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ORIGINAL ARTICLE

Epidemiology of thymic epithelial tumors: 22-years experience from a single-institution

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Abstract

Background: To assess the correlation of WHO histological classification and Masaoka–Koga staging system of thymic epithelial tumors (TETs) with prognosis.

Methods: We retrospectively analyzed 83 patients with TETs in the Instituto Nacional de Enfermedades Neoplasicas between 1996 to 2018. We analyzed the clinical stages, histological types and treatment modalities and attempted to determine the impact on overall survival. The data was retrieved from clinical files and reviewed by a pathologist who reclassificated according to the 2004 WHO classification system. The staging was performed with the Masaoka–Koga staging system. Survival curves were constructed with Kaplan-Meir method.

Results: There was a total of 83 patients with a median age of 55 years old included in the study. The histological type corresponded to thymoma (T) in 63.8% (n = 53) and to thymic carcinoma (TC) in 36.1%. T were type A, AB, B1, B2 and B3 in 14.4%, 18%, 12%, 3.6%, 7.4% of cases, respectively. The proportion of advanced disease (Masaoka stage III–IV) was high (65%). With a median follow-up of 88.4 months, median overall survival (OS) was 81.6 months for T and 12.3 months for TC (P = 0.01). Univariate analysis showed that sex, histological type, clinical stage and surgery (P = 0.01) were significant independent prognostic factors. On multivariate analysis, histology type and Masaoka–Koga staging had an effect on survival.

Conclusions: The results indicates a clear association between the WHO histological classification and Masaoka–Koga staging system with survival. We found a higher proportion of TETs with advanced disease at diagnosis. Further research are required and collaboration is important to foster knowledge focused on classification and treatment.

Key points

Significant findings of the study: The WHO histological classification, the Masaoka–Koga system and surgery treatment were associated with overall survival.

What this study adds: To determine prognosis factors in TETs.

Introduction

Thymic epithelial tumors (TETs) compose a heterogeneous group of rare neoplasms with an incidence of less than 1%; however, they represent the most common entity of the anterior-superior mediastinum.[1]TETs are divided into thymomas (T) and thymic carcinomas (TC).

The first staging for TETs was introduced in 1978 by Bergh *et al.*[2] and the main feature was the extent of surgical resection but it was not enough to explain the clinical staging before the management. This is the reason why Masaoka[3] in 1981 proposed a staging system, that was subsequently modified by Koga *et al.*[4] based on the extent of disease, focusing on the thymus capsule infiltration and micro-macroscopic invasion into neighboring organs.

In 1999,[5] the World Health Organization (WHO) published a classification system according to the morphology of epithelial cells and lymphocyte-to-epithelial cell ratio; it was updated in 2004[6] with descriptions of clinical symptoms, immunohistological and genetic features.

These two variables, staging (Masaoka–Koga system) and histology (WHO classification)[3,4,7] are the most important factors influencing outcomes. This study describes the epidemiology and survival of TETs and evaluates the prognostic impact of staging, histology and other clinicopathological characteristics.

Methods

We retrospectively reviewed data of patients with histological diagnosis of T or TC, treated at the Instituto Nacional de Enfermedades Neoplasicas (INEN) in Lima, Peru, from 1996 to 2018.

Clinical and pathological characteristics were retrospectively collected from clinical files, and included age, sex, smoking history, stage at diagnosis, histological classification, treatment, and outcomes. All pathology specimens were reviewed by an expert pathologist and reclassified according to the 2004 WHO classification system.[2] Staging was performed with the Masaoka–Koga staging system.[4] Treatment was divided into four groups: (i) Only surgery; (ii) only concurrent chemoradiation; (iii) systemic chemotherapy for advanced disease; and (iv) no treatment.

Descriptive statistics analyses are reported through distribution tables. Overall survival (OS) was defined as the time from diagnosis to the date of death. Survival curves were constructed with the Kaplan-Meier method and compared with long-rank test. A level of $P < 0.05$ was considered statistically significant. The importance of prognostic factors for survival was identified by multivariable Cox regression analysis. The statistical package SPSS v19 (IBM SPSS Statistics for Windows, Version 19.0. Armonk,NY: IBM Corp) was used for the data analysis. This study was approved by the institutional IRB.

Table 1 Clinical and pathological characteristics of TET patients

	Studied population N (%)
Sex	
Male	43 (48.1%)
Female	40 (52.8%)
Median age	54 (19–83)
Status performance	
0	3 (3.6%)
1	55 (66.2%)
2	21 (25.3%)
3	4 (4.9%)
Smoker	
Yes	19 (22.8%)
No	33 (39.7%)
Not registered	31 (37.3%)
Histological types	
Thymoma	53 (63.8%)
Thymic carcinoma	30 (36.1%)
Clinical stage	
I	25 (30.1%)
II	2 (2.4%)
III	12 (14.4%)
IV	42 (50.6%)
Not registered	2 (2.4%)

Results

Clinical data

Over a 22-year period, 105 patients were diagnosed with TETs. A total of 22 cases without an adequate tissue specimen for pathological review were excluded. There were 83 cases finally included in the study. The general characteristics are shown in Table 1. Of the 83 cases, 48.1% ($n = 40$) were male and 51.8% ($n = 43$) were female. Median age at time of diagnosis was 55 years old (range: 19– 84). Most patients (70%) had good status performance (Zubrod 0–1) and 36.5% were smokers. Myasthenia gravis was present in four patients.

Histological classification and staging

The histological type corresponded to T in 63.9% of cases ($n = 53$) and TC in 36.1% of cases ($n = 30$). Among T, WHO types A, AB, B1 tumors were the most common and represented 44.4% of cases (Table 2).

For T, the distribution by stage was as follows: stage I, 44.4% ($n = 20$); stage II, 4.4% ($n = 2$); stage III, 17.7% ($n = 8$) and stage IV, 33.3% ($n = 15$). For TC: stage I, 10.3% ($n = 3$); stage III, 10.3% ($n = 3$) and stage IV, 79.3%

Table 2 Masaoka stage versus World Health Organization (WHO) histology

Masaoka stage	A	AB	B1	B2	B3	TC	Unknown	Total
I	5	8	4	2	1	3	2	25
II	0	1	1	0	0	0	0	2
III	2	5	0	0	1	3	1	12
IV	5	1	5	1	3	23	4	42
NR	0	0	0	0	1	1	0	2
Total	12 (14.4%)	15 (18%)	10 (12%)	3 (3.6%)	6 (7.4%)	30 (36.1%)	7 (8.4%)	83

Table 3 Treatment data by Masaoka stage

	I	II	III	IV	Total
Surgery	16	2	5	2	25 (30%)
Chemotherapy	1	0	2	27	30 (36%)
RT/QT concurrence	0	0	0	1	1 (1%)
No treatment	8	0	5	14	27 (32%)
Total	25 (30.12%)	2 (2.4%)	12 (14.46%)	44 (53%)	83 (100%)

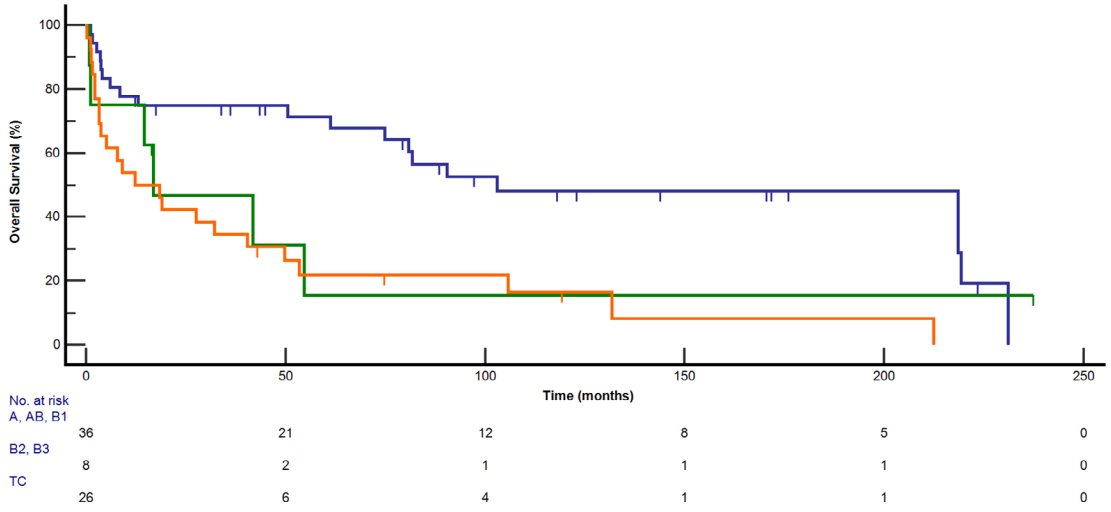

Figure 1 OS according to histological types (——) A, AB, B1 (——) B2, B3 (——) TC.

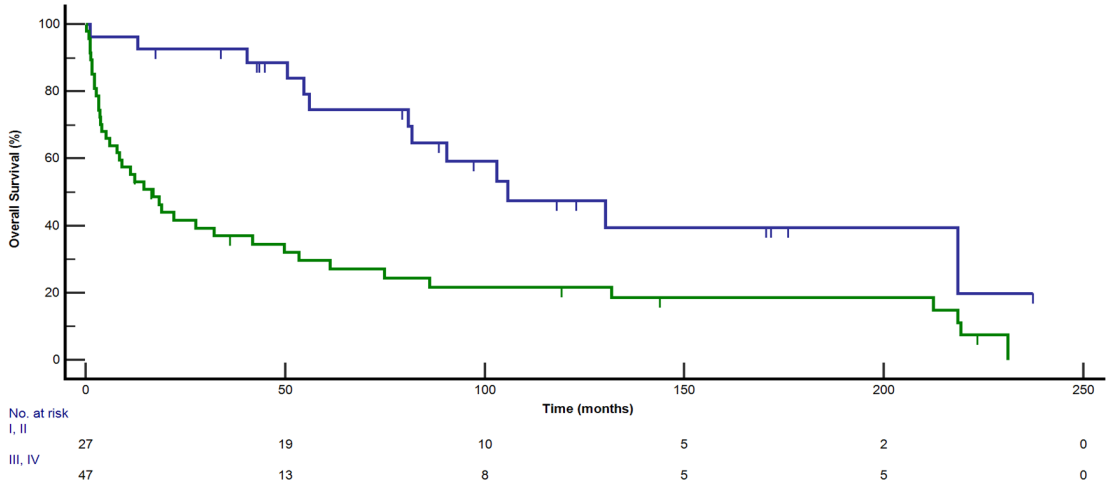

Figure 2 OS according to Masaoka-Koga staging system (——) i, ii (——) iii, iv.

Table 4 Univariate analysis to identify factors associated with overall survival (OS)

	Number	Median OS (months)	(95% confidence interval)	*P*-value
Sex				0.037
Male	35	22.03	(0.00–52.29)	
Female	40	86.1	(47.92–124.27)	
Age				0.792
<55	35	41.76	(0.23–83.30)	
≥ 55	40	56.03	(23.46–88.60)	
Histological type				0.002
A,AB,B1	36	102.967	11.74–194.19	
B2,B3	8	16.767	0–48.62	
TC	26	12.300	0–79.30	
Clinical stage				0.001
I, II	27	105.667	60.83–150.50	
III, IV	47	16.767	6.80–26.72	
Surgery				0.003
Yes	24	90.433	52.29–128.57	
No	51	16.767	8.03–25.50	

Table 5 Multivariate analysis associated with overall survival (OS)

	Hazard ratio (95% confidence interval)	*P*-value
Age		
>55 years (vs. > 55 years)	0.63(0.28–1.4)	0.25
Gender		
Male (vs. female)	0.60(0.27–1.36)	0.22
Histological type		
B2, B3 (vs. A, AB, B1)	0.47 (0.24–0.91)	0.049
B2, B3 (vs. CT)	0.93 (0.35–2,45)	0.897
Clinical stage		
III, IV (vs. I, II)	2,48(1.1–5.6)	0.03

(n = 23). A detailed distribution of staging according to histological types is shown in Table 2.

Treatment

Surgery was performed in 30% of patients, most of them in stage I. Chemotherapy was the most used treatment in 36% of cases, mostly to patients in stage IV, concurrent chemoradiation was delivered only once and overall 32% of patients received only BSC/no treatment (Table 3).

Survival

With a median follow-up of 88.4 months, median OS for T was 81.6 months and 12.3 months for TC (P = 0.01). OS by T histological type was 102 months for types A-B-B1 and 16.7 months for stages B2–B3 (P = 0.01). (Fig 1). The OS for Masaoka stages I–II and III–IV patients was 105 and 16 months, respectively (Fig 2).

Univariate analysis

In the univariate analysis, we found that gender (P = 0.03), WHO histological type (P = 0.0029), Masaoka stages (P = 0.001) and surgery treatment (P = 0.003) were associated with OS, while age was not (P = 0.792) (Table 4).

Multivariate analysis

A multivariate analysis was performed according to the Cox proportional hazard model. We found that patients with histology types (B2, B3) and Masaoka–Koga stages (III–IV) had a significantly worse prognosis (Table 5).

Discussion

We retrospectively analyzed the characteristics and outcomes of patients with TETs diagnosed at our institution over a 22-year period. This is, as far as we know, the largest series of cases describing this disease in the Latin American region.[8] It is well known that TETs are uncommon around the world with a reported annual incidence ranging from 1.3 to 3.2 per million.[9]

TETs typically occur in adults of 40 to 70[9] years old with a median age at diagnosis of 52 years. In our study, the median age at diagnosis was 55 years (19–85 years), 53 for T and 54 for TC. In contrast with what has been previously reported[1,6,10,11] we found a female predominance in TC.

The classification of TETs has been a subject of debate. The WHO in an effort to unify terminology, proposed a classification system,[5,6] using numbers and letters to designate tumor entities. There are five types of thymoma (A, AB, B1-3) and a more aggressive group of thymic carcinoma called type C thymomas.[12,13] The WHO classification system has prognostic impact which has been validated by many studies.[14,15]

According to the literature worldwide, T accounts for most thymic neoplasms. The reported incidence of T ranges between 85% and 95%, while TC are more rare and represent 5% to 15%.[16–18] In our study, while T were still the most frequent, we found a higher than expected frequency of TC (36.1%) and one of the highest incidences ever reported. Previously, geographical differences in incidence have been described for TC.[19] The reasons behind this finding require further research.

Critical differences exist between the biology of T and TC, and consequently between their clinical behavior.[14,20] Most studies and meta-analyses report a more indolent behavior for patients with histological types A, AB and B1 when compared with types B2, B3 or TC.[9,20–23] Okumura *et al.*[24] reviewed 273 cases of TETs and classified them

according to the WHO system. Their results suggested that types B2 and B3 exhibited a more malignant behavior in terms of survival, invasiveness, and tumor recurrence, compared with types A, AB and B1. Likewise, Strobel *et al.*[7] reported that types A, AB and B1 behaved in a benign fashion, while types B2 and B3 behaved more aggressively. The present study confirms what has been previously reported with a median OS of 102 months for types A, AB and B1, 16.7 months for types B2 and B3, and 12.3 months for TC.

The Masaoka–Koga staging system is the most widely accepted system for staging and predicting TET prognosis.[22,25,26] While T diagnosed in patients in stage I–III have been reported to have a five-year survival of 85%, stage IV T patients exhibit a five-year OS of 65%.[27,28] Survival rates for TC also depend on stage at diagnosis; stage I–II patients have been reported to have a five-year survival rate of 91% while for stage III–IV patients it is only 31%.[29] This is confirmed by our study, in which the prognosis of patients with stage I–II TETs was significantly better than for stage III and IV ($P = 0.01$).

A relationship between histological type and stage at diagnosis has been previously reported.[1,7] In general, the majority of patients with A and AB thymomas were in Masaoka stage I or II, while Masaoka stages III and IV were seen mainly in B2 and B3 thymomas,.[14,22,28,30] The fact that 50% of the TET cases of the present series were diagnosed at advanced Masaoka stages is highlighted. A possible explanation for this is that in Peru, access to imaging and a biopsy for early diagnosis is frequently difficult, especially for patients coming from the periphery.[31]

Treatment of TETs includes multimodality strategies[32] with the objective of achieving complete resection, long-term survival, and avoiding local or distant recurrence; however, there are no randomized clinical trials that provide definitive guidance for the management. Surgery is considered as the main curative-intent treatment for patients with Masaoka–Koga stages I/II and selected cases of stage III.[33] As has been previously shown, undergoing surgery is a favorable prognostic factor.[1] In our series, patients who received operative intervention, either primarily or after neoadjuvant treatment achieved a better OS of 90 months.

The role of adjuvant radiotherapy or chemoradiation after surgery is debatable. It has been found especially useful for stage II patients.[34] For unresectable, metastatic, or recurrent tumors, chemotherapy is the palliative-intent treatment. Regimens based on cisplatin are frequently administered.[33,35] Given the high rate of advanced disease in our series, this was the most common treatment strategy administered.

In the univariate analysis, we found that male gender, WHO histological type B2, B3 and CT, Masaoka stages III–IV and patients who had not undergone surgery were unfavorable prognostic factors for OS. The multivariate analysis was performed to determine if the prognostic relevance of the B2, B3 WHO histology type and Masaoka stages III–IV were independent prognostic factors. The findings in our study are consistent with those in previous studies.[7,18,20,22,23]

The present study has strengths and limitations. Its main strength is that it includes a large number of patients from a single institution. The limitations include its retrospective nature, and the long period encompassed which may influence treatment strategies and therefore impact survival. For these reasons, the results in our study should be interpreted with caution.

In conclusion, the present study provides confirmatory results on the prognostic impact of Masaoka staging and WHO histological types. Surgery is the mainstay of treatment of thymic malignancies and the favorable outcome of TETs after surgery was reaffirmed in our study. The remarkably high incidence of TC and the high proportion of T diagnosed at advanced stages make it difficult for us to compare our results to those of other series where patients with advanced disease are limited. However, the large number of advanced TET diseases and the 22-year follow-up time in our single-institution allowed us to obtain reliable data on the epidemiology, disease evolution and prognostic factors that directly influence patient survival. These findings require further research in the future and multicenter collaborative studies focused on epidemiology and treatment are essential.

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The authors assume full responsibility for analyses and interpretation of these data.

Disclosure

No authors report any conflict of interest.

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