoperative lung function: conditional recurrence-free survival (A, D, G, J, M, P), conditional overall survival (B, E, H, K, N, Q), and conditional relative survival (C, F, I, L, O, R). Events for recurrence-free survival included recurrence only and deaths were censored. DLCO, single-breath carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second. *(Continued to the next page)*



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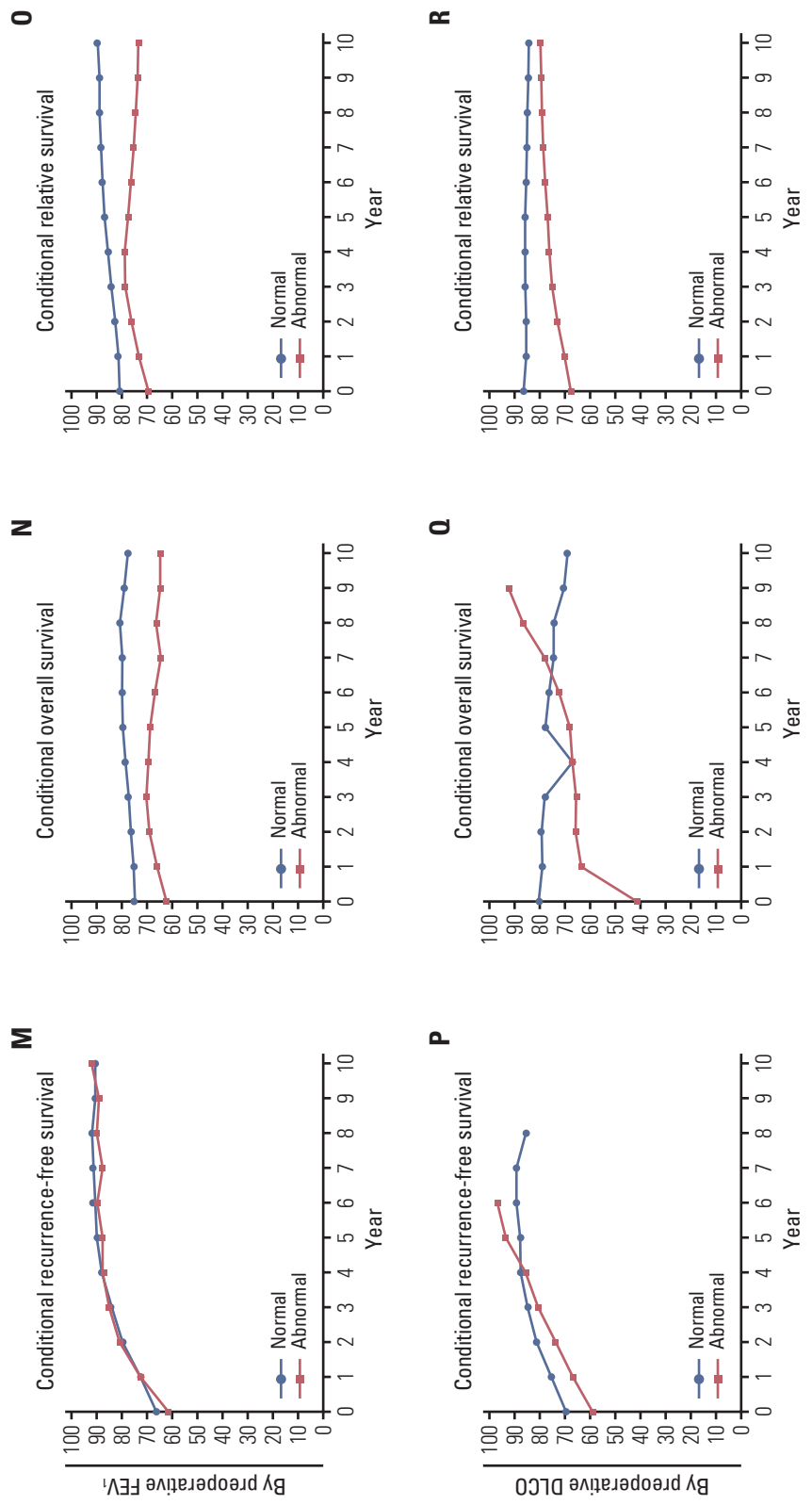

Fig. 3. *(Continued from the previous page)*

disappeared after 4-5 years of survival. Recurrence rate was significantly higher with higher stage disease at baseline, but difference in 5Y CRFS according to stage at diagnosis almost disappeared after 5 years. No significant difference in 5Y CRFS was observed by histologic type, except for slightly higher estimated in other/mixed type. Smoking status at baseline did not significantly affect 5Y CRFS throughout the period. There were no significant trends based on the presence of comorbidities or preoperative pulmonary function.

5Y COS showed different pattern by age: in younger age group, COS increase with survival time, but in older age group, it decreased with survival. By sex, male showed initial increase but became stable after 4-5 years, and female showed initial decrease but also became stable after 3-4 years. Patients who received surgery in 1990 showed increasing OS at initial years, while those who received surgery after 2010 showed stable estimates from the initial years. Patients who had stage II and stage III disease showed increment 5Y COS until 5 years and then became stable, while stage I disease showed stable 5Y COS from the baseline. Adenocarcinoma showed stable 5Y COS at around 80%, which was higher than that of squamous cell carcinoma through to 10 years. Non-smoker showed highest and stable 5Y COS, and past and current smoker showed lower 5Y COS. Patients with comorbidities and poor FEV_1 had worse 5Y COS. Patients who had poor DLCO had worse survival at first, but 5Y COS increased to a higher rate than patients with normal DLCO after 7 years of survival.

5Y CRS was lower in older patients and did not converge to that of younger patients even after 10 years. Female has higher 5Y CRS at baseline, and while it converged by sex at 4-5 years, it diverged again. Those who received surgery after 2010 has better 5Y CRS at initially than those who were treated before, but the difference disappeared with longer survival. Difference in 5Y CRS by stage was slightly reduced with longer survival, but persisted through the 10-year period after diagnosis. 5Y CRS of adenocarcinoma did not change much and only slightly increased, while 5Y CRS of squamous cell carcinoma was lower but increased upto 4 years although it began to decrease thereafter. 5Y CRS of non-smokers and smokers showed different pattern, the latter showed initial increase upto 4 years and decrease after that. Patients with comorbidities (except for hypertension) and poor preoperative pulmonary function had lower 5Y CRS throughout the period compared with patients who had no comorbidities (Figs. 2 and 3).

Discussion

In this study, we investigated dynamic prognosis of resected NSCLC with a large cohort of patients applying conditional survival methodology. We showed that CRFS and CRS improved over time, but significant risk of recurrence and significant excess mortality compared to general population remained even after 5 years. The strength of our study is that we presented CRFS and CRS in addition to the COS, the formers were rarely found in previous studies. In addition, our study has relatively large sample size (8,798 patients) compared to previous studies which reported conditional survivals in patients with resected NSCLC [10,11]. By limiting the subjects to patients who received curative surgery, our conditional survival estimates would be helpful to thoracic surgeons and their patients, compared to conditional survival estimates from population-based registry, which mainly includes unresectable patients.

Conditional survival estimates are useful to answer the question of a survivor's current prognosis. Lack of information on current prognosis could lead to higher level of fear of recurrence, resulting in lower quality of life and unnecessary medical use. Therefore, it is critical to determine the optimal follow-up strategy such as up testing frequency and duration of surveillance to be based on a patient's updated risk reflecting change of likelihood of recurrence or survival [3,11]. In this study, the 5Y CRFS of lung cancer patients was 65.5% at baseline, but increased rapidly, and it reached 89.7 % after 5 years, and then remain stable at around 90% upto 10 years. This has two-sided messages: the risk of recurrence rapidly drops at initial years suggesting that long-term survivors do not need to worry too much about. However, at the same time, it means that long-term survivors (> 5 years) still has around 2% of risk of recurrence even after 5 years. This is consistent to American Thoracic Society recommendation which recommends annual low-dose computed tomography (LDCT) scan for all lung cancer survivors up to age of 79 [16].

The 5Y CRS of lung cancer patients was 79.0% at baseline and improved steadily, however it reached only up to 86.8% after 5 years suggesting considerable excess in mortality remained compared with the general population even if patients live without recurrence for more than 5 years from surgery. Comorbidities, such as chronic obstructive pulmonary disease (COPD) or cardiovascular disease, may contribute to the excess mortality [12], as indicated by the lower COS and CRS in patients with comorbidities from our stratified analyses. This finding suggests that long-term management is warranted for so-called 'cured' long-term survivors.

Age had a marked influence on the conditional survival of patients with NSCLC. Older patients had worse 5Y CRFS throughout the observation period, 5Y COS and CRS even diverged with time. This means that higher risk of recurrence and death in older patients persist over time. Previous studies suggested higher risk of recurrence in older person [17].

In addition, while not confined to those with curative resection, previous studies have shown that age still influenced COS of lung cancer patients up to 5 years after diagnosis [5]. This is quite different from other types of cancer, which show the influence of age on CRS largely disappeared after survival for 5-10 years [18]. Therefore, age seems to be the main factor to influence conditional survival even after survival for 5-10 years from surgery. Young survivors persistently showed higher CS than older survivors, probably due to earlier detection [19], better endurance with invasive surgery or chemotherapy, and lack of competing morbidities [12].

There was no difference in 5Y CRFS between two sex. However, 5Y CRS and COS was better in women than in men. Several studies revealed that female have more favorable survival in lung cancer than men [20,21]. Better survival in female might be attributable to differences of younger age at diagnosis, histologic type (e.g., more adenocarcinoma), genetic factor (such as epidermal growth factor receptor [*EGFR*] mutation, etc.), and lower comorbidity and smoking rate [22-24].

The findings of the current study revealed that the probability of recurrence in patients with pathologic stage II or III disease decreases rapidly over time, to the level comparable to that of stage I patients at 5 years after surgery. However, gaps in COS and CRS decreased but did not converge, stage remains an important prognostic factor for overall survival after 5 years [6]. There might be several reasons: patients with stage II or III disease might have worse baseline health status or health behaviors (e.g., smoking) compared to stage I patients who had been more likely to be diagnosed with LDCT screening [25], long-term effect of more extensive of surgery, such as respiratory difficulty [26], or long-term effect of chemo or radiotherapy, such as increased risk of cardiovascular disease [27], etc.

The conditional survival for patients with adenocarcinoma, squamous cell carcinoma, large cell carcinoma and others showed different curves in the present study. The CRFS for patients with adenocarcinoma and squamous cell carcinoma increased with succeeding year survived from surgery with similar estimates, indicating a similar hazard for recurrence. However, COS and CRS were better in patients with adenocarcinoma than in squamous cell carcinoma over 10 years from surgery. This may be due to the different approach of patients with lung adenocarcinoma compared with patients with squamous cell carcinoma in the era of personalized medicine: recurred adenocarcinoma is currently managed long-term with new anti-cancer therapy targeted to EGFR or anaplastic lymphoma kinase, etc. [28].

No significant difference was noted in 5Y CRFS by smoking status. This is contrast to the evidence that baseline smoking [29] or persistent smoking after surgery [30] are known to be a risk factor for recurrence after curative resection of NSCLC. On the other hand, 5Y COS or CRS remained persistently worse in current smoker at baseline, suggesting they are at higher risk of cardiovascular, respiratory, and other non-cancer-related death caused by smoking [31]. Intervention for smoking cessation is warranted for patients diagnosed with NSCLC.

In the current study, 5Y COS, CRFS, and CRS in early survivorship period gradually improved from 1994-1999 periods, and 2000-2009 periods to 2010-2016 periods. However, later than 5 years from surgery, there was no significant difference between patients who underwent surgery in earlier year and who had it in later year. Advance in surgical technique and peri-operative care might have prevented early mortality, and chemo and radiotherapy might prolong survival, explaining improvement of short-term conditional survival. However, long-term survivors in earlier years are likely to be those who had survived without modern treatment (i.e., natural selection), and had similar conditional survival compared to recent survivors.

Patients with lung disease and poor preoperative pulmonary function showed poor COS and CRS, although their CRFS was not different. This highlights the importance of proper management of comorbid COPD and preoperative and postoperative respiratory rehabilitation. However, these findings should be confirmed by further studies.

There are several limitations. First, the representativeness is limited as this study is an analysis of a retrospective cohort from a single institution. Second, although much larger than previous studies with resected NSCLC, the size of some of the subgroups was too small to yield sufficient number of events and stable estimates. Third, information on disease status after 5 years might have been insufficient, as most patient were routinely followed up for 5 years. Fourth, our data might not be generalizable to other countries: Korea has universal health coverage, and lung cancer screening by LDCT is quite widely available in private health screening program [32]. Validation of our results in other ethnic group and in other health care system would allow general application of our finding.

CRFS improved over time, but significant recurrence risk remained even after 5 years. CRS slightly improved over time, but did not reach 90% suggesting significant excess mortality compared to general population. Conditional survival estimates were different by age and stage, even several years after surgery. Our conditional survival estimates would be helpful in the survivorship management in that the patients and clinicians to make informed decision based on a patient's current status at a certain point after surgery.

Ethical Statement

The study was approved by Institutional Review Board (IRB) of that Samsung Medical Center and informed consent were waived as we used di-identified data only (IRB no. SMC 2019-01-159-001).

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Obtained funding: Shin DW, Shim YM.
Administrative, technical, or material support: Lee G, Shim YM.
Integrity of the data and the accuracy of the data analysis: Shim YM.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

This work was supported by intramural research grants from the Samsung Medical Center and by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2019R1A2C2009751). The funding source played no role in the study's design, data collection and analysis, writing of the report, or decision to submit the report for publication.

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