Heliyon 9 (2023) e19750

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Impact of time-to-treatment initiation on survival in single primary non-small cell lung Cancer: A population-based study

Jun Teng [a,1], Yan Liu [a,1], Junyan Xia [b], Yi Luo [a], Heng Zou [a], Hongwu Wang [a,*]

[a] Respiratory Disease Center, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, 100700, Beijing, China
[b] Department of Cardiology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, 100700, Beijing, China

ARTICLE INFO

Keywords:
Non-small cell lung cancer
SEER database
Time-to-treatment initiation
Propensity score matching
Competing risk model

ABSTRACT

Background: Understanding the effects of a delayed time-to-treatment initiation(TTI) for non-small cell lung cancer (NSCLC) is vital.
Methods: We analyzed NSCLC data from the Surveillance, Epidemiology, and End Results database, focusing on lung adenocarcinoma (LUAD) and lung squamous carcinoma (LUSC). TTI was studied as both continuous and dichotomous variables. Restricted cubic splines were employed to identify potential nonlinear dependency between the hazard ratio (HR) and TTI. Propensity score matching was used to ensure a balanced patient allocation, and then survival differences between groups were assessed using Kaplan-Meier analysis and competing risk models. We used overall survival (OS) as the primary outcome and cancer-specific cumulative mortality (CSCM) as a complementary indicator. Finally, sensitivity analyses were performed on censored data.
Results: A total of 80,020 with NSCLC were analyzed. TTI was assessed as a continuous variable, showing a noticeable increase in the HR for stage I to II NSCLC with TTI >1 month. Conversely, the trend for stage III to IV NSCLC was the opposite. In stage I LUAD, the 'early' group demonstrated a higher OS compared to the 'delayed' group (Log-rank $P = 0.002$), while there was no significant difference in CSCM (Fine-gray $P = 0.321$). In stage I LUSC, there was no significant difference in OS(Log-rank $P = 0.260$), but the 'early' group had a lower CSCM (Fine-gray $P = 0.018$). For stage II-IV NSCLC, the 'delayed' group did not exhibit a negative impact on OS or CSCM. The sensitivity analysis further supported the results of the main analysis.
Conclusion: Prolongation of TTI ≥31 days has a negative impact on OS or CSCM in stage I NSCLC only. Further exploration and validation are needed to determine whether these results can be used as evidence for a 'safe' TTI threshold setting for future NSCLC.

1. Introduction

Lung cancer is a global public health problems and the main cause of cancer deaths in the United States. By 2023, 127,070, or 21%, of all cancer deaths in the United States are expected to be due to lung cancer [1]. Non-small cell lung cancer (NSCLC) is the leading type of lung cancer, accounting for approximately 85% of all cases. The most common histological subtypes are lung adenocarcinoma (LUAD) and lung squamous carcinoma (LUSC) [2]. NSCLC treatment has become increasingly sophisticated, with choices such as

* Corresponding author.
E-mail address: wanghongwu2015@126.com (H. Wang).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e19750
Received 15 May 2023; Received in revised form 17 August 2023; Accepted 31 August 2023
Available online 2 September 2023

surgery, radiation, chemotherapy, targeted therapy, immunotherapy, palliative care, or any combination of these. However, because of the complexities of therapy alternatives, the time-to-treatment decision (or Time-to-treatment initiation, TTI) is frequently prolonged, despite the fact that timeliness is one of the fundamental goals of healthcare delivery [3,4].

Considerable heterogeneity exists among studies on the impact of prolonged TTI on survival in patients with NSCLC. Some studies have reported a positive correlation between shorter TTI and higher survival rates [5–8], whereas others have found no correlation [9, 10] or even a negative association between prolonged TTI and survival [11,12]. However, these studies may have limitations in controlling for confounding factors related to the histologic and clinical staging of NSCLC. Specifically, most studies have overlooked the single primary of NSCLC and employed the sixth or seventh edition(American Joint Committee on Cancer, AJCC) of the TNM staging system for assessing the disease stage, without AJCC eighth edition. Hence, these findings should be interpreted with caution. As the causes of TTI prolongation are complex, previous studies have primarily used overall survival (OS) as an indicator to assess the prognostic impact. However, this approach may not provide a comprehensive evaluation of the risk of cancer-related death when multiple competing events are present. Therefore, cancer-specific cumulative mortality (CSCM) is a suitable complementary indicator. Furthermore, previous studies have primarily focused on determining the 'safe' TTI interval for patients with early-stage NSCLC and evaluating specific management options such as surgery. However, limited attention has been given to the impact of TTI prolongation on full-stage NSCLC [7,10,13,14].

Given the varied response of different histological subtypes of NSCLC to treatment and prognosis [15], it is crucial to analyze full-stage NSCLC in multiple categories and determine the appropriate TTI range for each subtype. In this study, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to investigate the impact of TTI prolongation on patient survival in stage I to IV single primary NSCLC with selected histological subtypes. Our study focused on overall survival (OS) with CSCM as complementary evaluation indicators.

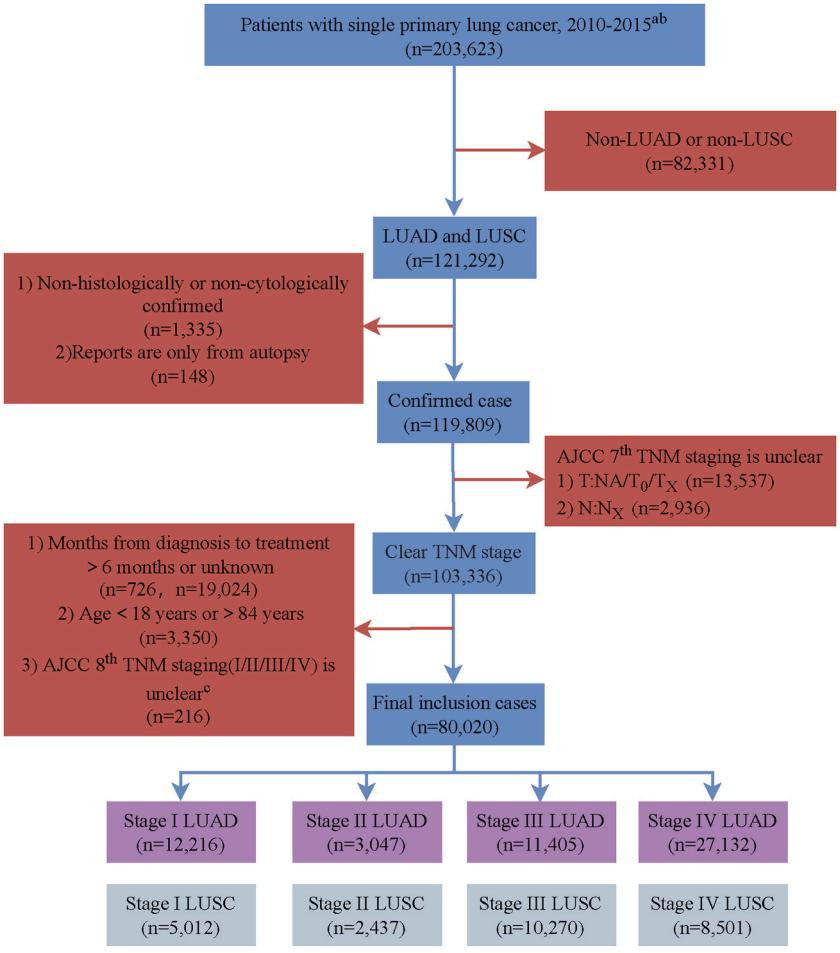

Fig. 1. The patients' selection process. [a]ICD-O-3 : C33.9 , C34.0 , C34.1 , C34.2 , C34.3 , C34.8 , C34.9;[b]Sequence number: 'One primary only in the patient's lifetime';[c]Excluding CS TUMOR SIZE (2004–2015) : 'code = 990–999' in AJCC 7th $T_{2a/2NOS}N_0M_0$ and $T_{2NOS}N_1M_0$.

2. Patients and methods

2.1. Data source

The data for this retrospective observational analysis were taken from the SEER database and focused on individuals with NSCLC. SEER*Stat 8.4.0.1 (IMS Inc., Calverton, MD, USA) was used to access the SEER (2000–2019) dataset, which provides trustworthy

Table 1
Baseline characteristics of patients with lung adenocarcinoma (LUAD).

Patient Characteristic	Subgroup	No. (%) of patients or median (range)			
		Stage[a] I (n = 12216)	Stage II (n = 3047)	Stage III (n = 11405)	Stage IV (n = 27132)
Age, mean (SD), y	–	67.5 (9.61)	67.3 (9.96)	65.9 (10.1)	64.3 (10.4)
Treatment Delays(m[b])	–	1 (0–6)	1 (0–6)	1 (0–6)	1 (0–6)
Survival Months(m[b])	–	61 (0–119)	49 (0–119)	25 (0–119)	8 (0–119)
Sex	Female	7341 (60.1)	1638 (53.8)	5878 (51.5)	13315 (49.1)
	Male	4875 (39.9)	1409 (46.2)	5527 (48.5)	13817 (50.9)
Race	White	9914 (81.2)	2410 (79.1)	8929 (78.3)	20524 (75.6)
	Black	1095 (9.0)	340 (11.2)	1438 (12.6)	3361 (12.4)
	other[c]	1162 (9.5)	291 (9.6)	1014 (8.9)	3219 (11.9)
	Unknown	45 (0.4)	6 (0.2)	24 (0.2)	28 (0.1)
Primary Site	C34.0	19 (0.2)	25 (0.8)	275 (2.4)	1059 (3.9)
	C34.1	7563 (61.9)	1729 (56.7)	6842 (60.0)	14379 (53.0)
	C34.2	661 (5.4)	163 (5.3)	543 (4.8)	1217 (4.5)
	C34.3	3810 (31.2)	1052 (34.5)	3007 (26.4)	6930 (25.5)
	other	163 (1.3)	78 (2.6)	738 (6.5)	3547 (13.1)
Grade	I	3140 (25.7)	337 (11.1)	826 (7.2)	830 (3.1)
	II	5086 (41.6)	1189 (39.0)	2700 (23.7)	3399 (12.5)
	III	2330 (19.1)	1050 (34.5)	3893 (34.1)	6617 (24.4)
	IV	42 (0.3)	29 (1.0)	76 (0.7)	143 (0.5)
	Unknown	1618 (13.2)	442 (14.5)	3910 (34.3)	16143 (59.5)
Laterality	Left	4835 (39.6)	1258 (41.3)	4265 (37.4)	10599 (39.1)
	Right	7380 (60.4)	1786 (58.6)	7102 (62.3)	15575 (57.4)
	other	1 (0.0)	3 (0.1)	38 (0.3)	958 (3.5)
T Stage	T1	8569 (70.1)	684 (22.4)	1709 (15.0)	3500 (12.9)
	T2	3647 (29.9)	2363 (77.6)	3061 (26.8)	7329 (27.0)
	T3	0 (0.0)	0 (0.0)	3894 (34.1)	6959 (25.6)
	T4	0 (0.0)	0 (0.0)	2741 (24.0)	9344 (34.4)
N Stage	N0	12216 (100.0)	1448 (47.5)	2709 (23.8)	6158 (22.7)
	N1	0 (0.0)	1599 (52.5)	1043 (9.1)	2184 (8.0)
	N2	0 (0.0)	0 (0.0)	5994 (52.6)	12264 (45.2)
	N3	0 (0.0)	0 (0.0)	1659 (14.5)	6526 (24.1)
M Stage	M0	12216 (100.0)	3047 (100.0)	11405 (100.0)	0 (0.0)
	M1	0 (0.0)	0 (0.0)	0 (0.0)	27132 (100.0)
Surgery	Performed	10240 (83.8)	2408 (79.0)	4606 (40.4)	1445 (5.3)
	None/Unknown	1976 (16.2)	639 (21.0)	6799 (59.6)	25687 (94.7)
Radiation	Performed	2087 (17.1)	718 (23.6)	6780 (59.4)	15590 (57.5)
	None/Unknown	10129 (82.9)	2329 (76.4)	4625 (40.6)	11542 (42.5)
Chemotherapy	Performed	802 (6.6)	1576 (51.7)	8757 (76.8)	20773 (76.6)
	None/Unknown	11414 (93.4)	1471 (48.3)	2648 (23.2)	6359 (23.4)
Marital Status[d]	Single	4998 (40.9)	1246 (40.9)	1645 (14.4)	4351 (16.0)
	Married	6622 (54.2)	1677 (55.0)	9288 (81.4)	21713 (80.0)
	Unknown	596 (4.9)	124 (4.1)	472 (4.1)	1068 (3.9)
Income[e]	35 k-	252 (2.1)	66 (2.2)	277 (2.4)	623 (2.3)
	35 k to 55 k	2822 (23.1)	806 (26.5)	3034 (26.6)	7161 (26.4)
	55 k to 75 k	5607 (45.9)	1367 (44.9)	5037 (44.2)	11836 (43.6)
	75 k+	3535 (28.9)	808 (26.5)	3056 (26.8)	7511 (27.7)
	Unknown	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
County[f]	Metropolitan	10753 (88.0)	2646 (86.8)	9778 (85.7)	23324 (86.0)
	Not Metropolitan	1453 (11.9)	401 (13.2)	1613 (14.1)	3782 (13.9)
	Unknown	10 (0.1)	0 (0.0)	14 (0.1)	26 (0.1)

[a] Stage: 8th edition of AJCC.
[b] Median values.
[c] other defined as the Asian/Pacific Islanders and American Indians/Alaska Natives.
[d] Patient's marital status at the time of diagnosis for the reportable tumor (with 'married' including those who are divorced, separated, or widowed, and 'single' including those who are unmarried or in domestic partnerships).
[e] Median household income inflation adjusted to 2019 (median household income was categorized as $< \$35{,}000$, \$35,000-\$54,999, \$55,000-\$74,999, and $\geq \$75{,}000$).
[f] County of residence at diagnosis.

information on cancer diagnosis and treatment from 17 population-based cancer registries. Due to the absence of individually identifiable information in the SEER database and the data's public availability, our study was exempt from the need for ethical approval.

2.2. Study population

This study focused on patients diagnosed with a single primary NSCLC, precisely stage I to IV LUAD and LUSC, using pathology

Table 2
Baseline characteristics of patients with LUSC.

Patient Characteristic	Subgroup	No. (%) of patients or median (range)			
		Stage[a] I (n = 5012)	Stage II (n = 2437)	Stage III (n = 10270)	Stage IV (n = 8501)
Age, mean (SD), y	–	70.3 (8.16)	68.8 (8.99)	67.5 (9.16)	66.8 (9.41)
Treatment Delays(m[b])	–	1 (0–6)	1 (0–6)	1 (0–6)	1 (0–6)
Survival Months(m[b])	–	49 (0–119)	32 (0–119)	15 (0–119)	6 (0–118)
Sex	Female	2273 (45.4)	875 (35.9)	3526 (34.3)	2852 (33.5)
	Male	2739 (54.6)	1562 (64.1)	6744 (65.7)	5649 (66.5)
Race	White	4414 (88.1)	2117 (86.9)	8480 (82.6)	6848 (80.6)
	Black	381 (7.6)	215 (8.8)	1167 (11.4)	1113 (13.1)
	other[c]	207 (4.1)	103 (4.2)	611 (5.9)	531 (6.2)
	Unknown	10 (0.2)	2 (0.1)	12 (0.1)	9 (0.1)
Primary Site	C34.0	46 (0.9)	87 (3.6)	817 (8.0)	725 (8.5)
	C34.1	3089 (61.6)	1309 (53.7)	5839 (56.9)	4342 (51.1)
	C34.2	212 (4.2)	91 (3.7)	349 (3.4)	287 (3.4)
	C34.3	1583 (31.6)	875 (35.9)	2647 (25.8)	2283 (26.9)
	other	82 (1.6)	75 (3.1)	618 (6.0)	864 (10.2)
Grade	I	164 (3.3)	61 (2.5)	202 (2.0)	106 (1.2)
	II	2084 (41.6)	881 (36.2)	2775 (27.0)	1613 (19.0)
	III	1899 (37.9)	1010 (41.4)	3644 (35.5)	2791 (32.8)
	IV	27 (0.5)	17 (0.7)	57 (0.6)	48 (0.6)
	Unknown	838 (16.7)	468 (19.2)	3592 (35.0)	3943 (46.4)
Laterality	Left	2201 (43.9)	1102 (45.2)	4288 (41.8)	3611 (42.5)
	Right	2811 (56.1)	1331 (54.6)	5916 (57.6)	4636 (54.5)
	other	0 (0.0)	4 (0.2)	66 (0.6)	254 (3.0)
T Stage	T1	3223 (64.3)	254 (10.4)	604 (5.9)	501 (5.9)
	T2	1789 (35.7)	2183 (89.6)	2574 (25.1)	2233 (26.3)
	T3	0 (0.0)	0 (0.0)	4028 (39.2)	2408 (28.3)
	T4	0 (0.0)	0 (0.0)	3064 (29.8)	3359 (39.5)
N Stage	N0	5012 (100.0)	1578 (64.8)	2508 (24.4)	1716 (20.2)
	N1	0 (0.0)	859 (35.2)	1217 (11.9)	756 (8.9)
	N2	0 (0.0)	0 (0.0)	5300 (51.6)	4126 (48.5)
	N3	0 (0.0)	0 (0.0)	1245 (12.1)	1903 (22.4)
M Stage	M0	5012 (100.0)	2437 (100.0)	10270 (100.0)	0 (0.0)
	M1	0 (0.0)	0 (0.0)	0 (0.0)	8501 (100.0)
Surgery	Performed	3428 (68.4)	1473 (60.4)	2457 (23.9)	377 (4.4)
	None/Unknown	1584 (31.6)	964 (39.6)	7813 (76.1)	8124 (95.6)
Radiation	Performed	1664 (33.2)	988 (40.5)	7603 (74.0)	5609 (66.0)
	None/Unknown	3348 (66.8)	1449 (59.5)	2667 (26.0)	2892 (34.0)
Chemotherapy	Performed	429 (8.6)	1126 (46.2)	7641 (74.4)	5924 (69.7)
	None/Unknown	4583 (91.4)	1311 (53.8)	2629 (25.6)	2577 (30.3)
Marital Status[d]	Single	578 (11.5)	335 (13.7)	1443 (14.1)	1364 (16.0)
	Married	4210 (84.0)	2017 (82.8)	8393 (81.7)	6795 (79.9)
	Unknown	224 (4.5)	85 (3.5)	434 (4.2)	342 (4.0)
Income[e]	35 k-	202 (4.0)	118 (4.8)	416 (4.1)	350 (4.1)
	35 k to 55 k	1638 (32.7)	774 (31.8)	3477 (33.9)	3038 (35.7)
	55 k to 75 k	2136 (42.6)	1040 (42.7)	4182 (40.7)	3451 (40.6)
	75 k+	1035 (20.7)	504 (20.7)	2195 (21.4)	1662 (19.6)
	Unknown	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
County[f]	Metropolitan	4065 (81.1)	1943 (79.7)	8256 (80.4)	6741 (79.3)
	Not Metropolitan	937 (18.7)	485 (19.9)	1990 (19.4)	1738 (20.4)
	Unknown	10 (0.2)	9 (0.4)	24 (0.2)	22 (0.3)

[a] Stage: 8th edition of AJCC.
[b] Median values.
[c] other defined as the Asian/Pacific Islanders and American Indians/Alaska Natives.
[d] Patient's marital status at the time of diagnosis for the reportable tumor (with 'married' including those who are divorced, separated, or widowed, and 'single' including those who are unmarried or in domestic partnerships).
[e] Median household income inflation adjusted to 2019 (median household income was categorized as $< \$35{,}000$, \$35,000-\$54,999, \$55,000-\$74,999, and $\geq \$75{,}000$).
[f] County of residence at diagnosis.

codes from the International Classification of Diseases for Oncology, Third Revision (ICD-*O*-3) between 2010 and 2015 (Table S1). We excluded patients younger than 18 or older than 84 years, those with a diagnosis of 'not available' (NA), T0, TX, or NX due to uncertainty about the primary tumor site, size, or lymph node metastasis, and those with a TTI exceeding 6 months or unknown TTI [16]. Patients whose lung cancer stage was not confirmed based on the eighth edition AJCC criteria were excluded. Fig. 1 provides a visual summary of the patient screening process.

2.3. Data elements

We collected extensive demographic and clinical information from the SEER database to obtain an all-encompassing comprehension of the patients. The data retrieved comprised personal details of the patients, such as their patient identification number, age, gender, and race, as well as their marital status at the time of diagnosis. Additionally, we gathered data on the median household income of the patients [17] and their county of residence.

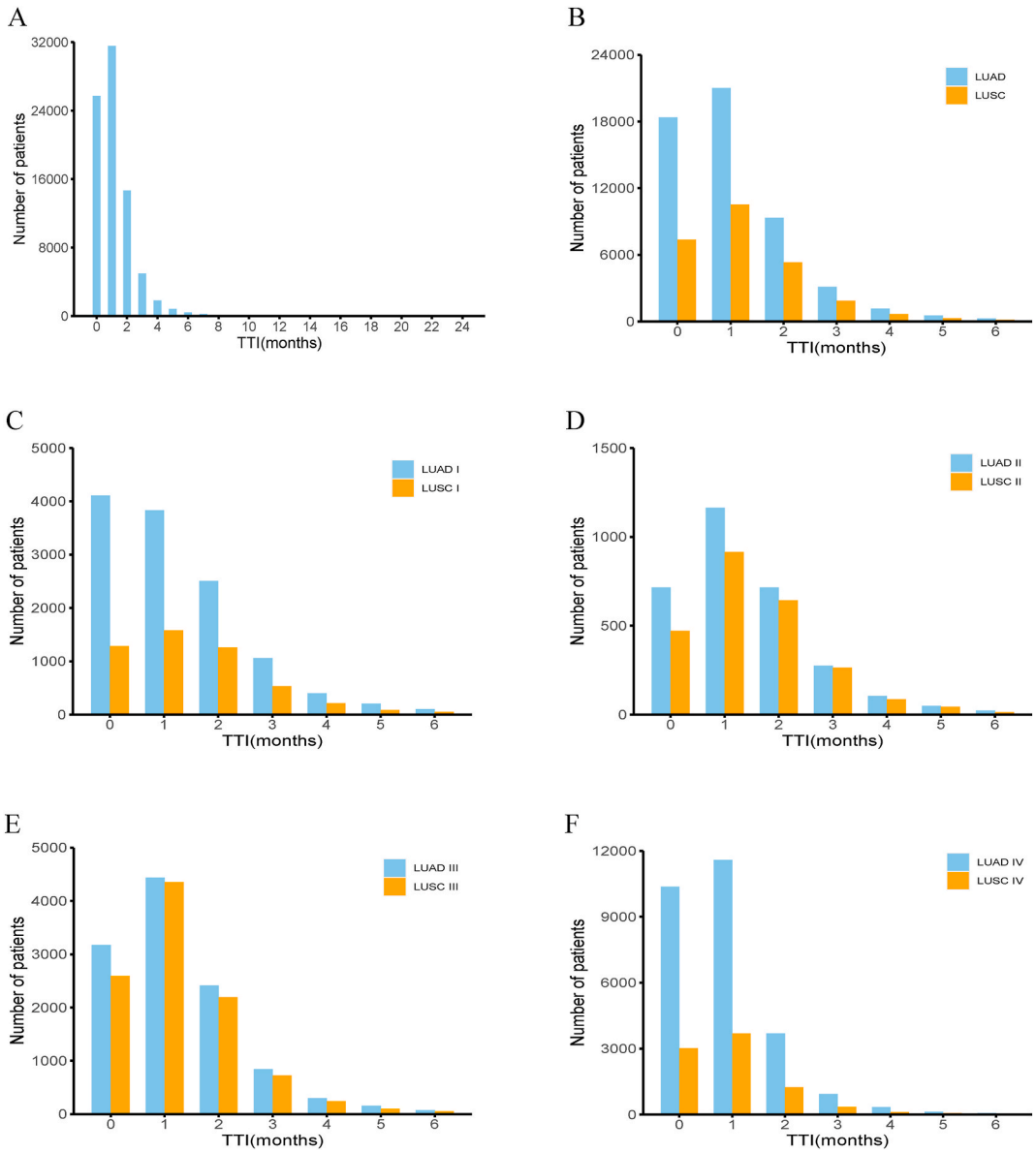

Fig. 2. Distribution of TTI for NSCLC and its major tissue subtypes. **A** Distribution of TTI(0–24 months) for NSCLC, **B** Distribution of TTI(0–6 months) for LUAD and LUSC, **C** Distribution of TTI(0–6 months) for stage I LUAD and stage I LUSC, **D** Distribution of TTI(0–6 months) for stage II LUAD and stage II LUSC, **E** Distribution of TTI(0–6 months) for stage III LUAD and stage III LUSC, **F** Distribution of TTI(0–6 months) for stage IV LUAD and stage IV LUSC.

In this study, we collected seven clinical covariates, namely histologic classification (LUAD and LUSC), differentiation grade (I to IV and unknown), primary site (C34.0-C34.3 and unknown), laterality (left lung, right lung, and unknown), TNM stage, NSCLC clinical stage (including I to IV) based on AJCC eighth edition, and cancer-related management options (surgery, radiotherapy, and chemotherapy). We also gathered time-related variables, including TTI and survival time (in months).

We analyzed TTI as both a continuous and dichotomous variable, with the latter separated into an 'early' group (TTI = 0 month) and a 'delayed' group (TTI = 2–6 months). We excluded patients with a TTI of 1 month due to how the SEER database calculates TTI, which defines months from diagnosis to treatment as ((year of initial treatment start * 12) + month of initial treatment start) - ((year of diagnosis * 12) + month of diagnosis). The calculation yields an actual TTI range of 1 month, which spans '1–59 days'. We opted to use a dichotomous variable to better distinguish between the 'early' group (TTI = 0 month or 0–29 days) and the 'delayed' group (TTI = 2–6 months or 31–179 days) (Table S2), although this method resulted in some missing data(TTI = 1 month).

The primary outcome metric for this study was OS, and the secondary metrics were CSCM, with a final follow-up date of December 31, 2019.

2.4. Statistical analysis

We employed restricted cubic spline(RCS) curves with three or four degrees of freedom to model TTI as a continuous variable to avoid overfitting and underfitting. We selected RCS due to their versatility and ability to capture potential nonlinear relationships.

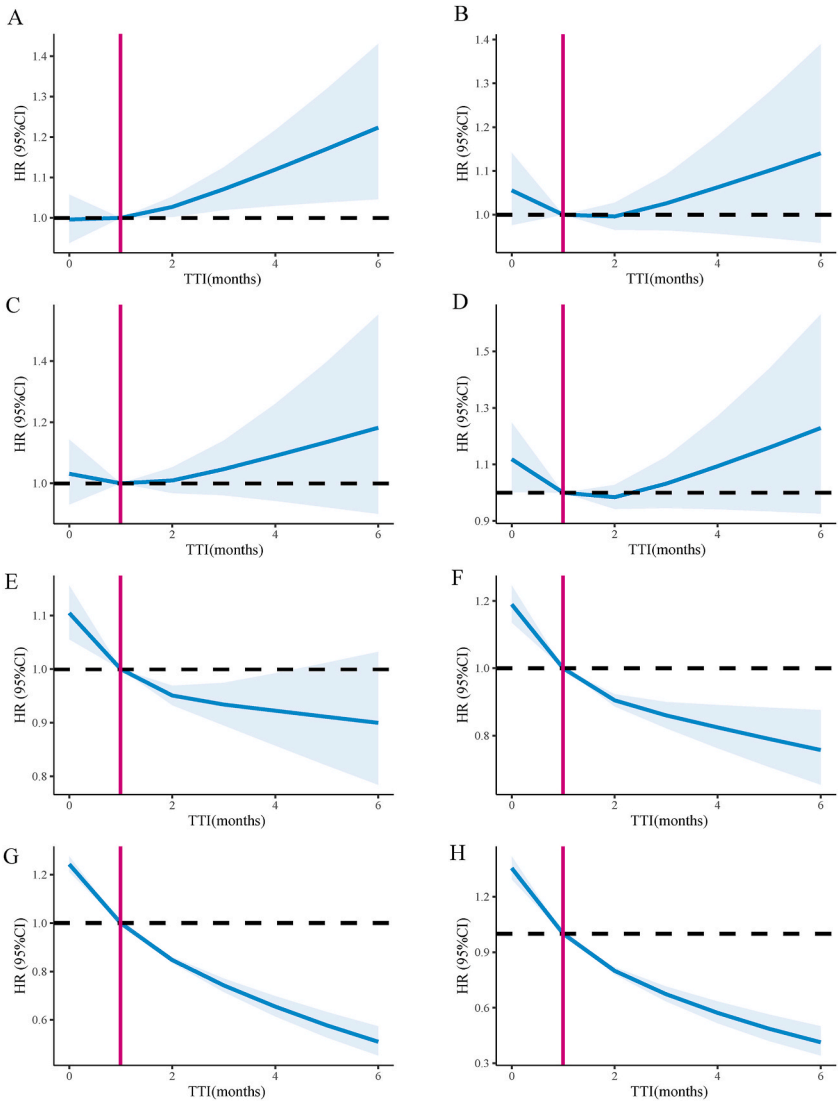

Fig. 3. Restricted cubic spline curve functions for TTI in LUAD and LUSC. **A** stage I LUAD,**B** stage I LUSC, **C** stage II LUAD, **D** stage II LUSC, **E** stage III LUAD,**F** stage III LUSC, **G** stage IV LUAD,**H** stage IV LUSC.

To assess the impact of treatment delay, we separated patients into two cohorts (an 'early' group and a 'delayed' group) based on their TTI. To minimize possible biases, we conducted a propensity score matching (PSM) analysis using a 1:1 ratio while accounting for various confounding factors, including age, gender, race, primary site, tumor grade, advanced stage, T stage, N stage (where applicable), and management options such as surgery, radiotherapy, chemotherapy, as well as marital status at diagnosis, median household income, and county of residence. Our nearest-neighbor matching algorithm is greedy without replacement, and the propensity scores have been calibrated with a fixed threshold of 0.01. We assessed the balance of the matches using p-values and the standardized mean differences (SMD) technique. Subsequently, Kaplan-Meier and a log-rank test were used to compare the OS and cancer-specific survival (CSS) of the matched 'early' and 'delayed' groups. Lastly, we addressed competing risk bias in the matched group by implementing a competing risk model and fine-gray test.

To investigate the impact of censored data on the findings of this study, a comparative analysis was performed between the 'early' group and the 'censored' group(TTI = 1 month).

We performed subgroup analyses by stratifying the data according to the histological subtype, and stage of NSCLC. Statistical analyses and graphical representations were performed using R-studio version 2022.12.0 + 353 (https://posit.co/downloads/) of R4.2.2 (http://www.r-project.org/). The following packages were utilized for the study: "survminer", "rms", "ggplot2″, "cmprsk", "MatchIt", "tableone", "survival", and "Magrittr".

3. Results

A total of 80,020 patients with stage I to IV single primary NSCLC met the inclusion criteria for the study, of which 53,800 had LUAD and 26,220 had LUSC (Fig. 1). Tables 1 and 2 provide detailed baseline characteristics of LUAD and LUSC patients, respectively. The population exhibited a right-skewed distribution, with only a few patients having a TTI longer than 6 months (Fig. 2A). The median duration of TTI was 1 month for each histologic subtype and clinical stage (Tables 1 and 2, Fig. 2B-F).

3.1. Restricted cubic splines analysis of treatment delay and prognosis

To investigate the association between TTI and prognosis, we employed the RCS model to illustrate this connection flexibly. We identified trends in the data using a median TTI of 1 month as a reference point. Our results demonstrated that the hazard ratio (HR) continuously rose with a prolonged TTI for individuals with stage I to II LUAD and LUSC(Fig. 3A-D). For patients with stage III to IV LUAD and LUSC, however, the HR steadily dropped with a prolonged TTI (Fig. 3E-H).

3.2. Kaplan-Meier for propensity score-matched analysis

We conducted a PSM analysis to compare the OS and CSS of patients who received 'early' versus 'delayed' treatment. Tables S3–S6 present the baseline characteristics of patients in the LUAD and LUSC cohorts after matching. After the matching process, we observed

Table 3
Kaplan-Meier OS and CSS for LUAD subgroup PSM analysis.

Cancer	OS			CSS		
	Early	Delayed		Early	Delayed	
	Survival (95% CI[b])	Survival (95% CI)	Log-rank *P* value	Survival (95% CI)	Survival (95% CI)	Log-rank *P* value
Stage[a] I	N = 3043	N = 3043	0.002	N = 3043	N = 3043	0.210
1-year(%)	92.2 (93.1,91.2)	93.6 (94.5,92.7)		95.0 (95.8,94.3)	96.8 (97.5,96.2)	
3-year(%)	81.3 (82.7,79.9)	80.0 (81.4,78.6)		87.5 (88.8,86.3)	87.8 (89.0,86.6)	
5-year(%)	71.5 (73.2,69.9)	69.0 (70.7,67.3)		81.6 (83.0,80.1)	81.0 (82.5,79.6)	
MST[c](mo)	N/A(N/A,N/A)	110 (101,N/A)		N/A(N/A,N/A)	N/A(N/A,N/A)	
Stage II	N = 676	N = 676	0.340	N = 676	N = 676	0.740
1-year(%)	83.8 (86.7,81.1)	87.4 (90.0,85.0)		87.0 (89.6,84.4)	90.2 (92.5,88.0)	
3-year(%)	61.5 (65.3,58.0)	61.3 (65.1,57.7)		67.4 (71.1,63.9)	67.9 (71.6,64.4)	
5-year(%)	50.6 (54.6,47.0)	47.4 (51.4,43.7)		57.6 (61.6,53.8)	56.2 (60.3,52.4)	
MST(mo)	63 (51,75)	54 (47,65)		97 (78,N/A)	76 (69,N/A)	
Stage III	N = 2926	N = 2926	0.046	N = 2926	N = 2926	0.002
1-year(%)	66.4 (68.2,64.7)	74.4 (76.0,72.9)		69.5 (71.2,67.8)	77.1 (78.7,75.6)	
3-year(%)	39.6 (41.5,37.9)	40.8 (42.6,39.0)		43.8 (45.7,41.9)	46.0 (47.9,44.2)	
5-year(%)	27.9 (29.6,26.3)	27.1 (28.8,25.5)		32.6 (34.5,30.9)	33.1 (35.0,31.3)	
MST(mo)	24 (22,26)	27 (26,29)		28 (26,30)	32 (30,35)	
Stage IV	N = 4789	N = 4789	< 0.0001	N = 4789	N = 4789	< 0.0001
1-year(%)	34.9 (36.3,33.6)	48.1 (49.6,46.7)		36.7 (38.2,35.4)	50.3 (51.8,48.9)	
3-year(%)	12.2 (13.1,11.3)	16.6 (17.7,15.6)		13.6 (14.6,12.6)	18.9 (20.1,17.8)	
5-year(%)	6.0 (6.7,5.3)	8.2 (9.1,7.5)		7.1 (8.0,6.4)	10.0 (10.9,9.1)	
MST(mo)	7 (7,8)	12 (11,12)		8 (7,8)	13 (12,13)	

[a] Stage: 8th edition of AJCC.
[b] CI indicates confidence interval.
[c] MST: Median survival time(month).

that the between-group *P*-values for all variables were more significant than 0.05, and the SMDs were less than 0.1, indicating a well-balanced sample. Tables 3and4 provide a summary of the Kaplan-Meier OS and CSS estimates at 1, 3, and 5 years, as well as the median survival time (in months) for each NSCLC stage in the 'early' and 'delayed' groups for the LUAD and LUSC cohorts.

The results showed that in stage I LUAD, the 'early' group had a higher OS compared with the 'delayed' group (Log-rank $P = 0.002$) (Fig. 4A), but there was no significant difference in CSS between the two groups(Log-rank $P = 0.210$). In stage II LUAD, there was no significant difference in OS and CSS between the 'early' and 'delayed' groups(Log-rank $P = 0.340$, $P = 0.740$). In stage III LUAD, the 'early' group had lower OS and CSS compared to the 'delayed' group (Log-rank $P = 0.046$, $P = 0.002$). In stage IV LUAD, the 'early' group had lower OS and CSS compared to the 'delayed' group (Log-rank $P < 0.0001$ for each).

In stage I LUSC, there was no significant difference in OS (Log-rank $P = 0.260$) (Fig. 5A),however, the 'early' group had a higher CSS compared with the 'delayed' group (Log-rank $P = 0.032$). In stage II LUSC, there was no significant difference in OS (Log-rank $P = 0.350$) (Fig. 5C),however, the 'early' group had a lower CSS compared with the 'delayed' group (Log-rank $P = 0.042$). In patients with stage III to IV LUSC, the 'early' group had lower OS and CSS compared with the 'delayed' group (Log-rank $P < 0.0001$ for each) (Fig. 5E,G).

3.3. Propensity score-matched analysis of competing risk model

In stages I to II of LUAD, CSCM did not differ significantly between the 'delayed' and the 'early' groups (Fine-gray $P = 0.321$, $P = 0.785$) (Fig. 4B, D). In contrast, in stage III to IV LUAD, the 'early' group showed a higher CSCM compared to the 'delayed' group(Fine-gray $P = 0.001$, $P < 0.001$) (Fig. 4F,H). For stage I LUSC, the CSCM was lower in the 'early' group (Fine-gray $P = 0.018$) (Fig. 5B). However, for stages II to IV of LUSC, the 'early' group showed a higher CSCM (Fine-gray $P = 0.038$, $P < 0.001$, $P < 0.001$) (Fig. 5D, F, and H).

3.4. Sensitivity analysis

In Table S7, we present the baseline characteristics of patients in the 'censored' group. We also conducted sensitivity analyses by repeating the previous analysis steps between the 'early' and 'censored' groups. Tables S8–S11 display the baseline characteristics of patients in the LUAD and LUSC cohorts in the matched 'early' and 'censored' groups. Tables S12–S13 and Figures S1 to S2 show the results of the sensitivity analysis. The study found that there was no significant difference in OS between the 'early' and 'censored' groups in stage I to II NSCLC (Log-rank $P = 0.099$). However, in stage I LUAD, the 'early' group had a higher CSCM (Fine-gray $P = 0.032$). In stage III to IV NSCLC, the 'early' and 'censored' groups exhibited similar differences in OS and CSCM as the 'early' and 'delayed' groups.

Table 4
Kaplan-Meier OS and CSS for LUSC subgroup PSM analysis.

Cancer	OS			CSS		
	Early	Delayed		Early	Delayed	
	Survival (95% CI[b])	Survival (95% CI)	Log-rank *P* value	Survival (95% CI)	Survival (95% CI)	Log-rank *P* value
Stage[a] I	N = 1208	N = 1208	0.260	N = 1208	N = 1208	0.032
1-year(%)	84.1 (86.2,82.0)	86.6 (88.5,84.7)		91.1 (92.8,89.5)	91.6 (93.2,90)	
3-year(%)	65.1 (67.9,62.5)	65.3 (68.0,62.6)		79.7 (82.1,77.3)	78.4 (80.9,76)	
5-year(%)	53.0 (55.9,50.2)	50.9 (53.8,48.1)		73.0 (75.8,70.3)	69.3 (72.2,66.5)	
MST[c](mo)	67 (61,78)	62 (57,69)		N/A (N/A,N/A)	N/A (N/A,N/A)	
Stage II	N = 463	N = 463	0.350	N = 463	N = 463	0.042
1-year(%)	72.7 (76.9,68.8)	79.6 (83.3,76.0)		78.0 (82.0,74.3)	85.8 (89.1,82.6)	
3-year(%)	49.7 (54.5,45.3)	52.7 (57.5,48.3)		58.0 (62.9,53.5)	63.2 (68.0,58.7)	
5-year(%)	38.8 (43.5,34.5)	40.0 (44.8,35.7)		49.9 (55.0,45.2)	54.2 (59.5,49.5)	
MST(mo)	36 (29,43)	43 (35,50)		59 (43,102)	91 (59,N/A)	
Stage III	N = 2383	N = 2383	< 0.0001	N = 2383	N = 2383	< 0.0001
1-year(%)	48.2 (50.3,46.3)	62.4 (64.4,60.5)		51.8 (53.9,49.8)	66.5 (68.5,64.6)	
3-year(%)	22.3 (24.1,20.7)	28.1 (30.0,26.4)		26.5 (28.4,24.7)	33.7 (35.8,31.8)	
5-year(%)	15.0 (16.6,13.7)	19.0 (20.7,17.5)		19.7 (21.5,18.1)	25.8 (27.8,24.0)	
MST(mo)	12 (11,13)	18 (17,19)		14 (12,15)	20 (19,21)	
Stage IV	N = 1744	N = 1744	< 0.0001	N = 1744	N = 1744	< 0.0001
1-year(%)	20.2 (22.2,18.4)	36.2 (38.5,34)		21.9 (24,20)	38.8 (41.2,36.5)	
3-year(%)	4.4 (5.5,3.5)	8.5 (9.9,7.3)		5.6 (6.9,4.6)	10.6 (12.3,9.2)	
5-year(%)	2.7 (3.6,2.0)	4.4 (5.5,3.5)		4.2 (5.4,3.3)	6.6 (8.1,5.4)	
MST(mo)	5 (4,5)	9 (8,9)		5 (5,5)	9 (9,10)	

[a] Stage: 8th edition of AJCC.
[b] CI indicates confidence interval.
[c] MST: Median survival time(month).

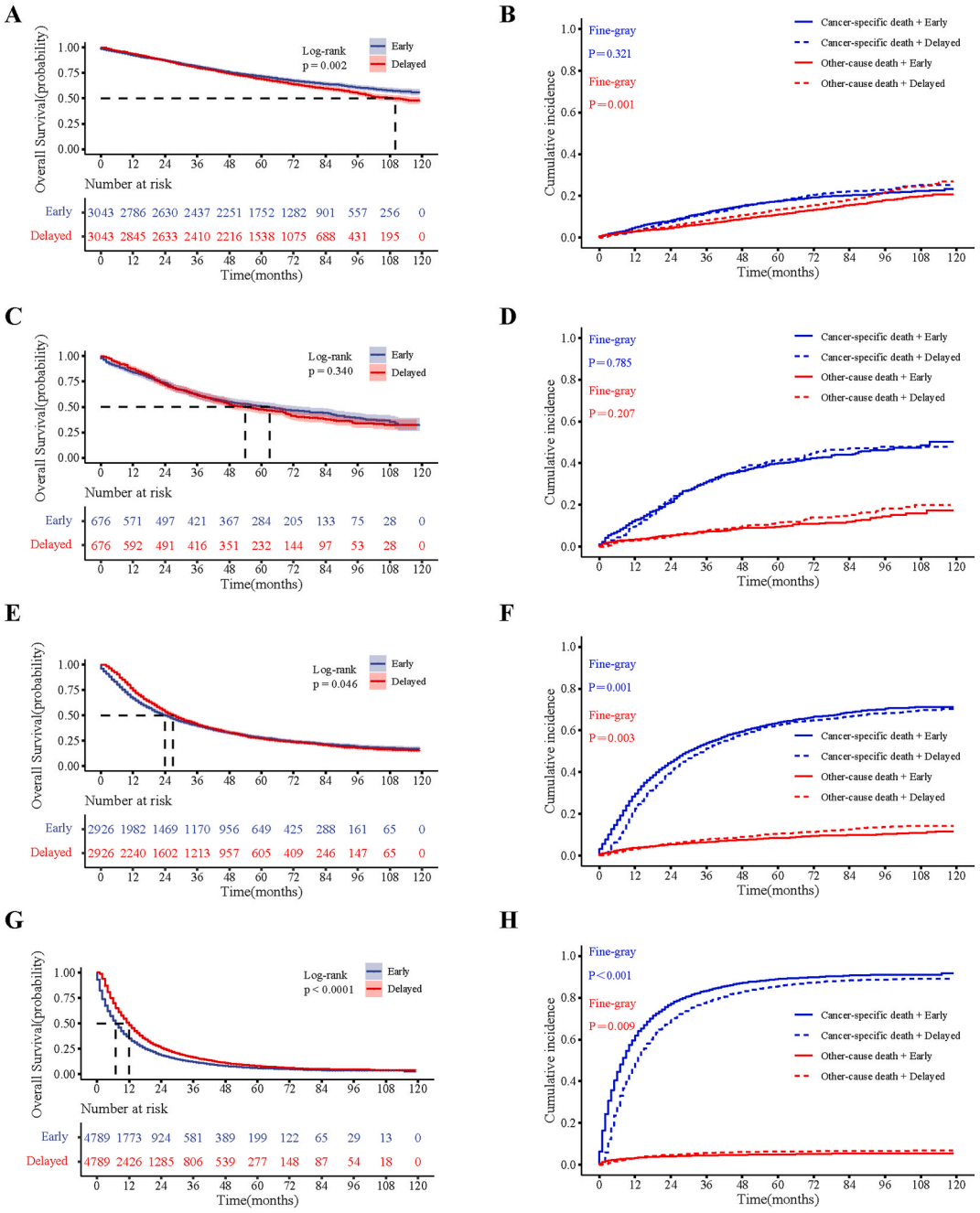

Fig. 4. Kaplan-Meier curves and competing risk models were utilized following adjustment for propensity score in LUAD. **A** stage I LUAD,**B** stage I LUAD, **C** stage II LUAD, **D** stage II LUAD, **E** stage III LUAD,**F** stage III LUAD, **G** stage IV LUAD,**H** stage IV LUAD.

4. Discussion

Timeliness of treatment is essential when assessing the quality of care provided to patients. Nevertheless, the influence of prolonged TTI on patients with a single primary NSCLC remains ambiguous. We conducted a retrospective study using the SEER database to address this issue. This study involved patients diagnosed with stage I to IV LUAD and LUSC. Subgroup analysis was based on histological subtype, and clinical stage. The study results indicated that the effect of TTI prolongation varied between subgroups, emphasizing the need for considering clinical stage, and histological subtype before delaying treatment.

Timely management standards for lung cancer have been established by some countries [18–22], but these standards are not well supported by evidence and are based mainly on expert consensus. Discrepancies exist between the recommendations and current

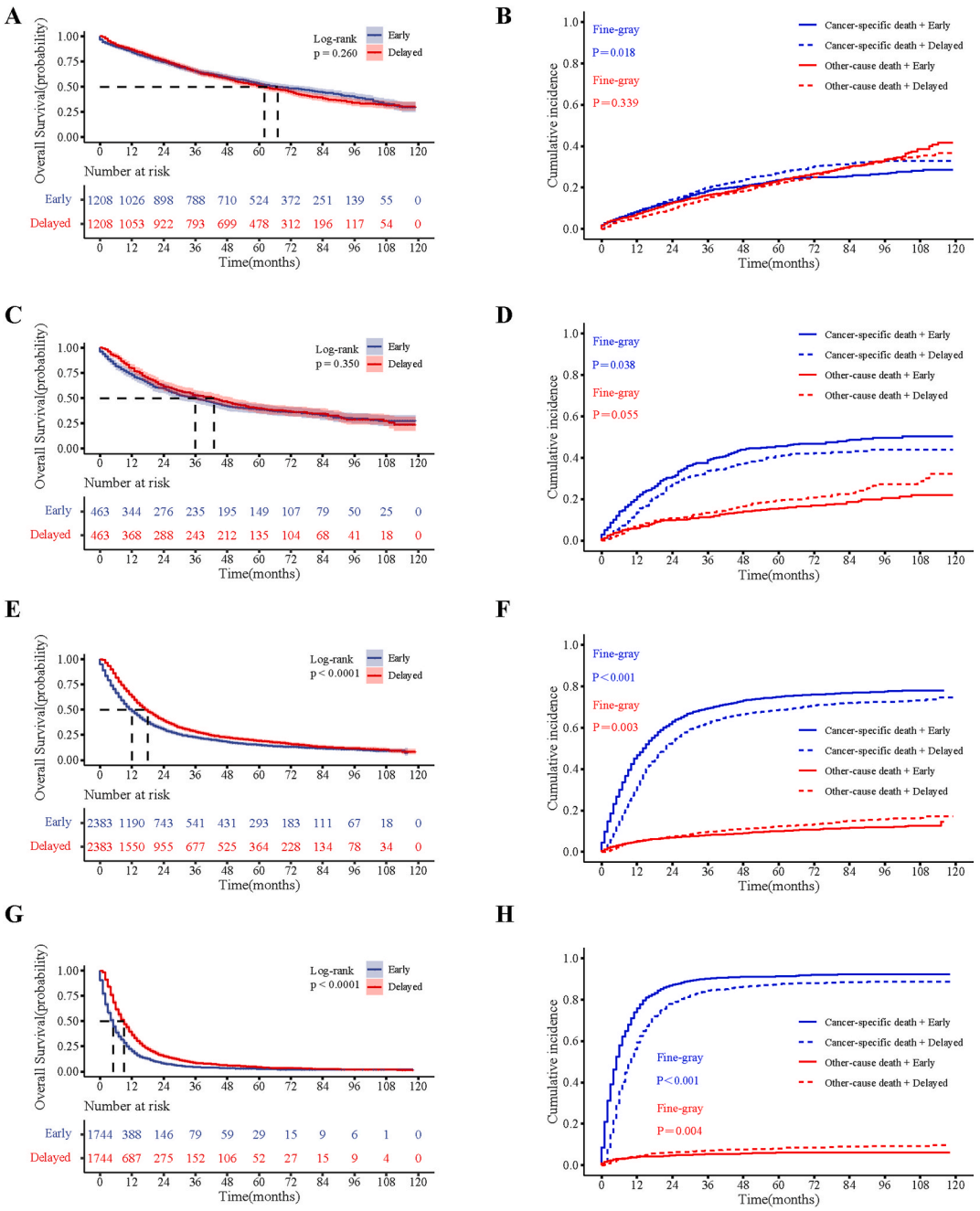

Fig. 5. Kaplan-Meier curves and competing risk models were utilized following adjustment for propensity score in LUSC. **A** stage I LUSC,**B** stage I LUSC, **C** stage II LUSC, **D** stage II LUSC, **E** stage III LUSC,**F** stage III LUSC, **G** stage IV LUSC,**H** stage IV LUSC.

practice. Olsson et al. [23] conducted a systematic review of the timeliness of lung cancer care, summarizing TTI from 49 studies published between 1995 and 2007. The median range of TTI was 12.5–52 days. Later, Jacobsen et al. [24]summarized 65 articles on lung cancer diagnosis and treatment published between 2007 and 2016 in 21 countries. The median range of TTI in their reports was 6–45 days. Guirado et al. [25] analyzed 38 articles published between 2010 and 2020 on waiting times for lung cancer diagnosis and treatment, and the median range of TTI was 6–121 days. These results suggest that TTIs for lung cancer have not improved in the last 30 years. However, the results may be even more unfavorable. According to a recent study published in the National Cancer Data Base (NCDB), from 33 days in 2010 to 39 days in 2018, the TTI for single primary NSCLC increased by over 15% [26].

The American College of Chest Physicians did not provide a 'safe' threshold for TTI in NSCLC, and only recommends timely and efficient care for patients with known or suspected lung cancer (Grade 2C) [27]. A review of United States NSCLC data indicates

significant heterogeneity among studies regarding the effect of TTI on survival in NSCLC [5–12]. This disparity may be due to several reasons. Firstly, patients with NSCLC presenting with acute malignancy, despite receiving prompt treatment, often have a poorer prognosis, referred to as 'waiting bias'. Waiting bias typically occurs in advanced or elderly patients [11,12,28]. Secondly, previous studies may have inadequately controlled for confounding factors related to NSCLC histology and clinical stage. Finally, TTI endpoints have frequently received not considered comprehensively in previous studies, such as limiting initial treatment to specific modalities like surgery [7,8,13,16,29]. In our study, we solely focused on single primary NSCLC and used the AJCC eighth edition of the TNM staging system to clinically re-stage the data included. This approach allowed us to control for confounding and effect modification in clinical staging and histology. We utilized restricted cubic spline analysis, without specifying specific management options as the endpoint of TTI, to fully evaluate the potential nonlinear relationship of time-dependent effects. The results indicate that in patients with stage I to II NSCLC, HR steadily increased with the prolongation of TTI. In contrast, in patients with stage III to IV NSCLC, TTI prolongation was negatively associated with a steady decrease in HR. These trends occurred after a TTI over 1 month (Fig. 3).

Based on the National Lung Screening Trial and NCDB databases, Mayne et al. [11,13] analyzed the effect of delayed treatment on OS in NSCLC in two studies. A study that focused on stage I NSCLC found that a delay of 90–120 days from diagnosis to surgical treatment was related to poorer OS in stage I LUAD (T1B-T1CN0M0, T2AN0M0) and stage IB LUSC. The results of the other study, which focused on patients with stage III to IV NSCLC, showed that even after sensitivity analysis, a delay of 90–120 days between the time of diagnosis and the start of any treatment did not result in significantly worse OS in patients with stage III to IV NSCLC. In contrast to previous studies, our study considers the impact of other competing mortality events and incorporates the use of competing risk models to provide a more comprehensive assessment of cancer-related mortality risk. The findings indicate that in stage I-II NSCLC, the Kaplan-Meier curves demonstrate that the 'delayed' group only exhibited lower OS in the stage I LUAD subgroup(Log-rank $P = 0.002$), while no significant difference in OS was observed between the 'delayed' and 'early' groups in the other subgroups. When utilizing competing risks models, the model revealed that the 'delayed' group had higher CSCM in the stage I LUSC subgroup (Fine-gray $P = 0.018$) , but this association was not observed in the other subgroups. Our findings for stage III to IV NSCLC were identical to those of Mayne et al. [11]. Across all subgroups, the 'delayed' group exhibited higher OS and lower CSCM compared to the 'early' group.

To further investigate the potential impact of censored data (i.e. TTI = 1 month) on the primary analysis results, we conducted a sensitivity analysis. This involved repeating the analysis we used between the 'early' and 'delayed' groups, but this time comparing the 'early' group with the 'censored' group. Based on the results of the sensitivity analysis and the trend observed in HR when TTI was treated as a continuous variable (Fig. 3), we have grounds to conclude that the exclusion of data would not have influenced the outcomes of the main analyses.

We partially explain the presence of protective phenomena due to delayed treatment in patients with advanced NSCLC. Clinical staging is not always determinable at the time of the patient's initial visit, and during delayed treatment, clinical stage may remain unchanged or progress. For example, in a study of 21 NSCLC patients scheduled for radical radiotherapy, PET/CT showed that the mean tumor volume increased from 105 cc to 198 cc during a median delay period of 23 days (ranging from 8 to 176 days), which resulted in 6 patients no longer being eligible for radical therapy [30]. Thus, the clinical stage at the time of treatment may ultimately determine the survival outcome, and patients with the progressive clinical stage (e.g., from stage II to III) (Figure S3.A) have longer mean delays but higher OS and CSCM compared to patients with the unchanged clinical stage (stage III) (Figure S3.B) [31].

This study, to our knowledge, is the first to investigate the relationship between TTI and survival in patients with a single primary full-stage NSCLC. The study has several notable strengths. Firstly, it was conducted in a contemporary period (2010–2015) and confirmed NSCLC re-staging according to the 8th edition AJCC criteria, which makes the results broadly generalizable. Secondly, the study assessed TTI as both a binary and continuous variable and analyzed the time-dependent effects of delayed treatment. Additionally, a competing risk model was used, and the CSCM was included as one of the complementary evaluation indicators to enhance the comprehensiveness of the prognostic risk assessment.

This study, however, has several limitations. Firstly, we lack precise information regarding the TNM stage of the patient at the time of diagnosis (Figure S3). This limitation is inherent in clinical settings and should be taken into consideration. Secondly, the analysis of the study was limited to the variables present in the database. Although propensity score matching was employed to reduce bias, several critical covariates, including past medical history, smoking history, lung function, and the details of radiotherapy and chemotherapy, were not available in the SEER database. Thirdly, our analysis solely focused on the most prevalent histological subtypes in NSCLC and exclusively examined the initial management options (surgery, radiotherapy, or chemotherapy) following diagnosis. To enhance the comprehensiveness and specificity of conclusions, future studies should incorporate a broader spectrum of histological subtypes and concentrate on the primary management options associated with each subtype.

5. Conclusions

This study revealed that in the subgroup of single primary stage I NSCLC, a TTI of 31 days or more had a negative impact on OS or CSCM. However, in the subgroup of stage III-IV NSCLC, neither OS nor CSCM were significantly affected by TTI prolonging. Further exploration and validation are needed to determine whether these results can be used as evidence for a 'safe' TTI threshold setting for future NSCLC, and should consider potential differences between the TNM stage at diagnosis and the TNM stage at initial treatment.

Funding

This research was funded by the Fundamental Research Funds for the Beijing University of Traditional Chinese Medicine 2022

Annual, grant number 2022-JYB-JBZR-029.

Author contribution statement

Jun Teng; Yan Liu: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Junyan Xia; Yi Luo; Heng Zou: Contributed analysis tools or data; Performed the experiments.
Hongwu Wang: Conceived and designed the experiments; Wrote the paper

Data availability statement

Data associated with this study has been deposited at the SEER database (https://seer.cancer.gov/seerstat/, data accessed on 29 January 2023), which is freely available to the public.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

NSCLC	Non-small cell lung cancer
LUAD	Lung adenocarcinoma
LUSC	Lung squamous carcinoma
TTI	Time-to-treatment initiation
AJCC	American Joint Committee on Cancer
OS	Overall survival
CSS	Cancer-specific survival
CSCM	Cancer-specific cumulative mortality
SEER	The Surveillance, Epidemiology, and End Results
ICD-*O*-3	The International Classification of Diseases for Oncology, Third Revision
RCS	Restricted cubic spline
HR	Hazard ratio
PSM	Propensity score matching
SMD	The standardized mean differences
NCDB	National Cancer Data Base

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19750.

References

[1] R.L. Siegel, K.D. Miller, N.S. Wagle, A. Jemal, Cancer statistics, 2023, Ca - Cancer J. Clin. 73 (2023) 17–48, https://doi.org/10.3322/caac.21763.
[2] X. Xie, X. Li, W. Tang, P. Xie, X. Tan, Primary tumor location in lung cancer: the evaluation and administration, Chin. Med. J. 135 (2021) 127–136, https://doi.org/10.1097/CM9.0000000000001802.
[3] D.R. Gomez, K.-P. Liao, S.G. Swisher, G.R. Blumenschein, J.J. Erasmus, T.A. Buchholz, S.H. Giordano, B.D. Smith, Time to treatment as a quality metric in lung cancer: staging studies, time to treatment, and patient survival, Radiother. Oncol. 115 (2015) 257–263, https://doi.org/10.1016/j.radonc.2015.04.010.
[4] G.S. Kaplan, Health care scheduling and access: a report from the iom, JAMA 314 (2015) 1449–1450, https://doi.org/10.1001/jama.2015.9431.
[5] T.R. Cushman, B. Jones, D. Akhavan, C.G. Rusthoven, V. Verma, R. Salgia, M. Sedrak, E. Massarelli, J.W. Welsh, A. Amini, The effects of time to treatment initiation for patients with non-small-cell lung cancer in the United States, Clin. Lung Cancer 22 (2021) e84–e97, https://doi.org/10.1016/j.cllc.2020.09.004.
[6] A.A. Khorana, K. Tullio, P. Elson, N.A. Pennell, S.R. Grobmyer, M.F. Kalady, D. Raymond, J. Abraham, E.A. Klein, R.M. Walsh, E.E. Monteleone, W. Wei, B. Hobbs, B.J. Bolwell, Time to initial cancer treatment in the United States and association with survival over time: an observational study, PLoS One 14 (2019), e0213209, https://doi.org/10.1371/journal.pone.0213209.
[7] K.C. Banks, J.R. Dusendang, J.A. Schmittdiel, D.S. Hsu, S.K. Ashiku, A.R. Patel, L.C. Sakoda, J.B. Velotta, Association of surgical timing with outcomes in early stage lung cancer, World J. Surg. 47 (2023) 1323–1332, https://doi.org/10.1007/s00268-023-06913-w.
[8] P. Samson, A. Patel, T. Garrett, T. Crabtree, D. Kreisel, A.S. Krupnick, G.A. Patterson, S. Broderick, B.F. Meyers, V. Puri, Effects of delayed surgical resection on short-term and long-term outcomes in clinical stage I non-small cell lung cancer, Ann. Thorac. Surg. 99 (2015) 1906–1912, https://doi.org/10.1016/j.athoracsur.2015.02.022, discussion 1913.
[9] D. Ha, A.L. Ries, P. Montgrain, F. Vaida, S. Sheinkman, M.M. Fuster, Time to treatment and survival in veterans with lung cancer eligible for curative intent therapy, Respir. Med. 141 (2018) 172–179, https://doi.org/10.1016/j.rmed.2018.07.005.
[10] N.R. Mayne, H. Elser, B.K. Lin, V. Raman, D. Liou, X. Li, T.A. D'Amico, C.-F. Jeffrey Yang, The impact of extended delayed surgery for indolent lung cancer or part-solid ground glass nodules, Ann. Thorac. Surg. 113 (2022) 1827–1834, https://doi.org/10.1016/j.athoracsur.2021.05.099.

[11] N.R. Mayne, S.S. Bajaj, J. Powell, H.C. Elser, B.S. Civiello, F.J. Fintelmann, X. Li, C.-F.J. Yang, Extended delay to treatment for stage III-IV non-small-cell lung cancer and survival: balancing risks during the COVID-19 pandemic, Clin. Lung Cancer 23 (2022) e362–e376, https://doi.org/10.1016/j.cllc.2022.05.001.
[12] P. Nadpara, S.S. Madhavan, C. Tworek, Guideline-concordant timely lung cancer care and prognosis among elderly patients in the United States: a population-based study, Cancer Epidemiology 39 (2015) 1136–1144, https://doi.org/10.1016/j.canep.2015.06.005.
[13] N.R. Mayne, H.C. Elser, A.J. Darling, V. Raman, D.Z. Liou, Y.L. Colson, T.A. D'Amico, C.-F.J. Yang, Estimating the impact of extended delay to surgery for stage I non-small-cell lung cancer on survival, Ann. Surg. 273 (2021) 850–857, https://doi.org/10.1097/SLA.0000000000004811.
[14] L. Zhang, M.-C. Hsieh, L. Rennert, P. Neroda, X.-C. Wu, C. Hicks, J. Wu, R. Gimbel, Diagnosis-to-surgery interval and survival for different histologies of stage I–IIA lung cancer, Transl. Lung Cancer Res. 10 (2021) 3043–3058, https://doi.org/10.21037/tlcr-21-168.
[15] V. Relli, M. Trerotola, E. Guerra, S. Alberti, Abandoning the notion of non-small cell lung cancer, Trends Mol. Med. 25 (2019) 585–594, https://doi.org/10.1016/j.molmed.2019.04.012.
[16] S.K. Vinod, A. Chandra, A. Berthelsen, J. Descallar, Does timeliness of care in non-small cell lung cancer impact on survival? Lung Cancer 112 (2017) 16–24, https://doi.org/10.1016/j.lungcan.2017.07.032.
[17] Y. Min, Z. Liu, R. Huang, R. Li, J. Jin, Z. Wei, L. He, Y. Pei, N. Li, Y. Su, X. Hu, X. Peng, Survival outcomes following treatment delays among patients with early-stage female cancers: a nationwide study, J. Transl. Med. 20 (2022) 560, https://doi.org/10.1186/s12967-022-03719-7.
[18] E. Jakobsen, A. Green, K. Oesterlind, T.R. Rasmussen, M. Iachina, T. Palshof, Nationwide quality improvement in lung cancer care: the role of the Danish Lung Cancer Group and Registry, J. Thorac. Oncol. 8 (2013) 1238–1247, https://doi.org/10.1097/JTO.0b013e3182a4070f.
[19] BTS recommendations to respiratory physicians for organising the care of patients with lung cancer. The lung cancer working party of the British thoracic society standards of care committee, Thorax 53 (Suppl 1) (1998) S1–S8, https://doi.org/10.1136/thx.53.suppl_1.s1.
[20] F. Barata, P. Fidalgo, S. Figueiredo, F.S. Tonin, F. Duarte-Ramos, Limitations and perceived delays for diagnosis and staging of lung cancer in Portugal: a nationwide survey analysis, PLoS One 16 (2021), e0252529, https://doi.org/10.1371/journal.pone.0252529.
[21] A. Malalasekera, H.M. Dhillon, P.L. Blinman, S.C. Kao, J.L. Vardy, Delays to diagnosis and treatment of lung cancer in Australia: healthcare professional perceptions of actual versus acceptable timeframes: delays in lung cancer care, Intern. Med. J. 48 (2018) 1063–1071, https://doi.org/10.1111/imj.13970.
[22] T. Watanabe, R. Rikitake, T. Kakuwa, Y. Ichinose, M. Niino, Y. Mizushima, M. Ota, M. Fujishita, Y. Tsukada, T. Higashi, Time to treatment initiation for six cancer types: an analysis of data from a nationwide registry in Japan, World J. Surg. 47 (2023) 877–886, https://doi.org/10.1007/s00268-022-06883-5.
[23] J.K. Olsson, E.M. Schultz, M.K. Gould, Timeliness of care in patients with lung cancer: a systematic review, Thorax 64 (2009) 749–756, https://doi.org/10.1136/thx.2008.109330.
[24] M.M. Jacobsen, S.C. Silverstein, M. Quinn, L.B. Waterston, C.A. Thomas, J.C. Benneyan, P.K.J. Han, Timeliness of access to lung cancer diagnosis and treatment: a scoping literature review, Lung Cancer 112 (2017) 156–164, https://doi.org/10.1016/j.lungcan.2017.08.011.
[25] M. Guirado, E. Fernández Martín, A. Fernández Villar, A. Navarro Martín, A. Sánchez-Hernández, Clinical impact of delays in the management of lung cancer patients in the last decade: systematic review, Clin. Transl. Oncol. 24 (2022) 1549–1568, https://doi.org/10.1007/s12094-022-02796-w.
[26] Z. Muslim, S. Stroever, S.S. Razi, K. Poulikidis, M.Z. Baig, C.P. Connery, F.Y. Bhora, Increasing time-to-treatment for lung cancer: are we going backward? Ann. Thorac. Surg. 115 (2023) 192–199, https://doi.org/10.1016/j.athoracsur.2022.06.016.
[27] D.E. Ost, S.-C. Jim Yeung, L.T. Tanoue, M.K. Gould, Clinical and organizational factors in the initial evaluation of patients with lung cancer, Chest 143 (2013) e121S–e141S, https://doi.org/10.1378/chest.12-2352.
[28] R.D. Neal, P. Tharmanathan, B. France, N.U. Din, S. Cotton, J. Fallon-Ferguson, W. Hamilton, A. Hendry, M. Hendry, R. Lewis, U. Macleod, E.D. Mitchell, M. Pickett, T. Rai, K. Shaw, N. Stuart, M.L. Tørring, C. Wilkinson, B. Williams, N. Williams, J. Emery, Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review, Br. J. Cancer 112 (Suppl 1) (2015) S92–S107, https://doi.org/10.1038/bjc.2015.48.
[29] A. Malalasekera, S. Nahm, P.L. Blinman, S.C. Kao, H.M. Dhillon, J.L. Vardy, How long is too long? A scoping review of health system delays in lung cancer, Eur. Respir. Rev. 27 (2018), 180045, https://doi.org/10.1183/16000617.0045-2018.
[30] S. Everitt, N. Plumridge, A. Herschtal, M. Bressel, D. Ball, J. Callahan, T. Kron, M. Schneider-Kolsky, D. Binns, R.J. Hicks, M. Mac Manus, The impact of time between staging PET/CT and definitive chemo-radiation on target volumes and survival in patients with non-small cell lung cancer, Radiother. Oncol. 106 (2013) 288–291, https://doi.org/10.1016/j.radonc.2013.02.010.
[31] P.V.S. Zuniga, D.E. Ost, Impact of delays in lung cancer treatment on survival, Chest 160 (2021) 1934–1958, https://doi.org/10.1016/j.chest.2021.08.051.