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Original Article / *Özgün Makale*

Outcomes of thymoma after multimodal therapy and determinants of survival: A 16-year experience of a tertiary cancer center

Multimodal tedavi sonrası timoma hastalığının seyri ve hastalarda sağkalımın belirleyicileri: Üçüncü basamak kanser merkezinin 16 yıllık deneyimi

Naziye Ak[1], Alper Toker[2], Murat Kara[2], Berker Özkan[2], Melike Ülker[2], Erkan Kaba[3], Gülçin Yeğen[4], Şule Karaman[5], Nergiz Dağoğlu[5], Esra Kaytan Sağlam[5], Ethem Nezih Oral[5], Ahmet Kızır[5], Soley Bayraktar[6], Rian Dişçi[7], Ferhat Ferhatoğlu[1], Esra Aydın[1], Sezai Vatansever[1], Yeşim Eralp[1], Adnan Aydıner[1]

Institution where the research was done:
Istanbul University, Institute of Oncology, Istanbul, Turkey

Author Affiliations:
[1]Department of Medical Oncology, Istanbul University, Institute of Oncology, Istanbul, Turkey
[2]Department of Thoracic Surgery, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey
[3]Department of Thoracic Surgery, Istanbul Florence Nightingale Hospital, Istanbul, Turkey
[4]Department of Pathology, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey
[5]Department of Radiation Oncology, Istanbul University, Institute of Oncology, Istanbul, Turkey
[6]Department of Medical Oncology, Biruni University School of Medicine, Istanbul, Turkey
[7]Department of Biostatistical Science, Beykent University, Istanbul, Turkey

ABSTRACT

Background: In this study, we aimed to evaluate the factors that contribute to survival outcomes in patients with thymoma treated with multimodal approaches.

Methods: A total of 203 patients (105 males, 98 females; median age: 49 years; range, 17 to 77 years) with Masaoka-Koga Stage II-IV thymoma between January 2002 and December 2018 were retrospectively analyzed. Data including diagnosis of myasthenia gravis, diagnosis of diabetes mellitus, disease stage, histological type of tumor, capsule invasion and surgical margin status, lymphadenectomy, adjuvant radiotherapy or chemotherapy, time from surgery to the first day of adjuvant treatment, length of hospital stay, and overall and disease-free survival rates were recorded.

Results: Of the patients, 91 had Stage II, 67 had Stage III, and 45 had Stage IV disease. A total of 123 patients (61%) had myasthenia gravis. Seventy-six patients received adjuvant radiotherapy and 48 patients received either neoadjuvant (n=35) or adjuvant (n=25) chemotherapy. Higher disease stage, presence of R1 resection, and treatment with chemotherapy were significant factors for decreased disease-free survival time. Older age, higher disease stage, longer postoperative hospital stay, chemotherapy, and disease recurrence were effective contributors to decreased overall survival time. Adjuvant radiotherapy had a statistically significant positive effect on overall survival only in patients with completely resected Stage IV disease (five-year overall survival: 94.7% *vs*. 79.1%, respectively; p=0.015). In the multivariate analysis, older age (hazard ratio: 4.26), higher disease stage (hazard ratio: 2.95), and longer hospitalization time (hazard ratio: 3.81) were significant prognostic factors for overall survival. Patients with local recurrence who underwent complete resection had a survival time comparable to non-recurrent patients (p=0.753).

Conclusion: For patients with thymoma, higher disease stage, age ≥50 years, longer hospitalization, and need for chemotherapy are associated with worse survival rates. Adjuvant chemotherapy has a positive impact on Stage IV disease. Resection of recurrent lesions has a valuable impact on survival.

Keywords: Aggressive surgery, chemotherapy, Masaoka-Koga Staging, radiotherapy, survival, thymoma.

ÖZ

Amaç: Bu çalışmada, multimodal yaklaşımlar ile tedavi edilen timoma hastalarının sağkalım sonuçlarına katkıda bulunan faktörler değerlendirildi.

Çalışma planı: Ocak 2002 - Aralık 2018 tarihleri arasında Masaoka-Koga Evre II-IV timomalı toplam 203 hasta (105 erkek, 98 kadın; medyan yaş: 49 yıl; dağılım, 17-77 yıl) retrospektif olarak incelendi. Myastenia gravis tanısı, diabetes mellitus tanısı, hastalık evresi, tümörün histolojik türü, kapsül invazyonu ve cerrahi sınır durumu, lenfadenektomi, adjuvan radyoterapi veya kemoterapi, cerrahiden adjuvan tedavinin ilk gününe kadar geçen süre, hastanede yatış süresi ve genel ve hastalıksız sağkalım oranları kaydedildi.

Bulgular: Hastaların 91'inde Evre II, 67'sinde Evre III ve 45'inde Evre IV hastalık izlendi. Toplam 123 hastada (%61) myastenia gravis vardı. Yetmiş altı hastaya adjuvan radyoterapi ve 48 hastaya neoadjuvan (n=35) veya adjuvan (n=25) kemoterapi verildi. Yüksek hastalık evresi, R1 rezeksiyon varlığı ve kemoterapi azalmış hastalıksız sağkalım süresinin anlamlı faktörleriydi. İleri yaş, yüksek hastalık evresi, ameliyat sonrası uzun süreli hastane yatışı, kemoterapi ve hastalık nüksü genel sağkalım süresinin azalmasına katkıda bulunan faktörlerdi. Yalnızca tam rezeke Evre IV hastalığı olan hastalarda, adjuvan radyoterapinin genel sağkalım üzerinde istatistiksel olarak anlamlı bir pozitif etkisi vardı (beş yıllık genel sağkalım: sırasıyla %79.1'e kıyasla %94.7; p=0.015). Çok değişkenli analizde ileri yaş (risk oranı: 4.26), yüksek hastalık evresi (risk oranı: 2.95) ve daha uzun hastanede yatış süresi (risk oranı: 3.81) genel sağkalımın anlamlı prognostik faktörleriydi. Tam rezeksiyon uygulanmış lokal nüks saptanan hastalardaki sağkalım süresi, hiç nüks saptanmayan hastalar ile benzer bulundu (p=0.753).

Sonuç: Timomalı hastalarda yüksek hastalık evresi, ≥50 yaş, daha uzun süreli hastanede yatış ve kemoterapi ihtiyacı, daha kötü sağkalım oranları ile ilişkilidir. Adjuvan radyoterapi, Evre IV hastalık üzerinde olumlu etkiye sahiptir. Tekrarlayan lezyonların rezeksiyonunun sağkalım üzerinde önemli bir etkisi vardır.

Anahtar sözcükler: Agresif cerrahi, kemoterapi, Masaoka-Koga Evrelemesi, radyoterapi, sağkalım, timoma.

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Correspondence: Naziye Ak, MD. İstanbul Üniversitesi Onkoloji Enstitüsü, Tıbbi Onkoloji Anabilim Dalı, 34093 Fatih, İstanbul, Türkiye.
Tel: +90 551 - 102 28 66 e-mail: naziyeak@hotmail.com

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Thymomas are the most commonly diagnosed mediastinal tumors that present with anterior mediastinal masses.[1,2] Thymomas typically occur between 40 and 70 years of age, with similar incidences in both sexes.[3] Approximately 30 to 50% of patients with thymoma have myasthenia gravis (MG), and a wide range of other autoimmune paraneoplastic syndromes have been also reported.[4] The World Health Organization's (WHO) classification of thymic tumors was revised in 2015 and divided into six types: A, AB, B1, B2, B3, and thymic carcinoma.[5] The American Joint Committee on Cancer (AJCC) and the Masaoka-Koga staging system are two widely used staging modalities.[6-8] and surgery with a clear margin is the primary treatment modality.[9] The role of adjuvant radiotherapy (RT) remains controversial due to conflicting survival results, particularly after R0-resection for advanced stage thymomas.[10-12]

There is a dearth of randomized studies showing benefits of adjuvant therapy in completely resected patients, despite the high sensitivity of the tumor to chemotherapeutic agents. Due to the rarity of this tumor, prospective studies are unlikely and existing data mostly rely on retrospective or institutional reports, with current guidelines based on expert opinions. In the present study, we, therefore, aimed to evaluate the factors that contribute to outcomes in patients with thymoma treated with multimodal therapy.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Istanbul University, Institute of Oncology, Department of Medical Oncology between January 2002 and December 2018. Patients with Masaoka-Koga Stage II-IV thymoma were screened. Inclusion criteria were as follows: *(i)* patients with pathologically confirmed Masaoka-Koga Stage II-IV thymoma, *(ii)* patients with adequate follow-up, and *(iii)* patients who completed all suggested treatment modalities for standardization. Exclusion criteria were as follows: *(i)* patients with Masaoka-Koga Stage I thymoma, *(ii)* final pathology that also revealed a squamous cell carcinoma, *(iii)* incomplete clinical or pathological data, *(iv)* presence of synchronous active malignancy, and *(v)* refusal to give consent for the study. Accordingly, a total of 203 patients (105 males, 98 females; median age: 49 years; range, 17 to 77 years) were included in the study. A written informed consent was obtained from each patient. The study protocol was approved by the Istanbul University, Istanbul Faculty of Medicine Ethics Committee (No: 62576/2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

We performed histopathological confirmation before the definitive treatment, either via Tru-cut biopsy, mediastinotomy, or video-assisted thoracic surgery (VATS) biopsy, in patients whose thymic mass could not be resected with minimally invasive VATS. Lung resections, including lobectomies, were performed when there was an invasion of the lung or the hilar vessels of the lung. Parietal pleurectomy and/or partial or total diaphragmatic and pericardial resections were performed when there was an invasion, or thymoma implants were recognized. The phrenic nerve was sacrificed, when there was a unilateral invasion, and the diaphragm was plicated on the ipsilateral side. When the phrenic nerve was invaded bilaterally, the residual tumor was left behind on both or either side of the nerve. The indications for lymph node dissection were as follows: *(i)* pathological nodal enlargement in tomography and/or increased uptake in positron emission tomography, *(ii)* detection of positive lymph nodes during dissection, *(iii)* all open surgeries performed after 2014. When complete resection seemed impossible (according to the pre-surgical radiological assessment), we carefully discussed it with a multidisciplinary council and opted for neoadjuvant chemotherapy (CT) as a part of the curative-intent strategy. Two definite indications for neoadjuvant CT were the unfeasibility of R0 resection and the presence of a tumor too close to the main vascular structures. Neoadjuvant CT was omitted after experiencing difficulties in dissection and vascular reconstructions. Clinical restaging after induction CT was performed with computed tomography after the third cycle, and the decision for surgery suitability was made within a multidisciplinary council. For patients with an insufficient response, treatment continued until surgery could be performed. The Masaoka-Koga Stage system was used for staging, and the WHO classification system was used for histological classification. When the results were reported as mixed histological types, the tumor was reclassified according to the most histologically aggressive type. To illustrate, when the tumor had B1 and B3 components, the tumor was classified as type B3. Patients who recurred with resectable disease underwent three types of surgeries: *(i)* local excision of pleural, pericardial, and diaphragmatic implants, *(ii)* pleurectomy/decortication, *(iii)* chest wall/diaphragmatic resection and reconstruction. In general, posterolateral thoracotomy and median sternotomy were used in this group. A single incision with double-level thoracotomy was applied

to achieve implantations. In addition, pericardial defects were reconstructed with polypropylene or polytetrafluoroethylene (PTFE) patches and diaphragmatic defects with PTFE patches.

Regarding the decisions for postoperative treatment, stage and completeness of resection were the most relevant criteria considered, followed by histological evaluation. We used three-dimensional conformal radiotherapy (RT) with doses of 50.4 Gy/1.8-2 Gy per fraction in adjuvant CT and 54 to 56 Gy/1.8-2 Gy per fraction for microscopically positive resection margins and neoadjuvant CT. The CT regimen was based on the physician's preference. The regimens used for neoadjuvant and adjuvant settings were CAP (cyclophosphamide 500 mg/m^2, cisplatin 50 mg/m^2, doxorubicin 50 mg/m^2, intravenous day one every

Table 1. Baseline characteristics of patients and treatment modalities

	Total		Masaoka-Koga Stage			Resection type*	
Characteristics	n	%	II	III	IV	R0	R1
Age (year)							
<50	106	52.2	49	32	25	102	4
≥50	97	47.8	42	35	20	88	5
Sex							
Male	105	51.7	48	32	25	97	6
Female	98	48.3	43	35	20	93	3
MG							
Yes	123	60.6	63	38	22	117	4
No	80	39.4	28	29	23	73	4
Acetylcholine receptor antibodies (Patients with MG)							
Yes	113	91.9	56	37	20	107	4
No	10	8.1	7	1	2	10	0
WHO histology							
A†	14	6.9	7	5	2	13	0
AB	21	10.3	16	3	2	20	1
B1†	39	19.2	24	7	8	38	0
B2†	75	36.9	28	28	19	70	4
B3†	50	24.6	13	23	14	45	4
Micronodular thymoma	1	0.5	1	0	0	1	0
Not classified	3	1.5	2	1	0	3	0
NACT type*							
Cis/etoposide			1	6	1	8	0
CAP	35	17.6	2	6	17	20	2
Pac/carbo			0	1	1	4	1
Adjuvant CT type*							
Cis/etoposide			0	2	7	8	1
CAP	25	12.6	0	6	6	11	1
Pac/carbo			1	1	2	4	0
Adjuvant RT*							
50			21	15	14	49	1
54	76	38.2	5	11	7	18	5
56			0	1	2	0	3
Surgery after recurrence*							
Yes	21	10.6	3	6	12	19	2

MG: Myasthenia gravis; WHO: World Health Organization; NACT: Neoadjuvant chemotherapy; Cis: Cisplatin; CAP: Cyclophosphamide/adriamycin/cisplatin; CT: Chemotherapy; RT: Radiotherapy; * Total N: 199 with exclusion of four inoperable patients; † Histology of a metastatic patient.

Table 2. Characteristics of patients with lymph node involvement

Patient no	Age (year)	Tumor size (mm)	Histology type	Masaoka-Koga Stage	Cervical lymph node dissection	Station of positive lymph nodes
1	36	80	Thymoma type B1	Stage 4A	+	Cervical
2	42	71	Thymoma type B2	Stage 4A	_	4R
3	44	50	Thymoma type B2	Stage 3	_	4R
4	33	80	Thymoma type B3	Stage 4A	+	Cervical 4R
5	55	60	Thymoma type B3	Stage 3	_	2L

three weeks), CE (cisplatin 75 mg/m^2 intravenous day one, etoposide 100 mg/m^2 intravenous day 1-3 every 3 weeks), and paclitaxel with carboplatin (paclitaxel 80 mg/m^2 intravenous day 1, carboplatin AUC 2 intravenous day 1 weekly).

Patients who did not undergo complete surgery during the course of their disease were excluded from survival analysis with the aim of preserving accurate survival factors. The overall survival (OS) was defined from the date of histological diagnosis to the date of death from any cause. Disease-free survival (DFS) was defined from the date of histological diagnosis until recurrence.

Data including median age, sex, diagnosis of MG, diagnosis of diabetes mellitus (DM), Masaoka-Koga Stage, WHO histological type of tumor, capsule invasion and surgical margin status, lymphadenectomy, adjuvant RT or CT, days from surgery to the first day of adjuvant treatment (before and after 60 days), and length of hospital stay were analyzed.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The distribution of categorical variables was compared using the chi-square test, while continuous variables were compared after normality tests using the Mann-Whitney U or Kruskal-Wallis H test. Multivariate Cox regression analysis with 95% confidence interval (CI) was used to evaluate the effects of risk factors on survival. The Kaplan-Meier method was used for survival analysis, and factors were compared using the log-rank test. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic data

The most common complaints were myasthenia-related symptoms (n=70, 34.5%), while a total of

Table 3. Characteristics of patients with lymph node involvement

Characteristic	n	%
Sex		
Male	10	47.6
Female	11	52.4
Type of surgery		
Pleural implantation/pleurectomy	12	57.1
Cardiac implantation	5	23.8
Diaphragmatic implantation/reconstruction	11	52.4
Chest wall resection/ reconstruction	4	19
Complications		
None	11	52.4
Pneumonia	4	19
Wound infection	4	19
Hemorrhage (without revision)	3	14.3
Cardiac arrhythmia	2	9.5

15.3% of the patients (n=31) were asymptomatic. Other presenting symptoms included fatigue, mass-related symptoms such as coughing, chest pain, hoarseness, and dyspnea. Totally 123 (61%) patients had associated MG during any course of the disease, most frequently in B2 thymomas (n=53, 43.1% of patients with MG). Other autoimmune diseases associated with disease were hypothyroidism, hypogammaglobulinemia, uveitis, ankylosing spondylitis, and pure red cell aplasia. Type B2 and B3 thymomas were more invasive, and had more cases at either Stage III or IV (p<0.001). Four patients (2%) had metastatic disease.

Treatment modalities

The baseline disease characteristics of the patients, treatment modalities according to stage, and resection data are shown in Table 1. We operated the majority of patients within the first

Table 4. Univariate survival analysis of patients (n=199)*

Factors	Disease free survival results			Overall survival results		
	% of 5-years survival	SE	*p*†	% of 5-years survival	SE	*p*†
Age (year)						
<50	79	4.6	0.260	96.5	2	0.043
≥50	89.4	3.8		86.3	4.4	
Sex						
Female	85.1	4.4	0.876	92.2	3.1	0.660
Male	82.3	4.3		91.5	3.5	
Myasthenia gravis						
No	79.9	5.9	0.566	88.8	4.9	0.843
Yes	85.4	3.6		94.4	2.2	
Histology						
A	100	0	0.887	87.5	11.7	0.583
AB	87.8	8.1		100	0	
B1	84.2	6.5		91.6	4.7	
B2	76.7	6.0		92.8	3.5	
B3	85.4	6.1		91.4	5	
Masaoka-Koga Stage						
II	95.7	2.4	<0.001	96	2.3	0.003
III	89	4.7		88.4	5	
IV	46.7	9.5		88.2	5.6	
Hospitalization						
≤8	90.8	2.8	0.088	95.6	1.9	0.008
>8	74.3	7.9		79.8	6.9	
Resection						
R0	84.9	3.1	0.042	92.2	2.3	0.823
R1	47.4	22.8		80	17.9	
Adjuvant radiotherapy						
No	87.6	3.7	0.231	90.5	3.3	0.400
Yes	78.5	5.2		93.6	3.7	
Adjuvant chemotherapy						
No	91.6	2.6	<0.001	90.3	2.7	0.970
Yes	37.3	11.5		100	0	
Neoadjuvant chemotherapy						
No	88.8	2.8	<0.001	91.5	2.6	0.146
Yes	54.0	11.0		86.9	7.2	

† Log-rank test; SE: Standard error; * Total n: 199 with exclusion of four inoperable patients.

two months post-neoadjuvant CT, with a median of 51 days. We performed 103 (50.7%) upper partial or total sternotomy operations, 54 (26.6%) VATS, including unilateral, bilateral, and subxiphoid VATS approaches, 37 (18.2%) thoracotomies, and five (2.5%) robot-assisted thoracoscopic surgery. Overall, most patients (n=190) underwent R0 resection, and nine patients received R1-resection. During surgery, frozen sections confirmed complete resection without a suspicion of residual tumor. Thirty-five (17.25%) patients were treated with neoadjuvant CT, nine of whom underwent concomitant RT. However, none of them showed a complete pathological response in the final pathology. Superior vena cava resection and reconstruction were performed in 22 (1.1%) patients. We performed lymphadenectomy in 95 (4.7%) patients, of which five showed metastatic lymph node invasion (Table 2). The mean duration of postoperative hospitalization was 8.3±8.6 (range, 2 to 71) days. The number of total operative mortality was three, and 45 (22.2%) patients had operative complications. The most common complications were infection, transient arrhythmia, and hemorrhage. Forty-nine (24.1%) patients were hospitalized for more than eight days due to complications. Postoperative pathological reports showing invasive tumor characteristics such as invasion to adjacent tissues (n=48) and capsule (n=52) or close surgical margins (n=36) were the most common indications for the use of adjuvant treatment modalities. A total of 76 (37.3%) and 25 patients (12.3%) received adjuvant RT and adjuvant CT, respectively. Four (2%) patients with distant metastasis underwent CT with palliative intent.

Recurrence and survival results

Out of four patients with inoperable disease, complete follow-up data were available for 182 cases, and recurrence was observed in 30 (16.5%) patients. Nineteen (9.5%) patients died across all patient groups, and disease-related mortality was very low with seven patients (23.3% of patients with recurrence). Three (1.5%) patients died within one month after surgery. One (0.5%) patient died on the first postoperative day due to hypotensive shock after extended surgery. The second patient died two weeks after surgery due to postoperative pneumonia and MG crisis. The last patient, previously diagnosed with chronic renal failure, died with infectious hemodialysis complications at the end of the first postoperative month. All patients with local recurrence in our cohort (n=21) underwent a second surgery. Type of a second surgery depended on the region of recurrence, most frequently: lobectomy, pleurectomy, excision of the involved chest wall and rib. Although operative morbidity was relatively high (47.6%), there was no operative mortality (Table 3).

At a mean follow-up of 198.2±6.5 months (95% CI: 184.4-212), the five-year OS and DFS rates were 91.9% and 83.5%, respectively. In the univariate analyses, higher Masaoka-Koga Stage (p<0.001), R1 resection (p=0.042), and treatment with CT (p<0.001) were significant factors for decreased DFS (Table 4).

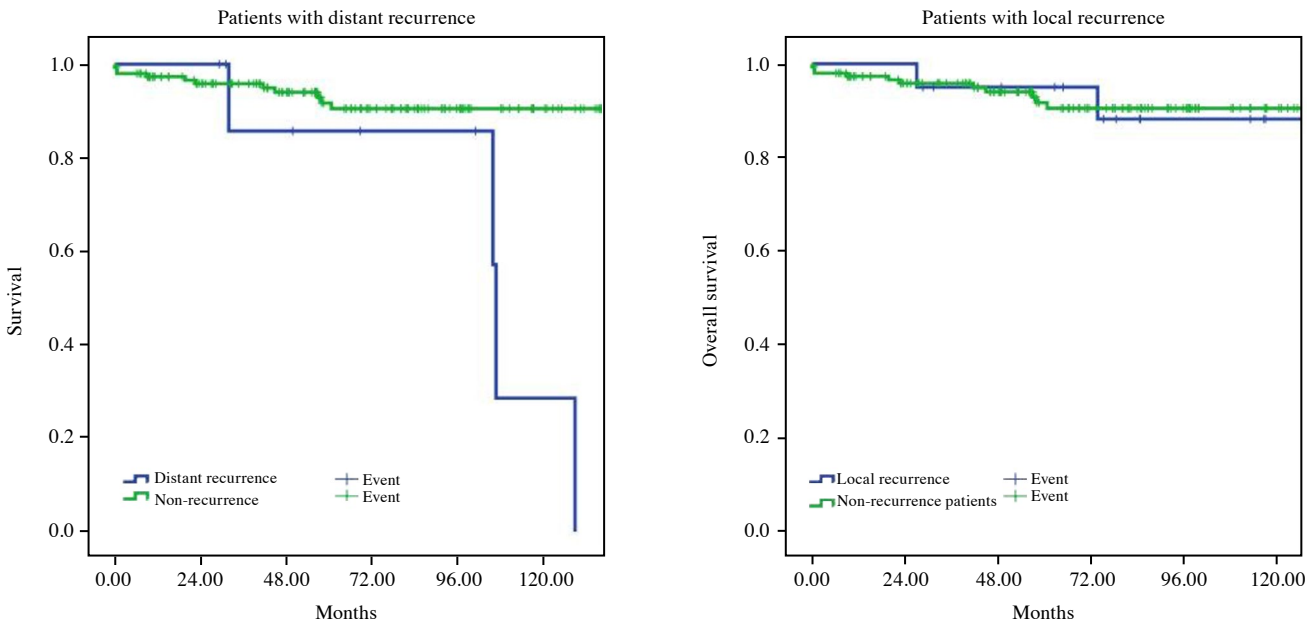


Figure 1. Survival results of patients after resection of local recurrence and distant recurrence.

Table 5. Multivariate analysis of factors on survival

	Overall survival			Disease-free survival		
Factors	HR	95% CI	*p*	HR	95% CI	*p*
Age (Ref: <50)	4.265	1.349-13.479	0.014	0.570	0.170-1.912	0.362
History of MG (Ref: Yes)	0.469	0.135-1.633	0.234	0.918	0.308-2.740	0.878
Hospitalization time (Ref: <8)	3.815	1.282-11.353	0.016	0.746	0.247-2.252	0.603
Histologic subtype (Ref: A)	0.714	0.444-1.148	0.164	0.615	0.370-1.022	0.061
Neoadjuvant CT (Ref: No)	1.305	0.316-5.401	0.713	0.907	0.273-3.013	0.873
Adjuvant CT (Ref: No)	0.590	0.112-3.100	0.533	5.320	1.685-16.800	0.004
Adjuvant RT (Ref: No)	0.536	0.181-1.583	0.259	2.097	0.774-5.680	0.145
Masaoka-Koga Stage (Ref: II)	2.955	1.452-6.016	0.003	2.780	1.267-6.101	0.011

Ref: Reference value; HR: Hazard ratio; CI: Confidence interval; MG: Myasthenia gravis; RT: Radiotherapy; CT: Chemotherapy.

The MG history had a negative impact on DFS for patients with Masaoka-Koga Stage III, although the number of events was low (n=7, five-year DFS; 82.4% *vs*. 100%, respectively; p=0.026). For patients with Masaoka-Koga Stage IV disease, DFS rates were higher if they had a history of MG, but the results did not reach statistical significance (five-year DFS: 60.2% *vs*. 33.6%, respectively; p=0.091). Older age (p=0.043), higher Masaoka-Koga Stage (p=0.002), longer postoperative hospitalization (p=0.008), treatment with CT (p=0.046), and disease recurrence (p=0.037) were significant factors for poor OS (Table 4). Notably, if the patients' first recurrence was local disease (n=21), OS was similar to non-recurrent patients (p=0.753) (Figure 1). The adjuvant RT resulted in statistically insignificant, but numerically higher OS rates in all patient populations (five-year OS: 93.6% *vs*. 89.5%, respectively; p=0.315). Only in patients with completely resected Masaoka-Koga Stage IV disease, was adjuvant RT found to have a significant positive effect on OS (five-year OS: 94.7% *vs*. 79.1%, respectively; p=0.015). Adjuvant CT, timing of adjuvant therapy (RT or CT), and histology showed no significant effects on patient outcomes. In the multivariate analysis, older age, higher Masaoka-Koga Stage, and longer hospitalization time retained their prognostic significance on OS; Masaoka-Koga Stage and need for postoperative CT had prognostic significance for DFS (Table 5).

DISCUSSION

Although rare, thymomas constitute the most frequently occurring tumors of the anterior thoracic region.[3] Due to its rarity and indolent course, retrospective experiences of reference centers are of utmost importance to understand the ailment and improve treatment recommendations. In this study, we present our experiences in the long-term in a high-volume reference center.

In our cohort, the median age of the patients was 49 years, and most patients presented with myasthenia-related symptoms. We observed significantly higher OS results in patients younger than 50 years old. Previous reports showing age-related outcomes have conflicting results.[10,13] Upon diagnosis of MG, asymptomatic patients may be examined for thymoma, thereby, contributing to early detection. Based on this hypothesis, Wilkins et al.[14] reported that MG was associated with a good prognosis. The effect of MG on survival is controversial, as is evident from other negative studies.[15,16] In our cohort, there were two different results for Masaoka-Koga Stage III-IV disease, and it is difficult to comment on this association.

The current WHO classification is the most widely used system for histological classification.[5,17] Histological subtypes of thymoma not only show pathological results, but also provide information on

the course of the disease. Although we were unable to show the survival effect of histological subtypes, we found that histology was strongly associated with the disease stage. Similar to our results, there have been a few reports demonstrating no relationship between OS and histology;[18,19] however, some studies have shown a correlation.[12,20,21] The relationship with disease stage could be interpreted as a survival result, when the cohort had a longer follow-up or higher sample size.

The implication of performing lymphadenectomy in patients is still controversial. However, the new Tumor, Node, Metastasis (TNM) staging system for thymic tumors prompts the recommendation for locoregional lymphadenectomy.[22] In our study, we detected only five patients with metastasis on nodal evaluation. We were not able to evaluate the survival effect of lymph node metastasis due to the small number of patients. However, lymphadenectomy did not have an effect on treatment choice and survival in our cohort. In our patient population, the mean hospitalization duration was 8±8.5 days. Interestingly, longer postoperative hospital stays were related to OS, evident from a multivariate analysis with a hazard ratio of 3.6. This could be attributed to the extensive nature of the surgery conducted. When we analyzed factors other than surgical complications that might affect the duration of hospitalization, age, history of DM or MG, and disease histology were similar between the long and short hospitalized groups. Although multivariate analysis showed both disease stage and hospitalization time to be independent factors, clinically, they are not totally independent. This result may be used to relate surgical outcome to disease outcome and, for oncologists, it could be an indicator of the need for treatment and/or high frequency follow-up. Notably, more patients with Masaoka-Koga Stage IV disease and a history of neoadjuvant CT were hospitalized for eight days.

In the Surveillance, Epidemiology, and End Results (SEER) registry, adjuvant RT was associated with superior OS and DFS rates and subgroup analyses suggested that the OS benefit was limited to patients with Masaoka-Koga Stage III-IV disease.[23] In our study, we found no survival benefit of adjuvant RT for Stage II-III, but in patients with completely resected Masaoka-Koga Stage IV disease, there was a significant survival benefit with adjuvant RT (p=0.015). Moreover, only one patient with adjuvant RT within this subgroup (n=38) died from the disease. The current data also have conflicting results for CT as the sole adjuvant setting. Guidelines do not recommend postoperative CT for R0-R1 resected Stage I-IVA disease.[11] We administered neoadjuvant and/or adjuvant CT to 48 patients, and if the patient had clinical indication of CT, they showed significantly lower survival rates. Consistent with our results, two separate studies also showed worse survival results with CT.[10,24] However, these results may depend on the clinical characteristics of patients, leading to the employment of CT.

Recurrence of thymic tumors is not uncommon, with a rate of 10 to 15%.[25] Local recurrence is more common and should be managed as newly diagnosed tumors.[11] A total of 16.5% of our patients experienced recurrence after complete surgery, and recurrence was associated with lower OS (p=0.013). Noteworthy, we demonstrated that patients with local recurrence subjected to a second surgery had survival rates equal to their non-recurrent counterparts. Therefore, we strongly suggest a second surgery for a disease-free status. Patients are usually resistant to repeated surgeries; therefore, these results can be attributed to strong encouragement for patients to undergo surgery.

There are several limitations to this study. Patient selection bias was inevitable due to the retrospective nature of the study. However, this is one of the largest cohorts of thymoma in a single center, representing the comprehensive surgical, pathological, and oncological results of the patients. Considering the difficulties of performing prospective studies on this rare disease, retrospective real-life experiences are of clinically significant value for guiding treatment approaches.

In conclusion, higher Masaoka-Koga stage, age ≥50 years, longer hospitalization time, and the need for chemotherapy are significantly correlated with worse survival results. More importantly, patients with Masaoka-Koga Stage IV disease can benefit from adjuvant radiotherapy, and resection of recurrent lesions has a significant effect on survival.

Declaration of conflicting interests

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