



Impact of prior cancer history on outcomes in thymoma: a propensity score, population-based study

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Background: Prior cancer history is a common exclusion in thymoma trials. However, whether prior cancer impacts the survival of thymoma patients and the outcomes of clinical trials remains uncertain. The aim of this study is to identify the impact of prior cancer on outcomes in thymoma.

Methods: Patients with thymoma diagnosed between 1975 to 2017 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Age, histologic types, and thymoma size were stratified to analyze. Propensity score matching (PSM), Kaplan-Meier methods and Cox proportional hazard models were used to analyze the prognostic effect of prior cancer on overall survival (OS).

Results: A total of 3,827 thymoma patients were enrolled, of whom 13.22% had a prior cancer history. The Kaplan-Meier curves showed statistically significantly different survival before ($P < 0.001$) and after PSM ($P = 0.0003$). Subgroup analyses stratified by histologic types and thymoma size showed that thymoma patients with prior cancer had inferior survival. But thymoma patients with prior cancer displayed similar OS among patients older than 65 years ($P = 0.693$). In multivariate analyses, patients with prior cancer displayed inferior OS [hazard ratio (HR) = 1.39, 95% confidence interval (CI), 1.18 to 1.63].

Conclusions: Prior cancer conveys an inferior OS among patients with thymoma. But it does not affect the survival adversely in older patients thus broader inclusion trial criteria may be adopted in thymoma patients with a prior cancer history.

Keywords: Thymoma; prior cancer; prognosis; clinical trial; Surveillance, Epidemiology, and End Results database (SEER database)

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Introduction

Thymomas are rare neoplasms driving from the epithelial component of the thymus and usually located in the anterior mediastinum. Many thymomas manifest an indolent clinical course and are usually incidentally discovered by computed tomography scan (1). Based on the Surveillance, Epidemiology, and End Results (SEER) database, the

overall incidence of thymoma is 0.13 to 0.15 per 100,000 person-years in America (2,3). With the primary treatment of complete resection, the 10-year overall survival (OS) of different stages thymoma ranges from 50% to 80% (4). Thymomas have a long natural history and peak in the seventh decade of life, thus increasing the prevalence of multiple primary cancers (2,5).

Numerous clinical trials are necessary to improve the

treatment of thymoma. But randomized trials are lacking, most published researches come from retrospective studies. Fewer than 5% of cancer patients are enrolled into clinical trials because of extreme restrictive exclusion criteria, one of which is cancer history (6,7). This is mainly attributed to the long-held assumption that cancer history could adversely affect clinical trials conduct and outcomes. It remains unclear whether cancer history impacts the survival of thymoma patients and the outcomes of clinical trials that exclude thymoma patients with cancer history apply equally to first primary thymoma patients.

Up to now, no research has specially reported the impact of cancer history on thymoma outcomes and the characteristics of thymoma patients with cancer history. With this in mind, we conducted this study to determine the characteristics and impact of cancer history on patients with thymoma using the SEER database.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/gs-20-880>).

Methods

Data source and study population

The population-based data were extracted from the SEER 18 Regs research data through SEER*Stat software version 8.3.8, broadly representing approximately 27.8% of the U.S. population (<https://seer.cancer.gov/data-software/documentation/seerstat/nov2018/>). Patients with thymoma diagnosed between 1975 to 2017 were included in this study. Thymoma was identified by histology of the International Classification of Diseases for Oncology, 3rd edition. Cancer history was derived from the SEER first malignant primary indicator. Exclusion criteria were as follows: (I) patients younger than 18 years at diagnosis; (II) patients with incomplete follow-up information or survival data; (III) patients diagnosed at autopsy or death certificates. All the data were extracted from the SEER database. Institutional review board approval was waived for this study because this is a public anonymized database.

Variables

Demographic data were extracted, including age, sex, year of diagnosis, marital status, race, Masaoka-Koga stage, WHO

histological subtype, size, treatment method, and cause of death. Stage was based on Masaoka-Koga staging system which was proposed by Fernandes *et al.* (8). Patients were classified into three groups: I/IIA (“an invasive neoplasm confined entirely to the organ of origin” or “localized, not otherwise specified”), IIB (“adjacent connective tissue”), and III/IV (“adjacent organs/structures” or “further contiguous extension”, or “metastasis”). I/IIA and III/IV were unable to be distinguished because of insufficient clinicopathological data. Treatment methods were divided into four groups: (I) surgery alone; (II) surgery plus chemotherapy or surgery plus radiation; (III) chemotherapy or radiation; (IV) no treatment. The survival time was recorded in months, and the survival time of 0-month was transformed into 0.5-month to include those who died within 1 month after thymoma diagnosis.

Statistical analysis

Patients included in this study were divided into two groups based on prior cancer history. Data were presented as median with standard deviation for continuous variables and as frequencies with proportions for categorical variables. Categorical variables were assessed by Pearson chi-squared and continuous variables were assessed by *t*-test as appropriate. Propensity score matching (PSM) method was employed to balance baseline characteristics. Propensity scores were calculated based on age, sex, marital status, year of diagnosis, Masaoka-Koga stage, WHO histological subtype, size, treatment method. A one-to-two PSM with a caliper of 0.05 was performed.

The primary endpoint of the study was OS. Survival time was calculated as the time from thymoma diagnosis date until the SEER date of death. Survival analysis was performed using the Kaplan-Meier method and the differences between subgroups were compared using log-rank tests. Propensity score-adjusted multivariate Cox proportional hazards model was built to identify whether prior cancer history impact prognosis independently. Hazard ratios (HRs) and their 95% confidence intervals (CI) were calculated. A two-tailed *P* value less than 0.05 was considered statistical significance. All analyses were performed using Stata 16.0 (StataCorp, College Station, TX, USA).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Baseline patient characteristics

From 1975 to 2017, a total of 3,827 patients with thymoma were identified. The median age of the patient population was 59 years old (range, 18–95 years), 48.5% were female, 68.1% were Caucasian, 64% were diagnosed with thymoma between 2003 and 2017. Among these patients, 506 (13.22%) had prior cancer history. Compared with first primary thymoma patients, patients with prior cancer history were more common among the elderly (89.1% vs. 66.7%, $P < 0.01$), Caucasians (77.7% vs. 66.6%, $P < 0.01$), and married individuals (63.4% vs. 59.8%, $P < 0.01$). Detailed baseline demographic and clinical characteristics before PSM were shown in *Table 1*. After 1:2 PSM, baseline characteristics were well balanced between the two cohorts (*Table 2*).

Survival

The median follow-up time was 54 months (range, 0.5–394 months) after PSM. The Kaplan-Meier curves showed statistically significantly different survival between patients with and without a prior cancer before ($P < 0.001$) and after PSM ($P = 0.0003$), demonstrating an adverse effect of prior cancer on OS (*Figure 1*). Kaplan-Meier survival curves stratified by age (cut-off value of 65 years), tumor size (cut-off value of 73 mm), and histologic types were shown in *Figures 2–4*, respectively. Histologic types were divided into two subgroups according to prognosis. *Figure 2* depicted that younger patients with a prior cancer had inferior survival than those without a prior cancer history ($P = 0.005$) and older patients had similar survival ($P = 0.693$). Subgroup analysis stratified by tumor size and histologic types displayed that prior cancer had worse survival compared with patients with no prior cancer (*Figures 3,4*). In multivariate Cox proportional hazards models, patients with prior cancer had worse OS [HR = 1.39, 95% CI, 1.18 to 1.63] compared to patients without a prior cancer (*Table 3*).

Discussion

The assumption that prior cancer history may impact the research outcomes has led to the practice of excluding patients with a prior cancer history (9). In the present study of more than 3,800 thymoma patients from the SEER database, we found that 13.22% thymoma patients with a

history of prior cancer. On the whole, univariate analysis, multivariate analysis, and subgroup analysis stratified by tumor size all revealed that prior cancer history conveyed an adverse impact on the survival of thymoma patients. However, in patients aged ≥ 65 years, prior cancer did not adversely impact OS. Thus, the long-held assumption which excluded patients with prior cancer history from study need to be rethought.

Unlike most other cancers, survival of thymoma patients can periodically be measured in decades (3,4). They can be cured, be undergoing treatment or follow-up in clinical (10). Long-term survival means a higher risk of cancer diagnosis (11). It was reported that approximately 15% of patients with thymoma had a prior cancer history and about 4% to 8% of patients had a cancer history on different sites (12,13). Zhou *et al.* (14) conducted a pan-cancer analysis to research the impact of prior cancer history on patients. Specific cancer types were classified into two groups according to different effects of prior cancer on OS: (I) “prior cancer inferior (PCI)” group, in which patients with prior cancer history had inferior OS than those without prior cancer; (II) “prior cancer similar (PCS)” group, which patients with prior cancer history had similar OS compared to patients without prior cancer. They found that cancers with relatively favorable outcomes are more likely to be impacted by prior cancer, whereas relatively aggressive cancers are more likely to be unrelated to prior cancer. From this point of view, thymoma is indolent cancer and a sort of PCI. As is reported by Lin *et al.* (15), the OS of patients with prior cancer history depend on the malignancy of cancer biology between index cancer and prior cancer. Our research shows that setting exclusion criteria rationally according to subgroups.

Thymomas are exceedingly uncommon in children and adolescents, and rise in incidence in middle age (2). The age distribution of thymoma patients is broad, with a peak around 30 to 40 years in patients with myasthenia gravis, and 60 to 70 years in those without myasthenia gravis. The 5-year survival among patients with thymoma was 60%, 72%, and 78% for older than 65 years, 25 to 64 years, and less than 25 years, respectively (4). The age-related rise in incidence reflects the accumulation of gene damage with age and applies to many other cancers (16). It is interesting that the incidence of thymoma increases with age, whereas involution of the thymus progresses with age (17). In this study, older patients with thymoma have a worse prognosis than younger patients. Patients with prior cancer had worse OS among the younger patients but had similar OS among

Table 1 Baseline characteristics of patients with thymoma before propensity score matching

Characteristics	Total, N=3,827 (%)	First primary cancer, N=3,321 (%)	Prior cancer history, N=506 (%)	P value
Age (years), mean \pm SD	58.26 \pm 15.04	56.96 \pm 14.96	66.82 \pm 12.57	<0.01
Gender				
Female	1,855 (48.5)	1,606 (48.4)	249 (49.2)	0.72
Race				<0.01
White	2,605 (68.1)	2,212 (66.6)	393 (77.7)	
Black	565 (14.8)	503 (15.1)	62 (12.3)	
Other/unknown	657 (17.2)	606 (18.2)	51 (10.1)	
Marital status				<0.01
Married	2,308 (60.3)	1,987 (59.8)	321 (63.4)	
Single	633 (16.5)	581 (17.5)	52 (10.3)	
Separated/divorced/widowed	715 (18.7)	608 (18.3)	107 (21.1)	
Unknown	171 (4.5)	145 (4.4)	26 (5.1)	
Year of diagnosis				<0.01
1975–1988	371 (9.7)	345 (10.4)	26 (5.1)	
1989–2002	1,007 (26.3)	901 (27.1)	106 (20.9)	
2003–2017	2,449 (64.0)	2,075 (62.5)	374 (73.9)	
Masaoka-Koga stage				<0.01
I/IIA	301 (7.9)	263 (7.9)	38 (7.5)	
IIB	754 (19.7)	689 (20.7)	65 (12.8)	
III/IV	311 (8.1)	283 (8.5)	28 (5.5)	
Unknown	2,461 (64.3)	2,086 (62.8)	375 (74.1)	
WHO type				0.02
A	261 (6.8)	219 (6.6)	42 (8.3)	
AB	474 (12.4)	400 (12.0)	74 (14.6)	
B1	373 (9.7)	318 (9.6)	55 (10.9)	
B2	390 (10.2)	338 (10.2)	52 (10.3)	
B3	505 (13.2)	427 (12.9)	78 (15.4)	
NOS	1,824 (47.7)	1,619 (48.8)	205 (40.5)	
Size (mm), mean \pm SD	75.50 \pm 60.74	76.33 \pm 60.20	70.19 \pm 63.90	0.07
Treatment				<0.01
Surg only	1,146 (29.9)	959 (28.9)	187 (37.0)	
Surg and Chemo/Radia	1,812 (47.3)	1,624 (48.9)	188 (37.2)	
Chemo/Radia	588 (15.4)	510 (15.4)	78 (15.4)	
No treatment	281 (7.3)	228 (6.9)	53 (10.5)	
Cause of death				<0.01
Alive	2,034 (53.1)	1,801 (54.2)	233 (46.0)	
Thymoma specific death	734 (19.2)	734 (22.1)	0 (0.0)	
Other death	1,059 (27.7)	786 (23.7)	273 (54.0)	

WHO, World Health Organization; SD, standard deviation; NOS, not otherwise specified; Surg, surgery; Chemo, chemotherapy; Radia, radiation.

Table 2 Baseline characteristics of patients with thymoma after propensity score matching

Characteristics	Total, N=1,318 (%)	First primary cancer, N=821 (%)	Prior cancer history, N=497 (%)	P value
Age (years), mean \pm SD	63.93 \pm 12.80	63.42 \pm 12.86	65.91 \pm 12.32	0.08
Gender				
Female	632 (48.0)	388 (47.3)	244 (49.1)	0.52
Race				0.20
White	1,022 (77.5)	637 (77.6)	385 (77.5)	
Black	144 (10.9)	82 (10.0)	62 (12.5)	
Other/unknown	152 (11.5)	102 (12.4)	50 (10.1)	
Marital status				0.59
Married	818 (62.1)	503 (61.3)	315 (63.4)	
Single	156 (11.8)	104 (12.7)	52 (10.5)	
Separated/divorced/widowed	281 (21.3)	177 (21.6)	104 (20.9)	
Unknown	63 (4.8)	37 (4.5)	26 (5.2)	
Year of diagnosis				0.97
1975–1988	71 (5.4)	45 (5.5)	26 (5.2)	
1989–2002	278 (21.1)	172 (21.0)	106 (21.3)	
2003–2017	969 (73.5)	604 (73.6)	365 (73.4)	
Masaoka-Koga stage				0.31
I/IIA	84 (6.4)	46 (5.6)	38 (7.6)	
IIB	192 (14.6)	128 (15.6)	64 (12.9)	
III/IV	75 (5.7)	47 (5.7)	28 (5.6)	
Unknown	967 (73.4)	600 (73.1)	367 (73.8)	
WHO type				0.46
A	104 (7.9)	64 (7.8)	40 (8.0)	
AB	217 (16.5)	145 (17.7)	72 (14.5)	
B1	130 (9.9)	75 (9.1)	55 (11.1)	
B2	142 (10.8)	90 (11.0)	52 (10.5)	
B3	181 (13.7)	105 (12.8)	76 (15.3)	
NOS	544 (41.3)	342 (41.7)	202 (40.6)	
Size (mm), mean \pm SD	73.07 \pm 68.72	74.72 \pm 71.15	70.27 \pm 64.39	0.33
Treatment				0.09
Surg only	448 (34.0)	264 (32.2)	184 (37.0)	
Surg and Chemo/Radia	555 (42.1)	367 (44.7)	188 (37.8)	
Chemo/Radia	197 (14.9)	121 (14.7)	76 (15.3)	
No treatment	118 (9.0)	69 (8.4)	49 (9.9)	
Cause of death				<0.01
Alive	689 (52.3)	459 (55.9)	230 (46.3)	
Thymoma specific death	180 (13.7)	180 (21.9)	0 (0.0)	
Other death	449 (34.1)	182 (22.2)	267 (53.7)	

WHO, World Health Organization; SD, standard deviation; NOS, not otherwise specified; Surg, surgery; Chemo, chemotherapy; Radia, radiation.

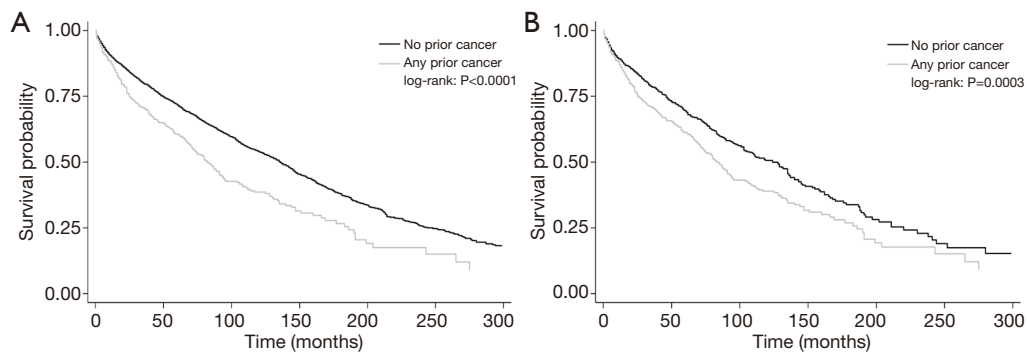


Figure 1 Overall survival for thymoma patients with or without prior cancer diagnosis. (A) Overall survival before propensity score matching. (B) Overall survival after propensity score matching.

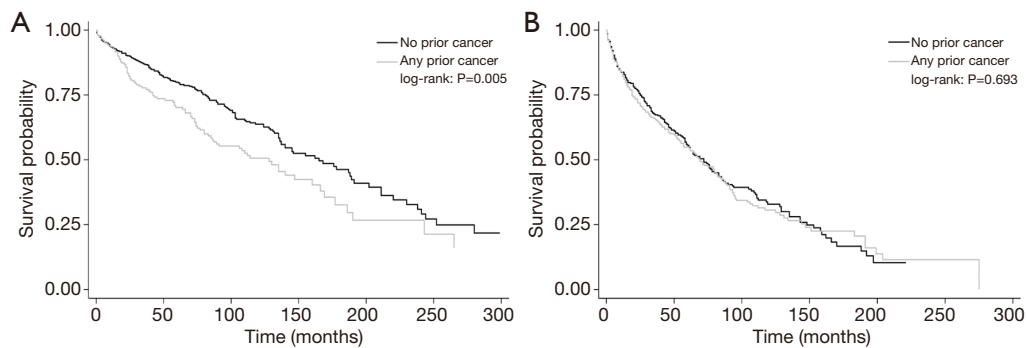


Figure 2 Subgroup analysis of prior cancer impact on the overall survival stratified by age. (A) Overall survival for age ≤ 65 years. (B) Overall survival for age > 65 years.

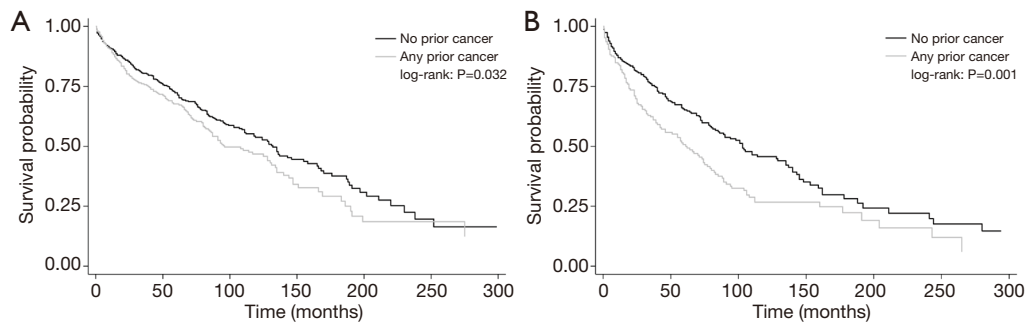


Figure 3 Subgroup analysis of prior cancer impact on the overall survival stratified by size. (A) Overall survival for size < 73 mm. (B) Overall survival for size ≥ 73 mm.

the older patients group. Younger patients with thymoma have better survival and are more likely to be cured than older patients. Prior cancer treatment can increase the risk of treatment intolerance and immune dysregulation, therefore prior cancer may worsen the prognosis among

younger patients (18). From this perspective, we should exclude younger patients with prior cancer history, but older patients may be considered for enrollment in clinical trials. Still, further investigation is required.

The World Health Organization (WHO) histologic

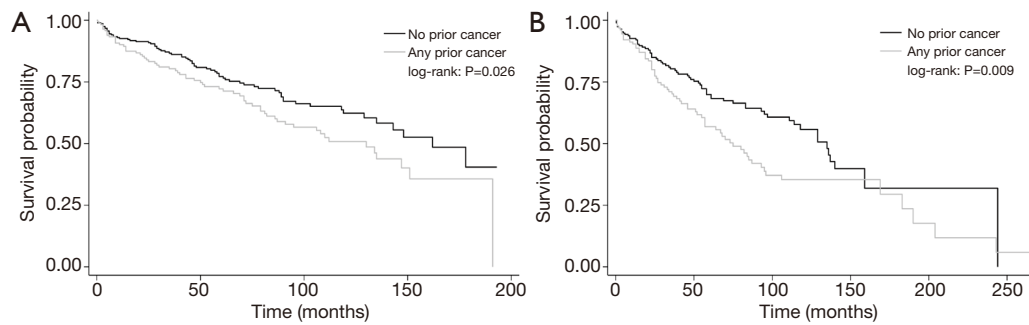


Figure 4 Subgroup analysis of prior cancer impact on the overall survival stratified by histologic types. (A) Overall survival for types A, AB, and B1. (B) Overall survival for types B2 and B3.

Table 3 Cox regression analysis of prior cancer history impact on patients with thymoma

Variables	Hazard ratio (95% CI)	P value
Age (years)		
≤65	Reference	
>65	2.22 (1.65–3.00)	<0.001
Gender		
Male	Reference	
Female	0.84 (0.71–0.99)	0.034
Race		
White	Reference	
Black	1.10 (0.85–1.39)	0.493
Other/unknown	0.81 (0.61–1.09)	0.165
Marital status		
Married	Reference	
Single	1.20 (0.91–1.57)	0.201
Separated/divorced/ widowed	1.51 (1.24–1.83)	< 0.001
Unknown	0.92 (0.60–1.41)	0.693
Year of diagnosis		
1975–1988	Reference	
1989–2002	1.11 (0.82–1.50)	0.505
2003–2017	0.75 (0.52–1.09)	0.137
Masaoka-Koga stage		
I/IIA	Reference	
IIB	1.44 (1.05–1.97)	0.025
III/IV	2.23 (1.54–3.24)	<0.001
Unknown	1.37 (0.93–2.01)	0.111

Table 3 (continued)

Table 3 (continued)

Variables	Hazard ratio (95% CI)	P value
WHO type		
A	Reference	
AB	0.68 (0.44–1.04)	0.072
B1	0.85 (0.56–1.30)	0.457
B2	1.03 (0.68–1.57)	0.875
B3	1.08 (0.74–1.59)	0.693
NOS	0.97 (0.69–1.37)	0.859
Size (mm)		
<73	Reference	
≥73	1.22 (1.04–1.45)	0.017
Treatment		
Surg only	Reference	
Surg and Chemo/Radia	1.07 (0.87–1.32)	0.498
Chemo/Radia	2.97 (2.33–3.79)	<0.001
No treatment	2.42 (1.80–3.26)	<0.001
Prior cancer history		
No	Reference	
Yes	1.39 (1.18–1.63)	0.017

HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; NOS, not otherwise specified; Surg, surgery; Chemo, chemotherapy; Radia, radiation.

classification of thymomas has been widely adopted. Thymomas are divided into five categories, that is, thymoma types A, AB, B1, B2, and B3. Types A, AB, B1 thymoma take a favorable outcome with 10 years OS between 90% and 95%. Whereas B2 and B3 thymoma have worse OS rates of

75% and 70% at 5 years (10,19-21). The clinical parameters such as thymoma size and age also have prognostic value. Large thymoma size has worse OS and is an independent predictor of recurrence and prognosis (21,22). In our study, subgroup analysis stratified by thymoma size and histologic type displayed that thymoma patients with prior cancer had worse survival compared with patients without prior cancer. It indicated that enrollment of thymoma patients with prior cancer history should be cautious.

The rarity of thymoma makes it difficult to conduct large phase II and III clinical trials, and new drugs are slow in development. More researches are necessary to explore and improve current treatment guidelines. The treatment of thymoma usually requires multidisciplinary therapy. Surgery is the mainstay of treatment as long as thymoma can be removed. Systemic chemotherapy is the current standard treatment for inoperable refractory, metastatic, or recurrent thymoma (10). However, chemotherapy may influence the ability of the thymus to reconstitute T cells and leads to immunosuppression. Preexposure to the prior cancer treatment may influence the study outcomes, such as the adverse and efficacy events.

This study also has a number of limitations. First, prior cancer history was derived from the SEER first malignant primary indicator. Prior cancer can be accurately identified but without detailed characteristics of prior cancer. So we could not include the timing and the type of prior cancer in this study. Second, some valuable information was lacking, such as comorbidities, adverse events, and detailed treatment methods. Therefore, further study is warranted to validate and confirm the generality of our findings.

Conclusions

Among patients with thymoma, prior cancer has an inferior effect on survival, regardless of the histologic types and tumor size. But prior cancer has a variable impact on survival when patients with thymoma are stratified by age. Prior cancer history is associated with inferior survival for younger patients with thymoma and does not adversely impact survival among older patients with thymoma. We suggest that including prior cancer history as a stratification variable in analysis and emphasize that exclusion criteria should be modified based on age. However, further studies are warranted to confirm the conclusions.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/gs-20-880>). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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