Original Article

The risks and trends of cardiac-specific mortality associated with chemotherapy or radiotherapy in a large cohort of non-elderly patients with non-small cell lung cancer

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Background: Anticancer treatment-related heart events is a major concern. However, the frequent occurrence time of cardiac death and the association between cardiac-specific mortality (CSM) and various lung lobes among non-elderly non-small cell lung cancer (NSCLC) patients after chemotherapy or radiotherapy (RT) are uncertain.

Methods: Data of patients aged 20–59 years and diagnosed with NSCLC during 1975–2014 were extracted from the Surveillance, Epidemiology and End Results (SEER) database. We divided them into four groups: no chemotherapy or RT, chemotherapy-only, RT-only and chemoradiation therapy (CRT). The Fine and Gray model was applied to evaluate the risks; the cumulative curves of CSM were established by Gray's test. Furthermore, the forest graphs delineated the hazards of different tumor subsites to CSM as the survival time prolonged. Eventually, we analyzed and elucidated the tendency of CSM decade by decade.

Results: We identified 121,302 patients and 3,423 died of heart diseases. In chemotherapy-only group, age, sex, race, marital status and surgery were significantly correlated to CSM while the subsite location of tumor was the key risk among RT-only patients. The hazard ratio (HR) of CSM was greatest in 2–5 years after RT (P=0.008, HR =2.30). CSMs of chemotherapy (P=0.130, HR =2.480) and CRT (P=0.028, HR =2.600) peaked in 1985–1994 and decreased sharply hereafter, whereas the CSMs of RT-only declined over time.

Conclusions: The risks of CSM after chemotherapy were similar to the common hazards of heart diseases; tumor in the left-lower lobe was a remarkable risk for patients receiving RT-only and the frequent occurrence of cardiac death was from the second year after RT. The CSMs of chemotherapy and CRT culminated in 1985–1994 and then descended; it declined all the time in RT-only group.

Keywords: Non-small cell lung cancer (NSCLC); non-elderly; chemotherapy; radiotherapy (RT); cardiac mortality

Submitted Oct 03, 2020. Accepted for publication Dec 12, 2020.
doi: 10.21037/tcr-20-2981
View this article at: http://dx.doi.org/10.21037/tcr-20-2981

Introduction

During the last four decades, the incidence of lung cancer was increasing and it remains the leading and lethal cancer (1). Around 85% of lung cancer are non-small cell lung cancer (NSCLC) and approximately 10% of the patients are younger than 55 years (2), which cannot be neglected. Data, based on the Surveillance, Epidemiology and End Results (SEER) database, showed that the 5-year relative survival rate increased from 12% in the mid-1970s to 18% during 2003–2009 (2). At present, chemotherapy and radiotherapy (RT) are still indispensable in clinical practice and their side effects need to be further studied with the extension of overall survival time. According to previous reports, cardiac-specific death is one of the major and devastating causes other than lung cancer itself since intensive cancer treatments have led to a variety of early and late cardiovascular toxicities, such as myocardial ischemia, cardiomyopathy, conduction disorders, heart failure and others (3,4). Therefore, as an inter-discipline, cardio-oncology emerged to study cardiovascular diseases in cancer patients due to the cardiotoxicities of anticancer therapies and many shared risk factors of two diseases (5).

Chemotherapeutic agents target cells at a specific growth pattern, meaning that cancer or normal cells at the same growing stage will be destroyed after taking medicines. Cardiotoxicity is one of the crucial side effects of chemotherapy (6). For instance, paclitaxel combined with high-dose anthracyclines increases the risk of left ventricle dysfunction to 20% and leads to cardiac myocyte cell death (7). The development of new chemotherapeutic regimens may lower the treatment-related cardiovascular mortality but it has not been evaluated in the population of non-elderly patients with NSCLC on a historical scale.

RT for thoracic cancer induces heart injury and cardiac-related death, especially when the tumor is in the left lung, left breast and the middle/lower thoracic esophageal cancer (8-10). Traditionally, RT-related cardiac diseases are thought to occur in more than 10 years after treatment (11), so they have long been recognized as a concern only for long-survivors of breast cancer and Hodgkin lymphoma (9,12). Nevertheless, it reported recently that the ratio of cardiac events is much higher and earlier for patients with left-laterality lung cancer compared with the opposite side after RT (8,13). From our perspective, although laterality is an easy-to-distinguish indicator, it is not precise enough to predict the radiation-induced CSM. Hereby, we highlight to investigate the association between the subsite location (lobe) of NSCLC and therapy-related CSM.

To the best of our knowledge, no research has exploited the SEER database to examine the CSM in such a large cohort of non-elderly NSCLC patients. In this research, we aimed to study the risk factors and tendency of CSM in association with chemotherapy and RT from 1985 to 2014. Meanwhile, we are the first to conduct a competing risk model to identify the risks of cardiovascular death for this population. Subsequently, we studied the association of the anatomic locations of the primary tumor with CSM as the survival time extended in the groups involving RT. Eventually, we assessed the evolution of CSM in every group during 1975–2014. As a whole, this study has a potential influence on the optimization of treatment strategy, the prevention of anticancer treatment-induced cardiac death and the improvement of therapeutic outcomes. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2981).

Methods

Source of data and population of this study

Patients aged 20–59 years old and diagnosed with NSCLC during 1975–2014 were enrolled from the National Cancer Institute SEER database (https://seer.cancer.gov/data) using SEER Stat 8.3.6 software. Therefore, it did not need to be approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital, and individual consent for this retrospective analysis was waived. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

We also extracted the demographic data (age, sex, race, marital status and year of diagnosis), clinicopathologic parameters (histology and subsite location of the primary cancer), treatment records [chemotherapy, RT, chemoradiation therapy (CRT) and surgery], survival status and death cause of each patient from the SEER database. The exclusion criteria were patients with unknown survival time or unspecific information of the subsite location of primary NSCLC. We collected the original data till the final year 2014 in order to divide patients into four decades and to ensure adequate follow-up to evaluate post-treatment CSM. This study population was divided into four different treatment groups: no chemotherapy or RT, chemotherapy-only, RT-only and CRT. According to the International Classification of Diseases for Oncology-3 codes, NSCLC included the following

histologies: adenocarcinoma (8140/2/3, 8141/3, 8147/3, 8480/3, 8481/3, 8260/3, 8550/3, 8570–8576), squamous cell carcinoma (8070/2/3, 8071/3, 8072/3, 8073/3, 8074/3, 8075/3, 8076/2, 8076/3, 8078/3), and others (8250–8257, 8012/3, 8013/3, 8014/3, 8031/3, 8046).

Statistical analysis

The Fine and Gray model was employed to determine the risk factors of heart death in every group. Herein, cardiac-specific death and death of other causes are two competing events. Cumulative incidence curves were plotted to display the accumulative CSM of tumor in various lobes and in four different eras using the Gray test. Moreover, forest graphs depicted the hazard ratios (HRs) of subsite locations of NSCLC to CSM among groups involving RT as the survival years increased; no chemotherapy or RT was tested as the control group. Finally, we calculated the percentage of cardiac death in every decade and compared the CSMs decade by decade with Gray test to elucidate the CSM trends after different treatments from 1975 to 2014.

All statistical analyses were carried out with the R software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). The R package "cmprsk" was used to perform the Fine and Gray model and cumulative CSM curves. Statistical significance was set at two-sided $P<0.05$.

Results

Demographic and clinicopathologic characteristics

There were 121,302 eligible patients in this investigation. Of these, 45.26% received no chemotherapy or RT, 38.43% received chemotherapy-only, 6.22% received RT-only and 10.09% received chemoradiation. The average follow-up time of the whole cohort was 41.1 months and 55.0, 23.9, 48.6, 39.3 months in no chemotherapy or RT, chemotherapy-only, RT-only and CRT, respectively. They were predominantly males, in their 50s, white race and adenocarcinoma. The number and percentage distribution of demographic and clinicopathologic characteristics in four different groups was displayed in *Table 1*.

In total, 3,423 (2.8%) died of cardiovascular diseases, 84,821 (69.9%) of NSCLC and 14,788 (12.2%) of other causes. The RT-only group exhibited the highest CSM and maximum (CSM/other mortality); the chemotherapy-only division had the lowest CSM and (CSM/other mortality) but highest cause-specific mortality; the minimum cause-specific mortality was from no chemotherapy or RT group.

Multivariate analysis of risk factors

Results from the Fine and Gray model (*Table 2*) demonstrated that patients aged 50–59 ($P=0.015$, HR =2.983), subsite location (other lobes *vs.* left-lower lobe, all $P<0.05$, HR <1), and decade of diagnosis were associated with CSM in RT-only group. The risk factors were similar in no chemotherapy or RT and chemotherapy-only groups: female, no surgery and married status were protective features whilst the black race and relatively older age increased CSM. Note that patients with squamous cell carcinoma revealed a higher probability of cardiac-specific death in all groups.

The indicator of high and early CSM in RT

According to *Figure 1* and *Table 2*, in the RT-only group, tumor in the left-lower lobe was significantly correlated to high CSM compared with any other lobes at the same survival time, which could not be observed in other three groups. Furthermore, the forest plots indicated that tumor in the left-lower lobe increased the risk vastly in the RT-only group overall, particularly during 2–5 years after RT ($P=0.008$, HR =2.30, 95% CI: 1.24–4.28), while no obvious discrepancy was illustrated in no chemotherapy or RT and CRT groups (*Figure 2*).

The trends of CSM from 1975 to 2014

To illuminate the changes of CSMs over a historical time course, we drew the line chart of percentage distribution (*Figure 3*) and the CSM cumulative curves (*Figure 4*) in four decades. Moreover, we compared the CSM decennium by decennium in four groups (*Table 3*). The outcomes suggested that the CSM declined all the way in no chemotherapy or RT and RT-only groups while it peaked in 1985–1994 and descended gradually after this period in chemotherapy-only and CRT groups.

Discussion

Anticancer treatment-induced cardiac events have received considerable attention from this century, particularly in elderly-patients. Nevertheless, we chose the non-elderly NSCLC patients because (I) there was no investigation on

Table 1 Demographic and clinicopathologic characteristics of 121,302 non-elderly patients with non-small cell lung cancer, stratified by treatments

Characteristic	No chemotherapy or radiotherapy (n=54,902), n (%)	Chemotherapy-only (n=46,619), n (%)	Radiotherapy-only (n=7,546), n (%)	Chemoradiation (n=12,235), n (%)
Age (years)				
20–39	1,204 (2.2)	1,611 (3.5)	255 (3.4)	479 (3.9)
40–49	10,293 (18.7)	10,666 (22.9)	1,796 (23.8)	3,164 (25.9)
50–59	43,405 (79.1)	34,342 (73.7)	5,495 (72.8)	8,592 (70.2)
Gender				
Male	30,760 (56.0)	25,385 (54.5)	4,521 (59.9)	6,426 (52.5)
Female	24,142 (44.0)	21,234 (45.5)	3,025 (40.1)	5,809 (47.5)
Race				
White	42,130 (76.7)	35,014 (75.1)	5,938 (78.7)	9,717 (79.4)
Black	9,505 (17.3)	7,876 (16.9)	1,193 (15.8)	1,725 (14.1)
Others	3,267 (6.0)	3,729 (8.0)	415 (5.5)	793 (6.5)
Marital status				
Married	30,179 (55.0)	26,821 (57.5)	4,753 (63.0)	7,490 (61.2)
Unmarried	22,460 (40.9)	18,220 (39.1)	2,587 (34.3)	4,378 (35.8)
Others	2,263 (4.1)	1,578 (3.4)	206 (2.7)	367 (3.0)
Decade of diagnose				
1975–1984	10,195 (18.6)	2,607 (5.6)	2,422 (32.1)	334 (2.7)
1985–1994	9,836 (17.9)	4,472 (9.6)	2,028 (26.9)	898 (7.3)
1995–2004	15,302 (27.9)	14,401 (30.9)	1,771 (23.5)	3,926 (32.1)
2005–2014	19,569 (35.6)	25,139 (53.9)	1,325 (17.6)	7,077 (57.8)
Subsite location				
Left-lower	6,622 (12.1)	5,636 (12.1)	844 (11.2)	1,231 (10.1)
Left-upper	15,812 (28.8)	13,301 (28.5)	2,338 (31.0)	3,570 (29.2)
Right-upper	21,721 (39.6)	18,408 (39.5)	3,117 (41.3)	5,308 (43.4)
Right-middle/lower	10,747 (19.6)	9,274 (19.9)	1,247 (16.5)	2,126 (17.4)
Histology				
Adenocarcinoma	30,592 (55.7)	25,701 (55.1)	4,064 (53.9)	6,881 (56.2)
Squamous carcinoma	14,856 (27.1)	10,113 (21.7)	2,291 (30.4)	2,760 (22.6)
Others	9,454 (17.2)	10,805 (23.2)	1,191 (15.8)	2,594 (21.2)
Surgery				
Yes	27,276 (49.7)	6,444 (13.8)	6,574 (87.1)	7,647 (62.5)
No	27,626 (50.3)	40,175 (86.2)	972 (12.9)	4,588 (37.5)
Death cause				
CSM	2,159 (3.9)	638 (1.4)	376 (5.0)	250 (2.0)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	No chemotherapy or radiotherapy (n=54,902), n (%)	Chemotherapy-only (n=46,619), n (%)	Radiotherapy-only (n=7,546), n (%)	Chemoradiation (n=12,235), n (%)
Cause-specific mortality	33,227 (60.5)	37,282 (80.0)	5,568 (73.8)	8,744 (71.5)
Other mortality	8,763 (16.0)	3,786 (8.1)	1,167 (15.5)	1,072 (8.8)
CSM/other mortality (%)	24.6	16.9	32.2	23.3

Total percent in variable groups by treatment categories is subject to rounding error. CSM, cardiac-specific mortality.

the risks and trends of CSM in this population; (II) by and large, the survival time decreases with age, so non-elderly patients are more suitable to study the long-term impact of anticancer-treatments on CSM; (III) the probability of cardiac comorbidities in this cohort is relatively lower than that in their old counterparts.

The risks and trend of CSM after chemotherapy

The results of our analysis indicated that the risks of cardiac death were analogical in groups of chemotherapy-only and no chemotherapy or RT: male, older, black race, unmarried, squamous cell carcinoma and surgery, most of which are also well-known risks of cardiovascular diseases. Strikingly, the CSM of left NSCLC was also significantly high in chemotherapy-only group. Left NSCLC is adjacent to the heart and most patients in this group were at the advanced stage, which could be reflected by the short survival time. Hence, metastasis and malignant pleural effusion might be two major reasons: advanced left NSCLC is easier to metastasize to the heart than the contralateral one, causing more cardiac-related events; on the other hand, severe malignant pleural effusion, common at late stage, may compress the heart and impair its function when the tumor is on the left.

Notably, the CSM was lowest among patients treated with chemotherapy-only in *Table 1* and *Figure 3*. There were several underlying causes. Primarily, in this group, most patients (80.0%, *Table1*) died of NSCLC itself due to the advanced stage. Moreover, the time was rather shorter to observe the serious adverse reactions of heart after the administration of chemotherapeutic drugs. Besides, the death causes and distributions were more widespread for these patients because chemotherapeutic medicines don't specifically target for cancer cells or cardiac cells but also other normal cells, which was confirmed by the lowest ratio of (CSM/other mortality) in *Table 1*. Above all, the highest percentage of cause-specific death and the lowest ratio in chemotherapy-only led to a relatively minimum CSM.

From *Table 2*, the CSM in the late period had no evident discrepancy compared with the first decade in chemotherapy group. However, it peaked in 1985–1994 and alleviated gradually when we studied deeply (*Figure 3*, *Table 3*), matching well with the changes of chemotherapeutic regimens historically. During 1985–1994, single gemcitabine was proved to enhance the risk of cardiac toxicity (14). Subsequently, the clinical trials in the next decade showed more favorable toxicity in the combination of cisplatin-gemcitabine (CG) or epirubicin-gemcitabine (EG) and gemcitabine-vinorelbine (6,15). Similarly, the more recent research also found no serious cardiac side-effects (16).

The hazards and the development of RT to CSM

Previously, researchers verified the discrepancy of cardiac morbidity and mortality between left/right-sided thoracic cancer associated with RT (8,9,13). Herein, we emphasized studying the association of subsite locations of tumor with CSM, which was more accurate but no study has reported this point hitherto. The multivariate analysis indicated a higher CSM in the left-lower lobe than that in any other lobes in RT-only group. Most importantly, only after 2 years of RT (*Figure 2B*), patients with left-lower tumor had an obviously higher probability of cardiac death, in line with the study of Defraene *et al*. in 2019 (17). They constructed models of multifactorial risk factors for mortality after RT and concluded that the largest impact of RT on mortality was at the 2-year time point. Other studies also demonstrated that cardiac disorders happened within 2 years and disastrous cardiac events occurred around the third year after RT as the irradiation doses to the heart were considerably higher for NSCLC patients than for those with other thoracic malignancies (8,18,19). Thus, the rule of thumb that RT-related cardiac toxicity is a late effect in more than 10 years is not applicable to NSCLC

Table 2 Multivariate analysis of risk factors of cardiac-specific mortality while accounting for other-cause mortality among non-elderly patients with non-small-cell lung cancer using the Fine and Gray model, sub-distributed by treatments

Characteristic	No chemotherapy or radiotherapy		Chemotherapy-only		Radiotherapy-only		Chemoradiation therapy	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)								
20–39	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
40–49	1.531 (1.003–2.336)*	0.048*	2.111 (1.033–4.316)*	0.040*	2.267 (0.922–5.573)	0.075	1.116 (0.536–2.325)	0.770
50–59	2.374 (1.576–3.576)*	<0.001*	2.882 (1.434–5.790)*	0.003*	2.983 (1.238–7.189)*	0.015*	1.141 (0.701–2.856)	0.330
Gender								
Male	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Female	0.628 (0.571–0.690)*	<0.001*	0.673 (0.570–0.795)*	<0.001*	0.824 (0.660–1.029)	0.088	0.528 (0.401–0.694)*	<0.001*
Race								
White	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Black	1.273 (1.141–1.421)*	<0.001*	1.390 (1.151–1.679)*	<0.001*	1.300 (0.991–1.707)	0.058	1.034 (0.716–1.493)	0.860
Marital status								
Married	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Unmarried	1.208 (1.105–1.321)*	<0.001*	1.230 (1.048–1.444)*	0.011*	0.994 (0.796–1.242)	0.960	1.157 (0.883–1.517)	0.290
Decade of diagnosis								
1975–1984	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
1985–1994	0.770 (0.688–0.861)*	<0.001*	1.351 (0.921–1.982)	0.120	0.848 (0.670–1.073)	0.170	2.535 (1.086–5.917)*	0.032*
1995–2004	0.498 (0.445–0.557)*	<0.001*	1.049 (0.742–1.484)	0.790	0.546 (0.406–0.734)*	<0.001*	1.598 (0.711–3.595)	0.260
2005–2014	0.410 (0.363–0.463)*	<0.001*	0.832 (0.591–1.171)	0.290	0.455 (0.274–0.757)*	0.002*	1.042 (0.459–2.367)	0.920
Subsite location								
Left-lower lobe	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Left-upper lobe	1.100 (0.951–1.263)	0.210	0.866 (0.677–1.108)	0.250	0.719 (0.525–0.985)*	0.040*	1.029 (0.682–1.553)	0.890
Right-upper lobe	0.976 (0.849–1.122)	0.730	0.765 (0.602–0.973)*	0.029*	0.738 (0.546–0.997)*	0.048*	0.706 (0.468–1.065)	0.097
Right-middle/low lobe	0.948 (0.811–1.108)	0.500	0.670 (0.505–0.886)*	0.005*	0.606 (0.416–0.883)*	0.009*	0.671 (0.411–1.097)	0.110
Histology								
Adenocarcinoma	1 (reference)		1 (reference)		1 (reference)		1 (reference)	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	No chemotherapy or radiotherapy		Chemotherapy-only		Radiotherapy-only		Chemoradiation therapy	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Squamous carcinoma	1.270 (1.159–1.391)*	<0.001*	1.551 (1.309–1.839)*	<0.001*	1.651 (1.340–2.035)*	<0.001*	1.385 (1.059–1.811)*	0.017*
Surgery								
Yes	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
No	0.332 (0.302–0.366)*	<0.001*	0.746 (0.602–0.926)*	0.008*	0.450 (0.230–0.879)*	0.019*	0.752 (0.552–1.025)	0.072

*, statistically significant hazard ratios and P. HR, hazard ratio; CI, confidence interval.

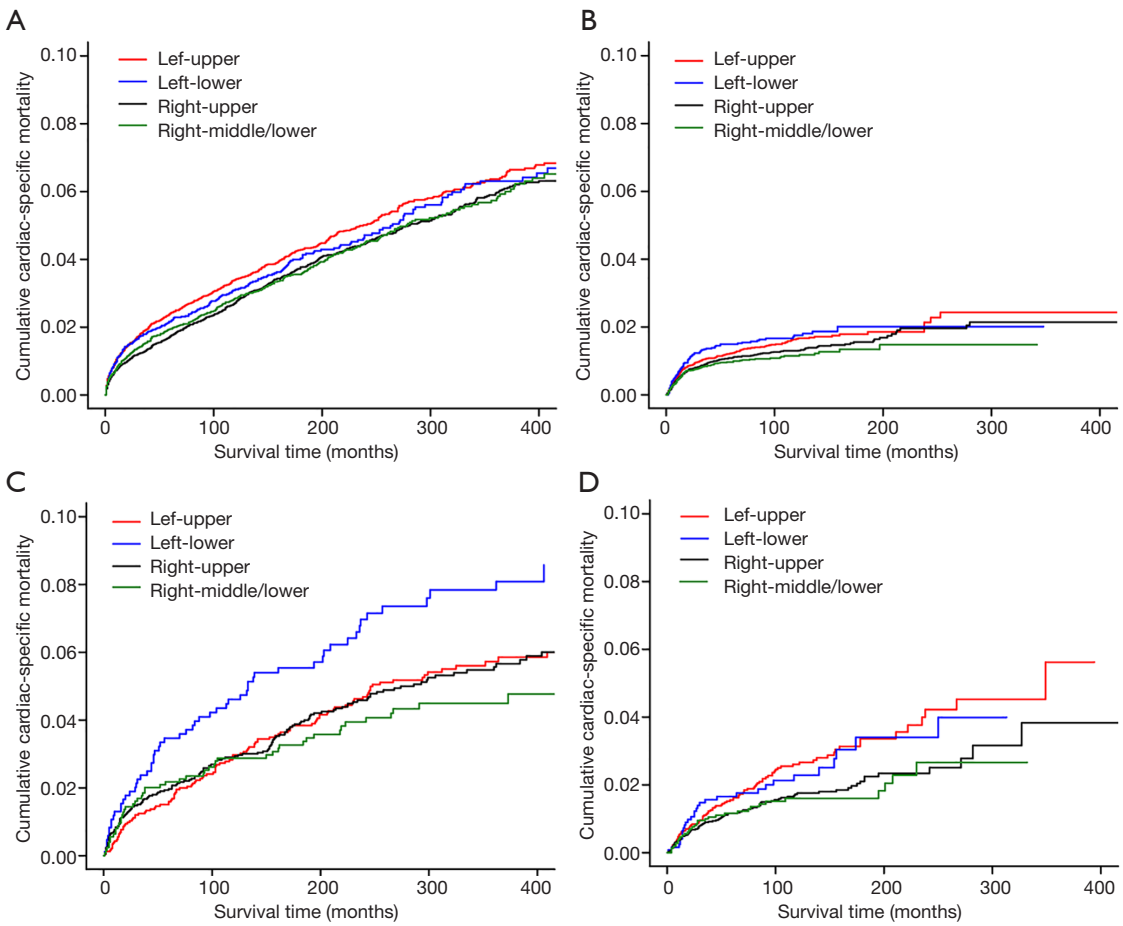

Figure 1 Cumulative incidence curves of cardiac-specific mortality for patients with different subsite locations of non-small cell lung cancer in four groups: (A) no chemotherapy or radiotherapy; (B) chemotherapy-only; (C) radiotherapy-only; (D) chemoradiation therapy.

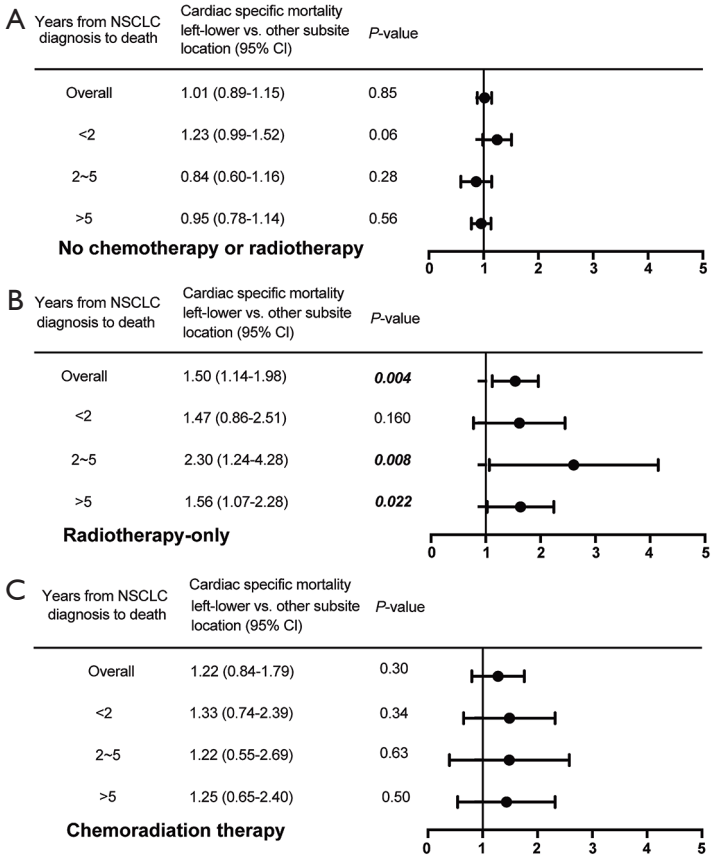

Figure 2 Forest graphs delineating the hazard ratios of subsite locations of tumor to CSM in the survival time of less than 2 years, 2–5 years and more than 5 years after diagnosis: (A) no chemotherapy or radiotherapy; (B) radiotherapy-only; (C) chemoradiation therapy. CI, confidence interval; NSCLC, non-small cell lung cancer.

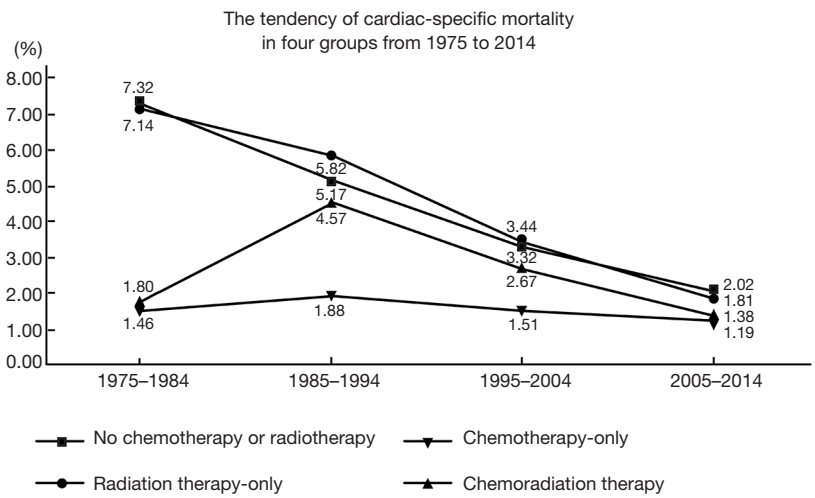

Figure 3 The line chart of percentage distribution of cardiac-specific mortality in four groups during 1975–2014.

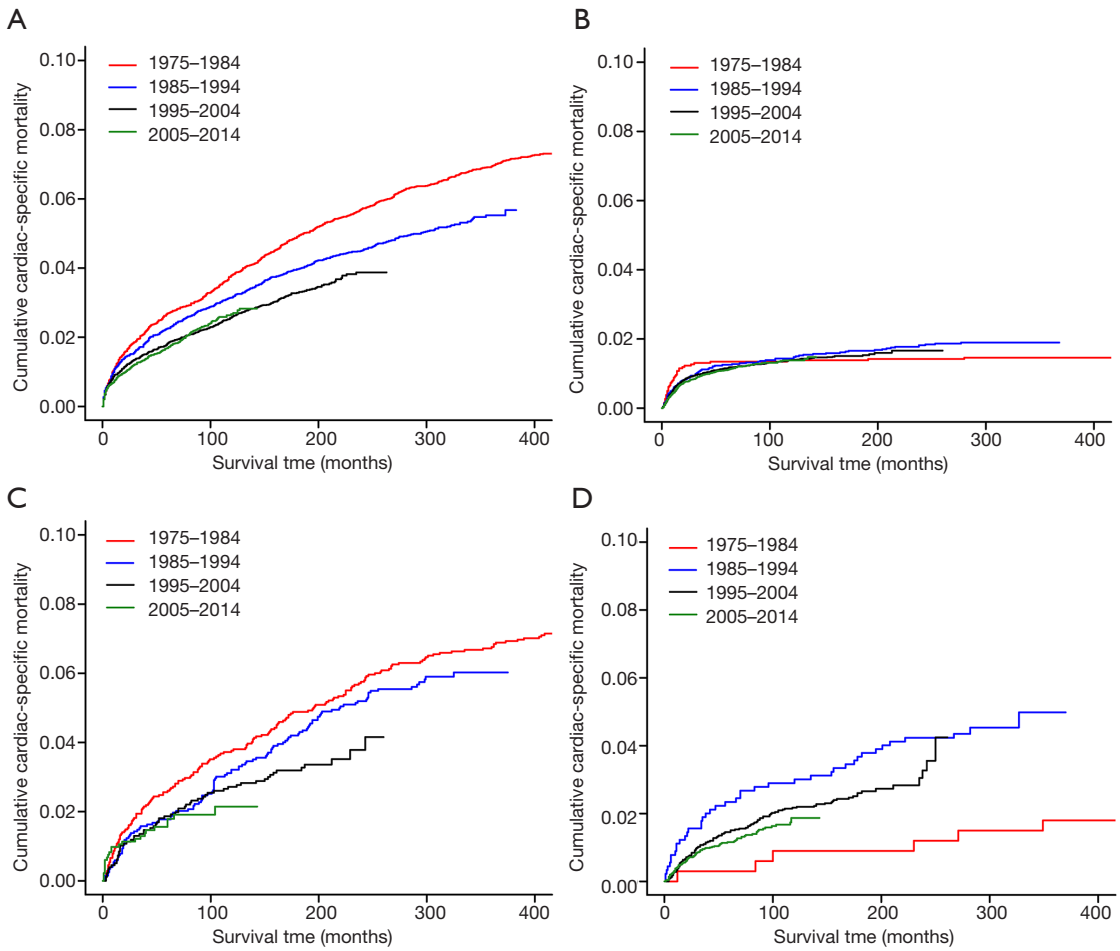

Figure 4 The tendency of cardiac-specific mortality from 1975 to 2014: (A) no chemotherapy or radiotherapy; (B) chemotherapy-only; (C) radiotherapy-only; (D) chemoradiation therapy.

Table 3 The comparison of cardiac-specific mortality decade by decade in four different treatment groups

Decades for comparison	No chemotherapy or radiotherapy		Chemotherapy-only		Radiation therapy-only		Chemoradiation therapy	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
1985–1994 *vs.* 1975–1984	0.709 (0.633–0.793)*	<0.001*	2.480 (0.761–8.050)	0.130	0.812 (0.643–1.030)	0.081	2.600 (1.110–6.090)*	0.028*
1995–2004 *vs.* 1985–1994	0.671 (0.595–0.758)*	<0.001*	0.411 (0.265–0.638)*	<0.001*	0.603 (0.443–0.821)*	0.001*	0.601 (0.420–0.860)*	0.0053*
2005–2014 *vs.* 1995–2004	0.728 (0.640–0.828)*	<0.001*	0.582 (0.383–0.883)*	0.011*	0.564 (0.354–0.901)*	0.017*	0.583 (0.445–0.764)*	<0.001*

*, statistically significant hazard ratios and P. HR, hazard ratio; CI, confidence interval.

patients. Accordingly, radiation oncologists should give more considerations to the dose and scope of radiation to the heart; clinical oncologists are supposed to pay close attention to the cardiovascular conditions just after patients receive RT.

The CSM reduced over time in the RT-only group, particularly since the mid-1990s, consistent with the research in the nonoperative but RT situation (8). This tendency could be attributed to the constraints of cardiac radiation dose, to the extensive application of advanced radiation techniques, and to the overall improvement of management, prevention and intervention of cardiovascular disease. In the 1990s, the three-dimensional conformal RT (3DCRT) came out. Combining the linear accelerator with computed tomography (CT) imaging, it delivered the irradiation more accurately, resulting in enough radiation doses to tumors and maximal protection for normal tissues (20). Compared with 1995–2004, the potential explanation for the decline of CSM in the era of 2005–2014 was the increasing use of intensity-modulated RT (IMRT) that further lowered heart doses (21). Consequently, our results perfectly represented the development and advancement in the RT field on a historical scale.

The traits in no chemotherapy or RT and CRT groups

The CSM reduced greatly all the time in no chemotherapy or RT group (*Tables 2*,*3*, *Figure 3*). The improvements of the medical care over decades and the incremental proportion of female patients in this group were the two major reasons. Indubitably, it benefited tremendously from the overall improvements in the precaution and treatment of cardiovascular disease and people's growing awareness of health care, proved by the decreasing CSMs all the time in both genders (Table S1). It was also one of the causes for the decline of CSM in other groups. Another reason was the incremental distribution of female patients, increasing from 34.9% to 49.1% during the study time (Table S1). It's universally acknowledged that the probability of cardiac events of non-elderly female is much lower than that of males, leading to a declining heart death.

In our current research, the CSM of CRT ascended during 1985–1994 and descended since the mid-1990s. In the literature, the impact of CRT on CSM was contradictory: some described that it increased the risk of cardiac toxicity (22,23) while others reported that it had acceptable toxicity (24-26). In reality, the influence of CRT on CSM might be too complicated to analyze thoroughly in a single study, such as the sequence of chemotherapy and RT, the kinds and doses of chemotherapeutics, the techniques of RT and so on.

Interestingly, the histological type of squamous cell carcinoma was an independent risk of CSM in every group (*Table 2*). Long-term and large-scale tobacco consumption might be a prime contributing factor since smoking is the shared culprit for both cardiac diseases and squamous cell carcinoma of NSCLC.

In summary, we proposed novel insights into the CSM for non-elderly NSCLC patients after RT or chemotherapy, but a few limitations should be stated. First, a majority of patients in the RT-only group also underwent surgery or other unknown treatments, which may also affect the CSM to some extent. Next, though we ensured that this population had less cardiac-related comorbidities generally, we did not verify it. Nevertheless, the SEER database still provided a large cohort of non-elderly NSCLC with enough information so that we could assess the therapy-related CSM in a long-time scale and put forward vital findings for better clinical anti-cancer strategies.

Conclusions

In a nutshell, male, older, black race, unmarried status, squamous cell carcinoma and surgery were the risks of CSM after chemotherapy. However, male, unmarried status, black race and surgery were no longer the adverse indicators of cardiovascular death in RT-only group and its dominating risk was tumor in left-lower lobe. Moreover, patients with left-lower sided NSCLC had the highest risk of cardiac death from the second years after RT, so earlier attention should be given to the cardiac conditions of patients receiving RT. The CSMs in chemotherapy and CRT culminated in 1985–1994 but descended gradually after this period; the tendency of CSM in RT-only decreased with time, especially since the mid-1990s.

Acknowledgments

We acknowledge the efforts of the National Cancer Institute and SEER database tumor registries for providing high-quality open resources for researchers.

Funding: This work was supported by the National Nature Science Foundation of China (grant number 81572321

to DZH).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2981

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2981). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval and individual consent are not needed.

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Cite this article as: Jiang KT, Huang DZ. The risks and trends of cardiac-specific mortality associated with chemotherapy or radiotherapy in a large cohort of non-elderly patients with non-small cell lung cancer. Transl Cancer Res 2021;10(2):842-853. doi: 10.21037/tcr-20-2981

Supplementary

Table S1 The distribution of NSCLC and the proportion of CSM in gender in the group of no chemotherapy or radiotherapy

Decade of diagnose	The distribution of NSCLC, n_0 (%)		Cardiac-specific mortality n_1 (%)	
	Male	Female	Male	Female
1975–1984 (n=10,195)	6,731 (66.0)	3,464 (34.0)	526 (7.8)	220 (6.4)
1985–1994 (n=9,836)	5,819 (59.2)	4,017 (40.8)	355 (6.1)	154 (3.8)
1995–2004 (n=15,302)	8,255 (53.9)	7,047 (46.1)	325 (3.9)	183 (2.6)
2005–2014 (n=19,569)	9,955 (50.9)	9,614 (49.1)	255 (2.6)	141 (1.5)

NSCLC, non-small cell lung cancer; CSM, cardiac-specific mortality.

http://dx.doi.org/10.21037/tcr-20-2981