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Prognostic Value of Preoperative Serum Carcinoembryonic Antigen for Overall Survival and Recurrence-Free Survival in Resectable Thymic Epithelial Tumors

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Abstract

Introduction: Tumor markers have been shown to be closely related to the long-term survival of patients with cancer and the recurrence of various malignant tumors. However, their role in thymic epithelial tumors (TETs) remains to be elucidated. We aimed to investigate whether the preoperative tumor biomarkers carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) could serve as independent predictors of postoperative prognosis in patients with TETs. **Materials and Methods:** We retrospectively included a total of 111 patients with TETs who underwent thymectomy at our hospital. Cox regression analysis was used to evaluate the statistical significance of CEA and NSE as independent predictors of overall survival (OS) and recurrence-free survival (RFS). Kaplan–Meier curves were used to present the results of our survival analyses. **Results:** Cox regression analysis showed that T stage, World Health Organization (WHO) histologic type, tumor size, and CEA levels served as independent prognostic factors for OS ($P < .05$). Whereas for RFS, multivariate analysis showed that only T stage, WHO histologic type, and drinking history were independently associated with it ($P < .05$). **Conclusion:** Our study found that preoperative serum CEA levels and tumor size may be strong predictors of postoperative OS in patients with TETs.

Keywords

thymic epithelial tumor, tumor biomarker, carcinoembryonic antigen, overall survival, recurrence-free survival, prognosis

Abbreviations

CIs, confidence intervals; CEA, carcinoembryonic antigen; ESTS, European Society of Thoracic Surgeons; NSE, neuron-specific enolase; OS, overall survival; RFS, recurrence-free survival; TETs, thymic epithelial tumors; WHO, World Health Organization

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Introduction

Thymic epithelial tumors (TETs), including thymoma, thymic carcinoma, and thymic neuroendocrine neoplasms, are rare tumors that mainly occur in the mediastinum.[1,2] Their incidence in Europe is only 1.7/million people per year, and the data registered in the United States is 0.13/100000 person-years.[3,4] According to the World Health Organization (WHO) histological classification, TETs can be divided into A, AB, B1-3, and other categories.[5] The current standard treatment for TETs is surgery.[6–9] A meta-analysis by Tateishi et al showed that postoperative adjuvant therapy can improve the overall survival (OS) of Masaoka stage II/III patients,[10] but the role of postoperative adjuvant therapy remains to be confirmed by prospective studies. A variety of clinical factors have been confirmed to be related to prognosis including tumor size,[11] T stage,[12] Masaoka

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stage,[13] WHO histologic types,[14] and tumor vascular invasion.[15] However, molecular biomarkers with prognostic value have not yet been identified or confirmed for this type of malignancy.

Since carcinoembryonic antigen (CEA) was discovered in intestinal adenocarcinoma in 1965,[16] it has gradually become an important diagnostic and prognostic indicator for patients with colorectal cancer. With the deepening of research, serum CEA levels have been found to increase in various cancers,[17] including pancreatic cancer, colorectal cancer, lung cancer,[18] gastric cancer,[19] and others. Meanwhile, CEA has been established as a prognostic marker in a variety of cancers, including colorectal cancer,[20] lung cancer,[21] and breast cancer.[22] However, its prognostic value in TETs has not yet been fully studied.

In a similar fashion, neuron-specific enolase (NSE) is often expressed at high levels in the brain and is elevated in some tumors of neuroendocrine cell origin, and it can be used as a prognostic biomarker for small cell lung cancer,[23] non-small cell lung cancer,[24] esophageal neuroendocrine cell carcinoma,[25] prostate cancer,[26] and other diseases. Some studies have shown that the expression of NSE may also be abnormal in TETs,[27] but its relationship with OS and recurrence-free survival (RFS) in this type of tumors remains to be elucidated.

Although a variety of tumor markers have prognostic roles in various tumors, given the rarity of TETs, research on their specific markers has not attracted a lot of interest from researchers. Therefore, this study explored the prognostic value of tumor markers CEA and NSE in these rare tumors by collecting patients' data for more than 10 years.

Materials and Methods

Study Design

This study was approved by the ethics review board of the Sun Yat-sen University Cancer Center (No. B2020-353-01), and we obtained the subject's informed consent exemption, the original dataset was uploaded to the Sun Yat-sen University Cancer Center database (RDDA2021002090). Our study has de-identified all patient details.

We retrospectively reviewed the medical records of patients with TETs who underwent thymoma resection at the Sun Yat-sen University Cancer Center between May 2004 and August 2015. The inclusion criteria were as follows: (1) age > 18 years, (2) presence of histopathologically confirmed TETs, including thymomas and thymic carcinomas (TCs), (3) complete surgical resection (R0, no residual disease), and (4) complete relevant laboratory tests (serum tumor marker examination) within 7 days before surgery. Patients were excluded if (1) they were administered radiotherapy or chemotherapy prior to surgery, before and after surgery, or in an unknown sequence of treatment with surgery, (2) they were followed-up for less than 5 years, (3) they had more than 1 malignancy or a history of other malignancies, (4) they had a postoperative survival time of less than 3 months, (5) they only underwent thymoma biopsy, (6) they were treated by cryoablation, and (7) or their follow-up information is incomplete (Figure 1).

Data Collection

Data were collected on the following clinical variables: CEA (ng/mL) and NSE (ng/mL) levels (recorded within 1 week before surgery), sex, age, smoking history, drinking history (alcohol consumption per day, specific alcohol consumption is not limited and described), family history of tumors, tumor size, myasthenia gravis symptoms, T stage, histological subtype, Masaoka stage, comorbidities (hypertension and/or diabetes), tumor capsule status, and other clinical information.

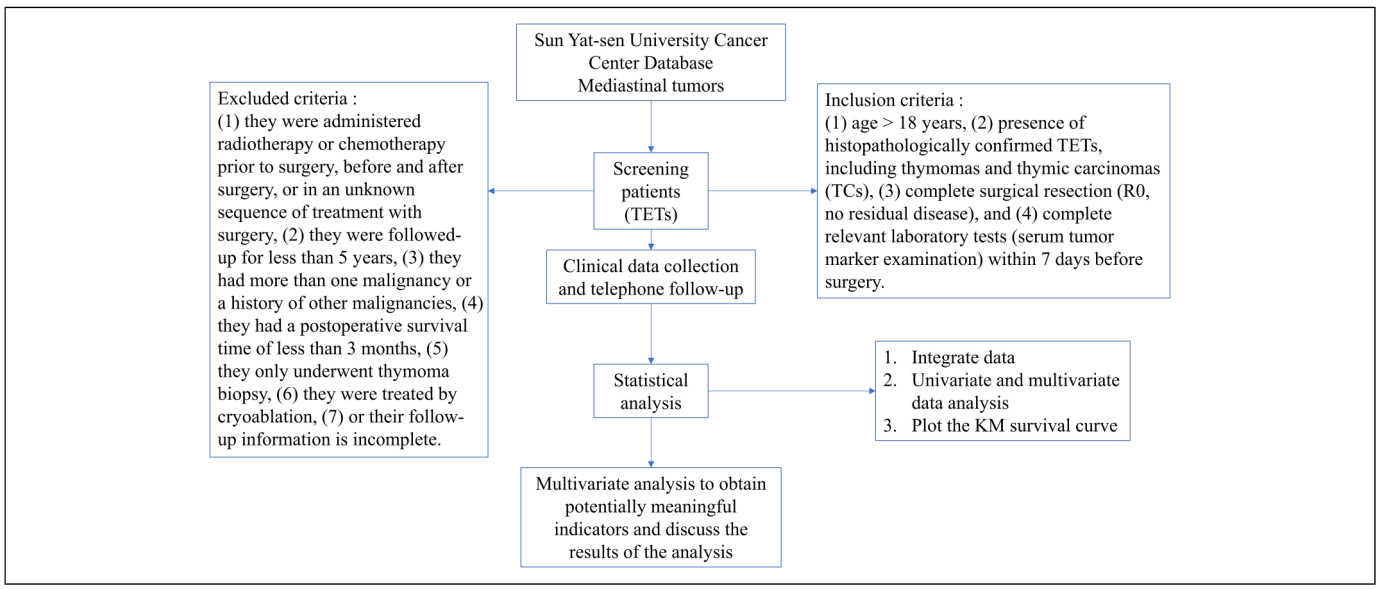

Figure 1. Flowchart.

Follow-up

The follow-up strategy was specific for the first 2 years, with follow-up every 6 to 12 months for all postoperative patients, every 12 months for the third to fifth years, and then every year. The follow-up examination items were chest computed tomography plain scan and hematological examination (eg, blood routine, biochemical routine, tumor markers, etc.). The last follow-up encounter was in August 2020. The primary endpoints of this study were OS and RFS.

Data Analysis

In this study, the X-Tile was used to obtain the best cut-off values for CEA and NSE (http://www.tissuearray.org/rimmlab). Statistical analyses were performed using SPSS (version 25.0; IBM) and R software (version 4.0.3; https://www.r-project.org/). Univariate and multivariate regression analyses were performed using Cox proportional hazards regression models in SPSS and relying on hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the risk value for each factor. Survival curves were drawn using the Kaplan–Meier method, and the log-rank test was used to compare the survival and recurrence of patients in different groups. All tests were two-way, with a significance level of $P < .05$.

Results

Patient Characteristics

A total of 111 patients with TETs were included in this study, including 58 men and 53 women, with an average age of 50.72 ± 12.09 years and an average tumor size of 6.63 ± 3.15 cm. Table 1 summarizes the patients' WHO histologic types, T staging, smoking history, drinking history, myasthenia gravis, and other relevant clinical information.

Table 1. Basic Demographic Data, Disease Specific Characteristics (n = 111).

Characteristic	N	%
Gender		
Male	58	52.3
Female	53	47.7
Age (years)		
≤60	87	78.4
>60	24	21.6
Smoking history		
Never	84	75.7
Ever	27	24.3
Drinking history		
No	96	86.5
Yes	15	13.5
Family history of tumor		
No	92	82.9
Yes	19	17.1
Tumor size (cm)		
≤6	63	56.8
>6	48	43.2
pT stage		
T1	88	79.3
T2-3	23	20.7
Masaoka stage		
I	54	48.6
II-III	57	51.4
WHO histologic type		
A-B1	67	60.4
B2-B3	35	31.5
C	9	8.1
Underlying diseases		
No	86	77.5
Yes	25	22.5
Myasthenia gravis		
No	104	93.7
Yes	7	6.3
Tumor capsule status		
Complete	66	59.5
Incomplete	45	40.5
CEA		
≤ 2.3	71	64.0
> 2.3	40	36.0
NSE		
≤ 12.5	55	49.5
> 12.5	56	50.5

Abbreviations: CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; pT stage, pathological T stage; WHO, World Health Organization.

Optimal cut-off Values for Preoperative CEA and NSE

Taking OS as the endpoint, the optimal cut-off value for preoperative CEA was 2.3 ($P < .01$) and the optimal cut-off value for NSE was 12.5 ($P = 0.592$) determined using X-Tile software. For further analysis, patients were divided into a high or low CEA group (> 2.3 or ≤ 2.3, respectively) and a high or low NSE group (> 12.5 or ≤ 12.5, respectively).

X`

Association of CEA and NSE With Survival Outcomes

Using OS and RFS as endpoints, we compared the OS (Figure 2C; $P < .05$) and RFS (Figure 4C; $P > .05$) of patients assigned to the low-and high-level CEA groups.

Univariate and Multivariate Survival Analyses Based on OS

Univariate Cox regression analysis showed that 7 variables were significantly associated with OS: WHO histologic types, T stage, Masaoka stage, drinking history, tumor size, CEA levels, and tumor capsule status (Table 2). Four parameters were defined as independent prognostic factors for OS by multivariate Cox regression analysis: WHO histologic types (A-B1 vs B2-B3, HR = 0.456, 95% CI [0.122-1.706]; A-B1 vs C, HR = 6.938, 95% CI [1.814-26.538]), T stage (HR = 12.418, 95% CI [2.610-59.085]), tumor size (HR = 4.995, 95% CI [1.410-17.697]), and CEA (HR = 5.421, 95% CI [1.344-21.858]) (Table 2) and finally the Kaplan-Meier(KM) survival curve was used to show all the significant Cox factors (Figures 2 and 3).

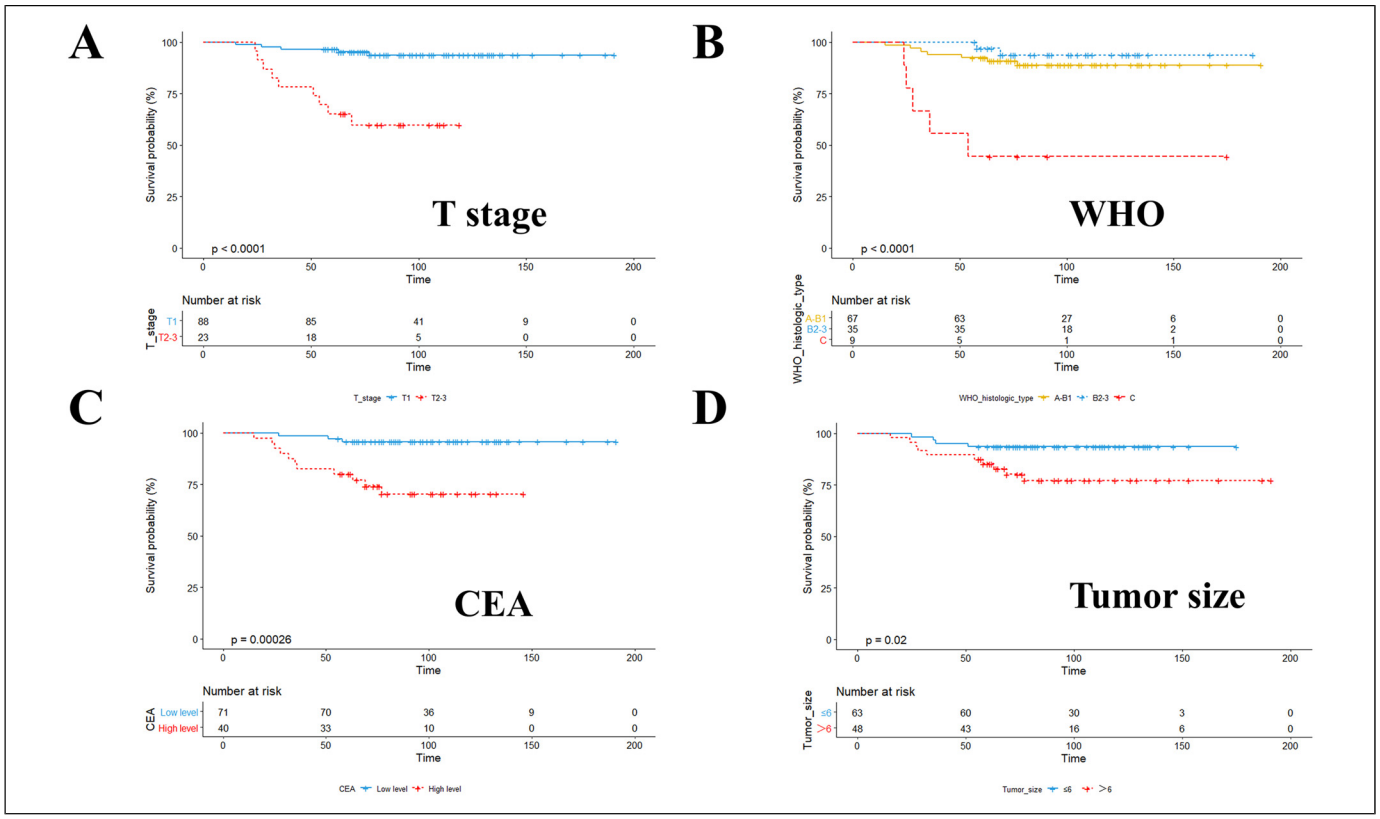

Figure 2. KM analysis of T stage (A), WHO (B), CEA (C), and tumor size (D) based on overall survival (OS).
Abbreviations: CEA, carcinoembryonic antigen; WHO, World Health Organization.

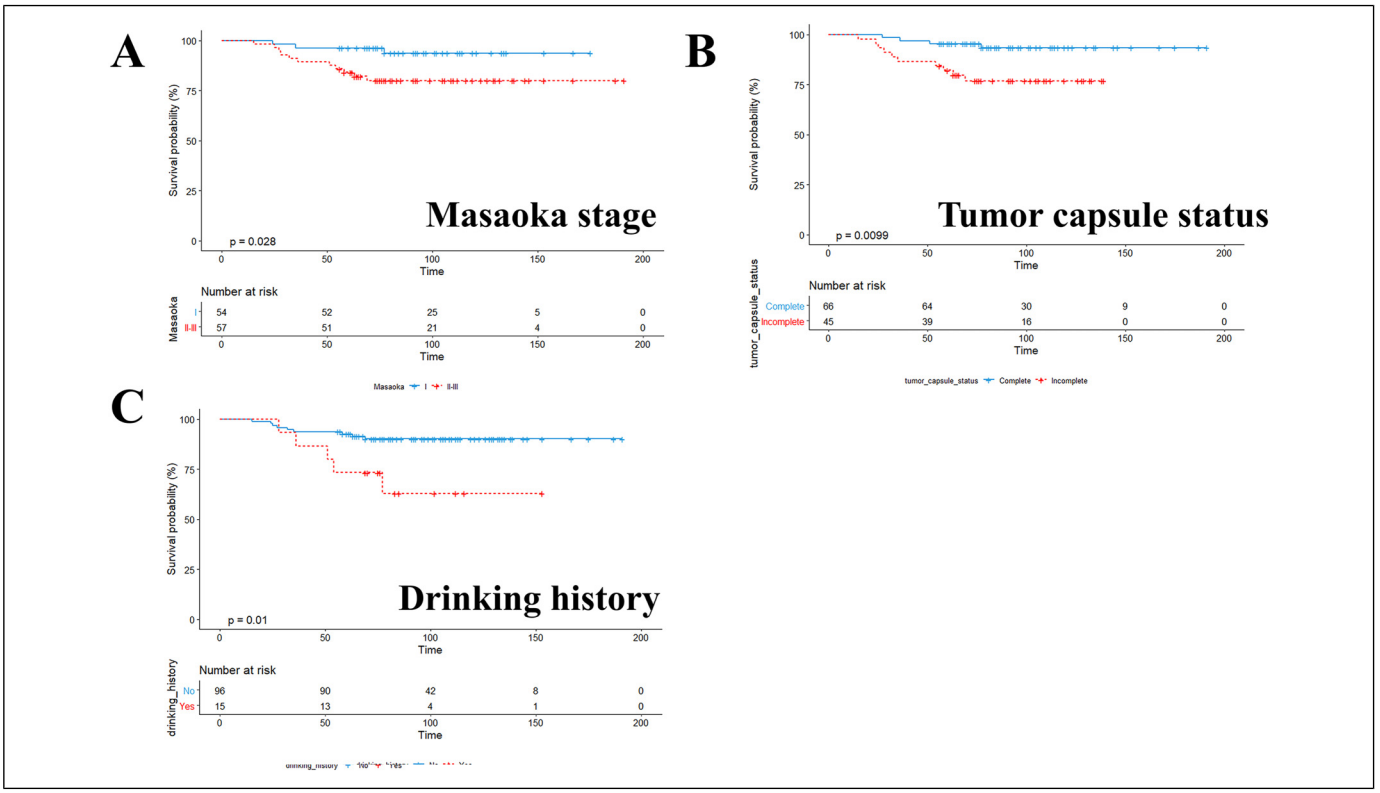

Figure 3. KM analysis of Masaoka stage (A), tumor capsule status (B), and drinking history (C) based on overall survival (OS).

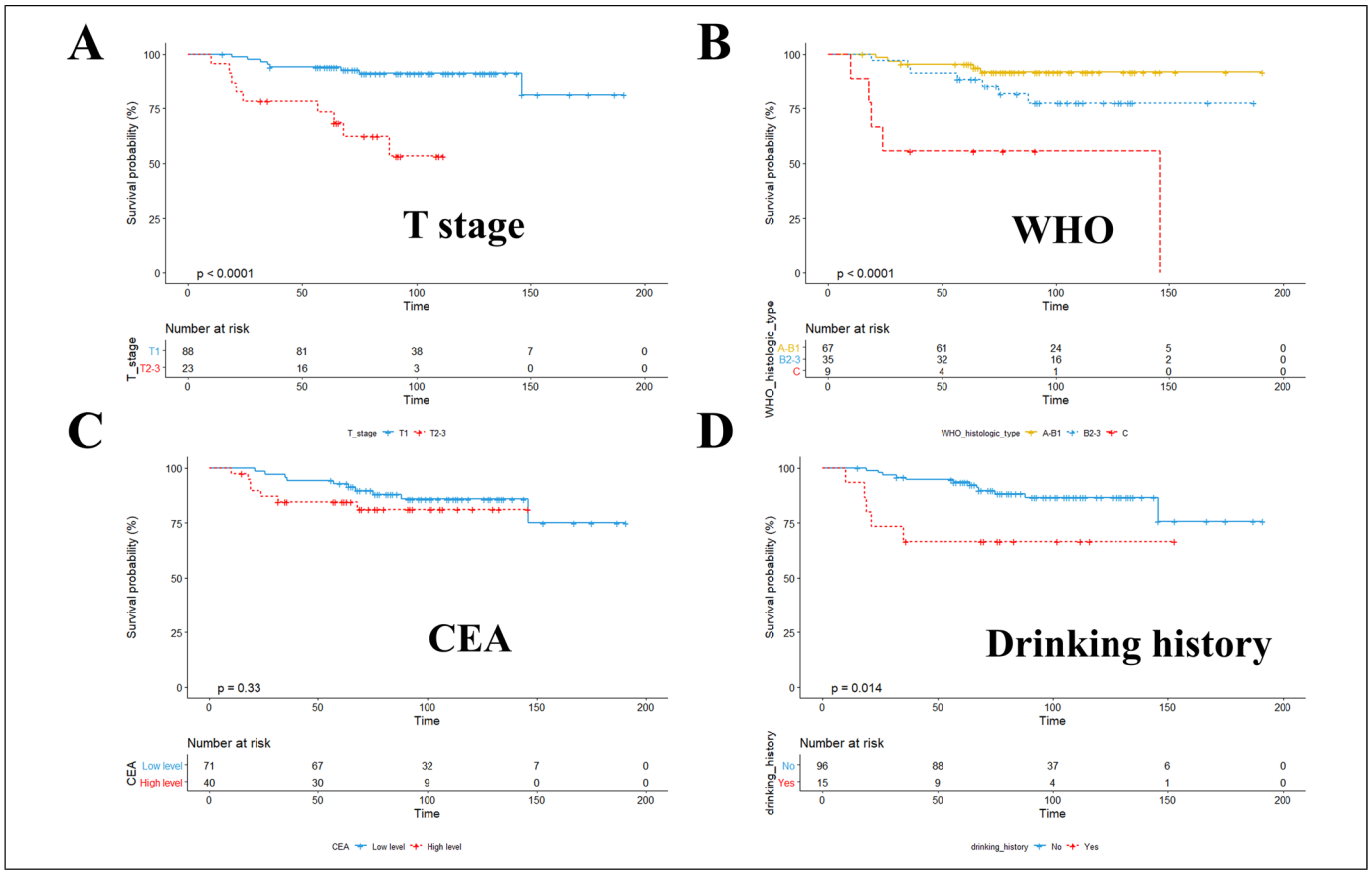

Figure 4. KM analysis of T stage (A), WHO (B), CEA(C), and drinking history (D) based on relapse-free survival (RFS).

Univariate and Multivariate Survival Analysis Based on RFS

In the univariate analysis, 5 variables were significantly associated with RFS: WHO histologic types, T stage, drinking history, Masaoka stage, and tumor capsule status (Table 3). However, multivariate Cox regression analysis showed that 4 parameters were defined as independent prognostic factors for RFS: WHO histologic types (A-B1 vs B2-B3, HR = 1.669, 95% CI [.485-5.743]; A-B1 vs C, HR = 6.431, 95% CI [1.675-24.693]), T stage (HR = 4.722, 95% CI [1.580-14.114]), drinking history (HR = 4.227, 95% CI [1.431-12.484]) and NSE(HR = .305, 95% CI [.105–.887]) (Table 3) and finally the KM survival curve was used to show all the significant Cox factors (Figures 4 and 5).

Discussion

This study confirmed the predictive effect of the tumor marker CEA on OS of patients with TETs through a rigorous Cox regression analysis. Interestingly, we also found that tumor size was an independent predictive factor of OS, and drinking history was an independent predictive factor of postoperative recurrence. However, NSE did not show any prognostic power for patients in our cohort.

It is well known that T stage,[12] WHO histologic types,[28] and Masaoka stage[13] have significant effects on the survival of patients with TETs and the recurrence of these tumors, which was also reflected in our study. In addition, the Masaoka-Koga staging system is widely accepted for the staging of TETs. However, Yanagiya et al found in their cohort that WHO histological type and age were important prognostic factors without including the Masaoka-Koga staging system.[29] Similarly, Fukui et al showed that a new classification system had a better prognostic effect than Masaoka-Koga staging for TETs.[30,31] Combined with our findings, T staging may be more accurate in prognostic prediction than Masaoka-Koga staging. This needs to be validated in a larger sample size database. Eriksson et al showed that drinking history may be a risk factor for thymic tumors,[32] but due to the rarity of TETs, few studies have investigated the relationship between drinking history and prognosis. Therefore, this may be an interesting research direction, which needs to be further confirmed by studies with larger sample sizes.

Whether tumor size affects the prognosis of TETs remains controversial. Okumura et al analyzed the clinical information of 2083 postoperative patients with thymomas by integrating multiinstitutional data and concluded that tumor size has an important impact on prognosis.[33] In addition, Fukui et al found that patients with tumors larger than 4 cm had worse RFS results, and this relationship was found even in patients

Table 2. Univariate and Multivariate Analysis Results in Thymic Epithelial Tumor (TET) Based on Overall Survival (OS) (n = 111).

Variable	Univariate analysis	Multivariate analysis		
	P	HR	95% CI	*P*
Gender	.353			
Male versus female				
Age(years)	.525			
≤60 versus >60				
Smoking history	.746			
Never versus ever				
drinking history	.017			.490
No versus Yes				
Family history of tumor	.277			
No versus Yes				
Tumor size	.030	Reference		
≤6 versus >6		4.995	1.410–17.697	.013
pT stage	.000	Reference		
T1 versus T2-3		12.418	2.610–59.085	.002
Masaoka stage	.041			
I versus II-III				.076
WHO histologic type	.000	Reference		
A-B1 versus B2-B3		.100	.015–.683	
A-B1 versus C		.966	.196–4.755	.026
Underlying diseases	.510			
No versus Yes				
Myasthenia gravis,	.506			
No versus Yes				
Tumor capsule status	.017			
Complete versus Incomplete				.692
CEA	.002	Reference		
Low level versus high level		5.421	1.344–21.858	.018
NSE	.592			
Low level versus high level				.536

Abbreviations: CI, confidence interval; CEA, carcinoembryonic antigen; HR, hazard ratio; NSE, neuron-specific enolase; pT stage, pathological T stage; WHO, World Health Organization.

with stage I disease.[9] There are other related studies supporting this conclusion.[34–36] However, Nicholson et al analyzed more than 8000 patients and found that tumor size did not have a prognostic significance in thymic malignancies.[37] Similarly, Tseng et al also found that tumor size did not improve the prognostic predictive power of the TNM staging.[38] Using the data of more than 2000 patients in the European Society of Thoracic Surgeons (ESTS) database, Ruffini et al found that tumor size did not predict OS and RFS but could predict incomplete resection and recurrence risk.[39] Finally, in this study, our data support an independent association between tumor size and OS after R0 resection in patients with TETs.

As a tumor marker first discovered in intestinal adenocarcinoma, CEA has shown a strong prognostic role in lung cancer, breast cancer, colorectal cancer, and other tumors.[20–22] In TETs, Savino et al found that CEA may play a role as a thymic epithelial cell growth factor,[40] and Tomita et al found that the expression of CEA in thymoma was correlated with clinical stage.[41] Additionally, Tomita et al found that CEA is highly expressed in thymic carcinomas, possibly indicating the aggressiveness of these carcinomas.[42] Due to the rarity of TETs, the sample size of previous studies was extremely limited. Based on previous research and considering that CEA may affect the malignant potential and invasiveness of TETs, the team further explored the value of CEA as a tumor biomarker in the prognosis prediction of patients with these tumors. Although CEA was not significantly associated with postoperative RFS, our team first found that CEA was an independent predictor of postoperative R0 resection of TETs.

Whether for OS or RFS, NSE did not show statistical significance in univariate analysis in this study. However, in multivariate analysis with RFS as the end point of the study, NSE showed a certain prognostic value, but we think it cannot be used as one of the conclusions of this study. First, NSE did not show a prognostic value in univariate analysis, and its reference value in multivariate analysis was limited in this study. Second, due to the small number of NSE patients in this study, the results may have certain errors. Third, as a traditional oncological marker, NSE mainly reflects the diagnosis and differential diagnosis of meningitis, cerebral infarction, cerebral hemorrhage, islet cell tumor, melanoma, neuroblastoma, seminoma, small cell lung cancer, and other diseases, from a clinical point of view, it is not closely related to epithelial tumors.

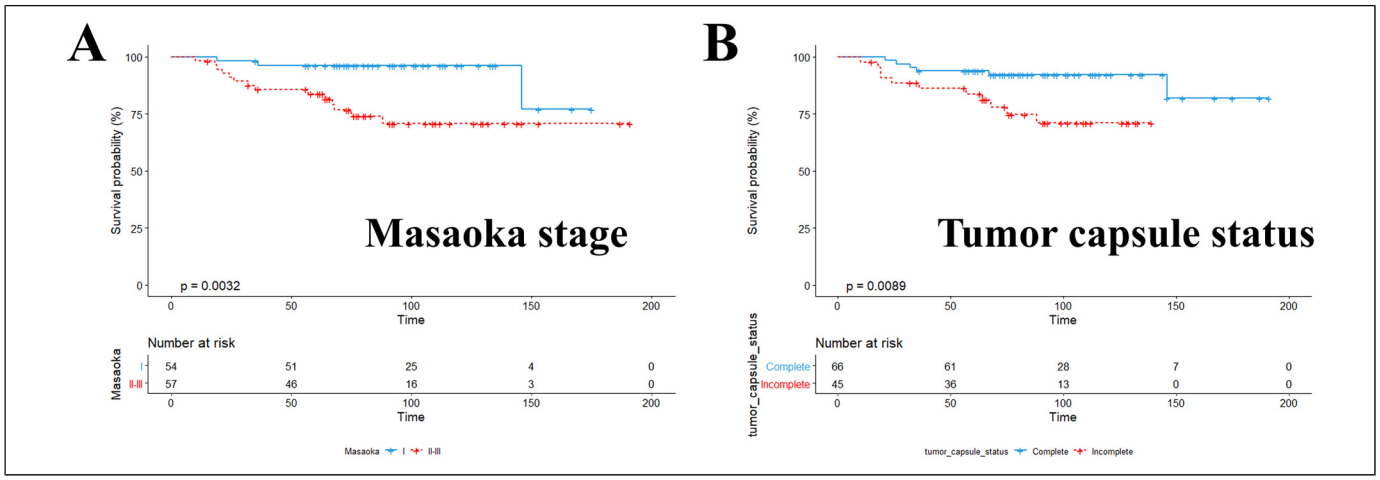

Figure 5. KM analysis of Masaoka (A) and tumor capsule status (B) based on relapse-free survival (RFS).

Table 3. Univariate and Multivariate Analysis Results in Thymic Epithelial Tumor (TET) Based on Relapse-Free Survival (RFS) (n = 111)

Variable	Univariate analysis	Multivariate analysis		
	P	HR	95% CI	*P*
Gender	.851			
Male versus female				
Age(years)	.351			
≤60 versus >60				
Smoking history	.990			
Never versus ever				
drinking history	.021	Reference		
No versus Yes		4.691	1.523–14.452	.007
Family history of tumor	.933			
No versus Yes				
Tumor size	.060			
≤6 versus >6				
pT stage	.000	Reference		
T1 versus T2-3		6.090	1.973–18.801	.002
Masaoka stage	.008			
I versus II-III				.113
WHO histologic type	.001	Reference		
A-B1 versus B2-B3		2.005	.596–6.741	
A-B1 versus C		6.728	1.712–26.440	.022
Underlying diseases	.530			
No versus Yes				
Myasthenia gravis	.463			
No versus Yes				
Tumor capsule status	.015			
Complete versus Incomplete				.537
CEA	.338			
Low level versus high level				.321
NSE	.200	Reference		
Low level versus high level		.305	.105–.887	.029

Abbreviations: CI, confidence interval; CEA, carcinoembryonic antigen; HR, hazard ratio; NSE, neuron-specific enolase; pT stage, pathological T stage; WHO, World Health Organization.

Fourth, it is well known that NSE is a risk factor in many benign and malignant diseases, and in our study, it is a protective factor, which violates the clinical common sense. In summary, we believe that the statistical significance of NSE in RFS should be held with skepticism. It is likely that this is just an accidental result and must be confirmed by a larger sample size or multiple centers to further determine its relationship with prognosis.

Although NSE did not show sufficient prognostic value in this study, it is important to consider the fact that this study mainly included thymoma and thymic carcinoma and did not consider other related thymic tumor types. Whereas NSE is mainly generated from neuroendocrine cells, and it can still show potential significance in future studies on thymic neuroendocrine neoplasms.

There is no doubt that the tumor capsule status is an important prognostic factor, but the prognostic value was not reflected in this study. The reason may be that, first, the tumor status in this study was relatively early, and all patients underwent complete surgical resection, so resection results are consistent regardless of tumor capsule status. Second, the data volume of this study is small, which may cause statistical errors.

This study had some limitations. First, this was a retrospective study conducted at a single center. In the future, multicenter, large sample studies are needed to confirm our results. Second, due to the extremely low incidence of thymic neuroendocrine neoplasms, this study did not include such patients, which may have affected the predictive effect of NSE on prognosis. At last, the dynamic changes in postoperative CEA and NSE levels were not included in the research scope, and their values need to be further explored.

Conclusion

Through retrospective analysis of more than 10 years of patient data, we found that preoperative serum CEA levels, WHO histologic types, and tumor size can independently predict OS in patients with TETs after R0 resection. On the other hand, patient drinking history and Masaoka stage were independently associated with postoperative RFS. Finally, the preoperative CEA level appears to be a powerful biomarker for the postoperative prognosis of TETs.

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Author's Contribution

Conception and design of the study: MGW and HYY. Provision of study materials or patients: MGW. Acquisition of data: HYY and LSH. Data analysis: HYY and LX. Interpretation of data: MGW and HYY. HYY drafted the manuscript alone. MGW, HY, LSH, LX, and HYY substantially revised the manuscript. All authors have read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of Sun Yat-Sen University Cancer Center (B2020-353-01) and complied with the Declaration of Helsinki. Data were recorded at the Sun Yat-sen University Cancer Center under the record number: RDDA2021002090. At the same time, this study has obtained the exemption of informed consent application from the Ethics Committee of Sun Yat-sen University Cancer Center.

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