The Egyptian Journal of Hospital Medicine (January 2024) Vol. 94, Page 97-107

Survival Outcomes and Prognostic Factors of Thymic Epithelial Tumors a Single Center Experience

Hadeer Saber Abd El Rasoul*, Nawal Mohamed El Sayed El Kholy, Mohamed Saad El-deen El-zahi, Fatma Mohamed Farouk Akl

Department of Clinical Oncology & Nuclear Medicine, Faculty of Medicine, Mansoura University, Egypt

***Corresponding author:** Hadeer Saber Abd El Rasoul, **Mobile:** (+20)1141404031, **E-Mail:** hadersaber07@gmail.com

ABSTRACT

Background: Thymic epithelial tumors (TET) constitute the most common neoplasia in the anterior mediastinum, although they account for less than 1% of all neoplasms.

Objective: This is a retrospective study conducted to analyze clinic-epidemiological characteristics, prognostic factors, treatment modality and survival outcomes of patients with thymic epithelial tumors.

Patients and Methods: All patients diagnosed with Thymic epithelial tumors (TETs) over a period of 10 years (from 2010 to 2019) were reviewed. A clinical sheet was designed for 34 cases, and all clinicopathological data were collected. Data analysis was performed using both the Kaplan-Meier method and Cox proportional hazards modeling.

Results: seventy-six (76%) of patients presented with thymoma (N: 26) while only 8 patients had thymic carcinoma. By Masoaka staging system 35.3% of the patients were stage III. Myasthenia gravis presented in 11 patients (32.4%). Multiple treatment modalities were needed for 22 patients (64.7%) while single modality was used in 12 patients (35.3 %). Twenty-three of the patients (67.6%) underwent surgical resection. Twenty-nine (29%) of the patients received adjuvant RT.

Conclusion: For patients with TETs, surgery is statistically significant for Overall survival (OAS) prognostic factors and the *Masoaka* staging system is the only statistically significant factor of the progression-free survival (PFS) prognostic factors.

Keywords: Thymoma, Multi-modality treatment, Prognostic factors.

INTRODUCTION

Thymic epithelial tumors (TETs) make up less than 1% of all tumors. The most prevalent kind of TETs are thymomas [(1)]. TETs are the most common neoplasia in the anterior mediastinum, despite being rare. They sporadically develop ectopically, primarily in the neck. Reaching its height in the fourth and sixth decades [(2)].

Thymomas may behave like malignant tumors, but histologically, they seem to be benign tumors. Thymic carcinoma, on the other hand, has more aggressive tumor cells and a propensity to spread [(3)].

Types A and AB of thymomas are typically regarded as benign tumors, while type B1 is a low-grade malignant tumor with a 90% 10-year survival rate; type B2 exhibits a higher degree of malignancy; and type B3, which resembles thymic carcinoma in that it has a poor prognosis[(4)].

Over the past few decades, at least fifteen distinct stage classification schemes for thymic malignancies have been put up and put into practice. The Masaoka-Koga classification is still the most often used clinical staging system, nevertheless. A new categorization for thymic malignancies has been proposed by the International Thymic Malignancy Interest Group (ITMIG) and the International Association for the Study of Lung Cancer (IASLC) [(5)].

One-third to one-half of thymoma patients exhibit no symptoms, while the remaining third show localized symptoms because of the tumor's encroachment on nearby structures. A third of cases are unintentionally discovered during radiographic exams done as part of a myasthenia gravis (MG) workup [(6)].

Favorable characteristics like younger age, thymoma histologic type, earlier stage, and higher rate of complete resection status are linked to paraneoplastic/autoimmune (PN/AI) syndromes [(7)].

In 10% of myasthenic cases, thymoma coexists with myasthenia gravis. This is a common combination. Up until now, there has been no connection between thymic carcinoma and myasthenia gravis [(8)].

Imaging is essential to the treatment of patients with thymic carcinoma and thymoma. Imaging plays a key role in the initial diagnosis, patient staging, especially for identifying locally invasive disease distant and metastases [(9)].

For the most part, thymomas can be surgically resected without a prior diagnosis [(10)]. The standard therapy for TET is still resection, with the desired outcome being total excise of the tumor and any affected organs [(11)].

PORT is advised for thymomas that have not been fully excised, if stage II or above. Every stage of thymic carcinoma that shows positive surgical margins should be considered for PORT treatment [(12)].

Neoadjuvant therapy, such as radiotherapy and possibly chemotherapy, may be beneficial for patients who had locally advanced TET to facilitate complete excision, enhance local control, and improve survival [(13)]. Radiotherapy plays an important role in the management of unresectable locally advanced TET [(14)].

This work was aimed to assess progression free survival and overall survival and to determine the prognostic factors that could influence survival of thymic tumors.

Received: 15/10/2023
Accepted: 15/12/2023

PATIENTS AND METHODS

This retrospective study included a total of thirty-four patients with thymic epithelial tumors (thymoma or thymic carcinoma) who were treated at the Department of Clinical Oncology and Nuclear medicine, Mansoura University Hospital (MUH) from January 2010 to December 2019.

A clinical sheet was designed of 34 cases that were reviewed from medical records and the following data were collected: age, gender, ECOG, smoking, comorbidities, presenting symptoms, histopathological type, stage, laboratory profile, radiological investigations, treatment modality, survival (OAS, and PFS) and follow-up.

Inclusion criteria: Patients with pathologically proven thymic epithelial tumor, aged ≥ 18 years, without major co-morbidities, and at different tumor stages.

Exclusion criteria: Patients with other malignancies.

Ethical consent:

Approval of the study was obtained from Mansoura University Academic and Ethical Committee. Every patient signed an informed written consent for the acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The software tool SPSS version 26 is using for All performed statistics. Quantitative data were summarized as median, minimum and maximum values (range) or mean±SD. Qualitative data as percentages. Comparison of group medians was done by using the Mann Whitney U test and Kruskal-Wallis test, while Chi-square test was used for comparisons of percentages. The significance of prognostic factors was analyzed by using Cox regression analysis. The survival was shown by the Kaplan-Meier survival curve. Over-all survival (OAS) is defined as the time since the patient was diagnosed till died or lost follow-up. The progression-free survival (PFS) took into account all data from the beginning of treatment until the date of progression, death, or the final follow-up. If the p-value was less than 0.05, the findings were significant.

RESULTS

Thymic epithelial tumors distribution among our cases was 76% of patients presented with thymoma (N: 26) while only 8 patients had thymic carcinoma. Twenty-five patients (73.5%) were above 35 years old. The median age was 46.5% (19 – 70) years. Male to female ratio was 2.09:1. As in Table 1.

Most of patients (N: 22, 64.7%) had good performance status (ECOG 1 and 2). Dyspnea was the commonest presentation (N: 22, 64.7%). Myasthenia gravis presented in 11 patients (32.4%).

Most of the patients (41.4%) were B2 by WHO histological classification and (23.5 %) of them had thymic carcinoma. By Masoaka staging system 35.3% of the patients were stage III. As shown in Table 1.

The recurrence rate in thymic carcinoma was 37.5% which was higher than that of Thymoma which was 34.6% as presented at table 1.

Table (1): Clinical and pathological Characteristics of the Patients

Characteristics	Thymoma N:26	Thymic carcinoma N:8	Over all N:34

	N:26	%	N:8	%	N:34	%
Age Group						
≤45	12	46.2	5	62.5	17	50
>45	14	53.8	3	37.5	17	50
Gender						
Male	18	69.2	5	62.5	23	67.6
Female	8	30.8	3	37.5	11	32.4
ECOG						
0	5	19.2	0	0	5	14.7
1	13	50	4	50	17	50
2	7	26.9	4	50	11	32.4
3	1	3.9	0	0	1	2.9
Smoking						
Yes	12	46.2	2	25	14	41.2
No	14	53.8	6	75	20	58.8
Symptoms						
Dyspnea	9	34.6	3	37.5	12	35.3
Cough	3	11.7	3	37.5	6	17.6
Chest pain	2	7.8	0	0	2	5.9
Muscle weakness	5	19.2	1	12.5	6	17.6
Accidently	2	7.8	0	0	2	5.9
Hoarseness of voice	1	3.9	1	12.5	2	5.9
Others	4	15.4	0	0	4	11.8
WHO Histology classification						
A	2	7.8	0	0	2	5.9
AB	3	11.7	0	0	3	8.8
B1	4	15.4	0	0	4	11.8
B2	14	53.8	0	0	14	41.4
B3	3	11.7	0	0	3	8.8
Thymic carcinoma	0	0	8	100	8	23.5
Masoaka staging system						
Stage I	7	26.9	0	0	7	20.6
Stage IIA	3	11.7	0	0	3	8.8
Stage IIB	4	15.6	0	0	4	11.8
Stage III	8	31.2	4	50	12	35.3
Stage IVA	4	15.4	2	25	6	17.6
Stage IVB	0	0	2	25	2	5.9
Myasthenia gravis	10	38.4	1	12.5	11	32.4
Recurrence	9	34.6	3	37.5	12	35.3
Status						
• **Alive**	22	84.6	6	75	28	82.4
• **Missed follow up**	4	15.4	2	25	6	17.6

Table 2 shows treatment modalities. Multiple treatment modalities were needed for disease control in 22 patients (64.7%) while single modality was used in 12 patients (35.3 %). Nine out of 10 Thymoma patients were treated by surgery as a single modality. Twenty-three of the patients (67.6%) underwent surgery, fifteen (44.1%) of them were R0. twenty-nine 29% of the patients had adjuvant RT.

Table (2) Different Treatment modalities:

Characteristics	Thymoma N:26	Thymic carcinoma N:8	Over all N:34

	N	%	N	%	N	%
Treatment Modality						
Tri-modality	2	7.7	3	37.5	5	14.7
Bimodality	14	53.8	3	37.5	17	50
Single modality	10	38.4	2	25	12	35.3
Treatment received						
Surgery only	9	34.6	0	0	9	26.5
Surgery + Radiotherapy	5	19.2	0	0	5	14.7
Surgery + chemotherapy	4	15.6	0	0	4	11.8
Surgery + RT + ChT	2	7.8	3	37.5	5	14.7
Chemotherapy + RT	5	19.2	3	37.5	8	23.5
Chemotherapy only	1	3.9	2	25	3	8.8
Surgical resection						
R0	14	53.8	1	12.5	15	44.1
R1	3	11.7	1	12.5	4	11.8
R2	3	11.7	1	12.5	4	11.8
No surgery	6	23.4	5	62.5	11	32.4
Radiotherapy						
No	14	53.8	2	25	16	47.2
Neoadjuvant	1	3.8	0	0	1	2.9
Adjuvant	7	26.9	3	37.5	10	29.4
Definitive	4	15.4	2	25	6	17.6
Palliative	0	0	1	12.5	1	2.9

Survival analysis was performed to asses overall survival (OAS) and progression-free survival (PFS). The 5- and 7-year OAS of all patients were 88.2 % and 57.7 % respectively. As illustrated in **Figure 1.** Longer 5year OAS in thymoma patients vs thymic carcinoma patients, although it was non statically significant (p value 0.184), as represented in **Figure 2**. The mean PFS of all patients was 61.9 ± SD19.57 months and the 5-year PFS was 70.6 %. As shown in **Figure 3.** Thymoma patients had longer 3year PFS than Thymic carcinoma patients In **Figure 4.**

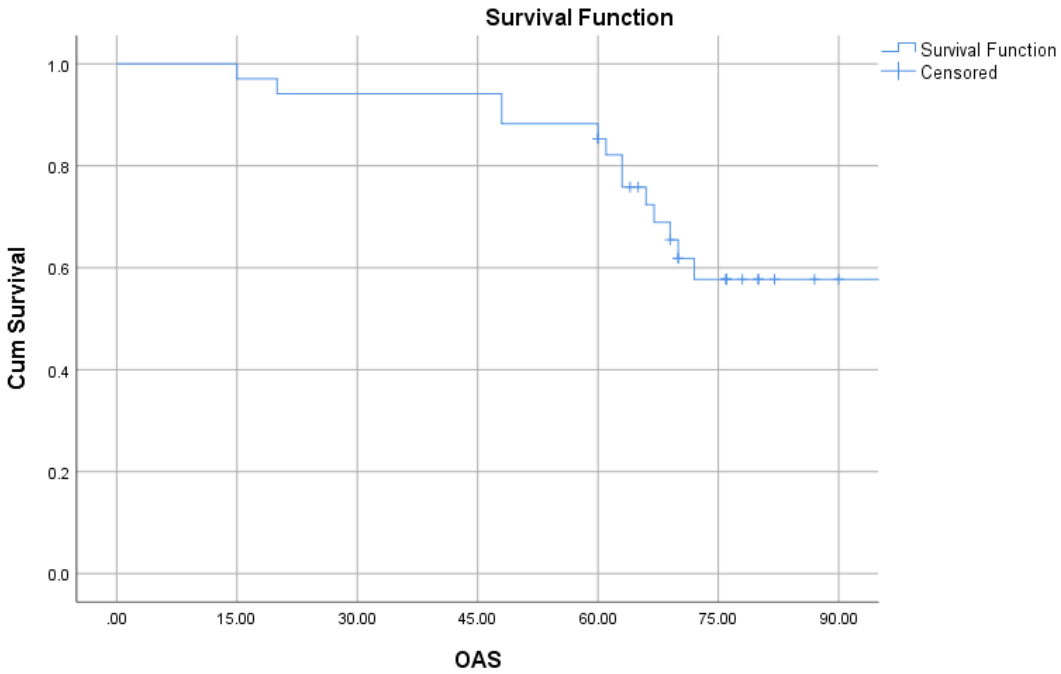

Figure (1): The OAS of all patients.

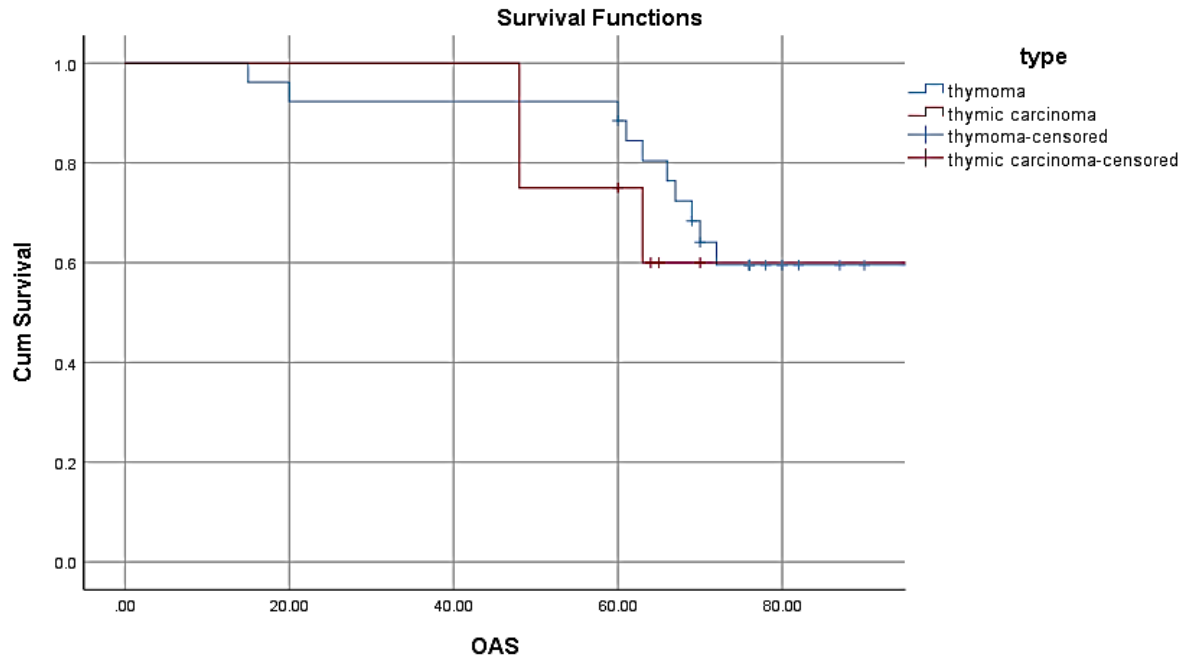

Figure (2): The OAS in thymoma versus thymic carcinoma patients

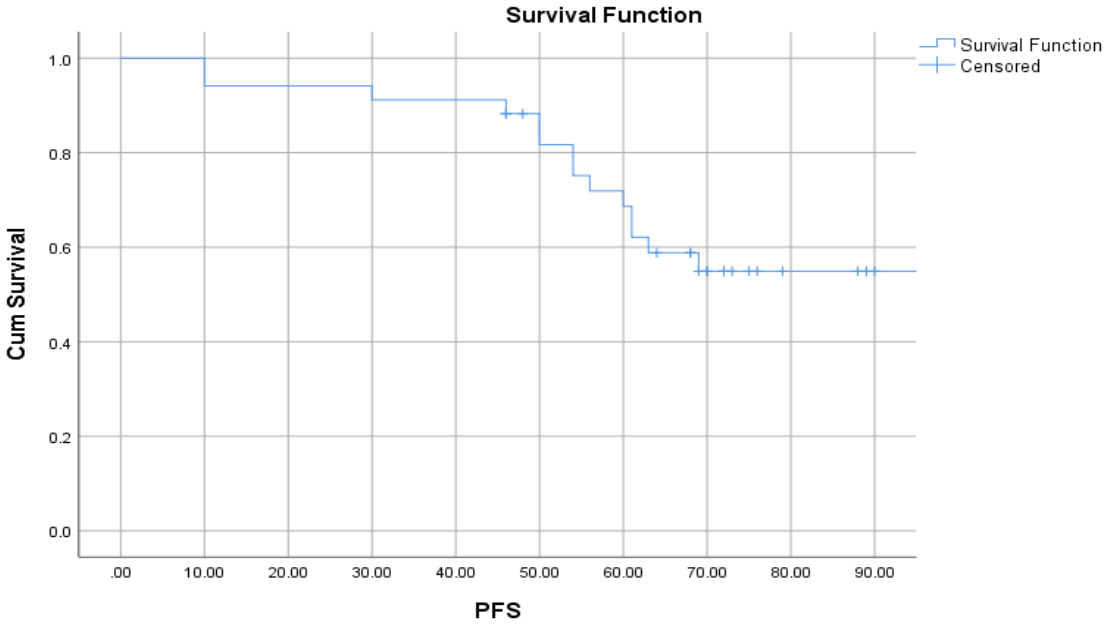

Figure (3): The PFS of all patients.

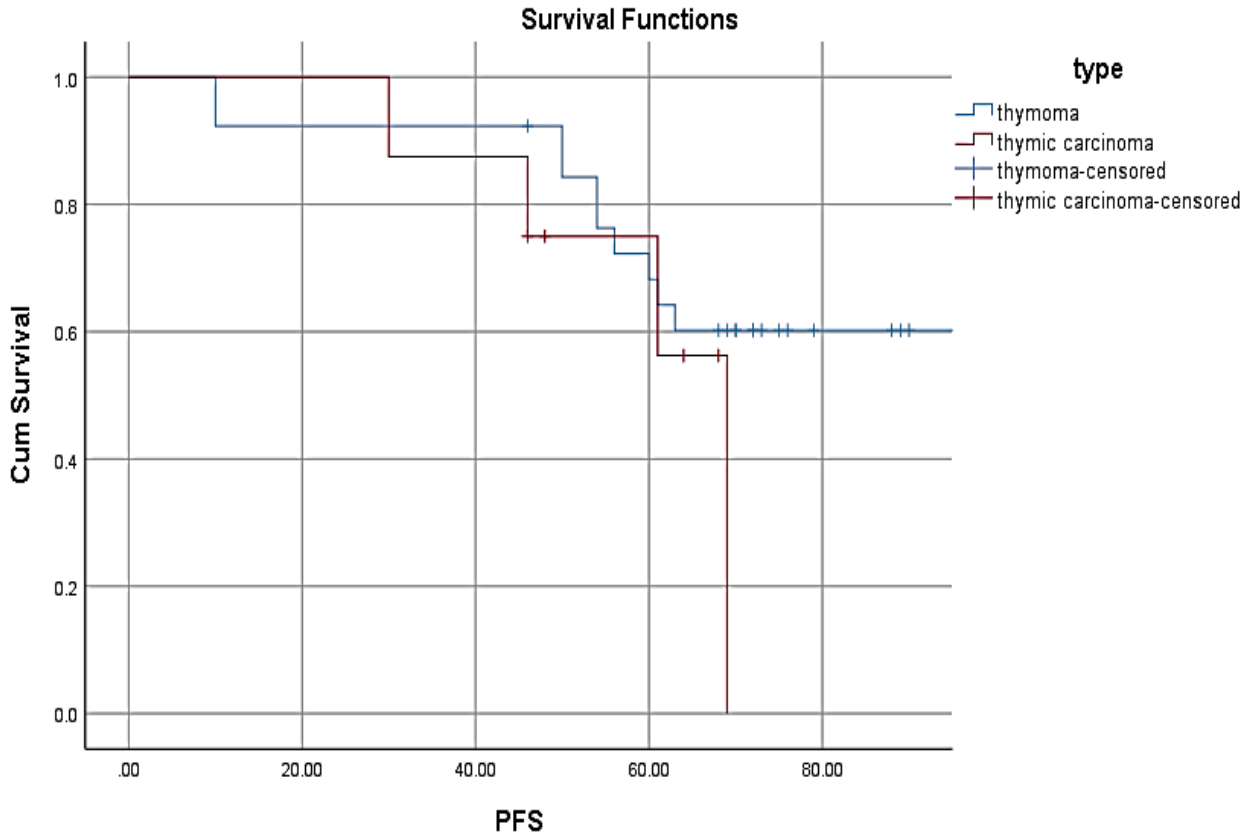

Figure (4): The PFS in thymoma versus thymic carcinoma patients.

the univariate analysis of different prognostic factors with OAS revealed that age, ECOG, Masoaka staging system, and surgery were statistically significant as OAS prognostic factors with p value (0.033, 0.041, <0.001, and 0.033 respectively as illustrated in **table 3** while in the multivariate analysis of OAS prognostic factors, the tumor stage was the most independent prognostic factor (p value 0.039). shown in **Table 4**. PFS prognostic factors as shown in **Table 3** revealed that Masoaka staging system was the only statistically significant factor ($p < 0.001$). These impacts were shown in **Figure (5-8).**

Table (3): Univariate analysis of different prognostic factors of OAS and PFS.

		5-Years OAS %	95%CI	P-value	5-years PFS %	95%CI	p-value
Age Group							
	≤ 45	50	(0.096-0.108)	**0.033****	38.2	(0.718-0.738)	0.452
	>45	38.2			32.4		
Gender							
	Male	58.8	(1-1)	0.738	47.1	(1-1)	0.850
	Female	29.4			23.5		
ECOG							
	0	14.7	(0.123-0.136)	**0.041****	11.8	(0.698-0.716)	0.369
	1	44.1			38.2		
	2	29.4			20.6		
	3	0			0		
Smoking			0.626-0.645)			(0.157-0.172)	
Yes		43.3		0.484	31.8		
No		56.7			68.2		0.133
MG							
	Yes	55.9	(0.270-0.288)	0.141	44.1	(0.700-0.718)	0.32
	No	32.4			26.5		
Histology classification							
	Thymoma	70.6	(0.222-0.238)	0.184	58.8	(0.407-0.426)	0.144
	Thymic carcinoma	17.6			11.8		
Masoaka staging system							
	Stage I-III	76.5	(0.001-0.002)	**<0.001****	67.6	**(**0.000-0.002)	**<0.001****
	Stage IV	11.8			2.9		
Treatment modality							
	Trimodality	11.8	(1-1)	0.557	5.9	(0.542-0.562)	0.266
	Bimodality	47.1			38.2		
	Single modality	29.4			26.5		
	Surgery	50	(0.029-0.035	**0.033****	41.2	(0.277-0.295)	0.132
	Non surgery	38.2			29.4		
Resection							
	Complete	65.2%		0.161	52.2	(0.654-0.673)	0.363
	Incomplete	30.4%	(0.344-0.363)		21.7		

Notes: CI = confidence interval.

Table (4): Multivariate analysis of overall survival prognostic factors

	Hazard Ratio	95% CI		P-value
	Exp(B)	Min	Max	
Age group	6.641	0.431	102.404	0.175
ECOG	3.160	0.541	18.470	0.201
Stage	17.917	1.154	278.072	0.039*
Surgery	0.116	0.006	2.271	0.156

Notes: CI = confidence interval.

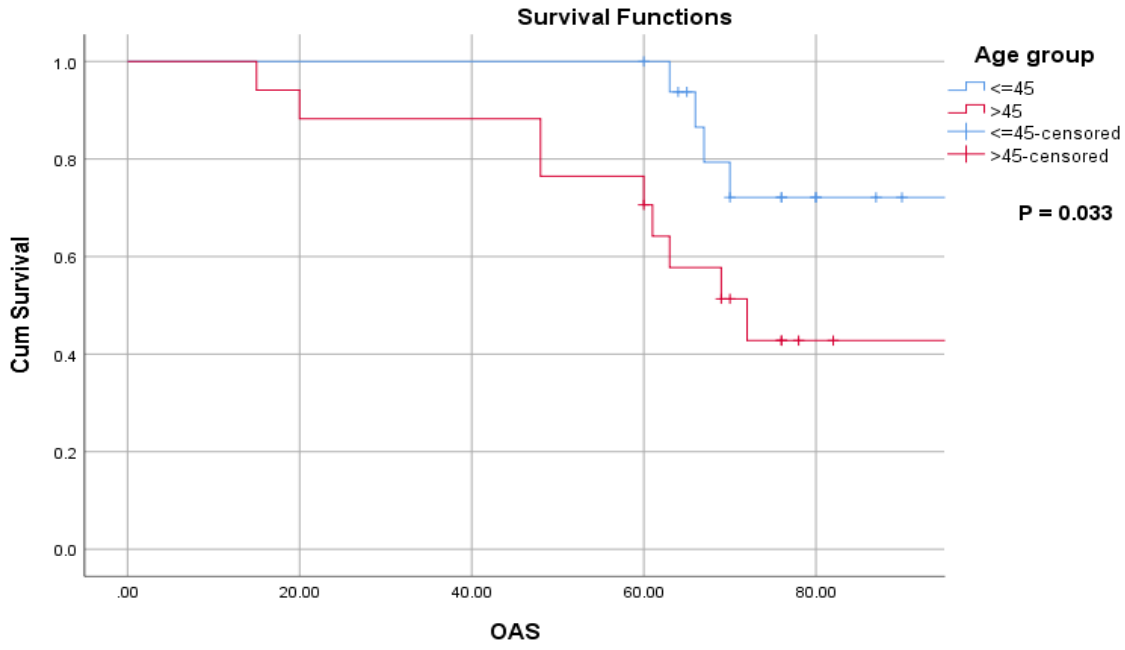

Figure (5): The impact of age on OAS.

There is Significant correlation between age and OAS where patients ≤ 45 years old had longer OAS than patients ≥45 years old.

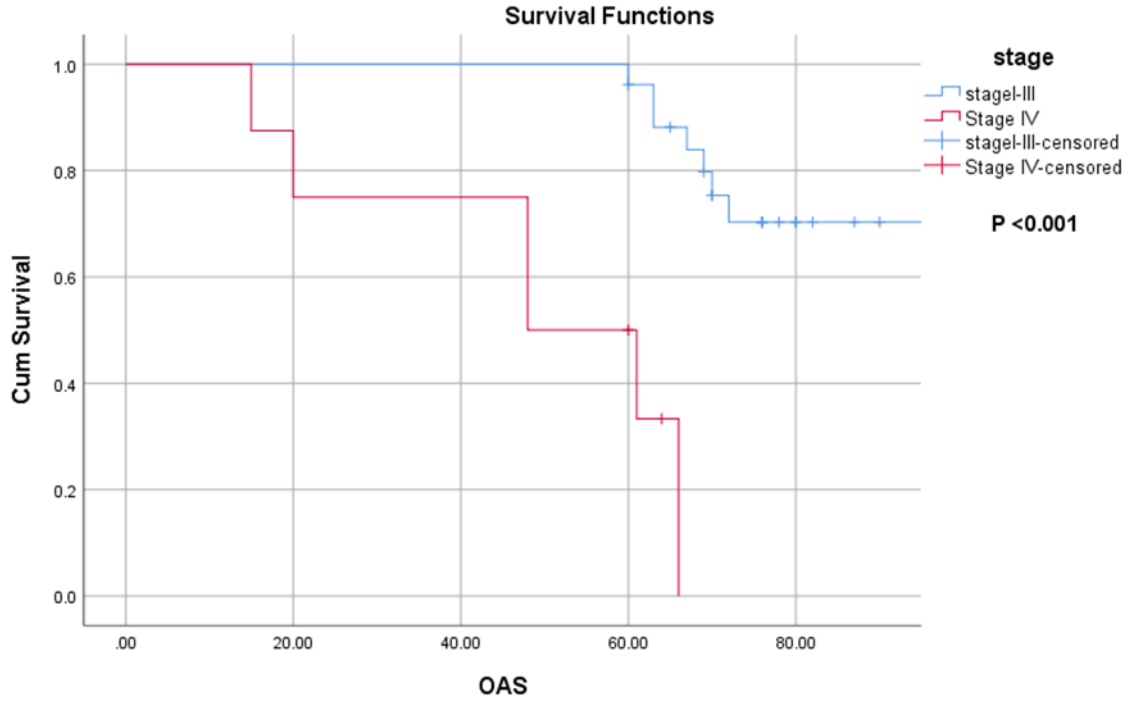

Figure (6): The impact of disease stage on OAS.

Patients with stages I-III had longer survival than those with stage IV.

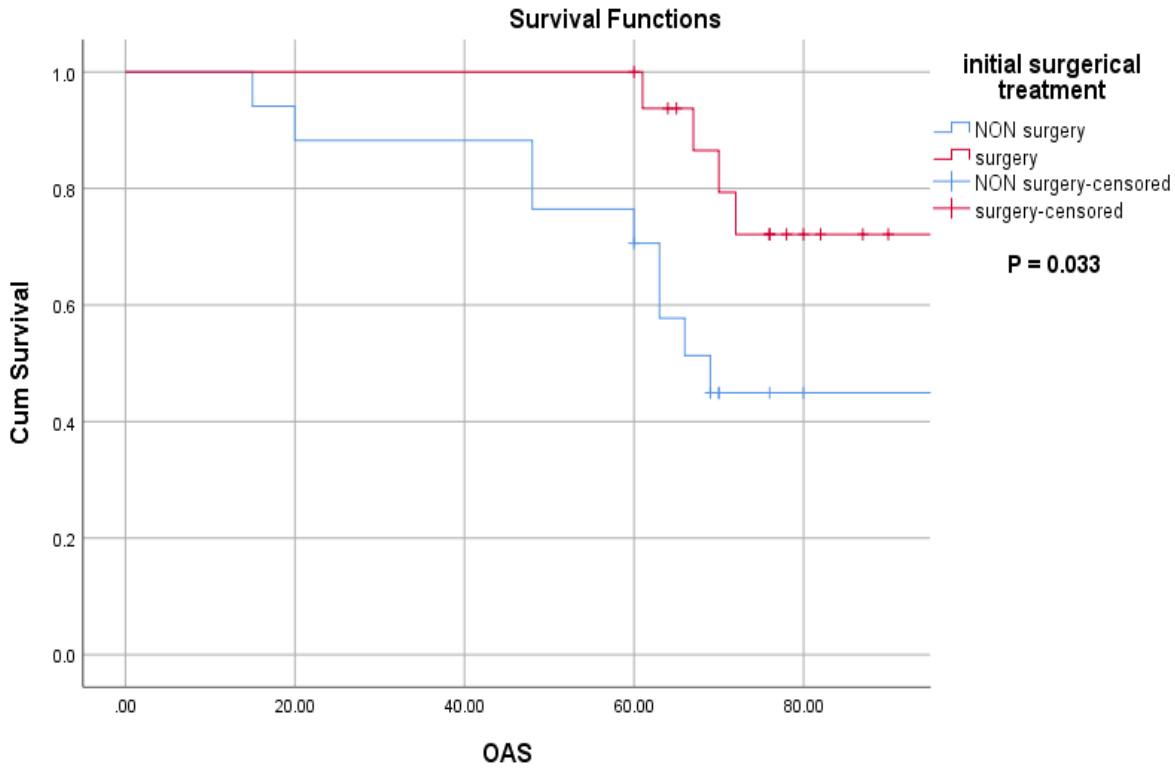

Figure (7): The impact of surgery on OAS.
Surgery had a statistical significance on OAS with p value 0.033, so that patients who were treated by surgery had longer survival in comparison to those who weren't treated by surgery.

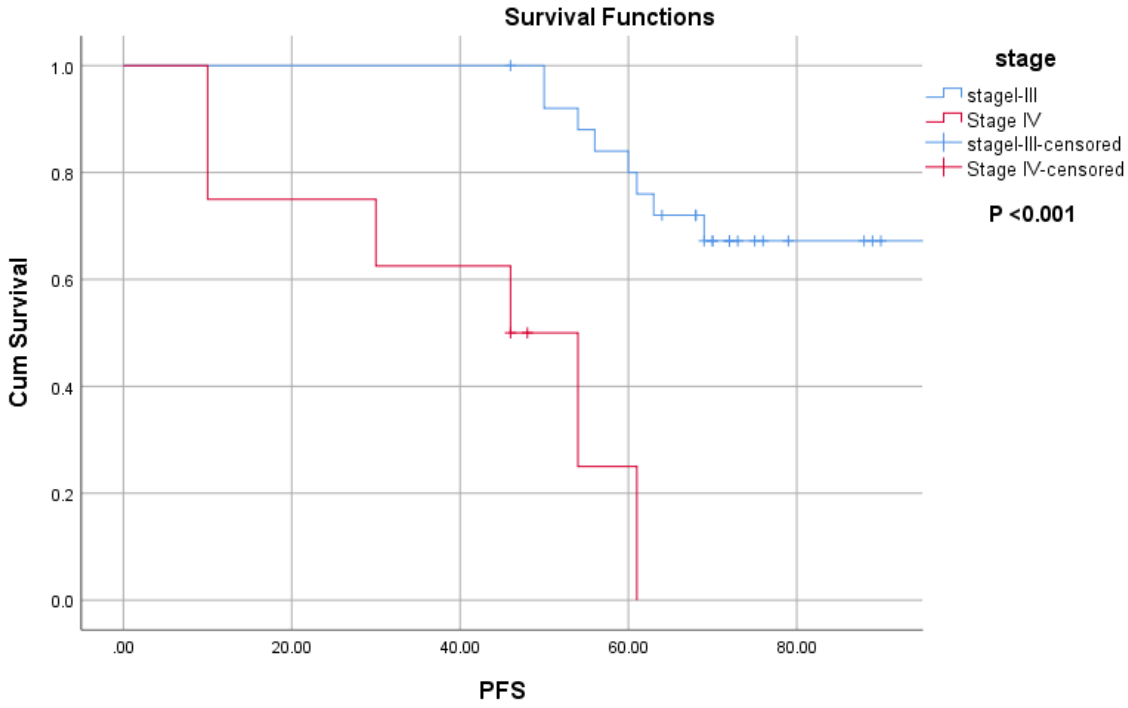

Figure (8): The impact of disease stage on PFS.
It demonstrates the significant correlation between disease stage and PFS as patients with stage IV had recurrence rate higher than those of early stages.

DISCUSSION

Our study involved 34 patients with epithelial thymic tumors. Most of them (N: 26) had thymoma while only 8 patients had thymic carcinoma. The median age was 46.5 years which correlated with results of **Valavanis *et al.*** [15], who reported that thymoma affects all age groups most commonly middle-aged adults (40-50 years) but it was lower than age reported by **Conforti *et al.*** [16], who reported age peak was in the seventh decade which may can be explained with different races and availability of health care services.

Most of our cases were males (N: 23, 67.6%) that went parallel with results of **Bluthgen *et al.*** [17]. In his study female to male's ratio was (1:1.2) and also slightly higher than **Lee *et al.*** [4] who reported male was 55.4% of patients.

The low risk of thymoma in consider to WHO classification includes A, AB, and B1 subtypes which represent 26.4 % of our study cases (N: 9), that correlated with **Lee *et al.*** [4] who reported 25.3 % of his cases was low risk thymoma. While High-risk thymoma (B2, B3) represented 50 % (N: 17) of our patients vs 53 % (N: 321) in the study of **Nakajima *et al.*** [18]. Thymic carcinoma represented 23.5 % of our cases which was a little bit higher than the results reported by **Alothaimeen and Memon** [3] who reported that thymic carcinoma represents 19.46% of his cases.

According to Masoaka staging system, our cases were distributed as follows: stage I (20.6 %), stage II (20.6%), stage III (35.3%), and stage IV (23.5%) that coped with the results of **Altshuler *et al.*** [19] who reported stage II 22.5% (N:9) and stage IV 23.4% (N: 11).

Patients with thymomas, especially type B1 and B2, were noticed to develop autoimmune disorders and myasthenia gravis (MG) was the most common, as it represented 30% of cases, while systemic lupus erythematosus (2%-5%) and red cell aplasia (1%) explained by an immune activation against antigens similar or in common between cancer and a self-tissue **Agrafiotis *et al.*** [20] and **Conforti *et al.*** [16]. In our study myasthenia gravis was presented in 10 patients (38.4%). Our study confirmed the theory that correlated thymoma and autoimmune disease, especially myasthenia gravis.

Twenty-three patients (67.65%) of our study were treated with surgery ± adjuvant treatment either radiotherapy, chemotherapy, or both.

While in **Lococo *et al.*** [21] 203 patients registered in a database from the European Society of Thoracic Surgeons (ESTS). All had undergone surgery to remove the tumor, alone or in combination with chemotherapy and/or radiotherapy. Their mean follow-up was 60 months (around five years). Before surgery, 22 patients (10.8%) underwent induction therapy to shrink the tumor before it was removed.

The 5-year OAS in our study was 88.2 % near to the results obtained by **Li *et al.*** [22] **and Dai *et al.*** [23] both results were slightly lower than ours (5-year OAS was 84% and 86% respectively.

Our 5-year PFS was 70.6%, which was adherent to results of **Alothaimeen and Memon** [3]. In Alothaimeen's study the OAS ranged between 80-100% according to stages and PFS ranged between 55- 87.5% accord disease stage.

In our study 12 patients (35.3%) had recurrence. As in **Ahmad *et al.*** [24] the 5-years cumulative recurrence incidence was 35% (95% CI, 30%-40%)

Age, ECOG, Masoaka staging system, and surgery were the statistically significant OAS prognostic factors.

Both of our study and **Agrafiotis *et al.*** [20] confirmed that gender has no impact on OAS. **Knetki-Wroblewska *et al.*** [25] results agreed with our results as regard performance status of patient impact on OAS ($P < 0.0001$).

Masaoka Stage was the only statistically significant prognostic factor as regard PFS ($p < 0.001$) that go parallel with results of **Lee *et al.*** [4] ($p = 0.001$).

In our study, Masaoka stages had significance for OAS ($P < .0001$). The 5-year OAS of stage I/ III was 70.6%, and stage IV was 17.6. Which agree with **Ahmad *et al.*** [24] where Masaoka stage had ($P < .0001$) with OAS, that was significantly associated. The 5-year OAS by stage was 80% for stage I/II, 63% for stage III, 42% for stage IVa, and 30% for stage IVb.

A systematic review and meta-analysis of 60 studies reported where the age was in a significant relation with OAS in 9 out of 14 studies, while unfavorable relation to in the age 5 studies (HR, 1.04; 95% CI, 1.02–1.04; $P < .001$). As regard Masaoka Stage, a total 11 studies demonstrated the lower OAS of stage III tumors than stage I tumors (HR, 3.38; 95% CI, 2.69–4.26; $P < .001$). The stage IV disease showed lower OAS than stage I disease (HR, 8.02; 95% CI, 6.12–10.50; $P < .001$) in 9 studies. The OAS of stage III/IV were lower than that of stage I/II disease (HR, 2.74; 95% CI, 2.12–3.55; $P < .001$) as resulted in 4 studies. The initial treatment with induction therapy was an independent prognostic factor for OAS[22], which is in accordance with our study.

The surgery had a statistical significance on OAS had p value <0.01 **Altshuler *et al.*** [19] vs 0.033 in our study. resectability and ability to get R0 with no residual either microscopic or gross residual is a significant survival prognostic factor in Agrafiotis2022 [20]. While in our study it had no impact and that may be explained by small sample and small number of patients with R1 and R2.

In current study myasthenia gravis had no statistical significance on OAS ($p = 0.32$) vs ($p = 0.082$) in the results of **Altshuler *et al.*** [19] and ($p= 0.062$) in the results of **Nakajima *et al.*** [18]. While other studies showed the significance correlation between myasthenia gravis and OAS $p <0.05$ [22, 26].

CONCLUSION

For patients with TETs, surgery is statistically significant for Overall survival (OAS) prognostic factors and the Masoaka staging system is the only statistically significant factor of the progression-free survival (PFS) prognostic factors.

STUDY LIMITATION

The limitation of our study was the small number of cases. Further studies with larger numbers are needed to confirm the data of our results.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

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