Impact of Prior Cancer History on Outcomes in Thymoma

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Research article

Keywords: Prior cancer history, Thymoma, Survival, SEER database, Clinical trial

Posted Date: July 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-41041/v1

Abstract

Background: Thymoma is an uncommon intrathoracic malignant tumor and has a long natural history. It is uncertain whether the survival of thymoma patient is affected by prior cancer history. Finding out the impact of a prior cancer history on thymoma survival has important implications for both decision making and research.

Method: The Surveillance, Epidemiology, and End Results (SEER) database was queried for thymoma patients diagnosed between 1975 and 2015. Kaplan-Meier methods and Cox proportional hazards model were used to analyze overall survival across a variety of stages, age, and treatment methods with a prior cancer history or not.

Results: A total of 3604 patients with thymoma were identified including 507 (14.1%) with a prior cancer history. The 10-year survival rate of patients with a prior cancer history (53.8%) was worse than those without a prior cancer history (40.32%, 95%CI 35.24-45.33, P < 0.0001). However,

adjusted analyses showed that the impact of a prior cancer history was heterogenous across age and treatment methods. In subset analyses, prior cancer history was associated with worse survival among patients who were treated with chemoradiotherapy (HR: 2.80, 95% CI: 1.51-5.20, P = 0.001) and age ≤ 65 years (HR: 1.33, 95%CI: 1.02-1.73, P = 0.036).

Conclusions: Prior cancer history provides an inferior overall survival for patients with thymoma. But it does not worsen the survival in some subgroups and these thymoma patients should not be excluded from clinical trials.

Background

Thymoma is a rare tumor deriving from the epithelial cells of the thymus, but the most common primary tumor in the anterior mediastinum. According to a nation-wide report, the prevalence of thymoma is 0.13 per 100000 person-years in the United States[1]. Unlike most other cancers, thymoma has a long natural history and the overall survival of thymoma patients can regularly be measured in decades[2]. The thymoma patients with multiple primary cancers are still worth studying in oncology. Some studies found that patients with thymoma had a broadly increased risk for cancer, some even lead to worse survival[3–5]. But the impact of prior malignancy on thymoma outcomes is still unknown.

Clinical trials play a pivotal role in improving the survival of patients with cancer. However, cancer history is commonly used exclusion criteria in oncology clinical trials due to concerns that previous treatment and survival impact could interfere with clinical results. Whereas the exclusion of cancer history population may also be problematic. It is common for clinical trials to struggle to recruit enough patients with thymoma, especially for the restrictive criterion[6]. What's more, there have been no data clearly support that prior cancer history can impact the survival of patients with thymoma. And it is uncertain whether the results of clinical trials that exclude the patients with prior cancer history apply equally to

patients who have prior cancer. Therefore, illustrating the impact of prior cancer history on thymoma survival is important for both patients and the oncology community.

Until recently, no study has particularly evaluated the impact of prior cancer on thymoma outcomes, and we know little about the features of thymoma patients with prior cancer. In this study, we aimed to identify the relationship between thymoma patients with cancer history and its prognosis, the mortality risk related to a prior cancer history was evaluated in a cohort of thymoma patients in the Surveillance, Epidemiology, and End Results (SEER) database.

Method

Data source and study population

All the data were extracted from the SEER database through the SEER*Stat software version 8.3.6 (accession number: 15356-Nov2018). We searched all records of patients diagnosed with thymoma between 1975 and 2015. A diagnosis of thymoma excluding thymic carcinoma were identified by histology and primary site (tumor site code). The SEER sequence number variable represented the order of reportable tumors diagnosed in a lifetime and was used to determine the prevalence of prior cancer.

The thymoma patients were divided into two cohorts based on whether they had a prior history of cancer. The “prior cancer history” cohort – included patients that had a cancer diagnosis before the thymoma diagnosis. The “first primary” cohort – included patients who were diagnosed thymoma represented their only and first malignancy. All patients must be diagnosed with microscopic confirmation by cytology or histology. Exclusion criteria were listed as follows: (1) patients with only death certificates or autopsy records; (2) age at diagnosis younger than 18 years old; (3) patients with incomplete follow-up information or survival data.

Data elements

Demographic and clinicopathological characteristics were extracted from the SEER database, including age, sex, race, marital status, year of diagnosis, histological subtype, stage, surgery records, chemotherapy, and radiotherapy records. The survival data were calculated in months. The survival time of 0 months was recorded as 0.5 months. Masaoka–Koga staging was estimated using an approach modeled which was proposed by Fernandes et al.[6] Briefly, patients were categorized into four groups: I/IIA (“invasive tumor confined to gland of origin” or “localized, not otherwise specified”), IIB (“adjacent connective tissue”), III/IV (“adjacent organs/structures” or “further contiguous extension” or “any positive lymph nodes”), and unknown (unknown extent of disease).

Statistical analysis

Data were presented as mean value with standard deviation for continuous variables, and percentages for categorical variables. Continuous variables were compared using t-test. Categorical variables were analyzed using the Pearson’s χ 2 test. Survival curves were plotted by using the Kaplan-Meier method and

compared by using the log-rank test. Cox proportional hazards regression models were adjusted for demographic and clinicopathological characteristics. The survival time was calculated as months from diagnosis to death or end of follow-up. The primary endpoint of this study was overall survival and the end of the follow-up cutoff date was December 31, 2016. All P values were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Stata 16.0 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

A total of 3604 thymoma patients who met the inclusion criteria were collected from the SEER database, including 507 (14.1%) in the prior cancer history. The baseline patient characteristics were shown in Table 1. The median age was 58 years (SD, 15), and 1739 (48.3%) patients were female. A total of 1239 patients (34.4%) with thymoma were more than 65 years. The prevalence of patients with prior cancer history was concentrated between 2003 and 2015 (72%). None of the patients died of cancer in the “prior cancer history” cohort. In general, the “prior cancer history” cohort had more elderly patients, more deaths, and smaller tumors compared to the “first primary” cohort. Treatment was further divided into six subgroups: surgery only, surgery and adjuvant therapy, radiation only, chemotherapy only, radiation and chemotherapy, and no treatment.

Table 1
Baseline characteristics of patients with thymoma in each cohort

Characteristics	Full cohort N = 3604 (%)	First primary cohort N = 3097 (%)	Prior Cancer History N = 507 (%)	P-value
Age (years), mean (SD)	58.12 (15.05)	56.72 (14.97)	66.63 (12.55)	< 0.01
Gender				
Female	1739 (48.3%)	1478 (47.7%)	261 (51.5%)	0.12
Race				< 0.01
White	2455 (68.1%)	2062 (66.6%)	393 (77.5%)	
Black	531 (14.7%)	468 (15.1%)	63 (12.4%)	
Other/unknow	618 (17.1%)	567 (18.3%)	51 (10.1%)	
Marital status				< 0.01
Married	2178 (60.4%)	1857 (60.0%)	321 (63.3%)	
Single	585 (16.2%)	529 (17.1%)	56 (11.0%)	
Seprated/divorced/widowed	684 (19.0%)	576 (18.6%)	108 (21.3%)	
Unknow	157 (4.4%)	135 (4.4%)	22 (4.3%)	
Year of diagnosis				< 0.01
1975–1988	370 (10.3%)	343 (11.1%)	27 (5.3%)	
1989–2002	1005 (27.9%)	890 (28.7%)	115 (22.7%)	
2003–2015	2229 (61.8%)	1864 (60.2%)	365 (72.0%)	

SD, standard deviation; WHO, World Health Organization; NOS, not otherwise specified.

Characteristics	Full cohort N = 3604 (%)	First primary cohort N = 3097 (%)	Prior Cancer History N = 507 (%)	P-value
Masaoka-koga stage				< 0.01
I/IIA	298 (8.3%)	257 (8.3%)	41 (8.1%)	
IIB	749 (20.8%)	680 (22.0%)	69 (13.6%)	
III/IV	308 (8.5%)	278 (9.0%)	30 (5.9%)	
Unknow	2249 (62.4%)	1882 (60.8%)	367 (72.4%)	
WHO type				0.03
A	232 (6.4%)	195 (6.3%)	37 (7.3%)	
AB	433 (12.0%)	362 (11.7%)	71 (14.0%)	
B1	345 (9.6%)	290 (9.4%)	55 (10.8%)	
B2	350 (9.7%)	298 (9.6%)	52 (10.3%)	
B3	476 (13.2%)	397 (12.8%)	79 (15.6%)	
NOS	1768 (49.1%)	1555 (50.2%)	213 (42.0%)	
Size (mm), mean (SD)	75.50 (60.75)	76.49 (60.44)	69.61 (62.30)	0.04
Surgery	2782 (77.2%)	2399 (77.5%)	383 (75.5%)	0.34
Treatment				< 0.01
Surgery	1046 (29.0%)	856 (27.6%)	190 (37.5%)	
Surgery plus adjuvant therapy	1736 (48.2%)	1543 (49.8%)	193 (38.1%)	

SD, standard deviation; WHO, World Health Organization; NOS, not otherwise specified.

Characteristics	Full cohort N = 3604 (%)	First primary cohort N = 3097 (%)	Prior Cancer History N = 507 (%)	P-value
Radiation	177 (4.9%)	154 (5.0%)	23 (4.5%)	
Chemotherapy	196 (5.4%)	174 (5.6%)	22 (4.3%)	
Radiation plus chemotherapy	195 (5.4%)	166 (5.4%)	29 (5.7%)	
No treatment	254 (7.0%)	204 (6.6%)	50 (9.9%)	
Cause of death				< 0.01
Alive	1823 (50.6%)	1600 (51.7%)	223 (44.0%)	
Cancer death	730 (20.3%)	730 (23.6%)	0 (0.0%)	
Non-cancer death	1051 (29.2%)	767 (24.8%)	284 (56.0%)	

SD, standard deviation; WHO, World Health Organization; NOS, not otherwise specified.

Unadjusted survival comparisons

Kaplan-Meier survival analysis for surviving patients was analyzed with a median follow up of 68 months (range, 0-468 months). As shown in Fig. 1A, the 10-year overall survival rates of the “first primary” cohort (53.8%, 95% CI 51.76–55.86, P < 0.0001) was better than the “prior cancer history” cohort (40.32%, 95%CI 35.24–45.33, P < 0.0001). Figure 1B-D depicted stratified Kaplan-Meier survival curves by stage. Thymoma patients with prior cancer exhibited worse survival for stage I-IV and only stage II appeared to have a statistical difference (P = 0.005). Among patients with stage II thymoma, the 10-year overall survival rate for the “first primary” cohort and “prior cancer history” cohort were 48.24% (95%CI 44.42–51.95) and 37.68% (95%CI 26.4-48.91). Figure 2A-B presented stratified Kaplan-Meier curves by age. Patients with prior cancer displayed worse survival for age ≤ 65 years (P = 0.004). And patients with prior cancer showed similar survival for age > 65 years.

Adjusted survival comparisons

Cox proportional hazard models were adjusted for patient demographic and stratified by treatment. As shown in Fig. 3, prior cancer was associated with worse survival for 5.4% of thymoma patients, and the impact of prior cancer was no statistical difference for a total of 94.6% of thymoma patients. For the

patients who were treated with radiation and chemotherapy, the “prior cancer history” cohort was associated with worse survival compared to the “first primary” cohort (HR: 2.80, 95% CI: 1.51–5.20, P = 0.001). For the patients who were treated with other treatments, the impact of a prior cancer history was no statistical difference. Multivariate Cox proportional hazard model analysis showed that prior cancer history didn’t exhibit significantly worse survival for stages II thymoma (HR: 1.03, 95%CI: 0.72–1.46, P = 0.889) but displayed worse survival for age ≤ 65 years (HR: 1.33, 95%CI: 1.02–1.73, P = 0.036).

Discussion

As far as we know, this is the first study to analyze the impact of prior cancer history on outcomes in thymoma. Our study indicated that a prior cancer history had a significant but heterogenous effect on the survival of thymoma patients. To some degree, the unadjusted survival analyses show the prior cancer was associated with worse survival compared to the first primary cancer (Fig. 1A). Prior cancer had an adverse effect on overall survival in patients younger than 65 years. Patients with a prior cancer history shown worse survival for stages II (Fig. 1C) but had no statistic difference survival in multivariate Cox proportional hazard model analysis. Patients may have competing priorities to make treatment decisions and treatment modalities may have implications for survival[7, 8]. The adjusted survival analyses were stratified by treatment modalities for further analysis. It revealed that the prior cancer cohort had significantly worse survival in the chemoradiotherapy subgroup.

The cancer survivor population is rapidly growing in the USA over the past 30 years, largely driven by the aging population, the improvement of treatment, and expanding cancer screening efforts[9]. These factors have led to an increased prevalence of multiple primary cancer[10]. In our study, 20% of older (age > 65 years) and more than 10% of younger adult (age ≤ 65 years) diagnosed with thymoma had prior cancer history. As shown in Fig. 2A, the patients with a history of prior cancer had significantly worse prognosis among younger adult subgroup. The study led by Andrew et al found that prior cancer did not adversely affect on clinical outcomes and suggested the prior cancer history subset should not be excluded from clinical trials among advanced lung cancer patients[11, 12]. Older patients were more likely to die of the progression of cancer and comorbidities, thus prior cancer had less impact relatively. Younger patients with thymoma tended to have a better prognosis and were more likely to be cured than older patients[13]. Prior cancer treatment could increase the risks of treatment intolerance thus worsen the survival of younger patients[14].

Although several staging systems exist, the Masaoka staging classification is the most extensive used and is a wonderful predictor for the prognosis of thymoma[15, 16]. The 5-year overall survival rate were approximately 85% in the stage I to III thymoma patients and 65% in the stage IV thymoma patients [15, 17, 18]. For stage I and stage II thymoma, complete surgical resection is the recommended standard treatment. What’s more, postoperative radiotherapy is suggested in incompletely resected or high-risk stage II thymomas[19]. Adjuvant radiotherapy can reduce local recurrence rates and completely resected stage II tumors may benefit from adjuvant radiotherapy but without impact on overall survival[20, 21]. It is not yet clear whether stage II thymoma patients with a prior cancer history could benefit from

postoperative radiotherapy. We found that prior cancer didn't display significantly worse survival to those without prior cancer in patients with stage II thymoma.

Thymomas are representative slow-growing tumors that can spread locally. Metastases are usually restricted to the pericardium, diaphragm, or pleura, whereas extrathoracic region metastases are uncommon[20]. Because of their rarity, various studies are necessary to expore and improve current therapeutic standards. Surgery is the cornerstone of the treatment of thymomas and primary treatment in multimodality strategies. Complete removal of the tumor and total thymectomy are recommended for most resectable tumors[6, 20–22]. Incompletely resected tumors or tumors with a positive resection margin are generally treated with radiotherapy. Chemotherapy combined with radiotherapy is recommended in unresectable thymomas or advanced thymomas[20, 21]. It can be seen from Fig. 3 that the "prior cancer history" cohort was associated with worse survival compared to the "first primary" cohort among patients received radiation and chemotherapy. Intriguingly, our results showed that the impact of a prior cancer history was not statistically significant for advanced thymomas. On one hand, the prior cancer treatment increased the toxicity and intolerance of chemoradiotherapy, and on the other hand unresectable thymoma patients with a prior cancer history had a more complex condition.

The current study suggested that prior cancer history may have a significant impact on the selection of retrospective study and clinical trial. We suggested that including prior cancer history as a stratification or covariate variable when prior cancer history was known to modify the effect of one or more independent variables. The relation between survival and prior cancer history most probably reflected an interaction between: (1) the recurrence or lethality of prior cancer, (2) the recurrence or lethality of the newly diagnosed thymoma, and (3) the personal circumstances of patients.

Undeniably, the present study has several limitations. Firstly, we confirmed a prior cancer history according to the sequence number only, without detailed prior cancer characteristics. Hence we could not distinguish whether the index thymoma was from local recurrence. Secondly, the current study focused on prior cancer history, without description of the specific prior cancer type. Prior cancer type could affect results, as the previously diagnosed cancer could be "likely lethal" or "likely irrelevant" to prognosis. Thirdly, the SEER database lacked detailed information on therapeutic regimens for chemotherapy and radiotherapy or toxicity. Comorbidities and adverse events were not captured in the database, either. In addition, the data which acquired from the SEER database cover approximately 34.6% of the population in the United States. Further studies are required to confirm the generality of our findings.

Conclusions

In conclusion, a prior cancer history has variable impact on the survival of patients with thymoma according to age and treatment method. A prior cancer history is associated with worse survival for patients who were younger and treated with chemoradiotherapy. Older patients with a prior cancer history could adopt in broader inclusion trial criteria. However, further studies are required for confirmation.

Abbreviations

SEER: Surveillance, Epidemiology, and End Results.

Declarations

Ethics approval and consent to participate:

All the data were extracted from the SEER database. Institutional review board approval was waived for this study because the SEER database is a public anonymized database.

Consent for Publication:

Not applicable.

Competing interests:

The authors have no conflicts of interest to declare.

Funding:

None.

Authors' contributions:

(I) Conception and design: SL Wu, GL Peng; (II) Administrative support: GL Peng, JX He; (III) Provision of study materials or patients: SL Wu, GL Peng; (IV) Collection and assembly of data: SL Wu; (V) Data analysis and interpretation: SL Wu, MY Liu, WX Cui; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Acknowledgments:

None.

References

1. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol. 2010;5(10 Suppl 4):260–5.
2. Kim E, Thomas CR. Conditional survival of malignant thymoma using national population-based surveillance, epidemiology, and end results (SEER) registry (1973–2011). J Thorac Oncol. 2015;10(4):701–7.
3. Welsh JS, Wilkins KB, Green R, Bulkley G, Askin F, Diener-West M, Howard SP. Association between thymoma and second neoplasms. JAMA. 2000;283(9):1142–3.
4. Souadjian JV, Silverstein MN, Titus JL. Thymoma and cancer. Cancer. 1968;22(6):1221–5.

5. Pan CC, Chen PC, Wang LS, Chi KH, Chiang H. Thymoma is associated with an increased risk of second malignancy. Cancer. 2001;92(9):2406–11.
6. Berghmans T, Durieux V, Holbrechts S, Jungels C, Lafitte J-J, Meert A-P, Moretti L, Ocak S, Roelandts M, Girard N. Systemic treatments for thymoma and thymic carcinoma: A systematic review. Lung Cancer. 2018;126:25–31.
7. Murphy CC, Gerber DE, Pruitt SL. Prevalence of Prior Cancer Among Persons Newly Diagnosed With Cancer: An Initial Report From the Surveillance, Epidemiology, and End Results Program. JAMA Oncol. 2018;4(6):832–6.
8. Monsalve AF, Hoag JR, Resio BJ, Chiu AS, Brown LB, Detterbeck FC, Blasberg JD, Boffa DJ. Variable impact of prior cancer history on the survival of lung cancer patients. Lung Cancer. 2019;127:130–7.
9. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016;25(7):1029–36.
10. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist. 2007;12(1):20–37.
11. Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. Prior cancer does not adversely affect survival in locally advanced lung cancer: A national SEER-medicare analysis. Lung Cancer. 2016;98:106–13.
12. Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. **Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual**. *J Natl Cancer Inst* 2015, 107(4).
13. Zhao M, Yin J, Yang X, Jiang T, Lu T, Huang Y, Li M, Yang X, Lin M, Niu H, et al. Nomogram to predict thymoma prognosis: A population-based study of 1312 cases. Thorac Cancer. 2019;10(5):1167–75.
14. Liu J, Zhou H, Zhang Y, Fang W, Yang Y, Hong S, Chen G, Zhao S, Chen X, Zhang Z, et al: **Impact of prior cancer history on the overall survival of younger patients with lung cancer**. *ESMO Open* 2020, 5(1).
15. Masaoka A. Staging system of thymoma. J Thorac Oncol. 2010;5(10 Suppl 4):304–12.
16. Kondo K. Tumor-node metastasis staging system for thymic epithelial tumors. J Thorac Oncol. 2010;5(10 Suppl 4):352–6.
17. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma. A clinicopathologic review. Cancer. 1987;60(11):2727–43.
18. Park HS, Shin DM, Lee JS, Komaki R, Pollack A, Putnam JB, Cox JD, Hong WK. Thymoma. A retrospective study of 87 cases. Cancer. 1994;73(10):2491–8.
19. Hamaji M, Shah RM, Ali SO, Bettenhausen A, Lee H-S, Burt BM. A Meta-Analysis of Postoperative Radiotherapy for Thymic Carcinoma. Ann Thorac Surg. 2017;103(5):1668–75.
20. Falkson CB, Bezjak A, Darling G, Gregg R, Malthaner R, Maziak DE, Yu E, Smith CA, McNair S, Ung YC, et al. The management of thymoma: a systematic review and practice guideline. J Thorac Oncol. 2009;4(7):911–9.

21. Girard N, Mornex F, Van Houtte P, Cordier J-F, van Schil P. Thymoma: a focus on current therapeutic management. J Thorac Oncol. 2009;4(1):119–26.
22. Kondo K. Optimal therapy for thymoma. J Med Invest. 2008;55(1–2):17–28.

Figures

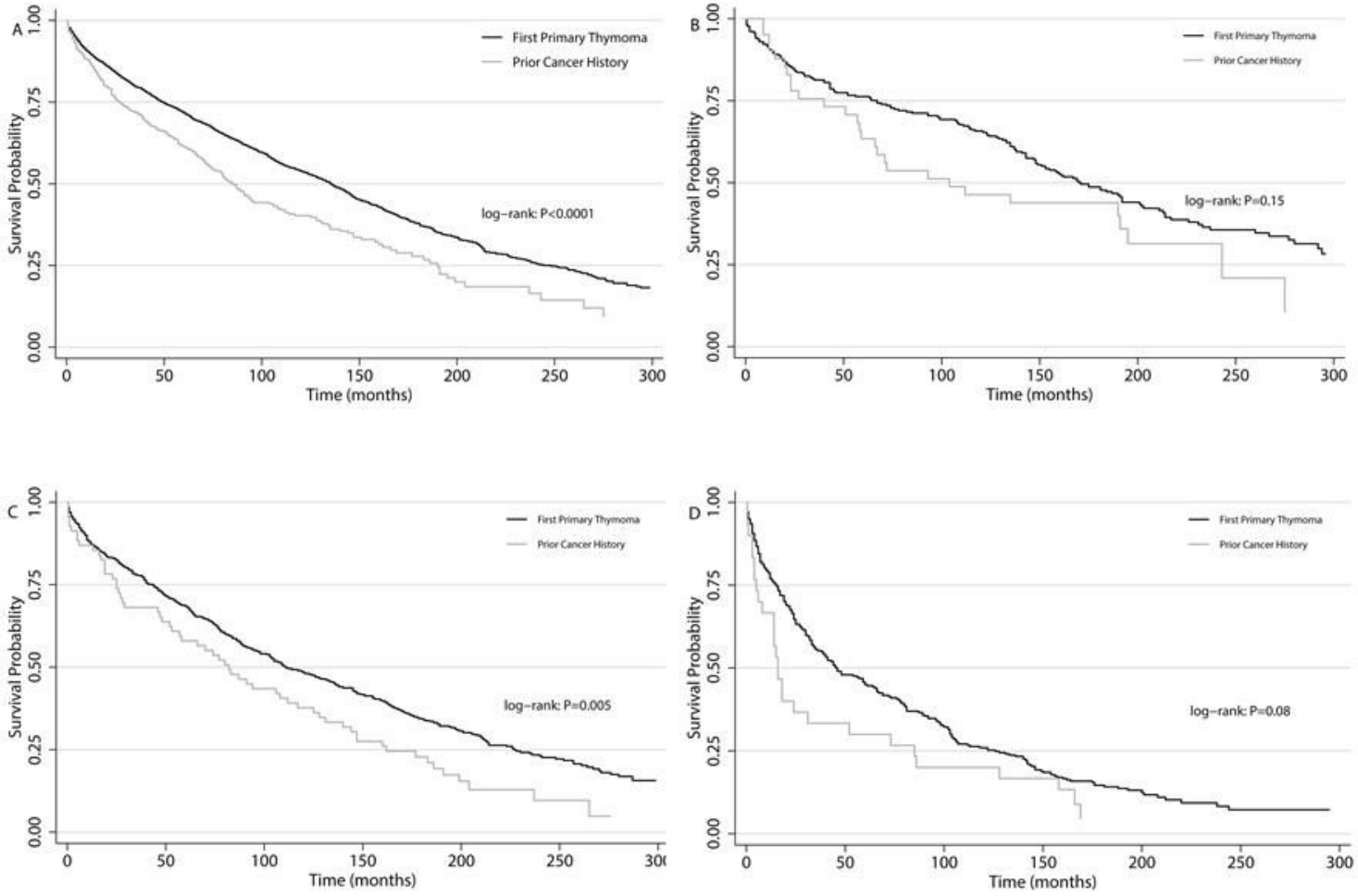

Figure 1

Kaplan-Meier survival plots for different stage. The survival curve of patients with prior cancer history compared with those in whom the thymoma represented their only and first malignancy (A) as well stratified by Masaoka-koga stage (B, Stage I/IIA; C, stage IIB; D, stage III/IV).

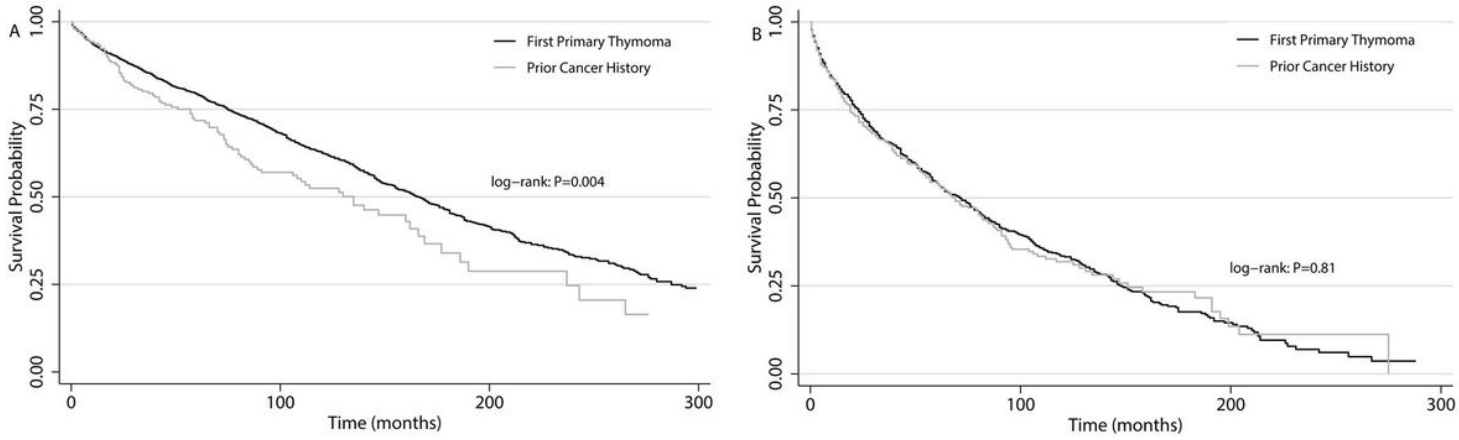

Figure 2

Subgroup analysis the impact of prior cancer history on the overall survival stratified by age. The survival curve of patients with prior cancer history compared with those in whom the thymoma represented their only and first malignancy stratified by age (A, age ≤ 65 years; B, age > 65 years).

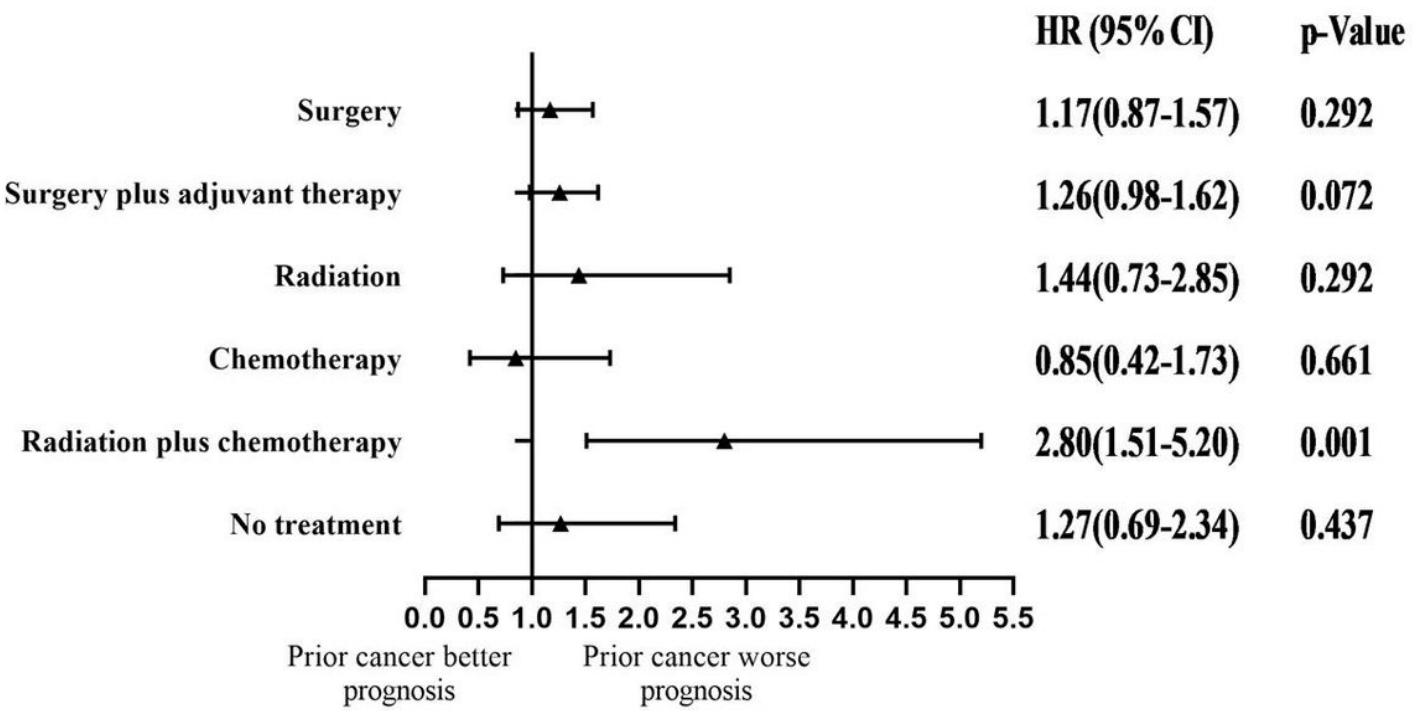

Figure 3

Multivariate Cox proportional Hazards of patients stratified by treatment. Analysis the impact of prior cancer history on overall survival by treatment. The model adjusted for Masaoka-koga stage, race, WHO type, size, marital status, age, and year of diagnosis.