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Research Article

Survival Analysis of Thymus Epithelial Tumors, Experience of an Oncological Center in Mexico

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Abstract

Background: Thymus epithelial neoplasms are rare tumors, with a reported incidence of 0.13:100,000 person/year. The basis of treatment is surgical and postoperative radiotherapy has shown improvement in overall survival. In case of being unresectable, the therapy of choice would be systemic. Due to the frequency of the disease, there are few studies to help us regulate our behavior. Our objective is To identify and describe the characteristics and the oncological results of this tumors. **Methods:** Retrospective, descriptive and analytical cohort study, conducted in a single center. A descriptive and exploratory analysis was done to know the behavior of the data. For survival analysis, Kaplan - Meier curves and Log Rank analysis were used. Univariate and multivariate analyses were performed. **Results:** in a period of 10 years, a sample of 18 patients was obtained. 17% were carcinomas and the rest thymomas. The median survival was 36.9 months; for thymoma 62.3 and carcinoma 27.2 (p=0.04). In relation to the clinical stages of both Masaoka and TNM, had a mean survival of 90.8 months for localized or crazy advanced stages, and 33.8 for stage IV (p = 0.022). **Conclusions:** In Mexico there is lack of information regarding these neoplasms. We found 18 cases, the characteristics of the cases have similarities in relation to other works. In the survival analysis we found higher risk to higher clinical stage, both Masaoka and TNM and histology of the WHO. We present one of the first cohorts of thymus epithelial tumors in Mexico.

Keywords: Thymus; Thymoma; Thymic Carcinoma; Masaoka;

Abbreviations: Overall Survival (OS); Clinical Stage (CS); Complete Resection (R0); Incomplete Resection With Microscopic Margins (R1); Incomplete Resection With Gross Margins (R2);

Introduction

Background

Thymus epithelial neoplasms are rare tumors, with an incidence of 0.13:100,000 people/year, of these, 10% are carcinomas, adopting the definition of orphan disease [1,2]. A tendency to increase frequency has been found in people originating from the Pacific Islands and Asia.

In Latin America there are two important reports, the first by Rioja et al, compiling 83 cases in 22 years; and the clinical data of the patients are described, finding thymomas in 63.7% and carcinoma in 36.3% [3]. In Mexico there are two reports, the first by Corona-Cruz [4], reporting 25 cases in 10 years, whose objective was to describe the techniques and surgical results of a center, and the second prepared by Cacho-Díaz [5], with the aim of describing patients with Myasthenia gravis.

Up to 30% of cases present as an incidental finding on chest imaging studies, and the rest with local symptoms. Paraneoplastic syndromes are found in 50% of cases; the most common is Myasthenia Gravis, present in 30-50% of patients with thymoma and 0.5% of patients with carcinoma [2,6]. The diagnostic approach can be performed with chest tomography; The most common findings are ovoid or spherical mediastinal mass with smooth edges and homogeneous reinforcement. Definitive histological diagnosis is challenging; An interobserver correlation of 70-80% has been reported [11]. The description and classification are made according to the one published by the WHO, modified in 2004 and 2021; [12,13] The correlation between this classification, the frequency of invasion and survival, has been studied and corroborated [14]. Staging is done according to the Masaoka and TNM systems. The first was originally published in 1991, and

reevaluated multiple times. A study in 2010 reassessed it finding lower overall survival at a higher clinical stage [15,16]. In 2014 the staging of TNM is published, which has greater discriminative capacity than the previous one [17,18].

The basis of treatment is surgical with curative intent, finding important differences in overall survival (RR 2.3) and disease-free survival according to the type of resection (R0: complete resection, R1: microscopic incomplete resection, R2: gross incomplete resection) [20,21]. In the context of incomplete resection, there is postoperative radiotherapy which has shown improvement in overall survival with HR 0.66 and progression-free survival with HR 0.54 [22].

In case of unresectable disease, the therapy of choice is systemic treatment with chemotherapy, with the intention of moving to a local therapy eventually and resecting the disease. The proposed schemes are based on platinum. Due to the frequency of the disease, there are few studies with a low level of evidence to help us regulate our behavior [23-27]. The most commonly used is CAP, which consists of: cisplatin, doxorubicin and cyclophosphamide.

Rationale and Knowledge Gap:

Thymus epithelial tumors are considered very rare diseases, with scarce data reported in Mexico [4], without guidelines. Therefore, it is important to document the cases presented in this cancer center, in order to generate an overview of thymus epithelial tumors in our country and describe their characteristics in our population.

Objective

Our main objective was to estimate overall survival of subjects with different types of thymic epithelial tumors and describe it according to clinical stage and histological classification.

Material and Methods

Our primary objectives are to estimate overall survival, defined as the time since the date of first diagnosis to last follow up or death, of subjects with different types of thymus epithelial tumors and describe survival based on clinical stage (Masaoka and TNM) and histological classification (WHO). The potential confounders are any comorbidity of the patient in case.

Other defined objectives are to characterize the demographic and clinical data of patients with epithelial thymic tumor, describe pathological features (clinical stage, histological type), describe the characteristics of treatments delivered.

Study Design

Retrospective, descriptive and analytical cohort study, conducted in a single center. The sample size is calculated to estimate a proportion of 1%, considering that it is a very rare entity. It is calculated with a 5% confidence limit with an estimated proportion of 1% of oncological diagnoses in our center estimating 16 cases.

Patients:

We included all the 18 year old or older patients with epithelial thymus tumor diagnosed by histopathology. Patients with duplicate records or with incomplete or inconclusive pathology or non-epithelial thymus tumors were excluded.

General Procedures

The records of all patients diagnosed from January 2012 to December 2022 with thymus epithelial tumors will be reviewed. Data from patients who meet the inclusion criteria were be added to the database. Which was collected from the following sources: Clinical laboratory database records, pathology records, TIMSA electronic medical record, physical record, PACS imaging platform.

The protection of the information consists of a database encrypted with a password, which is physically protected on a single computer and does not contain personal identification data of the patients.

Statistical Analysis

A descriptive and exploratory analysis will be carried out to know the behavior of the data, that is, to detect the distribution of each of the variables and verify an adequate data capture. It will be detected by means of measures of central tendency and dispersion, which variables had a normal behavior to be evaluated with parametric or non-parametric statistics as appropriate. Dichotomous variables will be analyzed by one-tailed Fischer test.

For survival analysis, curves were performed with Kaplan-Meier method, as well as analysis with Log Rank. Univariate and multivariate analyses were performed to evaluate prognostic factors associated with survival.

Ethical Aspects

The project complies with international and local regulations for human research studies, in accordance with the General Health Law and the Declaration of Helsinki. This study is considered to have less than a minimum risk, so the ethics committee is asked to waive the signing of informed consent, as it could entail a greater risk for the patient. No contact of any kind will be made with patients. It was approved by the corresponding bioethics, teaching and research committee. The probability of data breach is considered a risk. Once the database is processed, sensitive data that could lead to the identification of patients will be censored.

Results

Clinical Data

In a period of 10 years, 21 patients were identified, 3 were excluded because they were non-epithelial tumors of time (one lymphoma, two neuroendocrine), no patients with missing data were detected. The general characteristics are shown in Table 1. Of the 18 cases, 61% were men, the mean age was 66 years, 44% were diagnosed with overweight and obesity and 39% had a history of smoking (Table 1).

Characteristics	N =18	%
Gender		
Male	11	61
Female	7	39
Age		
Median (Years)	67	9.7
Autoimmune disease		
Yes	5	28
No	13	72
Myasthenia gravis		
Yes	3	17
No	15	83
Masaoka Clinical stage		
I	9	50
II	3	17
III	2	11
Iva	1	6
IVb	3	17
TNM Clinical Stage		
I	12	66
II	0	0
III	0	0
IV	6	33
OMS classification		
A	0	0
AB	5	28
B1	6	33
B2	4	22
B3	0	0
C	3	17
Surgery		
Yes	15	83
No	3	17
Surgical Results		
R0	11	73
R1	2	13
R2	2	13
Radiotherapy		
Yes	4	22
No	14	78
Radiotherapy intention		
Adjuvant	3	75
Palliative	1	25
Chemotherapy		
Yes	6	33
No	12	67
Immunotherapy		
Yes	2	11
No	16	89

Table 1: Population Characteristics.

Regarding the history of autoimmune diseases, they are observed in 33% of thymomas and 0% of carcinomas; this scenario is similar in the context of Myasthenia Gravis found in 20% of thymomas and 0% of carcinomas. (Table 2). There were 6 autoimmune diseases in 4 patients: hepatitis and colitis in one patient, Bechet syndrome, Guillain Barre syndrome, systemic lupus erythematosus and antiphospholipid antibody syndrome in another patient.

Histological Classification and Staging

The most frequent clinical stage of presentation according to Masaoka staging was I representing 50% of patients, followed by clinical stage IVb in 17% of cases; according to TNM staging, 67% presented in stage I and 33% in stage IV. At diagnosis, 67% of cases were resectable. Regarding the WHO classification, 17% were carcinomas (C), and the rest were thymomas (Table 1). Of the thymomas, 80% were clinical stage I by TNM and 60% by Masaoka, of the carcinomas 100% was clinical stage IV by TNM and 67% IVb by Masaoka (Table 2).

Treatment

Regarding treatment modalities, surgery was performed on most patients (83%), of these, 73% achieved complete resection (R0) (Table 1). 97% of thymomas and 33% of carcinomas underwent surgery (Table 2). 22% of patients received radiotherapy, of which 75% were with adjuvant intent and 25% palliative (1 patient for superior vena cava syndrome).

Of all cases, 33% had chemotherapy as a therapeutic indication; the most frequently used regimen was CAP (cisplatin + doxorubicin + cyclophosphamide) in 3 patients, in another epirrubicin + cisplatin + etoposide and finally one with single drug carboplatin. Due to intolerance to CAP in one case, treatment had to be changed to Pembrolizumab (Table 1). Of the patients with carcinoma, 100% received chemotherapy, and 20% of the cases with thymoma, of which one was B1, and one was B2, both clinical stage IV by TNM and Masaoka (Table 2).

Only 2 patients (11%) received immunotherapy, one with indication for thymic carcinoma and one as treatment for metastatic melanoma prior to thymoma resection; the latter patient had grade 4 immune-mediated toxicity, characterized by myocarditis, myositis, and Miller Fischer syndrome; After thymoma resection, an attempt was made to restart immunotherapy, with recurrence of myocarditis. The other patient, who received immunotherapy for the management of thymic carcinoma, had a partial response (Table 1).

Differences Between Thymoma and Thymic Carcinoma

	Thymoma		Carcinoma		
Characteristics	N =15	%	N =3	%	p
Gender					0.674
Male	9	60	2	67	
Female	6	40	1	33	
Autoimmune disease					NA
Yes	5	33	0	0	
No	19	67	3	100	
Masaoka Clinical stage					
I	9	60	0	0	NA
II	3	20	0	0	
III	1	7	1	33	
Iva	1	7	0	0	
IVb	1	7	2	67	
TNM Clinical Stage					NA
I	12	80	0	0	
II	0	0	0	0	
III	0	0	0	0	
IV	3	20	100	100	
Surgery					
Yes	14	93	1	33	0.999
No	1	7	2	67	
Surgical Results					NA
R0	11	79	0	0	
R1	2	14	0	0	
R2	1	7	1	100	
Radiotherapy					0.108
Yes	2	13	2	67	
No	13	87	1	33	
Radiotherapy Intention					NA

Adjuvant	2	100	1	50	
Palliative	0	0	1	50	
Chemotherapy					NA
Yes	3	20	3	100	
No	12	80	0	0	
Immunotherapy					0.314
Yes	1	7	1	33	
No	14	93	2	67	

Table 2: Differences Between Thymoma and Thymic Carcinoma.

Survival

With a median follow-up of 31.4 months, survival was 36.9 months; for thymoma 62.3 and for carcinoma 27.2 months (HR 15.5, 95% CI 1.4-165.9 p=0.04) (Figure 1). According to Masaoka's clinical stages, the median was 90.8 for clinical stage I-III, and 33.8 for IV (p=0.025) (Figure 2). According to TNM staging, the median survival for clinical stage I was 90.8 months and clinical stage IV 33.8 months (HR 15.5 95% CI 1.46-165.9 p=0.022) (Figure 3).

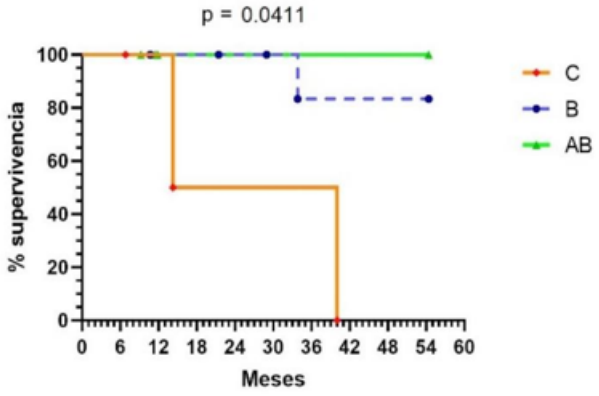

Figure 1: Overall Survival According to WHO Classification.

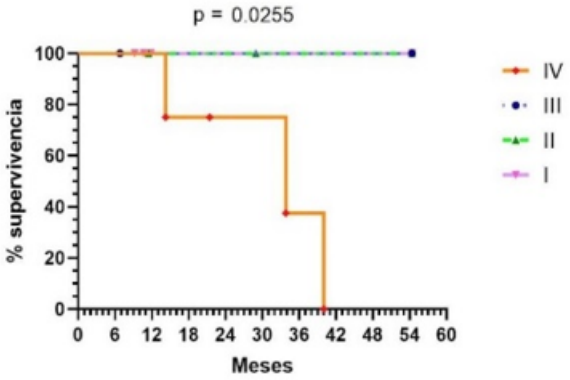

Figure 2: Overall Survival According to Staging of Masaoka.

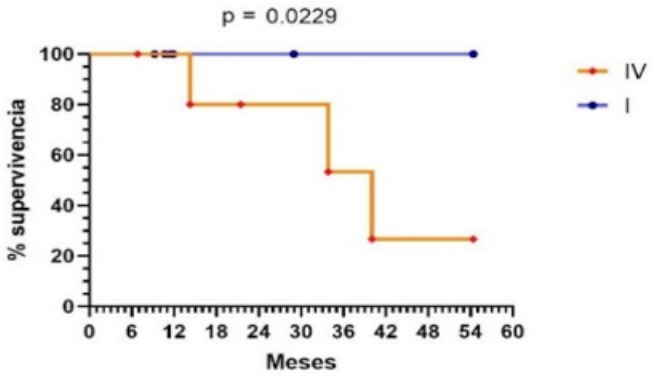

Figure 3: Overall Survival According to TNM Staging.

In the univariate analysis for survival, we did not obtain statistical significance in any area, but a tendency releate to clinical stage of Masaoka (p = 0.070), clinical stage of TNM (p = 0.070), WHO classification (p = 0.067), and application of chemotherapy (p = 0.070). No statistical significance was found in the multivariate analysis (Table 3).

Univariate and Multivariate Analysis for Overall Survival

Independent Variable	OR (IC)	p	HR	P
Age	0.59 (0.88-1.12)	0.95		
Personal History of cancer	1 (0.10-0.94)	0.039		
Autoimmune Disease	1 (NA)	NA		
Myasthenia gravis	2 (0.13-30)	0.61		
Local symptoms	1 (0.08-31.8)	0.057		
Masaoka Clinical Stage	11 (0.81-147)	0.07	4.06 (0.11-146)	0.44
TNM Clinical Stage	11 (0.81-147)	0.07	4.06 (0.11-146)	0.44
OMS Classification	4.4 (0.90-21)	0.067	1.93 (0.27-13.8)	0.66
Irresectability Criteria	11 (0.81-147.8)	0.07		
Overweight or obesity	5.4 (0.43-66.6)	0.188		
Smoking history	1.8 (0.19-16.9)	0.608		
Surgery	0.49 (0.033-7.5)	0.617		
Surgical Results	6 (0.50-70)	0.154		
Radiotherapy	6 (0.50-70)	0.154		
Radiotherapy intention	1 (NA)	NA		
Chemotherapy	11 (0.81-147)	0.07	4.06 (0.11-146)	0.443
Immunotherapy	1 (NA)	NA		
Immune mediated adverse events	1 (NA)	NA		

Table 3: Univariate and Multivariate Analysis for Overall Survival.

Discussion

We performed a retrospective analysis, emphasizing the characteristics and outcomes of thymus epithelial tumors found in a center, over a period of 10 years. We managed to collect 18 cases, of which 3 (17%) were carcinomas, in other retrospective studies, such as the one in Rioja [3] carcinoma was reported in 36% of patients, and in Buitrago-Ramirez, in 12.9% of cases [29]. In a study conducted in the United States of America, with the SEER database, 13586 cases were found, of which 66% were thymomas and 20.4% carcinomas [30]. In Mexico, it is the first study whose objective is to report the epidemiology of these neoplasms.

Regarding the WHO classification, in a series of 250 cases the following frequencies were reported: A 21.6%, AB 15.2%, B1 13.2%, B2 3.2%, B 3 9.2%; No carcinomas were reported in this study [31]. In our study we reported the following frequencies: AB 28%, B1 33%, B2 22%, C 17%; we do not report type A or type B3 cases; These diverge from what was reported in other series. But being a very rare disease, it is difficult to establish standard frequencies.

For staging, a study was conducted including 76 patients, finding according to Masaoka's staging system: 9 cases Clinical Stage (CS) I, 14 CS II, 20 III, 28 IVa and 5 IVb. According to TNM 23 CS I, 1 CS II, 17 CS III, 30 IVa and 5 IVb [17].In our study we found according to Masaoka 50% CS I, 17% CS II, 11% CS III, 6% IVa and 17% IVb. As for the TNM 67% CS I and the rest CS IV, finding and according to other studies, better discriminatory capacity of TNM staging.

In our sample, Complete surgical resection has been associated with increased overall survival as in other reported studies [20,21]. 83% of cases received surgery as the first therapeutic intention, achieving complete resection in 74% of cases; the remainder received adjuvant radiation therapy.

As for systemic treatment, due to the rarity of the disease, they are small studies, mostly non-randomized. The greatest evidence is found in platinum-based chemotherapy [23]. In our study 6 patients received chemotherapy.

Immunotherapy has been tested in 2 studies reported so far. One evaluated pembrolizumab for advanced thymic carcinoma, reporting objective response rate of 23%, stable disease 53%, and overall survival of 24.9 months [28]. Another phase 2 study evaluated the effect of immunotherapy also on thymomas, finding objective response rate of 28.6% and stable disease in 71% of cases with thymoma, but the frequency of immune-mediated adverse events was higher in the thymoma group compared to the carcinoma group (71.4% vs 15.4%) [32].

The main strength of our study is the number of cases recorded in a single center, and for the rarity of the disease; which may be useful to describe the behavior of these tumors in the Mexican population. As for limitations, the main one is the retrospective nature of the study; and that despite being a significant number of patients in relation to prevalence, it is difficult to obtain results with statistical significance, and the results of Log Rank should be taken with reservation, another point to take into consideration is the heterogeneity in terms of diagnosis and management because they are multiple operators.

In conclusion, a retrospective analysis of thymus epithelial tumors was performed in a single center, finding 18 cases. The clinical characteristics and survival are described, and prognostic factors are assessed, finding relevant the clinical stage of Masaoka, the clinical stage of TNM and the histological classification of the WHO.

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Author Contributions:

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Jose Fabian Martinez Herrera: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Supervision; Validation; Visualization; Roles/Writing - original draft and Writing - review & editing.

Raquel Gerson Cwilich: Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Resources; Supervision; Validation; Visualization; Roles/Writing - original draft; and Writing - review & editing.

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