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The Impact of Extended Delayed Surgery for Indolent Lung Cancer or Part-Solid Ground Glass Nodules

Nicholas R. Mayne, BSE, Holly Elser, PhD, Belle K. Lin, BS, Vignesh Raman, MD, MHS, Douglas Liou, MD, Xiao Li, PhD, Thomas A. D'Amico, MD, and Chi-Fu Jeffrey Yang, MD

Department of Surgery, Duke University, Durham, North Carolina; Stanford School of Medicine, Stanford, California; Division of Epidemiology and Biostatistics, University of California Berkeley School of Public Health, Berkeley, California; University of Arizona College of Medicine, Phoenix, Arizona; Department of Cardiothoracic Surgery, Stanford University, Stanford, California; Stanford Health Care ValleyCare, Stanford, California; Case Western University, Cleveland, Ohio; and Department of Surgery, Division of Thoracic Surgery, Massachusetts General Hospital, Boston, Massachusetts

ABSTRACT

BACKGROUND During the COVID-19 pandemic, patients with lung cancer may experience treatment delays. The objective of this study was to evaluate the impact of extended treatment delays on survival among patients with stage I typical bronchopulmonary carcinoid (BC), lepidic predominant adenocarcinoma (LPA) or invasive adenocarcinoma with a lepidic component (ADL).

METHODS Using National Cancer Database data (2004-2015), multivariable Cox regression analysis with penalized smoothing splines was performed to examine the association between treatment delay and all-cause mortality for stage I BC, LPA, and ADL. Propensity score–matched analyses compared the overall survival of patients who received "early" vs "delayed" surgery (ie, 0-30 vs 90-120 days after diagnosis) across the different histologic subtypes.

RESULTS During the study period, patients with stage I BC (n = 4947), LPA (n = 5340), and ADL (n = 6816) underwent surgery. Cox regression analysis of these cohorts showed a gradual steady increase in the hazard ratio the longer treatment is delayed. However, in propensity score–matched analyses that created cohorts of patients who underwent early and delayed surgery that were well-balanced in patient characteristics, no significant differences in 5-year survival were found between early and delayed surgery for stage I BC (87% [95% CI:77%-93%] vs 89% [95% CI: 80%-94%]), stage I LPA (73% [95% CI: 64%-80%] vs 77% [95% CI: 68%-83%]), and stage I ADL (71% [95% CI: 64%-76%] vs 69% [95% CI: 60%-76%]).

CONCLUSIONS During the COVID-19 pandemic, for early-stage indolent lung tumors and part-solid ground glass lung nodules, a delay of surgery by 3-4 months after diagnosis can be considered.

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During the COVID-19 pandemic, to preserve limited hospital resources and protect patients from potential exposure, national guidelines recommend delayed surgical management for lung tumors with indolent histology or for part-solid ground glass nodules, particularly in areas with severely high rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1-4] However, the implications of extended delays in the surgical management for patients with these types of lung cancers are unclear, and there have been no prospective or retrospective studies to date to support this recommendation.

The objective of this study was to use data from the National Cancer Database (NCDB) to evaluate overall survival in patients with stage I typical

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Address correspondence to Dr Yang, 55 Fruit St, Boston, Massachusetts 02114; email: cjyang@post.harvard.edu.

bronchopulmonary carcinoid (BC), lepidic predominant adenocarcinoma (LPA), or predominantly invasive adenocarcinoma with a lepidic component (ADL) who underwent surgery within 0-30 days after diagnosis vs patients who underwent surgery 90-120 days after diagnosis. We aimed to provide clinicians with quantifiable evidence that can be used to inform the treatment decision process for patients with indolent lung tumors or part-solid ground glass nodules during this COVID-19 pandemic or during subsequent events that severely strain health systems.

PATIENTS AND METHODS

DATA SOURCE: NCDB. The NCDB is a clinical oncology database and a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data collected from the NCDB are estimated to include upwards of 80% of newly diagnosed lung cancer cases nationwide in the United States.[5] Staging was reclassified using best available data according to American Joint Committee on Cancer, 8th edition, criteria.[6]

STUDY POPULATION. All patients with histologically confirmed clinical stage I BC, LPA, and ADL identified via International Classification of Diseases for Oncology, 3rd edition, histology and topography codes from 2004-2015 who were treated with surgical lung resection (including wedge resection, segmentectomy, lobectomy, bronchial sleeve resection, or pneumonectomy) were included. The specific histology codes used were 8240/3 for BC; 8250/3 for LPA; and 8254/3 and 8255/3 for ADL. The ADL category likely includes different subtypes of adenocarcinoma along with a lepidic component, but details of these subtypes are not delineated in the NCDB.

BC was chosen for analysis because of its known indolent nature and better prognosis than other non-small cell lung cancers.[7] LPA and ADL (formerly considered "bronchioloalveolar carcinoma," but now considered distinct histologic subtypes[8]) were chosen for analysis because they are also associated with better prognosis[8] and are known to have part-solid and part-ground glass components seen on computed tomography (CT).[9] Of the subtypes formerly classified as bronchioloalveolar carcinoma that also have ground glass components on CT, we excluded from the analysis adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive mucinous adenocarcinoma because, in the NCDB, too few patients with these subtypes received extended delayed surgery to perform any meaningful comparisons. We also excluded atypical adenomatous hyperplasia because the NCDB does not contain data on this type.

Follow-up is based on reports from physician follow-up, program inpatient or outpatient services, and death certificates and has been detailed previously.[10] Our analysis was restricted to patients with no history of prior malignancy.

DATE OF DIAGNOSIS. Diagnosis is defined in the NCDB using Surveillance, Epidemiology, and End Results registry guidelines (NAACCR Item #390), which state that date of diagnosis is the "date of initial diagnosis [identified] by a recognized medical practitioner for the tumor being reported whether clinically or microscopically confirmed." The NCDB further clarifies that "the first date of diagnosis whether clinically or histologically confirmed," should be used and that "if the physician states that in retrospect the patient had cancer at an earlier date, then use the earlier date as the date of diagnosis." For example, if the nodule was biopsied on April 1, 2021, but on CT scan was seen on March 1, then March 1 was the date of diagnosis.

DAYS FROM DIAGNOSIS TO TREATMENT. The primary exposure of interest was days elapsed from diagnosis of lung cancer to surgery. We created 2 exposure metrics for measuring delay from diagnosis to surgery. First, we created a continuous measure of days from diagnosis to surgery. Second, we categorized surgery as "early" (0-30 days between time of diagnosis and time of surgery)[11-13] or "delayed" (90-120 days between diagnosis and surgery)[1,2,4] based on guidelines and observations noted from previous literature.

ALL-CAUSE MORTALITY. The primary outcome of interest was overall survival. We considered all-cause mortality in Cox proportional hazards regression analysis and cumulative survival. In all analyses, survival was measured from the date of surgery to the date of death or last follow up.

COVARIATES. The covariates used in the modeling, as described below, are the following: age, sex, race, Charlson comorbidity score, tumor size, T-status (when indicated), tumor location, facility type, distance from the hospital, hospital volume, insurance type, education, income, type of surgery, and year of diagnosis. All patient and disease characteristics used in the present study are directly defined by or were created using variables described in the NCDB 2016 PUF Data Dictionary.[10]

STATISTICAL ANALYSIS. Pearson's χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables were used to determine differences in patient characteristics and unadjusted outcomes between the early and delayed surgery groups.

Cox Proportional Hazards Regression With Penalized Smoothing Splines. We used Cox proportional hazards regression to model the instantaneous mortality rate as a

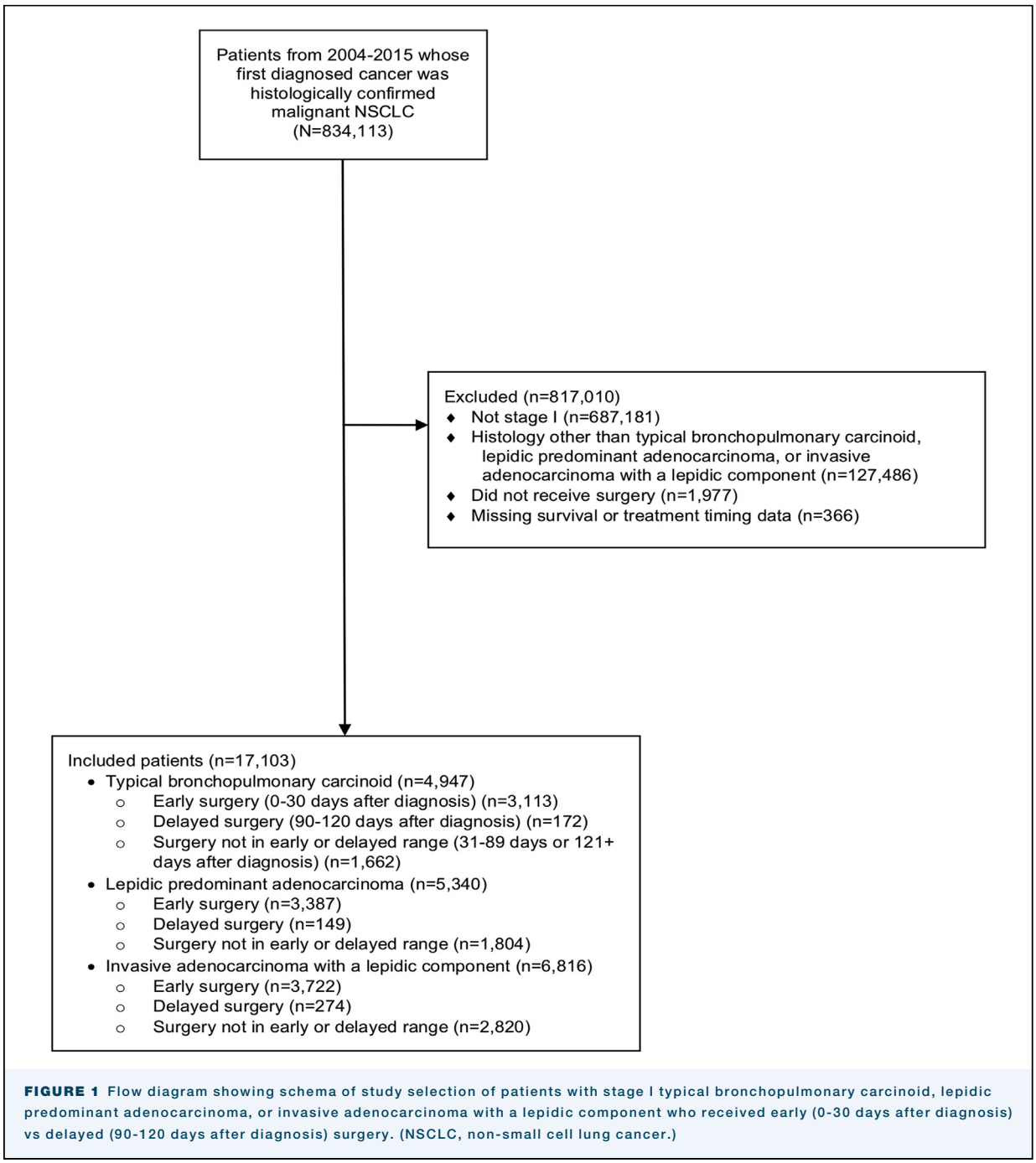

FIGURE 1 Flow diagram showing schema of study selection of patients with stage I typical bronchopulmonary carcinoid, lepidic predominant adenocarcinoma, or invasive adenocarcinoma with a lepidic component who received early (0-30 days after diagnosis) vs delayed (90-120 days after diagnosis) surgery. (NSCLC, non-small cell lung cancer.)

function of time from diagnosis to surgery. We controlled for a priori specified covariates listed above, as these could plausibly confound the association between time from diagnosis to surgery and mortality, and included the covariates listed above.

We modeled time from diagnosis to surgery with penalized smoothing splines with 3 degrees of freedom. Penalized smoothing splines have the advantage of flexibility and can capture potential nonlinearities in the dose-response between time from diagnosis to surgery and mortality.[14,15] Within each subgroup of interest, we used fitted models to plot the hazard ratio as a function of days from diagnosis to surgery with surgery on the day of diagnosis (ie, zero days between diagnosis and surgery) as the referent. After analyzing the cohorts of patients with stage I BC, LPA, and ADL, we repeated the above analysis by substage (IA and IB).

TABLE 1 Baseline Characteristics for Patients with Stage I Indolent Lung Cancer or Part-Solid Ground Glass Nodules Who Were Treated With Surgery

Patient Characteristic	Typical Bronchopulmonary Carcinoid (n = 4947)	Lepidic Predominant Adenocarcinoma (n = 5340)	Invasive Adenocarcinoma With a Lepidic Component (n = 6816)
Age, years	62 (52, 69)	69 (61, 75)	68 (61, 75)
Female Sex	3640 (74)	3623 (68)	4236 (62)
Race			
White	4539 (92)	4700 (88)	5839 (86)
Black	275 (6)	362 (7)	480 (7)
Other	89 (2)	237 (4)	411 (6)
Unknown	44 (1)	41 (1)	86 (1)
CDCC			
0	3237 (65)	3005 (56)	3,34 (53)
1	1293 (26)	1674 (31)	2240 (33)
2	324 (7)	494 (9)	704 (10)
3+	93 (2)	167 (3)	238 (3)
Clinical T-status			
T1a	522 (11)	381 (7)	309 (5)
T1b	2211 (45)	2122 (40)	2593 (38)
T1c	1391 (28)	1648 (31)	2175 (32)
T2a	823 (17)	1189 (22)	1739 (26)
Tumor size, cm	1.7 (1.3, 2.4)	2.0 (1.4, 2.5)	2.0 (1.5, 2.6)
Tumor location			
Main bronchus	43 (1)	<10	<10
Right upper lobe	697 (14)	2002 (37)	2463 (36)
Right middle lobe	1065 (22)	304 (6)	381 (6)
Right lower lobe	1088 (22)	992 (19)	1278 (19)
Left upper lobe	934 (19)	1306 (24)	1706 (25)
Left lower lobe	1120 (23)	735 (14)	987 (14)
Insurance status			
Uninsured	95 (2)	81 (2)	82 (1)
Private insurance/ managed care	2558 (52)	1730 (32)	2235 (33)
Medicaid	235 (5)	147 (3)	293 (4)
Medicare	1940 (39)	3270 (61)	4110 (60)
Other government insurance	51 (1)	38 (1)	45 (1)
Unknown	68 (1)	74 (1)	51 (1)
Facility type			
Community cancer program	184 (4)	334 (6)	206 (3)
Comprehensive community clinic	1740 (35)	2405 (45)	1471 (22)
Academic/research program	1920 (39)	1867 (35)	4347 (64)
Integrated network cancer center	699 (14)	717 (13)	766 (11)
Unknown	404 (8)	17 (0)	26 (0)
Hospital volume quartile			
First quartile (lowest volume)	120 (2)	128 (2)	124 (2)
Second quartile	473 (10)	696 (13)	403 (6)
Third quartile	995 (20)	1340 (25)	957 (14)
Fourth quartile (highest volume)	3359 (68)	3176 (59)	5332 (78)
Distance from hospital, miles	12.2 (5.5, 29.5)	9.2 (4.2, 23.3)	11.7 (4.9, 27.7)

(*Continued*)

Propensity Score–Matched Analysis. Next, we examined differences in cumulative survival in patients who received "early" (0-30 days after diagnosis) vs "delayed" (90-120 days after diagnosis) surgery for stage I BC, LPA, and ADL in the NCDB. We used propensity scores to match patients in the "early" and "delayed" surgery groups, using methodology previously described.[16] In brief, the propensity score reflects the probability of

TABLE 1 Continued

Patient Characteristic	Typical Bronchopulmonary Carcinoid (n = 4947)	Lepidic Predominant Adenocarcinoma (n = 5340)	Invasive Adenocarcinoma With a Lepidic Component (n = 6816)
Income[a]			
First quartile	703 (14)	809 (15)	877 (13)
Second quartile	1008 (20)	1035 (19)	1059 (16)
Third quartile	1150 (23)	1239 (23)	1394 (20)
Fourth quartile	2017 (41)	2148 (40)	3414 (50)
Unknown	69 (1)	109 (2)	72 (1)
Education[b]			
First quartile	836 (17)	916 (17)	1121 (16)
Second quartile	1146 (23)	1247 (23)	1491 (22)
Third quartile	1539 (31)	1562 (29)	1949 (29)
Fourth quartile	1365 (28)	1487 (28)	2190 (32)
Unknown	61 (1)	98 (2)	65 (1)
Surgery type			
Wedge resection	1090 (23)	1058 (20)	1121 (16)
Segmentectomy	225 (5)	195 (4)	390 (6)
Lobectomy	3488 (71)	4063 (76)	5281 (77)
Pneumonectomy	81 (2)	22 (0)	23 (0)
Sleeve lobectomy	63 (1)	<10	<10
Days from diagnosis to surgery	20 (0, 44)	20 (0, 42)	28 (0, 49)
Year of diagnosis	2013 (2011, 2014)	2009 (2007, 2011)	2012 (2010, 2014)

Values are presented as median (interquartile range) or n (%). [a]National Cancer Database codes income level as average household income of the zip code where the patient lives; [b]NCDB codes education level as the number of adults aged 25 years or older in the patient's zip code who did not graduate from high school. CDCC, Charlson comorbidity score.

early surgery conditional on clinically relevant baseline characteristic variables (as described above).

To calculate propensity scores, we applied a greedy nearest neighbor matching algorithm without replacement with a caliper of 0.01. Standardized differences were used to assess the balance of the match. We examined the cumulative survival in the matched "early" and "delayed" surgery groups using the Kaplan-Meier method and log-rank test. After analyzing the cohorts of patients with stage I BC, LPA, and ADL, we repeated the above analysis by substage (IA and IB).

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 13.0 (StataCorp LP, College Station, TX). This study was approved by the institutional review boards at Duke University, Stanford University, and Massachusetts General Hospital.

RESULTS

In this study, there were 4947 patients with stage I BC, 5,40 with LPA, and 6816 with ADL who underwent surgery (Figure 1). Of patients with stage I BC, 3113 (63%) underwent early surgery and 172 (3%) underwent extended delayed surgery. Of patients with stage I LPA, 3387 (63%) underwent early surgery and 149 (3%) underwent extended delayed surgery. Of patients with stage I ADL, 3722 (55%) underwent early surgery and 274 (4%) underwent extended delayed surgery. Patient and tumor characteristics are detailed in Table 1. The median follow-up was 45.6 months (interquartile range 23.7-72.5 months). There were 3689 total deaths in the overall cohort with 2037 deaths in the early surgery group and 137 deaths in the extended delayed surgery group.

COX PROPORTIONAL HAZARDS REGRESSION WITH PENALIZED SMOOTHING SPLINES. In our analysis using multivariable Cox proportional hazards regression with penalized smoothing splines, the hazard ratio increased gradually with greater time elapsed from diagnosis to surgery as compared with individuals treated the same day as their diagnosis for stage I BC, LPA, and ADL (Figures 2A-2C). An analysis of substages was also performed (Figures 2D-2I). The pattern observed in mortality risk with time elapsed from diagnosis to treatment within these subgroups is largely consistent with that seen in the primary analysis, although the confidence interval overlaps with hazard ratio equal to 1 for stage IB BC (Figure 2E) during delayed timepoints because of a small sample size.

PROPENSITY SCORE–MATCHED ANALYSIS. Propensity-score matching was used to create 2 groups of an equal number of patients who underwent early vs delayed surgery and were well-matched with regard to baseline characteristics for stage I BC (n = 157 per group), LPA

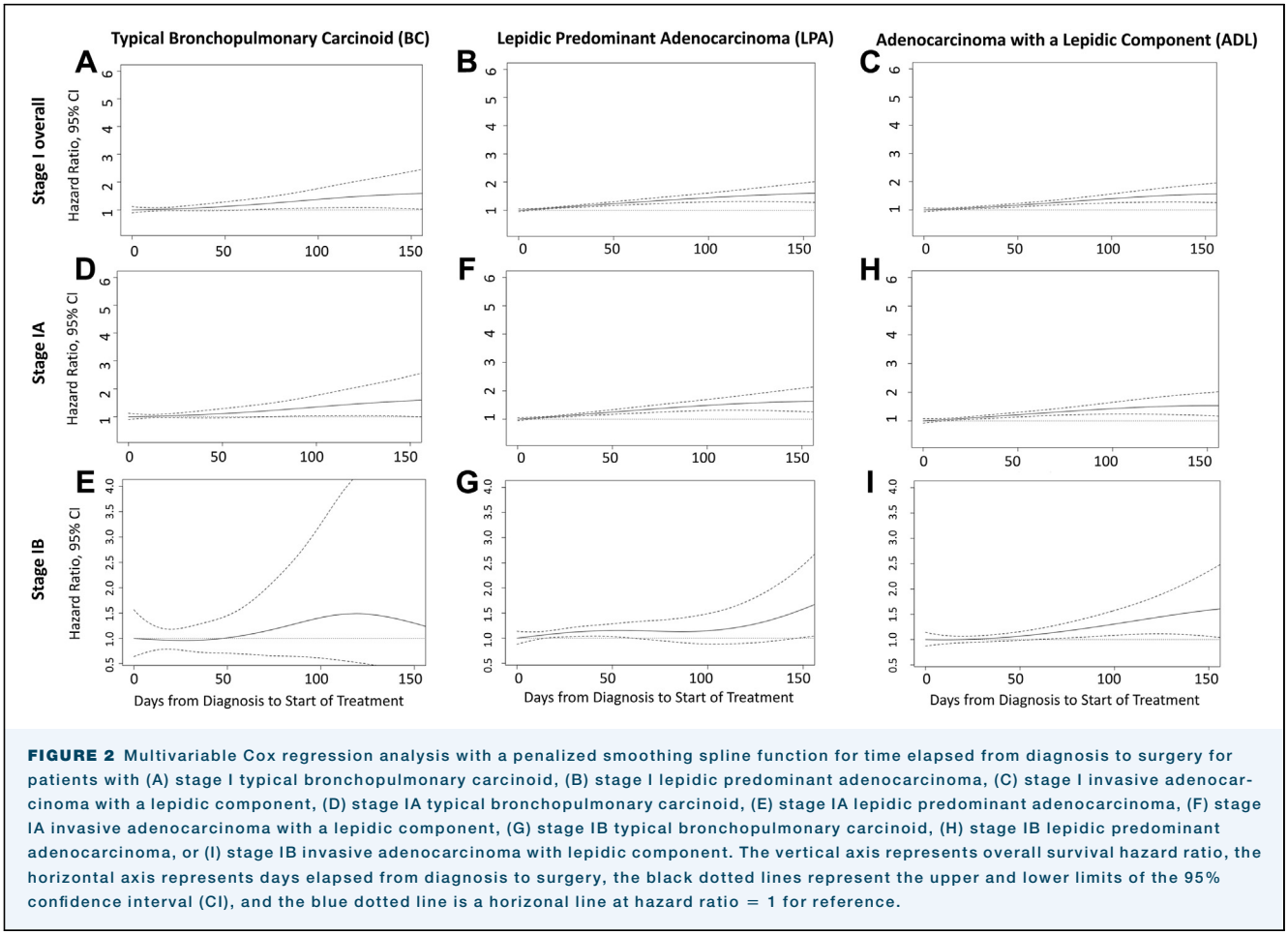

FIGURE 2 Multivariable Cox regression analysis with a penalized smoothing spline function for time elapsed from diagnosis to surgery for patients with (A) stage I typical bronchopulmonary carcinoid, (B) stage I lepidic predominant adenocarcinoma, (C) stage I invasive adenocarcinoma with a lepidic component, (D) stage IA typical bronchopulmonary carcinoid, (E) stage IA lepidic predominant adenocarcinoma, (F) stage IA invasive adenocarcinoma with a lepidic component, (G) stage IB typical bronchopulmonary carcinoid, (H) stage IB lepidic predominant adenocarcinoma, or (I) stage IB invasive adenocarcinoma with lepidic component. The vertical axis represents overall survival hazard ratio, the horizontal axis represents days elapsed from diagnosis to surgery, the black dotted lines represent the upper and lower limits of the 95% confidence interval (CI), and the blue dotted line is a horizonal line at hazard ratio = 1 for reference.

(n = 142 per group), and ADL (n = 263 per group) (Supplemental Tables S1-S3). All standardized mean differences were less than or equal to 14.3% for all comparisons. We found no significant differences between the 2 groups for stage I BC, LPA, and ADL with regard to perioperative outcomes (Supplemental Table S4). Delayed surgery was associated with similar survival compared to early surgery across all the histologic subtypes (Figure 3).

An analysis of stage I overall and its substages (IA and IB), stratified by histologic subtype, was also performed, using the same methodology as in the primary analysis. The results of stage I overall and the subgroup analysis are consistent with the results from our primary analysis and show that there were no significant differences in overall survival between early and delayed surgery (Figure 3).

COMMENT

In this study, we analyzed data from the NCDB to examine the impact of delayed surgery on the survival of patients with early-stage indolent lung tumors and part-solid ground glass nodules. We evaluated both the relationship between timing of treatment and survival, and the impact of extended delays (>3 months) for stage I BC, LPA, and ADL. Previous studies that consider the implications of the timing of treatment on survival for lung cancer have not evaluated these particular subtypes of non-small cell lung cancer.[17-22] Because BC, LPA, and ADL are associated with much better prognoses than other histologic subtypes of lung cancers,[7,8] national guidelines have recommended different management algorithms for these tumors than for other types of lung cancer during the COVID-19 pandemic. However, to date, there is no available evidence to support these guidelines. Collectively, our results suggest that delaying surgery in patients for stage I BC, LPA, and ADL may not produce any significant disadvantages in morbidity or mortality.

In the present study, the multivariable Cox regression analysis with penalized smoothing splines for each cohort demonstrated an increased mortality risk with greater time elapsed between diagnosis and treatment.

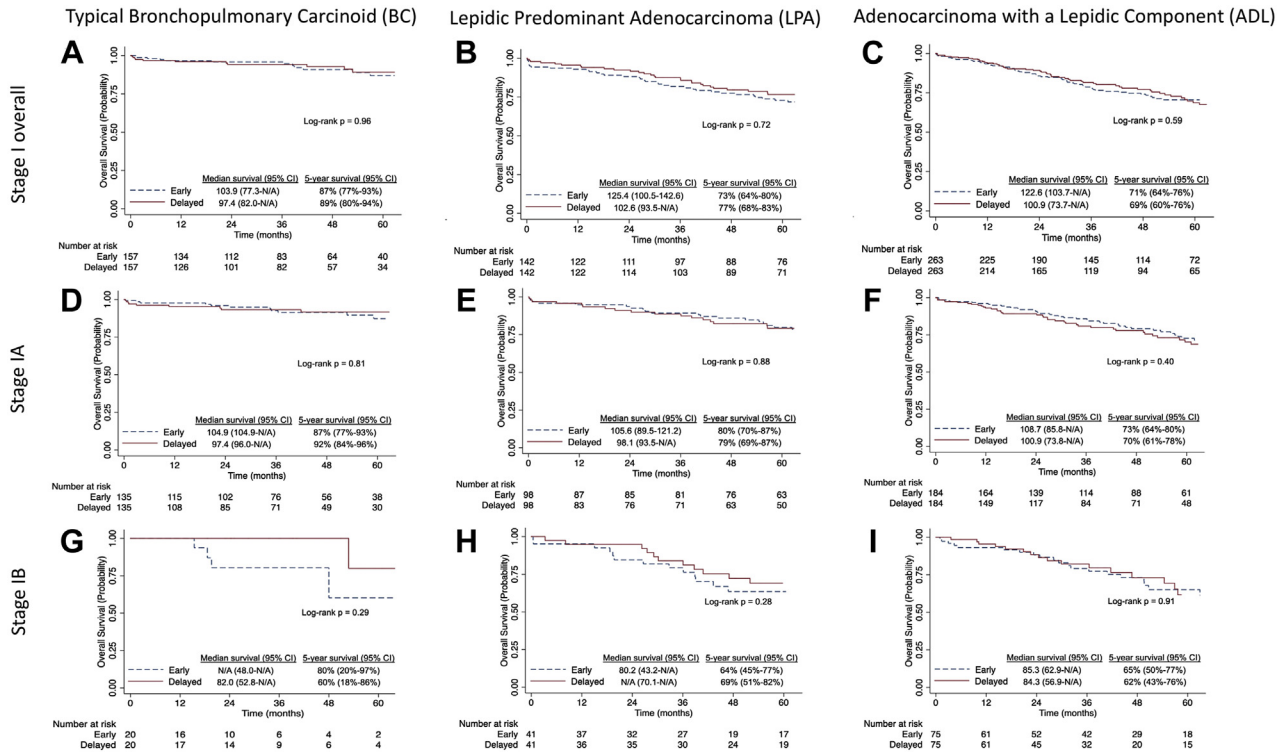

FIGURE 3 Kaplan-Meier analysis of overall survival for propensity score–matched patients who received early (0-30 days after diagnosis) vs delayed (90-120 days after diagnosis) surgery for (A) stage I typical bronchopulmonary carcinoid, (B) stage I lepidic predominant adenocarcinoma, (C) stage I invasive adenocarcinoma with a lepidic component, (D) stage IA typical bronchopulmonary carcinoid, (E) stage IA lepidic predominant adenocarcinoma, (F) stage IA invasive adenocarcinoma with a lepidic component, (G) stage IB typical bronchopulmonary carcinoid, (H) stage IB lepidic predominant adenocarcinoma, or (I) stage IB invasive adenocarcinoma with lepidic component.

However, the slopes of the dose-response curves are generally quite gradual, which suggests only a slight or modestly increased mortality risk with increasing delay to surgery. When we compared the cumulative survival in patients who received "early" treatment (0-30 days after diagnosis) to a matched sample of otherwise similar patients who received "delayed" treatment (90-120 days after diagnosis), we found little evidence of survival differences between the "early" and "delayed" treatment groups for stage I BC, LPA, and ADL.

There are several limitations to the study. First, there are other histologic subtypes that have part-solid part-ground glass components seen on CT that were not analyzed due to small sample sizes. Thus, our results are not necessarily generalizable to other types of part-solid ground glass nodules. Our results are also not generalizable to other histologic subtypes of non-small cell lung cancer. Second, because of the study's observational design, there is potential for residual confounding and selection bias. The delays experienced by patients in this study predated the COVID-19 pandemic, and therefore we do not know the reason why some patients experienced a delay to surgery whereas others received prompt treatment. There are important covariates such as pulmonary function data that are not available in the NCDB. However, in our multivariable analysis and propensity-score matching, we were able to include key covariates such as comorbidity scores. Third, details regarding the CT findings of the tumors are not available in the NCDB and thus detailed information about the size of the ground glass vs solid opacity was not available for analysis. Certainly, tumors that are mostly solid will have worse prognosis than tumors that have only a small solid component. Tumors of the ADL histology will more likely have higher percentages of solid components when compared with LPA histology (according to the IASLC Lung Cancer Staging Project).[9] Fourth, data regarding complications does not exist in the NCDB. Fifth, the NCDB does not contain data on cancer-specific and recurrence-free survival and we were unable to directly evaluate whether delay in treatment correlates to cancer progression.

In the treatment of early-stage indolent lung tumors and part-solid ground glass nodules, timely surgery is preferable to any delay. However, delays to surgery of up to 4 months may have similar implications for survival as more timely treatment for these tumors. The findings from the study can be used to inform treatment

decisions during the COVID-19 pandemic and in future settings where extended delays in surgery are either required due to catastrophic events affecting the health care system or preferred by the patient due to significant life events affecting the patient or patient's family.

The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. Vignesh Raman was supported by a National Institutes of Health T-32 grant 5T32CA093245 in surgical oncology.

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