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Prognostic Factors as a Function of Disease-Free Interval after Definitive (Chemo)radiation for Non-Small Cell Lung Cancer using Conditional Survival Analysis

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Abstract

Purpose—We analyzed overall and disease-free survival (OS and DFS) after definitive (chemo)radiation for stage III non-small cell lung cancer (NSCLC) with two statistical methods: Kaplan-Meier (KM) analysis, with diagnosis as index date, and conditional survival (CS) analysis, with a variety of disease-free index dates, and determined if prognostic factors varied based on the reference date.

Methods—All 651 patients analyzed received definitive (chemo)radiotherapy for stage III NSCLC in November 1998–December 2010 at a single institution; all had Karnofsky performance status scores ≥ 60 and received ≥ 60 Gy. OS and DFS were first calculated with the KM method, and then CS was used to calculate two outcomes: OS conditioned on DFS time (OS|DFS) and DFS conditioned on DFS time (DFS|DFS). Factors predicting OS and DFS conditioned on 1-, 2-, and 3-year DFS were sought in univariate and multivariate analyses.

Results—KM analysis produced 1-, 2-, and 3-year DFS rates of 48%, 30%, and 26%; OS rates were 64%, 41%, and 29%. By CS analysis, both OS|DFS and DFS|DFS showed an increase in 5-year OS after 6 months, and CS after 30 months approached 100%. On multivariate analyses, age and concurrent chemoradiation predicted OS|DFS; age, smoking history, tumor histology, disease stage, and radiation dose predicted DFS|DFS.

Conclusions—CS analysis showed that the probability of long-term survival increases sharply after 6 months with no evidence of disease; factors predicting survival differed based on the method and endpoint used.

Keywords

conditional survival; Kaplan-Meier analysis; survival; non-small cell lung cancer

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Conflicts of Interest: None

Introduction

Numerous studies have examined survival outcomes for patients with non-small cell lung cancer (NSCLC); 5-year survival rates for patients with locally advanced disease are usually said to be 15%–20% (1). These statistics are typically reported from the time of diagnosis. Although this approach is useful for comparing outcomes across studies or institutions, it has limitations: specifically, for patients who have already survived for some period after diagnosis, assessing survival with a fixed time point provides limited information about how the probability of survival may change over time. In fact, patients inquiring about the chance of long-term survival after treatment have often already remained disease-free for some time. Although information on survival outcomes based on disease-free interval can be extrapolated from standard Kaplan-Meier (KM) analysis, gleaming specific estimates (e.g., 2-year survival after a 2-year disease-free interval) is often not straightforward.

In contrast to KM analysis, conditional survival (CS) analysis involves presenting probability estimates according to the period a patient has already survived (2). CS estimates have been reported for several types of malignancies, including pancreatic cancer (3), colon cancer (4), glioblastoma (5), head and neck cancer, and gastric cancer (6). Although a limited number of analyses have assessed CS in patients with NSCLC (7–9), none have specifically focused on patients with locally advanced disease treated with modern techniques. The purposes of the current study were thus two-fold. First, we sought to identify factors predicting survival in a large group of patients with locally advanced NSCLC treated at a tertiary cancer center. Second, we present estimates of CS in this setting, conditioned on both disease-free survival (DFS) and overall survival (OS). Our aim in both analyses was to provide a comprehensive report of factors predicting survival for patients with locally advanced disease, which could guide both patients and physicians in discussions about prognosis.

Materials and Methods

Study inclusion criteria and patient characteristics

This single-institution study was approved by the relevant institutional review board. We included patients who had received definitive radiotherapy for NSCLC, with or without chemotherapy, from November 1998 through December 2010. Patients were selected from an in-house database of 765 patients who had received definitive radiotherapy on the basis of the following criteria: (1) histologic confirmation of stage III NSCLC, (2) Karnofsky performance status (KPS) score ≥ 60 , and (3) radiation dose ≥ 60 Gy (Figure 1). Ultimately, 651 patients met these criteria. Disease was staged per the 6th (2002) version of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (10). Prior chemotherapy, radiotherapy, or surgery for NSCLC were causes for exclusion.

Characteristics of the 651 patients analyzed are summarized in Table 1. Most were male, and the vast majority (92%) had a history of smoking. The distribution of stage IIIA and IIIB disease was approximately even. Although T-status distribution varied, most patients had N2 disease. Most patients (82%) also had a KPS score of at least 80, most (86%, n=563) had received concurrent chemoradiation, and most (95%, n=536) had been treated with platinum

doublet therapy. All patients received three-dimensional conformal radiation therapy (3D-CRT) (53%) or intensity-modulated radiation therapy (IMRT) (47%).

Kaplan-Meier analysis of survival and assessment of prognostic factors with the Cox proportional hazards model

OS and DFS were calculated by KM analysis, with the index date being the end of RT; 1-year, 2-year, and 5-year estimates of each of these two endpoints were reported. The Cox proportional hazards model was then used to determine the prognostic significance, if any, of the variables listed in Table 1. All of the variables were analyzed as categorical except for age, radiation dose, and gross tumor volume, which were continuous. Notably, performance status was treated as a categorical variable because a discrete number of classifications were used (70, 80, 90, or 100). Backward selection was used to select variables in univariate analysis for inclusion in multivariate analysis.

Conditional survival analysis

CS calculates the changing risk of cancer death over time, and provides estimates of ongoing survival given the precondition of having already survived to a certain point after the index date. The index date for CS was the same as that for KM analysis, i.e., the end of RT. Specifically, CS [(y/x) on OS|OS] is the probability of surviving an additional y years for a patient who has already survived x years. The measure can be obtained by dividing the cumulative survival at x+y years by the cumulative survival at x years (2). For example, to compute the 5-year conditional OS for survival of patients who have survived 1 year, the 6-year OS rate is divided by the 1-year OS. Using the technique of Zamboni et al. (4), we defined three specific endpoints: (1) OS|OS, the probability of OS for a patient who has survived for x years; (2) OS|DFS, or the probability of OS for a patient who has survived *without disease* for x years; and (3) DFS|DFS, the probability of DFS for a patient who has survived *without disease* for x years.

We first calculated 5-year rates of OS and DFS conditioned on DFS for 6-month intervals of x, beginning at the index date. We then estimated the probability of 1-year OS|OS, OS|DFS, and DFS|DFS at 6-month intervals of x, with the same index date. Next, we used the parameter OS|DFS to identify variables that were associated with survival based on achieving DFS at 1, 2, and 3 years, using both univariate and multivariate analyses. Again, backward selection was used to select variables for inclusion in multivariate analysis. Finally, we calculated OS|DFS and DFS|DFS stratified by factors that were significantly associated with surviving an additional year in multivariate analysis. Confidence intervals (CIs) were calculated by using the modified Greenwood formula.

Results

Kaplan-Meier estimates of OS and DFS and factors predicting survival

The median follow-up time in this study was 17.1 months, and 78.5% of patients (n=511) were censored in the analysis. By the KM method, the 1-year, 2-year, and 3-year DFS rates were 49.8%, 30.4%, and 25.6%, and the corresponding OS rates were 64.1%, 41.1%, and 29.4% (Suppl. Fig. 1). According to the Cox proportional hazards model, age, gross tumor

volume, N status (N3 vs. N0/N1), and the absence of concurrent chemoradiation were associated with worse OS and DFS on multivariate analysis (Table 2). Finally, we examined various chemotherapeutic regimens on DFS and OS (platinum-etoposide vs. platinum-taxol vs. other), and found that all regimens were either statistically significant or trending towards significance with regard to both OS and DFS (Table 2).

Conditional survival analysis

CS estimates of 5-year total survival at 6-month intervals after RT with the parameters OS|OS, OS|DFS, and DFS|DFS are shown in Figure 2A–C. We also estimated the probability of an *additional* 1 year of OS and DFS given survival at 6-month intervals for the same three analysis parameters (OS|OS, OS|DFS, and DFS|DFS) (Fig. 2D–F).

We then assessed factors predicting OS conditioned on DFS (OS|DFS) and DFS conditioned on DFS (DFS|DFS) at 1- and 2-year landmark dates, with both univariate and multivariate analyses. Although multivariate analysis showed that concurrent chemoradiation predicted OS conditioned on DFS (2-year landmark HR=0.33, 95% CI 0.12–0.90, $p=0.03$), several factors were associated with DFS conditioned on DFS, including a history of smoking (1-year landmark HR=0.49, 95% CI 0.28–0.88, $P=0.02$), tumor histology (1-year landmark non-squamous cell carcinoma HR=1.77, 95% CI 1.10–2.85, $P=0.02$), and N status (1-year landmark HR for N3 vs. N0/N1 disease HR=2.71, 95% CI=1.11–6.61, $P=0.03$). Both smoking history and histology were also associated with 2-year landmark DFS|DFS. Interestingly, when examining individual chemotherapeutic regimens, platinum-etoposide improved OS at both 1-year and 2-year DFS, while platinum-taxol regimens had the most substantial benefit using a 2-year landmark. The “other” category of chemotherapy regimens did not affect survival significantly using either a 1-year or 2-year landmark time (Table 3). Figure 3 illustrates stratified CS curves for three factors found to be associated with survival outcomes on multivariate analysis: concurrent chemoradiation (Fig. 3A), tumor histology (squamous vs. non-squamous; Fig. 3B), and N status (Fig. 3C). Notably, year of treatment (1998–2003 vs. 2004–2010) was not significantly associated with any outcome on CS analysis ($p>0.05$ for all analyses).

From this depiction, survival estimates for 1 additional year based on the time of OS or DFS can be obtained. Although the shapes of these survival curves are similar overall, clear differences are apparent at various time points. For instance, for a patient with stage N0/N1 disease, the probability of 1 additional year of DFS at 12 months is approximately 80%, whereas for a patient with N3 disease it is 50%. These survival probabilities then converge by 24 months, such that at this time the CS probabilities are both 85%. This change in relative survival reflects the risk of disease failure with time associated with specific patient, disease, and treatment characteristics.

Discussion

The purpose of this study was to report OS and DFS outcomes for a large cohort of patients with stage III NSCLC treated with definitive radiotherapy, with outcomes as calculated both by the fixed reference point of diagnosis with KM analysis and by a dynamic timepoint characteristic with the CS method. Our findings from these two survival analyses

complemented each other, and were as follows. First, DFS and OS rates with the index date being the end of treatment, determined with KM analysis, were both approximately 20% at 5 years, but in patients who were free of disease for 2 years, the probability of long-term (5-year) DFS and OS were both 75% or higher. This trend was indicative of a sharp increase in the likelihood of long-term survival if patients were disease-free at 6 months after treatment. Second, the probability of being free of disease or surviving an additional year did not substantially change (and even slightly decreased) during the first 6 months after RT, but after 30 months this probability approached 100%. Finally, prognostic factors varied slightly depending on the index date and method used, with gross tumor volume being associated with survival outcomes only in KM analysis, and tumor histology, smoking status, and N status being correlated with DFS when survival time was measured at 1 year and 2 years after RT. This discrepancy underscores the fluidity of risk factors over time and emphasizes that prognostic factors may change depending on the disease-free interval.

The value of CS analysis is that by using a different index date that is dependent on being disease-free, patients and physicians can quickly reference survival estimates for individual patients at follow-up visits. In addition, with regard to identifying predictive factors, an inherent presumption in the Cox model is that the risk *ratio* over time is constant, but the *absolute risk* may vary. Variations on the Cox model, such as time-varying effects on covariates, can be used to provide these estimates, but they can be more difficult to interpret than CS. Therefore, in the current analysis we hoped to provide a clear distinction between survival and clinically relevant covariates directly after treatment versus at various time points through the initial follow-up period in a large cohort of patients. As hypothesized, we found that the disease-free interval was an important factor influencing these estimates.

The variety of studies used to assess CS provides a basis for comparison in other malignancies. For example, the conditional probability of surviving an additional year with glioblastoma decreases substantially over the first year, and then sharply increases over the next 2 years (5). For colon cancer, 5-year CS estimates change very little in the first 5 years after diagnosis, varying from 75% to 90% (4). In head and neck cancer, CS estimates of an additional year of survival increase from 60% to 80% in the first 24 months and reach a plateau after that time (11). These varying relative prognoses reflect differences in the “risk windows” for specific malignancies; in other words, the risk is more constant over time for head-and-neck and colon cancer, as compared with high rates of failure in the first 1–2 years after treatment for glioblastoma and lung cancer, followed by sharp declines and improved prognosis.

Recent reports of CS in lung cancer have been somewhat limited, with most studies grouping patients with different disease stages or using relatively nonspecific staging systems such as that defined by the Surveillance, Epidemiology, and End Results (SEER) database. For instance, investigators at Brigham Young University used CS to study patients treated 20–30 years ago and found that tumor histology, SEER stage, and age affected outcomes, although 5-year CS estimates were lower than those observed in the current study (ranging from approximately 10% to 60% regardless of survival up to that point) (7). This difference potentially reflects improvements in treatment options over the past several decades, particularly the increased probability of being a long-term survivor after a disease-

free interval of approximately 2 years. In another study using the SEER database, the investigators found that 5-year CS rates varied by ethnicity, with African Americans having the lowest 5-year CS rates (9). In a study of patients from Denmark that examined CS for four major histologic subtypes of lung cancer, survival outcomes were similar for disease subtypes within NSCLC (versus SCLC). Moreover, although CS differed greatly by extent of disease (localized vs. regional) in the first year, it did converge with time and became approximately equal at 5 years (8).

Our analysis differs from prior studies using population-based data in our use of a stage- and treatment-specific patient population in which most patients received relatively “standard” management (concurrent chemotherapy with high-dose radiation). In addition, we could confirm some information that is not available in sources such as the SEER database, such as tumor size, performance status, and radiation dose. Focusing our investigation in this manner allows us to better apply these results to an individual patient who fits the criteria of this study and who will receive treatment according to national guidelines. This uniformity in treatment approach may explain why our CS estimates are higher than those reported in previous studies.

The predictors of survival identified in this study, such as age, tumor histology and size, and nodal status, are similar to those reported previously (12–15). As alluded to above, because the prognostic factors differed somewhat after treatment vs. at 1–2 years after the completion of RT, we presented both sets of results to provide a greater breadth of information as to what factors are most important in DFS and OS, both directly after diagnosis (Cox model) as well as during the first 2 years of follow-up. Not surprisingly, these different index dates also had some similarities, but the findings can be used collectively to ascertain outcomes over time. For instance, at 1 year after treatment, a patient who received concurrent chemoradiation is more likely to be a long-term survivor of stage III lung cancer compared with patients who did not receive concurrent chemotherapy, both at diagnosis and even after 1 year of DFS. In contrast, a patient with N3 disease has reduced OS at diagnosis, but after a 1-year disease-free interval, the OS rates approach those of patients with N0–N1 disease. And when categorizing chemotherapy regimens, we found that there was consistent association with both DFS and OS when using Cox analysis. However, when using landmark analysis, only platinum-etoposide regimens were correlated with survival consistently (at 1 and 2 years), while for platinum-taxol regimens the effect for OS was substantially stronger at a 2-year DFS compared to no concurrent chemotherapy. This difference highlights the utility of examining survival rates over time to better inform patients who are at varying follow-up periods.

Other than the constraints of any retrospective study, interpretation of our findings is subject to several limitations. First, the dataset, although large, was from a single tertiary cancer center, and thus ideally these results would be validated with more patients and from multiple centers. Second, contrary to what was observed in the Cox model, a discrepancy was found between predictors of DFS and OS in multivariate analysis of CS. The reason for this difference is likely that for patients who are free of disease for 1–2 years, OS may have been influenced by confounding variables not assessed in this study, such as non-malignant comorbid conditions or treatment toxicity. Finally, although these results are useful for

providing prognostic information and counseling patients, the study was not designed to change treatment recommendations. Rather, our purpose here was to report survival outcomes based on two different statistical methods for a relatively large number of patients who underwent standard treatment approaches. That is, the novelty of this report is not to change treatment paradigms, but rather to compare and contrast survival outcomes with CS in a manner that has not been published for patients with locally advanced NSCLC, and thus to add to the current literature regarding the dynamic nature of survival for patients with this malignancy.

In conclusion, we estimated DFS and OS in a group of patients with stage III NSCLC treated with definitive (chemo)radiation over a 14-year period in the modern era by using two different methods: standard KM/Cox survival analysis and CS. We found that the CS approach provided both complementary and novel results compared with KM/Cox analysis and with prior CS studies reported in the literature. Indeed, after a DFS interval of 2–3 years, the probability of long-term survival as well as an additional year of DFS approached 90%–100%. We further found that factors predicting improved DFS after a disease-free interval were not necessarily concordant with those found in KM/Cox analysis, nor did they typically predict OS. Reasons for these discrepancies include factors that are important primarily during the first 1–2 years after RT, as well as the increasing influence of other variables with time. Given the relevant clinical information that CS analysis can provide, we believe that there is value to validating these results and reporting additional studies that incorporate this method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. CONSORT diagram demonstrating patient selection, beginning with 765 patients in our institutional database that received definitive radiation therapy.

Fig. 2.

Conditional survival estimates depicting the probability of survival at 5 years at various time points. (A) Probability of 5-year overall survival (OS) given survival from 0–54 months at 6-month intervals (OS|OS). (B) Probability of 5-year OS given disease-free survival (DFS) from 0–54 months at 6-month intervals (OS|DFS). (C) Probability of 5-year DFS given DFS from 0–54 months at 6-month intervals (DFS|DFS). (D) Probability of 1 additional year of OS given OS from 0–54 months at 6-month intervals (OS|OS). (E) Probability of 1 additional year of OS given DFS from 0–54 months at 6-month intervals (OS|DFS). (F) Probability of 1 additional year of DFS given DFS from 0–54 months at 6-month intervals (DFS|DFS).

Fig. 3. Stratified conditional survival curves with 95% confidence intervals. (A) Probability of 1 additional year of OS based on DFS time from 0–60 months stratified by receipt of concurrent chemotherapy. (B) Probability of 1 additional year of DFS based on DFS time from 0–60 months stratified by squamous vs. non-squamous tumor histology. (C) Probability of 1 additional year of DFS based on DFS time from 0–60 months stratified by N status (N0/N1 vs. N2 vs. N3).

Table 1

Clinical and treatment characteristics of 651 patients with stage III non-small cell lung cancer

Characteristic	Value or No. of Patients (%)
Karnofsky performance status score	
<80	119 (18.3)
80	532 (81.7)
Age, years	
Median (range)	71 (37–94)
Race	
White	547 (84.0)
Other	104 (16.0)
Sex	
Male	364 (55.9)
Female	287 (44.1)
Current smoking	
No	492 (75.6)
Yes	151 (23.2)
Unknown	8 (1.2)
Ever smoking	
No	45 (6.9)
Yes	602 (92.5)
Unknown	4 (0.6)
Tumor histology	
Squamous	231 (35.5)
Non-squamous	420 (64.5)
Gross tumor volume, cm ³	
Median(range)	132.70(3.6–1256.0)
Clinical disease stage	
IIIA	308 (47.3)
IIIB	343 (52.7)
N status	
N0/N1	67 (10.3)
N2	404 (62.1)
N3	180 (27.6)
Concurrent chemoradiation	
No	88 (13.5)
Yes	563 (86.5)
Radiation dose, Gy	
Median (range)	63 (60–76)
Year of Treatment	
1998–2003	261 (40.0)
2004–2010	390 (60.0)

Abbreviations: 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

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Multivariate analysis of predictors of overall survival and disease-free survival in a Cox proportional hazards model

Table 2

Variables	Overall Survival			Disease-Free Survival		
	HR	95% CI	P value	HR	95% CI	P value
Age (continuous)	1.01	1.00–1.02	<0.01	0.99	0.98–1.00	0.12
Gross tumor volume (continuous)	1.18	1.12–1.24	<0.01	1.17	1.10–1.23	<0.01
N status						
N0–I	ref	—	—			
N2	1.25	0.92–1.70	0.16	1.37	0.96–1.96	0.09
N3	1.61	1.15–2.26	<0.01	1.83	1.24–2.70	<0.01
Concurrent chemoradiation						
None	ref	—	—			
Platinum-Etoposide	0.60	0.43–0.83	<0.01	0.69	0.46–1.03	0.07
Platinum-Taxol	0.57	0.44–0.74	<0.01	0.65	0.47–0.90	0.01
Other	0.62	0.44–0.89	0.01	0.64	0.42–0.97	0.04

Table 3

Multivariate analysis of prognosis of OS | DFS and DFS | DFS at 1-year and 2-year landmarks

Variable	Multivariate analysis at 1-year landmark					Multivariate analysis at 2-year landmark				
	OS DFS	HR	95% CI	P	DFS DFS	OS DFS	HR	95% CI	P	DFS DFS
Age, years (continuous)	1.04	1.02–1.07	<0.01	1.03	1.00–1.05	0.03	1.05	1.01–1.10	0.01	
Ever-smoking										
No				Ref	—	—			Ref	—
Yes				0.49	0.28–0.88	0.02			0.35	0.12–1.02
Histology										
Squamous	Ref	—	—	Ref	—	—	Ref	—	Ref	—
Non-squamous				1.77	1.10–2.85	0.02			3.38	1.17–9.77
N status										
N0–1	Ref	—	—	Ref	—	—	Ref	—	—	—
N2				1.58	0.68–3.66	0.29				
N3				2.71	1.11–6.61	0.03				
Concurrent chemoradiation										
None	Ref	—	—	Ref	—	—	Ref	—	—	—
Platinum-Etoposide	0.39	0.19–0.83	0.01				0.27	0.80–0.89	0.03	
Platinum-Taxol	0.62	0.34–1.12	0.11				0.30	0.11–0.86	0.02	
Other	0.67	0.31–1.47	0.32				0.71	0.21–2.35	0.57	

Abbreviations: OS | DFS, probability of surviving an additional *y* years for patients with disease-free survival *x* years; DFS | DFS, probability of surviving disease-free an additional *y* years for patients who have been alive and disease-free for *x* years; HR, hazard ratio; CI, confidence interval.