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Effect of clinicopathologic features on survival of patients with thymic carcinomas and thymic neuroendocrine tumors: A population-based analysis

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ABSTRACT

Background: Thymic carcinomas (TCs) and thymic neuroendocrine tumors (TNETs) are aggressive cancers with poor survival outcome and limited investigation. This study is to investigate clinicopathologic features on TC and TNET patients' prognosis of a large cohort. *Materials and Methods:* The Surveillance, Epidemiology, and End Results database were used to identify a total of 362 TC and TNET patients with documented clinicopathologic features we investigated. The characteristics and overall survival of the TC and TNET patients were studied. *Results:* Two hundred and forty TC and 122 TNET patients were identified. For the entire cohort of TC and TNET, histologic type ($P < 0.001$), tumor size ($P = 0.015$), Masaoka-Koga stage ($P = 0.008$), regional node positive ($P = 0.004$), surgery of primary site ($P < 0.001$), lymph node surgery ($P = 0.013$), and chemotherapy ($P = 0.001$) were considered as significant clinicopathologic features that could affect prognosis of TC and TNET patients in univariate analysis. More importantly, histologic type ($P < 0.001$), regional nodes positive ($P = 0.03$) and surgery of primary site ($P < 0.001$) were able to independently predict overall survival of those patients. In addition, for the cohort of TC, we found that regional nodes positive ($P = 0.034$) and surgery of primary site ($P = 0.001$) could be independent predictors of TC patients' survival. *Conclusion:* Regional nodes detection is essential for TC and TNET patients. Surgery of primary site is the preferred primary treatment for those patients.

Abbreviations: TCs, thymic carcinomas; TNETs, thymic neuroendocrine tumors; SEER, Surveillance, Epidemiology, and End Results; WHO, World Health Organization; OS, overall survival; ESTS, The European Society of Thoracic Surgeons; NCI, National Cancer Institute; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; HR, hazard ratio; CI, confidence interval; MST, median survival time.

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Introduction

Thymic tumors are rare malignancies mainly originated from thymic epithelial cells, which are described as the most common lesion of the anterior mediastinum in adults.[1] According to the latest histologic classification of World Health Organization (WHO), thymic carcinomas (TCs) are distinguished from thymic neuroendocrine tumors (TNETs). Both of the 2 types of tumor belong to thymic epithelial tumors.[2] Although thymic tumors are rarer than other tumors, it has been shown that TCs and TNETs have a low overall survival (OS) rate as a result of the high possibility of recurrence and lymphatic or distant metastases incidence together with an aggressive biological behavior.[3,4]

Because of the rarity of this type of tumor, studies concentrated on thymic tumors are still limited to small retrospective investigations. Groups like the European Society of Thoracic Surgeons have developed a retrospective database of thymic tumors between 1990 and 2010. However, the number of patients in the group used for medical research is restricted in small size.[5] For patients with TCs or TNETs, the main treatment is surgery, with radiation therapy and chemotherapy serving as adjuvant treatment.[6] Efforts have been made to evaluate the OS of patients after surgery. Besides, there have been many studies investigating the prognostic factors of TCs and TNETs, such as stage, age, tumor size, and surgery.[7-10] Nevertheless, these investigations have limitations of small sample size and included evaluated prognostic factors.

With the purpose of overcoming these limitations, we utilized the Surveillance, Epidemiology, and End Results (SEER) database which is a public-use cancer dataset registered from the National Cancer Institute to collect a total of 362 patients with TCs or TNETs.[11] We investigated plenty of clinicopathologic features that can give a strong prognostic impact in TC and TNET patients. This study is to find out clinicopathologic factors that have an impact on thymic tumor patients' prognosis and evaluate whether the intervention of surgery, radiation therapy, and chemotherapy can benefit TC and TNET patients.

Materials and method

Data source and patient sample

This study identified information of patients diagnosed with TCs or TNETs that were recorded in the SEER database, which is publicly available and comprises of patients' records from a total of 18 population-based geographically distinct cancer registries that cover 28% of the population in the United States. To include all cases of TCs and TNETs, the SEER 18 submission (1973-2015) was queried. Tumors of thymus were confirmed by the "Primary Site" variable C37.9 on the basis of the International Classification of Diseases for Oncology, Third Edition for topography codes. The histology of TC and TNET was identified by utilizing the International Classification of Diseases for Oncology, Third Edition codes including 8002, 8010, 8012, 8013, 8020, 8021, 8023, 8033, 8041, 8045, 8070-8072, 8074, 8082, 8123, 8140, 8200, 8240, 8260, 8246, 8249, 8310, 8430, 8480, 8560, 8576, and 8586. Then, we excluded patient samples according to the criteria including not providing enough information of prognostic factors, survival time and survival status, age $<$18 years. The final patient cohort used for analysis included 240 TC patients and 122 TNET patients.

Extracted variables

We extracted variables of interest mainly including clinicopathologic features and survival information of TC and TNET patients. Clinicopathologic features we used for analysis contained age at diagnosis, histology type, sex, race/ethnicity, tumor size, the extension of tumor, Masaoka-Koga stage, whether with other tumors, regional nodes positive, surgery of primary site, surgery of lymph node and surgery of other sites, radiation therapy, and chemotherapy. Extension of tumor was classified into local extension and adjacent organ extension and metastasis. Masaoka-Koga stage was based on the Masaoka-Koga classification. Because of the difficulty to differentiate Masaoka-Koga stage I from stage II using the available data provided by the SEER, we classified Masaoka-Koga stage into stage I/IIA, stage IIB, stage III, and stage IV. Surgery of other site referred to the dissection of distant lymph nodes or the removal of other tissues or organs apart from the primary site. Survival information includes survival time of patients calculated from the day of diagnosis of TC or TNET to the last vital status and survival status.

Statistical analysis

Kaplan-Meier OS curves were used to estimate the prognostic factor of survival outcome for patients of TC and TNET stratified by clinicopathologic features. The log-rank test was performed to compare differences in survival by clinicopathologic features. We used the Cox univariate model to calculate hazard ratio (HR) as well as 95% confidence interval (CI). Cox multivariate proportional hazard model was used for analysis of independent prognostic variables which have P values <0.05 in univariate analysis. The P values of two side <0.05 were considered to be statistically significant. IBM SPSS Statistics version 23.0 (IBM, Armonk, NY) was used for all statistical analyses in this study.

Results

Patient characteristics

Basic characteristics of TC and TNET patients are shown in Table 1. A total of 325 patients were included in our analysis, of which 240 patients (66.3%) were diagnosed with TC and 112 patients with TNET (33.7%). The median age at diagnosis of the patients was 61 years (range 19-91 years) with 231 males (70.7%) and 256 white people (70.7%). The tumor size ranges from 0.4 to 22 cm with median size 6.5 cm. One hundred and eighty-five patients (51.1%) had a tumor of TC or TNET bigger than 6.5 cm. Extension of tumor was divided into local extension and adjacent organ extension and metastasis, which were respectively observed in 120 (33.1%) and 242 (66.9%) patients. According to Masaoka-Koga classification, there were 120 (33.1%) Masaoka-Koga stage I/IIA patients, 53 (14.6%) stage IIB patients, 148 (41.0%) stage III patients, and 41 (11.3%) stage IV patients. The majority of patients had only 1 tumor of TC or TNET in their lives (75.1%, $n = 272$), while patients with other tumors except for TC or TNET were less common (24.9%, $n = 90$). Patients with regional lymph node positive were 124 (34.3%), and patients with no lymph node metastasis accounted for approximately two thirds.

As for the treatment for patients with TC or TNET, the majority of patients received surgery of primary site (73.2%, $n = 265$). There were 141 patients (39.0%) undergoing regional lymph node surgery, while there were only 35 patients (9.7%) receiving surgery of other sites like distant lymph nodes or other metastases. One hundred and ninety-six (54.1%) patients underwent radiation therapy and 178 (49.2%) patients underwent chemotherapy.

Survival outcomes of both TC and TNET patients

Median survival time (MST) of all the patients was 29.5 months. In the univariate analysis of the entire cohort, there were 7 clinicopathologic features considered as significant

Table 1
Basic characteristics of thymic carcinoma and thymic neuroendocrine tumor patients.

Characteristic		
Total [*n* (%)]	362	(100)
Median duration of survival time, years (range)	3.1	(0-16.9)
Median age at diagnosis, years (range)	61	(19-91)
<61 [*n* (%)]	170	(47.0)
≥61 [*n* (%)]	192	(53.0)
Histologic type [*n* (%)]		
Thymic carcinoma	240	(66.3)
Thymic neuroendocrine tumor	122	(33.7)
Sex [*n* (%)]		
Male	231	(63.8)
Female	131	(36.2)
Race/Ethnicity [*n* (%)]		
White	256	(70.7)
Other	106	(29.3)
Tumor size, median (range, cm)	6.5	(0.4-22)
<6.5 [*n* (%)]	177	(48.9)
≥6.5 [*n* (%)]	185	(51.1)
Extension of tumor [*n* (%)]		
Local extension	120	(33.1)
Adjacent organ extension and metastasis	242	(66.9)
Masaoka-Koga stage [*n* (%)]		
Stage I and IIA	120	(33.1)
Stage IIB	53	(14.6)
Stage III	148	(41.0)
Stage IV	41	(11.3)
Whether with other tumor [*n* (%)]		
Only one tumor	272	(75.1)
With other tumor	90	(24.9)
Regional nodes positive [*n* (%)]		
Negative	238	(65.7)
Positive	124	(34.3)
Surgery of primary site [*n* (%)]		
Yes	265	(73.2)
No	97	(26.8)
Lymph node surgery [*n* (%)]		
Yes	141	(39.0)
No	221	(61.0)
Surgery of other site [*n* (%)]		
Yes	35	(9.7)
No	327	(90.3)
Radiation therapy [*n* (%)]		
Yes	196	(54.1)
No	166	(45.9)
Chemotherapy [*n* (%)]		
Yes	178	(49.2)
No	184	(50.8)

clinicopathologic features that could affect the prognosis of TC and TNET patients (Table 2, Fig 1). Histologic type used TNET with MST of 92 months comparing to the TC with MST of 52 months (HR = 0.466, 95% CI = 0.318-0.682, $P < 0.001$). Patients with larger tumor size (MST = 59 months) had a poor survival outcome than those with smaller size (MST = 88 months; HR = 1.502, 95% CI = 1.083-2.081, $P = 0.015$). Masaoka-Koga stage was classified into 4 stage, including stage I/IIA (MST = 81 months), stage IIB (MST = 113 months), stage III (MST = 61 months), stage IV (MST = 37 months; HR = 1.247, 95% CI = 1.060-1.466, $P = 0.008$). Patients with regional node positive had shorter MST than those with regional node negative (46 vs 81 months) (HR = 1.635, 95% CI = 1.175-2.275, $P = 0.004$). Besides, patents not receiving surgery of primary site (MST = 23 months) had poorer OS than those receiving (MST = 90 months;

Table 2
Survival analysis of thymic carcinoma and thymic neuroendocrine tumor patients.

Variable	HR	95% CI	*P* value
Age at diagnosis, years (≥61 vs <61)	1.160	0.838-1.605	0.370
Histologic type (thymic neuroendocrine tumor vs thymic carcinoma)	0.466	0.318-0.682	<0.001
Sex (female vs male)	1.048	0.747-1.469	0.787
Race/Ethnicity (other vs White)	1.006	0.704-1.439	0.973
Tumor size, median (≥6.5 vs <6.5)	1.502	1.083-2.081	0.015
Extension of tumor (adjacent organ extension and metastasis vs local extension)	1.244	0.874-1.771	0.225
Masaoka-Koga stage (stage IV vs III vs IIB vs I/IIA)	1.247	1.060-1.466	0.008
Whether with other tumor (with other tumor vs only one tumor)	1.052	0.734-1.508	0.783
Regional nodes positive (positive vs negative)	1.635	1.175-2.275	0.004
Surgery of primary site (No vs Yes)	3.699	2.628-5.206	<0.001
Lymph node surgery (No vs Yes)	1.547	1.098-2.179	0.013
Surgery of other site (No vs Yes)	0.911	0.542-1.531	0.724
Radiation therapy (No vs Yes)	1.161	0.840-1.602	0.366
Chemotherapy (No vs Yes)	0.570	0.411-0.791	0.001

HR, hazard ratio; CI, confidence interval.

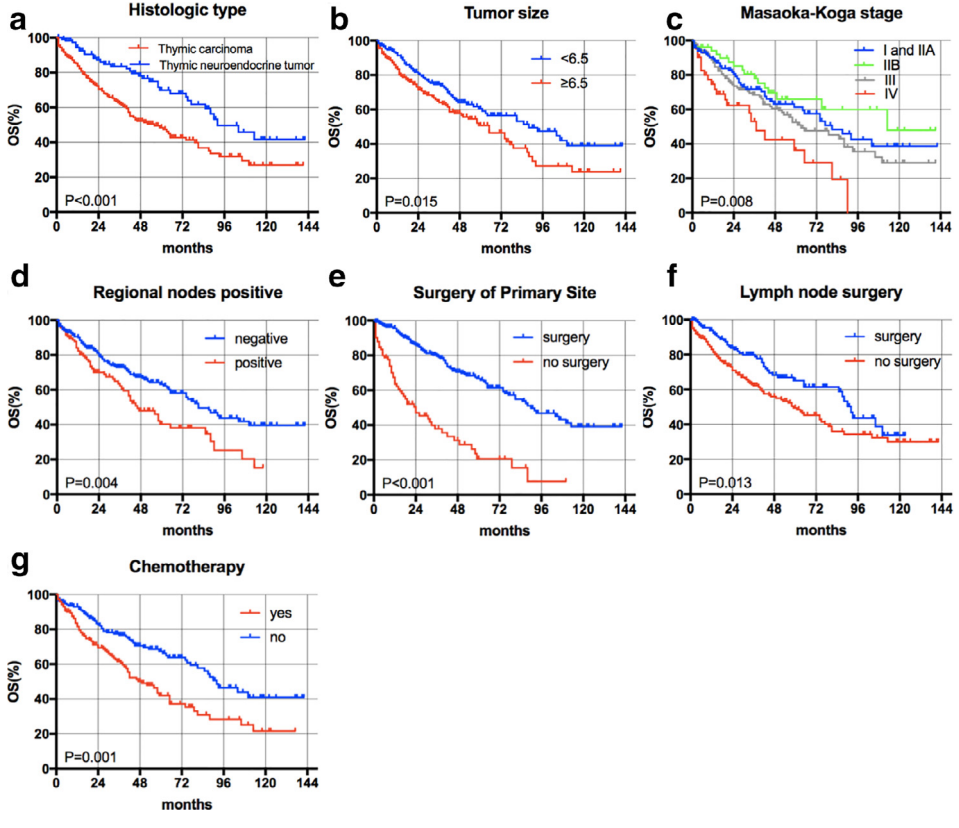

Fig. 1. Kaplan-Meier survival curves of 240 thymic carcinoma and 122 thymic neuroendocrine tumor patients. (a) Overall survival of patients of thymic carcinoma vs thymic neuroendocrine tumor patients. (b) Overall survival of patients of tumor size ≥6.5 vs tumor size <6.5. (c) Overall survival of patients with Masaoka-Koga stage IV vs III vs IIB vs I/IIA. (d) Overall survival of patients with regional nodes positive vs negative. (e) Overall survival of patients with no surgery of primary site vs those with surgery. (f) Overall survival of patients with no surgery of lymph node vs those with surgery. (g) Overall survival of patients with no chemotherapy vs those with chemotherapy.

Table 3
Multivariate analysis of thymic carcinoma and thymic neuroendocrine tumor patients.

Variable	HR	95% CI	*P* value
Histologic type (thymic neuroendocrine tumor vs thymic carcinoma)	0.467	0.312-0. 699	<0.001
Masaoka-Koga stage (stage IV vs III vs IIB vs I/IIA)	1.056	0.887-1.258	0.540
Regional nodes positive (positive vs negative)	1.532	1.043-2.253	0.030
Surgery of primary site (No vs Yes)	2.960	1.870-4.686	<0.001
Lymph node surgery (No vs Yes)	1.077	0.690-1.683	0.743
Chemotherapy (No vs Yes)	1.058	0.720-1.555	0.774
Tumor size, median (≥6.5 vs <6.5)	1.334	0.951-1.870	0.095

HR, hazard ratio; CI, confidence interval.

HR = 3.699, 95% CI = 2.628-5.206, $P < 0.001$). Patients not conducting the surgery of lymph node (MST = 58 months) also had poorer OS than those conducting (MST = 90 months; HR = 1.547, 95% CI = 1.098-2.179, $P = 0.013$). Interestingly, we found that patients who did not undergo chemotherapy (MST = 90 months) had a better OS than those who underwent chemotherapy (MST = 47 months; HR = 0.570, 95% CI = 0.411-0.791, $P = 0.001$). However, clinicopathologic features including age at diagnosis, sex, race/ethnicity, extension of tumor, whether with other tumor, surgery of other site, and radiation therapy were not statistically significant. Then, we conducted multivariate analysis to identify clinicopathologic features that were able to function as independent prognostic factors of TC and TNET patients (Table 3). TNET patients demonstrated a better survival outcome than TC patients (HR = 0.467, 95% CI = 0.312-0.699, $P < 0.001$). Regional nodes positive was an independent significant predictor of OS of TC and TNET patients, with those of one or more positive regional lymph node metastases demonstrating worse survival rate than those of no regional lymph nodes metastases (HR = 1.532, 95% CI = 1.043-2.253, $P = 0.03$). Surgery of primary site was an independent good predictor of patients' survival, with patients who were not surgery had poorer OS (HR = 2.960, 95% CI = 1.870-4.686, $P < 0.001$). However, the adjusted analysis showed that tumor size, Masaoka-Koga stage and lymph node surgery, and chemotherapy had no effect on patients' OS.

Survival outcomes of TC patients

We then conducted survival analysis for 240 TC patients, considering higher morbidity of TC than TNET. The univariate analysis demonstrated that 5 clinicopathologic features were statistically significant (Table 4, Fig 2). Patients with bigger tumor size had a poor OS than those with smaller tumor size (HR = 1.568, 95% CI = 1.081-2.274, $P = 0.018$). Masaoka-Koga stage was another predictor for patients' OS (HR = 1.320, 95% CI = 1.090-1.598, $P = 0.004$). As for regional node status, patients with the positive node (MST = 33 months) was associated to poorer OS than those with the negative node (MST = 74 months) (HR = 2.055, 95% CI = 1.405-3.005, $P < 0.001$). Surgery of primary site (MST = 81 months) was a positive feature of patients' OS, with patients not receiving surgery (MST = 18 months) having poor OS (HR = 3.487, 95% CI = 2.375-5.122, $P < 0.001$). Besides, patients not receiving lymph node surgery (MST = 41 months) had poorer OS than those receiving (MST = 88 months) (HR = 1.745, 95% CI = 1.169-2.603, $P = 0.006$), while other factors were not associated with TC patients' survival. The statistically significant factors were then used for multivariate analysis. Poor prognostic significance was strongly related to regional lymph node metastases (HR = 1.604, 95% CI = 1.037-2.479, $P = 0.034$). In contrast, surgical treatment of primary site (HR = 2.539, 95% CI = 1.497-4.307, $P = 0.001$) was considered as valuable independent predictors of OS, with TC patients who underwent primary site and lymph node metastases had a better survival outcome than those not (Table 5). Other factors including the tumor size, Masaoka-Koga stage, and lymph node surgery were not statistically significant in multivariate analysis.

Table 4
Survival analysis of thymic carcinoma patients.

Variable	HR	95% CI	*P* value
Age at diagnosis, years (≥61 vs <61)	0.946	0.651-1.375	0.772
Sex (female vs male)	0.921	0.629-1.349	0.673
Race/Ethnicity (other vs White)	1.009	0.674-1.509	0.967
Tumor size, median (≥6.5 vs <6.5)	1.568	1.081-2.274	0.018
Extension of tumor (adjacent organ extension and metastasis vs Local extension)	1.435	0.935-2.203	0.098
Masaoka-Koga stage (stage IV vs III vs IIB vs I/IIA)	1.320	1.090-1.598	0.004
Whether with other tumor (with other tumor vs only one tumor)	0.999	0.660-1.511	0.996
Regional nodes positive (positive vs negative)	2.055	1.405-3.005	<0.001
Surgery of primary site (No vs Yes)	3.487	2.375-5.122	<0.001
Lymph node surgery (No vs Yes)	1.745	1.169-2.603	0.006
Surgery of other site (No vs Yes)	0.895	0.511-1.567	0.698
Radiation therapy (No vs Yes)	1.317	0.908-1.910	0.147
Chemotherapy (No vs Yes)	0.714	0.490-1.040	0.079

HR, hazard ratio; CI, confidence interval.

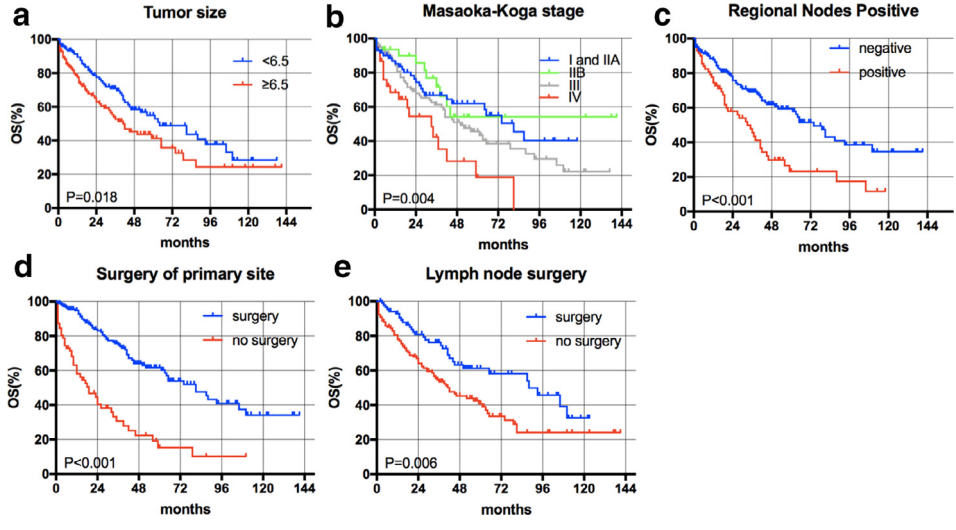

Fig. 2. Kaplan-Meier survival curves of 240 thymic carcinoma patients. (a) Overall survival of patients of tumor size ≥6.5 vs tumor size <6.5. (b) Overall survival of patients with Masaoka-Koga stage IV vs III vs IIB vs I/IIA. (c) Overall survival of patients with regional nodes positive vs negative. (d) Overall survival of patients with no surgery of primary site vs those with surgery. (e) Overall survival of patients with no surgery of lymph node vs those with surgery.

Table 5
Multivariate analysis of thymic carcinoma patients.

Variable	HR	95% CI	*P* value
Tumor size, median (≥6.5 vs <6.5)	1.266	0.865-1.855	0.225
Masaoka-Koga stage (stage IV vs III vs IIB vs I/IIA)	1.128	0.922-1.379	0.243
Regional nodes positive (positive vs negative)	1.604	1.037-2.479	0.034
Surgery of primary site (No vs Yes)	2.539	1.497-4.307	0.001
Lymph node surgery (No vs Yes)	1.207	0.709-2.053	0.488

HR, hazard ratio; CI, confidence interval.

Discussion

With the growing number of patients of thymic tumor, TC and TNET, as the major malignant tumors of the thymus, are also with an increasing incidence. Hence, it is essential to obtain more information about clinic characteristics of TC and TNET. But few studies with large cohort have comprehensively evaluated the clinicopathologic features of TC and TNET patients. In our population-based investigation of 240 TC patients and 122 TNET patients, we retrospectively investigated the impacts of both clinical and pathologic factors on patients' survival. We found that histologic type, regional nodes positive, and surgery of primary site were able to serve as independent prognostic factors for OS of the entire cohort of TC and TNET patients. Besides, we demonstrated that regional nodes positive, surgery of primary site were independent survival predictors for TC patients, which suggests a favorable treatment modality for TC and TNET patients. To our knowledge, our study is the first SEER analysis with an updated patient cohort which shows the lymph node surgery is a survival predictor for TC patients.

Lymph node involvement is a not uncommon event for TC and TNET patients.[12] However, data reporting whether the regional lymph node positive has an impact on patients' OS are available in few researches. Kondo et al demonstrated that thymoma and TC patients with node metastasis had worse survival rate.[13] Weksler et al used the SEER database to investigate the impact of positive nodal metastases in 229 TC and TNET patients.[14] Both of the 2 findings were in accordance with ours that the positive lymph nodes were independently associated with TC and TNET patients' survival. Besides, our study is an updated research on SEER database with up to a total of 362 patients, which is more convincing than previous studies. This relationship between lymph node involvement and patients' OS can give a practical importance of sampling and dissection of patients' lymph node. And the lymph node map based on this relationship is able to give a recommendation of choosing sampling or dissection of the lymph node to TC and TNET patients with different disease conditions.[15,16] In addition, Park et al reported that patients with lymph node metastases were more likely to have adjacent organ extension,[9] which confirms our investigation. However, due to lack of information about the location of regional lymph nodes in SEER database, it is difficult for us to predict patients' survival according to the location of sentinel lymph nodes.

Surgery of thymus is considered as the major treatment modality for TC and TNET patients. In our research, the surgery of primary site was able to obviously improve the survival rate of both TC and TNET patients. Fu et al made a retrospective analysis of 329 TC patients and concluded that complete resection was preferred as the primary treatment for TC.[17] However, our study included more histology types than theirs including basaloid carcinoma, mucoepidermoid carcinoma, lymphoepithelial carcinoma, clear cell carcinoma, sarcomatoid carcinoma, and adenocarcinomas, which is more representative. Besides, their studies are limited to the race of Chinese. Ruffini et al conducted a cohort study of the European Society of Thoracic Surgeons and indicated that survival of 229 TC patients was better after complete surgical resection than those not surgery.[5] Nevertheless, Ruffini's research did not include TNET that is rarer than TC but more invasive and less studied. Above all, our study showed a more convincing relationship that patients with TC or TNET had a better OS after undertaking surgery of primary site. Therefore, TC or TNET patients should make a choice of surgical management of thymus whenever possible.

For the cohort of TC in our analysis, we additionally found that lymph node surgery could be a predictor of TC patients' survival. Up to date, our study is the first one to find lymph node surgery is positively associated with OS of TC patient. This is in support of the study of Park's team in which they retrospectively reviewed 37 patients and found outcomes of patients with lymph node dissection was better than those not.[9] For TC patients who have nodal metastases, lymph node dissection has gradually become an essential part of surgical procedures. But there has been no study proving that lymph node dissection could really be a beneficial factor for those patients. Our result can provide a guideline for clinical surgical management for TC patients with lymph node metastasis.

It needs to mention that our analysis found there was no difference between Masaoka-Koga stage and patients' OS in multivariate analysis, which indicates that Masaoka-Koga stage maybe not enough for predicting TC and TNET patients' survival. This can be the result of lacking in including the information of lymph node status in the final staging and just classified lymph node involvement as stage IVB, leading to the inaccurate prediction of patients' survival and likely discouraging surgeons from considering lymph node surgery for patients with TC or TNET.[18] Except for that, we found that there is no correlation between other clinicopathologic features and patients' survival. Interestingly, we found that neither radiation therapy nor chemotherapy could serve as an independent predictor for survival outcome of TC and TNET patients, which may be the reason that the side effects of radiation therapy and chemotherapy overweighed the therapeutic effects. Further studies with a large cohort were needed to further verify these relations.

There are some limitations in our study. First, because of the lack of patient sample of TNET, we are unable to conduct a convincing survival analysis that is statistically significant for TNET cohort. Second, this study is a retrospective analysis of TC and TNET with the unbalanced control group. Third, some clinicopathologic features in the SEER database are not available, which limits us for further investigation. Despite the limitations, our research can provide important insights on the clinicopathologic factors and survival outcome of TC and TNET patients. Besides, the limitations can be solved by constructing an international multi-institutional system of thymic tumor to get more useful evidence and conducting a prospective study of the large cohort in the future.

In conclusion, this SEER analysis unearths clinicopathologic factors that can be critically important for surgical management and survival outcomes of TC and TNET. The statistically significant features include regional nodes positive and surgery of primary site for the entire cohort of TC and TNET. With these factors, clinicians are able to more precisely evaluate patients' condition and make a better choice for treatment modality to improve OS of TC and TNET patients.

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