



Diagnosis-to-surgery interval and survival for different histologies of stage I–IIA lung cancer

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Background: Guidelines on timeliness of lung cancer surgery are inconsistent. Lung cancer histologic subtypes have different prognosis and treatment. It is important to understand the consequences of delayed surgery for each lung cancer histologic subtype. This study aimed to examine the association between diagnosis-to-surgery time interval and survival for early stage lung cancer and selected histologic subtypes.

Methods: Patients diagnosed with stage I–IIA lung cancer between 2004 and 2015 receiving definitive surgery and being followed up until Dec. 31, 2018, were identified from Surveillance, Epidemiology, and End Results database. Histologic subtypes included adenocarcinoma, squamous or epidermoid carcinoma, bronchioloalveolar carcinoma, large cell carcinoma, adenosquamous carcinoma, carcinoid carcinoma, and small cell carcinoma. Diagnosis-to-surgery interval was treated as multi-categorical variables (<1, 1–2, 2–3, and ≥3 months) and binary variables (≥1 *vs.* <1 month, ≥2 *vs.* <2 months, and ≥3 *vs.* <3 months). Outcomes included cancer-specific and overall survival. Covariates included age at diagnosis, sex, race, marital status, tumor size, grade, surgery type, chemotherapy, radiotherapy, and study period. Kaplan-Meier survival curves and Cox proportional hazards regression models were applied to examine the survival differences.

Results: With a median follow-up time of 51 months, a total of 40,612 patients were analyzed, including 40.1% adenocarcinoma and 24.5% squamous or epidermoid carcinoma. The proportion of patients receiving surgery <1, 1–2, 2–3, and ≥3 months from diagnosis were 34.2%, 33.9%, 19.8%, and 12.1%, respectively. Delayed surgery was associated with worse cancer-specific and overall survival for all lung cancers, adenocarcinoma, squamous or epidermoid, bronchioloalveolar, and large cell carcinoma (20–40% increased risk). Dose-dependent effects (longer delay, worse survival) were observed in all lung cancers, adenocarcinoma, and squamous and epidermoid carcinoma. No significant association between surgery delay and survival was observed in adenosquamous, carcinoid, and small cell carcinoma.

Conclusions: Our findings support the guidelines of undertaking surgery within 1 month from diagnosis in patients with stage I–IIA lung cancer. The observed dose-dependent effects emphasize the clinical importance of early surgery. Future studies with larger sample size of less frequent histologic subtypes are warranted to provide more evidence for histology-specific lung cancer treatment guidelines.

Keywords: Lung cancer; histologic subtype; surgery delay; survival

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Introduction

Lung cancer is the deadliest cancer in the United States (U.S.) (1). In 2017, lung cancer caused more deaths than breast, prostate, colorectal, and brain cancers combined (1). A large randomized controlled trial found that annual screening can decrease lung cancer mortality by 20% in the high risk population (2), which indicates the effect of early detection and timely treatment on lung cancer survival. Timely treatment has been associated with improved survival for many types of cancer, especially for the early stage diseases (3–6). However, there is a lack of consensus on the impact of timely care on lung cancer survival. Although surgery is the initial treatment recommended to the operable diseases (7,8), the major clinical guidelines on the timing of lung cancer surgery are inconsistent. Rand Corporation recommended lung cancer surgery within 6 weeks from diagnosis in 2000 and did not update the guidelines since then (9). American College of Chest Physicians (ACCP) recommended surgery within 4–8 weeks of referral in 2003 guidelines (10), but in its most recent guidelines from 2013, only ‘interventions to improve timeliness should be developed locally by addressing barriers to providing timely care that are specific to the local setting’ was recommended (11). British Thoracic Surgery (BTS) suggested a maximum of 8 weeks from respiratory specialist consultation to surgery in 1998 (12), however, no specific recommendations on the timing of treatment was provided in its 2019 guidelines (13). Danish Lung Cancer Group and Registry recommended less than 14 days from diagnosis to treatment (14). The reason for the inconsistency in the clinical guidelines could be the conflicting findings from the previous research. Thus, well designed epidemiological studies with more contemporary data and larger sample size is needed to describe the association between timely surgery and lung cancer survival.

Intensive work has been done to differentiate histologic subtypes of lung cancer, which can be used to predict prognosis and personalize treatment. Generally, two broad classes of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is a group of several histologies, representing about 85% of all lung cancer cases. The recommended initial treatment for early stage NSCLC is surgery (7). SCLC has a higher tumor growth rate and worse prognosis than NSCLC (15). Surgical resection is also recommended to operable SCLC, however, most SCLC has spread at diagnosis, for which the mainstay treatment is chemotherapy (8). In the past

two decades, more attention has been paid to the histologic subtypes (16). For example, adenocarcinoma is the most common histology of lung cancer, representing almost half of lung cancer cases (17). Squamous cell carcinoma accounts for about 30% of NSCLC, which has a shorter doubling time, lower sensitivity to targeted therapy, and poorer survival than adenocarcinoma (18,19). Other histologic subtypes, such as bronchioloalveolar carcinoma and carcinoid carcinoma, are rare but usually well-differentiated and have high survival rates if resected at an early stage (20,21). Given the different prognoses and responses to the treatment, it is important to determine the timeliness of treatment for each histologic subtype of lung cancer. In this study, we aimed to examine the association between diagnosis-to-surgery time interval and survival for stage I-IIA lung cancers and selected histologic subtypes. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/tlcr-21-168>).

Methods

Data source and study population

The Surveillance, Epidemiology, and End Results (SEER) program, which is supported by National Cancer Institute, collects cancer incidence data from population-based cancer registries covering approximately 34.6% of the U.S. population (22). The SEER registries routinely collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, and first course of treatment. By linking with National Death Index and state death file, patients’ vital status, date of last contact, and cause of death can be identified (22).

In this study, patients diagnosed with the American Joint Committee on Cancer (AJCC) stage I–IIA lung cancer during 2004 and 2015 (AJCC 6th Edition used for 2004–2009 cases and AJCC 7th Edition used for 2010–2015 cases) were identified from the SEER database, including data from 18 cancer registries. Patients whose lung cancer was diagnosed as the only cancer or as the first primary cancer if more than one cancer were diagnosed, with negative lymph node involvement, receiving surgery of lobectomy, bilobectomy, or pneumonectomy, were included in the analyses. Exclusion criteria included: (I) patients with missing information on time interval between tumor diagnosis and treatment initiation, (II) patients receiving radiation before or before/after surgery or with sequence

between radiation and surgery unknown; and (III) patients with less than one-month follow-up. All patients were followed until December 31, 2018.

All procedures performed in studies were in accordance with the Helsinki Declaration (as revised in 2013).

Lung cancer histologic subtype

Following the categorization proposed by SEER, lung cancer histologic subtype was determined based on the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3): adenocarcinoma (8140–8149), squamous or epidermoid carcinoma (8070–8079), bronchioloalveolar carcinoma (8250), large cell carcinoma (8012), adenosquamous carcinoma (8560), carcinoid (8240–8249), and small cell carcinoma (8041–8045) (23).

Variables

The primary exposure variable was the time interval between tumor diagnosis and surgery. The original variable in the SEER database was the interval between tumor diagnosis and treatment initiation (in months). We used this variable to approximate the interval between tumor diagnosis and surgery, as the initial treatment was highly likely to be surgery in this selected patient population. Three inclusion/exclusion criteria were applied to ensure the selected population receiving surgery as the initial treatment: (I) we included stage I–IIA lung cancer patients, for whom the recommended initial treatment is surgery if the cancer is operable (both NSCLC and SCLC) (7,8); (II) we included only the patients who received a definitive surgery (lobectomy, bilobectomy, or pneumonectomy); and (III) we excluded the patients whose radiation therapy was given before the surgery or before/after the surgery and the patients whose sequence between radiation and surgery was unknown. In other words, stage I–IIA lung cancer patients who received surgery and the surgery was the only treatment or prior to radiation were included in the analyses, thus, we used the time interval between diagnosis and treatment initiation as a substitute for the time interval between diagnosis and surgery.

The time interval between tumor diagnosis and surgery was examined in a multi-categorical format: less than 1 month (<1 month), 1 month or longer but less than 2 months (1–2 months), 2 months or longer but less than 3 months (2–3 months), 3 months or longer (≥ 3 months). With multi-categorical variables, potential dose-dependent

effect (longer delay, worse survival) can be detected by the trend analyses. Furthermore, to detect any non-linear associations (no trend for the worse survival associated with the increased time interval, but delay beyond a single cut-off point in the interval associated with worse survival) and maintain the sample size in multivariable analyses, especially for the less frequent histologic subtypes, a secondary exposure variable of the diagnosis-to-surgery interval was examined in a binary format: ≥ 1 vs. <1 month, ≥ 2 vs. <2 months, and ≥ 3 vs. <3 months.

The outcome variables included lung cancer-specific survival and overall survival. In the analyses of lung-cancer specific survival, patients dying from other causes or alive at the end of follow-up were censored, and patients dying from unknown causes were excluded. Patients' survival time was calculated as the time interval between tumor diagnosis and date of last contact (death or end of the follow-up) in months.

Covariates included age at diagnosis (<50, 50–59, 60–69, ≥ 70 years), sex, race (white, other), marital status (married, single or divorced or separated or widowed or unmarried or domestic partner, unknown), tumor size (AJCC tumor size T1, T2), grade (well differentiated, moderately differentiated, poorly differentiated or undifferentiated, unknown), histologic subtype, surgery type (resection of one lobe or bilobectomy, lobectomy or bilobectomy with dissection of lymph nodes or pneumonectomy), chemotherapy (yes, no or unknown), radiation therapy (yes, no or unknown), and study period (2004–2009, 2010–2015).

Statistical analysis

We used Chi-square tests to compare patient's sociodemographic and clinical characteristics. Kaplan-Meier survival curves were created to present the cancer-specific survival and overall survival distribution by diagnosis-to-surgery interval, among all patients and stratified by histologic subtypes. Log-rank tests were conducted to examine the statistical differences in the Kaplan-Meier survival curves. We additionally applied Cox proportional hazards regressions to evaluate the survival differences associated with the diagnosis-to-surgery interval, with and without adjustment of covariates. In the analyses of the multi-categorical variable of diagnosis-to-surgery interval (<1, 1–2, 2–3, ≥ 3 months), as <1 month was set as the reference group, the crude and adjusted odds ratio of each time interval compared to <1 month was calculated and reported. To examine the dose-dependent effect (whether

increased time interval is associated with worse survival), *P* for trend was calculated by treating the time interval as a continuous variable. All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA) and statistical tests of significance were based on a two-sided test with significance levels of 0.05.

Results

A total of 40,612 patients were analyzed in this study (Table 1), including 53.3% female and 84.8% white. Adenocarcinoma was the most frequent histologic subtype (40.1%), followed by squamous or epidermoid carcinoma (24.5%), and SCLC was the least frequent histologic subtype (0.9%). The follow-up time ranged from 1 to 155 months, with a median of 51 months (interquartile 1–3: 26–87 months). During the follow-up, 39.8% of the patients died from any causes, while 23.1% of the patients died from cancer-specific causes.

The proportion of the patients receiving surgery <1, 1–2, 2–3, and ≥3 months from diagnosis were 34.2%, 33.9%, 19.8%, and 12.1%, respectively (Table 1). Younger, female, white, married patients and those with well-differentiated or T1 size tumor had shorter time interval to surgery, compared to their counterparts (*P*<0.0001). Within each histologic subtype, the proportion of patients receiving surgery within 1 month from diagnosis ranged from 28.9% for squamous or epidermoid carcinoma to 41.3% for bronchioloalveolar carcinoma; and the proportion of receiving surgery ≥3 months after diagnosis ranged from 8.5% for SCLC to 13.9% for squamous or epidermoid carcinoma. Both the proportions of cancer-specific death (from 21.7% to 25.5%) and all-cause death (from 37.5% to 44.8%) increased as the diagnosis-to-surgery interval increased (*P*<0.0001).

Figure 1 shows the Kaplan-Meier cancer-specific survival curves by the time to surgery among all lung cancer patients and patients with each histologic subtype. Among all lung cancer patients, those receiving earlier surgery had better survival than those receiving later surgery (*P*<0.0001). Among adenocarcinoma patients, those with <1 month diagnosis-to-surgery interval had the best survival and those with ≥3 months interval had the worst survival, while the survival curves for patients with intervals of 1–2 and 2–3 were greatly overlapped. For squamous or epidermoid carcinoma, except in the first 6 years of follow-up when 2–3 and ≥3 months to surgery showed similar survival, earlier surgery was associated with better survival. For bronchioloalveolar carcinoma, the cancer-specific survival

was very similar in the first 5 years of follow-up regardless of time to surgery, but patients receiving surgery within 1 month from diagnosis had best survival during the rest of the follow-up time. Large cell lung cancer patients receiving surgery 3 months or later from diagnosis had worst survival than their counterparts who received earlier surgery. Time to surgery from diagnosis was not associated with cancer-specific survival for patients with adenosquamous carcinoma, carcinoid carcinoma, or small cell carcinoma.

Figure 2 shows the overall survival curves by the time interval between diagnosis and surgery. Similar to cancer-specific survival curves, earlier treatment was associated with better survival among all lung cancer patients and adenocarcinoma patients. For squamous or epidermoid carcinoma patients, those receiving surgery ≥3 months had the worst survival, while <1 and 1–2 months diagnosis-to-surgery interval had very similar survival curves. Early surgery showed better survival in bronchioloalveolar patients, except no obvious survival differences among those with 2–3 and ≥3 months intervals. No significant overall survival differences due to time to surgery were observed in patients with large cell carcinoma, adenosquamous carcinoma, carcinoid carcinoma, or small cell carcinoma.

Table 2 presents the results from Cox proportional hazards regressions, with and without adjusting covariates. Similar as shown in Kaplan-Meier survival curves, compared to lung cancer patients receiving surgery <1 month from diagnosis, delayed surgery was associated with 15%, 25%, and 37% increased hazard of cancer-specific death for 1–2, 2–3, and ≥3 months from diagnosis, respectively, without controlling for covariates (*P*<0.0001 for each, *P* for trend <0.0001). With adjustment of covariates, the increased hazard was 3% [hazard ratio (HR): 1.03; 95% confidence interval (CI): 0.98–1.09], 10% (HR: 1.10; 95% CI: 1.04–1.16), and 22% (HR: 1.22; 95% CI: 1.14–1.30) for the three groups of patients, respectively (*P* for trend <0.0001). When using binary exposure variable, patients receiving surgery one month or later after diagnosis had 1.08 times the hazard of cancer-specific death (HR: 1.08; 95% CI: 1.04–1.13) than those receiving surgery within one month from diagnosis; ≥2 months diagnosis-to-surgery interval was associated with 1.12 times the hazard of cancer-specific death compared to <2 month interval (HR: 1.12; 95% CI: 1.07–1.17); the HR for ≥3 months interval was 1.17 (95% CI: 1.10–1.25) compared to <3 months interval. After stratified by histologic subtype, extended timeline to surgery was associated with worse cancer-specific survival and dose-dependent relationship was significant for

Table 1 Characteristics of patients diagnosed with stage I-IIA lung cancer in Surveillance, Epidemiology, and End Results registries between 2004 and 2015

Characteristics	All patients		Time interval between diagnosis and treatment initiation (row %)				P value
	N	%	<1 month (N=13,907)	1–2 months (N=13,754)	2–3 months (N=8,026)	≥3 months (N=4,925)	
All	40,612		34.2	33.9	19.8	12.1	
Age, years							<0.0001
<50	2,048	5.0	42.5	35.4	13.6	8.5	
50–59	6,885	17.0	37.3	32.9	18.4	11.5	
60–69	14,427	35.5	35.2	33.6	19.0	12.2	
≥70	17,252	42.5	31.2	34.3	21.7	12.8	
Sex							<0.0001
Male	18,949	46.7	33.2	33.8	20.0	13.1	
Female	21,663	53.3	35.2	34.0	19.6	11.3	
Race							<0.0001
White	34,345	84.8	34.9	34.4	19.3	11.4	
Other	6,160	15.2	30.3	30.8	22.5	16.5	
Marital status							<0.0001
Married	23,430	57.7	35.4	35.6	19.0	9.9	
Single, divorced, separated, widowed, unmarried or domestic partner	15,740	38.8	32.1	31.5	20.9	15.5	
Unknown	1,442	3.55	38.7	30.7	19.8	11.6	
Grade							<0.0001
Well differentiated	7,433	18.3	39.6	32.7	17.0	10.8	
Moderately differentiated	17,020	41.9	33.4	33.7	20.4	12.5	
Poorly differentiated or undifferentiated	13,137	32.4	31.5	35.6	20.7	12.2	
Unknown	3,022	7.4	37.8	29.9	19.3	13.0	
Tumor size							<0.0001
T1	22,018	54.2	39.0	31.4	18.1	11.6	
T2	18,594	45.8	28.6	36.8	21.8	12.8	
Surgery type							0.0003
Resection of one lobe or bilobectomy	8,906	21.9	36.0	32.6	19.1	12.2	
Lobectomy or bilobectomy with dissection of lymph nodes or pneumonectomy	31,706	78.1	33.7	34.2	19.9	12.1	
Radiation therapy							0.0002
Yes	1,071	2.6	29.1	39.5	20.0	11.4	
No/unknown	39,541	97.4	34.4	33.7	19.8	12.2	

Table 1 (continued)

Table 1 (continued)

Characteristics	All patients		Time interval between diagnosis and treatment initiation (row %)				P value
	N	%	<1 month (N=13,907)	1–2 months (N=13,754)	2–3 months (N=8,026)	≥3 months (N=4,925)	
Chemotherapy							<0.0001
Yes	4,639	11.4	30.4	40.7	19.6	9.3	
No/unknown	35,973	88.6	34.7	33.0	19.8	12.5	
Histologic subtype							<0.0001
Adenocarcinoma	16,269	40.1	34.8	34.5	18.9	11.7	
Squamous or epidermoid	9,954	24.5	28.9	34.8	22.4	13.9	
Bronchioloalveolar	2,414	5.9	41.3	31.2	18.4	9.2	
Large cell	627	1.5	38.4	31.4	20.9	9.3	
Adenosquamous	926	2.3	29.2	34.9	22.4	13.6	
Carcinoid	1,870	4.6	39.1	30.9	16.4	13.6	
Small cell	377	0.9	39.8	34.5	17.2	8.5	
Other	8,175	20.1	36.6	33.3	20.7	13.4	
Cancer-specific death	9,381	23.1	21.7*	23.4*	24.1*	25.5*	<0.0001
All-cause death	16,153	39.8	37.5*	39.0*	42.0*	44.8*	<0.0001
Follow-up time, months, median [IQR]		51 [26–87]	57 [29–93]	52 [26–87]	47 [23–82]	44 [22–77]	<0.0001

*, proportion of death (%) in each subgroup. IQR, inter-quartile range.

adenocarcinoma, squamous or epidermoid carcinoma, and bronchioloalveolar carcinoma. For large cell carcinoma, >3 month from diagnosis to surgery was associated with significant worse survival (HR: 1.63; 95% CI: 1.09–2.44) than <3 months interval, controlling for covariates. No significant association was observed between time to surgery and cancer-specific survival for adenosquamous carcinoma, carcinoid carcinoma, and small cell carcinoma.

Table 3 shows the overall survival differences from Cox proportional hazards regressions. When using multi-categorical exposure variable of the diagnosis-to-surgery interval, 2–3 and ≥3 months were associated with significantly worse overall survival compared to <1 month for patients with any lung cancer, adenocarcinoma, squamous or epidermoid carcinoma, and bronchioloalveolar carcinoma (P for trend <0.0001 for each), after adjusting for covariates. When using binary exposure variable, the longer time interval between diagnosis and surgery was associated with worse overall survival at each cut-off point for patients with any lung cancer, adenocarcinoma, squamous or epidermoid carcinoma, and bronchioloalveolar carcinoma.

No significant overall survival differences were observed for other histologic subtypes when adjusting for covariates.

Discussion

With a median follow-up of 51 months of a SEER retrospective cohort of 40,612 stage I-IIA lung cancer patients who received surgery, we examined the association between diagnosis-to-surgery time interval and the cancer-specific and overall survival. We found that extended diagnosis-to-surgery interval was associated with worse survival in all lung cancer patients and a few selected histologic subtypes. A strong dose-dependent effect from delayed surgery was detected in patients with adenocarcinoma and squamous or epidermoid carcinoma (longer delay, worse survival). No significant survival differences due to delayed surgery were observed among patients with adenosquamous carcinoma, carcinoid carcinoma, and small cell carcinoma. Findings on cancer-specific survival and overall survival were consistent.

In the past two decades, many studies examined the

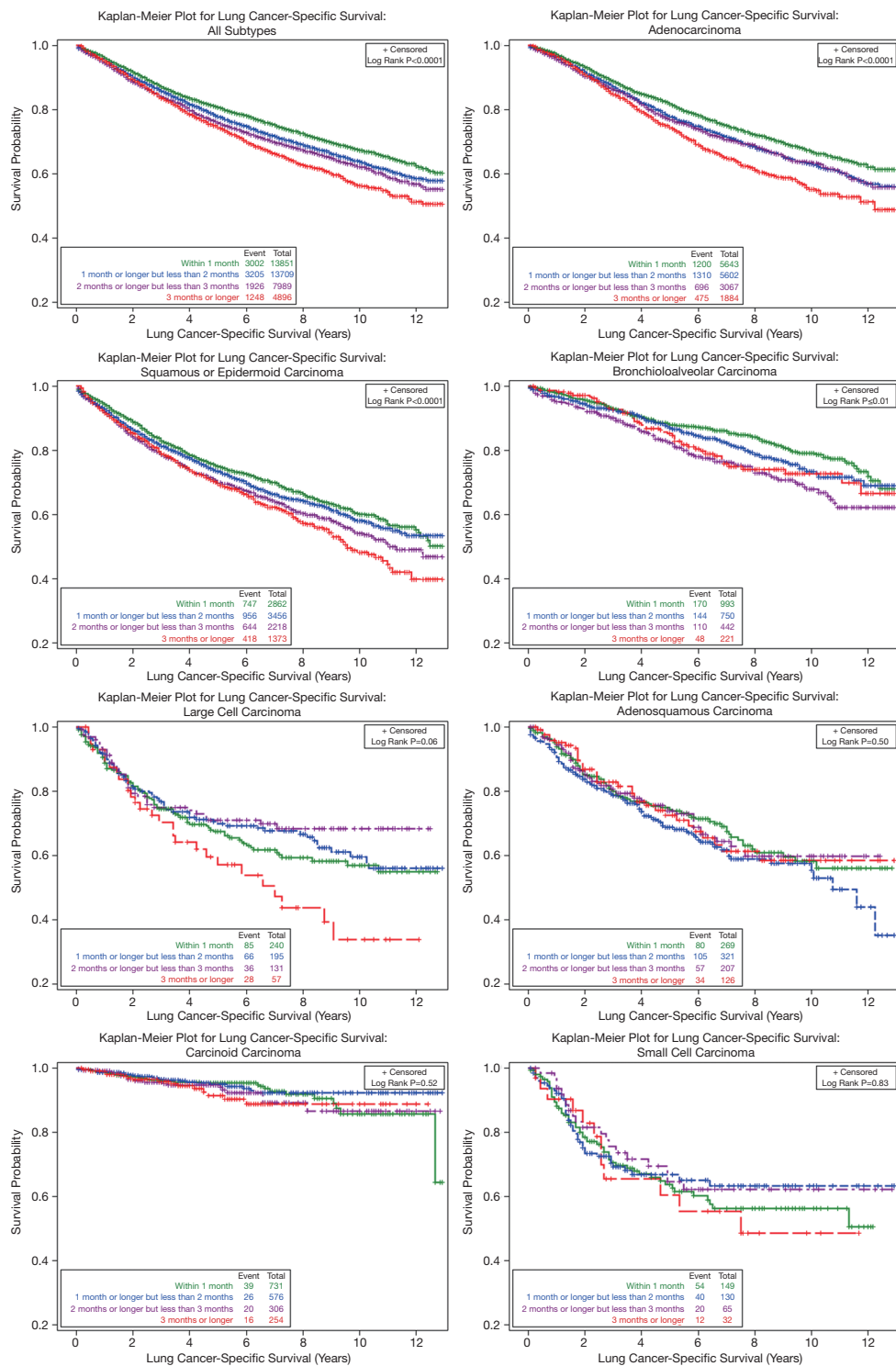


Figure 1 Kaplan-Meier plot of lung cancer-specific survival by time interval between cancer diagnosis and surgery.

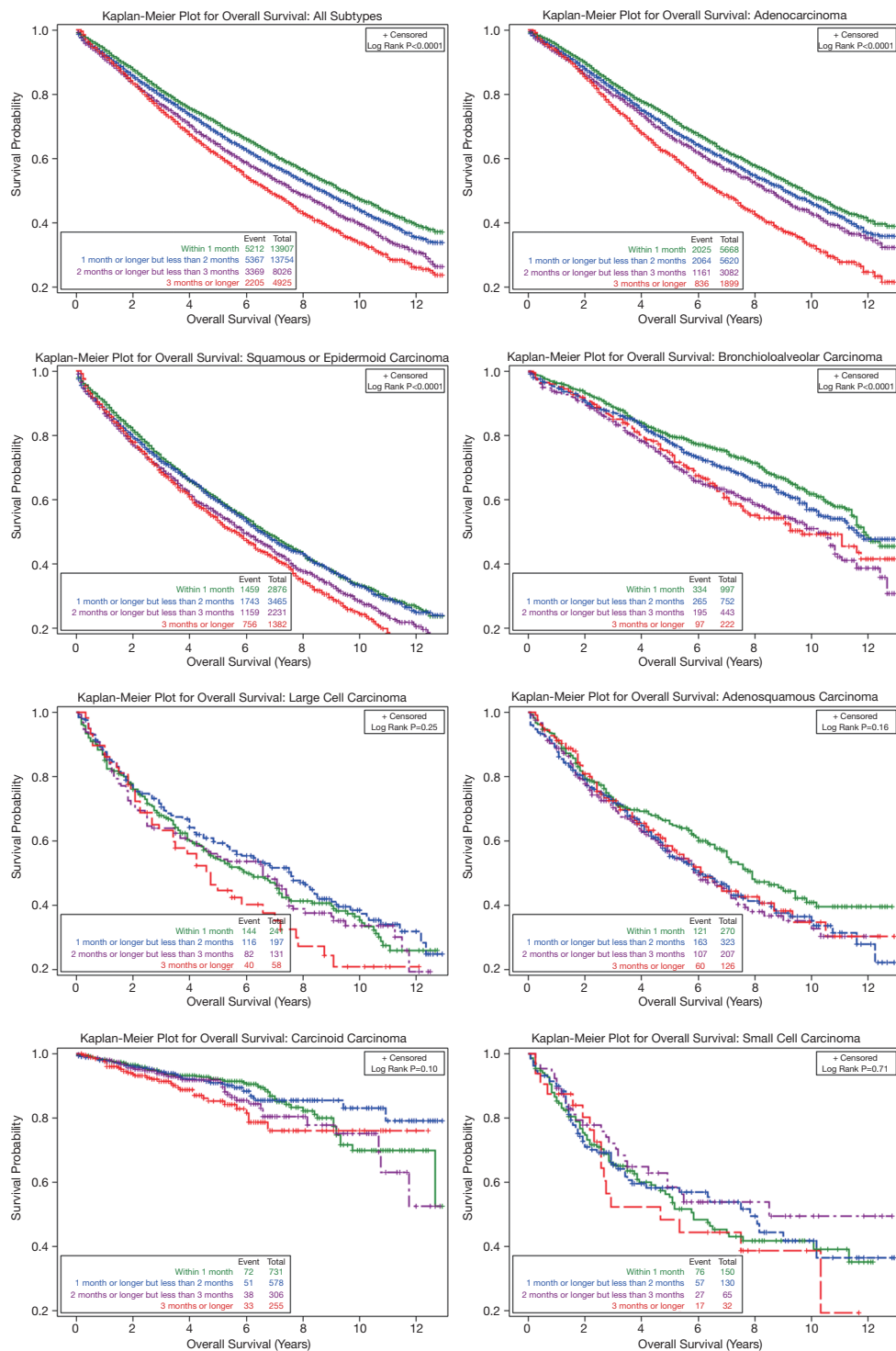


Figure 2 Kaplan-Meier plot of overall survival by time interval between cancer diagnosis and surgery.

Table 2 Hazard ratios (95% confidence intervals) of cancer-specific death by the time interval between lung cancer diagnosis and surgery, among all patients with stage I–IIA disease and stratified by histologic subtype

Variable	Crude	Adjusted*
All patients		
1–2 vs. <1 month	1.15 (1.09–1.21) [¶]	1.03 (0.98–1.09)
2–3 vs. <1 month	1.25 (1.18–1.32) [¶]	1.10 (1.04–1.16) [‡]
≥3 vs. <1 month	1.37 (1.29–1.47) ^{¶§}	1.22 (1.14–1.30) ^{¶§}
≥1 vs. <1 month	1.22 (1.17–1.27) [¶]	1.08 (1.04–1.13) [¶]
≥2 vs. <2 months	1.21 (1.16–1.26) [¶]	1.12 (1.07–1.17) [¶]
≥3 vs. <3 months	1.24 (1.17–1.32) [¶]	1.17 (1.10–1.25) [¶]
Adenocarcinoma		
1–2 vs. <1 month	1.18 (1.09–1.28) [¶]	1.10 (1.02–1.19) [†]
2–3 vs. <1 month	1.22 (1.11–1.33) [¶]	1.11 (1.01–1.22) [†]
≥3 vs. <1 month	1.44 (1.29–1.60) ^{¶§}	1.29 (1.16–1.44) ^{¶§}
≥1 vs. <1 month	1.23 (1.15–1.32) [¶]	1.13 (1.06–1.22) [¶]
≥2 vs. <2 months	1.19 (1.11–1.28) [¶]	1.12 (1.04–1.20) [‡]
≥3 vs. <3 months	1.29 (1.17–1.42) [¶]	1.22 (1.11–1.34) [¶]
Squamous or epidermoid carcinoma		
1–2 vs. <1 month	1.10 (1.00–1.21)	1.03 (0.94–1.14)
2–3 vs. <1 month	1.24 (1.12–1.38) [¶]	1.16 (1.04–1.29) [‡]
≥3 vs. <1 month	1.32 (1.17–1.48) ^{¶§}	1.23 (1.09–1.38) ^{¶§}
≥1 vs. <1 month	1.18 (1.09–1.29) [¶]	1.11 (1.02–1.20) [†]
≥2 vs. <2 months	1.21 (1.12–1.31) [¶]	1.17 (1.08–1.26) [¶]
≥3 vs. <3 months	1.20 (1.08–1.33) [‡]	1.16 (1.05–1.29) [†]
Bronchioalveolar carcinoma		
1–2 vs. <1 month	1.22 (0.97–1.52)	1.08 (0.86–1.35)
2–3 vs. <1 month	1.62 (1.28–2.06) [¶]	1.44 (1.13–1.83) [‡]
≥3 vs. <1 month	1.39 (1.01–1.91) ^{¶§}	1.19 (0.86–1.66) [¶]
≥1 vs. <1 month	1.37 (1.13–1.65) [‡]	1.21 (1.00–1.46)
≥2 vs. <2 months	1.42 (1.17–1.72) [¶]	1.31 (1.08–1.59) [‡]
≥3 vs. <3 months	1.17 (0.87–1.57)	1.07 (0.79–1.44)
Large cell carcinoma		
1–2 vs. <1 month	0.89 (0.65–1.23)	0.85 (0.62–1.19)
2–3 vs. <1 month	0.76 (0.52–1.13)	0.65 (0.43–0.96) [†]
≥3 vs. <1 month	1.46 (0.95–2.23)	1.40 (0.91–2.15)
≥1 vs. <1 month	0.93 (0.71–1.22)	0.86 (0.65–1.13)
≥2 vs. <2 months	1.01 (0.76–1.36)	0.91 (0.68–1.23)
≥3 vs. <3 months	1.60 (1.08–2.39) [†]	1.63 (1.09–2.44) [†]

Table 2 (continued)

Table 2 (continued)

Variable	Crude	Adjusted*
Adenosquamous carcinoma		
1–2 vs. <1 month	1.22 (0.91–1.63)	1.19 (0.89–1.60)
2–3 vs. <1 month	1.03 (0.73–1.44)	1.00 (0.71–1.41)
≥3 vs. <1 month	1.01 (0.67–1.51) [#]	0.94 (0.62–1.42)
≥1 vs. <1 month	1.12 (0.86–1.45)	1.08 (0.83–1.41)
≥2 vs. <2 months	0.92 (0.71–1.18)	0.89 (0.69–1.14)
≥3 vs. <3 months	0.92 (0.64–1.31)	0.87 (0.61–1.26)
Carcinoid carcinoma		
1–2 vs. <1 month	0.90 (0.55–1.48)	0.82 (0.49–1.38)
2–3 vs. <1 month	1.22 (0.71–2.09)	0.93 (0.53–1.64)
≥3 vs. <1 month	1.37 (0.76–2.45)	1.25 (0.68–2.31)
≥1 vs. <1 month	1.09 (0.73–1.62)	0.94 (0.62–1.43)
≥2 vs. <2 months	1.34 (0.89–2.01)	1.14 (0.74–1.76)
≥3 vs. <3 months	1.36 (0.79–2.32)	1.36 (0.78–2.37)
Small cell carcinoma		
1–2 vs. <1 month	0.90 (0.59–1.35)	0.89 (0.57–1.40)
2–3 vs. <1 month	0.83 (0.50–1.38)	0.68 (0.40–1.17)
≥3 vs. <1 month	1.08 (0.58–2.03)	0.97 (0.50–1.88)
≥1 vs. <1 month	0.90 (0.63–1.28)	0.83 (0.57–1.22)
≥2 vs. <2 months	0.95 (0.64–1.42)	0.81 (0.53–1.22)
≥3 vs. <3 months	1.17 (0.64–2.12)	1.09 (0.58–2.04)

*, all model adjusted age at diagnosis, sex, race, marital status, tumor size, grade, surgery type, chemotherapy, radiation therapy, and study period. In the model for all patients, histologic subtype was also adjusted. [†], P<0.05; [‡], P<0.01; [§], P<0.001. [#], P for trend <0.05; [!], P for trend <0.01; [§], P for trend <0.0001.

correlation between timely care and lung cancer survival but yielded mixed and even paradoxical findings. Some studies reported better survival associated with timely diagnosis, staging, and treatment (24–27), some studies did not find any significant associations (28–31), while others found inverse associations (32,33). Three possible reasons could explain the inconsistent findings. The first reason could be the unnoticed effect modification from stage and histology. Compared to advanced stage diseases, early stage diseases have a longer wait time due to multiple diagnostic tests and staging studies but better prognosis (32,34). SCLC tends to have a shorter diagnosis-to-treatment interval but worse survival than NSCLC (32). Delayed diagnosis or treatment could impact survival differently across these patient

subgroups. Without stratifying by these effect modifiers, the conclusions could be misleading. The second reason could be the different definitions of timely treatment used in the literature, given the inconsistent guidelines. The third reason could be the different treatment modalities used in the previous studies. In our study, we focused on the early stage disease treated with surgery and stratified the sample by histologic subtype to control the confounding and effect modification from stage and histology. In addition, we used the multi-categorical time interval as the exposure variable to examine the dose-dependent effect from delayed treatment, which addressed the concerns associated with binary analysis based on inconsistent guidelines.

There were two studies using the SEER-Medicare

Table 3 Hazard ratios (95% confidence intervals) of all-cause death by the time interval between lung cancer diagnosis and surgery, among all patients with stage I–IIA disease and stratified by histologic subtype

Variable	Crude	Adjusted*
All patients		
1–2 vs. <1 month	1.12 (1.07–1.16) [¶]	1.02 (0.98–1.06)
2–3 vs. <1 month	1.28 (1.22–1.33) [¶]	1.13 (1.08–1.18) [¶]
≥3 vs. <1 month	1.43 (1.36–1.50) ^{¶§}	1.24 (1.18–1.31) ^{¶§}
≥1 vs. <1 month	1.22 (1.18–1.26) [¶]	1.09 (1.05–1.13) [¶]
≥2 vs. <2 months	1.26 (1.22–1.30) [¶]	1.16 (1.12–1.20) [¶]
≥3 vs. <3 months	1.29 (1.24–1.35) [¶]	1.20 (1.15–1.26) [¶]
Adenocarcinoma		
1–2 vs. <1 month	1.11 (1.04–1.18) [¶]	1.05 (0.99–1.12)
2–3 vs. <1 month	1.21 (1.13–1.30) [¶]	1.12 (1.04–1.20) [‡]
≥3 vs. <1 month	1.52 (1.41–1.65) ^{¶§}	1.36 (1.26–1.48) ^{¶§}
≥1 vs. <1 month	1.21 (1.14–1.27) [¶]	1.12 (1.06–1.19) [¶]
≥2 vs. <2 months	1.26 (1.19–1.33) [¶]	1.17 (1.11–1.24) [¶]
≥3 vs. <3 months	1.41 (1.31–1.51) [¶]	1.30 (1.21–1.40) [¶]
Squamous or epidermoid carcinoma		
1–2 vs. <1 month	1.03 (0.96–1.10)	0.99 (0.92–1.06)
2–3 vs. <1 month	1.17 (1.08–1.26) [¶]	1.11 (1.03–1.20) [‡]
≥3 vs. <1 month	1.24 (1.14–1.35) ^{¶§}	1.16 (1.06–1.26) ^{¶§}
≥1 vs. <1 month	1.11 (1.04–1.18) [‡]	1.06 (0.99–1.12)
≥2 vs. <2 months	1.18 (1.11–1.24) [¶]	1.14 (1.07–1.20) [¶]
≥3 vs. <3 months	1.18 (1.09–1.28) [¶]	1.13 (1.05–1.22) [‡]
Bronchioalveolar carcinoma		
1–2 vs. <1 month	1.14 (0.97–1.34)	1.05 (0.89–1.24)
2–3 vs. <1 month	1.48 (1.24–1.76) [¶]	1.32 (1.10–1.58) [‡]
≥3 vs. <1 month	1.42 (1.14–1.79) ^{¶§}	1.29 (1.03–1.62) ^{¶§}
≥1 vs. <1 month	1.29 (1.13–1.48) [¶]	1.17 (1.02–1.35) [‡]
≥2 vs. <2 months	1.38 (1.20–1.59) [¶]	1.28 (1.11–1.48) [¶]
≥3 vs. <3 months	1.25 (1.01–1.55) [‡]	1.19 (0.96–1.47)
Large cell carcinoma		
1–2 vs. <1 month	0.89 (0.70–1.14)	0.89 (0.69–1.14)
2–3 vs. <1 month	1.03 (0.78–1.35)	0.88 (0.66–1.16)
≥3 vs. <1 month	1.28 (0.90–1.82)	1.21 (0.85–1.72)
≥1 vs. <1 month	0.99 (0.80–1.21)	0.93 (0.75–1.15)
≥2 vs. <2 months	1.16 (0.93–1.44)	1.02 (0.82–1.27)
≥3 vs. <3 months	1.33 (0.96–1.84)	1.29 (0.93–1.80)

Table 3 (continued)

Table 3 (continued)

Variable	Crude	Adjusted*
Adenosquamous carcinoma		
1–2 vs. <1 month	1.27 (1.00–1.61) [†]	1.21 (0.95–1.53)
2–3 vs. <1 month	1.30 (1.00–1.68) [†]	1.24 (0.95–1.62)
≥3 vs. <1 month	1.20 (0.88–1.64)	1.09 (0.80–1.50)
≥1 vs. <1 month	1.26 (1.03–1.56) [†]	1.19 (0.97–1.48)
≥2 vs. <2 months	1.11 (0.91–1.34)	1.07 (0.88–1.30)
≥3 vs. <3 months	1.02 (0.78–1.34)	0.96 (0.73–1.26)
Carcinoid carcinoma		
1–2 vs. <1 month	0.96 (0.67–1.37)	0.95 (0.66–1.37)
2–3 vs. <1 month	1.25 (0.85–1.86)	0.98 (0.66–1.47)
≥3 vs. <1 month	1.55 (1.02–2.34) ^{†#}	1.35 (0.88–2.07)
≥1 vs. <1 month	1.16 (0.87–1.56)	1.04 (0.77–1.41)
≥2 vs. <2 months	1.40 (1.05–1.88) [†]	1.15 (0.85–1.56)
≥3 vs. <3 months	1.50 (1.03–2.18) [†]	1.38 (0.94–2.03)
Small cell carcinoma		
1–2 vs. <1 month	0.94 (0.67–1.33)	0.96 (0.66–1.39)
2–3 vs. <1 month	0.81 (0.52–1.26)	0.71 (0.45–1.12)
≥3 vs. <1 month	1.13 (0.67–1.91)	1.06 (0.61–1.85)
≥1 vs. <1 month	0.93 (0.69–1.25)	0.89 (0.65–1.22)
≥2 vs. <2 months	0.94 (0.67–1.32)	0.82 (0.58–1.18)
≥3 vs. <3 months	1.20 (0.73–1.98)	1.16 (0.68–1.96)

*, all model adjusted age at diagnosis, sex, race, marital status, tumor size, grade, surgery type, chemotherapy, radiation therapy, and study period. In the model for all patients, histologic subtype was also adjusted. [†], P<0.05; [‡], P<0.01; [§], P<0.001. [#], P for trend <0.05; [!], P for trend <0.01; [§], P for trend <0.0001.

dataset examining the consequences of delayed care on lung cancer survival. Both studies examined the survival effect of the time interval from diagnosis to any treatment initiation among all stage lung cancer patients. One study evaluated NSCLC patients from 2004–2007 and found that diagnosis-to-treatment interval ≤ 35 days was associated with better survival among patients with localized disease, which was similar with our findings (34). Another study analyzed 2002–2007 NSCLC and SCLC patients but found a paradoxical association between timely treatment and overall survival (32). After stratified by stage, the association between timely care and worse survival was significant only among stage III & IV patients, and there was a trend for a positive but insignificant association among stage I &

II patients (32). Compared to these two studies, we used more contemporary data of curative patients and focused on the effect of timely surgery, i.e., stage I & IIA patients who received definitive surgery. The more restricted study population can explain the higher prevalence of delayed treatment in our study (34% of patients receiving treatment within 1 month from diagnosis in our study *vs.* higher than 60% of patients receiving timely care in the other two studies), as both early stage and receiving surgery are the risk factors of delayed treatment (32,35). Among the studies focusing on the effect of timely surgery, two studies using National Cancer Data Base (NCDB) reported higher likelihood of pathologic upstaging and worse survival associated with delayed surgical resection among stage I

NSCLC patients (25,26), which was consistent with our findings. One study reported 4% increased hazard of death for every one week delay to surgery among stage I & II community diagnosed NSCLC patients (36). Two studies analyzing stage I & II NSCLC patients from single institution did not find significant association between delayed surgical resection and survival, for which the small sample size could be the reason (29,37).

To our knowledge, our study is the first one examining the impact of delayed surgery on survival for each lung cancer histologic subtype. It was proposed that the faster growing tumors are more sensitive to extended wait time to treatment, as the longer diagnosis-to-treatment interval can result in worse outcomes due to the higher tumor growth rate (38). However, our data did not show this pattern. In our study, delayed surgery was associated with worse survival for adenocarcinoma, squamous cell carcinoma, bronchioloalveolar carcinoma, and large cell carcinoma, and the strength of the association was similar for these histologic subtypes. Similarly, another study found the survival effect of delay in any treatment was similar for NSCLC and SCLC, for all stages combined (32). One previous study analyzing a patient population with clinical stage IA lung squamous cell carcinoma from NCDB, reported 36% of patients receiving surgery within 30 days from diagnosis and 11–13% increased risk of all-cause mortality associated with delayed surgery, which is very similar with our findings for squamous cell carcinoma (10–20% increased risk) (39). Another recent study analyzing 286 propensity score matched clinical stage I lung adenocarcinoma patients found that delayed surgery (>21 days from histologic diagnosis to surgery) is associated with two-fold risk of all-cause mortality (HR =2.03, P=0.038), which is higher than 10–36% increased risk in our adenocarcinoma patients. Additionally, for adenocarcinoma and squamous or epidermoid carcinoma, the longer interval between diagnosis and surgery was associated with worse cancer-specific and overall survival in our study (P for trend <0.0001).

No previous research investigated the effect of timely care on survival for other less frequent histologic subtypes of lung cancer. Our data was not able to detect significant survival differences associated with delayed surgery for adenosquamous carcinoma, carcinoid carcinoma, and SCLC, for which the smaller sample size could be a reason. Adenosquamous carcinoma contains both adenocarcinoma and squamous component, with each component constituting at least 10% of the tumor, and has higher tumor growth rate than adenocarcinoma (16). Our data

showed that using 1 month as cutoff point to define delayed surgery tends to have stronger effect than using 3 months as cutoff point among adenosquamous carcinoma patients. Carcinoid carcinoma is a rare and well-differentiated neuroendocrine tumor (21), which had about 90% cancer-specific survival rate in our study. Undertaking surgery 3 months or later after diagnosis tended to be associated with worse cause-specific and overall survival for carcinoid carcinoma. Regarding SCLC, as majority of the diseases are inoperable at diagnosis in the clinical practice, for which the chemotherapy is the mainstay treatment, future studies with detailed information on the timing of other treatment are needed to determine the effect of timely care.

Our findings emphasize the clinical importance of timely care for lung cancer, which has been considered as a practice gap (40). In addition to survival benefit, timely care can relieve patients' stress and anxiety, and improve quality of life. However, multiple diagnostic tests and consultations could make the timely lung cancer management challenging. Previous studies examined the effects of nurse-led care coordination (41), multidisciplinary clinics via telemedicine (42), and outpatient diagnostic process (43,44) to shorten the time to active treatment. More recent studies proposed the target time window to improve timely care (34,36). Based on these findings, how to overcome the institutional challenges to provide timely management is a priority for lung cancer care.

Our study has several strengths. The first strength is the exclusive study population from a contemporary national database. We included only stage I-IIA patients who received surgery, which can avoid the confounding effect from stage and medical complexity (medically inoperable patients were excluded). Secondly, while most previous studies defined the delayed treatment into a single binary variable, we investigated the delayed treatment in both multi-categorical and binary format. By comparing the survival of patients receiving surgery 1–2, 2–3, and ≥3 months to <1 month and providing P value for trend, we can evaluate the dose-dependent effect from delayed treatment, which can provide stronger evidence on the association. By using 1, 2, and 3 months as cutoff points to generate three binary variables, we have higher chance to identify the most appropriate interval for timely treatment for each histologic subtype. Thirdly, as majority of previous studies included only overall survival as the outcome, we additionally used cancer-specific survival as the outcome. Cancer-specific survival is a more sensitive indicator of the effect from cancer treatment and prognosis, especially for

the old patient population.

Despite strengths, our study is also subjected to limitations. First of all, the exact date of surgery was not available in the original dataset. The time interval between the diagnosis and treatment initiation was used to approximate the diagnosis-to-surgery interval. Although we believe this approximation was appropriate as surgery was highly likely to be the initial treatment in the study population, future studies with exact surgery date are needed to confirm the findings. The second limitation is the lack of information on patient's comorbidity and performance status, which can be important confounders of timely surgery. We alleviated the confounding effect from comorbidity and performance status by including only patients who received surgery and using cancer-specific survival as an outcome. Patients with severe comorbid conditions or poor performance status who were not eligible for surgery were excluded in the analysis. Cancer-specific survival is less likely to be confounded by other health conditions and comorbidities. Thirdly, for the variables of chemotherapy utilization and radiation therapy utilization, no treatment and treatment unknown were grouped together. This is an inherent limitation of cancer registry data. The last limitation is the small sample size for less frequent histologic subtypes, especially SCLC. Larger sample size can provide more power to detect significant differences.

In summary, as the first study systematically examining the impact of delayed surgery on survival by histologic subtype, we found the delayed surgery is associated with worse survival in a large cohort of stage I-IIA lung cancer patients. The effect of delayed surgery was especially profound in adenocarcinoma, squamous or epidermoid carcinoma, bronchioloalveolar carcinoma, and large cell carcinoma. Our findings support the guidelines of receiving surgery within one month from tumor diagnosis in patients with stage I-IIA lung cancer. The observed dose-dependent effects emphasize the clinical importance of early treatment. Future studies with a larger sample size of less frequent histologic subtypes are warranted to provide more evidence for histology-specific lung cancer treatment guidelines.

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