Clinics in Oncology

Research Article
Published: 20 Nov, 2024

# Time-Dependent Alteration in the Causes of Death in Long-Term Thymoma Survivors

*Xu K, Sun H, Jiao R, Liang J and Jiang W**

*Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China*

## Abstract

**Objectives:** It was suggested that thymoma is a chronic disease and that cardiovascular disease is the most common non-cancer-related cause of death in survivors after thoracic radiotherapy. We aimed to evaluate time-related survival and causes of death in patients with thymoma.

**Methods:** The survival and cause of death in patients with thymoma were assessed using the Surveillance, Epidemiology, and End Results data. We performed conditional survival, annual hazard rate, and Fine-Gray competing risk analyses.

**Results:** We identified 3,105 patients with thymoma. The 10-year overall survival and cancer-specific survival rates were 55.5% (95% CI, 53.4-57.6%) and 74.4% (95% CI, 72.4-76.3%), respectively. The annual smoothed hazard for all-cause mortality increased steadily, while that of thymoma-related mortality decreased by the 4th year and was surpassed by other causes starting at 4.5 years. The annual hazard of thymoma-related mortality remained at about 1% to 2% between years 5 and 25. Conditional survival showed a similar trend. The 10-, 15-, and 25-year cumulative incidences of the most common death causes were 23.1, 28.5, and 31.8% for thymoma, 5.4, 8.3, and 11.8% for heart disease, and 3.9, 7.0, and 10.8% for a second cancer, respectively. Heart disease was the leading non-thymoma cause of death in 5-year survivors and posed a high mortality risk in 10-year survivors aged ≥ 65 years or who received radiotherapy (adjusted P<0.001, P=0.015).

**Conclusion:** The risk of cancer-specific and non-cancer-specific causes of death shifted over time in patients with thymoma. Non-cancer-specific causes, particularly heart disease, were major competing causes of death that increased with survival.

**Keywords: Thymoma; Conditional survival; Annual hazard; Heart disease**

**OPEN ACCESS**

***Correspondence:***
*Wei Jiang, Department of Radiation Oncology, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China,*

**Received Date**: *03 Oct 2024*
**Accepted Date:** *14 Nov 2024*
**Published Date:** *20 Nov 2024*

***Citation:***
*Xu K, Sun H, Jiao R, Liang J, Jiang W. Time-Dependent Alteration in the Causes of Death in Long-Term Thymoma Survivors. Clin Oncol. 2024; 9: 2114.*

***ISSN: 2474-1663***



## Introduction

Thymoma originates from the thymic epithelium and is a rare neoplasm with a low morbidity rate of 1.3 per million person-years in the United States. Nevertheless, it remains the most common neoplasm in the anterior mediastinum [1]. The thymoma tumor grows slowly and rarely spreads to other body parts. However, it often invades nearby tissues, including the pericardium, great vessels, lungs, and pleura [1,2]. Surgical resection is the cornerstone treatment, but complete resection can be difficult, and local or regional recurrence is common [3,4]. Radiotherapy was shown to confer a survival advantage in patients with Masaoka-Koga stage II-IV disease beyond the benefits of surgery [5-7].

Thymoma is a limited malignant tumor with excellent survival prospects. Even patients with aggressive recurrent or progressing thymoma have a favorable long-term survival with appropriate treatment [8,9]. Non-cancer-related deaths tend to occur in long-term cancer survivors. Cardiovascular disease is the most common nonmalignant cause of death in thoracic radiotherapy cancer survivors, including patients with Hodgkin's lymphoma, breast cancer, and lung cancer. A significant association was noted between high radiation doses and the risk of cardiovascular disease [10-14]. Advances in treatment have increased the number of long-term survivors. However, few studies have focused on cardiovascular disease and other causes of death in patients with thymoma. Moreover, data on the cause of morbidity in long-term thymoma survivors are limited. Previous research has suggested that thymoma is a chronic disease rather than a curable cancer, as the conditional survival rate for thymoma does not change over time [15]. However, the reason for this incurability and the causes of mortality in long-term thymoma survivors remains unclear. To

address this knowledge gap, we conducted this large retrospective analysis using data from the Surveillance, Epidemiology, and End Results (SEER) database to evaluate survival over time and causes of death in patients with thymoma.

## Materials and Methods

### Database and patient selection

We systematically identified patients with thymoma in the SEER database between January 1975 and December 2016 (database 1975-2016). The SEER database provides information on the patients' baseline characteristics (age, sex, race), tumor (stage, histology, sites), and treatment (surgery, radiotherapy, chemotherapy). The database lacks data on comorbidities, performance status, medical imaging, radiation dose, and treatment failure events. Our database search included the terms "primary site labeled by ICD-O-3 is to C37.9," "histological type ICD-O-3 is to 8580–8585," and "the behavior code is to /3." Cases with primary thymoma were selected in patients aged ≥ 18 years between 1975 and 2016. All patients had to have a cytological or histological diagnosis. Patients with a previous cancer diagnosis, loss to follow-up, unknown treatment, or missing death information were excluded from the analysis. The flowchart was shown in supplement Figure S1.

Patients were staged according to the Masaoka-Koga staging system as follows:

I-IIA (Localized): Localized only

IIB-III (Regional): Regional by direct extension only

IV (Distant): Regional lymph node involvement only or regional by direct extension with lymph node involvement unknown.

### Statistical analysis

The Kaplan-Meier method evaluated Overall Survival (OS) and Cancer-Specific Survival (CSS). The Fine-Gray competing risks method determined cumulative incidence functions for competing events. Fine-Gray sub-distributional hazard regression identified risk factors for thymoma specific deaths, with other cause-specific deaths treated as competing risks. Univariable and multivariable Fine-Gray and Cox regressions assessed risks associated with various factors. Multivariable models included covariates with $P \leq 0.1$ in the univariable analysis.

For patients who have survived for at least t0(≥ 0) years, conditional survival was defined as the probability that they will live for additional *t* years, denoted as S(t/t0) and referred to as the conditional survival function [16].

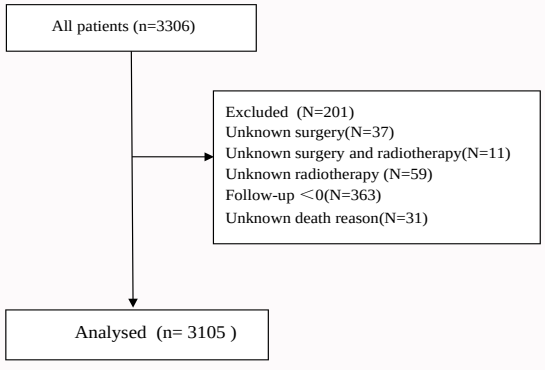


**Figure S1:** The flowchart of research.

$S(t/t0) = S(t+t0)/S(t0)$ for $t \geq 0$

For example, the 5-year conditional survival of patients surviving two years is estimated by dividing the 7-year cumulative survival by the 2-year cumulative survival. The conditional survival estimates were obtained using the Kaplan-Meier method. As an extension of the conditional survival concept, conditional CSS was defined as the probability of surviving for a given number of years with thymoma-specific mortality. The annual hazard rate curves were based on a weighted kernel smoothing [17,18]. The smoothed annual hazards of deaths from thymoma, other causes, and any cause were calculated.

Statistical analysis was performed using STATA software, Version 16.0 (Stata Corp, College Station, TX), and the cmrsk package in R, Version 3.6.3. All statistical tests were two-tailed, and statistical significance was set at $P<0.05$.

### Data availability

After identification, individual participant data will be made available to investigators who provide a methodologically sound proposal for individual patient based meta-analyses. Proposals should be directed to Wei Jiang. Data requestors should sign a data access agreement.

## Results

### Cohort characteristics

The study included 3,105 patients, whose baseline information is shown in Table 1. The median age was 58 (18–93) years, with male patients accounting for 52.0%, and patients aged ≥ 65 years accounted for 33.1%. The most common primary histological diagnoses were B3 (13.1%) and AB (12.4%). Locally advanced disease (IIB-III) was diagnosed in 1,360 (43.8%) patients. Most patients (2,461, 79.3%) underwent surgery, and 1,644 (52.9%) also received radiotherapy.

### Survival and conditional survival

With a median follow-up of 9.7 (95% CI, 9.2-10.1) years, the 10-year OS and CSS rates were 55.5% (95% CI, 53.4-57.6%) and 74.4% (95% CI, 72.4-76.3%), respectively (Figure 1A). Smoothed hazard plots showed that the hazard of death from other causes exceeded that of thymoma by approximately 4.5 years after diagnosis and that the overall annual hazard of death increased steadily. The annual hazard of thymoma-related mortality increased from diagnosis to the 4$^{th}$ year and then decreased annually and remained stable at approximately 1% to 2% from the 5$^{th}$ to the 25$^{th}$ year after diagnosis.

The OS-based conditional survival decreased slowly over time, while the CSS-based conditional survival increased slowly. For patient with thymoma who already survived 6 or 12 years after diagnosis, the probability of surviving to 15 years after diagnosis without dying from thymoma was 72.3% and 74.1%, respectively, while the probability of surviving 15 years without dying from any cause was 36.4% and 32.7%, respectively (Table 2). Notably, the hazard curve for death from any cause was parallel to that for death from other factors from the 5$^{th}$ year onward (Figure 1B).

### Risk factors of cancer-specific and other cause mortality

Age, sex, time of diagnosis, marital status, stage, surgery, and chemotherapy were independent risk factors for all-cause mortality. Compared to young patients, those aged ≥ 65 years were predicted to have poor OS (HR, 1.51; 95% CI, 1.27-1.79; $P<0.001$). Compared with TNM stage I-IIA, the HR was 1.66 (95% CI, 1.26-2.17) for patients at stage IIB-III and 3.15 (95% CI, 2.36-4.22) for those at stage IV.

**Table 1:** Demographic and clinical characteristics of the patients with thymoma.

| Variable | *n* | % | 10 y OS | 10 y CSS |
|---|---|---|---|---|
| **Age (years)** | | | | |
| **<65** | 2,077 | 66.9 | 64.4 (63.0-65.8) | 77.6 (75.3-79.7) |
| **≥65** | 1,028 | 33.1 | 36.5 (34.4-38.7) | 67.4 (63.4-71.1) |
| **Marital status** | | | | |
| **Married** | 1,861 | 59.9 | 58.3 (56.8-59.9) | 75.8 (73.4-78.0) |
| **Unmarried** | 1,120 | 36.1 | 49.2 (47.1-51.2) | 67.3 (61.4-72.5) |
| **Unknown** | 124 | 4 | 70.7 (63.7-76.7) | 75.1 (70.4-79.1) |
| **Race** | | | | |
| **White** | 2,061 | 66.4 | 56.4 (54.9-57.8) | 75.8 (73.4-78.0) |
| **Black** | 474 | 15.3 | 48.4 (45.1-51.5) | 67.3 (61.4-72.5) |
| **Other** | 570 | 18.4 | 58.6 (55.7-61.4) | 75.1 (70.4-79.1) |
| **Sex** | | | | |
| **Female** | 1,490 | 48 | 56.9 (55.1-58.7) | 76.5 (73.6-79.0) |
| **Male** | 1,615 | 52 | 54.3 (52.6-55.9) | 72.6 (69.8-75.2) |
| **Diagnosis time** | | | | |
| **1,975_1,987** | 269 | 8.7 | 38.8 (33.0-44.6) | 55.8 (49.2-62.0) |
| **1,988_2,003** | 1,005 | 32.4 | 51.2 (48.1-54.3) | 71.1 (67.9-73.9) |
| **2,004_2,016** | 1,831 | 59 | 63.0 (59.6-66.2) | 80.9 (78.0-83.4) |
| **Stage** | | | | |
| **I-IIa** | 869 | 28 | 75.1 (72.9-77.2) | 90.1 (88.0-93.0) |
| **IIB-III** | 1,360 | 43.8 | 56.3 (54.5-57.9) | 77.5 (74.7-80.1) |
| **IV** | 670 | 21.6 | 32.9 (30.3-45.5) | 48.8 (43.6-53.8) |
| **Unknown** | 206 | 6.6 | 48.4 (44.0-52.7) | 66.2 (58.2-73.1) |
| **Histology, Thymoma** | | | | |
| **A** | 202 | 6.5 | 55.1 (49.6-60.2) | 88.1 (80.4-92.9) |
| **AB** | 384 | 12.4 | 67.6 (_63.5-71.3) | 86.7 (80.7-90.7) |
| **B1** | 303 | 9.8 | 64.3 (60.0-68.3) | 81.0 (74.4-86.0) |
| **B2** | 310 | 10 | 66.9 (62.1-71.3) | 78.9 (70.3-85.3) |
| **B3** | 406 | 13.1 | 56.5 (52.9-59.9) | 74.9 (68.8-80.0) |
| **Unknown** | 1,500 | 48.3 | 49.6 (48.0-51.2) | 68.3 (65.5-70.9) |
| **Surgery** | | | | |
| **Yes** | 2,461 | 79.3 | 63.3 (61.9-64.6) | 82.5 (80.5-84.3) |
| **No** | 644 | 20.7 | 27.1 (24.8-29.5) | 42.8 (37.9-47.6) |
| **Radiotherapy** | | | | |
| **Yes** | 1,644 | 52.9 | 56.2 (52.9-59.4) | 75.2 (72.1-78.0) |
| **No** | 1,443 | 46.5 | 55.1 (52.3-57.8) | 73.8 (71.1-76.2) |
| **Chemotherapy** | | | | |
| **Yes** | 861 | 27.7 | 40.3 (36.3-44.3) | 54.4 (50.2-58.5) |
| **No** | 2,244 | 72.3 | 61.4 (58.9-63.8) | 82.2 (80.1-84.1) |

As expected, surgical inventions were a protective factor for OS (HR, 0.42; 95% CI, 0.32-0.50).

The thymoma-specific mortality in young people was lower than in older adults ($P$<0.001) and at an early stage than at an advanced stage ($P$<0.001). Similarly, the hazard of mortality due to another cancer was higher in older patients (≥ 65 years) than in younger ones. Surgery decreased the hazard of death (adjusted Sub-distribution Hazard Regression (SHR), 0.42; 95% CI, 0.3-0.50; $P$<0.001) without increasing the hazard of death due to other causes. The multivariable analysis results are summarized in Table 3.

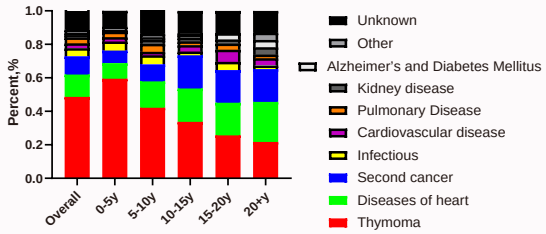


**Figure 1:** The survival (A) and smoothed annual hazard (B) of the entire group.

Smoothed hazard plots showed that the hazard of death from other causes exceeded that of death from stage I-IIA thymoma since diagnosis. The overall annual hazard of death increased steadily (Figure 2A). This cross point was delayed in patients at more advanced thymoma stages (Figure 2B, 2C). The critical points were seven years for patients <60 and three years for those ≥ 65 years (Figure 2D, 2E). The hazard of death from other causes exceeded that of death from thymoma after surgery from diagnosis onward (Figure 2F).

The hazard of thymoma-specific death decreased over the treatment period (for 1988–2003: adjusted SHR, 0.60; 95% CI, 0.48-0.76; $P$<0.001; for 2004–2016: adjusted SHR, 0.35; 95% CI, 0.27-0.45; $P$<0.001).

### The incidence of causes of death and time-dependent changes

The 10-, 15-, and 25-year cumulative incidences of the most common causes of death were 23.1, 28.5, and 31.8% for thymoma, 5.4, 8.3, and 11.8% for heart disease, and 3.9, 7.0, and 10.8% for a second cancer. Mortality from heart disease and a second cancer increased annually (Figure 3A, 3B). For those surviving five years, heart disease was the leading cause of death after thymoma (Supplementary Table S1).

Age, years of diagnosis, and race were associated with mortality due to heart disease in those who already survived 0 and 10 years. Patients aged ≥ 65 years who already survived 0 and 10 years had an increased risk of dying from heart disease ($P$<0.001; Supplementary Table S2 and Figure 3C). Patients who received radiotherapy and survived ten years were at a higher risk of heart-specific death (adjusted HR, 2.22; 95% CI, 1.17-4.22; $P$=0.015; Supplementary Table S2 and Figure 3D).

## Discussion

In this study, patients with thymoma were more likely to die from causes other than thymoma 4.5 years after diagnosis or later. Thymoma-related deaths decreased very slowly with time, but the annual risk remained at about 1% to 2% even 25 years after diagnosis. Like the annual risk, the conditional probability of OS increased slowly, and the CSS decreased slowly over the same period. These results highlighted the likelihood of other causes of death replacing those related to thymoma during follow-up and reflected the dynamic changing trend of causes of death. The reported 20-year cumulative incidence of recurrence by pathological T categories (9$^{th}$ TNM) in N0M0 thymoma cases was 2.8% for T1a, 5.0% for T1b, 2.0% for T2, 31.7% for T3, and 37.5% for T4 [19]. The lower recurrence in the early thymoma stages also showed favorable survival. Therefore, follow-up

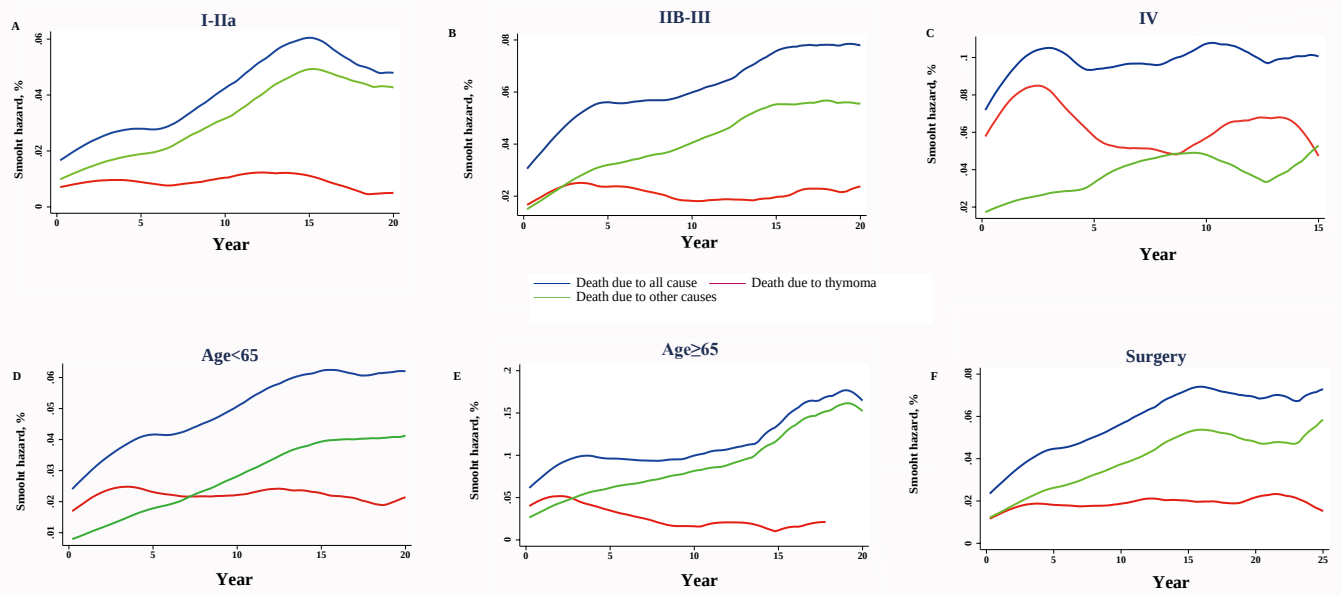


**Figure 2:** The annual death hazard due to any cause, thymoma, and other causes. The annual death hazard based on the stage (A-C), the patients' age (D-E), and the surgical treatment (F).

**Table 2:** The conditional overall and cancer-specific survival after thymoma diagnosis.

| Total survival (years) | Already survived (years) | | | | | |
|---|---|---|---|---|---|---|
| | 3 | 6 | 9 | 12 | 15 | 18 |
| **Conditional overall survival, %** | | | | | | |
| **6** | 71.6 (63.9-73.7) | | | | | |
| **9** | 60.3 (57.7-62.8) | 56.9 (53.6-60.1) | | | | |
| **12** | 48.8 (45.8-51.7) | 43.7 (39.8-47.5) | 43.5 (38.6-48.3) | | | |
| **15** | 37.4 (34.1-40.8) | 36.4 (32.3-40.4) | 34.5 (29.2-39.9) | 32.7 (25.8-39.7) | | |
| **18** | 31.2 (27.7-34.9) | 28.9 (24.4-33.5) | 27.6 (21.8-33.6) | 26.7 (19.5-34.3) | 23.1 (14.2-33.2) | |
| **21** | 24.8 (20.9-28.8) | 23.1 (18.3-28.3 | 22.5 (16.5-29.0) | 18.7 (11.6-27.1) | 10.3 (2.5-24.4) | 13.4 (3.2-31.1) |
| **Conditional thymoma-specific survival, %** | | | | | | |
| **6** | 86.5 (84.7-86.1) | | | | | |
| **9** | 81.2 (78.9-83.3) | 81.5 (78.5-84.1) | | | | |
| **12** | 75.5 (72.6-78.2) | 76.3 (72.4-79.7) | 77.4 (72.2-81.7) | | | |
| **15** | 70.7 (67.0-74.0) | 72.3 (67.-76.5) | 71.3 (64.3-77.1) | 74.1 (65.8-80.6) | | |
| **18** | 66.8 (62.4-71.0) | 66.6 (60.1-72.4) | 69.6 (61.9-76.0) | 74.1 (65.8-80.6) | 72.9 (55.6-84.4) | |
| **21** | 61.7 (55.8-67.1) | 65.0 (57.9-71.2) | 69.6 (61.9-76.0) | 67.9 (52.5-79.3) | 72.9 (55.6-84.4) | 84.4 (58.3-89.3) |

For example, for a patient who had survived for six years after thymoma diagnosis, the probability of surviving until 9 years after thymoma diagnosis without dying of thymoma is 81.5%, and the probability of surviving for 15 years after thymoma diagnosis without dying of any cause is 36.4%

with Computed Tomography (CT) should be performed at 12-month intervals for early-stage patients who underwent surgery, every 6 to 12 months for patients at a locally advanced stage, and every six months for those at an advanced stage.

A previous study reported that five-year conditional OS and CSS remained static ten years after thymoma diagnosis, suggesting that thymoma was a chronic disease rather than a curable cancer [15]. This could be explained by the steady increase in the other causes of death, while thymoma as the cause of death remained stable at around 2%. Furthermore, among non-cancer-related deaths, heart disease was suggested as the main cause. We found that the annual hazard of thymoma-specific death increased during the first 4.5 years and then decreased, while other causes of death increased continuously. The difference in trend suggested that the other causes of death were the main cause of increased mortality. Our study suggest that heart disease is an important long-term mortality cause for thymoma. Focusing on the changing risk and cause of death could help develop rational strategies for surveillance and screening for survivors. The cause of death dynamics changed over time. Age has been reported to be associated with survival and conditional survival in patients with lung cancer [20]. We saw a higher risk of cancer-specific and non-cancer-specific mortality in older patients. The results concord with those of a large population study from England [21]. This reflects the competing risk of more comorbidities in older patients and partly explains the variability in mortality risk and the shift in the causes of mortality over time. The increased risk of death from

**Table 3:** Multivariable analysis for cause of death for patients with thymoma.

| Item | OS | | | | CSS | | | | Other cause of death | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HR | CI | CI | *P* | SHR | CI | CI | *P* | SHR | CI | CI | *P* |
| **Age (years)** | | | | | | | | | | | | |
| **<65** | Ref | | | <0.001 | | | | <0.001 | | | | <0.001 |
| **≥ 65** | 2.53 | 2.256 | 2.831 | | 1.51 | 1.272 | 1.79 | | 2.35 | 2,032 | 2.729 | |
| **Marital status** | | | | | | | | | | | | |
| **Married** | Ref | | | | | | | 0.093 | Ref | | | |
| **Unmarried** | 1.23 | 1.102 | 1.382 | <0.001 | 1.15 | 0.976 | 1.363 | | 1.15 | 0.989 | 1.34 | 0.069 |
| **Unknown** | | | | | | | | | | | | |
| **Race** | Ref | | | | | | | | | | | |
| **White** | 1.12 | 0.967 | 1.301 | 0.13 | 1 | 0.802 | 1.25 | 0.988 | | | | 0.193 |
| **Black** | 0.93 | 0.804 | 1.078 | 0.338 | 1 | 0.828 | 1.263 | 0.835 | | | | 0.043 |
| **Other** | | | | | | | | | | | | |
| **Sex** | Ref | | | 0.001 | Ref | | | 0.081 | | | | |
| **Female** | 1.2 | 1.079 | 1.341 | | 1.14 | 0.976 | 1.3421 | | | | | |
| **Male** | | | | 0.002 | | | | | | | | |
| **Diagnosis time** | Ref | | | | Ref | | | | Ref | | | |
| **1,975_1,987** | 0.72 | 0.614 | 0.835 | <0.001 | 0.6 | 0.481 | 0.758 | <0.001 | 0.83 | 0.682 | 1.001 | 0.058 |
| **1,988_2,003** | 0.46 | 0.385 | 0.56 | <0.001 | 0.35 | 0.265 | 0.454 | <0.001 | 0.58 | 0.453 | 0.738 | <0.001 |
| **2,004_2,016** | | | | <0.001 | | | | | | | | |
| **Stage** | Ref | | | | Ref | | | | Ref | | | |
| **I-IIa** | 1.49 | 1.278 | 1.742 | <0.001 | 1.66 | 1.261 | 2.174 | <0.001 | 1.29 | 1.081 | 1.542 | 0.005 |
| **IIB-III** | 2.43 | 2.031 | 2.903 | <0.001 | 3.15 | 2.359 | 4.223 | <0.001 | 1.08 | 0.843 | 1.378 | 0.547 |
| **IV** | 1.51 | 1.204 | 1.886 | <0.001 | 2.21 | 1.58 | 3.099 | <0.001 | 0.93 | 0.683 | 1.253 | 0.616 |
| **Unknown** | | | | 0.314 | | | | | | | | |
| **Histology, Thymoma** | Ref | | | | Ref | | | | Ref | | | |
| **A** | 0.72 | 0.519 | 0.985 | 0.04 | 1.25 | 0.682 | 2.296 | 0.468 | 0.55 | 0.,379 | 0.808 | 0.002 |
| **AB** | 0.86 | 0.625 | 1.184 | 0.355 | 1.7 | 0.943 | 3.075 | 0.077 | 0.55 | 0.364 | 0.827 | 0.004 |
| **B1** | 0.83 | 0.591 | 1.17 | 0.29 | 1.63 | 0.89 | 2.98 | 0.114 | 0.52 | 0.33 | 0.813 | 0.004 |
| **B2** | 0.95 | 0.709 | 1.268 | 0.719 | 1.9 | 1.09 | 3.326 | 0.024 | 0.63 | 0.434 | 0.907 | 0.013 |
| **B3** | 0.9 | 0.697 | 1.165 | 0.427 | 1.68 | 0.993 | 2.852 | 0.053 | 0.66 | 0.489 | 0.892 | 0.007 |
| **Unknown** | | | | | | | | | | | | |
| **Surgery** | Ref | | | <0.001 | | | | <0.001 | | | | |
| **Yes** | 0.52 | 0.457 | 0.589 | | 0.42 | 0.352 | 0.497 | | | | | |
| **No** | | | | | | | | | | | | |
| **Radiotherapy** | Ref | | | 0.001 | | | | <0.001 | Ref | | | <0.001 |
| **Yes** | 1.25 | 1.1 | 1.417 | | 1.88 | 1.568 | 2.265 | | 0.67 | 0.489 | 0.892 | |

CI: Confidence Interval; Ref: Reference

cardiopulmonary and other systemic diseases in long-term survivors highlights the need for comprehensive pre-treatment assessment and ongoing clinical surveillance.

We also identified factors that might be associated with cardiovascular-related death in survivors at different time intervals. Age, time of diagnosis, and race were associated with cardiac death in those surviving 0 and 10 years. Long-term survivors who underwent radiotherapy were observed to have a higher incidence of cardiovascular-related death. A large dataset analysis had shown that radiotherapy in patients with breast and lung cancers was associated with increased mortality from heart disease 10 to 20 years after treatment [10]. Another study also showed that a higher heart radiation dose was associated with an increased risk of cardiovascular disease in long-term survivors, with the median time to cardiovascular disease diagnosis being 8.4 years after treatment [22]. Therefore, the role of radiotherapy for thymoma should also focus on cardiac morbidity in long-term survivors.

Due to the lack of information on health function and comorbidities, the cumulative incidence and hazard of death from other causes might be overestimated for some cohorts in the current study. Lung or cardiac function should be assessed during long-term follow-up. The lack of available data on treatment failure events

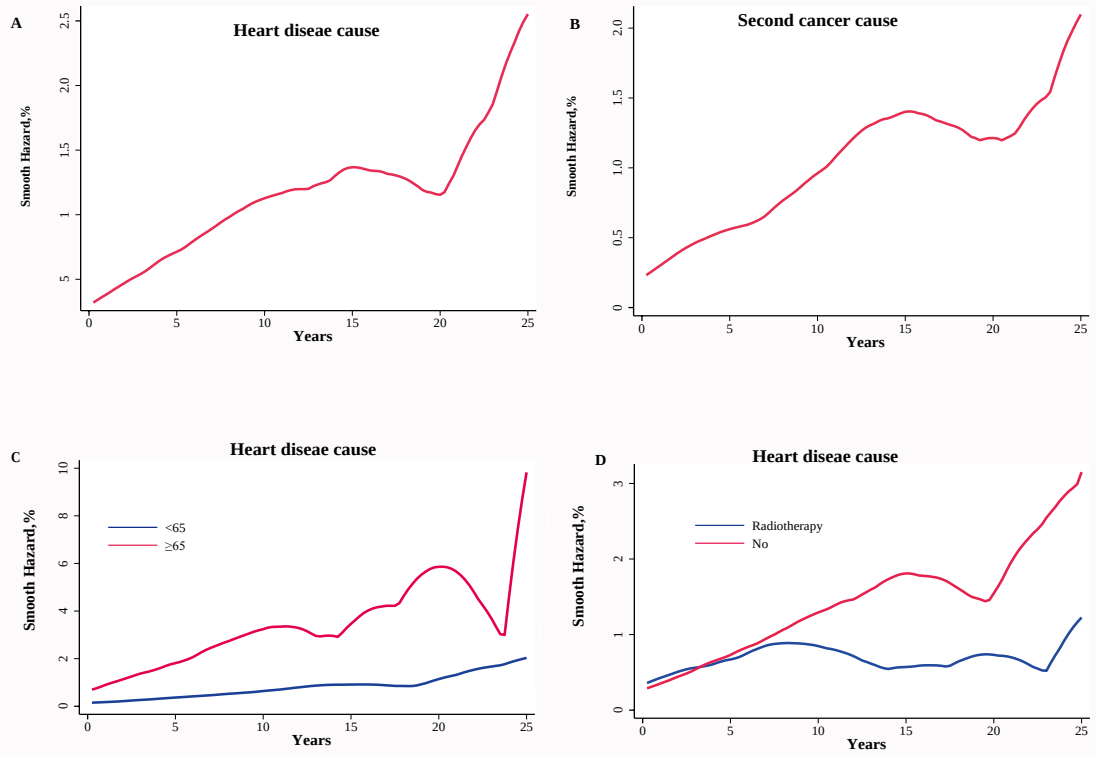


**Figure 3:** The mortality from heart disease (A) and a second cancer (B) against survival time with thymoma. Heart disease as the cause of death for patients of various ages (C) and those who underwent radiotherapy (D).

highlights the urgent need for further surveillance research to address this limitation. Various treatment details should be considered in future analyses. The dynamic changes in survival probabilities and hazards in patients with thymoma need further verification.

In conclusion, our study showed that the risks and causes of cancer-related and non-cancer-related mortality tend to change over time in patients with thymoma. The non-cancer-related causes, especially cardiorespiratory diseases, emerged as major competing causes of mortality with increasing survival time. These findings underscore the importance of surveillance tailored and adapted to the length of follow-up and the individual's pre- and post-treatment status

## Acknowledgement

This trial was supported by Shenzhen Key Medical Discipline Construction Fund (No. SZXK013); Sanming Project of Medicine in Shenzhen (No. SZSM202211030); Shenzhen High-level Hospital Construction Fund; Shenzhen Clinical Research Center for Cancer (No. [2021] 287); Supported by Hospital Research Project (E010322032).

## References

1. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol. 2010;5:S260-65.
2. Kondo K, Monden Y. Lymphogenous and hematogenous metastasis of thymic epithelial tumors. Ann Thorac Surg. 2003;76:1859-64; discussion 1864-5.
3. Falkson CB, Bezjak A, Darling G, Gregg R, Malthaner R, Maziak DE, et al. The management of thymoma: A systematic review and practice guideline. J Thorac Oncol. 2009;4:911-9.
4. Chiappetta M, Lococo F, Zanfrini E, Moroni R, Aprile V, Guerrera F, et al. The International Thymic Malignancy Interest Group classification of thymoma recurrence: Survival analysis and perspectives. J Thorac Oncol. 2021;16:1936-45.
5. Patel S, Macdonald OK, Nagda S, Bittner N, Suntharalingam M. Evaluation of the role of radiation therapy in the management of malignant thymoma. Int J Radiat Oncol Biol Phys. 2012;82:1797-801.
6. Lim YJ, Kim HJ, Wu HG. Role of postoperative radiotherapy in nonlocalized thymoma: Propensity-matched analysis of surveillance, epidemiology, and end results database. J Thorac Oncol. 2015;10:1357-63.
7. Fan C, Ge H, Zhang S, Xing W, Ye K, Zheng Y, et al. Impact of definitive radiotherapy and surgical debulking on treatment outcome and prognosis for locally advanced Masaoka-Koga stage III thymoma. Sci Rep. 2020;10:1735.
8. Safieddine N, Liu G, Cuningham K, Ming T, Hwang D, Brade A, et al. Prognostic factors for cure, recurrence and long-term survival after surgical resection of thymoma. J Thorac Oncol. 2014;9:1018-22.
9. Liu H, Gu Z, Qiu B, Detterbeck FC, Roden AC, Ruffini E, et al. A Recurrence predictive model for thymic tumors and its implication for postoperative management: A Chinese Alliance for research in thymomas database study. J Thorac Oncol. 2020;15:448-56.
10. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol. 2005;6:557-65.
11. Nolan MT, Russell DJ, Marwick TH. Long-term risk of heart failure and myocardial dysfunction after thoracic radiotherapy: A systematic review. Can J Cardiol. 2016;32:908-20.
12. Stewart FA. Mechanisms and dose-response relationships for radiation-induced cardiovascular disease. Ann ICRP. 2012;41:72-9.

13. Maraldo MV, Giusti F, Vogelius IR, Lundemann M, van der Kaaij MAE, Ramadan S, et al. Cardiovascular disease after treatment for Hodgkin's lymphoma: An analysis of nine collaborative EORTC-LYSA trials. Lancet Haematol. 2015;2:e492-502.

14. Xavier AC, Epperla N, Taub JW, Costa LJ. Excess mortality among 10-year survivors of classical Hodgkin lymphoma in adolescents and young adults. Am J Hematol. 2018;93:238-45.

15. Kim E, Thomas CR, Jr. Conditional survival of malignant thymoma using national population-based Surveillance, Epidemiology, and End Results (SEER) registry (1973-2011). J Thorac Oncol. 2015;10:701-7.

16. Jung S-H, Lee HY, Chow S-C. Statistical methods for conditional survival analysis. J Biopharm Stat. 2018;28:927-38.

17. Susarla VJM. Kernel estimation of a smooth distribution function based on censored data. Springer Nature. 1990;37:71-86.

18. Tu D. Under-smoothed kernel confidence intervals for the hazard ratio based on censored data. Biom J. 2007;49:474-83.

19. Ruffini E, Huang J, Cilento V, Goren E, Detterbeck F, Ahmad U, et al. The International Association for the Study of Lung Cancer Thymic Epithelial Tumors Staging Project: Proposal for a Stage Classification for the Forthcoming (Ninth) Edition of the TNM Classification of Malignant Tumors. J Thorac Oncol. 2013;18:1655-71.

20. Skuladottir H, Olsen JH. Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. J Clin Oncol. 2003;21:3035-40.

21. Wong KF, Lambert PC, Mozumder SI, Broggio J, Rutherford MJ. Conditional crude probabilities of death for English cancer patients. Br J Cancer. 2019;121:883-9.

22. Liao J, Liu T, Zhang H, Cai F, Chen J, Dang J. The role of postoperative radiation therapy for completely resected stage III thymoma and effect of higher heart radiation dose on risk of cardiovascular disease: A retrospective cohort study. Int J Surg. 2018;53:345-9.