Aus der Klinik für Thoraxchirurgie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Risikofaktoren für Lymphknotenmetastasen bei epithelialen Thymustumoren und prognostische Bedeutung von Lymphknotendissektion bei Thymuskarzinomen und neuroendokrinen Tumoren des Thymus.

Risk factors correlated to lymph node metastasis in thymic epithelial tumors and the prognostic significance of lymph node dissection for thymic carcinomas and thymic neuroendocrine tumors.

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I. Contents

II. Abstract German

Thymustumore werden im Allgemeinen als wenig maligne Tumore, mit geringer Wahrscheinlichkeit einer Lymphknotenmetastasierung (LNM) angesehen. Diese Studie zielt darauf ab, die Faktoren, die mit einer möglichen LNM bei Thymusepithelialtumoren (TETs) stehen zusammenhängen , zu analysieren und den Einfluss der Lymphknotendissektionen (LND) bei pathologisch gesicherten Hochrisikotypen (Thymuskarzinomen, TCs und Nuroendokrinen Tumoren des Thymus, TNETs) auf die Prognose zu untersuchen.

Diese Studie analysierte systematisch die klinisch-pathologischen Informationen von Pat. mit Thymus Malignomen in der Surveillance, Epidemiology, and End Results Datenbank. Zunächst wurde die Inzidenz von diesen Tumoren zusammengefasst, dann wurden die relevanten klinisch-pathologischen Faktoren von Pat. mit Thymomen (A-B3), Thymuskarzinomen (TCs) und Thymus neuroendokrinen Tumoren (TNETs), die operiert und bei denen Lymphknoten exsipiert wurde, gesammelt. Außerdem wurden unabhängig von der LNM in Beziehung stehende Variablen mittels Logistik-Regression bestimmt. Schließlich wurden Pat., bei denen die diagnostizierten TCs und TNETs chirurgisch behandelt wurden, gesammelt und die Prognose bei unterschiedlichem Lymphknotenstatus analysiert. Die Cox-Analyse wurde verwendet, um die Variablen im Zusammenhang mit der Prognose des Gesamtüberlebens (OS) und des krebsspezifischen Überlebens (CSS) zu analysieren. Propensity Score Matching (PSM) wurde für die Subgruppenanalyse von Pat. mit unterschiedlichem Lymphknotenstatus verwendet.

Insgesamt wurden 5934 Pat. mit pathologisch gesicherten Thymus-Malignomen eingeschlossen am häufigsten waren Thzmome gefolgt von TCs und TNETS. Insgesamt wurden 1048 TETs Pat. operiert und erhielten eine LND. Der Gesamtanteil der TETs Pat.. mit LNM betrug 1,1%. Die LNM-Rate bei Thymomen, TCs und TNETs betrug 6,8%, 30,2% bzw. 61,1%. Histologietyp sowie T-Stadium waren unabhängige Faktoren, die mit LNM in der multivariaten Logistikanalyse korrelierten. Es gab 812 Pat. mit TCs und TNETs, die sich einer chirurgischen Behandlung unterzogen hatten, darunter waren 76,7% TCs und 11,6% TNETs. Etwa 398 Pat. erhielten eine LND und von diesen hatten 36,2% eine LNM. In der multivariaten Cox-Analyse von OS und CSS war die Prognose von LND- Pat. signifikant schlechter als die von N0 Pat.. Der

prognostische Unterschied zwischen N+ und LND- Pat. war nicht statistisch signifikant. Nach PSM ist in der univariaten Analyse und in der multivariaten Subgruppenanalyse von OS und CSS das Überleben von N0 Pat. immer noch besser als das von LND- und N+ Gruppen, jedoch zeigte der Prognoseunterschied zwischen LND- und N+ Pat. keine statistische Signifikanz in der multivariaten Analyse (P >0.05).

Lymphknotenbeteiligung ist bei TETs nicht ungewöhnlich. Hauptfaktoren im Zusammenhang mit LNM in TETs sind der Histologietyp sowie das T-Stadium. LND in TCs und TNETs kann dabei helfen einen genaueren Lymphknotenstatus, sowie die Langzeitprognose von Patienten besser zu beurteilen.

III. Abstract English

Thymic tumors are generally considered with low degree of malignancy, and the probability of lymph node metastasis (LNM) is low. This study aims to further comprehensively analyze the related factors of LNM in thymic epithelial tumors (TETs) and investigate the impact of lymph node dissection (LND) in high-risk pathological types (thymic carcinomas, TCs and thymic neuroendocrine tumors, TNETs) on the prognosis.

The present research systematically analyzed the clinicopathological information of patients with thymic malignancies in the Surveillance, Epidemiology, and End Results (SEER) database. The overall incidence of tumors was firstly analyzed. Furtherly, the relevant clinicopathological factors of thymoma (A-B3), thymic carcinomas (TCs), and thymic neuroendocrine tumors (TNETs) who had surgical treatment and underwent ≥1 lymph node examined were collected, and variables independently related to LNM were determined via Logistics regression. Finally, the patients diagnosed TCs and TNETs undergoing operative treatment were collected, and the differences in the prognosis of patients with different lymph node status were analyzed. Univariate and multivariate Cox analysis was used to analyze the variables related to the prognosis of overall survival (OS) and cancer-specific survival (CSS). Propensity score matching (PSM) was used for subgroup analysis of patients with different lymph node status.

An overall of 5934 patients was involved with pathologically confirmed thymic malignancies (1975-2016), of which the highest proportion was thymoma (63.3%), followed by TCs (18.5%) and TNETs (5.6%). A total of 1048 TETs individuals underwent surgery and LND. The overall proportion of TETs patients with LNM was 19.1%. The rate of LNM in thymoma, TCs, and TNETs was 6.8%, 30.2%, and 61.1%, respectively. Histology type and T stage were independent factors correlated with LNM in the multivariate Logistics analysis. There were 812 patients with TCs and TNETs underwent surgical treatment, including 76.7% cases of TCs and 11.6% cases of TNETs. About 398 patients underwent LND and 36.2% of patients among them had LNM. In the multivariate Cox analysis of OS and CSS, the prognosis of LND- patients was significantly worse than that of N0 patients (OS: P =0.019; CSS: P =0.012), and the prognostic difference between N+ and LND- patients was not statistically significant (OS: P =0.561, CSS: P =0.759). After PSM, in the univariate analysis and multivariate

subgroup analysis of OS and CSS, the survival of N0 patients is still better than that of LND- and N+ groups, however, the prognosis (OS and CSS) difference between LND- and N+ patients did not show statistical significance in multivariable analysis (P >0.05).

Nodal involvement was not uncommon in TETs. Main factors related to LNM in TETs were histology type and T stage. LND in TCs and TNETs can achieve a clearer lymph node status and assess the long-period prognosis of patients with more accuracy.

1. Introduction

As a significant lymphoid organ that could gradually degenerate with the development of the adaptive immune system in childhood, the thymus is ultimately replaced with fat tissue in adulthood (1). Under certain circumstances, the residual epithelial tissue can develop into tumor. Thymic malignancies are a relatively rare type of thoracic solid tumor, including tumors stemming from epithelial cells, germ cells, lymphocytes, and soft tissues. According to the pathological classification detailed in the 4th edition of the World Health Organization (WHO), a large majority of thymic epithelial tumors (TETs) are categorized as malignant tumors. TETs can be further classified into either thymomas, thymic carcinomas (TCs), or thymic neuroendocrine tumors (TNETs) (2). According to the studies of Surveillance, Epidemiology, and End Results (SEER) database in the United States, it was found out that the incidence of thymoma in North America was 2.14/ 1 million, and the incidence in Asians (3.74/ 1 million) was higher compared to Caucasians (1.89/ 1 million) (3, 4).

With the increase in the number of patients screened with CT as a result of screening programs, the number of patients in whom a thymic tumor was detected has also increased. As revealed by four major lung cancer screening studies, such as ELCAP, COXMOS, Farmingham and Seoul University Hospital in South Korea, the proportion of anterior mediastinum nodular lesions ranged from 0.50 to 0.77%, while the proportion of pathologically diagnosed TETs was in the range of 0.02-0.06%, which was far higher than previously reported for thymic malignancies (5-8). According to the cancer registration data collected, the incidence ratio between males and females was approximately 1.4:1. The incidence of thymoma among children and adolescents is extremely low, and increases gradually with the atrophy of thymus and age (1, 9).

TETs are mostly located in the anterior mediastinum. The exact etiology is still unclear. In previous studies, there was still no characteristic process of precancerous evolution found. The abnormal proliferation of epithelial cells and lymphocytes in tumor tissues are frequently mixed, and the heterogeneity is evident. Up to now, the molecular characteristics exhibited by various subtypes of thymic epithelial tumors remain unknown, and they are still predominantly distinguished by histological cell morphology and immunohistochemical characteristics. According to the classification performed by

Müller Hermelink in 1985, thymoma is classified mainly into several subtypes, including A (medullary thymoma), AB (mixed thymoma), B1 (cortical dominant thymoma), B2 (cortical thymoma), B3 (well differentiated carcinoma) and C (poorly differentiated carcinoma) (10).

According to the 2015 WHO thymoma pathological classification, the biological behavior code of all thymoma types (A-B3) is /3 (malignant). TNETs and TCs are separated from the classification of thymoma as well (2). However, it is widely believed that the malignant degree of type A and AB thymomas is relatively low. Comparatively, B1, B2 and B3 thymomas are more aggressive, with type B3 thymomas in particular, which are most likely to invade other tissues. Besides, they show similar morphological and histological features to TCs. TNETs stem from thymic neuroendocrine cells, as first suggested by Rosai and Higa in 1972 (11). It is known as a rare disease with greater invasiveness and poorer prognosis compared to other NETs (12). It is often associated with ectopic adrenocorticotropic hormone (adrenocorticotropic hormone, ACTH) syndrome. TNETs are characterized by low incidence, strong heterogeneity and relatively poor prognosis. Early-stage thymic tumors often show no obvious clinical signs. with the increase of tumor volume, patients could manifest such symptoms as chest pain, cough or dyspnea due to the local compression or invasion of adjacent tissue structures in the mediastinum. Some patients may even develop systemic autoimmune diseases and paraneoplastic syndrome, such as myasthenia gravis, good syndrome and so on (13).

At present, surgery remains the most preferred treatment of resectable thymic tumors. The 10-year survival rates of patients with stage I, II, III and IV TETs with R0 resection are 80%, 78%, 75% and 42%, respectively (1). Radiotherapy plays an important role in the treatment of the patients with stage III or R1-2 resection, while chemotherapy is still the major choice for the patients with unresectable and metastatic thymomas (14). The goal of surgical treatment is to remove the entire thymus and surrounding structures that may be infiltrated by the tumor to achieve complete resection (R0). The prognosis is largely determined by the tumor stage at diagnosis and the integrity of tumor resection. The first-ever thymectomy was performed in 1911 by Ferdinand Sauerbruch, a German surgeon, through the cervical approach (15). Since then, with the constant

development of surgical techniques and novel instruments, it has gradually evolved from a transsternal approach to multiple or single port thoracoscopic assisted subxiphoid and intercostal approach, and to a da Vinci robot surgery-based resection so far. With such advantages as higher resolution stereoscopic 3D field of vision, higher accuracy and stable operation, robot-assisted surgery is increasingly being used in clinical practice on a daily basis (16).

Lymph node metastases (LNM) are an important prognostic indicator for patients with thymic malignancies (17). In the past, it was generally believed that LNM are rare in TETs, thus lymph node dissection (LND) or sampling was rarely done during surgical resection. However, in recent years, LNM in TETs has garnered greater attention (18). Previously, the commonly used staging system for thymic malignancies is Masaoka-Koga staging system. Patients with LNM are classified as stage IVb, which is the same staging as distant metastases (19). In the 8th edition of the UICC/AJCC stage program, TNM staging is used to distinguish thymic tumors from distant metastases and to identify the corresponding lymph node (LN) region (N1 and N2) in thymic tumors. Presently, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines emphasize the importance of LND in thymectomy, though the importance of lymphadenectomy in TETs has still not received widespread attention in current clinical practice (20, 21).

In order to further study this project, comprehensive research was conducted on the tumor registration database for further determining and analyzing the overall incidence of thymic malignancies and lymph nodes metastases in different pathological types of TETs and to investigate the impact of lymph node resection on long-term survival for the patients with TCs and TNETs.

2. Methodology

2.1 Data sources

Our research presents a retrospective observation investigation carried out according to the declaration of Helsinki and its amendments. The data of patients was acquired from the Surveillance, Epidemiology, and End Results (SEER) program database. It is a large-scale cancer registry database constructed by the National Cancer Institute of the United States containing a variety of comprehensive data of anonymized cancer patients accounting for more than 30% American population (22). Besides, SEER stat software (8.3.5) was applied to gain access to the publicly available database. Researchers consecutively screened and extracted the data of Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying), National Cancer Institute, Surveillance Research Program, released in Apr 2019, based on the Nov 2018 submission. The use of anonymous data complies with the requirements set out by the ethics committees for institutional review.

2.2 Design of studies

The data collected from those patients with histologically confirmed primary malignancies (/3) located in the thymus (Primary Site-labeled: C37.9) was first analyzed to understand the overall state of the database from the earliest documented patient in 1975 to the latest recorded in 2016. In line with the 2015 WHO histology classification codes for tumors of the thymus (International Classification of Diseases for Oncology, 3rd Edition, ICD-O-3), the malignant neoplasms were classified into thymoma (8580-8585), thymic carcinomas (8123, 8310, 8430, 8082, 8070-8074, 8140, 8033, 8480, 8200, 8020, 8586, 8588 and 8589), and TNETs (8240, 8246, 8249, 8013, 8041 and 8045) (2).

The inclusion criteria set for the study investigating the influencing factors for LNM in TETs are detailed as follows:

1) Since the specifics regarding dissected and positive lymph nodes were documented from 1988 onwards, the period of the study lasted from 1988 to 2016.

2) The patients who underwent surgical treatment, with one or more lymph nodes surgically resected and pathologically examined.

3) The pathological groups of the patients were determined either as thymoma (type A-

B3: 8581-8585), TCs or TNETs.

The inclusion criteria set in the study for evaluating the status of LN on the prognostic results of TCs and TNETs are detailed as follows:

1) The label “Type of Reporting Source” was used to preclude those patients with only autopsy or certifications of death as they could not be taken into account for survival analysis.

2) Patients with less survival time than one month were defined as postoperative mortality and got excluded from the published research.

3) Patients with a histological confirmed diagnosis of TCs and TNETs were included in this study.

4) The label “Therapy. Rx Sum-Surg Prim Site (1998+)” was used to recognize sufferers undergoing surgical treatment and also the surgery type they received.

5) The recorded information of operation types had become available since 1998, so that the period of study for this part of the research stretched from 1998 to 2016.

2.3 Research variables

2.3.1 Clinicopathological characteristics

From the SEER database, the diagnosis time, age, gender, ethnicity, region, marital status and other details recorded at the time of diagnosis were obtained, while the variables were unified and coded. The specifics of tumor pathology mainly include tumor size, pathological type, the number of LND, the number of LNM positive, and tumor stage. As for treatment-related information, it mainly involves whether or not surgery, surgery type, radiotherapy and chemotherapy. To be specific, the surgery types include thymectomy, extended thymectomy, and debulking, depending on the coding of SEER variables.

2.3.2 Prognosis related information

The details of prognosis were obtained from the follow-up information contained in SEER database. The variable "survival months" was used to identify survival time. The primary endpoint of this research is overall survival (OS) and the secondary one is cancer-specific survival (CSS). OS was obtained through calculation performed by the difference in months from the diagnosis to death caused by any reason as listed under

the variable "vital status recode". While CSS was obtained through calculation from the date of diagnosis to the date of cancer-related death (attributable to this cancer dx), in line with the SEER cause-specific classification of death.

2.4 Regression analysis

2.4.1 Logistic regression analysis

Logistic regression analysis was conducted to determine the parameters related to LNM in TETs using the *rms* R package. All of the research variables were factored into the univariable logistic regression analysis, during which a comparison was performed between the odds ratio (OR) and 95% confidence interval (CI) of different parameters. The factors showing a significant association with LNM ($P < 0.05$) in the univariable analysis were taken into account for the multivariable analysis, so as to identify the independent risk factors to LNM.

2.4.2 Cox regression analysis

Univariable survival analysis was completed via Kaplan-Meier (K-M) curves and through Log-rank test. K-M curves were plotted using *survival* R package and Log-rank test was performed to draw comparison in the survival probability of OS and CSS between different groups. The parameters with a smaller *P*-value than 0.05 on Log-rank test were factored into the multivariable Cox proportional hazard model for identifying the independent prognostic factors of statistical significance. Moreover, hazard ratio (HR) and 95% CI were calculated as well.

2.5 Propensity score matching (PSM) analysis

PSM was performed to make adjustment accordingly for the diversities in general features of patients between the three LN status groups and subgroup analysis was further conducted. Based on logistic regression modeling performed using the *matchit* R package, the propensity scores included all the clinicopathological variables and a 1:1 matching protocol with no replacement, via a caliper width of 0.2 standard deviation (SD) from the logit of the propensity score. The chi squared test or Fisher's exact test was completed for the contrast between the matched groups. In addition, similar univariate and multivariate analysis Cox proportional hazards models were applied to speculate the LND significance for the matched sub-groups.

2.6 Statistical analysis

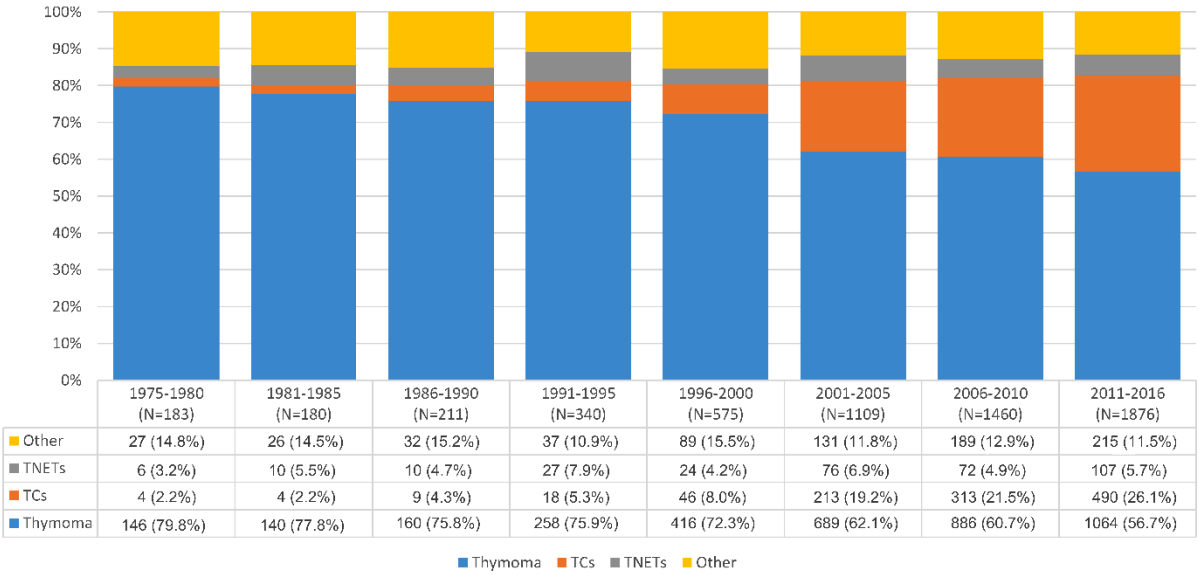
The statistical analyses required for this research were conducted using R software 4.0.5 (https://www.r-project.org) and SPSS Statistics 24.0 (IBM Corp., Armonk, New York, USA). The number of observations and the proportions of categorical variables were calculated, while the significant differences between different groups were contrasted through chi-squared test or Fisher's exact test. As for the normally distributed continuous variables, they were analyzed through the independent samples' t-test or paired student's t-test and indicated by mean ± SD. The variables failing to meet the normal distribution, median and intermediate range (IQR) were analyzed by means of the Mann Whitney test (U) test or Wilcox signed rank test and represented. All the tables and figures were visualized on the researcher's own. Two-sided *P*-value <0.05 were treated as statistically significant.

3. Results

3.1 The overview of thymic malignancies in the database.

An overall of 5934 patients with histologically confirmed malignancy were identified. Of them, there were 63.3% (3759/5934) of thymoma, 18.5% (1097/5934) of TCs, 5.6% (332/5934) of TNETs and 12.6% (746/5934) of other malignant tumors. Among the pathological classifications of thymoma, the proportion of thymoma type A, AB, B1, B2, B3 and NOS (8580/3: Not Otherwise Specified) was 6.7% (253/3759), 12.6% (473/3759), 9.8% (369/3759), 10.2% (384/3759), 13.3% (500/3759), and 47.4% (1780/3759), respectively. The number of diagnosed thymic malignancies showed an increasing trend on an annual basis. TNETs accounted for 3.3-7.9% of the total on a continued basis. The proportion of TCs increased gradually, from 2.2% to 26.1%.

In the whole cohort of patients, the proportion of male patients was higher, reaching 54.3% (3224/5934). Among the thymic malignancy of all types, the incidence of TETs was significantly higher in males (thymoma: 51.6%; TCs: 60.1%; TNETs: 68.1%). The median age was 59 years (IQR: 46-69). The age of high incidence group varied from 61 to 70 years. As the major race in this cohort, Caucasian accounted for 69.6% (4129/5934). The proportion was similar among the pathological types of different races. Thymoma (62.1-66.8%) had the highest proportion among the three groups, followed by TCs (17.4-19.5%) and TNETs (3.3-6%). The median size of tumor in thymoma, TCs and TNETs was 6.9 (IQR: 5.0-9.5) cm, 6.5 (IQR: 4.5-8.6) cm, and 7.0 (IQR: 4.7-9.9) cm, respectively. Surgery was considered the primary approach to treatment for the whole group of patients, with 70.4% (4178/5934) of them undergoing surgical treatment. There were 36.8% (2183/5934) of the patients receiving chemotherapy, 38.2% undergoing radiotherapy, of whom 4.8% received preoperative radiotherapy and 94.5% underwent postoperative radiotherapy.



	1975-1980 (N=183)	1981-1985 (N=180)	1986-1990 (N=211)	1991-1995 (N=340)	1996-2000 (N=575)	2001-2005 (N=1109)	2006-2010 (N=1460)	2011-2016 (N=1876)
Other	27 (14.8%)	26 (14.5%)	32 (15.2%)	37 (10.9%)	89 (15.5%)	131 (11.8%)	189 (12.9%)	215 (11.5%)
TNETs	6 (3.2%)	10 (5.5%)	10 (4.7%)	27 (7.9%)	24 (4.2%)	76 (6.9%)	72 (4.9%)	107 (5.7%)
TCs	4 (2.2%)	4 (2.2%)	9 (4.3%)	18 (5.3%)	46 (8.0%)	213 (19.2%)	313 (21.5%)	490 (26.1%)
Thymoma	146 (79.8%)	140 (77.8%)	160 (75.8%)	258 (75.9%)	416 (72.3%)	689 (62.1%)	886 (60.7%)	1064 (56.7%)

Figure 1. The number and proportion of patients with thymic malignances in different year groups.

3.2 Analysis of the associated factors to LNM in TETs.

An overall of 1048 patients reached the research criteria and were involved in this retrospective study. Among them, 59.4% (622/1048) had thymoma, 31.6% (331/1048) had TCs and 9.1% (95/1048) had TNETs. A majority of these patients were male (53.6%, 562/1048) and Caucasian (71.1%, 745/1048), with a median age of 60 years (IQR: 49-70). The median tumor size of all patients was 6.5 cm (IQR: 4.8-9.0), while the median number of LND was 3 (IQR: 1-6).

Overall, the proportion of LNM in thymic tumors was 19.1% (200/1048). The rate of LNM in thymomas, TCs, and TNETs was 6.8% (42/622), 30.2% (100/331), and 61.1% (58/95), respectively (P <0.001), as listed in Table 1. The percentage of LNM in the T3/4 group (24.5%, 120/490) was remarkably greater in contrast to the T1/2 group (12.6%, 58/460). Figure 2 shows the details of the LNM percentages in different pathological subtypes of TETs.

Univariable logistic analysis was performed on the entire variables of patients undergoing LND to explore the factors that correlated with LNM. Race (P =0.011), histology type (P <0.001), T stage (P <0.001), surgery type (P < 0.001), and number of LND (P =0.001) significantly correlated with LNM (Table 2). These factors were included

into the multivariate logistic regression model analysis. The results revealed that B3 thymoma (OR =3.616, 95%CI: 1.729-7.563, *P* <0.001), TCs (OR =8.536, 95%CI: 4.569-15.950, *P* <0.001), TNETs (OR =39.360, 95%CI: 18.803-84.430, *P* < 0.001) and T3/4 stage (OR =1.141, 95%CI: 1.042-1.250, *P* =0.004) were independent risk parameters for LNM. As T stage increases (T3/T4) and histologic type progresses (≥ B3), the likelihood of LNM increases (Table 3).

Table 1. Patients and malignancies features. (N = 1048)

Variable	N0 [N = 848 (100%)]	N1/2 [N = 200 (100%)]	*P*
Gender			0.064
Female	405 (47.8%)	81 (40.5%)	
Male	443 (52.2%)	119 (59.5%)	
Age			0.249#
Mean (± SD)	60.0 (± 14.4)	57.5 (±15.2)	
Median (IQR)	60.0 (49.0-70.0)	58.5 (48.0-69.8)	
Race			0.010
White	588 (69.3%)	157 (78.5%)	
Other	260 (30.7%)	43 (21.5%)	
Marriage			0.133
Married	524 (61.8%)	135 (67.5%)	
Other	324 (38.2%)	65 (32.5%)	
Histology Type			<0.001
A	67 (7.9%)	0 (0.0%)	
AB	132 (15.6%)	8 (4.0%)	
B1	93 (11.0%)	5 (2.5%)	
B2	137 (16.2%)	5 (2.5%)	
B3	151 (17.8%)	24 (12.0%)	
TCs	231 (27.2%)	100 (50.0%)	
TNETs	37 (4.4%)	58 (29.0%)	
T Stage			<0.001
T1/T2	402 (47.4%)	58 (29.0%)	
T3/T4	370 (43.6%)	120 (60.0%)	
Unknown	76 (9.0%)	22 (11.0%)	
Tumor Size (cm)			0.446#
Mean (± SD)	6.5 (±7.1)	7.4 (± 3.8)	
Median (IQR)	6.5 (4.8-9.0)	7.0 (4.9-8.6)	
No. LND			0.003
1-3	457 (53.9%)	81 (40.5%)	
>3	328 (38.7%)	99 (49.5%)	
Number Unknown	63 (7.4%)	20 (10.0%)	
No. LNP			--
1	--	113 (56.5%)	
>1	--	72 (36.0%)	
Number Unknown	--	15 (7.5%)	
Surgery Type			<0.001
Debulking	20 (2.4%)	13 (6.5%)	
Extend Thymectomy	212 (25.0%)	66 (33.0%)	
Thymectomy	583 (68.8%)	106 (53.0%)	
NOS	33 (3.9%)	15 (7.5%)	

SD: Standard Deviation; IQR: Interquartile Range; LND: Lymph Node Dissection; LNP: Lymph Node Positive; No.: Number of; NOS: Not otherwise specified.
#: Not normally distributed, analyzed by Mann–Whitney test.

Table 2. Univariable logistic regression analysis on risk factors for LNM in the whole cohort.

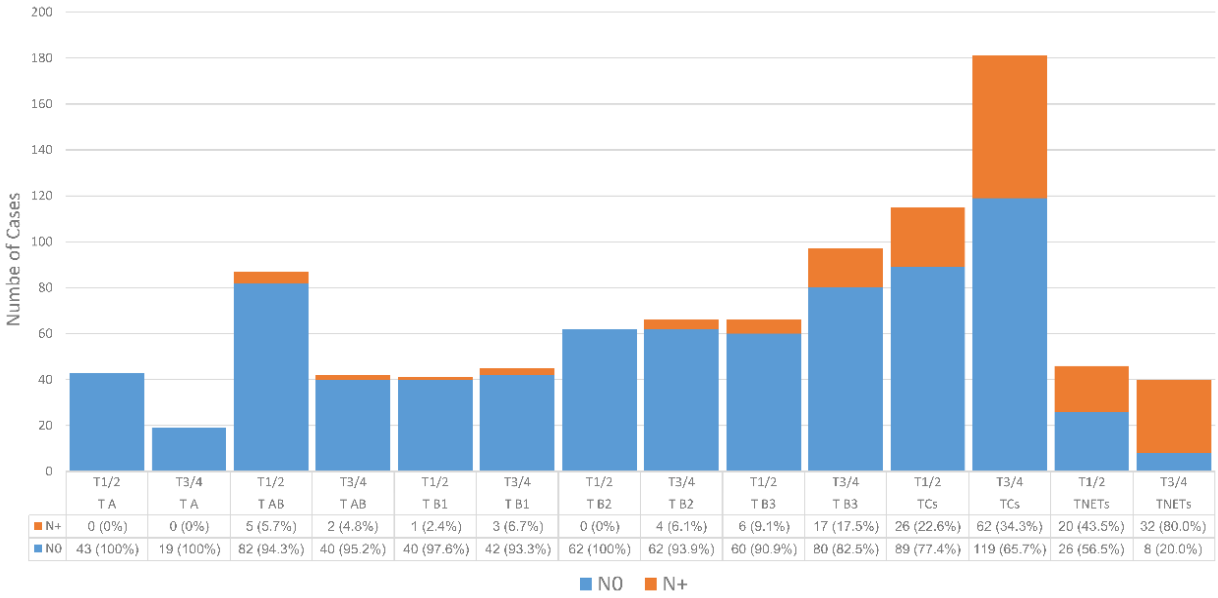
Variable	OR (95%CI)	*P*
Gender		
Female vs. Male	0.745 (0.545-1.018)	0.065
Age	0.993 (0.983-1.004)	0.203
Race		
Other vs. White	0.619 (0.429-0.895)	0.011
Marriage		
Other vs. Married	0.779 (0.562-1.080)	0.133
Histology Type		<0.001
B3 vs. A+AB+B1+B2	3.788 (2.000-7.174)	<0.001
TCs vs. A+AB+B1+B2	10.317 (6.093-17.471)	<0.001
TNETs vs. A+AB+B1+B2	37.360 (19.969-69.899)	<0.001
Tumor Size	1.000 (0.997-1.002)	0.815
T Stage		
T3/4 vs. T1/2	1.176 (1.098-1.260)	<0.001
No. LND		
>3 vs. 1-3	1.703 (1.229-2.359)	0.001
Surgery Type		<0.001
Debulking vs. Thymectomy	3.575 (1.726-7.406)	0.001
Extend Thymectomy vs. Thymectomy	1.712 (1.212-2.418)	0.002

LND: Lymph Node Dissection; No.: Number of. OR: Odds Ratio; CI: Confidence Interval.

Table 3. Multivariable logistic regression analysis on risk factors for LNM in the whole cohort.

Variable	OR (95%CI)	*P*
Race		
Other vs. White	0.802(0.502-1.280)	0.355
Histology Type		<0.001
B3 vs. A+AB+B1+B2	3.616(1.729-7.563)	0.001
TCs vs. A+AB+B1+B2	8.536(4.569-15.950)	<0.001
TNETs vs. A+AB+B1+B2	39.844(18.803-84.430)	<0.001
T Stage		
T3/4 vs T1/2	1.141(1.042-1.250)	0.004
No. LND		
>3 vs 1-3	1.377(0.918-2.064)	0.122
Surgery Type		0.166
Debulking vs. Thymectomy	2.047(0.864-4.850)	0.103
Extend Thymectomy vs. Thymectomy	1.360(0.869-2.128)	0.178

LND: Lymph Node Dissection; LNP: Lymph Node Positive; No.: Number of; OR: Odds Ratio; CI: Confidence Interval.



	T1/2 TA	T3/4 TA	T1/2 TAB	T3/4 TAB	T1/2 TB1	T3/4 TB1	T1/2 TB2	T3/4 TB2	T1/2 TB3	T3/4 TB3	T1/2 TCs	T3/4 TCs	T1/2 TNETs	T3/4 TNETs
N+	0 (0%)	0 (0%)	5 (5.7%)	2 (4.8%)	1 (2.4%)	3 (6.7%)	0 (0%)	4 (6.1%)	6 (9.1%)	17 (17.5%)	26 (22.6%)	62 (34.3%)	20 (43.5%)	32 (80.0%)
N0	43 (100%)	19 (100%)	82 (94.3%)	40 (95.2%)	40 (97.6%)	42 (93.3%)	62 (100%)	62 (93.9%)	60 (90.9%)	80 (82.5%)	89 (77.4%)	119 (65.7%)	26 (56.5%)	8 (20.0%)

Figure 2. The number and proportion of patients with LNM in different TETs pathological subtypes.

3.3 The prognostic significance of LND for TCs and TNETs patients.

3.3.1 Features of enrolled patients.

A total of 812 patients were included in the study of prognostic impact of LND, of which TCs accounted for 76.7% (623/812) and TNETs accounted for 23.2% (189/812). Among the enrolled patients, 36.8% (299/812) were female, 11.6% (94/812) were African American, and 17.6% (143/812) were Asian. The median age of patients in the total cohort was 62 (51-71) years. The median age of patients with TNETs was 63 (IQR: 53-71) years and that of TCs patients was 59 (IQR: 42-66) years. The age of TNETs patients was significantly younger compared to those with TCs (P <0.001). The median size of TNETs was 6.7 (IQR: 4.2-9.6) cm, while that of TCs was 6.0 (4.0-8.0) cm. The difference in tumor size between TNETs and TCs reached a statistically significant extent (P =0.049). The primary pathological type of TCs was 8586/3 (Thymic carcinoma, NOS, 63.9%, 398/623), while squamous cell carcinoma accounted for 27.9% (174/623). The main pathological type of TNETs was carcinoid (57.7%, 106/189). In terms of treatment, 32.6% (265/812) of these patients underwent only surgical treatment. Among those patients receiving adjuvant therapy, 15.7% (86/547) received adjuvant chemotherapy alone, 39.5% (216/547) received adjuvant radiotherapy alone, and 44.8% (245/547) received a combination of radiotherapy and chemotherapy. Other detailed

general information of patients has been shown in the selected Publication (Table 1) (23).

Over half of the patients did not undergo lymph node resection. A total of 49.0% (398/812) patients received LND. The proportion of lymph node metastasis positive was 36.2% (144/398). Among the 183 patients undergoing lymph node resection in the subgroup of LND 1-3, 27.3% (50/183) had positive lymph node metastasis. Additionally, 188 patients received 4+ lymph node dissection, of whom 44.1% (83/188) examined positive for lymph node metastasis. The positive ratio of LNM was observed to be significantly higher in those sufferers with more than 4 lymph nodes resected (*P* =0.001).

3.3.2 Survival analysis.

The median follow-up time was 49.0 (IQR: 18.5-100.0) months across the cohort. The median OS and CSS were 85 and 169 months, respectively. The 3-year, 5-year and 10-year OS were 75.8%, 60.0% and 37.0%, respectively, while CSS was 84.2%, 73.4% and 61.8%, respectively. According to univariate Cox regression analysis, age, histology type, grade, tumor size, lymph node status, M-K stage, surgery type, and chemotherapy were associated with OS. Moreover, grade, tumor size, lymph node status, M-K stage, surgery type, and chemotherapy were associated with the prognosis of CSS (Table 4). The K-M survival curves of patients with these factors are shown as follows.

3.3.2.1 Age

In the whole group, the 5- and 10-year OS were 65.4% and 44.2% respectively for patents in age ≤60 years group, and 54.7% and 30.2% respectively for patents in age >60 years group. The prognosis of OS difference between the two groups was statistically significant (Fig 3. Log-rank *P* <0.001). The 5- and 10-year CSS of patients aged ≤60 years were 72.7% and 59.8% respectively, while they were74.0% and 62.6% for those aged >60 years, respectively. There was no significant difference found in the prognosis of CSS between the two age groups (Fig 3. Log-rank *P* =0.716).

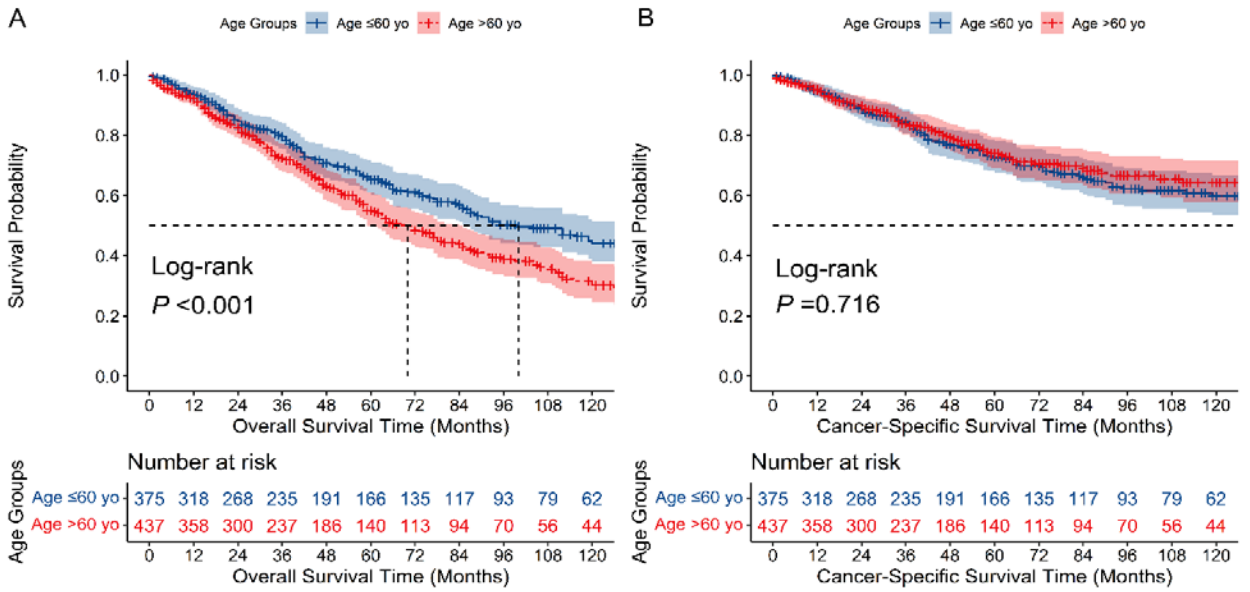


Figure 3. The OS (A) and CSS (B) K-M survival curves of patients in different age groups. yo: years old.

3.3.2.2 Histology type

In the total cohort, the 5- and 10-year OS were 56.9% and 36.5% for patents in the TCs group, respectively, while they were 70.2% and 39.7% for those in the TNETs group, respectively. The OS difference between the two groups was of statistical significance (Fig 4. Log-rank *P* =0.036). The 5- and 10-year CSS were 71.8% and 63.5% for those patients in the TCs group, respectively, while they were 78.3% and 57.3% for those patients in the TNETs group, respectively. There was no significant difference observed in the prognosis of CSS between these two groups (Fig 4. Log-rank *P* =0.724).

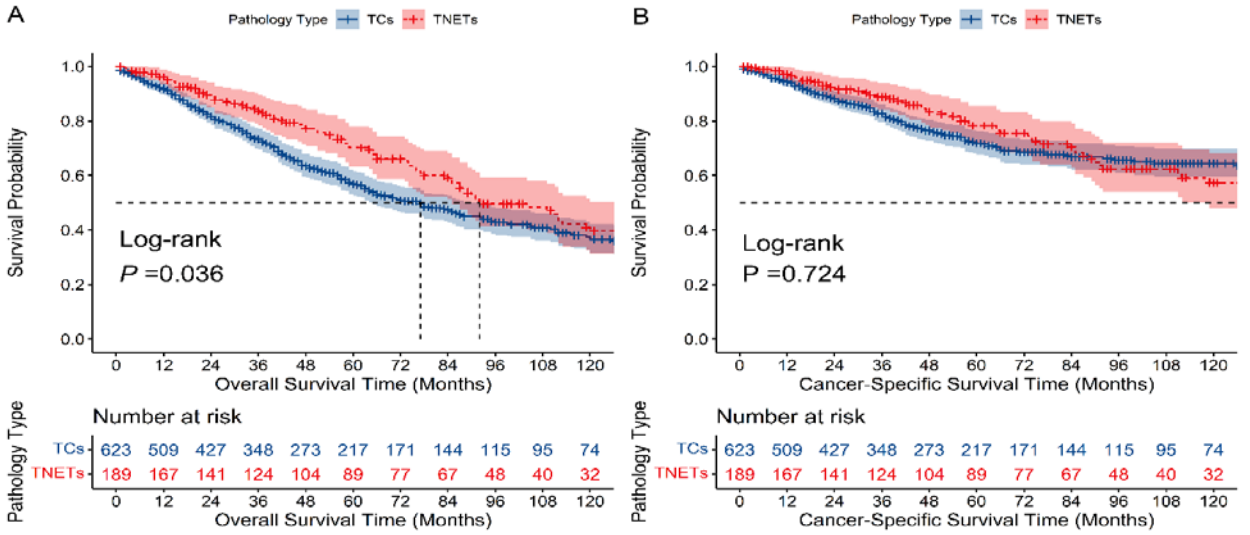


Figure 4. The OS (a) and CSS (b) K-M survival curves of patients in different histology type groups.

Table 4. Univariable and multivariable Cox proportional hazard regression model analysis on risk factors of CSS in the whole cohort.

Variables	Univariable analysis of CSS		Multivariable analysis of CSS	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Gender				
Male vs. Female	1.052 (0.791-1.400)	0.726		
Age (years)				
>60 vs. ≤60	0.951 (0.723-1.250)	0.717		
Race				
Other vs. Caucasoid	0.985 (0.706-1.300)	0.782		
Marriage				
Other vs. Married	0.837 (0.624-1.123)	0.236		
Histopathologic subtypes				
TENTs vs. TCs	0.945 (0.692-1.292)	0.725		
Region		0.510		
Northern Plains vs. East	1.001 (0.594-1.686)	0.997		
Pacific Coast vs. East	1.166 (0.859-1.581)	0.325		
Southwest vs. East	1.511 (0.817-2.795)	0.189		
Grade		0.009		
II vs. I	2.702 (1.184-6.170)	0.018	3.845(1.149-12.868)	0.029
III/IV vs. I	3.260 (1.512-7.028)	0.003	4.347(1.340-14.099)	0.014
Tumor Size (cm)				
>6.0 vs. ≤6.0	2.319 (1.686-3.190)	<0.001	1.736(1.126-2.676)	0.013
LND				
LND+ vs. LND-	0.978 (0.743-1.286)	0.872		
Lymph Node Status		<0.001		
N0 vs. LND-	0.622 (0.436-0.889)	0.009	0.514 (0.305-0.866)	0.012
N+ vs. LND-	2.009 (1.450-2.783)	<0.001	0.915 (0.521-1.609)	0.759
M-K Stage		<0.001		
IIb vs. I/IIa	3.556 (2.103-6.013)	<0.001	2.830 (1.301-6.155)	0.009
III/IV vs. I/IIa	8.174 (4.883-13.682)	<0.001	4.284 (1.843-9.958)	0.001
Surgery Type		0.006		
Thymct vs. Ext Thymct	1.120 (0.833-1.505)	0.454	1.650 (1.070-2.545)	0.023
Debulking vs. Ext Thymct	2.284 (1.381-3.776)	0.001	1.587 (0.739-3.409)	0.237
Chemotherapy				
No vs. Yes	0.494 (0.375-0.650)	<0.001	0.776 (0.497-1.214)	0.267
Radiotherapy				
No vs. Yes	0.775 (0.585-1.027)	0.076		

CSS: Cancer-Specific Survival; HR: Hazard Ratio; CI: Confidence Interval; LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; Thymct: Thymectomy.

3.3.2.3 Grade

In the whole group of patients, the 5-year OS was 72.4%, 68.3%, 47.6% for those patients with pathological grade of I, II, and III/IV, respectively, while the 10-year OS was 52.3%, 37.7%, and 25.4%, respectively. Besides, there was significant difference observed in the prognosis of OS between the groups (Fig 5. Log-rank *P* =0.003). The 5-year CSS was 88.5%, 69.4%, and 61.3% for those patients with pathological grade of I, II, and III/IV, respectively, while the 10-year CSS was 77.8%, 49.0%, and 47.7%, respectively. Moreover, there were significant statistical differences detected in the

prognosis of CSS among sufferers in each group (Fig 5. Log-rank *P* =0.006).

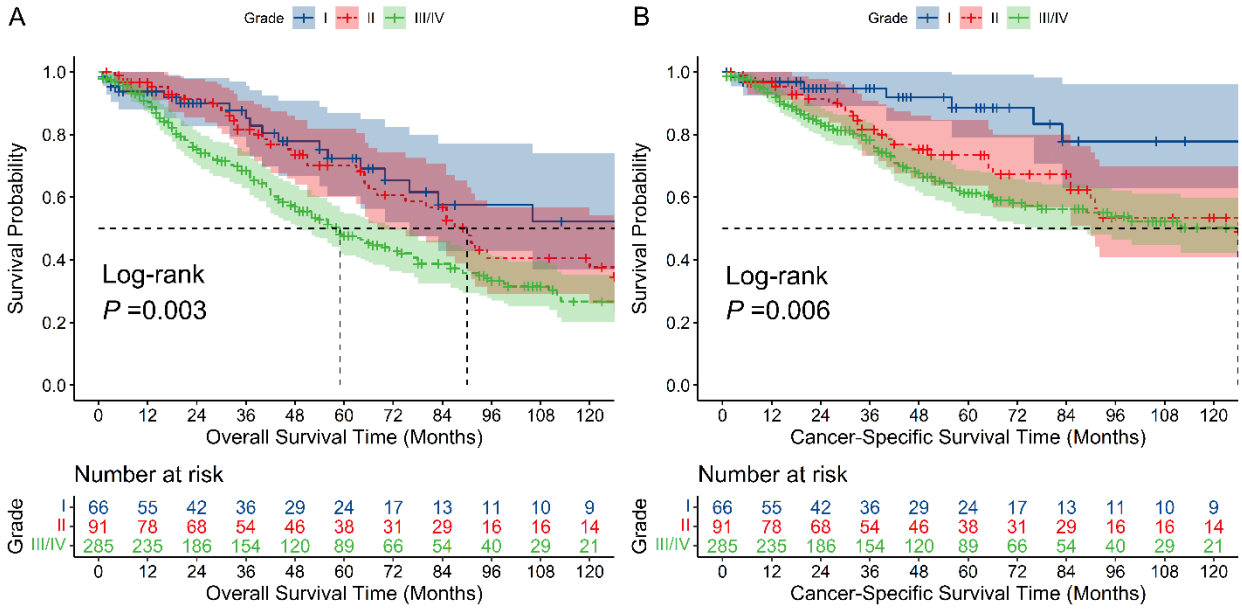


Figure 5. The OS (A) and CSS (B) K-M survival curves of patients in different grade groups.

3.3.2.4 Tumor size

In the total cohort, the 5- and 10-year OS were 65.5% and 55.9% for those patients with a tumor size ≤6.0 cm, respectively, while they were 41.6% and 31.1% for those patients with a tumor size >6.0 cm, respectively. The difference in the prognosis of OS between these two groups of patients reached a statistically significant extent (Fig 6. Log-rank *P* =0.001). The 5- and 10-year CSS of patients in the tumor size ≤6.0 cm group were 83.0% and 75.7%, respectively, while they were 65.6% and 49.3% for those patients with a tumor size >6.0 cm, respectively. The difference in the prognosis of CSS between the two groups of patients was observed as statistically significant (Fig 6. Log-rank *P* <0.001).

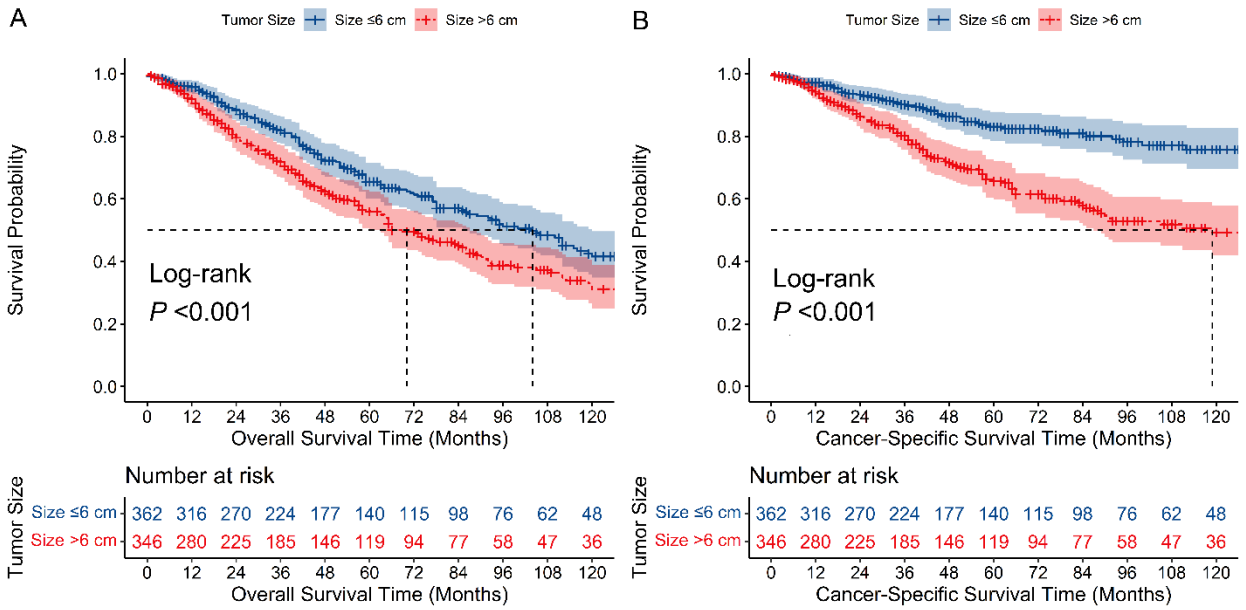


Figure 6. The OS (A) and CSS (B) K-M survival curves of patients in different tumor size groups.

3.3.2.5 Lymph node status

In the whole group of patients, the 5-year OS of patients in the pathological N0, LND-, and N+ groups was 70.6%, 59.8%, and 41.9%, respectively, while the 10-year OS of patients in the pathological N0, LND-, and N+ groups was 44.5%, 37.4%, and 20.5%, respectively. The difference in the prognosis of OS between the three groups of patients showed statistical significance (Fig 7. Log-rank *P* <0.001. Part of the results have been shown in the doctoral Publication Figure 1A (23).). The 5-year CSS of sufferers in the pathological N0, LND-, and N+ groups was 82.6%, 73.6%, and 53.7%, respectively. Comparatively, the 10-year CSS of patients in the pathological N0, LND-, and N+ groups was 74.8%, 60.1%, and 31.1%, respectively. The difference in the prognosis of CSS between the three groups of patients was statistically significant (Fig 7. Log-rank *P* <0.001). In the N0 subgroup, the 10-year OS of LND ≥4 group and LND 1-3 group were 54.6% and 38.1%, respectively; CSS were 81.3% and 76.6% respectively. The long-term survival of LND ≥4 group was better than that of LND 1-3 group, but there was no significant difference between the two groups (OS: Log-rank *P* = 0.203; CSS: Log-rank *P* =0.665).

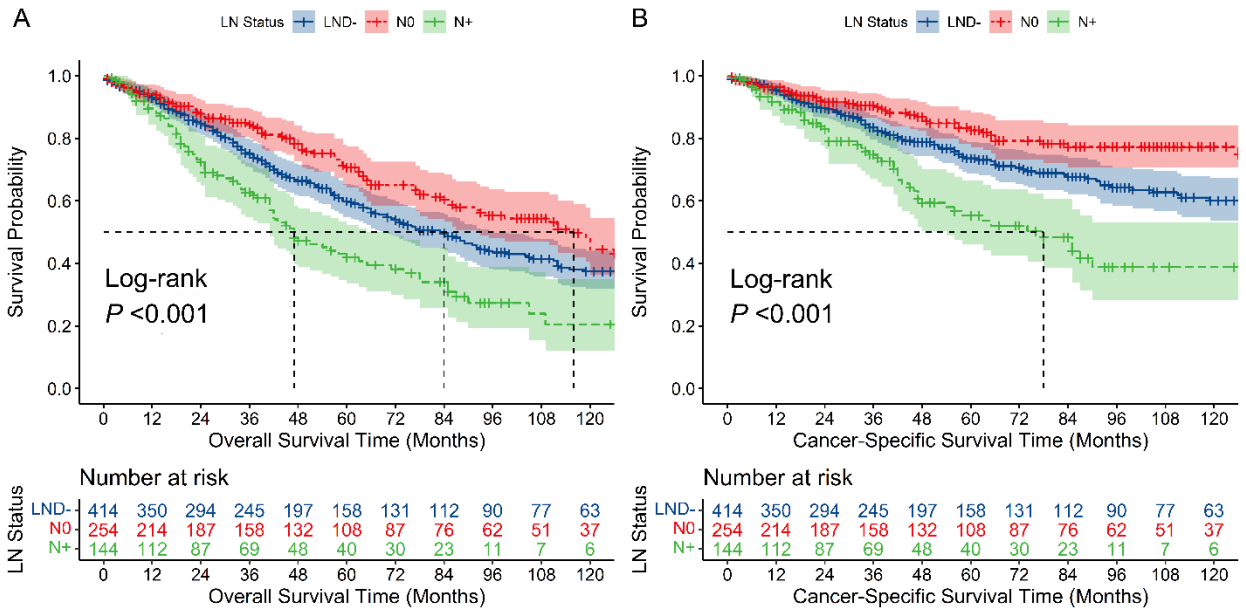


Figure 7. The OS (A) and CSS (B) K-M survival curves of patients in different lymph node status groups. LN: Lymph Node; LND: Lymph Node Dissection.

3.3.2.6 M-K Stage

In the whole group of patients, the 5-year OS of patients in M-K stage I/IIa, IIb, and III/IV groups was 77.6%, 62.4%, and 41.5%, respectively, while the 10-year OS of patients in M-K stage I/IIa, IIb, and III/IV groups was 53.8%, 42.0%, and 15.6%, respectively. The difference in the prognosis of OS between the three groups of patients was observed as statistically significant (Fig 8. Log-rank *P* <0.001). The 5-year CSS of sufferers in M-K stage I/IIa, IIb, and III/IV groups was 91.4%, 75.0%, and 54.4%, respectively. In comparison, the 10-year CSS of patients in M-K stage I/IIa, IIb, and III/IV groups was 85.7%, 63.3%, and 33.0%, respectively. The CSS between the three groups of patients was statistically significant (Fig 8. Log-rank *P* <0.001).

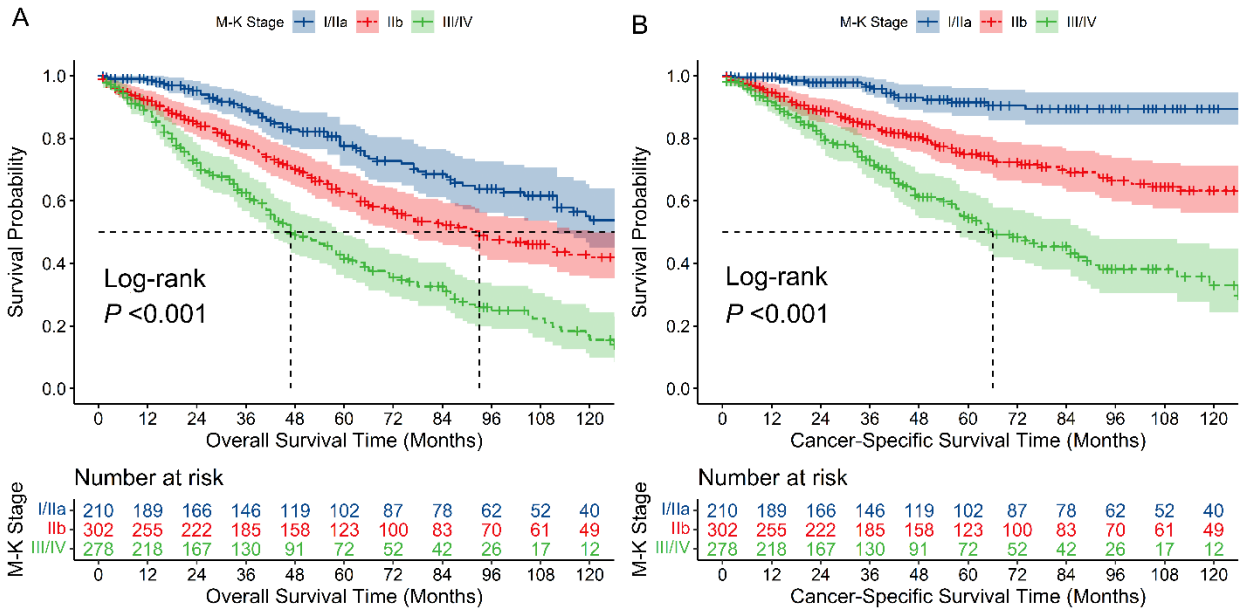


Figure 8. The OS (A) and CSS (B) K-M survival curves of patients in different M-K stage groups. M-K: Masaoka-Koga.

3.3.2.7 Surgery type

In the whole cohort, the 5-year OS of patients in the extended thymectomy, thymectomy, and debulking surgery type groups was 65.0%, 58.8%, and 25.8%, respectively, while the 10-year OS of patients in the extended thymectomy, thymectomy, and debulking surgery type groups was 39.8%, 37.4%, and 16.1%, respectively. The difference in the prognosis of OS between the three groups of patients was statistically significant (Fig 9. Log-rank *P* =0.003). The 5-year CSS of patients in the extended thymectomy, thymectomy, and debulking surgery type groups was 76.9%, 74.1%, and 44.8%, respectively. While the 10-year CSS of patients in the extended thymectomy, thymectomy, and debulking surgery type groups was 64.4%, 62.0%, and 28.0%, respectively. The difference in the prognosis of CSS between the three groups of patients showed statistical significance (Fig 9. Log-rank *P* =0.004).

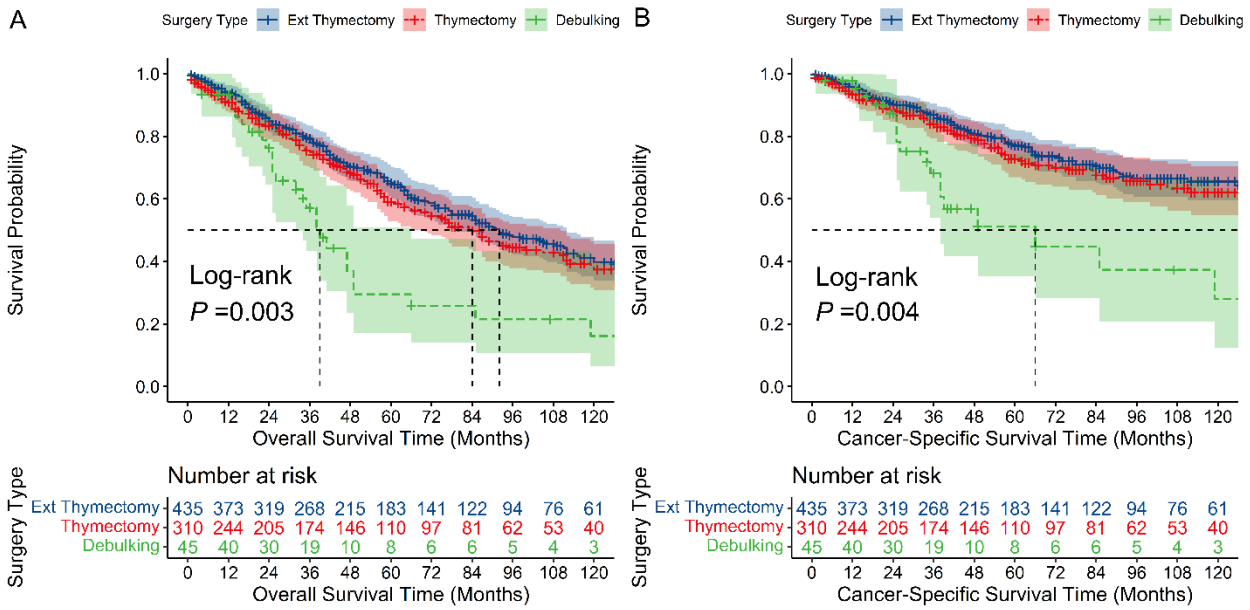


Figure 9. The OS (A) and CSS (B) K-M survival curves of patients in different surgery type groups. Ext: Extended.

3.3.2.8 Chemotherapy

In the entire group of patients, the 5- and 10-year OS of patients undergoing chemotherapy were 51.0% and 29.5%, respectively, while the 5- and 10-year OS of patients receiving no chemotherapy were 66.0% and 41.8%, respectively. The difference in the prognosis of OS between the two groups of patients was shown to be statistically significant (Fig 10. Log-rank *P* =0.001). The 5- and 10-year CSS of patients undergoing chemotherapy were 61.5% and 47.3%, respectively, while the 5- and 10-year CSS of patients undergoing no chemotherapy were 80.7% and 70.2%, respectively. The difference in the prognosis of CSS between the two groups of patients exhibited statistical significance (Fig 10. Log-rank *P* <0.001).

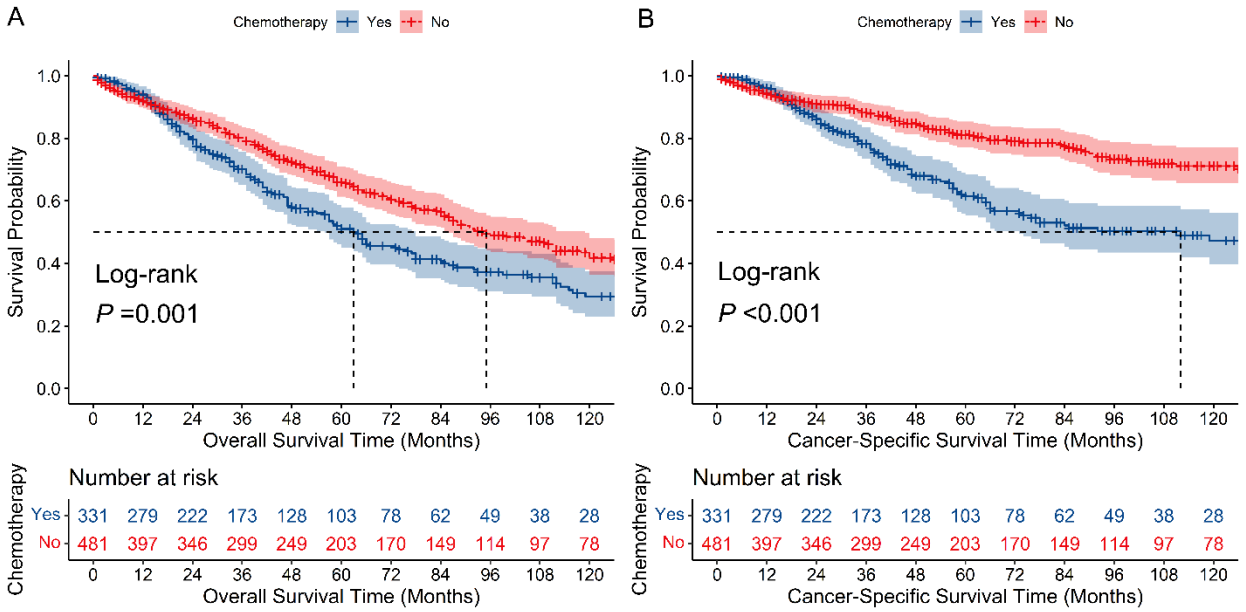


Figure 10. The OS (A) and CSS (B) K-M survival curves of patients in different chemotherapy treatment groups.

3.3.3 Multivariate Cox regression analysis.

As suggested by the results of multivariate Cox analysis, those patients with pathological N0 had a better prognosis in terms of OS and CSS. According to multivariate analysis, however, there was no statistically significant difference observed in prognosis between LND- and N+ patients with regard to OS and CSS. The patients who underwent debulking performed worse in OS when compared to patients with extended thymectomy. Patients after thymectomy had worse CSS than patients after extended thymectomy. Compared to patients with TCs and stage III/IV tumors, patients with TNETs and stage I/IIa tumors had a better OS. Besides, tumor grade, tumor size, and M-K stage were considered as independent risk parameters of CSS. With increasing pathological stage, advancing M-K stage, and enlarging tumor size, tumor-specific survival of patients became worse. Figure 11 details the results of multivariate analysis.

3.3.4 Characteristics of patients before and after PSM.

3.3.4.1 Clinicopathological characteristics of between N0 and N+ patients before and after PSM

The general information about patients in the N0 group (N =254) and the N+ group (N =144) before PSM is shown in Table 5 (Some of the results have been demonstrated in

the doctoral Publication Supplementary-table 1 (23).). In the TCs group, 65.3% of the patients had LNM, which was significantly higher than 34.7% of TCs (*P* <0.001). The tumor size in the N+ group was considerably larger than in the N0 group (*P* =0.048). After PSM analysis, the information on patients in each group was collected, as shown in Table 5. Apart from M-K staging, there was no significant statistical difference exhibited in other variables between the N0 and N+ groups (N =52).

3.3.4.2 Clinicopathological characteristics of patients between N0 and LND- groups before and after PSM.

The basic information on patients in the N0 (N =254) group and the LND- (N =144) group before PSM is shown in Table 6 (Part of the results have been presented in the doctoral Publication Supplementary-table 2 (23).). There were significant statistical differences found between the two groups in region, histology type, tumor size, M-K stage, and surgery type. In the LND- group most patients underwent extended thymectomy. In the N0 group, most patients received thymectomy. The baseline factors of the patients in the two groups (N =254) were found to be well balanced after PSM, with no statistical differences observed in all the variables.

3.3.4.3 Clinicopathological characteristics of patients between N+ and LND- groups before and after PSM.

The general clinicopathological information about patients in the N0 group (N =144) and the LND- group (N =414) before PSM is shown in Table 7 (Some of the results have been shown in the doctoral Publication Supplementary-table 3 (23).). A significant statistical difference between the two groups of patients was detected in such factors as race, histology type, grade, tumor size, M-K stage, surgery type, chemotherapy, and radiotherapy. After PSM analysis, the information on patients in the two groups (N=136) was collected, as summarized in Table 7. Since all of the enrolled patients in the N+ group were in stage III/IV, there remained significant difference observed in the variable of M-K stage, while other factors were found well balanced after PSM.

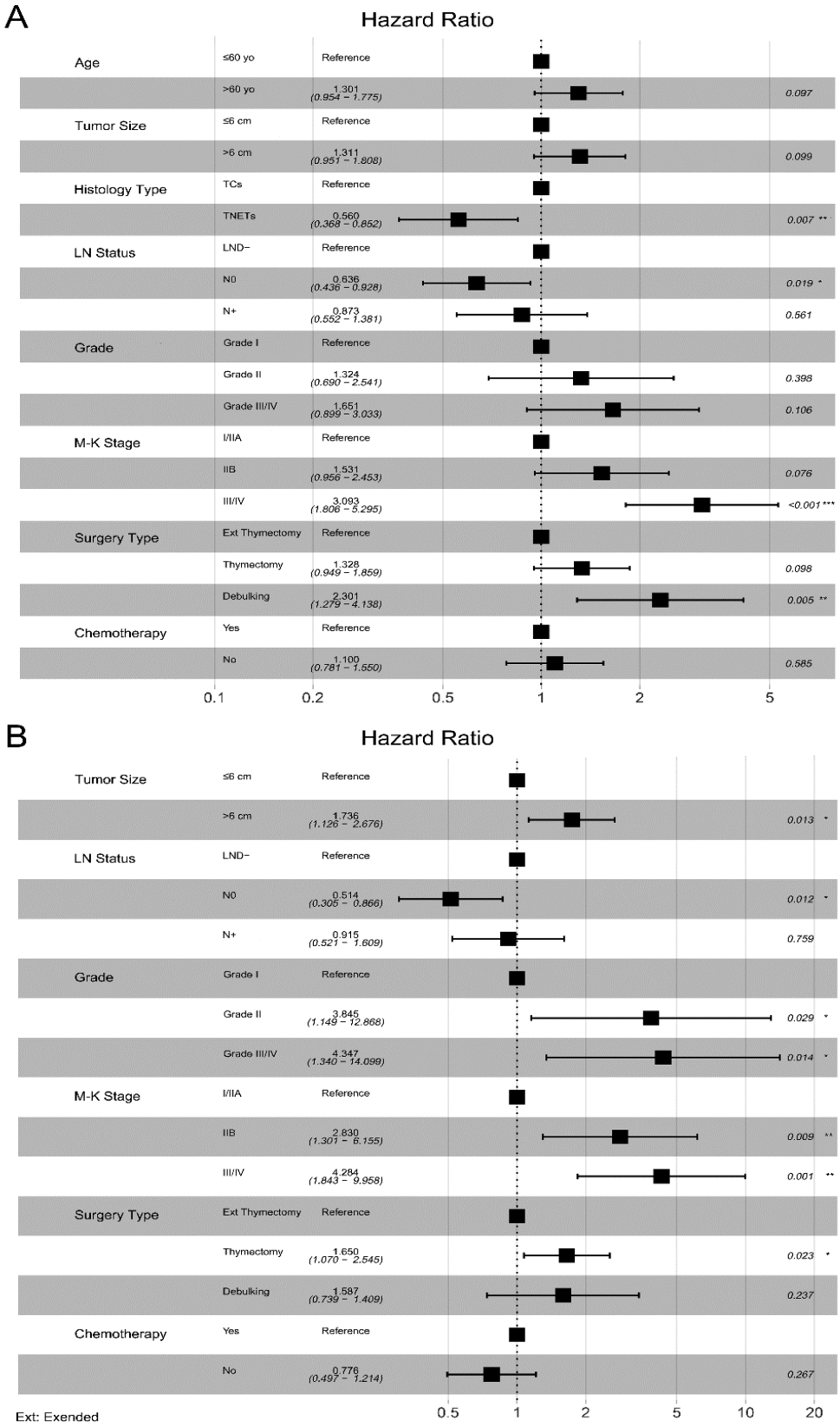


Figure 11. Forest plot of multivariable Cox proportional hazard regression model analysis on risk factors of OS (A) and CSS (B) in the whole cohort. LN: Lymph Node; M-K: Masaoka-Koga; Ext: Extended.

Table 5. Patients and tumor characteristics of subgroup N0 and N+ before and after PSM.

Variables	Before Matching			After Matching		
	N0 (N=254)	N+ (N=144)	*P*	N0 (N=52)	N+ (N=52)	*P*
Gender			0.745			0.687
Female	103 (40.6)	56 (38.9)		21 (40.4)	19 (36.5)	
Male	151 (59.4)	88 (61.1)		31 (59.6)	33 (63.5)	
Age			0.095			0.844
≤60	112 (44.1)	76(52.8)		23 (44.2)	24 (46.2)	
>60	142 (55.9)	68(47.2)		29 (55.8)	28 (53.8)	
Race			0.070			0.813
Caucasoid	180 (70.9)	114(79.2)		40 (76.9)	41 (78.8)	
Other	74 (29.1)	30(20.8)		12 (23.1)	11 (21.2)	
Marriage			0.804			0.842
Married	168 (66.1)	97(67.4)		30 (57.7)	31 (59.6)	
Other	86 (33.9)	47(32.6)		22 (42.3)	21 (40.4)	
Region			0.116			0.573
East	81 (31.9)	54(37.5)		16 (30.8)	19 (36.5)	
Northern Plains	37 (14.6)	10(6.9)		6 (11.5)	3 (5.8)	
Pacific Coast	126 (49.6)	72(50.0)		28 (53.8)	26 (50.0)	
Southwest	10 (3.9)	8(5.6)		2 (3.8)	4 (7.7)	
Histology Type			<0.001			0.183
TCs	219 (86.2)	94 (65.3)		45 (86.5)	49 (94.2)	
TNETs	35 (13.8)	50 (34.7)		7 (13.5)	3 (5.8)	
Grade			0.153			0.292
I	17 (6.7)	10 (6.9)		2 (3.8)	0 (0)	
II	26 (10.2)	14 (9.7)		4 (7.7)	2 (3.8)	
III/IV	92 (36.2)	68 (47.2)		20 (38.5)	27 (551.9)	
Unknown	119 (46.9)	52 (36.1)		26 (50.0)	23 (44.2)	
Tumor Size (cm)			0.048			0.587
≤6.0	121 (47.6)	55 (38.2)		20 (38.5)	25 (48.1)	
>6.0	109 (42.9)	80 (55.6)		27 (51.9)	22 (42.3)	
Unknown	24 (9.4)	9 (6.3)		5 (9.6)	5 (9.6)	
M-K Stage			<0.001			0.027
I/IIa	73 (28.7)	0 (0)		0 (0)	0 (0)	
IIb	132 (52.0)	0 (0)		4 (7.7)	0 (0)	
III/IV	47 (18.5)	144 (100.0)		46 (88.5)	52 (100.0)	
Unknown	2 (0.8)	0 (0)		2 (3.8)	0 (0)	
Surgery Type			0.441			0.764
Ext Thymectomy	158 (62.2)	92 (63.9)		32 (61.5)	34 (65.4)	
Thymectomy	79 (31.1)	40 (27.8)		13 (25.0)	14 (26.9)	
Debulking	10 (3.9)	10 (6.9)		5 (9.6)	2 (3.8)	
NOS.	7 (2.8)	2 (1.4)		2 (3.8)	2 (3.8)	
Chemotherapy			<0.001			0.841
Yes	99 (39.0)	88 (61.1)		32 (61.5)	31 (59.6)	
No	155 (61.0)	56 (38.9)		20 (38.5)	21 (40.4)	
Radiotherapy			0.021			0.691
Yes	143 (56.3)	98 (68.1)		29 (55.8)	31 (59.6)	
No	111 (43.7)	46 (31.9)		23 (44.2)	21 (40.4)	

LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; NOS.: Not otherwise specified.

Table 6. Patients and tumor characteristics of subgroup LND- and N0 before and after PSM

Variables	Before Matching			After Matching		
	LND- (N=414)	N0 (N=254)	*P*	LND- (N=254)	N0 (N=254)	*P*
Gender			0.079			0.412
Female	140 (33.8)	103 (40.6)		94 (37.0)	103 (40.6)	
Male	274 (66.2)	151 (59.4)		160 (63.0)	151 (59.4)	
Age			0.786			0.591
≤60	187 (45.2)	112 (44.1)		106 (41.7)	112 (44.1)	
>60	227 (54.8)	142 (55.9)		148 (58.3)	142 (55.9)	
Race			0.285			0.388
Caucasoid	277 (66.9)	180 (70.9)		171 (67.3)	180 (70.9)	
Other	137 (33.1)	74 (29.1)		83 (32.7)	74 (29.1)	
Marriage			0.289			0.925
Married	257 (62.1)	168 (66.1)		167 (65.7)	168 (66.1)	
Other	157 (37.9)	86 (33.9)		87 (34.3)	86 (33.9)	
Region			0.022			0.113
East	152 (36.7)	81 (31.9)		82 (32.3)	81 (31.9)	
Northern Plains	30 (7.2)	37 (14.6)		20 (7.9)	37 (14.6)	
Pacific Coast	216 (52.2)	126 (49.6)		141 (55.5)	126 (49.6)	
Southwest	16 (3.9)	10 (3.9)		11 (4.3)	10 (3.9)	
Histology Type			<0.001			0.704
TCs	310 (74.9)	219 (86.2)		216 (85.0)	219 (86.2)	
TNETs	104 (25.1)	35 (13.8)		38 (15.0)	35 (13.8)	
Grade			0.284			0.878
I	39 (9.4)	17 (6.7)		19 (7.5)	17 (6.7)	
II	51 (12.3)	26 (10.2)		30 (11.8)	26 (10.2)	
III/IV	125 (30.2)	92 (36.2)		85 (33.5)	92 (36.2)	
Unknown	199 (48.1)	119 (46.9)		120 (47.2)	119 (46.9)	
Tumor Size (cm)			0.020			0.858
≤6.0	186 (44.9)	121 (47.6)		127 (50.0)	121 (47.6)	
>6.0	157 (37.9)	109 (42.9)		105 (41.3)	109 (42.9)	
Unknown	71 (17.1)	24 (9.4)		22 (8.7)	24 (9.4)	
M-K Stage			0.003			0.275
I/IIa	137 (33.1)	73 (28.7)		89 (35.0)	73 (28.7)	
IIb	170 (41.1)	132 (52.0)		116 (45.7)	132 (52.0)	
III/IV	87 (21.0)	47 (18.5)		44 (17.3)	47 (18.5)	
Unknown	20 (4.8)	2 (0.8)		5 (2.0)	2 (0.8)	
Surgery Type			<0.001			0.055
Ext Thymectomy	191 (46.1)	79 (31.1)		118 (46.5)	158 (62.2)	
Thymectomy	185 (44.7)	158 (62.2)		111 (43.7)	79 (31.1)	
Debulking	25 (6.0)	10 (3.9)		16 (6.3)	10 (3.9)	
NOS.	13 (3.1)	7 (2.8)		9 (3.5)	7 (2.8)	
Chemotherapy			0.274			0.409
Yes	144 (34.8)	99 (39.0)		90 (35.4)	99 (39.0)	
No	270 (65.2)	155 (61.0)		164 (64.6)	155 (61.0)	
Radiotherapy			0.426			0.858
Yes	220 (53.1)	143 (56.3)		145 (57.1)	143 (56.3)	
No	194 (46.9)	111 (43.7)		109 (42.9)	111 (43.7)	

LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; NOS.: Not otherwise specified.

Table 7. Patients and tumor characteristics of subgroup LND- and N+ before and after PSM.

Variables	Before Matching			After Matching		
	LND- (N=414)	N+ (N=144)	*P*	LND- (N=136)	N+ (N=136)	*P*
Gender			0.272			0.705
Female	140 (33.8)	56 (38.9)		48 (35.3)	51 (37.5)	
Male	274 (66.2)	88 (61.1)		88 (64.7)	85 (62.5)	
Age			0.115			0.627
≤60	187 (45.2)	76 (52.8)		74 (54.4)	70 (51.5)	
>60	227 (54.8)	68 (47.2)		62 (45.6)	66 (48.5)	
Race			0.006			0.543
Caucasoid	277 (66.9)	114 (79.2)		111 (81.6)	107 (78.7)	
Non-Caucasoid	137 (33.1)	30 (20.8)		25 (18.4)	29 (21.3)	
Marriage			0.257			0.604
Married	257 (62.1)	97 (67.4)		94 (69.1)	90 (66.2)	
Other	157 (37.9)	47 (32.6)		42 (30.9)	46 (33.8)	
Region			0.840			0.941
East	152 (36.7)	54 (37.5)		52 (38.2)	53 (39.0)	
Northern Plains	30 (7.2)	10 (6.9)		9 (6.6)	10 (7.4)	
Pacific Coast	216 (52.2)	72 (50.0)		68 (50.0)	68 (50.0)	
Southwest	16 (3.9)	8 (5.6)		7 (5.1)	5 (3.7)	
Histology Type			0.026			0.898
TCs	310 (74.9)	94 (65.3)		90 (66.2)	91 (66.9)	
TNETs	104 (25.1)	50 (34.7)		46 (33.8)	45 (33.1)	
Grade			0.003			0.074
I	39 (9.4)	10 (6.9)		16 (11.8)	8 (5.9)	
II	51 (12.3)	14 (9.7)		23 (16.9)	14 (10.3)	
III/IV	125 (30.2)	68 (47.2)		48 (35.3)	63 (46.3)	
Unknown	199 (48.1)	52 (36.1)		49 (36.0)	51 (37.5)	
Tumor Size (cm)			<0.001			0.409
≤6.0	186 (44.9)	55 (38.2)		59 (43.4)	50 (36.8)	
>6.0	157 (37.9)	80 (55.6)		66 (48.5)	77 (56.6)	
Unknown	71 (17.1)	9 (6.3)		11 (8.1)	9 (6.6)	
M-K Stage			<0.001			<0.001
I/IIa	137 (33.1)	0 (0)		18 (13.2)	0 (0)	
IIb	170 (41.1)	0 (0)		60 (44.1)	0 (0)	
III/IV	87 (21.0)	144 (100.0)		47 (34.6)	136 (100.0)	
Unknown	20 (4.8)	0 (0)		11 (8.1)	0 (0)	
Surgery Type			<0.001			0.344
Ext Thymectomy	185 (44.7)	92 (63.9)		74 (54.4)	85 (62.5)	
Thymectomy	191 (46.1)	40 (27.8)		46 (33.8)	39 (28.7)	
Debulking	25 (6.0)	10 (6.9)		10 (7.4)	10 (7.4)	
NOS.	13 (3.1)	2 (1.4)		6 (4.4)	2 (1.5)	
Chemotherapy			<0.001			0.805
Yes	144 (34.8)	88 (61.1)		82 (60.3)	80 (58.8)	
No	270 (65.2)	56 (38.9)		54 (39.7)	56 (41.2)	
Radiotherapy			0.002			0.898
Yes	220 (53.1)	98 (68.1)		90 (66.2)	91 (66.9)	
No	194 (46.9)	46 (31.9)		46 (33.8)	45 (33.1)	

LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; NOS.: Not otherwise specified.

3.3.5 Univariate and multivariate Cox regression analysis of patients after PSM.

3.3.5.1 Univariate and multivariate Cox analysis of patients in N0 and N+ cohort after PSM.

As revealed by the univariate Cox survival analysis of patients in the N0 group and N+ group, the status of LN and surgical type can be taken as the prognostic factors for OS, while the status of lymph node can be treated as the prognostic factor for CSS (Table 8). These factors were factored into multivariate Cox analysis, and N0 was considered an independent superior factor in OS and CSS prognosis. The surgery type is regarded as a prognostic factor of OS. Table 9 lists the results of multivariate analysis. Some of the results in Table 8 and 9 have been shown in the doctoral Publication Table 3 (23).

Table 8. Univariate Cox proportional hazard regression model analysis on risk factors of OS and CSS in N0 and N+ subgroup cohort after PSM.

Variables	Univariable analysis of OS HR (95% CI)	*P*	Univariable analysis of CSS HR (95% CI)	*P*
Gender				
Male vs. Female	0.791 (0.446-1.402)	0.423	0.893 (0.430-1.855)	0.762
Age (years)				
>60 vs. ≤60	1.697 (0.951-3.027)	0.073	1.395 (0.676-2.877)	0.368
Race				
Other vs. Caucasoid	0.993 (0.442-2.231)	0.986	0.888 (0.306-2.574)	0.827
Marriage				
Other vs. Married	0.915 (0.512-1.636)	0.764	1.041 (0.503-2.155)	0.913
Histology Type				
TENTs vs. TCs	1.089 (0.427-2.779)	0.858	1.291 (0.448-3.719)	0.636
Region		0.870		0.861
Northern Plains vs. East	0.733 (0.246-2.184)	0.577	0.580 (0.128-2.624)	0.479
Pacific Coast vs. East	1.145 (0.609-2.155)	0.674	1.122 (0.507-2.481)	0.777
Southwest vs. East	1.086 (0.315-3.739)	0.896	1.026 (0.226-4.667)	0.973
Grade		0.265		0.618
II vs. I	9008.378 (0.001-7.808E+131)	0.952	14558.111 (0.000-1.765E+142)	0.953
III/IV vs. I	30362.498 (0.001-2.624E+132)	0.945	27527.210 (0.000-3.684E+142)	0.950
Tumor Size (cm)				
>6.0 vs. ≤6.0	1.858 (0.988-3.495)	0.054	2.224 (0.951-5.205)	0.065
Lymph Node Status				
N+ vs. N0	2.158 (1.190-3.914)	0.011	2.271 (1.055-4.886)	0.036
M-K Stage				
III/IV vs. IIb	21.775 (0.040-11978.741)	0.339	21.723 (0.011-43902.551)	0.428
Surgery Type		0.014		0.065
Thymct vs. Ext Thymect	0.299 (0.108-0.827)	0.020	0.314 (0.090-1.096)	0.069
Debulking vs. Ext Thymct	0.258 (0.104-0.644)	0.004	0.264 (0.086-0.808)	0.020
Chemotherapy				
No vs. Yes	1.197 (0.672-2.131)	0.542	1.250 (0.605-2.592)	0.545
Radiotherapy				
No vs. Yes	1.464 (0.827-2.591)	0.190	0.962 (0.457-2.025)	0.918

OS: Overall Survival; CSS: Cancer-Specific Survival; HR: Hazard Ratio; CI: Confidence Interval; LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; Thymct: Thymectomy.

Table 9. Multivariate Cox proportional hazard regression model analysis on risk factors of OS and CSS in N0 and N+ subgroup cohort after PSM.

Variables	Multivariable analysis of OS		Multivariable analysis of CSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Lymph Node Status				
N+ vs. N0	2.394 (1.283-4.466)	0.006	2.271 (1.055-4.886)	0.036
Surgery Type				
Thymct vs. Ext Thymct	0.248 (0.088-0.696)	0.008		
Debulking vs. Ext Thymct	0.207 (0.081-0.526)	0.001		

OS: Overall Survival; CSS: Cancer-Specific Survival; HR: Hazard Ratio; CI: Confidence Interval; Ext: Extended; Thymct: Thymectomy.

3.3.5.2 Univariate and multivariate Cox analysis of patients in N0 and LND- cohort after PSM.

According to the univariate Cox survival analysis of patients in the LND- group and the N0 group, age, grade, tumor size, lymph node status, M-K stage and surgery type were prognostic factors for OS, while tumor size, lymph node status, M-K stage, surgery type and chemotherapy were prognostic factors for CSS, as shown in Table 10. With these factors factored into the multivariate Cox analysis, it was discovered that there were independent factors in the correlation with good OS and CSS prognosis for patients with N0. Pathological grade, M-K stage and the extent of the performed resection were determined as independent risk factors for OS, while tumor size and M-K stage were identified as the independent risk factors for CSS. The results of multivariate Cox analysis are shown in Table 11. Part of the results in Table 10 and 11 have been demonstrated in the doctoral Publication Table 4 (23).

Table 10. Univariate Cox proportional hazard regression model analysis on risk factors of OS and CSS in LND- and N0 subgroup cohort after PSM.

Variables	Univariable analysis of OS		Univariable analysis of CSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender				
Male vs. Female	1.064 (0.806-1.405)	0.663	1.054 (0.710-1.566)	0.793
Age (years)				
>60 vs. ≤60	1.496 (1.131-1.981)	0.005	0.866 (0.589-1.274)	0.466
Race				
Other vs. Caucasoid	1.233 (0.924-1.646)	0.154	1.149 (0.760-1.737)	0.511
Marriage				
Other vs. Married	0.892 (0.669-1.189)	0.434	0.682 (0.442-1.052)	0.084
Histology Type				
TENTs vs. TCs	0.675 (0.447-1.019)	0.061	0.785 (0.447-1.381)	0.401
Region		0.695		0.497
Northern Plains vs. East	0.975 (0.605-1.572)	0.917	0.935 (0.455-1.919)	0.854
Pacific Coast vs. East	1.169 (0.859-1.591)	0.320	1.296 (0.831-2.021)	0.253
Southwest vs. East	1.229 (0.630-2.397)	0.545	1.591 (0.660-3.836)	0.301

Table 10. (*continued*)

Variables	Multivariable analysis of OS		Multivariable analysis of CSS	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Grade		0.043		0.053
II vs. I	1.509 (0.694-3.280)	0.299	4.511 (1.025-19.857)	0.046
III/IV vs. I	2.159 (1.087-4.288)	0.028	5.558 (1.353-22.840)	0.017
Tumor Size (cm)				
>6.0 vs. ≤6.0	1.459 (1.092-1.949)	0.011	2.653 (1.709-4.119)	<0.001
Lymph Node Status				
N0 vs. LND-	0.717 (0.546-0.942)	0.017	0.614 (0.415-0.909)	0.015
M-K Stage		<0.001		<0.001
IIb vs. I/IIa	1.542 (1.107-2.148)	0.010	3.773 (2.033-7.002)	<0.001
III/IV vs. I/IIa	3.143 (2.119-4.662)	<0.001	7.318 (3.724-14.383)	<0.001
Surgery Type		0.030		0.032
Thymct vs. Ext Thymct	1.132 (0.845-1.517)	0.406	1.208 (0.796-1.833)	0.375
Debulking vs. Ext Thymct	2.087 (1.209-3.604)	0.008	2.581 (1.266-5.261)	0.009
Chemotherapy				
No vs. Yes	0.904 (0.682-1.198)	0.482	0.635 (0.431-0.935)	0.021
Radiotherapy				
No vs. Yes	1.163 (0.887-1.526)	0.275	0.920 (0.623-1.359)	0.675

OS: Overall Survival; CSS: Cancer-Specific Survival; HR: Hazard Ratio; CI: Confidence Interval; LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; Thymct: Thymectomy.

Table 11. Multivariate Cox proportional hazard regression model analysis on risk factors of OS and CSS in LND- and N0 subgroup cohort after PSM.

Variables	Multivariable analysis of OS		Multivariable analysis of CSS	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age (years)				
>60 vs. ≤60	1.421 (0.945-2.139)	0.092		
Grade		0.026		
II vs. I	1.922 (0.793-4.659)	0.148		
III/IV vs. I	2.742 (1.239-6.064)	0.013		
Tumor Size (cm)				
>6.0 vs. ≤6.0	1.367 (0.908-2.059)	0.134	2.014 (1.271-3.191)	0.003
Lymph Node Status				
N0 vs. LND-	0.550 (0.365-0.828)	0.004	0.533 (0.344-0.827)	0.005
M-K Stage		0.000		<0.001
IIb vs. I/IIa	1.519 (0.904-2.551)	0.114	3.255 (1.614-6.562)	0.001
III/IV vs. I/IIa	3.969 (2.155-7.311)	0.000	5.859 (2.694-12.744)	<0.001
Surgery Type		0.016		0.098
Thymct vs. Ext Thymct	1.470 (0.946-2.284)	0.087	1.509 (0.949-2.401)	0.082
Debulking vs. Ext Thymct	2.844 (1.285-6.295)	0.010	1.941 (0.867-4.346)	0.107
Chemotherapy				
No vs. Yes			0.768 (0.490-1.204)	0.250

OS: Overall Survival; CSS: Cancer-Specific Survival; HR: Hazard Ratio; CI: Confidence Interval; LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; Thymct: Thymectomy.

3.3.5.3 Univariate and multivariate Cox analysis of patients in N+ and LND- cohort after PSM.

As revealed by the univariate Cox survival analysis of patients in the LND- group and the N+ group, age, histology type, lymph node status, M-K stage, and surgery type are the influencing factors in the prognosis of OS, while grade, tumor size, lymph node

status, M-K stage, chemotherapy are the prognostic factors for CSS (Table 12). With these factors were included in the multivariate Cox regression analysis, it was found out that the prognostic difference between the LND- group and the N+ group was insignificant. Histology type is regarded as an independent factor for OS prognosis, while tumor size and grade are the independent factors for the prognosis of CSS. The outcomes of the multivariate analysis are presented by Table 13. Some of the results in Table 12 and 13 have been shown in the doctoral Publication Table 5 (23).

Table 12. Univariate Cox proportional hazard regression model analysis on risk factors of OS and CSS in LND- and N+ subgroup cohort after PSM.

Variables	Univariable analysis of OS		Univariable analysis of CSS	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Gender				
Male vs. Female	0.980 (.698-1.377)	0.908	1.137 (0.745-1.735)	0.551
Age (years)				
>60 vs. ≤60	1.527 (1.100-2.118)	0.011*	1.214 (0.816-1.806)	0.340
Race				
Other vs. Caucasoid	0.824 (0.542-1.253)	0.366	0.711 (0.416-1.215)	0.213
Marriage				
Other vs. Married	0.949 (0.662-1.359)	0.774	0.785 (0.498-1.238)	0.298
Histology Type				
TENTs vs. TCs	0.615 (0.429-0.882)	0.008*	0.775 (0.509-1.180)	0.234
Region		0.479		0.545
Northern Plains vs. East	1.413 (0.735-2.714)	0.300	1.680 (0.771-3.659)	0.191
Pacific Coast vs. East	1.052 (0.741-1.493)	0.779	1.232 (0.795-1.908)	0.351
Southwest vs. East	0.578 (0.209-1.600)	0.292	0.952 (0.336-2.696)	0.926
Grade		0.125		0.047
II vs. I	1.253 (0.582-2.696)	0.565	3.500 (1.019-12.021)	0.047
III/IV vs. I	1.800 (0.922-3.511)	0.085	4.280 (1.330-13.772)	0.015
Tumor Size (cm)				
>6.0 vs. ≤6.0	1.211 (0.856-1.714)	0.280	1.708 (1.100-2.652)	0.017
Lymph Node Status				
N+ vs. LND-	1.271 (1.076-1.501)	0.005	1.270 (1.036-1.555)	0.021
M-K Stage		0.004		0.021
IIb vs. I/IIa	0.839 (0.365-1.927)	0.679	1.008 (0.342-2.971)	0.989
III/IV vs. I/IIa	1.668 (0.775-3.590)	0.191	1.977 (0.721-5.419)	0.185
Surgery Type		0.040		0.068
Thymct vs. Ext Thymct	0.537 (0.287-1.005)	0.052	0.557 (0.263-1.180)	0.127
Debulking vs. Ext Thymct	0.467 (0.259-.843)	0.011	0.440 (0.216-0.899)	0.024
Chemotherapy				
No vs. Yes	0.775 (0.554-1.084)	0.136	0.626 (0.411-0.954)	0.029
Radiotherapy				
No vs. Yes	1.094 (0.775-1.543)	0.611	0.902 (0.584-1.393)	0.643

OS: Overall Survival; CSS: Cancer-Specific Survival; HR: Hazard Ratio; CI: Confidence Interval; LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; Thymct: Thymectomy.

Table 13. Multivariate Cox proportional hazard regression model analysis on risk factors of OS and CSS in LND- and N+ subgroup cohort after PSM.

Variables	Multivariable analysis of OS		Multivariable analysis of CSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)				
>60 vs. ≤60	1.384 (0.970-1.973)	0.073		
Histology Type				
TENTs vs. TCs	0.580 (0.395-0.853)	0.006		
Grade				0.046
I vs. I			8.768 (1.138-67.552)	0.037
III/IV vs. I			12.123 (1.571-93.529)	0.017
Tumor Size (cm)				
>6.0 vs. ≤6.0			2.186 (1.181-4.046)	0.013
Lymph Node Status				
N+ vs. LND-	0.999 (0.799-1.250)	0.995	0.810 (0.570-1.149)	0.237
M-K Stage		0.055		0.165
IIb vs. I/IIa	0.787 (0.341-1.820)	0.576	0.424 (0.112-1.598)	0.205
III/IV vs. I/IIa	1.556 (0.669-3.617)	0.305	0.858 (0.223-3.305)	0.824
Surgery Type		0.059		
Thymct vs. Ext Thymct	0.528 (0.278-1.001)	0.050		
Debulking vs. Ext Thymct	0.483 (0.265-0.879)	0.017		
Chemotherapy				
No vs. Yes			1.031 (0.555-1.915)	0.923

OS: Overall Survival; CSS: Cancer-Specific Survival; HR: Hazard Ratio; CI: Confidence Interval; LND: Lymph Node Dissection; M-K: Masaoka-Koga; Ext: Extended; Thymct: Thymectomy.

4. Discussion

In this study, a systemic analysis was conducted using the data of TETs patients as collected from the cancer registration database who had received surgical treatment and LND. On this basis, the potential correlating factors in LNM were identified through both univariable and multivariable logistic regression analyses. The pathological type and T stage of TETs were determined as the independent factors related to LNM. Besides, an analysis was carried out on the prognostic significance of LND in TCs and TNETs. The status of lymph node (pathological N0) was identified as an independent prognostic factor in OS and CSS. However, there was no significant difference observed in the prognostic results between LND- and LNM positive patients in OS and CSS, as confirmed in the PSM subgroup analysis. The patients with pathological N0 had a significantly better prognosis than N+ and LND- patients. In spite of this, there was no significant difference found in the long-term prognosis between the patients undergoing no LND and those with N+.

At present, the staging criteria of TETs are not completely consistent in clinical practice. In 1978, Bergh *et al.* first proposed the staging criteria of thymoma, with thymoma divided into three stages (24). On this basis, Masaoka *et al.* performed an analysis of 96 patients with thymomas treated at Osaka University between 1954 and 1979 (25). According to the surgical findings and pathological diagnosis, thymoma was divided into four stages. Koga *et al.* went further to construct the Masaoka-Koga staging system recognized by International Thymic Malignancy Interest Group (ITMIG) (19). Since then, this staging system had been widely applied in the clinical practice of diagnosing and treating TETs. In spite of this, there remain some ambiguities in this stage. Back in the 1990s, tumor TNM staging gradually matured, but there was still no staging system in place for thymoma. In particular, some scholars found out that metastatic lymph nodes existed in the resected mediastinal fat of thymoma, which was linked to prognosis. In 1991, Yamakawa *et al.* analyzed the prognosis of 207 patients with TETs on the basis of Masaoka staging, based on which the concept of thymic TNM staging was proposed for the first time ever (26). However, the criteria specified by Masaoka staging still apply to the T staging of tumors. Subsequently, Bedini *et al.* made attempt to construct another TNM staging system, which is called Istituto Nazionale Tumori (INT) (27). The staging is designed to be treatment-oriented. Due to its complexity, however, it is not extensively

applied in clinical practice. In 2014, ITMIG conducted research and analysis on more than 6000 cases using the global collaborative multi-center database, and then published the eighth edition of TNM staging opinions. This staging method can be used to evaluate the severity of tumor invasion more systematically and comprehensively in the multi-dimensional of tumor, lymph node and metastasis (28). In T stage, the tumor was divided into T1a, T1b, T2, and T3/4 depending on whether the tumor was localized or invaded the mediastinal pleura, pericardium and surrounding tissue structure. With the map of mediastinal lymph nodes built, the lymph nodes were divided into anterior mediastinum (N1) and deep mediastinum (N2) (29). In the evaluation of metastasis, the solitary pleural and pericardial nodules were identified as M1a, while the pulmonary lesions or other distant metastases were identified as M1b.

In addition to thymoma, TCs and TNETs, rare diseases with higher malignancy, are the two most common malignant tumors in TETs. After our retrieve for the latest NCCN, ESMO, and American Society of Clinical Oncology (ASCO) guidelines, it was found that most of the therapeutic specifications for TNETs refer to TCs. The staging criteria for both TCs and TNETs could also be found in the Masaoka-Koga or TNM stage system (25, 28). Due to the low incidence, the survival difference between such two kinds of tumors remains unclear. Although the previous studies from the ITMIG database demonstrated no differences in the OS and recurrence-free survival (RFS) between these two types of histology (Table 14), a difference was still observed in OS, rather than in CSS, which is possibly attributed to the patient cohorts being different among these studies. Therefore, it is believed that the biological characteristics of these two types of tumors remain worthy of further exploration. Some conclusions drawn in this study can serve as reference in this regard. Moreover, it was demonstrated in this study that TNETs had a higher number of lymph node metastases than TCs, which is similar to the results obtained by Fang *et al.* (30).

In recent years, some scholars have studied LNM in TETs and the impact of LNM on prognosis. Kondo *et al.* conducted a retrospective study using the data collected from 1320 TETs patients at 115 medical centers in 2003. It was discovered that the rate of LNM was 1.8% in thymoma, 26.8% in TCs, and as high as 27.5% in TNETs (31). In 2015, Weksler *et al.* analyzed the data collected from the SEER database between

1988 and 2011 to find out that the proportion of LNM in the cases of thymoma, TCs, and TNETs was 13.3%, 33.5% and 62.3%, respectively (32, 33). The prognoses of patients who were LNM positive were found to be significantly worse compared to those negative. In the study of Weksler, the similar inclusion criteria to this study were applied. The proportion of TCs and TNETs positive for LNM was similar to what was reported in prior studies. However, this study focused on analyzing the occurrence of LNM in different thymoma pathological subtypes, so that the thymomas of unclear pathological types (8580/3: Not Otherwise Specified) were excluded. Differently, these were included in the study of Weksler *et al.* The percentage of thymomas with LNM was found to be 6.8% in this study, which was different than in the different one (13.3%). Similar to our study, Hwang *et al.* found an LNM rate of 5.1% in thymomas in a Korean cohort study (34). In a prospective multicenter clinical study conducted by the Chinese Alliance for Research in Thymomas (ChART), it was found out that 275 patients with TETs underwent intentional lymph node sampling or dissection (30). The proportion of thymoma, TCs, and TNETs patients with LNM in this study was 2.1%, 25% and 50%, respectively, which is similar to the percentage of patients with LNM as found out in our study.

In addition to the pathological subtypes of TETs, the T stage is another significant influencing factor for LNM. The rate of LNM showed more significance as the tumor T-stage increased. In this study, it was revealed that T3/4 was an independent risk factor for LNM in TETs. In addition, the relationship between tumor size and LNM was examined through univariable analysis, but with no significant correlation observed. Therefore, despite the relationship between LNM and tumor size remaining inconclusive, the correlation between LNM and tumor local invasion is likely (15). According to the similar findings in prior studies, the LNM in TETs is associated with the invasiveness of tumors to some extent. The greater the degree of tumor invasion, the higher the rate of LNM (12, 15).

Table 14. Recent literature on the studies of the survival analyses between TCs and TNETs.

Author	Study design	TCs/TNETs	Comments
Kim S. 2020. (35)	RC/ NCDB	578/54	No survival analysis between TCs and TNETs.
Ruffini E. 2019. (36)	PC/ 75 ESTS institutions.	207/49	No survival analysis between TCs and TNETs.
Zhao Y. 2017. (37)	RC/ signal ITMIG center	287/56	There was no significant difference between OS (*P* =0.159) and DFS (*P* =0.696) in TCs and TNETs. Individuals with TNETs were found a significantly greater risk of LNM.
Gu Z. 2017. (18)	RC/ ChART database	265/42 (T: A/AB/B1 =769; T B2/B3=541)	On multivariable analysis, TNETs had a greater proportion of lymph node metastases (TCs vs TNETs: OR =0.351 (95% CI: 0.129–0.957), *P* =0.041). On multivariable survival analysis, tumor histology grade (*P* =0.019) and complete resection (*P* =0.047) were independently related factors to OS.
Filosso PL. 2016. (38)	RC/ ESTS & ITMIG database	728/132	On univariate analysis, tumor histology was not correlated to neither OS (*P* =0.19) nor RFS (P =0.35).
Weksler B. 2015. (32)	RC/ SEER database	176/53	Patients who underwent surgical resection of TCs or TNETs with documented pathological of lymph nodes. On univariate analysis, tumor histology did not influence OS (TC vs. TNET: 1.066 (0.660–1.720), *P* =0.795)

T: Thymoma; RC: Retrospective Cohort; PC: Prospective Cohort; NCDB: National Cancer Database; ESTS: European Society of Thoracic Surgeons; ITMIG: International Thymic Malignancy Interest Group; ChART: Chinese Alliance for Research in Thymomas; SEER: Surveillance, Epidemiology, and End Results; OS: Overall Survival; DFS: Disease-Free Survival; RFS: Recurrence-Free Survival.

According to the description of LND as made in the guidelines, it is necessary for all suspicious lymph nodes to be removed (29). The dissection of lymph nodes around the tumor and anterior mediastinum is recommended for those patients with the TETs in clinical stages I and II. For those patients in clinical stage III, both a systematic dissection of anterior mediastinal lymph nodes and the sampling of some intrathoracic lymph nodes are recommended. For those patients with either suspected or confirmed TCs or TNETs, it is recommended that the systematic sampling should be performed for at least the anterior mediastinal, intrathoracic, supraclavicular, and inferior cervical lymph nodes stations (17). Since the right paratracheal lymph nodes are a major site for LNM of thymic malignancies, LND including that region is recommended for those patients with stage II or later TETs (39). It is necessary for the management of the lymph nodes (the specific location, sampling, or dissection of the lymph nodes) to be recorded in the operative notes (40).

At present, it is recommended by the NCCN, ESMO, and ITMIG guidelines that lymph nodes should be resected at the time of dissection for tumors and thymus, given a large proportion of LNM in TCs as a significant factor for poor prognosis (20, 21, 41). However, there is still no further data supporting the oncology-related survival analysis in this respect, such as the conclusion about whether undergoing LND makes difference to the prognosis of patients with TCs or TNETs. In previous studies, an analysis was conducted to assess the impact of LND on the prognosis of patients with thymoma and TCs, which led to the finding that there was no difference in the 10-year freedom from recurrence rate between the LND+ and LND- groups regardless of whether patients were diagnosed with thymoma or TCs (34). Therefore, an attempt was made in this study to further explore the significance of LND for the long-period prognostic results of TCs and TNETs.

According to a survey by ITMIG, 54% found the lymph node map helpful, but only 48% used it in clinical practice (20). As per the nodal map, LND of the N1 stations was performed in thymomas from 50% of respondents (N =107) and in TCs from 66% of respondents (N =144). LND of the N2 stations was carried out in thymomas from 21% of respondents (N =45) and TCs from 41% of respondents (N =88), respectively. Up until very recently, LND has been rarely conducted after the removal of primary thymic malignancies, and the effect of lymphatic node spread has been long-period undervalued. Therefore, when taking these into considerations, this study was aimed to increase public awareness, that is, LND is supposed to be routinely performed for the surgery of thymic malignancies. On this basis, it might be advisable to further assess the impact of different types of LND (stations, number, and extent) on the prospect of long-term survival for TCs and TNETs patients. As shown in Table 15 below, there is a brief review conducted of the recent publications on the prognosis-related impact of LND in thymic malignancies.

Because this study focused on the significance of LND in TCs and TNETs, patients who did not undergo lymph node resection were assigned to the reference group. Univariable survival analysis was performed between patients who underwent LND and those who did not (LND+ vs. LND-). No remarkable differences in prognosis were found between these groups. Obviously, there are patients with LNM positive mixed in the two

groups: a factor that can have a significant negative impact on the prognosis.

Table 15. Recent publications on the prognosis influence of LND in thymic malignancies.

Author	T/TCs/TNETs	Comments
Park. 2013. (39)	0/37/0	The DFS probability of the sufferers with and without LNM were not significantly different (*P* =0.11).
Fang. 2018. (30)	243/24/8	On multivariate analysis, type B3/TCs/TNETs, stage T3/4, and N2 LND predicted a higher probability of LNM.
Hwang. 2018. (34)	594/182/0	The 10-year FFR ratio of pN1/2 was remarkably inferior in contrast to pN0 (*P* <0.001). LND was a safe procedure without increasing postoperative complication and mortality. The 10-year FFR ratio of patients undergoing LND or not were similar in thymoma (*P* =0.46) subgroup and TCs subgroup (*P* =0.42).
Cheufou. 2019. (42)	0/43/10	LNM was related to unsatisfactory OS (*P* =0.044). M-K stage (IV vs. I to III) was another significant prognosticator (*P* =0.0002). Organ metastasis occurred in 18 sufferers at the time of thymectomy and were associated with worse survival results (*P* =0.001).

T: Thymoma; LND: Lymph Node Dissection; FFR: Freedom from Recurrence; DFS: Disease-Free Survival; OS: Overall survival.

For this reason, LND+ was split into two groups, namely N0 and N+. Then, the survival analysis was conducted, and the two groups were compared with LND-, respectively, so as to reveal the significance of LND in assessing the accuracy of long-term prognosis for patients and the impact on the OS. In order to confirm the results, subgroup analyses were conducted for patients in these three groups after PSM. It was discovered that N+ had a clearly worse prognosis than N0. When the group of patients underwent no LND, compared with N0 and N+ groups respectively, it was found out that those patients with N0 had benefited more statistically than those undergoing no LND. There was no statistical difference observed in the multivariable analysis between those patients with N+ and those not undergoing LND, suggesting that LND contributed to assessing the LNM status and was more accurate in predicting long-period prognostic results for patients, which coincides with the outcomes acquired from the entire cohort study before PSM. Apart from that, a survival analysis was conducted through comparison between the two subgroups of patients suffering LND to different extents (LND 1-3 vs. LND ≥4) in N0 group. Though the difference in survival between the two groups showed no statistical significance, the median OS of sufferers in the LND ≥4 subgroup remained more satisfactory as compared to those patients in the LND 1-3

subgroup.

The randomized controlled trial (RCT) studies provide the most rigorous and robust evidence to determining whether a causal relationship exists between an intervention and the outcome, with a much higher level of proof obtained than those general retrospective studies. Given that TCs and TNETs are rare malignancies, however, there is still no randomized studies on these diseases currently. It is believed as challenging among some scholars to conduct the randomized trials due to the low annual incidence of TCs (43, 44). For a retrospective study, there are some inherent drawbacks. Currently, the guidelines applied in the U.S. and Europe recommend that LND needs to be performed at the time of thymectomy, which is due to a high proportion (20%) of lymph nodes metastasis in TCs (in our study it was 30% for TCs and 58.8% for TNETs) (6, 21). However, there was no further data supporting the analysis of oncology-related survival (6).

Given the rarity of these diseases and the recommendations made in the current guidelines for TCs and TNETs, it is inadvisable to explore the significance of LND through prospective RCT studies in the future, which is because this might contravene the guidelines or even the medical ethical requirements. In case that some patients with TCs were randomly enrolled into the cohort with reluctance to accept LND in the experimental design, it might be in breach of the relevant clinical guidelines or even the medical ethics. Since the real-world evidence (RWE) research has already used cumulative data, there wouldn’t be any infringement on the rights and benefits or detriments with respect to the physical states of patients. As argued by some scholars, if clinical RWE is made good use of, it will be easy to study various controversial issues, thus improving future treatment guideline modalities (45). Therefore, the RWE research conducted using the national database is expected to address the small sample size of rare diseases, while the data collected from the real world can be used to reveal the adverse effects of existing methods of non-standard treatment. Additionally, further data support can be provided to demonstrate the importance of lymph node dissection for those patients with TCs and TNETs. On this basis, it is worth expecting that more prospectively designed databases or clinical trials will help provide a higher level of evidence required to conduct further studies on the scope of standardized lymph node

resection for this rare disease in the future.

In the meantime, there still exist some limitations in this research. This is a retrospective study, which makes it inevitable for some natural deviations to occur. The data was collected from the cancer registry database, but there were some important clinicopathological variables that could not be wholly included in the study (e.g., specific N1 or N2 stations of LND and metastasis), which might affect the comprehensiveness of the study to some extent.

In this study, a systematic analysis was conducted on the clinical and pathological information about TETs sufferers in the SEER database, based on which the proportion of each pathological subtype of TETs emerging in recent decades was evaluated. In TETs, pathological type and T stage were treated as independent risk factors for LNM. Especially in TCs and TNETs, lymph node involvement is relatively high. LND can lead to more accurate staging for these patients. Pathological N0 is an independent superior prognostic factor for OS and CSS. For the patients who did not undergo LND, there was no significant difference observed in the prognosis between the patients with LNM positive and this group of patients.

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6. Affidavit

Statutory Declaration

"I, [Ziming, Wang], by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic [*Risikofaktoren für Lymphknotenmetastasen bei epithelialen Thymustumoren und prognostische Bedeutung von Lymphknotendissektion bei Thymuskarzinomen und neuroendokrinen Tumoren des Thymus; Risk factors correlated to lymph node metastasis in thymic epithelial tumors and the prognostic significance of lymph node dissection for thymic carcinomas and thymic neuroendocrine tumors*], independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

[In the case of having conducted your doctoral research project completely or in part within a working group:] Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date Signature

Declaration of your own contribution to the publication

[Ziming Wang] contributed the following to the below listed publications:

Publication: Effect of Lymph Node Dissection on the Prognosis of Thymic Carcinomas and Thymic Neuroendocrine Tumors.
Zi-Ming Wang, Feng Li, Xin-Ying Liu, Dania Nachira, Harun Badakhshi, Jens-C Rückert, Mahmoud Ismail
Seminars in Thoracic and Cardiovascular Surgery (official publication of The American Association for Thoracic Surgery)
Submitted and accepted year: 2020

Contribution: In this research, Ziming Wang systematically reviewed the related literature on the current research status and latest advances in TETs, combined with the situation of daily clinical practice, and carried out the development work of this scientific topic. Harun Badakhshi and Mahmoud Ismail approved the research protocol and scientific study plan. Ziming Wang was responsible for the conceptualization and design work of this study, research materials acquisition from the database, and data curation. Xin-Ying Liu and Mahmoud Ismail reviewed the enrollment criteria and selection process of the study. The statistical methods involved in this research have been reviewed by Feng Li. Ziming Wang made use of the statistical software (SPSS [IBM Corp, Armonk, USA], R project [Vienna, Austria]) and analysis packages (‘rms’, ‘matchit’, ‘survival’, ‘ggplot2’ R software packages) to analyze the data and summarize the research results. Jiani Wang from the Institute for Social Medicine, Epidemiology and Health Economics at the Charité Berlin conducted the statistical assistance and the supervision work of the data analysis process. Ziming Wang completed the visualization works of all the figures and tables in this study and wrote the original draft of the manuscript. The accuracy of all the critical interpretation including statistical evaluations, tables, and figures were then checked by Feng Li, Dania Nachira, Harun Badakhshi, and Mahmoud Ismail. Harun Badakhshi, Jens-C Rückert, and Mahmoud Ismail supervised the process of this study and reviewed the first draft manuscript. Ziming Wang revised the manuscript based on the suggestions and comments from Harun Badakhshi, Mahmoud Ismail, and other co-authors. All co-authors reviewed the final manuscript and agreed to submit it for publication.

_____
Signature, date and stamp of first supervising university professor / lecturer

_____
Signature of doctoral candidate

7. Excerpt of the Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI Selected Categories: **"CARDIAC and CARDIOVASCULAR SYSTEMS"** Selected Category Scheme: WoS

Gesamtanzahl: 138 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	CIRCULATION	158,218	23.603	0.205020
2	EUROPEAN HEART JOURNAL	59,968	22.673	0.140620
3	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	101,927	20.589	0.190280
4	Nature Reviews Cardiology	7,100	20.260	0.021130
5	CIRCULATION RESEARCH	51,539	14.467	0.071470
6	JAMA Cardiology	4,740	12.794	0.030110
7	JACC-Cardiovascular Imaging	10,110	12.740	0.027550
8	BASIC RESEARCH IN CARDIOLOGY	4,704	11.981	0.006380
9	EUROPEAN JOURNAL OF HEART FAILURE	12,784	11.627	0.028700
10	JACC-Heart Failure	4,117	8.750	0.019180
11	JACC-Cardiovascular Interventions	11,371	8.432	0.037330
12	CARDIOVASCULAR RESEARCH	21,526	8.168	0.019950
13	JOURNAL OF HEART AND LUNG TRANSPLANTATION	12,465	7.865	0.028140
14	Cardiovascular Diabetology	6,179	7.332	0.011390
15	PROGRESS IN CARDIOVASCULAR DISEASES	4,193	6.763	0.008340
16	European Heart Journal-Cardiovascular Pharmacotherapy	521	6.696	0.001640
17	Circulation-Heart Failure	6,773	6.033	0.018490
18	European Journal of Preventive Cardiology	5,589	5.864	0.015370
19	HEART RHYTHM	12,246	5.731	0.028620
20	Circulation-Cardiovascular Imaging	5,574	5.691	0.016320

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	JOURNAL OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY	11,347	5.508	0.018230
22	Circulation-Cardiovascular Interventions	5,012	5.493	0.018140
23	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	5,205	5.361	0.011120
24	Clinical Research in Cardiology	3,321	5.268	0.007280
25	HEART	18,108	5.213	0.030140
26	Circulation-Cardiovascular Quality and Outcomes	4,728	5.071	0.014350
27	CANADIAN JOURNAL OF CARDIOLOGY	6,980	5.000	0.017630
28	European Heart Journal-Cardiovascular Imaging	6,359	4.841	0.023110
29	TRENDS IN CARDIOVASCULAR MEDICINE	2,695	4.755	0.003920
30	REVISTA ESPANOLA DE CARDIOLOGIA	3,672	4.642	0.004610
31	Journal of the American Heart Association	17,149	4.605	0.070620
32	Circulation-Cardiovascular Genetics	3,090	4.534	0.008600
33	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	28,491	4.451	0.034300
34	Circulation-Arrhythmia and Electrophysiology	6,344	4.393	0.016630
35	AMERICAN HEART JOURNAL	19,814	4.153	0.026810
36	JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY	14,031	4.133	0.017960
37	CARDIOVASCULAR DRUGS AND THERAPY	2,114	4.069	0.003340
38	Circulation-Genomic and Precision Medicine	375	4.063	0.002220
39	Hellenic Journal of Cardiology	987	4.047	0.001000
40	EUROPACE	9,973	4.045	0.024750

Selected JCR Year: 2019; Selected Categories: "CARDIAC and CARDIOVASCULAR SYSTEMS"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
41	EuroIntervention	5,542	3.993	0.016590
42	ATHEROSCLEROSIS	24,587	3.919	0.036590
43	Frontiers in Cardiovascular Medicine	1,303	3.915	0.004020
44	ESC Heart Failure	1,276	3.902	0.004120
45	AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY	26,114	3.864	0.020400
46	Global Heart	1,074	3.862	0.003180
47	European Heart Journal-Acute Cardiovascular Care	1,555	3.813	0.005430
48	NUTRITION METABOLISM AND CARDIOVASCULAR DISEASES	6,026	3.700	0.008820
49	ANNALS OF THORACIC SURGERY	35,221	3.639	0.040380
50	HEART FAILURE REVIEWS	2,697	3.538	0.005130
51	EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY	16,682	3.486	0.025820
52	JOURNAL OF CARDIAC FAILURE	4,983	3.435	0.008730
53	JOURNAL OF NUCLEAR CARDIOLOGY	3,600	3.366	0.004570
54	Journal of Cardiovascular Translational Research	1,656	3.312	0.003140
55	INTERNATIONAL JOURNAL OF CARDIOLOGY	31,193	3.229	0.068160
56	RESPIRATORY MEDICINE	11,934	3.095	0.013490
57	Annals of Cardiothoracic Surgery	1,828	3.058	0.005060
58	CURRENT PROBLEMS IN CARDIOLOGY	567	2.966	0.000740
59	Journal of Cardiovascular Computed Tomography	1,809	2.892	0.004850
60	American Journal of Cardiovascular Drugs	1,063	2.674	0.001580

Selected JCR Year: 2019; Selected Categories: "CARDIAC and CARDIOVASCULAR SYSTEMS"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
61	Cardiovascular Diagnosis and Therapy	1,081	2.615	0.003050
62	JOURNAL OF CARDIOVASCULAR PHARMACOLOGY	5,340	2.598	0.003810
63	AMERICAN JOURNAL OF CARDIOLOGY	35,187	2.570	0.039490
64	CIRCULATION JOURNAL	9,860	2.540	0.014780
65	Cardiovascular Therapeutics	1,351	2.538	0.002120
66	Journal of Geriatric Cardiology	1,231	2.491	0.003270
67	Archives of Cardiovascular Diseases	1,628	2.434	0.003570
67	Current Cardiology Reports	2,127	2.434	0.005990
69	JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY	6,886	2.424	0.010110
70	Heart Failure Clinics	1,020	2.327	0.002330
71	JOURNAL OF CARDIOVASCULAR PHARMACOLOGY AND THERAPEUTICS	1,358	2.322	0.002140
71	Korean Circulation Journal	1,335	2.322	0.002430
73	European Journal of Cardiovascular Nursing	1,723	2.296	0.002700
74	Cardiovascular Toxicology	1,272	2.284	0.001730
75	JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA	5,371	2.258	0.007310
76	CLINICAL CARDIOLOGY	4,233	2.248	0.008620
77	Journal of Cardiology	3,243	2.246	0.006090
78	Pulmonary Circulation	1,651	2.205	0.004290
79	Heart Lung and Circulation	2,889	2.194	0.006490
80	CURRENT OPINION IN CARDIOLOGY	2,051	2.149	0.003530
81	Seminars in Thoracic and Cardiovascular Surgery	1,320	2.133	0.002210

Selected JCR Year: 2019; Selected Categories: "CARDIAC and CARDIOVASCULAR SYSTEMS"

8. Appendix

Publication: Effect of Lymph Node Dissection on the Prognosis of Thymic Carcinomas and Thymic Neuroendocrine Tumors.

Wang ZM, Li F, Liu XY, Nachira D, Badakhshi H, Rückert JC, Ismail M. Semin Thorac Cardiovasc Surg. 2021 Summer;33(2):568-578. Epub 2020 Nov 9.

DOI: 10.1053/j.semtcvs.2020.11.004.

Link: https://doi.org/10.1053/j.semtcvs.2020.11.004.

9. Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

10. Publications

1. **Wang ZM**, Li F, Liu XY, Nachira D, Badakhshi H, Rückert JC, Ismail M. Effect of Lymph Node Dissection on the Prognosis of Thymic Carcinomas and Thymic Neuroendocrine Tumors. Semin Thorac Cardiovasc Surg. 2021 Summer;33(2):568-578. Impact Factor: 2.133 (2019)

2. **Wang ZM**, Xu QR, Kaul D, Ismail M, Badakhshi H. Significance of tumor mutation burden and immune infiltration in thymic epithelial tumors. Thorac Cancer. 2021 Jul;12(13):1995-2006. Impact Factor: 3.502 (2020)

3. **Wang ZM**, Swierzy M, Balke D, Nachira D, González-Rivas D, Badakhshi H, Ismail M. Dynamic nomogram for long-term survival in patients with non-small cell lung cancer after pneumonectomy. J Thorac Dis. 2021 Apr;13(4):2276-2287. Impact Factor: 2.894 (2020)

4. Dai L, **Wang ZM**, Xue ZQ, He M, Yuan Y, Shang XQ, Chen KN; Chinese Cooperative Primary Malignant Melanoma of the Esophagus Group (CCPMMEG). Results of surgical treatment for primary malignant melanoma of the esophagus: A multicenter retrospective study. J Thorac Cardiovasc Surg. 2020 Mar 20:S0022-5223(20)30571-7. Impact Factor: 5.204 (2020)

5. Badakhshi H, **Wang ZM**, Li RJ, Ismail M, Kaul D. Survival and Prognostic Nomogram for Primary Gastrointestinal Melanoma (PGIM): A Population-based Study. Anticancer Res. 2021 Feb;41(2):967-974. Impact Factor: 2.481 (2020)

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I want to thank Dr. Diego Gonzalez-Rivas. As a well-known scholar in the field of thoracic surgery, he demonstrated with practical actions how thoracic surgeons should keep innovating and influence the development of thoracic surgery in the world. I hope I could be as enthusiastic and energetic as him, and he will be a role model for my career development.

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