Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Original Study

Extended Delay to Treatment for Stage III-IV Non–Small-Cell Lung Cancer and Survival: Balancing Risks During the COVID-19 Pandemic

Nicholas R. Mayne,[1] Simar S. Bajaj,[2] Joseph Powell,[3] Holly C. Elser,[4,5] Barbara S. Civiello,[6] Florian J. Fintelmann,[7] Xiao Li,[3] Chi-Fu Jeffrey Yang[2,6]

Abstract

During the coronavirus disease 2019 pandemic, patients may encounter lung cancer care delays. Using Cox regression analysis with penalized smoothing splines, propensity score-matched analysis, and least absolute shrinkage and selection operator regression models for 275,590 patients, we found that extended treatment delay from diagnosis was not associated with decreased survival compared to prompt treatment. These findings can help guide care priorities and decision-making during the pandemic.

Background: Due to the coronavirus disease 2019 (COVID-19) pandemic, patients may encounter lung cancer care delays. Here, we sought to examine the impact of extended treatment delay for stage III-IV non–small-cell lung cancer on patient survival. **Materials and Methods:** Using National Lung Screening Trial (NLST) and National Cancer Data Base (NCDB) data, Cox regression analysis with penalized smoothing splines was performed to examine the association between treatment delay and all-cause mortality for stage III-IV lung adenocarcinoma and squamous cell carcinoma. In the NCDB, propensity score-matched analysis was used to compare cumulative survival in patients who received "early" versus "delayed" treatment (ie, 0-30 vs. 90-120 days following diagnosis). **Results:** Cox regression analysis of the NLST ($n = 392$) and NCDB ($n = 275{,}198$) cohorts showed a decrease in hazard ratio the longer treatment was delayed. In propensity score-matched analysis, no significant differences in survival were found between early and delayed treatment for patients with stage IIIA, IIIB (T3-4,N2,M0), IIIC, and IV (M1B-C) adenocarcinoma and patients with IIIA, IIIB, IIIC, and IV squamous cell carcinoma (all log-rank $P > .05$). For patients with stage IIIB (T1-2,N3,M0) and stage IV (M1A) adenocarcinoma, delayed treatment was associated with improved survival (log-rank $P = .03$, $P = .02$). The findings were consistent in sensitivity analysis accounting for wait time bias. **Conclusion:** In this national analysis, for patients with stage III-IV adenocarcinoma and squamous cell carcinoma, an extended treatment delay by 3 to 4 months was not associated with significantly decreased overall survival compared to prompt treatment. These findings can be used to guide decision-making during the ongoing COVID-19 pandemic.

Clinical Lung Cancer, Vol. 23, No. 6, e362–e376
Keywords: Lung cancer, Delay, COVID-19, Outcomes

Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, hospitals postponed elective surgeries[1-4] and cancer operations[3,5] and delayed systemic cancer treatment[6,7] to preserve limited resources and decrease the risk of nosocomial transmission. Simultaneously, patients sometimes independently elected to postpone cancer treatment for fear of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[8,9] With the global spread of the Omicron variant, society has borne witness to repeated overwhelming global surges of COVID-19 cases.[10,11] Given current trajectories, experts predict that the development of even more infectious, deadly variants might ensue.[12] For patients with stage III non–small-cell lung cancer (NSCLC), particularly those from areas with severely high COVID-19 cases, many medical societies have recommended a delay or postponement in treatment.[2,6,13-16] Given that patients with lung cancer have significantly greater SARS-CoV-2 infection risk[17] and that palliative chemotherapy may further exacerbate that risk,[18] patients with stage IV NSCLC may similarly, in

FJF, XL, and CJY contributed equally to this manuscript as co-senior authors.

[1]Department of Medicine, Duke University, Durham, NC
[2]Department of Surgery, Massachusetts General Hospital, Boston, MA
[3]Case Western Reserve University School of Medicine, Cleveland, OH
[4]Stanford University School of Medicine, Stanford, CA
[5]Division of Epidemiology and Biostatistics, UC Berkeley School of Public Health, Berkeley, CA
[6]Seacoast Cancer Center at Wentworth Douglass Hospital, Dover, NH
[7]Department of Radiology, Massachusetts General Hospital, Boston, MA

Submitted: Feb 4, 2022; Revised: Apr 28, 2022; Accepted: May 1, 2022; Epub: 5 May 2022

Address for correspondence: Chi-Fu Jeffrey Yang, Division of Thoracic Surgery, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114.
E-mail contact: cjyang@mgh.harvard.edu

1525-7304/$ - see front matter
https://doi.org/10.1016/j.cllc.2022.05.001

conversation with their physician, be recommended to delay care or independently postpone cancer treatment.[8,9]

The impact of extended delays in treatment for patients with stage III and stage IV lung cancer is unclear. Although past research has evaluated timeliness of care,[19] previous studies did not assess the survival outcomes associated with extended treatment delays—potentially as long as 3 to 6 months—currently proposed by medical societies and enacted by some clinicians during the ongoing pandemic.

The objective of this study was to use data from the National Lung Screening Trial (NLST) and the U.S. National Cancer Data Base (NCDB) to characterize the impact of extended delays in treatment for stage III-IV NSCLC on survival. We aimed to provide clinicians with stage- and substage-specific data on stage III-IV lung adenocarcinoma and squamous cell carcinoma that could be used to inform treatment decision-making for patients during the COVID-19 pandemic and to prepare for future pandemic waves.

Materials and Methods

The data for this retrospective analysis are derived from the NLST and the NCDB.

Data Source: National Lung Screening Trial (NLST)

The NLST was a randomized controlled trial that compared screening for lung cancer with low-dose helical computed tomography versus screening via chest radiography for individuals at high risk of developing lung cancer.[20] The study design has been described previously.[21] The NLST enrolled 53,454 individuals between August 2002 and April 2004. Data collection ended December 31, 2009, with a median follow-up time of 6.5 years. During the study period, 1971 patients developed biopsy-confirmed lung cancer. AJCC sixth edition was used for staging in the NLST study;[22] however, we reclassified the staging in the study using best available data according to AJCC eighth edition criteria.[23]

Data Source: National Cancer Database (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 >80% of newly diagnosed lung cancer cases in the U.S.[24] Although clinical staging information is directly recorded in the NCDB using American Joint Committee on Cancer sixth and seventh edition TNM classifications for the years of study inclusion (2004-2015),[22,25] we reclassified the staging in this study using best available data according to AJCC eighth edition criteria.[23]

Study Population

All NSCLC patients in the NLST from 2004 to 2009 with adenocarcinoma or squamous cell carcinoma histology (identified via International Classification of Diseases for Oncology, third edition histology and topography codes) who had clinical stage III-IV disease and were treated with surgery, chemotherapy, radiation therapy, or concurrent chemoradiation were included. For the analysis of the NCDB, all patients with clinical stage III-IV NSCLC with adenocarcinoma or squamous cell carcinoma histology from 2004 to 2015 who were treated with surgery, chemotherapy, radiation therapy, concurrent chemoradiation, or immunotherapy were included. Adenocarcinoma and squamous cell carcinoma were chosen for this analysis because they are the most common histologic subtypes of NSCLC.[26]

The treatment regimens investigated in the NLST and NCDB cohorts were selected in accordance with national practice guidelines and varied by stage (Supplemental Table 1).[27] Concurrent chemoradiation was defined as starting chemotherapy within one month of the start of radiation therapy, as previously described.[28] Overall survival of patients who underwent early versus delayed treatment for each stage and sub-stage were assessed using methods described below.

Methods of follow-up have been previously described (ie, reports from physician follow-up, program inpatient or outpatient services, and death certificates).[29] Our analysis excluded patients with a history of prior malignancy.

Days From Diagnosis to Treatment

The primary exposure of interest in this study was days elapsed from diagnosis of lung cancer to treatment. We created two exposure metrics: a continuous measure of days from diagnosis to treatment and a categorical measure as "early" (0-30 days between time of diagnosis and time of treatment) or "delayed" (90-120 days between diagnosis and treatment). These metrics were created given the 3-month pandemic treatment deferral recommended by the Thoracic Surgery Outcomes Research Network and American College of Surgeons Commission on Cancer.[30,31]

All-cause Mortality

The primary outcome of interest was overall survival. We considered all-cause mortality in Cox proportional hazards regression analysis in cohorts from both data sources. In the NCDB, we also examined cumulative survival. Survival was measured from the start date of treatment to death or date of last follow up.

Covariates

All patient and disease characteristics in the NLST and NCDB cohorts are directly defined by or were created using variables described in the NLST Participant, Lung Cancer, and Treatment Data Dictionaries[32] or the NCDB 2016 PUF Data Dictionary,[29] respectively.

Statistical Analysis

For our primary analysis, we examined differences in cumulative survival in patients who received "early" versus "delayed" treatment in the NCDB. We used propensity scores to match patients into "early" and "delayed" treatment groups.[33] Briefly, propensity scores reflect the probability of early treatment, conditional on clinically relevant patient baseline characteristic variables (including age, sex, race, CDCC score, tumor size, tumor location, tumor grade, facility type, distance from the hospital, hospital volume, insurance type, education, income, and year of diagnosis). Where applicable, we additionally matched for clinical T- and N-status, type of surgery, and treatment with induction chemotherapy ± radiation. We applied a greedy nearest neighbor matching algorithm without

replacement with a caliper of 0.01 to calculate propensity scores. Balance of the match was assessed using standardized differences. We examined cumulative survival in the matched "early" and "delayed" treatment groups using the Kaplan-Meier method and log-rank test.

Second, in each of the NLST and NCDB data cohorts, we used Cox proportional hazards regression to model the instantaneous mortality rate as a function of time from diagnosis to treatment within subgroups defined by stage and corresponding guideline-concordant treatment. We controlled for *a priori* specified covariates that could conceivably confound the association between time from diagnosis to treatment and mortality. For the NLST cohort, these variables included the following: sex, age, race, smoking history (current vs. former), pack year smoking history, clinical T-, N-, and M-status (when applicable), tumor size, histology (squamous cell carcinoma, adenocarcinoma), type of surgery (when applicable), history of obstructive lung disease, history of restrictive lung disease, history of heart disease, and history of stroke. For the NCDB cohort, these variables were the same as described in propensity score matching.

We modeled time from diagnosis to treatment with penalized smoothing splines with three degrees of freedom. Penalized smoothing splines were chosen because they have the advantage of flexibility and can capture potential nonlinearities in the dose-response between time from diagnosis to treatment and mortality rates.[34,35] Within each subgroup of interest, we used fitted models to plot the hazard ratio as a function of days from diagnosis to treatment with 0 days from diagnosis to treatment as the referent. As a secondary analysis, we repeated our Cox regression analysis, as described above, in finer subgroups defined by substage, histologic subtype, and guideline-concordant treatment using the NCDB cohort. We performed the subgroup analysis in the NCDB cohort because, for analysis stratified by substage and histologic subtype, only the NCDB could provide large enough cohorts for meaningful comparisons.

To address problems of variable selection and enhance results' prediction accuracy, we employed least absolute shrinkage and selection operator (LASSO).[36] In particular, we created binary logistic LASSO regression models to identify key features from our survival analysis that determine the short-term (less than 25th percentile) or long-term (greater than 75th percentile) survival of patients with stage III and stage IV disease. To control overfitting, models were cross validated through 10 × 10 × 10 nested cross-validation. The coefficients of all three models were compared to determine if selected features were specific to one subset of the cohort. Area under the receiver operating characteristics (AUROC) is reported to assess the fidelity of the model in the testing set with the *P*-value generated from DeLong test.[37]

Sensitivity Analysis

Some previous studies have shown that, paradoxically, individuals who experience long delays between diagnosis and cancer treatment may survive longer than those who are treated quickly.[38-42] This "wait time bias"[43] may reflect the possibility that patients with more aggressive tumor biology and worse disease will be treated sooner and have worse survival; that individuals who wait for an extended period to receive treatment represent a survivor population; or, most likely, some combination of these 2 explanations. To examine the influence of wait time bias in the present study, we repeated our main analysis for stage IV disease while excluding patients who had a time of diagnosis to treatment below the 10th or above the 90th percentile.

All statistical analyses were performed using R version 4.0.5 (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

The NLST study cohort consisted of 392 patients who met study inclusion criteria and who underwent treatment for clinical stage III-IV adenocarcinoma or squamous cell carcinoma (Supplemental Figure 1A). The NCDB study cohort, consisted of 275,198 patients who met study inclusion criteria and who underwent treatment for clinical stage III-IV adenocarcinoma or squamous cell carcinoma (Supplemental Figure 1B). Table 1 details baseline characteristics for patients in the NLST and NCDB cohorts.

Propensity Score-Matched Analysis of Cumulative Survival with "Early" versus "Delayed" Treatment

Our propensity score-matched analysis of the NCDB cohort compares cumulative survival in patients who received "early" treatment versus a matched sample of otherwise similar patients who received "delayed" treatment within substages of adenocarcinoma and squamous cell carcinoma. Propensity score-matching balanced all matching variables in the "early" and "delayed" groups with nearly every standardized mean differences less than 10% (pre-match data Supplemental Table 2, post-match data Supplemental Table 3, Supplemental Figure 2, and data not shown). Table 2 details a summary of 1-, 3-, and 5-year Kaplan Meier overall survival estimates, as well as median survival for each substage stratified by "early" versus "delayed" treatment.

For all substages of stage IIIA adenocarcinoma, there was no difference in overall survival between patients who underwent early versus delayed treatment via surgery (ie, lobectomy with either induction or adjuvant chemotherapy with or without radiation) or concurrent chemoradiation (Figure 1A-D). For all substages of IIIB adenocarcinoma, there was no difference in survival between early versus delayed treatment via concurrent chemoradiation (Figure 1E-F). Notably, for patients with stage IIIB (T1-2,N3,M0) adenocarcinoma, the log-rank value indicated significantly improved survival in patients who received delayed concurrent chemoradiation compared to early treatment; however, the 95% CI for all overall survival metrics overlapped for the 2 groups indicating 1-year, 3-year, 5-year, or median overall survival was not significantly different (Table 2). For patients with stage IIIC adenocarcinoma, there was no difference in overall survival between patients who underwent early versus delayed concurrent chemoradiation (Figure 1G).

For all substages of stage IIIA, IIIB, and IIIC squamous cell carcinoma, there was no difference in 5-year overall survival between patients who underwent early versus delayed treatment (Figures 1H-I and 2A-E).

Table 1 Baseline Characteristics for Patients in the National Lung Screening Trial (NLST) and National Cancer Database (NCDB) Study Cohorts.

NLST Patient Characteristic	NLST Cohort($n = 392$)	NCDB Patient Characteristic	NCDB Cohort($n = 275,198$)
Age (median, IQR),	62 (59, 67)	Age (median, IQR), y	66 (58, 73)
Height (median, IQR), inches	69 (66, 71)	Female sex, *n* (%)	121,229 (44)
Weight (median, IQR), pounds	175 (152, 197)	Race, *n* (%)	
Female sex, *n* (%)	134 (34)	White	230,307 (84)
Race, *n* (%)		Black	34,037 (12)
White	359 (92)	Other	9061 (3)
Black	15 (4)	Unknown	1793 (1)
Asian	6 (2)	CDCC score, *n* (%)	
Other	9 (2)	0	172,573 (63)
Unknown	3 (1)	1	70,836 (26)
Education		2	23,077 (8)
8th grade or less	8 (2)	3+	8712 (3)
9th-11th grade	23 (6)	Clinical T status, *n* (%)	
High school graduate or GED	129 (33)	T1a	3,073 (1)
Post high school training, excluding college	58 (15)	T1b	12,807 (5)
Associate degree/some college	83 (21)	T1c	18,561 (7)
Bachelor's degree	49 (13)	T2a	27,926 (10)
Graduate school	34 (9)	T2b	17,662 (6)
Unknown	8 (2)	T3	44,984 (16)
Cigarette smoker, *n* (%)		T4	112,052 (41)
Former	166 (42)	Unknown	38,133 (14)
Current	226 (58)	Clinical N status, *n* (%)	
Pack years (median, IQR)	62 (45, 82)	N0	49,987 (18)
Family history of lung cancer, *n* (%)	109 (28)	N1	25,342 (9)
Clinical T status, *n* (%)		N2	117,849 (43)
T1a	3 (1)	N3	48,824 (18)
T1b	43 (11)	Unknown	33,196 (12)
T1c	41 (10)	Clinical M status, *n* (%)	
T2a	53 (14)	M0	108,160 (39)
T2b	30 (8)	M1	155,476 (56)
T3	93 (24)	Unknown	11,562 (4)
T4	109 (28)	Clinical stage, *n* (%)	
Unknown	20 (5)	IIIA	53,850 (20)
Clinical N status, *n* (%)		IIIB	45,289 (16)
N0	58 (15)	IIIC	9021 (3)
N1	34 (9)	IV	167,038 (61)
N2	208 (53)	Tumor size (median, IQR), cm	4.5 (2.9, 6.5)
N3	78 (20)	Tumor location, *n* (%)	
Unknown	14 (4)	Main bronchus	13,140 (5)
Clinical M status, *n* (%)		Right upper lobe	81,846 (30)
M0	197 (50)	Right middle lobe	10,446 (4)
M1	185 (47)	Right lower lobe	37,107 (13)
Unknown	10 (3)	Left upper lobe	62,525 (23)
Clinical stage, *n* (%)		Left lower lobe	29,118 (11)
IIIA	127 (32)	Bilateral	4624 (2)
IIIB	65 (17)	Unknown	36,392 (13)
IIIC	11 (3)	Histology, *n* (%)	
IV	189 (48)	Adenocarcinoma	173,070 (63)

(*continued on next page*)

Table 1 (*continued*)

NLST Patient Characteristic	NLST Cohort($n = 392$)	NCDB Patient Characteristic	NCDB Cohort($n = 275,198$)
Tumor size (median, IQR), cm	3.8 (2.5, 5.6)	Squamous cell carcinoma	102,128 (37)
Tumor location, *n* (%)		Grade, *n* (%)	
Left lower lobe	46 (12)	Well differentiated	8844 (3)
Left upper lobe	88 (22)	Moderately differentiated	54,040 (20)
Right lower lobe	63 (16)	Poorly differentiated	88,806 (32)
Right middle lobe	23 (6)	Undifferentiated	1541 (1)
Right upper lobe	127 (32)	Unknown	121,967 (44)
Hilum	14 (4)	Insurance status, *n* (%)	
Main stem bronchus	8 (2)	Uninsured	12,389 (5)
Other	23 (6)	Private insurance/managed care	89,056 (32)
Histology, *n* (%)		Medicaid	22,609 (8)
Adenocarcinoma	222 (57)	Medicare	139,770 (51)
Squamous cell carcinoma	170 (43)	Other government insurance	4585 (2)
Asthma, *n* (%)	33 (8)	Unknown	6789 (2)
Restrictive lung disease, *n* (%)	11 (3)	Facility type, *n* (%)	
Bronchiectasis, *n* (%)	16 (4)	Community Cancer Program	29,196 (11)
Chronic bronchitis, *n* (%)	49 (13)	Comprehensive Community Clinic	120,418 (44)
COPD, *n* (%)	37 (9)	Academic/Research Program	87,368 (32)
Emphysema, *n* (%)	64 (16)	Integrated Network Cancer Center	35,837 (13)
Heart disease, *n* (%)	52 (13)	Unknown	2379 (1)
Hypertension, *n* (%)	126 (32)	Facility volume, *n* (%)	
Stroke, *n* (%)	14 (4)	First quartile (lowest volume)	15,586 (6)
Diabetes, *n* (%)	38 (10)	Second quartile	39,991 (15)
		Third quartile	72,999 (27)
		Fourth quartile (highest volume)	146,622 (53)
		Distance from hospital (median, IQR), miles	9.3 (4.1, 22.4)
		Income,[a] *n* (%)	
		First quartile	61,639 (22)
		Second quartile	66,686 (24)
		Third quartile	63,719 (23)
		Fourth quartile	79,029 (29)
		Unknown	4125 (1)
		Education,[b] *n* (%)	
		First quartile	62,897 (23)
		Second quartile	78,817 (29)
		Third quartile	76,264 (28)
		Fourth quartile	53,688 (20)
		Unknown	3532 (1)
		Treatment type, *n* (%)	
		Surgery	35,760 (13)
		Chemotherapy alone	73,607 (27)
		Radiation alone	71,833 (26)
		Chemoradiation	87,655 (32)
		Immunotherapy	6343 (2)
		Year of diagnosis, (median, IQR)	2011 (2008, 2013)

Abbreviation: CDCC = Charlson comorbidity score.
[a] NCDB 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 age 25 or older in the patient's zip code who did not graduate from high school.

Table 2 Kaplan Meier Overall Survival Estimates for each National Cancer Database. Propensity Score-Matched Subgroup Analysis.

Survival Group/Characteristic	EarlyTreatment	DelayedTreatment	Log-rank *P*-value
Stage III adenocarcinoma			
IIIA: T4 N0 M0 or T3-4 N1 M0 – Surgery + Chemo	*n* = 79	*n* = 79	
1-y survival (95% CI)	88% (78%, 94%)	89% (80%, 95%)	
3-y survival (95% CI)	68% (55%, 78%)	54% (41%, 66%)	.33
5-y survival (95% CI)	50% (36%, 63%)	44% (31%, 56%)	
Median survival (95% CI), mo	67.5 (41.6, 96.6)	42.7 (33.2, 68.9)	
IIIA: T1-2 N2 M0 – surgery	*n* = 96	*n* = 96	
1-y survival (95% CI)	85% (79%, 91%)	91% (84%, 96%)	
3-y survival (95% CI)	59% (48%, 69%)	64% (53%, 74%)	.98
5-y survival (95% CI)	44% (32%, 55%)	46% (34%, 58%)	
Median survival (95% CI), mo	49.7 (35.6, 69.5)	51.7 (37.8, 78.2)	
IIIA: T4 N0 M0 or T3-4 N1 M0 – Chemoradiation	*n* = 176	*n* = 176	
1-y survival (95% CI)	53% (45%, 60%)	57% (49%, 64%)	
3-y survival (95% CI)	22% (16%, 29%)	23% (17%, 30%)	.34
5-y survival (95% CI)	13% (8%, 19%)	16% (10%, 23%)	
Median survival (95% CI), mo	12.9 (10.4, 16.6)	15.8 (11.7, 19.6)	
IIIA: T1-2 N2 M0 – Chemoradiation	*n* = 237	*n* =237	
1-y survival (95% CI)	70% (64%, 76%)	69% (63%, 75%)	
3-y survival (95% CI)	39% (33%, 46%)	33% (26%, 39%)	.21
5-y survival (95% CI)	25% (19%, 32%)	18% (12%, 24%)	
Median survival (95% CI), mo	24.9 (20.1, 30.1)	20.7 (17.6, 24.0)	
IIIB: T1-2 N3 M0 – Chemoradiation	*n* = 81	*n* = 81	
1-y survival (95% CI)	59% (48%, 69%)	73% (62%, 82%)	
3-y survival (95% CI)	27% (17%, 37%)	37% (26%, 49%)	.03
5-y survival (95% CI)	17% (8%, 28%)	22% (12%, 34%)	
Median survival (95% CI), mo	14.7 (10.4, 20.5)	24.1 (19.0, 34.2)	
IIIB: T3-4 N2 M0 – Chemoradiation	*n* = 176	*n* =176	
1-y survival (95% CI)	56% (48%, 63%)	62% (54%, 69%)	
3-y survival (95% CI)	26% (19%, 33%)	27% (20%, 35%)	.49
5-y survival (95% CI)	17% (11%, 24%)	18% (11%, 25%)	
Median survival (95% CI), mo	15.7 (11.9, 18.8)	18.4 (14.3, 24.5)	
IIIC: T3-4 N3 M0 – Chemoradiation	*n* = 37	*n* = 37	
1-y survival (95% CI)	43% (27%, 58%)	62% (44%, 75%)	
3-y survival (95% CI)	11% (4%, 24%)	33% (18%, 48%)	.18
5-y survival (95% CI)	11% (4%, 24%)	11% (3%, 25%)	
Median survival (95% CI), mo	10.9 (6.3, 13.4)	16.9 (8.8, 32.1)	
Stage III squamous cell carcinoma			
IIIA: T4 N0 M0 or T3-4 N1 M0 – Surgery	*n* = 58	*n* = 58	
1-y survival (95% CI)	84% (71%, 91%)	88% (76%, 94%)	
3-y survival (95% CI)	51% (37%, 64%)	53% (38%, 65%)	.91
5-y survival (95% CI)	46% (31%, 59%)	48% (33%, 61%)	
Median survival (95% CI), mo	43.7 (22.1, 96.6)	50.4 (23.8, 109.2)	
IIIA: T1-2 N2 M0 – Surgery	*n* = 30	*n* = 30	
1-y survival (95% CI)	90% (72%, 97%)	86% (67%, 94%)	
3-y survival (95% CI)	53% (33%, 70%)	45% (26%, 63%)	.29
5-y survival (95% CI)	36% (18%, 54%)	23% (8%, 41%)	
Median survival (95% CI), mo	36.2 (24.3, 105.8)	25.1 (18.7, 45.1)	

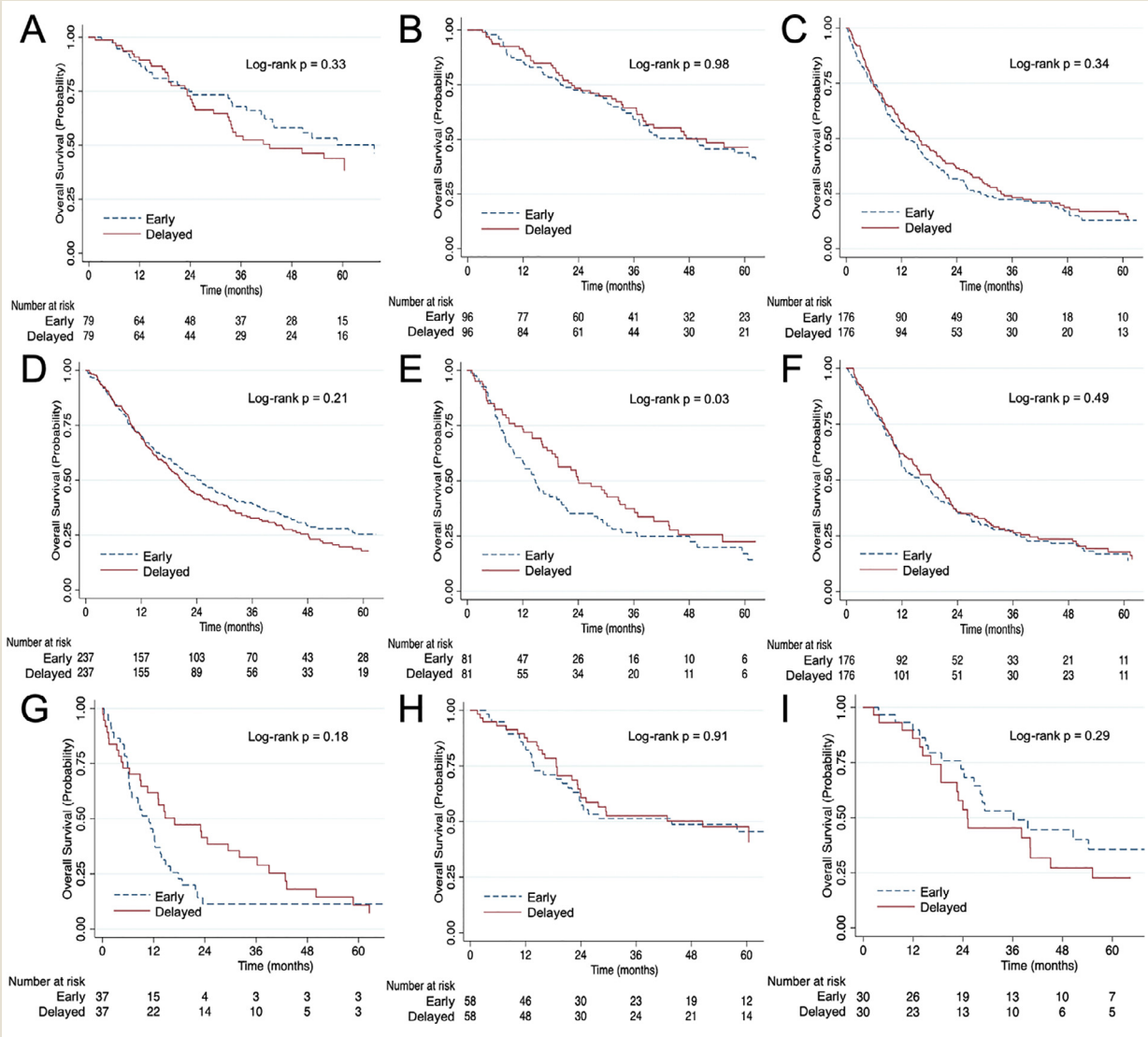
(*continued on next page*)

Table 2 (*continued*)

Survival Group/Characteristic	EarlyTreatment	DelayedTreatment	Log-rank *P*-value
IIIA: T4 N0 M0 or T3-4 N1 M0 – Chemoradiation	*n* = 223	*n* = 233	
1-y survival (95% CI)	52% (45%, 58%)	60% (53%, 66%)	
3-y survival (95% CI)	28% (22%, 34%)	27% (21%, 33%)	.60
5-y survival (95% CI)	15% (10%, 21%)	13% (8%, 19%)	
Median survival (95% CI), mo	13.0 (10.7, 17.8)	17.1 (12.6, 21.4)	
IIIA: T1-2 N2 M0 – Chemoradiation	*n* = 171	*n* = 171	
1-y survival (95% CI)	62% (54%, 69%)	63% (55%, 70%)	
3-y survival (95% CI)	26% (19%, 33%)	27% (20%, 34%)	.94
5-y survival (95% CI)	16% (10%, 23%)	16% (10%, 23%)	
Median survival (95% CI), mo	18.0 (13.3, 20.7)	17.6 (13.5, 22.5)	
IIIB: T1-2 N3 M0 – Chemoradiation	*n* = 48	*n* = 48	
1-y survival (95% CI)	62% (47%, 74%)	51% (36%, 64%)	
3-y survival (95% CI)	29% (17%, 43%)	17% (7%, 30%)	.14
5-y survival (95% CI)	20% (9%, 34%)	7% (2%, 19%)	
Median survival (95% CI), mo	14.8 (9.9, 28.9)	12.9 (8.2, 18.5)	
IIIB: T3-4 N2 M0 – Chemoradiation	*n* = 323	*n* = 323	
1-y survival (95% CI)	53% (48%, 59%)	61% (55%, 66%)	
3-y survival (95% CI)	21% (16%, 26%)	23% (18%, 29%)	.13
5-y survival (95% CI)	11% (7%, 16%)	15% (10%, 20%)	
Median survival (95% CI), mo	13.8 (11.3, 16.0)	15.9 (13.8, 19.6)	
IIIC: T3-4 N3 M0 – Chemoradiation	*n* = 55	*n* = 55	
1-y survival (95% CI)	47% (34%, 60%)	47% (34%, 60%)	
3-y survival (95% CI)	19% (10%, 30%)	25% (14%, 37%)	.69
5-y survival (95% CI)	17% (8%, 28%)	14% (5%, 26%)	
Median survival (95% CI), mo	11.4 (7.4, 17.3)	11.4 (7.5, 15.1)	
Stage IV adenocarcinoma			
IV: M1A – Chemotherapy ± surgery or radiation	*n* = 201	*n* = 201	
1-y survival (95% CI)	54% (47%, 61%)	61% (53%, 67%)	.02
3-y survival (95% CI)	22% (16%, 28%)	36% (29%, 43%)	
5-y survival (95% CI)	11% (7%, 18%)	15% (9%, 23%)	
Median survival (95% CI), mo	13.7 (10.6, 16.5)	19.0 (15.1, 22.0)	
IV: M1B-C – Chemotherapy ± surgery or radiation	*n* = 99	*n* = 99	
1-y survival (95% CI)	43% (39%, 46%)	48% (44%, 51%)	.71
3-y survival (95% CI)	16% (13%, 19%)	18% (15%, 21%)	
5-y survival (95% CI)	9% (6%, 12%)	9% (7%, 13%)	
Median survival (95% CI), mo	9.5 (8.5, 10.6)	11.2 (9.7, 12.4)	
Stage IV squamous cell carcinoma			
IV: M1A – Chemotherapy ± surgery or radiation	*n* = 773	*n* = 773	
1-y survival (95% CI)	50% (40%, 59%)	48% (38%, 57%)	.06
3-y survival (95% CI)	20% (13%, 29%)	18% (11%, 27%)	
5-y survival (95% CI)	10% (4%, 18%)	9% (3%, 17%)	
Median survival (95% CI), mo	11.9 (8.7, 14.2)	11.1 (7.1, 14.4)	
IV: M1B-C – Chemotherapy ± surgery or radiation	*n* = 177	*n* = 177	
1-y survival (95% CI)	39% (32%, 46%)	38% (30%, 45%)	.52
3-y survival (95% CI)	10% (5%, 16%)	14% (9%, 21%)	
5-y survival (95% CI)	8% (4%, 14%)	10% (5%, 16%)	
Median survival (95% CI), mo	8.1 (6.3, 9.8)	8.2 (6.7, 10.6)	

Abbreviation: CI = confidence interval.

Figure 1 Overall survival for propensity score-matched patients with non–small-cell lung cancer who received early (0-30 days after diagnosis) versus delayed (90-120 days after diagnosis) treatment for (A) stage IIIA, T4N0M0, or T3-T4N1M0, adenocarcinoma treated with lobectomy + adjuvant or induction chemotherapy with or without radiation, (B) stage IIIA, T1-T2N2M0, adenocarcinoma treated with lobectomy + adjuvant or induction chemotherapy with or without radiation, (C) stage IIIA, T4N0M0 or T3-T4N0M0, adenocarcinoma treated with concurrent chemoradiation, (D) stage IIIA, T1-T2N2M0, adenocarcinoma treated with concurrent chemoradiation, (E) stage IIIB, T1-T2N3M0, adenocarcinoma, (F) stage IIIB, T1-T2N3M0, adenocarcinoma treated with concurrent chemoradiation, (G) stage IIIC, T3-T4N3M0, adenocarcinoma treated with concurrent chemoradiation, (H) stage IIIA, T4N0M0, or T3-T4N1M0, squamous cell carcinoma treated with lobectomy + adjuvant or induction chemotherapy with or without radiation, (I) stage IIIA, T1-T2N2M0, squamous cell carcinoma treated with lobectomy + adjuvant or induction chemotherapy with or without radiation.

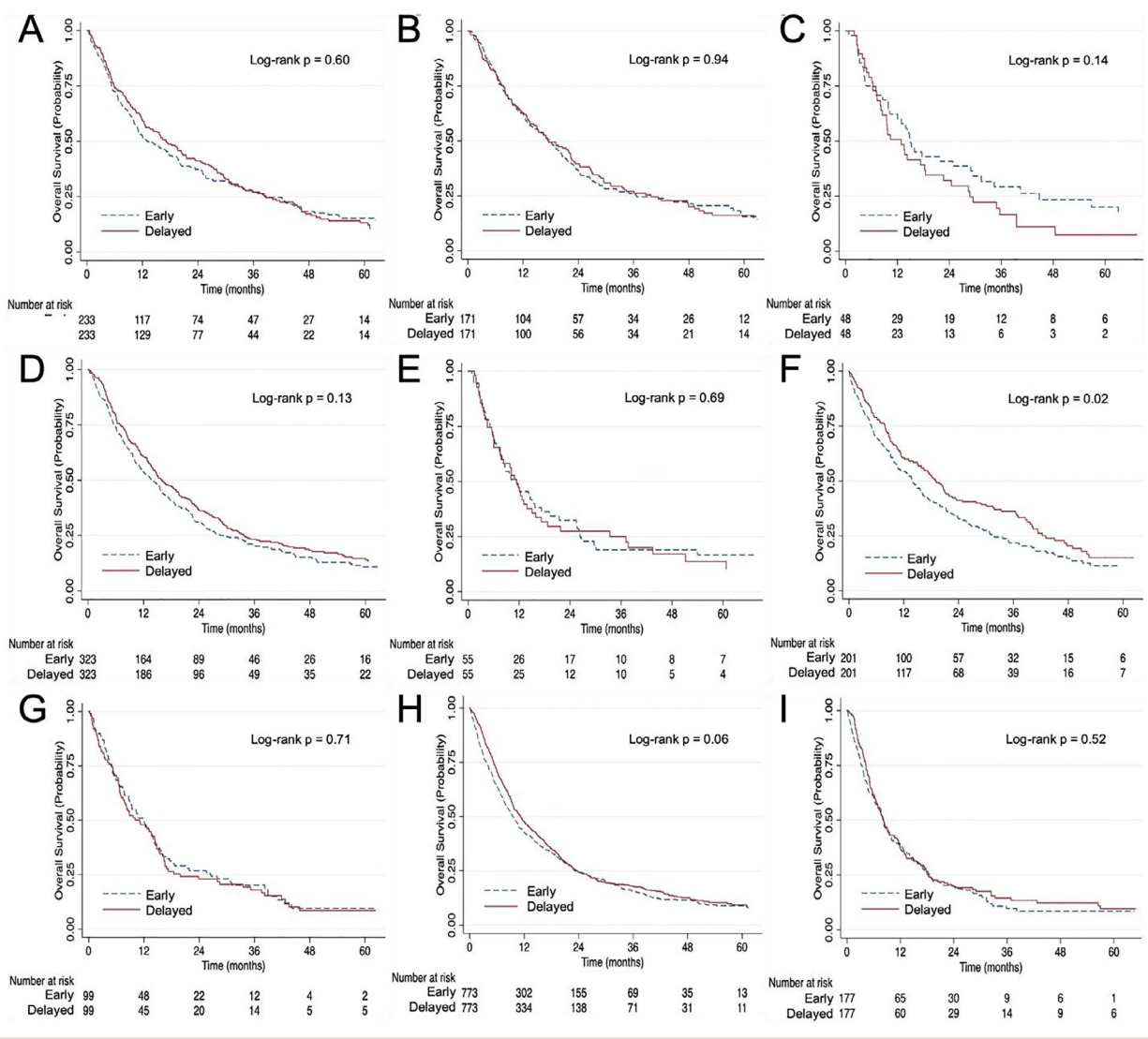


For stage IV (M1A) patients with adenocarcinoma, delayed treatment with curative intent chemotherapy was associated with better survival (Figure 2F); whereas, for patients with stage IV (M1A) squamous cell carcinoma, there was no difference in overall survival between early versus delayed treatment (Figure 2G). For stage IV (M1B-C) adenocarcinoma and squamous cell carcinoma, there was no difference in overall survival between early versus delayed curative-intent chemotherapy (Figure 2H-I).

Cox Proportional Hazards Regression with Penalized Smoothing Splines

Next, we used Cox proportional hazards regression to examine the implications of delayed treatment for all-cause mortality in the NLST and NCDB cohorts. Penalized smoothing splines were used to capture nonlinearities in the relationship between days elapsed from diagnosis to treatment and mortality. For this analysis, individuals treated on the day of diagnosis represented the referent group.

Figure 2 Overall survival for propensity score-matched patients with non–small-cell lung cancer who received early (0-30 days after diagnosis) versus delayed (90-120 days after diagnosis) treatment for (A) stage IIIA, T4N0M0 or T3-T4N0M0, squamous cell carcinoma treated with concurrent chemoradiation, (B) stage IIIA, T1-T2N2M0, squamous cell carcinoma treated with concurrent chemoradiation, (C) stage IIIB, T1-T2N3M0, squamous cell carcinoma, (D) stage IIIB, T1-T2N3M0, squamous cell carcinoma treated with concurrent chemoradiation, (E) stage IIIC, T3-T4N3M0, squamous cell carcinoma treated with concurrent chemoradiation, (F) stage IV, M1A, adenocarcinoma treated with curative intent chemotherapy, (G) stage IV, M1A, squamous cell carcinoma treated with curative intent chemotherapy, (H) stage IV, M1B-M1C, adenocarcinoma treated with curative intent chemotherapy, (I) stage IV, M1B-M1C, squamous cell carcinoma treated with curative intent chemotherapy.



Results stratified by stage and guideline-concordant treatment corresponding to that stage are shown in Figure 3A-D.

In both the NLST and NCDB cohort, for stage III and stage IV adenocarcinoma and squamous cell carcinoma, the HR decreased steadily with greater time elapsed from diagnosis to treatment as compared with individuals treated the same day as their diagnosis.

Secondary Analysis

As a secondary analysis, we repeated the Cox proportional hazards regression with penalized splines for subgroups defined by substage, histologic subtype, and guideline-concordant treatment within the NCDB cohort (Figures 4-5). The pattern observed in mortality risk with time elapsed from diagnosis to treatment within these subgroups is largely consistent with those seen in the subgroups assessed in the primary analysis defined only by stage and histologic subtype.

Sensitivity Analysis

In Figure 3E-F, we present the results from the sensitivity analysis in which stage IV patients who received very early or very delayed

Figure 3 National Cancer Database (NCDB) and National Lung Screening Trial (NLST) multivariable Cox regression analysis with a penalized smoothing spline function for time elapsed from diagnosis to treatment for (A) NCDB stage III patients treated with lobectomy + adjuvant or induction chemotherapy with or without radiation or treated with concurrent chemoradiation, (B) NLST stage III patients treated with lobectomy + adjuvant or induction chemotherapy with or without radiation or treated with concurrent chemoradiation, (C) NCDB stage IV patients treated with chemotherapy ± surgery, radiation, or immunotherapy, (D) NLST stage IV patients treated with chemotherapy ± surgery or radiation, (E) sensitivity analysis: NCDB stage IV patients treated with chemotherapy ± surgery, radiation, or immunotherapy excluding patients whose time to treatment was <10th and >90th percentile, (F) sensitivity analysis: NLST stage IV patients treated with chemotherapy ± surgery, radiation, or immunotherapy excluding patients whose time to treatment was <10th and >90th percentile.

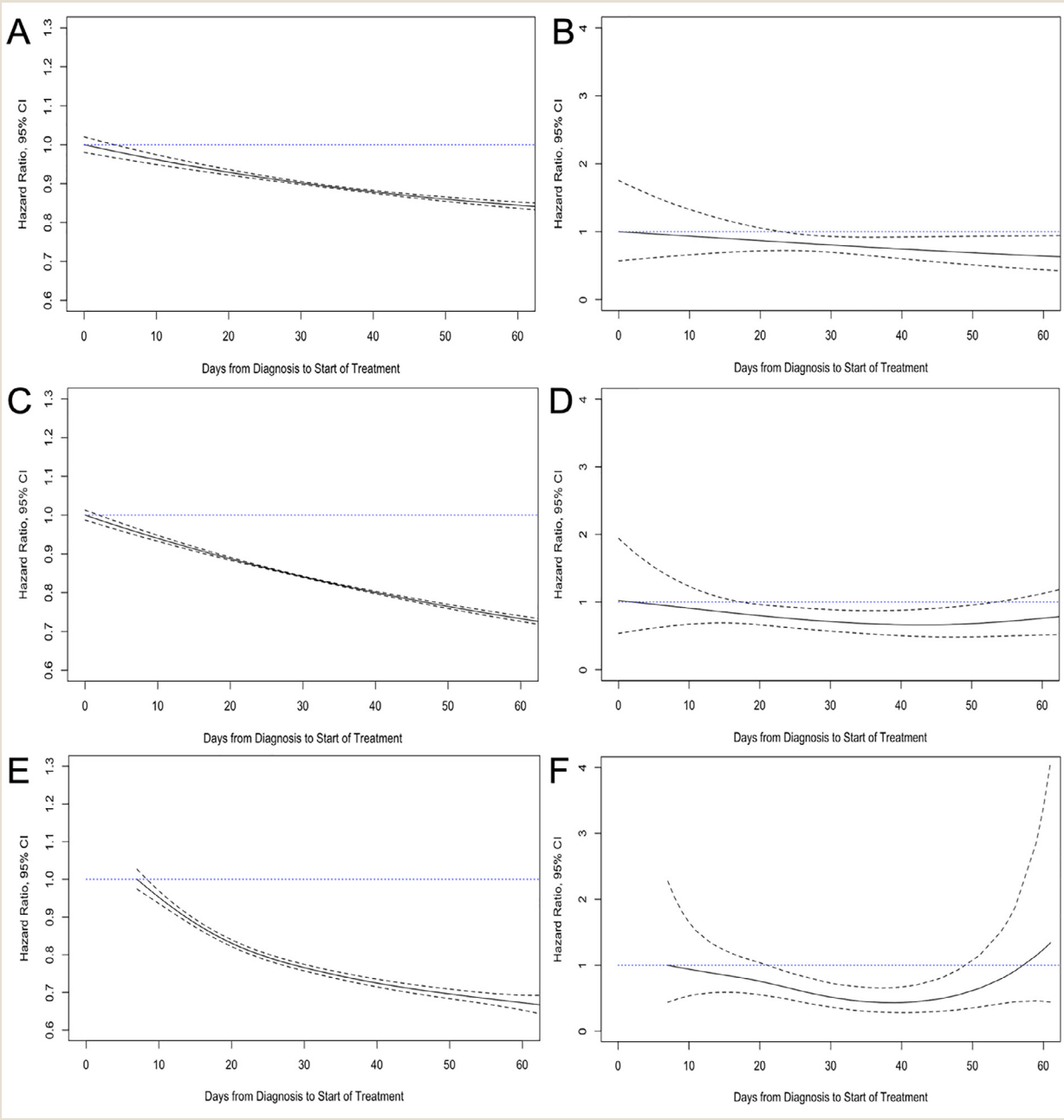
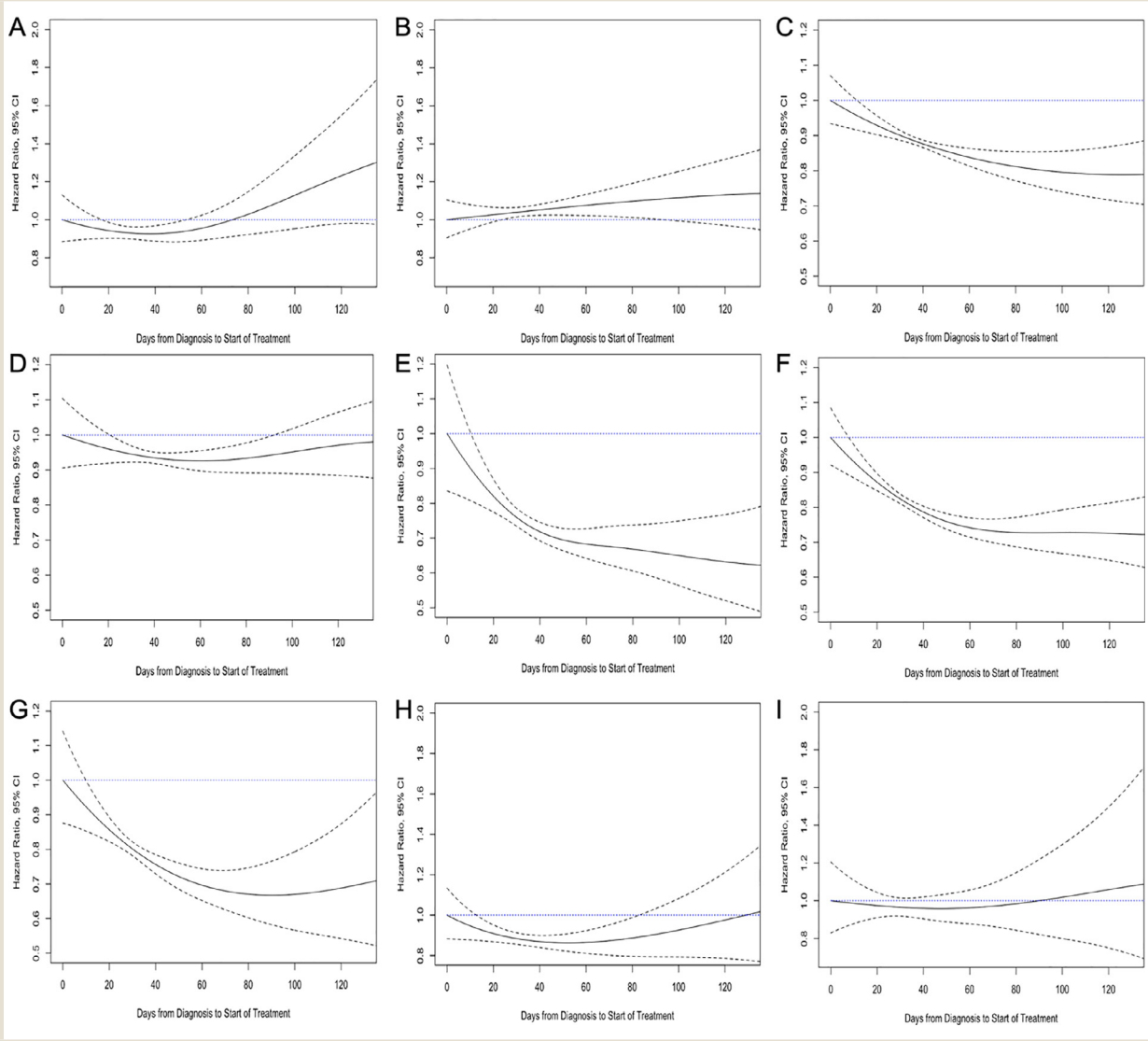


Figure 4 Multivariable Cox regression analysis with a penalized smoothing spline function for time elapsed from diagnosis to treatment for (A) stage IIIA, T4N0M0 or T3-T4N1M0, adenocarcinoma treated with lobectomy + adjuvant or induction chemotherapy with or without radiation, (B) stage IIIA, T1-T2N2M0, adenocarcinoma treated with lobectomy + adjuvant or induction chemotherapy with or without radiation, (C) stage IIIA, T4N0M0 or T3-T4N0M0, adenocarcinoma treated with concurrent chemoradiation, (D) stage IIIA, T1-T2N2M0, adenocarcinoma treated with concurrent chemoradiation, (E) stage IIIB, T1-T2N3M0, adenocarcinoma, (F) stage IIIB, T1-T2N3M0, adenocarcinoma treated with concurrent chemoradiation, (G) stage IIIC, T3-T4N3M0, adenocarcinoma treated with concurrent chemoradiation, (H) stage IIIA, T4N0M0 or T3-T4N1M0, squamous cell carcinoma treated with lobectomy + adjuvant or induction chemotherapy with or without radiation, (I) stage IIIA, T1-T2N2M0, squamous cell carcinoma treated with lobectomy + adjuvant or induction chemotherapy with or without radiation.

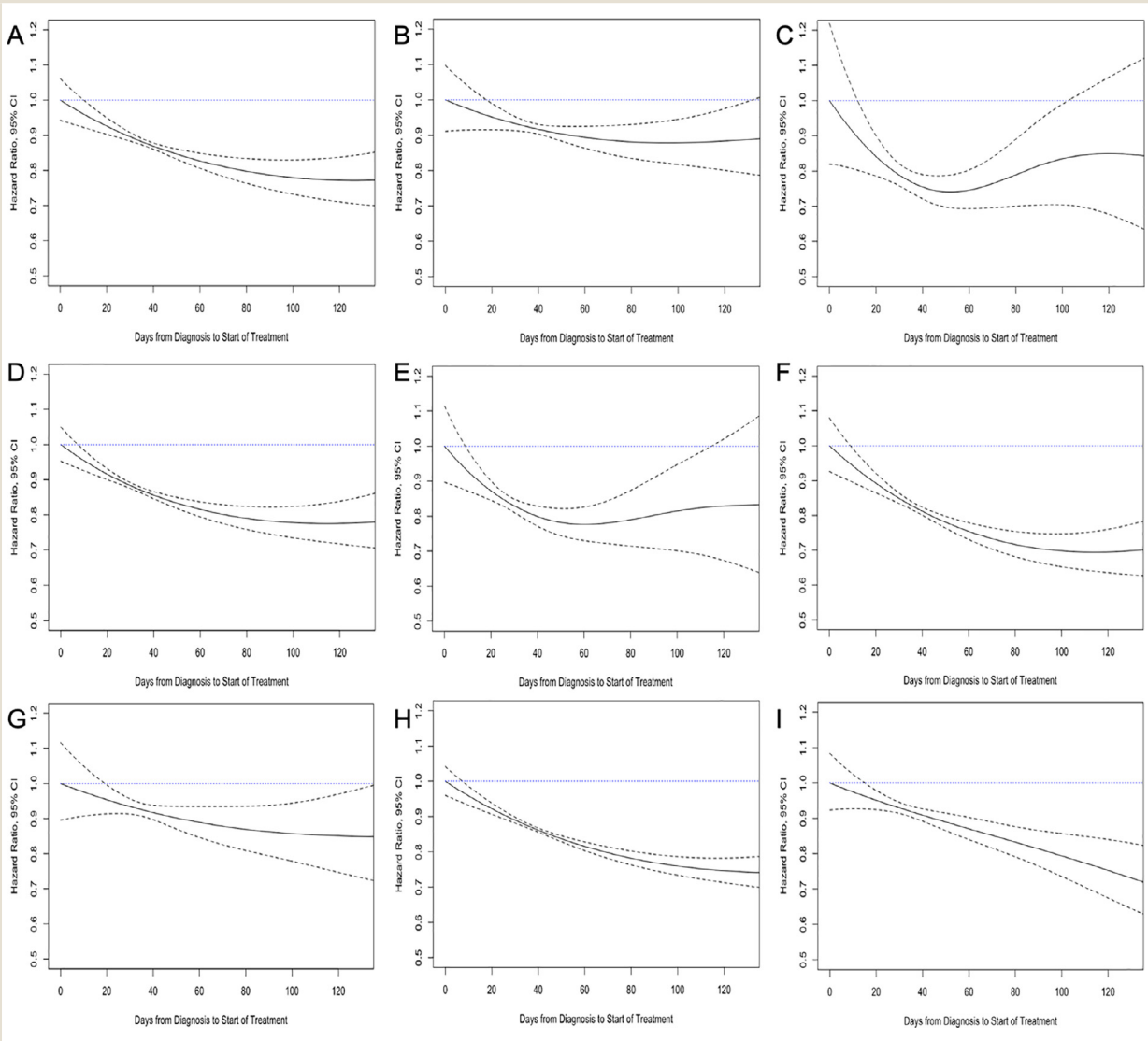


treatment (<10th percentile or >90th percentile) were excluded. The results from our sensitivity analysis are generally consistent with the results from our primary analysis.

LASSO Analysis

For stage III and stage IV lung cancer, the binary logistic LASSO regression model we developed represents a high-fidelity model, as determined by the AUROC,[44] for determining long-term survival (ie, ≥30.8 months posttreatment for stage III lung cancer and ≥15.5 months posttreatment for stage IV lung cancer) for all patients, patients with no treatment delay, and patients with treatment delay. For the entire study cohort, the most important features by magnitude of estimate are surgery (2.52 increase in log odds for stage III lung cancer and 2.22 increase in log odds for stage IV lung cancer), chemotherapy (1.72 increase and 2.79 increase), and radiation (0.66 increase and 0.36 increase) with a mean testing AUROC

Figure 5 Multivariable Cox regression analysis with a penalized smoothing spline function for time elapsed from diagnosis to treatment for (A) stage IIIA, T4N0M0, or T3-T4N0M0, squamous cell carcinoma treated with concurrent chemoradiation, (B) stage IIIA, T1-T2N2M0, squamous cell carcinoma treated with concurrent chemoradiation, (C) stage IIIB, T1-T2N3M0, squamous cell carcinoma, (D) stage IIIB, T1-T2N3M0, squamous cell carcinoma treated with concurrent chemoradiation, (E) stage IIIC, T3-T4N3M0, squamous cell carcinoma treated with concurrent chemoradiation, (F) stage IV, M1A, adenocarcinoma treated with curative intent chemotherapy, (G) stage IV, M1A, squamous cell carcinoma treated with curative intent chemotherapy, (H) stage IV, M1B-M1C, adenocarcinoma treated with curative intent chemotherapy, (I) stage IV, M1B-M1C, squamous cell carcinoma treated with curative intent chemotherapy.

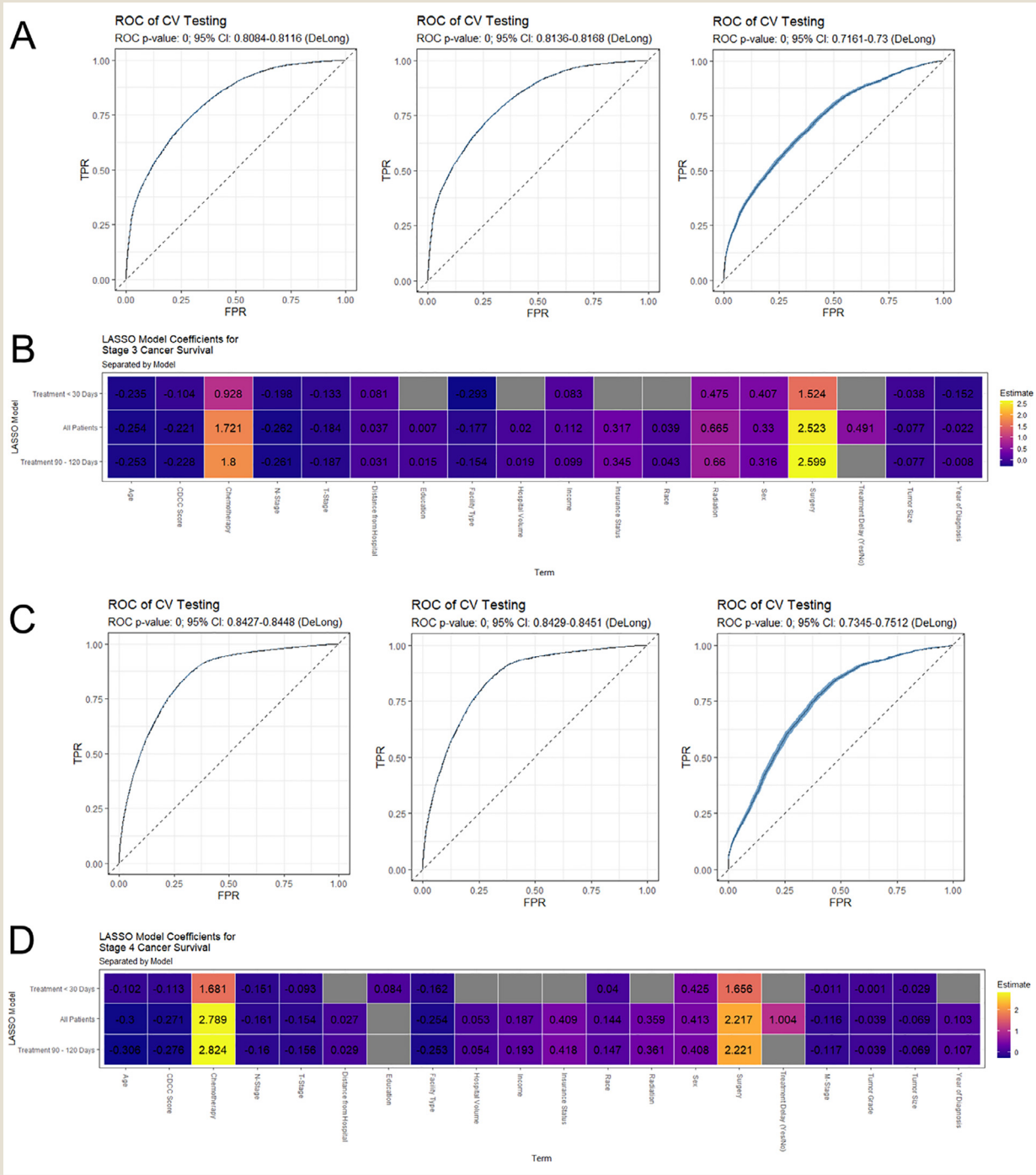


of 0.81 for stage III lung cancer and mean testing AUROC of 0.84 for stage IV lung cancer (Figure 4). In contrast, timing of treatment was not as important (0.49 increase in log odds for stage III lung cancer and 1.00 increase in log odds for stage IV lung cancer).

Discussion

In this study, we analyzed data from the NLST and NCDB to examine the impact of delayed cancer treatment on the survival of patients with clinical stage III-IV NSCLC. To our knowledge, this study is the first to evaluate the relationship between timing of treatment and survival, as well as the impact of extended delays (>3 months) of treatment by each substage of stage III-IV NSCLC and by specific histologic subtype (ie, adenocarcinoma and squamous cell carcinoma). Prior studies evaluating the timing of treatment on survival have mostly focused on assessing delays to treatment of up to 8 weeks[39,42,45-47] and have not studied effects within strata defined more precisely by substage and/or by histologic subtype. As a result, these previous studies are less relevant for decision-making regarding extended delays for cancer treatment per clinical guidelines and for practice in the setting of the

Figure 6 (A) The mean area under the receiver operating characteristic (AUROC), *P*-value, and 95% confidence intervals for training data of the least absolute shrinkage and selection operator (LASSO) model, from left to right, of all stage III patients, of stage III patients receiving early treatment (0 - 30 days after diagnosis), and of stage III patients receiving delayed treatment (90-120 days after diagnosis). (B) A heatmap of LASSO coefficients for the LASSO model, from top to bottom, for stage III patients who received early treatment, all stage III patients, and stage III patients who received delayed treatment. (C) The mean AUROC, *P*-value, and 95% confidence intervals for training data of the LASSO model, from left to right, of all stage IV patients, of stage IV patients receiving early treatment (0-30 days after diagnosis), and of stage IV patients receiving delayed treatment (90-120 days after diagnosis). (D) A heatmap of LASSO coefficients for the LASSO model, from top to bottom, for stage IV patients who received early treatment, all stage IV patients, and stage IV patients who received delayed treatment.



current COVID-19 pandemic. Collectively, our results suggest that extended delay to treatment for patients with stage III-IV NSCLC is not associated with significantly worse overall survival.

We first compared the cumulative survival in patients who received "early" treatment to a matched sample of otherwise similar patients who received "delayed" treatment in strata defined by stage and substage of lung adenocarcinoma and squamous cell carcinoma. For stage III-IV lung adenocarcinoma and squamous cell carcinoma, we found either no significant difference in cumulative survival or, unexpectedly, evidence of worse survival in the "early" versus "delayed" treatment groups in our propensity-score matched analysis.

Next, we performed multivariable Cox regression analyses with penalized smoothing splines for these specific substages and found also paradoxical trajectories (ie, longer delays in care were associated with better survival). Of note, studies from Australia,[42] Canada,[39] Finland,[40] Sweden,[41] and the U.S.[38] have similarly found shorter treatment delay to be associated with worse survival, which has been termed "wait time bias."[43] We examined the potential influence of "wait time bias" in the present study by repeating our main analysis for stage IV patients but with exclusion of individuals treated very early and very late. In this sensitivity analysis, we found similar trends as seen in our main analysis.

One interpretation of these unexpected findings is that, for stage III-IV NSCLC, extended delays to treatment by 3-4 months may be acceptable. However, it is important to recognize that the present analysis is conditional on treatment (ie, only individuals who underwent guideline-concordant treatment for NSCLC are included). Without complete information on individuals who are diagnosed with NSCLC but never treated, it is impossible to ascertain whether our findings are truly unbiased. Moreover, under no circumstances should the results from the present study be used to motivate extended delays in care for patients with advanced lung cancer nor justify untimely authorization of care by insurance companies. Nonetheless, they may provide some reassurance to patients who did not receive expeditious treatment during the COVID-19 pandemic or must delay care for any number of personal reasons during non-pandemic times.

Finally, our LASSO regression models indicate that any form of treatment following diagnosis of stage III and IV lung cancer is critical to impacting patient survival and outweighs delay in treatment in its impact. Whether a patient received treatment in a timely or delayed fashion is of lesser significance than if the patient received treatment at all.

Limitations

We used the NLST and NCDB data sources for the present study. The exposure was not randomized in either study population; therefore, the results presented here are subject to residual confounding. The NLST was a randomized controlled trial, and since trials typically have stringent inclusion and exclusion criteria to bolster internal validity, findings from the NLST may not be generalizable to all lung cancer patients. The NCDB includes an estimated 80% of all lung cancer diagnoses in the U.S.,[29] and the findings from its study population are likely much more generalizable. However, one advantage of the NLST is that data were prospectively collected and include high-quality information about patient comorbidities.

Although we used multivariable analysis and propensity score-matching to reduce bias, important covariates such as pulmonary function data and surgeon experience are not available in the NCDB. Data on EGFR tyrosine kinase inhibitor utilization, which began in 2007 in the midst of our study period, are also not available. However, the NCDB does have co-morbidity scores, and the NLST has detailed co-morbidity data, including data on obstructive and restrictive lung diseases and smoking history, that we used in our analyses.

Cancer-specific, recurrence-free, and disease-free survival are not recorded in the NCDB. Finally, our results are not necessarily generalizable to other histologic subtypes other than adenocarcinoma and squamous cell carcinoma.

Conclusion

During the COVID-19 pandemic, hospitals around the world may be forced to delay and postpone cancer treatment to preserve limited resources. Evidence regarding the impact of extended delayed treatment is critically needed to inform national guidelines.[48,49] The results from this national analysis demonstrate that extended delay to treatment, by 3-4 months, of advanced-stage lung adenocarcinoma and squamous cell carcinoma is not associated with worse overall survival. These findings can be used to provide reassurance to patients with stage III-IV disease who are unable to receive immediate care in areas of substantial SARS-CoV-2 transmission and to guide decision-making for administrators and public health officials during the ongoing COVID-19 pandemic and other future pandemic waves.

Clinical Practice Points

During the COVID-19 pandemic, hospitals may postpone cancer operations or delay systemic cancer treatment to preserve limited resources and decrease the risk of nosocomial transmission. The impact of extended delays in treatment for patients with stage III and stage IV lung cancer is unclear. Although past research has evaluated timeliness of care, previous studies did not assess the survival outcomes associated with extended treatment delays currently proposed by medical societies. In this national analysis of the National Lung Screening Trial and National Cancer Database, we found that, for patients with stage III-IV adenocarcinoma and squamous cell carcinoma, an extended treatment delay by 3-4 months was not associated with significantly decreased overall survival compared to prompt treatment. To our knowledge, this study is the first to evaluate the relationship between timing of treatment and survival, as well as the impact of extended delay to treatment by each substage of stage III-IV NSCLC and by specific histologic subtype. These findings can be used to provide reassurance to patients with stage III-IV disease who are unable to receive immediate care in areas of substantial SARS-CoV-2 transmission and to guide decision-making for administrators and public health officials during the ongoing COVID-19 pandemic and other future pandemic waves as services are re-integrated.

Acknowledgments

The authors thank the National Cancer Institute (NCI) for access to NCI's data collected by the National Lung Screening Trial. The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by the NCI.

The National Cancer Database (NCDB) 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 investigators. This work has no funding.

Disclosure

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.05.001.

References

1. Commins J. Surgeon general urges providers to 'consider stopping elective surgeries.' hospitals push back. *Health Leaders*. 2020.
2. Thoracic Surgery Outcomes Research Network IgCOVID-19 guidance for triage of operations for thoracic malignancies: a consensus statement from Thoracic Surgery Outcomes Research Network, The Society of Thoracic Surgeons and The American Association for Thoracic Surgery. *J Thorac Cardiovasc Surg*. 2020.
3. Stahel PF. How to risk-stratify elective surgery during the COVID-19 pandemic? *Patient Safety Surg*. 2020;14:8.
4. Iacobucci G. Covid-19: all non-urgent elective surgery is suspended for at least three months in England. *BMJ*. 2020;368:m1106.
5. Ueda M, Martins R, Hendrie PC, et al. Managing cancer care during the COVID-19 pandemic: agility and collaboration toward a common goal. *J Nat Compr Cancer Netw*. 2020;1:1–4.
6. Guckenberger M, Belka C, Bezjak A, et al. Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: an ESTRO-ASTRO consensus statement. *Radiother Oncol*. 2020.
7. Raghavan Derek, Jean Chai S, Plate Kevin, et al. levine cancer institute approach to pandemic care of cancer patients. *J Clin Oncol Oncol Pract*. 2020.
8. Cannistra SA, Haffty BG, Ballman K Challenges faced by medical journals during the COVID-19 pandemic. J Clin Oncol; 2020;38:2206-2207. doi:10.1200/JCO.20.00858.
9. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. *British Med J*. 2020.
10. Springer NatureDelta coronavirus variant: scientists brace for impact. *Nature*. 2021. Available at:. https://www.nature.com/articles/d41586-021-01696-3. Accessed: August 9, 2021.
11. Reuters. U.S. COVID-19 cases reach six-month high, Florida grapples with surge, 2021. Available at: https://www.reuters.com/world/us/us-covid-19-cases-hit-six-month-high-over-100000-reuters-tally-2021-08-05. Accessed: August 9, 2021.
12. Fauci A. Get vaccinated to stop risk of an even deadlier COVID variant. *USA Today*. 2021. Available at:. https://www.usatoday.com/story/opinion/2021/08/08/anthony-fauci-covid-vaccinate-mandate/5507400001 . Accessed: August 9, 2021.
13. Banna G, Curioni-Fontecedro A, Friedlaender A, Addeo A. How we treat patients with lung cancer during the SARS-CoV-2 pandemic: primum non nocere. *ESMO open*. 2020;5.
14. JM Marron, R Jagsi, FJ Hlubocky. Ethics and resource scarcity: ASCO recommendations for the oncology community during the COVID19 pandemic. J Clin Oncol.2020;38:2201-2205.
15. Passaro A, Addeo A, Von Garnier C, et al. ESMO management and treatment adapted recommendations in the COVID-19 era: lung cancer. ESMO Open 2020;5:e000820.
16. American College of Surgeons. COVID 19: elective case triage guidelines for surgical care thoracic cancer surgery. 2020.
17. Wang Q, Berger NA, Xu R. Analyses of risk, racial disparity, and outcomes among us patients with cancer and COVID-19 infection. *JAMA Oncol*. 2021;7:220–227.
18. Derosa L, Melenotte C, Griscelli F, et al. The immuno-oncological challenge of COVID-19. *Nature Cancer*. 2020;1:946–964.
19. Jacobsen MM, Silverstein SC, Quinn M, et al. Timeliness of access to lung cancer diagnosis and treatment: a scoping literature review. *Lung Cancer*. 2017;112:156–164.
20. Aberle DR, Adams AM, et al.National Lung Screening Trial Research T Reduced lung-cancer mortality with low-dose computed tomographic screening. *New England J Med*. 2011;365:395–409.
21. Aberle DR, Berg CD, et al.National Lung Screening Trial Research T The national lung screening trial: overview and study design. *Radiology*. 2011;258:243–253.
22. Greene FL. *American Joint Committee on Cancer., American Cancer Society*. 6th ed. New York: Springer; 2002 AJCC cancer staging manual.
23. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151:193–203.
24. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683–690.
25. Edge SB. *American Joint Committee on Cancer. AJCC cancer staging manual*. 7th ed. New York: Springer; 2010.
26. Barta JA, Powell CA, Wisnivesky JP. Global epidemiology of lung cancer. *Ann Glob Health*. 2019;85.
27. NCCN. Clinical practice guidelines in oncology: non–small cell lung cancer (version 3.2020). 2020.
28. Miller ED, Fisher JL, Haglund KE, et al. The addition of chemotherapy to radiation therapy improves survival in elderly patients with stage III non–small cell lung cancer. *J Thorac Oncol*. 2018;13:426–435.
29. National Cancer Database. American College of Surgeons, 1996-2019. Available at: https://www.facs.org/quality-programs/cancer/ncdb. Accessed: December 20, 2019.
30. Antonoff M, Backhus L, Boffa DJ, et al. COVID-19 guidance for triage of operations for thoracic malignancies: a consensus statement from Thoracic Surgery Outcomes Research Network. *J Thorac Cardiovasc Surg*. 2020;160:601–605.
31. American College of Surgeons. COVID-19 guidelines for triage of thoracic patients. 2020. Available at: http://www.facs.org/covid-19/clinical-guidance/elective-case/thoracic-cancer. Accessed: April 28, 2022.
32. NLST Datasets, Data Dictionaries. NIH National Cancer Institue Cancer Data Access System. Available at: https://cdas.cancer.gov/datasets/nlst/. Accessed: May 15, 2020.
33. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.
34. Eilers PH, Marx BD. Flexible smoothing with B-splines and penalties. *Stat Sci*. 1996:89–102.
35. Crainiceanu C, Ruppert D, Wand MP Bayesian analysis for penalized spline regression using WinBUGS. J Stat Software 2005;14:1–24.
36. Bajaj SS, Wang H, Williams KM, et al. New attending surgeons hired by their training institution exhibit greater research productivity. *Ann Thorac Surg*. 2020.
37. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
38. Nadpara P, Madhavan SS, Tworek C. Guideline-concordant timely lung cancer care and prognosis among elderly patients in the United States: a population-based study. *Cancer Epidemiol*. 2015;39:1136–1144.
39. Diaconescu R, Lafond C, Whittom R. Treatment delays in non–small cell lung cancer and their prognostic implications. *J Thorac Oncol*. 2011;6:1254–1259.
40. Salomaa ER, Sallinen S, Hiekkanen H, Liippo K. Delays in the diagnosis and treatment of lung cancer. *Chest*. 2005;128:2282–2288.
41. Myrdal G, Lambe M, Hillerdal G, Lamberg K, Agustsson T, Stahle E. Effect of delays on prognosis in patients with non–small cell lung cancer. *Thorax*. 2004;59:45–49.
42. Vinod SK, Chandra A, Berthelsen A, Descallar J. Does timeliness of care in non–small cell lung cancer impact on survival? *Lung Cancer*. 2017;112:16–24.
43. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *British J Cancer*. 2015;112(Suppl 1):S92–107.
44. Bradley AP. The use of the area under the ROC curve in the evaluation of machine learning algorithms. *Pattern Recognit*. 1997;30:1145–1159.
45. Samson P, Patel A, Garrett T, et al. Effects of delayed surgical resection on short-term and long-term outcomes in clinical stage I non–small cell lung cancer. *Ann Thorac Surg*. 2015;99:1906–1913.
46. Kanarek NF, Hooker CM, Mathieu L, et al. Survival after community diagnosis of early-stage non–small cell lung cancer. *Am J Med*. 2014;127:443–449.
47. Coughlin S, Plourde M, Guidolin K, et al. Is it safe to wait? The effect of surgical wait time on survival in patients with non–small cell lung cancer. *Canadian Journal of Surgery*. 2015;58:414.
48. Prachand VN, Milner R, Angelos P, et al. Medically necessary, time-sensitive procedures: scoring system to ethically and efficiently manage resource scarcity and provider risk during the COVID-19 pandemic. *J Am Coll Surg*. 2020.
49. American College of Surgeons. ACS guidelines for triage and management of elective cancer surgery cases during the acute and recovery phases of coronavirus disease 2019 (COVID-19) pandemic., 2020. Available at: https://www.facs.org/-/media/files/covid19/acs_triage_and_management_elective_cancer_surgery_during_acute_and_recovery_phases.ashx. Accessed: May 13, 2020.