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Treatment Outcomes and Prognostic Factors Affecting Survival in Thymic Carcinoma

Abdülkadir Koçanoğlu[1], Yakup Düzköprü[2], Esra Zeynelgil[3], Nesrin Gürçay[4], Serdar Karakaya[1], Doğan Yazılıtaş[3]

[1]*Health Sciences University Türkiye, Ankara Atatürk Sanatoryum Training and Research Hospital, Clinic of Medical Oncology, Ankara, Türkiye*
[2]*Aksaray Training and Research Hospital, Clinic of Medical Oncology, Aksaray, Türkiye*
[3]*Health Sciences University Türkiye, Etlik City Hospital, Clinic of Medical Oncology, Ankara, Türkiye*
[4]*Health Sciences University Türkiye, Ankara Atatürk Sanatoryum Training and Research Hospital, Clinic of Pathology, Ankara, Türkiye*

ABSTRACT

Aim: Treatment guidelines for thymic carcinoma, a rare cancer involving multiple clinical subgroups, are primarily derived from retrospective studies. We aimed to evaluate the frequency of histopathological subgroups, treatment modalities, clinicopathological characteristics, and to assess their correlation with the odds of survival of patients with thymic cancer.

Methods: A retrospective analysis was performed on data from 19 individuals monitored in outpatient oncology clinics following diagnosis of thymic carcinoma. Surgical history, margin status, sites of recurrence or metastasis, date of final follow-up, and date of death were among the clinical and demographic factors recorded and examined.

Results: For the whole group, the median overall survival (OS) was 20 months [95% confidence interval (CI): 2.25-37.75]. The median OS was ten months for individuals who were not operated on (95% CI: 7.43-12.56), compared with 68 months for operated patients (95% CI: 16.67-119.32) (p=0.010). The median OS for patients receiving mediastinal radiation was 68 months (95% CI: 15.67-120.32), compared with 8 months (95% CI: 3.19-12.80) for those not receiving RT. Although the difference did not reach statistical significance (p=0.064), patients with stage IV disease had a median OS of 14 months (95% CI: 6.45-21.55), whereas patients without stage IV disease had a median OS of 68 months (95% CI: 22.18-113.83).

Conclusion: Consistent with our findings, postoperative radiotherapy and surgical excision seem to be the most significant prognostic factors. Surgical options-including upfront surgery-and postoperative radiotherapy should be seriously considered in the treatment of thymic carcinoma.

Keywords: Thymic carcinoma, adjuvant radiotherapy, prognostic factors

Introduction

According to data from the World Health Organisation, thymic malignancies are uncommon cancers, with an incidence of 0.15-0.25 per 100,000 people. Histologically, they are classified into two major groups: thymomas and thymic carcinomas [1]. Roughly 20% of all thymic epithelial malignancies are thymic carcinomas, which have been reported to be more prevalent among Asia-Pacific [2]. In the United States, they are more common in men, and previous studies have reported a median age at diagnosis ranging from 54 to 65.5 years [3,4]. Squamous cell carcinoma (SCC) is the most frequently encountered histological subtype. Low-grade papillary adenocarcinoma, lymphoepithelial carcinoma, clear cell carcinoma, and basaloid carcinoma are further subtypes [5]. Thymomas are often diagnosed early and remain confined, in contrast to thymic carcinomas, which usually present with metastases. Given that total resection yields the most favorable survival outcomes, surgical management continues to be the preferred therapeutic option [6,7]. However, recommendations for metastatic disease are limited and mainly derived from small retrospective studies [8,9].

Several studies have demonstrated a survival benefit from postoperative radiotherapy (RT) in patients with thymic cancer

Address for Correspondence: Abdülkadir Koçanoğlu MD, Health Sciences University Türkiye, Ankara Atatürk Sanatoryum Training and Research Hospital, Clinic of Medical Oncology, Ankara, Türkiye
E-mail: kadirkocanoglu@hotmail.com **ORCID ID:** orcid.org/0000-0002-5579-2135
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who had positive surgical margins or received a total resection [10-12]. A multicenter European analysis reported that the most pronounced survival improvement with postoperative RT was observed in disease stages III and IV, and that it also conferred a statistically significant benefit among individuals with positive surgical borders [12].

For unresectable thymic carcinoma, platinum-based chemotherapy (CT) regimens combined with agents such as paclitaxel, anthracyclines, or etoposide may be used; these combinations have shown survival benefits [13,14]. In locally advanced cases that respond to CT, surgery is an feasible option for further treatment [15]. For metastatic thymic carcinoma, carboplatin plus paclitaxel is the preferred first-line regimen [16]. One study reported that this combination resulted in a 36% objective response rate and a median progression-free survival of 7.5 months [17]. Other platinum-based regimens are also used in clinical practice. Thymic carcinoma is a rare malignancy with multiple pathological subtypes, and treatment recommendations are largely based on retrospective data. We aimed to evaluate the frequencies of histopathological subgroups, treatment modalities, and clinicopathological characteristics, and their associations with survival in individuals with thymic carcinoma.

Methods

Patient Population and Data Collection

Information about individuals with thymic carcinoma who attended the outpatient cancer clinics of our hospital between January 1, 2012, and October 1, 2022, was examined retrospectively. Participants were included if they were at least 18 years old, had thymic carcinoma confirmed by histopathology, had an Eastern Cooperative Oncology Group performance status of 0-1 at diagnosis, and had comprehensive follow-up information available in clinical and electronic records. Patients with a history of another primary malignancy were not considered eligible. Nineteen of the twenty-four thymic cancer patients who were screened during the study period met the inclusion criteria and were included in the analysis.

Data were obtained from hospital files and electronic medical records. Collected variables included diagnostic date, disease location, histological subtype, disease stage, receipt of RT, CT regimens, comorbidities, smoking and alcohol history, surgical history, margin status, date and site of recurrence or metastasis, treatments received after recurrence or metastasis, date of death and date of most recent follow-up.

The Ethics Committee of Health Sciences University Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital approved the study (approval number: 141/13; date: 04.07.2022). The tenets of the 1964 Declaration of Helsinki were adhered to when carrying out the research protocol.

Statistical Analysis

IBM SPSS statistics (version 22.0; IBM Corp., Armonk, NY, USA) was used to perform statistical analyses. Utilising descriptive statistics to summarise clinical and demographic data. Non-normally distributed variables were expressed as median (range). Counts and percentages were used to present numerical and categorical variables (n, %). To compare categorical variables, the chi-square test was used. Overall survival (OS) was defined as the time from diagnosis to death or to last follow-up. The Log-Rank test was utilised to compare groups, and the Kaplan-Meier method was employed for survival analysis. For all analyses, a p value of less than 0.05 was deemed statistically significant.

Results

Three women and sixteen men comprised the study's 19 patients. The median age at diagnosis was 55 years (range: 20-80 years). Fifteen patients (78.9%) had a history of smoking. Stage IV disease was identified in 57.9% of the individuals. Thirteen patients (68.4%) underwent surgical resection. Among them, 9 (47.4%) had R0 resection and 4 (21.1%) had R1 resection. Regarding histopathological subtypes, the most prevalent type was SCC, observed in 15 cases (78.9%). Of the 13 patients who received curative treatment, 7 (53.8%) experienced recurrence. Six individuals (31.6%) had metastases in their lymph nodes, which were the most prevalent site. Thirteen patients received mediastinal RT; of these, 12 (63.2%) received it as adjuvant therapy and one for palliative purposes. Among them, 5 were stage I-II, 2 were stage III, and 6 were stage IV. Six patients (31.6%) underwent combined CT and RT after R0 resection, whereas four patients (21.1%) received the combination following R1 resection. All 8 patients who received adjuvant CT were treated with carboplatin plus paclitaxel. In first-line treatment for metastatic disease, the most commonly used regimen was carboplatin plus paclitaxel (n=7, 36.8%), followed by the cisplatin, doxorubicin, and cyclophosphamide (PAC) regimen (n=5, 26.3%). For second-line treatment, PAC was again the most commonly administered regimen (n=5, 26.3%). Table 1 summarizes the patients' clinicopathological and demographic characteristics.

In terms of OS, the cohort's median OS was 20 months [95% confidence interval (CI): 2.25-37.75]. The median OS was 10 months (95% CI: 7.43-12.56) in non-operated patients, whereas it was 68 months (95% CI: 16.67-119.32) in those who received surgery (p=0.010). Patients who did not receive mediastinal RT had a median OS of 8 months (95% CI: 3.19-12.80), while those who got RT had an OS median of whereas those who received RT had a median OS of 68 months (95% CI: 15.67-120.32). According to tumor, node, metastasis staging staging at diagnosis, the median OS for patients with stage IV disease was 14 months (95% CI: 6.45-21.55), while the median OS for those without stage IV disease was 68 months (95% CI: 22.18-113.83). This difference was not statistically significant (p=0.064). Table 2 summarises, and Figure 1 depicts, the relationship between clinicopathological features and OS.

Table 1. Clinicopathological and demographic characteristics of the patients

Features	n (%)
Age (median, minimum-maximum)	55 (20-80)
Gender	
Female	3 (15.8%)
Male	16 (84.2%)
Smoking status	
Yes	15 (78.9%)
No	4 (21.1%)
ECOG Performance Status	
0	5 (26.3%)
1	14 (73.7%)
Stage at diagnosis (TNM)	
I	4 (21.1%)
II	1 (5.3%)
III	3 (15.8%)
IV	11 (57.9%)
Surgery	
Performed	13 (68.4%)
Not performed	6 (31.6%)
Type of resection	
R0	9 (47.4%)
R1	4 (21.1%)
Histopathological subtype	
Squamous cell carcinoma	15 (78.9%)
Adenocarcinoma	2 (10.5%)
Basaloid type	1 (5.3%)
Adenosquamous carcinoma	1 (5.3%)
Mediastinal RT	
Yes	13 (68.4%)
No	6 (31.6%)
Site of metastasis	
Lymph nodes	6 (31.6%)
Lung	1 (5.3%)
Multiple sites	4 (21.1%)
First-line CT regimen for metastatic disease	
Carboplatin+paclitaxel	7 (36.8%)
PAC	5 (26.3%)
Cisplatin+gemcitabine	1 (5.3%)
Second-line CT regimen for metastatic disease	
PAC	5 (26.3%)
Carboplatin+paclitaxel	1 (5.3%)
Gemcitabine	1 (5.3%)

ECOG: *Eastern Cooperative Oncology Group,* CT: *Chemotherapy,* RT: *Radiotherapy,* PAC: *Cisplatin, doxorubicin, and cyclophosphamide, TNM: T*umor, node, metastasis staging

Discussion

Thymic carcinoma is an uncommon and serious cancer that develops from the epithelial cells of the thymus, characterized by its heterogeneous histopathological features and a generally unfavorable prognosis [18,19]. Despite improvements in diagnostic imaging, surgical techniques, and multimodal treatment strategies, the optimal management of thymic carcinoma remains a subject of ongoing debate. In the present investigation, our goal was to evaluate the clinicopathological characteristics, treatment preferences, survival rates, and prognostic variables in individuals with thymic carcinoma.

In our study, of all patients, 84.2% of patients were male; however, male and female patients did not differ significantly in OS. Overwhelmingly predominant pathologic subtype was SCC (78.9%), with adenocarcinoma, basaloid thymic carcinoma, and adenosquamous carcinoma following closely behind. No significant difference in OS was detected among histological subtypes. Similarly, Petat et al. [9] reported SCC as the predominant histological type (67%), followed by undifferentiated carcinoma, basaloid carcinoma, sarcomatoid carcinoma, and adenocarcinoma, in their cohort.

In the same study, 50% of the patients had stage IV cancer, including 15% with stage IVa; the presence or absence of surgery was identified as the most important prognostic factor, even among those who underwent upfront surgery. The PAC regimen was preferred by 62% of patients and the carboplatin-paclitaxel regimen by 22%, with PAC being linked to better progression-free survival (p=0.001) [9]. In our cohort, 57.9% of patients presented with stage IV disease, and 31.5% had stage IVa disease at diagnosis. Median OS was 68 months for surgically treated patients versus 10 months for those not operated on (p=0.010), underscoring the prognostic importance of surgical resection in thymic carcinoma. Among patients receiving CT as a first-line treatment for metastases, 36.8% received carboplatin-paclitaxel and 26.3% received the PAC regimen; there was no discernible variation in survival between regimens.

In a large analysis of 462 patients with thymic carcinoma, mediastinal RT after surgery did not significantly improve OS among stage I-II patients who underwent complete tumor resection (p=0.14). In contrast, OS was significantly better

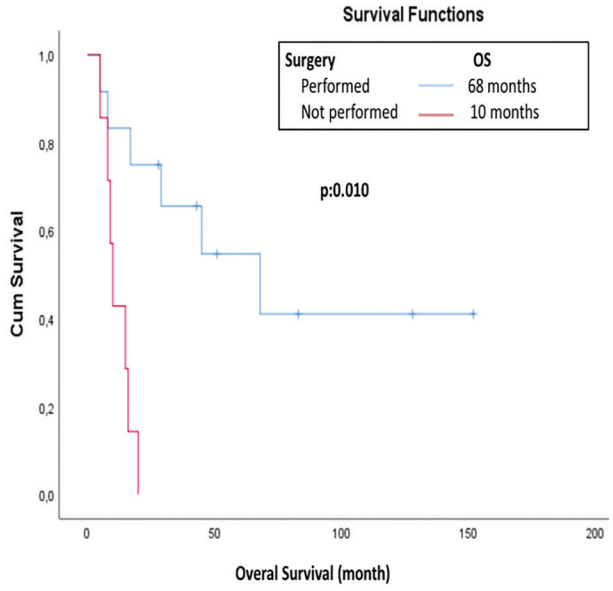

Figure 1. Kaplan-Meier curves of clinically significant prognostic factors (surgery and mediastinal RT)
RT: Radiotherapy, OS: Overal survival

Table 2. Univariate and multivariate analysis of prognostic factors for overall survival

Features	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Gender Female Male	0.64 (0.17-2.33)	0.49		
Histopathological subtype Squamous cell carcinoma Adenocarcinoma Basaloid type Adenosquamous carcinoma	2.09 (0.44-9.92)	0.144		
Smoking status Yes No	2.64 (0.57-12.16)	0.213		
ECOG PS 0 1	4.18 (0.90-19.50)	0.069		
At diagnosis, stage IV? Yes No	3.21 (0.94-10.97)	0.064		
Surgery Performed Not performed	5.56 (1.5-20.64)	0.010	Ref 0.872 (0.41-18.75)	0.930
Type of resection R0 R1	2.53 (0.41-15.62)	0.317		
Treatment modalities Total excision+CT+RT Total excision+RT No total excision, CT+RT No total excision, CT only No surgery, palliative CT		0.054		
Mediastinal RT Yes No	0.15 (0.04-0.54)	0.004	Ref 6.01 (0.27-132.12)	0.255
Adjuvant CT Yes No	0.66 (0.19-2.33)	0.522		
First-line CT regimen for metastatic disease PAC Carboplatin+Paklitaksel Sisplatin+Gemsitabin		0.321		

CI: Confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, CT: Chemotherapy, RT: Radiotherapy, PAC: Cisplatin, doxorubicin, and cyclophosphamide, HR: Hazard ratio

in stage III-IV patients with R0 resection (p=0.043) and in patients with residual disease after surgery (R1-2) (p=0.001). The authors reported that pathological stage, postoperative RT, and complete resection were independent predictors of survival [12]. Similarly, Nazzal et al. [20] analyzed data from patients with stage II thymic carcinoma and reported that adjuvant RT did not confer a survival benefit in early-stage R0-resected cases. In our study, the median OS was 8 months for those without mediastinal RT and 68 months for those who did receive mediastinal RT (p=0.004), suggesting a survival benefit associated with postoperative mediastinal RT. However, OS did not differ significantly by surgical margin status, likely because of the limited sample size and the relatively small proportion (21.1%) of R1-resected patients.

Previous studies have shown that disease stage at diagnosis is a crucial predictor of survival outcomes [12,21]. In our study, patients with stage IV disease had a median OS of 14 months, compared with 68 months for patients without stage IV disease. Although this difference did not reach statistical significance (p=0.064), which is likely due to the relatively small sample size, the numerical trend suggests a clinically meaningful impact of advanced stage on survival.

Study Limitations

Our study's retrospective design and relatively small patient population are its primary limitations. Because thymic carcinoma is rare, larger patient cohorts in multicentre prospective studies are needed to better define optimal treatment strategies and prognostic variables.

Conclusion

Thymic carcinoma is an infrequent malignancy with a challenging treatment course, and recommended treatment strategies are largely based on retrospective studies. As demonstrated in our study, postoperative RT and the extent of surgical resection are the most influential prognostic factors. Accordingly, management decisions should include a thorough evaluation of surgical strategies, including upfront surgery and postoperative RT.

Ethics

Ethics Committee Approval: The Ethics Committee of Health Sciences University Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital approved the study (approval number: 141/13; date: 04.07.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., Y.D., N.G., S.K., D.Y., Concept: A.K., Y.D., S.K., Design: A.K., E.Z., Data Collection or Processing: A.K., N.G., Analysis or Interpretation: A.K., Y.D., E.Z., N.G., S.K., Literature Search: A.K., D.Y., Writing: A.K.

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