Original Article

Postoperative radiotherapy after extirpative surgery may not improve survival in patients with Masaoka-Koga stage IIB thymoma: a propensity-matched study based on the SEER database

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Background: The exact role of postoperative radiotherapy (PORT) in patients with Masaoka-Koga stage IIB thymoma following extirpative surgery (defined as radical surgery or total thymectomy) is still under debate. This study was designed to evaluate the effect of PORT on survival in patients with stage IIB thymoma following extirpative surgery in a population-based registry.

Methods: Patients with Masaoka-Koga stage IIB thymoma who underwent extirpative surgery between 2000 and 2019 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. One-to-one propensity score matching (PSM) with Kaplan-Meier and Cox regression analyses were used to assess overall survival (OS) and cancer-specific survival (CSS). To identify potential patients who may benefit from PORT, exploratory subgroup analyses on survival and further analyses stratified by Asian patients were performed.

Results: A total of 273 eligible patients were included, 164 (60.1%) in the PORT group and 109 (39.9%) in the non-PORT group. After 1:1 PSM, OS and CSS were not significantly different between the two groups. The 10-year OS and CSS rates were 83.5% in the PORT group *vs.* 80.1% in the non-PORT group (P=0.95) and 97.8% *vs.* 97.7% (P=0.31), respectively. The multivariate analyses further demonstrated no significant association between PORT and either OS [hazard ratio (HR) =1.219, P=0.53] or CSS (HR =2.304, P=0.32). Exploratory subgroup analyses revealed that PORT did not significantly improve survival in any subgroup of patients with stage IIB thymoma, and further analyses based on the Asian patients yielded the same negative results.

Conclusions: According to the SEER database, adding PORT to extirpative surgery may not improve survival in patients with Masaoka-Koga stage IIB thymomas.

Keywords: Extirpative surgery; radiotherapy; thymoma

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Introduction

Despite its low incidence, thymoma remains the most common anterior mediastinal tumor (1). According to the World Health Organization (WHO) histologic grading system, thymomas are classified into A, AB and B1–3 subtypes and are often characterized by indolent behavior and a long natural history with a 5-year overall survival (OS) of approximately 90% (2,3). Currently, the Masaoka-Koga staging system, which primarily considers local extension into surrounding structures, is still the most widely used staging system for thymoma (4). Based on this staging system, surgical resection is the cornerstone in the management of thymomas. Nevertheless, multidisciplinary treatment is necessary due to the low annual incidence of the disease, which leads to a lack of prospective studies. Postoperative radiotherapy (PORT) has typically been recommended for patients with positive margins after surgical resection. For patients with totally resected Masaoka-Koga stage I thymomas, there are no improvements in survival given the excellent local control rates and long-term survival (5,6). However, there is no consensus on the indications for PORT in totally resected stage II thymoma patients. Several studies have shown an advantage of PORT in improving the prognosis of patients with completely resected stage II thymoma (7,8), while others have found no advantage of PORT in stage II patients (9-12). Notably, the sample sizes of most of these studies were all relatively small and did not distinguish between stage IIA and stage IIB. When further distinguishing between Masaoka-Koga stage IIA (included in T1a of the 8th tumor node metastasis staging system along with Masaoka-Koga stage I) and IIB (corresponding to T1b), the controversy is mostly focused on stage IIB, whereas for stage IIA thymoma, the addition of PORT is more consistent in most studies with no additional survival benefit; therefore, PORT is not routinely recommended for stage IIA in some guidelines (13-19). Although the role of PORT in thymoma has been extensively analyzed in several population-based studies, the population with stage IIB thymoma has only been analyzed as a subgroup, with no propensity score matching (PSM) analysis of this population or further analysis based on the extent of surgery, possibly leading to biased results. Therefore, we evaluated the role of PORT in patients with Masaoka-Koga stage IIB thymoma who underwent extirpative surgery (defined as radical surgery or total thymectomy) according to the Surveillance, Epidemiology, and End Results (SEER) database. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1061/rc).

Highlight box

Key findings

- The addition of postoperative radiotherapy (PORT) after extirpative surgery (radical surgery or total thymectomy) may not improve survival in patients with Masaoka-Koga stage IIB thymoma.

What is known and what is new?

- The exact role of PORT in patients with Masaoka-Koga stage IIB thymoma following extirpative surgery is still under debate.
- According to the Surveillance, Epidemiology, and End Results database, this study comprehensively investigated the role of PORT after extirpative surgery in Masaoka-Koga stage IIB thymoma and found no additional survival benefits. Further exploratory subgroup analysis confirmed the limited impact of PORT on survival in any subgroup of patients with stage IIB thymoma or in Asians, suggesting that PORT appears to be omitted in totally resected stage IIB patients.

What is the implication, and what should change now?

- This study suggests that extirpative surgery appears to be a sufficient treatment for Masaoka-Koga stage IIB thymoma, regardless of race. PORT might be omitted in totally resected stage IIB patients.

Methods

Patients and data extraction

The SEER database is a national cancer registry that has been used to track cancer incidence and patient survival since 1973 and is sponsored by the National Cancer Institute. For the present study, we analyzed patient data from the SEER 17-registry maintained by the National Cancer Institute (2000–2019; dataset submitted November 2021). SEER*Stat software (version 8.4.2) was used to extract clinicopathologic and survival information. All patients diagnosed with histologically confirmed thymoma were included in this analysis. The International Classification of Disease for Oncology, Third Edition (ICD-O-3) was used to determine the histology of thymic tumors. Histologic codes for thymoma [8580–8585] with corresponding topographic codes C37.9 (thymus) and C38.1 (anterior mediastinum) were used. The inclusion criteria were as follows: (I) aged ≥18 years; (II) had Masaoka-Koga stage IIB thymoma; (III) underwent cancer-directed surgery

with or without PORT; and (IV) underwent total resection or radical surgery. Patients with a survival time less than 3 months were excluded to rule out surgical death or substantial morbidity.

The covariates included age at diagnosis, race, gender, WHO histologic type, tumor size, and receipt of chemotherapy. The WHO histologic type was divided into three groups: low risk (defined as A, AB and B1), high risk (defined as B2 and B3) and not otherwise specified (NOS) (20). Although the Masaoka-Koga stage is not clearly defined in the database, the SEER database contains data [Extent of Disease (EOD) 10 1988–2003 and Collaborative Stage (CS) extension 2004, SEER Program Coding and Staging Manual, 2010] that specifically describe tumor invasion. Patients with thymomas invading into "adjacent connective tissue" were identified as Masaoka-Koga stage IIB. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Differences in patient characteristics between treatment groups were analyzed using the Chi-squared test or Fisher's exact test for categorical variables. One-to-one PSM with baseline characteristics was used to minimize confounding. OS and cancer-specific survival (CSS) were estimated by Kaplan-Meier analysis and evaluated by the log-rank test. When the univariate analysis yielded a P value ≤0.15, the variable was incorporated into the multivariate Cox regression analysis. A P value less than 0.05 was considered statistically significant. All the statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

A total of 273 patients with stage IIB thymoma who met the inclusion criteria were identified. Among them, 164 (60.1%) patients received PORT after extirpative surgery and the remaining 109 (39.9%) patients did not. The median age was 61 years (range, 20–90 years), and patients in the PORT group were younger than those in the non-PORT group. The white race constituted approximately two-thirds of the whole population. Among the other races, the majority were Asian (91.0%, 61/67). Among the patients who received chemotherapy, 13 patients received adjuvant chemotherapy, including 11 (6.7%) in the PORT group and 2 (1.8%) in the non-PORT group. After 1:1 PSM, the patients' characteristics were well balanced (*Table 1*).

Survival analysis before PSM

In the whole population, the 5- and 10-year OS rates were 90.2% and 80.2%, respectively, and the 5- and 10-year CSS rates were 98.3% and 97.3%, respectively. After a median follow-up of 8.4 years, patients who received PORT showed similar survival to those who did not receive PORT. The 5- and 10-year OS rates were 89.3% *vs.* 91.7% and 81.7% *vs.* 77.4%, respectively (P=0.74, *Figure 1A*). The 5- and 10-year CSS rates were 98.6% *vs.* 97.9% and 97.0% *vs.* 97.9%, respectively (P=0.27, *Figure 1B*). Univariate and multivariate analyses revealed that PORT was not an independent prognostic factor for survival (Tables S1,S2).

Survival analysis after PSM

After 1:1 PSM, a total of 99 patient-pairs were matched, and there were no significant differences in survival between the two groups. The median OS was not reached (NR) in both treatment groups, with a 5-year OS rate of 90.5% in the PORT group *vs.* 91.9% in the non-PORT group and a 10-year OS rate of 83.5% *vs.* 80.1% (P=0.95, *Figure 1C*). Median CSS was NR in both groups, with a 5-year CSS rate of 97.8% *vs.* 97.7% and a 10-year CSS rate of 97.8% *vs.* 97.7% (P=0.31, *Figure 1D*). The multivariate analyses further demonstrated no significant association between PORT and either OS or CSS (*Tables 2,3*).

Subgroup analysis

To identify patients who could benefit from PORT, an exploratory subgroup analysis was performed. *Figure 2* shows that PORT did not confer a significant improvement in OS in any other subgroup of the population. When a further 1:1 PSM analysis was performed with restriction to Asian patients, who made up the majority of the "other" race group, the results revealed that the addition of PORT not only did not significantly improve OS (10-year: PORT *vs.* non-PORT 87.8% *vs.* 79.3%, P=0.43) but also appeared to adversely affect patient CSS (10-year: PORT *vs.* non-PORT 94.1% *vs.* 100.0%, P=0.19) (Table S3, *Figure 3*).

Discussion

In this population-based study, we comprehensively

Table 1 Baseline characteristics before and after PSM

Characteristics	Before PSM			After PSM		
	Non-PORT (n=109), n (%)	PORT (n=164), n (%)	P	Non-PORT (n=99), n (%)	PORT (n=99), n (%)	P
Age			0.02			0.76
<65 years	61 (56.0)	113 (68.9)		61 (61.6)	63 (63.6)	
≥65 years	48 (44.0)	51 (31.1)		38 (38.4)	36 (36.4)	
Gender			0.38			0.67
Male	54 (49.5)	90 (54.9)		49 (49.5)	52 (52.5)	
Female	55 (50.5)	74 (45.1)		50 (50.5)	47 (47.5)	
Race			0.72			0.90
White	73 (67.0)	105 (64.0)		66 (66.7)	63 (63.6)	
Black	12 (11.0)	16 (9.8)		11 (11.1)	12 (12.1)	
Others	24 (22.0)	43 (26.2)		22 (22.2)	24 (24.2)	
WHO histology			0.32			0.86
Low risk	58 (53.2)	72 (43.9)		51 (51.5)	52 (52.5)	
High risk	31 (28.4)	54 (32.9)		28 (28.3)	25 (25.3)	
NOS	20 (18.3)	38 (23.2)		20 (20.2)	22 (22.2)	
Chemotherapy			0.23			0.97
No	70 (64.2)	89 (54.3)		61 (61.6)	63 (63.6)	
Yes	7 (6.4)	17 (10.4)		6 (6.1)	6 (6.1)	
Unknown	32 (29.4)	58 (35.4)		32 (32.3)	30 (30.3)	
Tumor size			0.78			0.42
<5.5 cm	37 (33.9)	57 (34.8)		31 (31.3)	24 (24.2)	
≥5.5 cm	67 (61.5)	102 (62.2)		63 (63.6)	72 (72.7)	
Unknown	5 (4.6)	5 (3.0)		5 (5.1)	3 (3.0)	

PSM, propensity score matching; PORT, postoperative radiotherapy; WHO, World Health Organization; NOS, not otherwise specified.

investigated the role of PORT after extirpative surgery in Masaoka-Koga stage IIB thymoma patients and found no additional survival benefits either before or after PSM. Further exploratory subgroup analysis confirmed the limited impact of PORT on survival in any subgroup of patients with stage IIB thymoma or in Asians, suggesting that PORT may be omitted in totally resected stage IIB patients. To our knowledge, the present study is the first propensity-matched SEER analysis of patients with stage IIB thymoma who underwent extirpative surgery.

Currently, the exact role of PORT after complete resection remains unclear, particularly for patients with Masaoka-Koga stage IIB thymoma. Limited by low annual incidence and long-term natural history of the disease, there are few large randomized clinical trials on the topic. Although the 2023 National Comprehensive Cancer Network guidelines recommend that PORT be considered for patients with stage II thymoma after R0 resection, it also acknowledges that patients may not benefit from PORT (21). Of note, most of these recommendations are based on small sample studies and the results are contradictory. According to an analysis of the International Thymic Malignancies Interest Group (ITMIG) retrospective database, the use of PORT improved OS in patients with completely resected stage II and III thymomas (8). Regrettably, this study did not further differentiate between stage IIA and IIB patients. In a subsequent meta-analysis of 4,746 patients, Tateishi

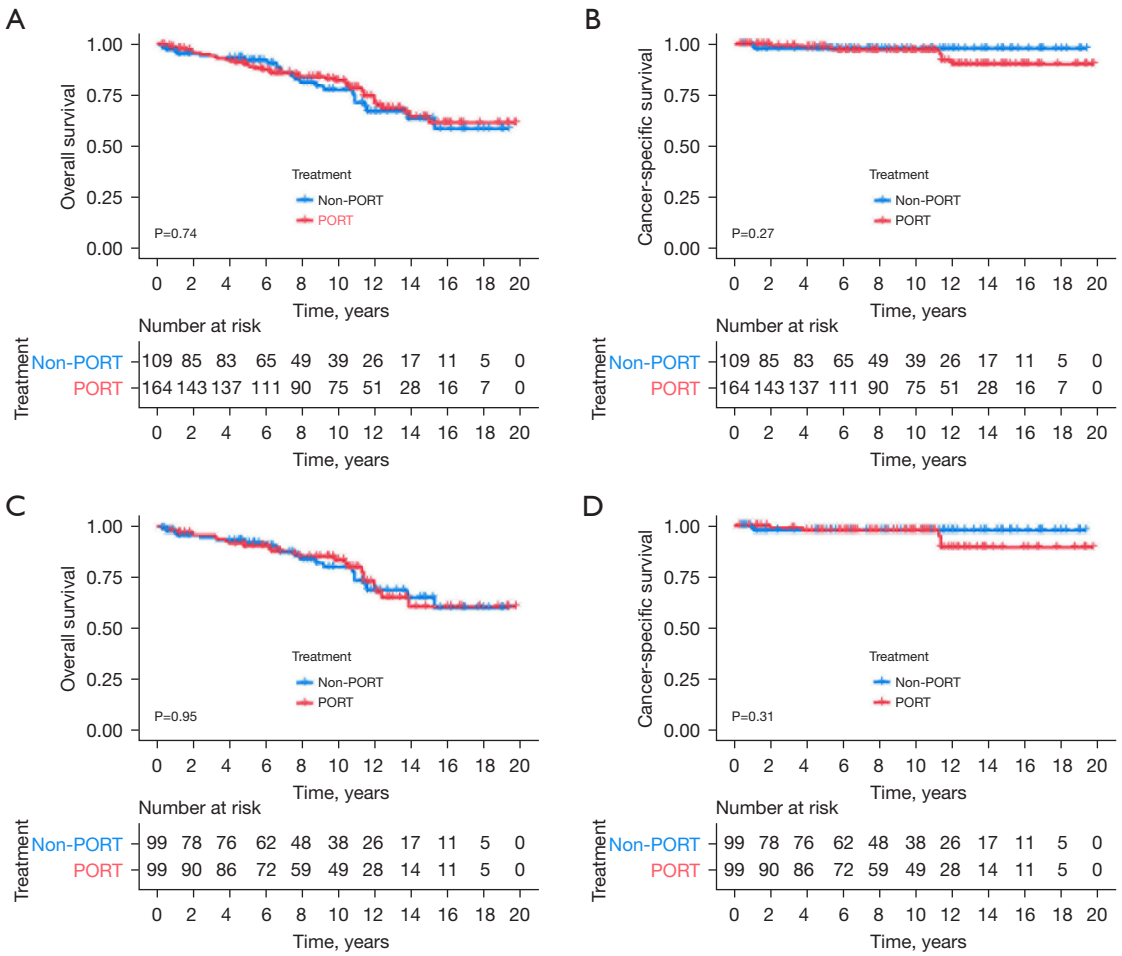

Figure 1 OS and CSS between the PORT group and the non-PORT group before and after PSM. (A) OS between the two treatment groups before PSM. (B) CSS between the two treatment groups before PSM. (C) OS between the two treatment groups after PSM. (D) CSS between the two treatment groups after PSM. PORT, postoperative radiotherapy; OS, overall survival; CSS, cancer-specific survival; PSM, propensity score matching.

et al. (22) found that thymoma patients with Masaoka stage II or III disease after complete resection showed improved OS but not improved DFS through the addition of PORT. However, due to the rarity of the disease, this meta-analysis included only 2 studies in the stage II subgroup. In a study based on the National Cancer Database (NCDB), Jackson *et al.* (15) reported that the addition of PORT significantly prolonged OS in patients with stage IIB thymoma after R0 resection. A subsequent population-based study published in 2022 showed similar results (16). However, two other studies based on the SEER database yielded negative results (14,18). It is worth noting that these studies all analyzed stage IIB patients as a subgroup, without further PSM analysis or further differentiation by extent of surgery, which may have contributed to these conflicting results. Considering the prognostic value of radical resection for outcomes (23), the inclusion of patients who received non-extirpative surgery may further bias the results. Therefore, we specifically restricted the surgical extent to total resection or radical surgery in patients with stage IIB thymoma and found no significant survival benefit of PORT in this population, similar to the findings of Forquer *et al.* (24). In this population-based analysis conducted by Forquer *et al.*, they demonstrated that no survival benefit was noted for PORT in "regional" (generally considered stage II–III) thymoma/thymic carcinoma after extirpative surgery. However, it should be noted that due to the lack of information on pathological resection margins in the

Table 2 Factors associated with OS in patients with stage IIB thymoma after PSM

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age				
<65 years	1.000 (reference)		1.000 (reference)	
≥65 years	4.055 (2.168, 7.586)	<0.001	4.667 (2.470, 8.818)	<0.001
Gender				
Male	1.000 (reference)		–	–
Female	0.737 (0.407, 1.335)	0.31	–	–
Race				
White	1.000 (reference)		–	–
Black	1.318 (0.577, 3.012)	0.51	–	–
Others	0.857 (0.391, 1.876)	0.69	–	–
WHO histology				
Low risk	1.000 (reference)		1.000 (reference)	
High risk	2.101 (1.001, 4.410)	0.050	2.770 (1.290, 5.950)	0.009
NOS	2.049 (0.997, 4.210)	0.051	2.070 (0.989, 4.334)	0.054
Chemotherapy				
No	1.000 (reference)		1.000 (reference)	
Yes	0.831 (0.109, 6.314)	0.85	1.094 (0.143, 8.399)	0.93
Unknown	1.801 (0.933, 3.479)	0.08	1.943 (0.972, 3.884)	0.06
Tumor size				
<5.5 cm	1.000 (reference)		–	–
≥5.5 cm	1.043 (0.533, 2.042)	0.90	–	–
Unknown	0.659 (0.147, 2.950)	0.58	–	–
PORT				
No	1.000 (reference)		1.000 (reference)	
Yes	0.982 (0.543, 1.775)	0.95	1.219 (0.653, 2.275)	0.53

OS, overall survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; NOS, not otherwise specified; PORT, postoperative radiotherapy.

SEER database, it is possible that some patients in our study may have had an R1 resection. Interestingly, patients with incomplete resections may have benefited more from the addition of PORT, but even in this setting, the addition of PORT still failed to significantly improve the prognosis of patients with stage IIB thymoma who received extirpative surgery, suggesting that the addition of PORT may not benefit this group of patients.

The incidence of thymoma, as well as its prognosis, varies among countries and races (25-28). The incidence of thymoma in China is 3.93/10,000, which is greater than that in European and American countries but similar to that in other Asian countries (28), suggesting the race-specificity of thymoma. Although the subgroup analysis in the present study suggested that there were no significant differences in the various races outcomes, given the highest incidence of thymoma in Asians and the lack of studies with large sample sizes investigating the value of PORT in Asian

Table 3 Factors associated with CSS in patients with stage IIB thymoma after PSM

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age				
<65 years	1.000 (reference)		–	–
≥65 years	2.833 (0.629, 12.765)	0.17	–	–
Gender				
Male	1.000 (reference)		–	–
Female	1.222 (0.273, 5.468)	0.79	–	–
Race				
White	1.000 (reference)		1.000 (reference)	
Black	3.725 (0.622, 22.299)	0.15	3.518 (0.581, 21.314)	0.17
Others	2.111 (0.352, 12.674)	0.41	1.790 (0.297, 10.771)	0.52
WHO histology				
Low risk	1.000 (reference)		1.000 (reference)	
High risk	1.038 (0.094, 11.445)	0.97	0.969 (0.086, 10.876)	0.98
NOS	3.934 (0.715, 21.627)	0.11	3.823 (0.694, 21.047)	0.12
Chemotherapy				
No	1.000 (reference)		–	–
Yes	0.000 (0.000, 0.000)	0.98	–	–
Unknown	2.841 (0.524, 15.400)	0.22	–	–
Tumor size				
<5.5 cm	1.000 (reference)		–	–
≥5.5 cm	0.843 (0.153, 4.631)	0.84	–	–
Unknown	2.092 (0.188, 23.246)	0.54	–	–
PORT				
No	1.000 (reference)		1.000 (reference)	
Yes	2.270 (0.440, 11.701)	0.32	2.304 (0.445, 11.927)	0.32

CSS, cancer-specific survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; NOS, not otherwise specified; PORT, postoperative radiotherapy.

patients, we therefore restricted the cases to Asian patients and performed further analysis and found that the addition of PORT still yielded the same negative results. The limited impact of PORT on survival in this study is similar to that reported in previous retrospective studies on Asians (9,29), indicating that extirpative surgery appears to be a sufficient treatment for stage II thymoma, regardless of race.

There are several shortcomings in this study. First, the SEER database lacks information on variables such as resection margin status, radiation dose and chemotherapy regimen. Although we restricted patients to those who underwent total resection or radical surgery, due to the absence of information on pathological resection margins, the results could not completely reflect the details of surgical procedures or the exact value of PORT after extirpative surgery. Second, the lack of information on recurrence or metastasis, the site of tumor recurrence, made it difficult to accurately assess the value of PORT and its effect on

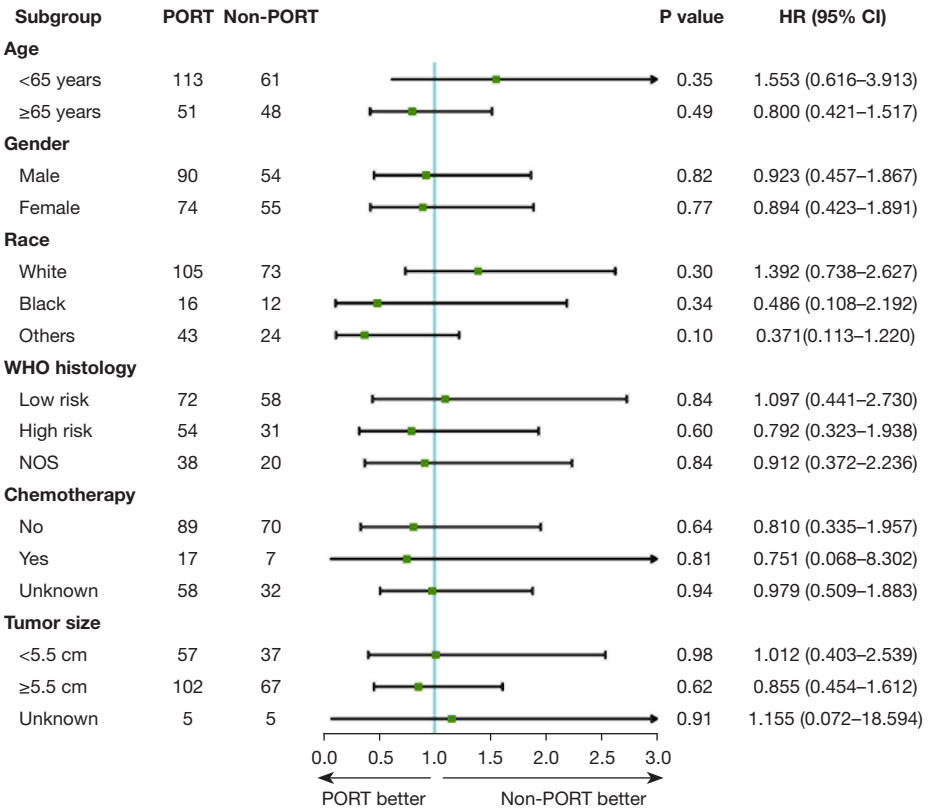

Figure 2 Subgroup analysis of prognostic factors for OS. PORT, postoperative radiotherapy; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; NOS, not otherwise specified; OS, overall survival.

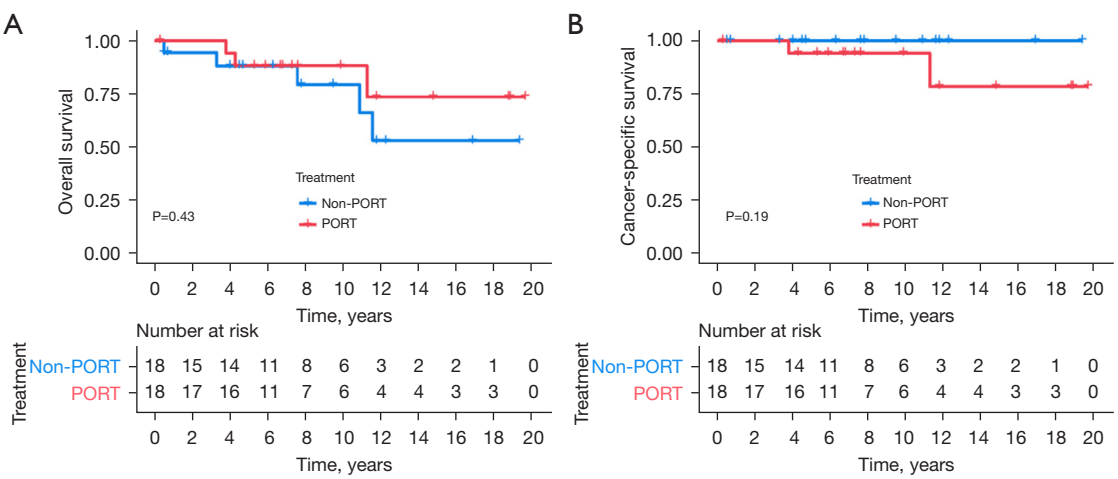

Figure 3 OS and CSS between the PORT group and the non-PORT group in Asians after PSM. (A) OS between the two treatment groups. (B) CSS between the two treatment groups. PORT, postoperative radiotherapy; OS, overall survival; CSS, cancer-specific survival; PSM, propensity score matching.

disease-free survival (DFS). Although OS, the current gold standard for assessing clinical benefit in tumors, may reflect the value of PORT to some extent, DFS is undoubtedly more reliable for tumors with indolent behavior such as thymoma. Third, the lack of descriptions of concurrent paraneoplastic syndromes and detailed treatment information, such as the use of corticosteroid therapy, which is useful for controlling thymoma and thymoma-related autoimmunity, may also have biased the results (30). Despite these limitations, our analysis demonstrated the limited impact of PORT on survival in patients with Masaoka-Koga stage IIB thymoma who underwent extirpative surgery in a moderate-sized population. To our knowledge, this is the first SEER PSM analysis focusing on the addition of PORT in patients with stage IIB thymoma after extirpative surgery. We believe that analyzing the SEER database can shed light on our clinical problems to some extent and contribute to the growing body of literature on the value of PORT in stage II thymoma and help guide clinical practice.

Conclusions

In conclusion, the present study demonstrated that adding PORT to extirpative surgery may not improve survival in patients with Masaoka-Koga stage IIB thymoma. Prospective and long-term studies on the value of PORT in patients with stage II thymoma are warranted.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1061/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1061/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1061/coif). 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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