JCS Journal of Chest Surgery
https://doi.org/10.5090/jcs.21.124
pISSN: 2765-1606 eISSN: 2765-1614
J Chest Surg. 2022;55(2):126-142

Clinical Research

An Overview of Surgical Treatment of Thymic Epithelial Tumors in Korea: A Retrospective Multicenter Analysis

Jun Oh Lee, M.D.[1,*], Geun Dong Lee, M.D., Ph.D.[1,*], Hyeong Ryul Kim, M.D., Ph.D.[1], Dong Kwan Kim, M.D., Ph.D.[1], Seung-Il Park, M.D., Ph.D.[1], Jong Ho Cho, M.D., Ph.D.[2], Hong Kwan Kim, M.D., Ph.D.[2], Yong Soo Choi, M.D., Ph.D.[2], Jhingook Kim, M.D., Ph.D.[2], Young Mog Shim, M.D., Ph.D.[2], Samina Park, M.D.[3], In Kyu Park, M.D., Ph.D.[3], Chang Hyun Kang, M.D., Ph.D.[3], Young Tae Kim, M.D., Ph.D.[3], Seong Yong Park, M.D., Ph.D.[2,4], Chang Young Lee, M.D., Ph.D.[4], Jin Gu Lee, M.D., Ph.D.[4], Dae Joon Kim, M.D., Ph.D.[4], Hyo Chae Paik, M.D., Ph.D.[4], for the Korean Association for Research on the Thymus

[1]Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, Ulsan University College of Medicine; [2]Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine; [3]Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine; [4]Department of Thoracic and Cardiovascular Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

ARTICLE INFO
Received October 5, 2021
Revised December 15, 2021
Accepted January 12, 2022

Corresponding author
Dong Kwan Kim
Tel 82-2-3010-3580
Fax 82-2-3010-6966
E-mail dkkim@amc.seoul.kr
ORCID
https://orcid.org/0000-0003-1984-0352

*These two authors contributed equally to this work as first authors.

Background: Thymic epithelial tumors (TETs) are rare, and information regarding their surgical outcomes and prognostic factors has rapidly changed in the past few decades. We analyzed surgical treatment practices for TETs and outcomes in terms of overall survival (OS) and freedom from recurrence (FFR) during a 13-year period in Korea.
Methods: In total, 1,298 patients with surgically resected TETs between 2000 and 2013 were enrolled retrospectively. OS and FFR were calculated using the Kaplan-Meier method and evaluated with the log-rank test. Prognostic factors for OS and FFR were analyzed with multivariable Cox regression.
Results: A total of 1,098 patients were diagnosed with thymoma, and 200 patients were diagnosed with thymic carcinoma. Over the study period, the total number of patients with surgically treated TETs and the proportion of patients who underwent minimally invasive thymic surgery (MITS) increased annually. The 5-year and 10-year survival rates of surgically treated TETs were 91.0% and 82.1%, respectively. The 5-year and 10-year recurrence rates were 86.3% and 80.0%, respectively. The outcomes of surgically treated TETs improved over time. Multivariable Cox hazards analysis for OS, age, tumor size, and Masaoka-Koga stage were independent predictors of prognosis. The World Health Organization classification and tumor-node-metastasis (TNM) staging were also related to the prognosis of TETs.
Conclusion: Surgical treatment of TETs achieved a good prognosis with a recent increase in MITS. The M-K stage was the most important prognostic factor for OS and FFR. The new TNM stage could also be an effective predictor of the outcomes of TETs.

Keywords: Thymic epithelial tumor, Thymectomy, Video-assisted thoracic surgery

Introduction

Thymic epithelial tumors (TETs) are rare tumors. However, the most common mediastinal tumors in adults arise from epithelial thymic cells and represent approximately 0.2% to 1.5% of all malignancies. TETs comprise a heterogeneous group with a wide spectrum, with thymoma and thymic carcinoma being the most frequent histologic subtypes.

Many previous studies have suggested a better prognosis in TETs with an early Masaoka-Koga (M-K) stage, complete resection status, and a World Health Organization (WHO) classification of medullary thymoma. Surgical resection, such as total thymectomy and complete excision of

the tumor, is the standard therapeutic approach for TETs. Patients with surgically unresectable TETs have alternatively been administered radiotherapy and chemotherapy in the setting of neoadjuvant, adjuvant, and palliative treatment, but the efficacy and results of non-surgical treatment remain unclear. Over the past few decades, clinical information regarding patients with surgically treated TETs has substantially changed. The new tumor-node-metastasis (TNM) staging system of TETs was established in 2014, and all TETs are now regarded as potentially malignant tumors. With recent developments in video- and robot-assisted thoracoscopic surgical instruments and practices, minimally invasive thymic surgery (MITS) has been increasingly indicated for thymoma.

The Korean Association for Research on the Thymus (KART) developed a retrospective database to define TETs' pathophysiologic and clinical profile with the participation of 4 medical institutions in Korea. We compiled data from 1,298 patients with thymoma and thymic carcinomas surgically treated between 2000 and 2013.

The aim of this study was to report recent changes in the surgical treatment of TETs and investigate a population-based series of TETs in Korea, with an analysis of the clinicopathologic and surgical outcomes.

Methods

Patients

The study was reviewed by the Institutional Review Board of Asan Medical Center (no., 2018-12963) and approved as a minimal-risk retrospective study that did not require individual consent according to the institutional guidelines for consent waivers. The KART established a multi-institutional database of patients who were surgically treated for TETs at 4 medical institutions in Korea. From January 2000 to December 2013, we compiled data on 1,325 patients with thymoma and thymic carcinoma. Among these, we excluded patients with other histologic types of mediastinal tumors, such as sarcoma, and patients who were surgically treated for recurrence of TETs. In total, 1,298 patients were included in this study, and their medical records were reviewed retrospectively.

Statistical analysis

The cumulative probability rate of achieving overall survival (OS) and freedom from recurrence (FFR) was estimated with the Kaplan-Meier method. The univariable analysis to potentially predict OS and FFR was conducted using a Cox proportional hazard model. Variables with p-values <0.20 were entered into the multivariable analysis. The proportional hazards assumption in the Cox model was assessed using Schoenfeld residuals. Continuous variables were compared using the Student t-test and 1-way analysis of variance. All results were expressed as the mean± standard deviation (SD) or as proportions. Statistical significance was considered with p-values <0.05. All statistical analyses were performed without correction for multiple testing. All statistical analyses were performed using the R software package ver. 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Results

Patient characteristics

Preoperative patients' characteristics and demographics are summarized in Table 1. The median follow-up period was 52.3 months, during which 139 patients died. Patients' age ranged from 15 to 81 years, with a mean age of 51.0± 13.00 years. Forty-eight percent of patients were women. The thymic carcinoma group was older and had a higher smoking rate (p<0.001). Fifty-five percent of patients were asymptomatic. In both the thymoma and thymic carcinoma groups, an incidental finding (asymptomatic) of TETs was the most common presentation. A comparison of clinical symptoms between thymoma and thymic carcinoma is shown in Fig. 1. Myasthenia gravis (MG), which represents a paraneoplastic syndrome, was observed more frequently in the thymoma group than in the thymic carcinoma group (25% versus 2%, p<0.001). The only other paraneoplastic phenomenon found in the study group was red cell aplasia, which was observed in 1 patient. The preoperative clinical MG profiles are shown in Appendix 1. The most common clinical symptom of MG patients was ptosis (274 patients, 86.2%). However, most of the patients had symptoms less than Myasthenia Gravis Foundation of America clinical classification III (274 patients, 86.2%). In total, 87.4% of patients received pyridostigmine (Mestinon) treatment and 7% of patients received steroid treatment preoperatively.

Operative details of the study population

The operative details of the overall study population are shown in Table 2. Standard median sternotomy was performed in more than half of the cases (748 patients, 57.6%).

https://doi.org/10.5090/jcs.21.124

Table 1. Baseline characteristics of the overall study population

Characteristic	Total (N=1,298)	Thymoma (N=1,098)	Thymic carcinoma (N=200)	p-value
Age (yr)	51.0±13.0	50.0±12.9	57.0±11.9	<0.001
Sex				<0.001
Male	681 (52.5)	540 (49.2)	141 (70.5)	
Female	671 (47.5)	558 (50.8)	59 (29.5)	
Symptomatic event	579 (44.6)	494 (45.0)	85 (42.5)	0.566
Previous malignancy	104 (8.0)	84 (7.7)	20 (10.0)	0.325
Underlying disease				
Diabetes mellitus	105 (8.1)	84 (7.7)	21 (10.5)	0.223
Hypertension	284 (21.9)	220 (20.0)	64 (32.0)	<0.001
Coronary artery occlusive disease	23 (1.8)	16 (1.5)	7 (3.5)	0.085
Tuberculosis	93 (7.2)	75 (6.8)	18 (9.0)	0.345
Hepatitis	51 (3.9)	43 (3.9)	8 (4.0)	1.000
Renal disease	13 (1.0)	11 (1.0)	2 (1.0)	1.000
Chronic obstructive pulmonary disease	13 (1.0)	6 (0.5)	7 (3.5)	0.001
Cerebro-vascular accident	24 (1.8)	18 (1.6)	6 (3.0)	0.304
Thyroid disease	32 (2.5)	26 (2.4)	6 (3.0)	0.778
Paraneoplastic syndrome				<0.001
Myasthenia gravis	316 (24.3)	310 (28.2)	6 (3.0)	
Red cell aplasia	1 (0.1)	1 (0.1)	0	
Smoking				<0.001
Never smoker	857 (66.0)	763 (69.5)	94 (47.0)	
Ex-smoker	228 (17.6)	170 (15.5)	58 (29.0)	
Current smoker	213 (16.4)	165 (15.0)	48 (24.0)	

Values are presented as mean±standard deviation or number (%), unless otherwise stated.

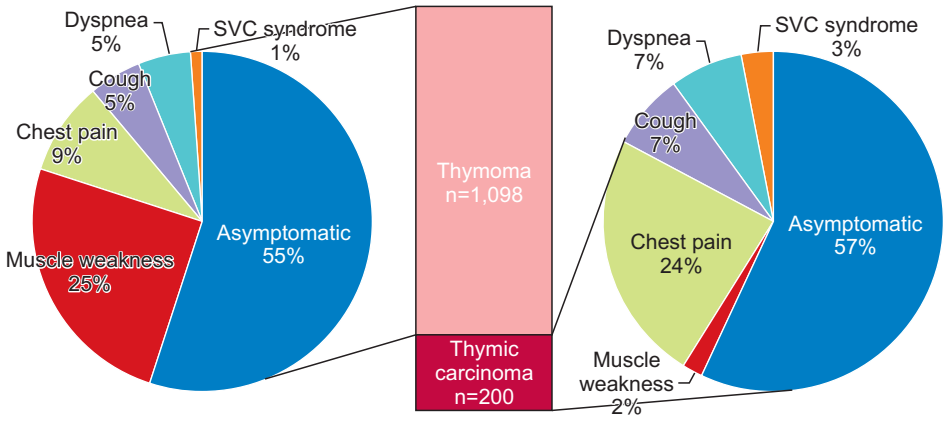


Fig. 1. Clinical symptoms compared between thymoma and thymic carcinoma. SVC, superior vena cava.

MITS was preferred more in the thymoma group compared to the thymic carcinoma group (p<0.001). Although complete resection was one of the primary goals of surgery, 4.7% of the patients had incomplete resections. In both thymoma and thymic carcinoma cases, complete thymectomy was the most frequently performed treatment, followed by thymothymectomy. A concurrent procedure was performed more frequently in thymic carcinoma (28.4% versus 71.0%, p<0.001). In both groups, concurrent lung resection was most common, followed by pericardium resection. The mean size of the tumor was 5.5±2.7 cm. There was no statistically significant difference in tumor laterality. During the observation period, lymph node dissection was performed in only 22.3% of all patients. Even in the thymic carcinoma group, lymph node dissection was only performed in 34% of cases.

Table 2. Operative details of the overall study population

Variable	Total (N=1,298)	Thymoma (N=1,098)	Thymic carcinoma (N=200)	p-value
Approach				<0.001
Open	824 (63.5)	667 (60.7)	157 (78.5)	
Sternotomy	748 (57.6)	610 (55.6)	138 (69.0)	
Thoracotomy	51 (3.9)	38 (3.5)	13 (6.5)	
Clamshell	10 (0.8)	8 (0.7)	2 (1.0)	
Others	15 (1.2)	11 (1.0)	4 (2.0)	
MITS	474 (36.5)	431 (39.3)	43 (21.5)	
VATS	427 (32.9)	388 (35.3)	39 (19.5)	
RATS	47 (3.6)	43 (3.9)	4 (2.0)	
Clinical resection status				<0.001
Complete	1,237 (95.3)	1,060 (96.5)	177 (8.5)	
Incomplete	61 (4.7)	38 (3.5)	23 (11.5)	
Operation				0.287
Thymomectomy	278 (21.4)	234 (21.3)	44 (22.0)	
Partial thymectomy	113 (8.7)	94 (8.6)	19 (9.5)	
Complete thymectomy	869 (66.9)	740 (67.4)	129 (64.5)	
Extended thymectomy	24 (1.8)	21 (1.9)	3 (1.5)	
Concurrent procedure	454 (35.0)	312 (28.4)	142 (71.0)	<0.001
Lung resection	323 (24.8)	214 (19.6)	109 (54.5)	
Wedge resection	291 (22.4)	195 (17.8)	96 (48.0)	<0.001
Segmentectomy	3 (0.2)	1 (0.1)	2 (1.0)	0.097
Lobectomy	24 (1.8)	16 (1.5)	8 (4.0)	0.030
Pneumonectomy	5 (0.4)	2 (0.2)	3 (1.5)	0.032
Pericardium	242 (18.6)	156 (14.2)	86 (43.0)	<0.001
Phrenic nerve	125 (9.6)	79 (7.2)	46 (23.0)	<0.001
Innominate vein	87 (6.7)	45 (4.1)	42 (21.0)	<0.001
Diaphragm	21 (1.6)	17 (1.5)	4 (2.0)	0.873
Pleural seeding	37 (2.9)	26 (2.4)	11 (5.5)	0.027
Other vessel	51 (3.9)	23 (2.1)	28 (14.0)	<0.001
Extrapleural pneumonectomy	8 (0.6)	6 (0.5)	2 (1.0)	0.793
Others	37 (2.9)	20 (1.8)	17 (8.5)	<0.001
Clinical tumor size (cm)	5.5±2.7	5.4±2.7	6.0±2.8	0.002
Tumor location				0.141
Median	388 (31.5)	319 (30.6)	69 (36.5)	
Right	450 (36.6)	392 (37.6)	58 (30.7)	
Left	393 (31.9)	331 (31.8)	62 (32.8)	
Concurrent LN dissection	289 (22.3)	221 (20.1)	68 (34.0)	<0.001
Enlarged LN	69 (5.3)	49 (4.5)	20 (10.0)	0.002

Values are presented as number (%) or mean±standard deviation, unless otherwise stated.
MITS, minimally invasive thymic surgery; VATS, video-assisted thoracoscopic surgery; RATS, robotic-assisted thoracoscopic surgery; LN, lymph node.

Pathologic profiles and distribution of thymoma classifications

The 5-year and 10-year OS rates were 91.1% (95% confidence interval [CI], 89.0%–92.7%) and 81.3% (95% CI, 77.4%–84.6%), respectively. The 5-year and 10-year FFR rates were 86.0% (95% CI, 83.4%–88.2%) and 80.1% (95% CI, 76.0%–83.6%), respectively. The distribution of thymoma classification is shown in Table 3. In the thymoma group, the WHO classification type A occupied the smallest proportion (5.6%) and other types (AB, B1, B2, B3) accounted for about 20%. The WHO classification was associated with the M-K stage (p<0.01) (Appendix 2).

Annual trends of surgically treated thymic epithelial tumors

Over the study period, the total number of patients with surgically treated TETs tended to gradually increase annually, and the proportion of patients who underwent MITS

https://doi.org/10.5090/jcs.21.124

Table 3. Postoperative outcomes of OS and FFR, pathologic profiles, and distribution of classifications

Variable	Total (N=1,298)	Thymoma (N=1,098)	Thymic carcinoma (N=200)	p-value
5-year OS (%)	91.1 (89.0–92.7)	93.3 (91.2–94.9)	79.2 (72.0–84.7)	<0.001
10-year OS (%)	81.3 (77.4–84.6)	85.3 (81.3–88.5)	58.5 (45.8–69.1)	<0.001
5-year FFR (%)	86.0 (83.4–88.2)	91.3 (88.9–93.2)	59.0 (50.2–66.8)	<0.001
10-year FFR (%)	80.1 (76.0–83.6)	85.2 (80.7–88.7)	55 (45.1–63.9)	<0.001
Final WHO type				<0.001
A	61 (4.7)	61 (5.6)	-	
AB	269 (20.7)	269 (24.5)	-	
B1	250 (19.3)	250 (22.8)	-	
B2	296 (22.8)	296 (27.0)	-	
B3	222 (17.1)	222 (20.2)	-	
C	200 (15.4)	-	200 (100.0)	
Pathologic Masaoka-Koga stage				<0.001
I	480 (37.2)	466 (42.5)	14 (7.1)	
IIa	294 (22.8)	264 (24.1)	30 (15.3)	
IIb	248 (19.2)	215 (19.6)	33 (16.8)	
III	166 (12.8)	97 (8.9)	69 (35.2)	
IVa	68 (5.3)	45 (4.1)	23 (11.7)	
IVb	36 (2.8)	9 (0.8)	27 (13.8)	
Pathologic TNM stage				<0.001
I	320 (69.3)	289 (79.6)	31 (31.3)	
II	10 (2.2)	5 (1.4)	5 (5.1)	
IIIa	67 (14.5)	41 (11.3)	26 (26.3)	
IIIb	1 (0.2)	0	1 (1.0)	
IVa	45 (9.7)	27 (7.4)	18 (18.2)	
IVb	19 (4.1)	1 (0.3)	18 (18.2)	
Final resection status				<0.001
R0 resection	1,183 (91.8)	1,022 (93.5)	161 (82.6)	
R1 resection	84 (6.5)	57 (5.2)	27 (13.8)	
R2 resection	21 (1.6)	14 (1.3)	7 (3.6)	

Values are presented as number (%) and OS and FFR are presented as rate (95% confidence interval).
OS, overall survival; FFR, freedom from recurrence; WHO, World Health Organization; TNM, tumor-node-metastasis.

(video-assisted thymic surgery and robot-assisted thymic surgery) increased from 0 case in 2000 to 100 cases (69.0%) in 2012 (Fig. 2).

As shown in Fig. 2, there was an upward trend of the 5-year OS from 66% in 2000 to 90% in 2010. When OS was analyzed using the Kaplan-Meier method depending on the year, 2007 was a significant cut-off point. After 2007, the annual OS dramatically increased (p=0.0014).

Extent of resection

In the total group, pathologic reports showed that 1,183 (91.8%) of patients underwent complete resection and 105 (8.1%) of patients underwent incomplete resection (R1 or R2 resection). The 5-year OS rates were 93.0% (95% CI, 91.1%–94.6%) in the complete resection group and 75.9% (95% CI, 65.5%–83.6%) in the incomplete resection group. As shown in Fig. 3, patients who underwent complete resection showed a significantly higher survival rate than who received incomplete resection (p<0.001). The 5-year and 10-year FFR rates of the complete resection group were 89.0% (95% CI, 86.5%–91.0%) and 82.1% (95% CI, 77.6%–85.8%), respectively.

Overall survival and freedom from recurrence by the World Health Organization histologic classification

Sixty-one patients (4.7%) were classified as WHO type A, 269 patients (20.7%) as WHO type AB, 250 patients (19.3%) as WHO type B1, 296 patients (22.8%) as WHO type B2, 222 patients (17.1%) as WHO type B3, and 200 patients (15.4%) as diagnosed with thymic carcinoma (WHO type C). Eighty-five percent of the patients were categorized as

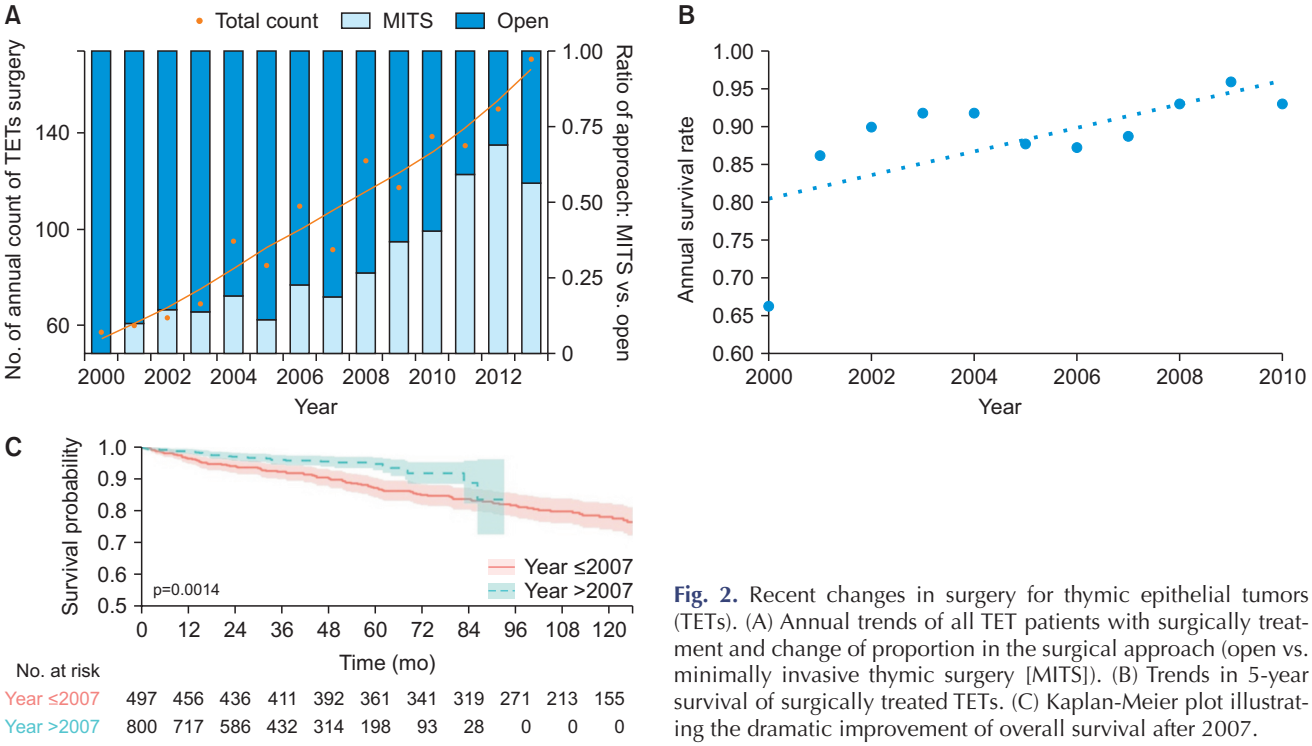


Fig. 2. Recent changes in surgery for thymic epithelial tumors (TETs). (A) Annual trends of all TET patients with surgically treatment and change of proportion in the surgical approach (open vs. minimally invasive thymic surgery [MITS]). (B) Trends in 5-year survival of surgically treated TETs. (C) Kaplan-Meier plot illustrating the dramatic improvement of overall survival after 2007.

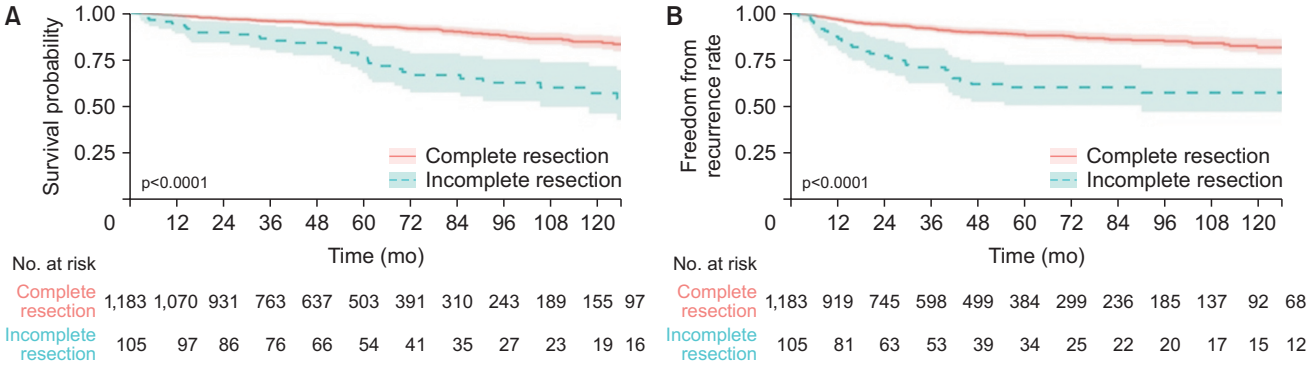


Fig. 3. Overall survival (OS) and freedom from recurrence (FFR) with complete resection and incomplete resection. (A) OS according to resection completeness. (B) FFR according to resection completeness.

having thymoma, and the subtypes (reflecting the nature of the malignancy) were categorized as the A&AB&B1 group, B1&B2 group, and C group.

OS and FFR according to M-K stage are shown in Fig. 4A and B. OS was significantly different among patients with thymoma compared to thymic carcinoma (p<0.001). The 5-year and 10-year OS rates in patients with thymoma were 93.3% (95% CI, 91.2%–94.9%) and 85.2% (95% CI, 81.2%–88.4%), respectively, compared to 79.1% (95% CI, 71.9%–84.6%) and 58.3% (95% CI, 45.6%–69.0%), respectively, in patients with thymic carcinoma. The OS among WHO subtype groups in thymoma was not significantly different (p=0.85). The 5-year and 10-year OS rates of the A&AB&B1 group were 94.5% (95% CI, 91.5%–96.4%) and 88.3% (95% CI, 82.9%–92.1%), respectively. The 5-year and 10-year OS rates of the B2&B3 group were 92.1% (95% CI, 88.9%–94.4%) and 82.2% (95% CI, 75.9%–87.0%), respectively. FFR was significantly different among the 3 WHO subtypes (p<0.001). The 5-year FFR of the A&AB&B1 group was 97.3% (95% CI, 95.0%–98.6%), that of the B2&B3 group was 86.4% (95% CI, 82.3%–89.6%), and that of the thymic carcinoma group was 58.8% (95% CI, 49.9%–66.6%).

https://doi.org/10.5090/jcs.21.124

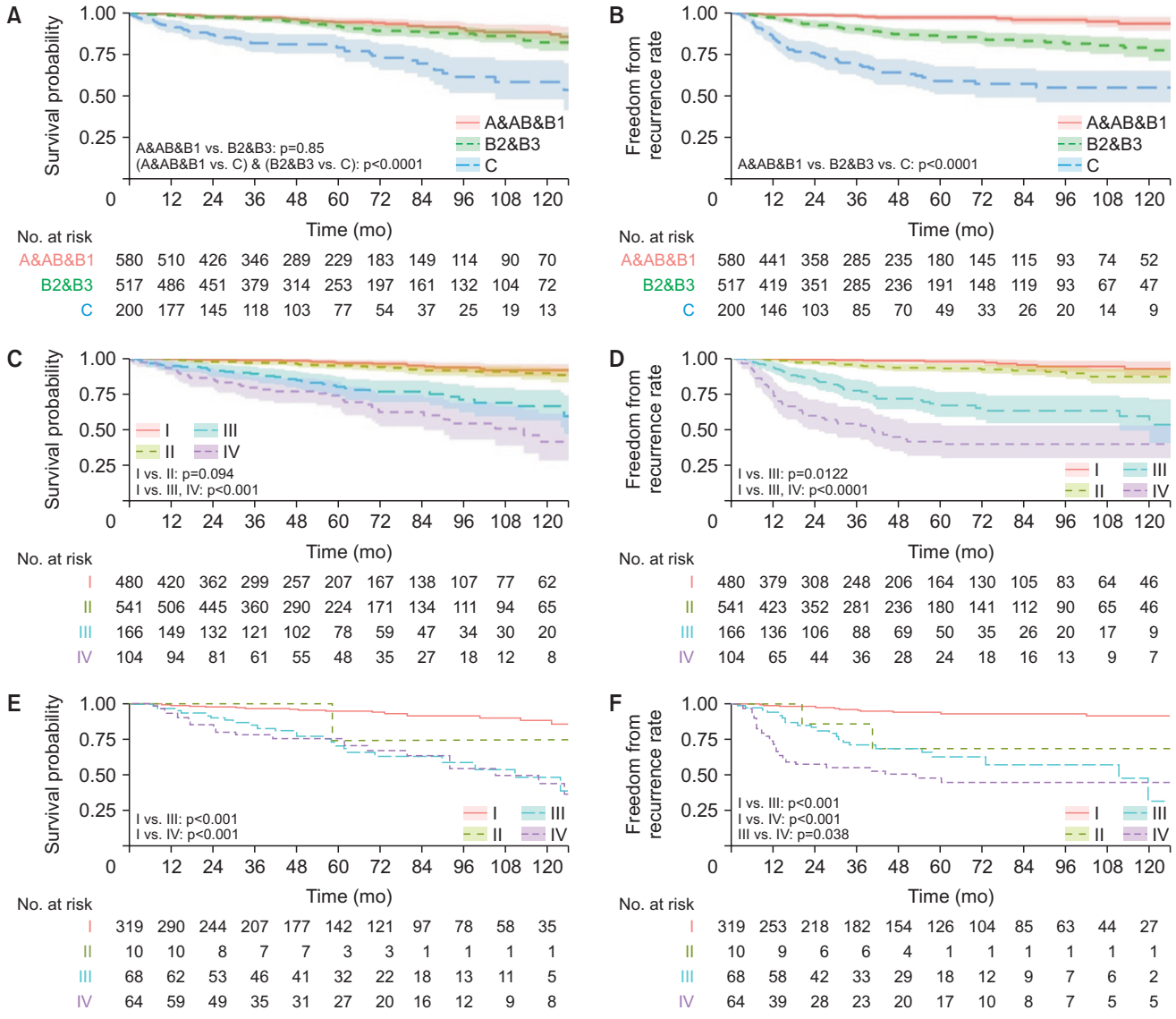


Fig. 4. Overall survival (OS) and freedom from recurrence (FFR) according to the thymic epithelial tumor (TET) classification. (A) OS with the World Health Organization (WHO) classification. (B) FFR with the WHO classification. (C) OS with Masaoka-Koga (M-K) staging. (D) FFR with M-K staging. (E) OS with tumor-node-metastasis (TNM) staging. (F) FFR with TNM staging.

Overall survival and freedom from recurrence by Masaoka-Koga staging

A total of 480 patients (37.2%) were classified as stage I, 294 patients (22.8%) as stage IIa, 248 patients (19.2%) as stage IIb, 166 patients (12.8%) as stage III, 68 patients (5.3%) as stage IVa, and 19 patients (4.1%) as stage IVb.

OS and FFR according to the M-K stage are shown in Fig. 4C and D. There was no significant survival difference between the M-K stage I and II groups (p=0.094). Stages III and IV each showed significantly lower OS rates than stage I. The 5-year and 10-year OS rates were as follows: M-K stage I, 96.4% (95% CI, 93.5%–98.19%) and 91.2% (95% CI, 85.6%–94.7%), respectively; M-K stage II, 94.6% (95% CI, 91.8%–96.5%) and 89.1% (95% CI, 83.7%–92.8%), respectively; M-K stage III, 79.7% (95% CI, 71.8%–85.6%) and 66.1% (95% CI, 54.2%–75.5%), respectively; M-K stage IV, 73.7% (95% CI, 63.2%–81.7%) and 41.3% (95% CI, 25.3%–56.7%), respectively. FFR showed a statistically similar pattern to that of OS. The FFR rates of M-K stages I and II were not significantly different (p=0.0122). However, M-K stages III and IV each showed higher rates FFR than that of stage I. The 5-year rates of FFR in patients were as follows: M-K stage I, 95.9% (95% CI, 91.9%–97.9%); M-K stage

II, 93.1% (95% CI, 89.9%–95.3%); M-K stage III, 66.8% (95% CI, 57.4%–74.7%); and M-K stage IV, 39.7% (95% CI, 28.5%–50.7%).

Overall survival and freedom from recurrence by TNM stage

From the entire study group, the TNM stage was estimated in only 461 patients owing to a lack of information on lymph nodes. A total of 319 patients (69.1%) were classified as stage I, 10 patients (2.1%) as stage II, 68 patients (14.7%) as stage III, and 64 patients (13.8%) as stage IV.

OS and FFR according to the TNM stage are shown in Fig. 4E and F. The 5-year and 10-year OS rates of the patients were as follows: stage I, 95.0% (95% CI, 91.2%–97.2%) and 88.4% (95% CI, 0.5%–93.2%), respectively; stage II, 81.7% (95% CI, 57.6%–92.8%) and 70.0% (95% CI, 37.2%–87.9%), respectively; stage III, 70.7% (95% CI, 56.5%–81.1%) and 48.5% (95% CI, 29.8%–64.9%), respectively; stage IV, 76.0% (95% CI, 62.7%–83.2%) and 44.0% (95% CI, 24.9%–61.6%), respectively. Stages III and IV each showed statistically significant differences in OS compared to stage I (p<0.001). The 5-year rate of FFR of patients were as follows: stage I, 93.8% (95% CI, 89.7%–96.3%); stage III, 62.4% (95% CI, 46.7%–74.7%), and stage IV, 47.6% (95% CI, 33.4%–60.5%). Statistically significant differences in FFR were found for stage I versus III, stage I versus IV, and stage III versus IV (p<0.05 each).

Perioperative therapy

Perioperative therapy according to the pathological M-K stage is shown in Appendix 3. Neoadjuvant treatment was administered in potentially resectable advanced TETs in 59 patients (4.6% in total, 2.6% in thymoma, and 15.5% in thymic carcinoma). Chemotherapy was administered especially frequently in M-K stages II, III, and IV. The OS of the neoadjuvant treatment group is shown in Fig. 5A. The 5-year OS of the neoadjuvant treatment group was 74% (95% CI, 59.7%–83.8%).

Approximately half of the entire study group and 74% of the thymic carcinoma group received adjuvant treatment after initial surgery. Radiation therapy was mainly administered in the adjuvant treatment group. In this study group, 42.4% of R0 resection patients, 77.4% of R1 resection patients, and 61.9% of R2 resection patients received adjuvant

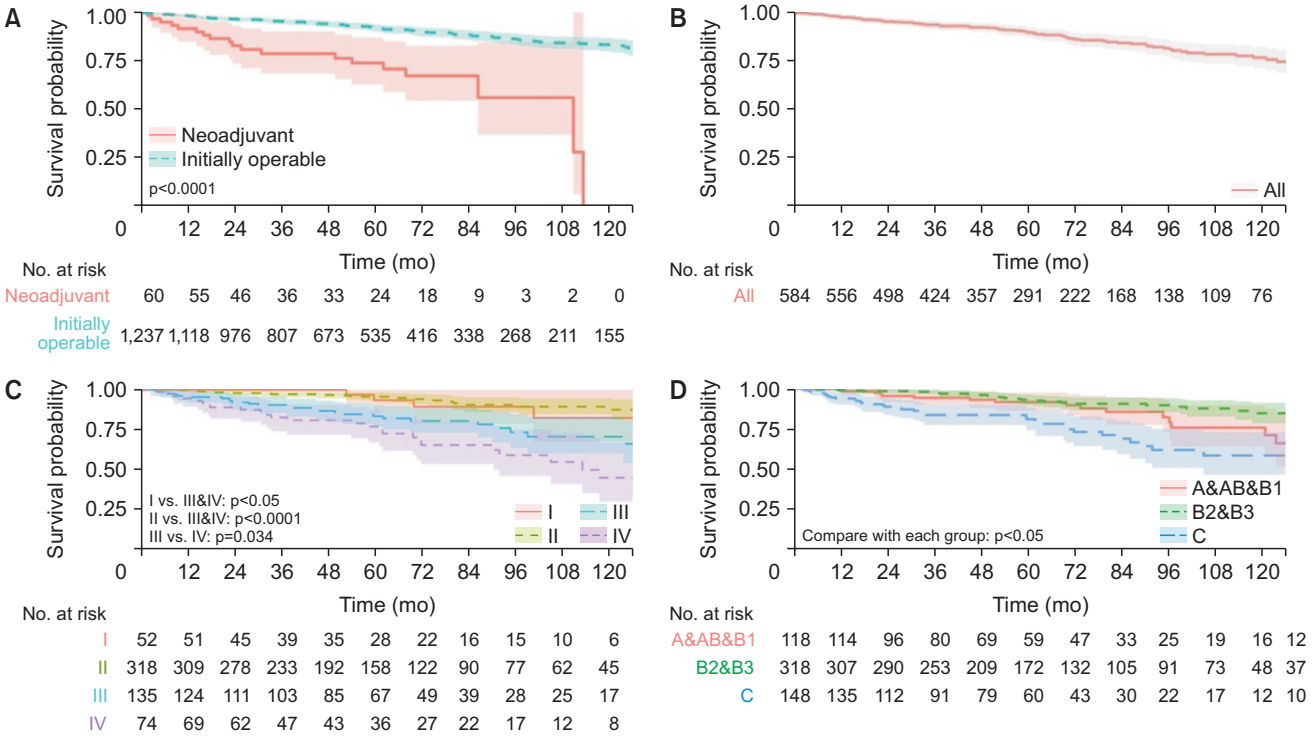


Fig. 5. Overall survival (OS) according to perioperative treatment. (A) OS compared between the initially inoperable group (neoadjuvant group) and the initially operable group. (B) OS in the entire adjuvant treatment group. (C) OS in the adjuvant treatment group according to the Masaoka-Koga (M-K) stage. (D) OS in the adjuvant treatment group according to the World Health Organization classification.

https://doi.org/10.5090/jcs.21.124

treatment (Appendix 4). The OS rates according to the M-K stage and WHO classification of adjuvant treatment group are shown in Fig. 5B–D. The 5-year and 10-year OS rates of the adjuvant treatment group were 89.7% (95% CI, 86.6%–92.2%) and 76.6% (95% CI, 70.6%–81.6%), respectively. The 5-year OS rates of each adjuvant treatment group according to M-K stage were as follows: stage I, 93.5% (95% CI, 76.5%–98.3%); stage II, 95.7% (95% CI, 92.2%–97.6%); state III, 83.5% (95% CI, 75.2%–89.2%); and stage IV, 76.9% (95% CI, 64.3%–85.5%). The 5-year OS rates of each adjuvant treatment group according to WHO classification were as follows: A&AB&B1 group, 91.6% (95% CI, 83.7%–95.8%); B2&B3 group, 93.0% (95% CI, 88.9%–95.6%); and C group, 80.9% (95% CI, 72.5%–86.9%).

Prognostic factors for overall survival and freedom from recurrence

The stepwise multiple Cox regression analysis of various potential prognostic factors for OS and FFR is shown in Table 4 and Table 5. Cox regression analysis for OS demonstrated age ≥60 (hazard ratio [HR], 2.489; 95% CI, 1.708–3.627; p<0.01), tumor size ≥6.5 cm (HR, 2.236; 95% CI, 1.508–3.315; p<0.01), M-K stage III (HR, 3.42; 95% CI, 1.757–6.654; p<0.01), and M-K stage IV (HR, 7.244; 95% CI, 3.548–14.789; p<0.01) as prognostic factors. Interestingly, the histological type, perioperative treatment, and resection status were not significantly associated with OS.

In the Cox regression analysis for FFR in R0 resection patients, WHO histologic type B2 or B3 (HR, 2.382; 95% CI, 1.192–4.762; p=0.014), type C (HR, 4.464; 95% CI, 2.108–

Table 4. Univariable and multivariable analyses of prognostic factors influencing overall survival

Variable	Category	Univariable		Multivariable	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Operation year	2000–2004	Reference			
	2005–2009	0.941 (0.635–1.396)	0.7638	0.688 (0.436–1.087)	0.109
	2010–2013	0.472 (0.263–0.847)	0.0119	0.487 (0.26–0.912)	0.0245
Age (yr)	<60	Reference			
	≥60	2.551 (1.826–3.565)	<0.0001	2.489 (1.708–3.627)	<0.0001
Sex	Male	Reference			
	Female	0.527 (0.369–0.752)	0.0004		
Smoking	Never smoker	Reference			
	Smoker	1.74 (1.241–2.441)	0.0013	1.354 (0.927–1.977)	0.1167
Symptom	Asymptomatic	Reference			
	Symptomatic	1.303 (0.931–1.824)	0.1223	1.785 (1.19–2.676)	0.0051
Myasthenia gravis	No	Reference			
	Yes	0.474 (0.307–0.734)	0.0008	0.638 (0.364–1.117)	0.1157
Tumor size (cm)	<6.5	Reference			
	≥6.5	2.918 (2.049–4.156)	<0.0001	2.236 (1.508–3.315)	<0.0001
Neoadjuvant	No	Reference			
	Yes	4.36 (2.666–7.132)	<0.0001		
Approach	Open	Reference			
	MITS	0.428 (0.259–0.708)	0.001		
WHO	A, AB, B1	Reference			
	B2, B3	1.351 (0.886–2.06)	0.1627	0.683 (0.402–1.158)	0.1567
	C	4.523 (2.949–6.937)	<0.0001	1.363 (0.751–2.473)	0.3087
Masaoka-Koga stage	I	Reference			
	II	1.597 (0.924–2.759)	0.0935	1.395 (0.765–2.545)	0.2778
	III	5.545 (3.241–9.488)	<0.0001	3.42 (1.757–6.654)	0.0003
	IV	9.396 (5.473–16.133)	<0.0001	7.244 (3.548–14.789)	<0.0001
Adjuvant	No	Reference			
	Yes	1.567 (1.115–2.203)	0.0098		
Resection status	Complete	Reference			
	Incomplete	3.235 (2.198–4.76)	<0.0001		

HR, hazard ratio; CI, confidence interval; MITS, minimally invasive thymic surgery; WHO, World Health Organization.

Table 5. Univariable and multivariable analyses of prognostic factors influencing freedom from recurrence after R0 resection

Variable	Category	Univariable		Multivariable	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Operation year	2000–2004	Reference		Reference	
	2005–2009	0.737 (0.447–1.215)	0.2317	0.583 (0.348–0.975)	0.0398
	2010–2013	1.594 (0.938–2.709)	0.0845	1.279 (0.738–2.217)	0.3802
Age (yr)	<60	Reference			
	≥60	0.789 (0.497–1.252)	0.314		
Sex	Male	Reference			
	Female	0.708 (0.479–1.047)	0.0834		
Smoking	Never smoker	Reference			
	Smoker	1.596 (1.085–2.348)	0.0175		
Symptom	Asymptomatic	Reference			
	Symptomatic	1.08 (0.737–1.584)	0.6923		
Myasthenia gravis	No	Reference			
	Yes	0.65 (0.402–1.050)	0.0782		
Tumor size (cm)	<6.5	Reference			
	≥6.5	1.813 (1.195–2.752)	0.0051		
Neoadjuvant	No	Reference		Reference	
	Yes	10.163 (6.137–16.83)	<0.0001	2.746 (1.538–4.9)	0.0006
Approach	Open	Reference			
	MITS	0.512 (0.324–0.81)	0.019		
WHO	A, AB, B1	Reference		Reference	
	B2, B3	4.434 (2.347–8.374)	<0.0001	2.382 (1.192–4.762)	0.014
	C	15.547 (8.249–29.303)	<0.0001	4.464 (2.108–9.452)	<0.0001
Masaoka-Koga stage	I	Reference		Reference	
	II	2.043 (1.058–3.945)	0.0333	1.212 (0.594–2.476)	0.5972
	III	11.425 (6.091–21.429)	<0.0001	4.013 (1.889–8.527)	0.0003
	IV	21.633 (11.102–42.152)	<0.0001	6.077 (2.703–13.665)	<0.0001
Adjuvant	No	Reference		Reference	
	Yes	3.551 (2.293–5.499)	<0.0001	1.404 (0.848–2.324)	0.1876

HR, hazard ratio; CI, confidence interval; MITS, minimally invasive thymic surgery; WHO, World Health Organization.

9.452; p<0.01), M-K stage III (HR, 4.013; 95% CI, 1.889–8.527; p<0.01), M-K stage IV (HR, 6.077; 95% CI, 2.703–13.665; p<0.01), and neoadjuvant treatment (HR, 2.746; 95% CI, 4.538–4.9; p<0.01) affected FFR.

Conventional open surgery and the recent trend of minimally invasive thymic surgery

As shown in Fig. 2, with recent developments in video- and robot-assisted thoracoscopic surgical instruments and practices, the rate of MITS has increased. However, MITS tends to be considered for early-stage TETs instead of conventional open thymic surgery. Propensity score matching was performed to compare operative outcomes (Appendix 5).

A comparison of OS and FFR between the open group and MITS group is shown in Appendix 6. There was no statistically significant difference in OS and FFR between the approaches (p=0.66 for OS and p=0.29 for FFR). In addition, MITS showed better results than open surgery in terms of postoperative outcomes and the hospital course (Appendix 7).

Discussion

This study is one of the largest unselected population-based reports of TETs in Korea. The clinical information and surgical treatment strategy for TETs are rapidly changing, and this topic warrants ongoing research in the future. The objective of this study was to present an integrated review of patients' clinicopathologic features, trends in surgical methods, and prognostic factors for survival and recurrence of this rare disease in Korea with a large volume of multi-institutional data.

The findings from the analysis of our database in this study are as follows: (1) The results of surgical treatment,

which were represented by OS, have improved in recent years, and the total number of thymic operations and the proportion of MITS also increased. (2) The M-K stage is an important prognostic factor for both OS and FFR. (3) The WHO classification is related to FFR. (4) Large tumor size is associated with a poor prognosis. (5) The TNM staging system could be an effective prognostic factor.

Patients with thymoma showed a favorable prognosis, with 5-year OS and FFR rates over 90%. However, unfortunately, patients with thymic carcinoma had poor outcomes, with a 5-year OS rate of less than 80% and an FFR rate of less than 60% despite aggressive treatment. A revolutionary new multimodal treatment strategy is needed for these patients.

In our data, the 5-year FFR rate was 86% in the entire group. The National Comprehensive Cancer Network (NCCN) guidelines (version 1.2021) recommend surveillance for recurrence with imaging studies every 6 months for 2 years, then annually for 5 years for thymic carcinoma and 10 years for thymoma. Because recurrences that are diagnosed early are usually local and treatable, it is important to increase patient compliance and educate patients regarding the importance of surveillance. Further study regarding the prognosis of recurrent TETs, which were excluded from this study population, is necessary.

TETs are associated with several paraneoplastic syndromes. Although there were only 2 types of paraneoplastic syndrome, MG and red cell aplasia, hypo-gamma-globulinemia is also one of the most frequent conditions that accompany TETs [1]. Patients with thymomatous MG usually underwent multimodal treatment, and thymectomy for thymomatous MG could lead to favorable neurological remission [2]. Whether the association of MG with TETs has an unfavorable effect on the prognosis remains unclear, but recent studies and our study have shown that the presence of MG is not an adverse factor in patients with TETs. Patients with MG are perhaps more likely to receive regular follow-up for medical therapy of MG, leading to earlier diagnoses of advanced thymoma.

In this study, tumor size was categorized using a cut-off ≥6.5 cm in the entire study population, and large tumors were associated with a poor prognosis in multivariable Cox analysis. In the current TNM staging system, tumor size is not considered as a factor in the T category, which was based on the International Association for the Study of Lung Cancer/International Thymic Malignancy Interest Group (ITMIG) project [3]. However, a previous study based on the KART database and recently published papers suggest that tumor size is an independent prognostic factor in thymoma [4,5]. From these recent studies, it appears that tumor size could be a factor of the T category in the future.

Traditionally, TETs are staged using the M-K staging system; this system, which has been established as an important prognostic factor in previous studies, was first proposed in 1981 and modified in 1994 [6,7]. Numerous reports have stated that the M-K stage is a suitable prognostic factor. Our study analysis reestablished that the M-K stage is a strong predictor of OS and FFR rate.

The WHO classification of TETs, which was published in 1999 and revised in 2004, categorized TETs into 6 histologic subtypes. Initially, the WHO classification was considered a powerful prognostic factor [8,9]. However, of late, disagreement has emerged regarding whether this histological characteristic is a reliable factor for predicting OS and reflects oncological features. In our study, the WHO classification was not a predictor for OS, but was related to FFR.

The Cancer Staging Prognostic Factors Committee and the ITMIG recently proposed the eighth edition of TNM-based staging system for TETs [3]. Unfortunately, our data were based on patients who underwent thymic surgery from 2000 to 2013, before the TNM classification system was proposed. In this period, surgeons overlooked the importance of lymph node dissection in thymic surgery. Owing to a lack of pathologic information on lymph nodes, only 462 of our 1,298 patients could be classified using the TNM staging system. In this study analysis, the number of stage II patients was too small to be statistically analyzed and the TNM stage was not observed to be a strong prognostic factor in multivariable Cox analysis. However, another study based on the KART database showed that the TNM staging system was superior to the M-K staging system in terms of FFR [10]. There were statistically significant differences in OS between stage I and stage III and between stage I and stage IV ($p<0.001$). Furthermore, there were statistically significant differences in FFR between stage I and stage III, between stage III and stage IV, and between stage I and stage IV ($p<0.05$). Our study showed that the TNM staging system could be a reasonable predictor of the outcomes of TETs in a limited group. In line with the current trend in which every thymoma is considered to have malignant potential, proactively performing lymph node dissection appears to be necessary in all thymic surgery procedures.

There is general acceptance that the treatment of choice for TETs is complete surgical resection. A previous study by Regnard et al. [11] reported that completeness of resection was the only significant prognostic factor. In our

study, completeness of resection was not a significant factor in the multivariable analysis. However, patients who underwent complete resection showed statistically significantly better OS and FFR than the incomplete resection group in the univariable analysis. From an oncological point of view, complete resection should always be considered in resectable thymoma surgery. However, in cases of advanced-stage of invasive thymoma or thymic carcinoma, when primary complete surgical resection would be difficult or impossible, neoadjuvant treatment could be applied. In this study, neoadjuvant treatment was demonstrated as a risk factor for FFR, which could be explained by the fact that the neoadjuvant group was in a more advanced state from the beginning. Many previous studies have investigated the use of neoadjuvant chemotherapy to increase the possibility of surgical resection [12]. However, the oncological advantage of neoadjuvant treatment compared with upfront surgical resection remains unclear [13]. Therefore, further studies, such as randomized controlled trials, are needed.

The NCCN guidelines (version 1.2021) recommend postoperative radiation therapy for R0 resected thymic carcinoma or stage II–IV thymoma and incompletely resected TETs of all types [14]. In our study, a simple comparison between the adjuvant treatment (advanced stage) and non-adjuvant treatment (early stage) groups showed 5-year and 10-year OS rates of 89.8% (86.6%–92.2%) and 73.7% (70.7%–80.1%), respectively, in the adjuvant treatment group compared to 92.3% (89.5%–94.4%) and 86.1% (81.0%–89.9%), respectively, in the non-adjuvant treatment group (p=0.009). The adjuvant treatment group consisted of patients with more advanced stages of TETs than the non-adjuvant treatment group. This could explain the result of multivariable Cox regression analysis that adjuvant treatment could be considered as a risk factor for a poor prognosis. A previous comparative study of postoperative therapy in stage II and III thymoma based on the KART database and other studies revealed that postoperative radiation therapy could significantly improve OS and FFR in patients with advanced-stage thymoma or with a positive resection margin [15].

The comparison of OS and FFR between open thymic surgery and MITS did not show a statistically significant difference. MITS could ensure not only the appropriate oncological outcome but also a better postoperative recovery course for patients. Recent developments in video-assisted thoracoscopic or robotic devices and improvements in surgical techniques, have made it possible for MITS to achieve total or extended thymectomy under the thoracoscopic view. In our data, when MITS was initially performed, the proportion of thymothymectomy was high; however, more recently, the proportion of total thymectomy has gradually increased. During the study period, the proportion of total or extended thymectomy was about 50% with MITS.

MITS can reduce perioperative trauma and shorten the recovery period, enabling patients to return to normal life more quickly [16,17]. However, the most important principle in thymic surgery is to confirm its oncological effectiveness. As we can see from our matched data and other previous reports, MITS might be ready to be considered as standard thymic surgery, but the long-term oncological outcome remains to be verified [13,18,19].

Limitations

There are several limitations to this study. Our study was limited by the retrospective nature of our database, which was not a randomized controlled trial. Although we used multivariate analysis to adjust for the covariates, there are still potential biases, such as limited setting of standardized regimens for multimodal treatment, the experience of surgeons and institutions, and the condition of individual patients. Additionally, since this study analyzed a multicenter database, it is possible that patients were treated with different diagnostic and therapeutic strategies, which were not incorporated into our analysis. Finally, information on lymph nodes was missing in a fairly substantial proportion of cases, and the analysis of the TNM stage as a prognostic factor was insufficient. This report is a comprehensive study of a rare disease, including broad clinical information still under investigation. Therefore, there were limitations in conducting in-depth research on each subtopic and follow-up studies are needed.

Conclusion

This study presents the characteristics of patients with TET, progress in surgical outcomes accompanying developments in surgical techniques, and possible prognostic factors of OS and FFR in Korea from 2000 to 2013. The total number of surgically treated TETs and the proportion of patients with MITS have significantly increased. There was a significant improvement in the 5-year OS rate during the study period. The M-K clinical staging system and tumor size are the most important prognostic factors for OS. The TNM stage could be an effective predictor for TETs.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

Members of the KART Study Group: Geun Dong Lee, Jae Kwang Yun, Sehoon Choi, Hyeong Ryul Kim, Yong-Hee Kim, Dong Kwan Kim, Seung-Il Park (Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, Ulsan University College of Medicine, Seoul, Korea); Sumin Shin, Jong Ho Cho, Hong Kwan Kim, Jhingook Kim, Young Mog Shim (Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea); Samina Park, In Kyu Park, Chang Hyun Kang, Young Tae Kim (Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea); and Chang Young Lee, Jin Gu Lee, Dae Joon Kim, Hyo Chae Paik (Department of Thoracic and Cardiovascular Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea).

ORCID

Jun Oh Lee: https://orcid.org/0000-0003-3373-1144
Geun Dong Lee: https://orcid.org/0000-0003-1890-7455
Hyeong Ryul Kim: https://orcid.org/0000-0002-6691-7693
Dong Kwan Kim: https://orcid.org/0000-0003-1984-0352
Seung-Il Park: https://orcid.org/0000-0002-8729-0498
Jong Ho Cho: https://orcid.org/0000-0003-3362-4621
Hong Kwan Kim: https://orcid.org/0000-0002-7815-3336
Yong Soo Choi: https://orcid.org/0000-0001-8492-7644
Jhingook Kim: https://orcid.org/0000-0002-3828-0453
Young Mog Shim: https://orcid.org/0000-0001-5924-9765
Samina Park: https://orcid.org/0000-0001-9625-2672
In Kyu Park: https://orcid.org/0000-0003-3550-5554
Chang Hyun Kang: https://orcid.org/0000-0002-1612-1937
Young Tae Kim: https://orcid.org/0000-0001-9006-4881
Sung Yong Park: https://orcid.org/0000-0002-5180-3853
Chang Young Lee: https://orcid.org/0000-0002-2404-9357
Jin Gu Lee: https://orcid.org/0000-0003-2767-6505
Dae Joon Kim: https://orcid.org/0000-0002-2182-010X
Hyo Chae Paik: https://orcid.org/0000-0001-9309-8235

References

1. Venuta F, Anile M, Diso D, et al. *Thymoma and thymic carcinoma*. Eur J Cardiothorac Surg 2010;37:13-25.
2. Na KJ, Hyun K, Kang CH, et al. *Predictors of post-thymectomy long-term neurological remission in thymomatous myasthenia gravis: an analysis from a multi-institutional database*. Eur J Cardiothorac Surg 2020;57:867-73.
3. Detterbeck FC, Stratton K, Giroux D, et al. *The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors*. J Thorac Oncol 2014;9(9 Suppl 2):S65-72.
4. Yun JK, Kim HR, Kim DK, et al. *Tumor size as a prognostic factor in limited-stage thymic epithelial tumors: a multicenter analysis*. J Thorac Cardiovasc Surg 2021;162:309-17.
5. Okumura M, Yoshino I, Yano M, et al. *Tumour size determines both recurrence-free survival and disease-specific survival after surgical treatment for thymoma*. Eur J Cardiothorac Surg 2019;56:174-81.
6. Masaoka A, Monden Y, Nakahara K, Tanioka T. *Follow-up study of thymomas with special reference to their clinical stages*. Cancer 1981;48:2485-92.
7. Koga K, Matsuno Y, Noguchi M, et al. *A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma*. Pathol Int 1994;44:359-67.
8. Okumura M, Ohta M, Tateyama H, et al. *The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients*. Cancer 2002;94:624-32.
9. Marchevsky AM, Gupta R, McKenna RJ, et al. *Evidence-based pathology and the pathologic evaluation of thymomas: the World Health Organization classification can be simplified into only 3 categories other than thymic carcinoma*. Cancer 2008;112:2780-8.
10. Yun JK, Lee GD, Kim HR, et al. *A nomogram for predicting recurrence after complete resection for thymic epithelial tumors based on the TNM classification: a multi-institutional retrospective analysis*. J Surg Oncol 2019;119:1161-9.
11. Regnard JF, Magdeleinat P, Dromer C, et al. *Prognostic factors and long-term results after thymoma resection: a series of 307 patients*. J Thorac Cardiovasc Surg 1996;112:376-84.
12. Weissferdt A, Moran CA. *The impact of neoadjuvant chemotherapy on the histopathological assessment of thymomas: a clinicopathological correlation of 28 cases treated with a similar regimen*. Lung 2013;191:379-83.
13. Pennathur A, Qureshi I, Schuchert MJ, et al. *Comparison of surgical techniques for early-stage thymoma: feasibility of minimally invasive thymectomy and comparison with open resection*. J Thorac Cardiovasc Surg 2011;141:694-701.
14. National Comprehensive Cancer Network. *NCCN guidelines version 1: thymomas and thymic carcinomas*. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2021.

15. Song SH, Suh JW, Yu WS, et al. *The role of postoperative radiotherapy in stage II and III thymoma: a Korean multicenter database study*. J Thorac Dis 2020;12:6680-9.
16. Takeo S, Tsukamoto S, Kawano D, Katsura M. *Outcome of an original video-assisted thoracoscopic extended thymectomy for thymoma*. Ann Thorac Surg 2011;92:2000-5.
17. Weksler B, Tavares J, Newhook TE, Greenleaf CE, Diehl JT. *Robot-assisted thymectomy is superior to transsternal thymectomy*. Surg Endosc 2012;26:261-6.
18. Manoly I, Whistance RN, Sreekumar R, et al. *Early and mid-term outcomes of trans-sternal and video-assisted thoracoscopic surgery for thymoma*. Eur J Cardiothorac Surg 2014;45:e187-93.
19. Friedant AJ, Handorf EA, Su S, Scott WJ. *Minimally invasive versus open thymectomy for thymic malignancies: systematic review and meta-analysis*. J Thorac Oncol 2016;11:30-8.

https://doi.org/10.5090/jcs.21.124

Appendix 1. Preoperative clinical profiles of patients with MG

Variable	MG (+) (N=318)
MG symptoms	
Ptosis	274 (86.2)
Fatigue	78 (24.5)
Muscle weakness	147 (46.2)
Swallowing difficulty	104 (32.7)
Others	158 (49.7)
Acetylcholine receptor antibody (nmol/L)	9.5±4.0
Preoperative MFGA clinical classification	
I	91 (28.6)
IIa	87 (27.4)
IIb	96 (30.2)
IIIa	8 (2.5)
IIIb	25 (7.9)
IVa	1 (0.3)
IVb	3 (0.9)
V	6 (1.9)
Preoperative MG treatment	
Pyridostigmine	278 (87.4)
Steroid	21 (6.6)
Plasmapheresis	7 (2.2)
IVIG	2 (0.6)
Pyridostigmine+steroid+IVIG	2 (0.6)
Pyridostigmine+plasmapheresis	2 (0.6)
Other	1 (0.3)
None	17 (5.3)
ECOG performance status	
0	243 (76.4)
1	57 (17.9)
2	12 (3.8)
3	1 (0.3)
4	5 (1.6)

Values are presented as number (%) or mean±standard deviation, unless otherwise stated.
MG, myasthenia gravis; MFGA, Myasthenia Gravis Foundation of America; IVIG, intravenous immunoglobulin; ECOG, European Cooperative Oncology Group.

Appendix 2. The relationship between the M-K stage and WHO classification

Variable	M-K stage						Total	p-value
	I	IIa	IIb	III	IVa	IVb		
WHO type								<0.001
A	38 (7.9)	13 (4.4)	7 (2.8)	3 (1.8)	0	0	61	
AB	157 (32.7)	78 (26.5)	31 (12.5)	3 (1.8)	0	0	269	
B1	141 (29.4)	64 (21.8)	28 (11.3)	12 (7.2)	3 (4.4)	1 (2.8)	249	
B2	102 (21.2)	62 (21.1)	77 (31.0)	31 (18.7)	23 (33.8)	1 (2.8)	296	
B3	28 (5.8)	47 (16.0)	72 (29.0)	48 (28.9)	19 (27.9)	7 (19.4)	221	
C	14 (2.9)	30 (10.2)	33 (13.3)	69 (41.6)	23 (33.8)	27 (75.0)	196	
Total	480	294	248	166	68	36		

Values are presented as number (%).
M-K, Masaoka-Koga; WHO, World Health Organization.

Appendix 3. Perioperative therapy according to the pathological M-K stage

Variable	Total (N=1,292)	M-K stage				p-value
		I (N=480)	II (N=542)	III (N=166)	IV (N=104)	
Preoperative therapy						0.014
CTx	50 (84.7)	2 (50.0)	4 (80.0)	21 (91.3)	23 (85.2)	
RTx	4 (6.8)	2 (50.0)	1 (20.0)	0	1 (3.7)	
CRTx	5 (8.5)	0	0	2 (8.7)	3 (11.1)	
Postoperative therapy						<0.001
CTx	44 (3.4)	3 (0.6)	7 (1.3)	11 (6.6)	23 (22.1)	
RTx	455 (35.2)	48 (10.0)	287 (53.0)	95 (57.2)	25 (24.0)	
CRTx	80 (6.2)	1 (0.2)	24 (4.4)	29 (17.5)	26 (25.0)	

Values are presented as number (%).
M-K, Masaoka-Koga; CTx, chemotherapy; RTx, radiation therapy; CRTx, chemoradiation therapy.

Appendix 4. Details of adjuvant treatment by pathologic resection status

Resection status	Total (N=1,288)	Resection status			p-value
		R0 (N=1,183)	R1 (N=84)	R2 (N=21)	
Adjuvant treatment	580 (45.0)	502 (42.4)	65 (77.4)	13 (61.9)	<0.001
RTx	455 (35.3)	412 (34.8)	39 (46.4)	4 (19.0)	
CRTx	80 (6.2)	58 (4.9)	16 (19.0)	6 (28.6)	
CTx	45 (3.5)	32 (2.7)	10 (11.9)	3 (14.3)	

Values are presented as number (%).
RTx, radiation therapy; CRTx, chemoradiation therapy; CTx, chemotherapy.

Appendix 5. Propensity score matching profiles between open thymic surgery and MITS

Covariates	Before propensity score matching				After propensity score matching			
	Open (N=824)	MITS (N=474)	p-value	SD	Open (N=424)	MITS (N=424)	p-value	SD
Age ≥60 yr	237 (28.8)	120 (25.3)	0.203	0.079	110 (25.9)	120 (28.3)	0.487	-0.054
Sex (female)	366 (44.4)	251 (53.0)	0.004	-0.079	220 (51.9)	233 (55.0)	0.409	0.054
WHO			<0.001				0.975	
A&AB&B1	316 (38.3)	264 (55.7)		0.171	213 (50.2)	214 (50.5)		0.061
B2&B3	351 (42.6)	167 (35.2)		-0.416	166 (39.2)	167 (39.4)		-0.011
C	157 (19.1)	43 (9.1)		0.096	45 (10.6)	43 (10.1)		-0.083
Charlson comorbidity index			0.237				0.465	
0–1	485 (58.9)	301 (63.5)		-0.094	271 (63.9)	254 (59.9)		0.058
2–3	268 (32.5)	134 (28.3)		-0.014	120 (28.3)	131 (30.9)		0.051
≥4	71 (8.6)	39 (8.2)		-0.064	33 (7.8)	39 (9.2)		-0.066
Smoker	289 (35.1)	152 (32.1)	0.298	-0.108	133 (31.4)	120 (28.3)	0.368	-0.121
MG symptoms	214 (26.0)	102 (21.5)	0.083	-0.19	122 (28.8)	101 (23.8)	0.119	-0.041
FEV1			0.002				0.856	
<80	122 (14.8)	44 (9.3)		-0.004	49 (11.6)	44 (10.4)		0.025
≥80	558 (67.7)	320 (67.5)		0.136	289 (68.2)	294 (69.3)		0
Unknown	144 (17.5)	110 (23.2)		-0.55	86 (20.3)	86 (20.3)		-0.023
Neoadjuvant treatment: none	769 (93.3)	469 (98.9)	<0.001	0.55	418 (98.6)	419 (98.8)	1	0.023
Tumor size on CT (cm)			<0.001				0.844	
<6.5	533 (64.7)	415 (87.6)		0.693	366 (86.3)	365 (86.1)		-0.007
≥6.5	252 (30.6)	42 (8.9)		-0.764	44 (10.4)	42 (9.9)		-0.017
Unknown	39 (4.7)	17 (3.6)		-0.062	14 (3.3)	17 (4.0)		0.038

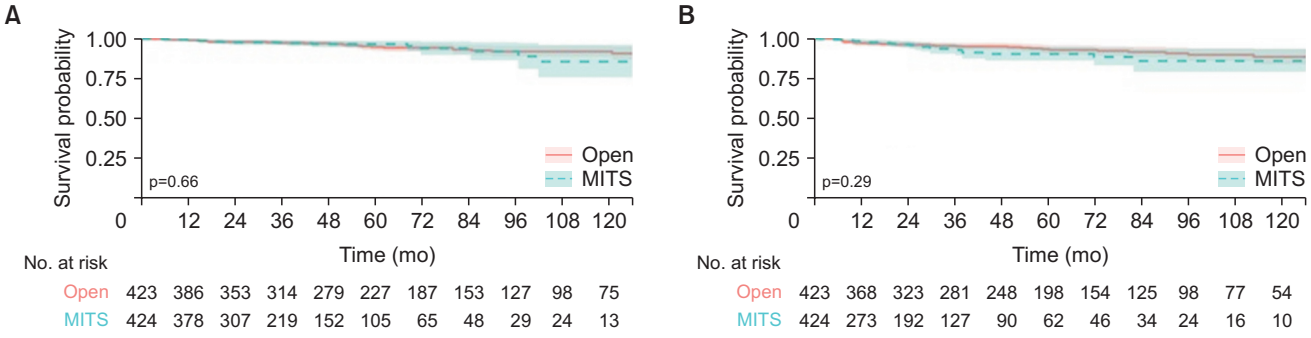
(Continued on next page)

https://doi.org/10.5090/jcs.21.124

Appendix 5. Continued

Covariates	Before propensity score matching				After propensity score matching			
	Open (N=824)	MITS (N=474)	p-value	SD	Open (N=424)	MITS (N=424)	p-value	SD
M-K stage			<0.001				1	
I	436 (52.9)	378 (79.7)		0.668	329 (77.6)	329 (77.6)		0
II	125 (15.2)	49 (10.3)		-0.159	48 (11.3)	48 (11.3)		0
III&IV	260 (31.6)	46 (9.7)		-0.738	46 (10.8)	46 (10.8)		0
Unknown	3 (0.4)	1 (0.2)		-0.033	1 (0.2)	1 (0.2)		0

Values are presented as number (%).
MITS, minimally invasive thymic surgery; SD, standard deviation; WHO, World Health Organization; MG, myasthenia gravis; FEV1, forced expiratory volume in 1 second; CT, computed tomography; M-K, Masaoka-Koga.



Appendix 6. Propensity matched overall survival and freedom from recurrence by surgical approach (open vs. minimally invasive thymic surgery [MITS]). (A) Overall survival with surgical approach. (B) Freedom from recurrence with surgical approach.

Appendix 7. Operative profiles and hospital course between propensity-matched patients who underwent open thymic surgery or MITS

Variable	Open (N=424)	MITS (N=424)	p-value
Operation			<0.001
Partial thymectomy	23 (5.4)	60 (14.2)	
Thymomectomy	39 (9.2)	157 (37.0)	
Total thymectomy	349 (82.3)	193 (45.5)	
Extended thymectomy	13 (3.1)	5 (1.2)	
Concurrent procedure	107 (25.2)	63 (14.9)	<0.001
Lymph node dissection	114 (26.9)	37 (8.7)	<0.001
Operation time (min)	158.1±54.4	118.3±67.9	<0.001
Events during operation	2 (0.5)	5 (1.2)	0.450
Transfusion	13 (3.1)	2 (0.5)	0.009
Chest tube duration (day)	4.3±2.0	2.9±2.1	<0.001
Operating room extubation	330 (78.4)	400 (94.3)	<0.001
Intensive care admission	221 (52.4)	57 (13.4)	<0.001
Hospital stay (day)	9.1±10.9	5.8±8.5	<0.001
Postoperative mortality	1 (0.2)	0	0.999
Postoperative complications	44 (10.4)	14 (3.3)	<0.001

Values are presented as number (%) or mean±standard deviation, unless otherwise stated.
MITS, minimally invasive thymic surgery.