Oncological resection, myasthenia gravis and staging as prognostic factors in thymic tumors: A Chilean case series

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Research

Keywords: thymic tumor, thymoma, myasthenia gravis, staging

Posted Date: February 24th, 2020

DOI: https://doi.org/10.21203/rs.2.24269/v1

Abstract

Background: Thymic epithelial tumors are rare and highly heterogeneous. Reports from the United States suggest an overall incidence of 0.15 per 100,000/year. In contrast, the incidence of these tumors in Latin America is largely unknown and reports are scarce, somewhat limited to case reports.

Methods: Herein, we report a series of 38 thymic tumors from a single institution, retrospectively incorporated into this study. Patient characteristics and outcomes including age, sex, stage, paraneoplastic syndromes, treatment regimens and the date of decease were obtained from medical records.

Results: Most cases in our series were females and young age (<50 years-old) and early stage by Masaoka-Koga or the Moran staging systems. Also, a 34% of patients had myasthenia gravis (MG). Next, we analyzed overall survival (OS) rates in our series and found that the quality of surgery (R0, R1 or R2), MG status, and staging (Masaoka-Koga or Moran) were prognostic factors. Finally, we compared our data to larger thymic tumor series.

Conclusions: Overall, our study confirms complete surgical resection as the standard, most effective treatment for thymic epithelial tumors. Also, the Masaoka-Koga staging system remains as a reliable prognostic factor but also the Moran staging system should be considered for thymomas.

Introduction

Thymic neoplasms are a rare and highly heterogeneous group of tumors. Reports from the United States indicate an overall incidence of 0.15 per 100,000/year (1). Histologically, thymic tumors can be classified as thymomas, thymic carcinomas or neuroendocrine thymic tumors. These tumors are frequently associated with paraneoplastic diseases, among these myasthenia gravis (MG) is by far the most commonly reported. Indeed, most studies demonstrate that MG prevalence on thymoma patients ranges from 30 to 50% (2). Although there is still no consensus on an official staging classification system for thymic malignancies (3) the system originally developed by Masaoka et al. (4) and subsequently modified by Koga et al. (5) remains as the most widely accepted. This system (hereafter called Masaoka-Koga) establishes 4 stages based on the local extent of the disease (6). More recently, Moran et al. (7) proposed a staging system based on pathological characteristics and specifically focused on thymomas and their invasiveness. Similarly, a number of histological classifications have been proposed for thymic tumors over the last decades, however the World Health Organization (WHO) histological classification system is the most accepted (8,9). Regarding treatment, the current gold standard for patients is complete resection surgery sometimes accompanied by radiation or chemotherapy (10).

As pointed above thymic tumors are rare, however their incidence in Latin America is largely undefined and the evidence is scarce and scattered, somewhat limited to case reports. Herein, we report a Chilean series of 38 thymic epithelial tumors from a single institution, most cases correspond to young patients

(< 50-year-old) and early stage thymomas. We also report survival rates and compare our results to other published thymoma series.

Materials And Methods

Patients and ethics approval

A total of 38 thymoma/thymic carcinoma patients were retrospectively incorporated into this study. Patients were diagnosed between December 1996 and April 2018. This study was approved by the Internal Review Board and Ethics committee at the Pontificia Universidad Catolica de Chile (approval #171004005 dated on November 7th 2017). A waiver of consent was granted for deceased patients. Patient characteristics and outcomes including age, sex, stage, paraneoplastic syndromes, treatment regimens including chemotherapy, surgery, and/or radiation therapy and the date of decease were obtained from medical records. Last date of follow-up was August 1st 2019. Overall Survival (OS) was defined as the time between diagnosis and death by any cause. Survival curves were estimated using the Kaplan-Meier method. Univariate associations between patient sex, age, stage, surgical resection and survival were analyzed by Log-rank test. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the R program software (version 3.5.1 R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria), applying the “survival” and “survminer” packages.

Results

Patients’ characteristics

Demographic and basic patient characteristics are summarized in Table 1. Briefly, most patients were female, younger than 50-year-old and early stage by Masaoka-Koga (50% were stage I). Similarly, most thymomas in our series were categorized as stage 0-I (84%) according to the staging system described by Moran (7). As expected, the most frequent paraneoplastic symptom was MG (34%). All patients had thymic resection surgery by sternotomy (84%), VATS (13%) or by thoracotomy (8%). Patients’ subsets also received chemotherapy or radiation therapy, 37% or 21% respectively.

Survival rates and current thymoma series versus other cohorts

Overall survival (OS) rates for the entire series are shown in Fig. 1A. As expected, tumor stage at initial diagnosis had a significant impact on OS ($p<0.0001$, Fig. 1B). Five-year OS was 89%, 100%, 80%, and 0% for Masaoka stage I, II, III, IV, respectively. On the other hand, all patients underwent surgical resection with curative intent. Negative resection margins pathologically confirmed (R0) was achieved in 33 (87%) patients. Otherwise, three (8%) and two (5%) patients had microscopic residual disease (R1) and gross residual disease (R2). Also as expected, patients with an optimal surgery (R0) had better OS versus suboptimal (R1 or R2) counterparts ($p<0.0001$, Fig. 1C). 5-year OS was 94%, 50% and 0%, for R0, R1, and R2 resection respectively. On the other hand, patients that were MG+ had better OS rates versus MG- counterparts ($p<0.05$, Fig. 1D). Then, we analyzed OS in the subset of thymomas (n=32) in our series

according to the Moran (7) staging system and found a significant impact on survival (Fig. 1E; $p<0.005$). Lastly, as shown by Table 2 we compared OS rates by Masaoka-Koga stage in our series against other previously published cohorts from Japan (4), Canada (11), the Netherlands (12) and China (13).

Discussion

Thymic tumors are infrequent neoplasms. Epidemiological studies in the US indicate an incidence of 0.15 cases per 100,000/year (1). In contrast, thymic tumor incidence in Latin America is largely unknown. Furthermore, regional studies on thymic tumors/thymomas are extremely scarce. Two retrospective single-institution studies in Mexico City have reported 64 (14) and 25 (15) patients, respectively. The first study reports a 10-year database 54.7% were males and average age (at diagnosis) was 51.4 years, also a 28% of patients were MG+. The second study reports clinical characteristics of patients recruited in the period January 2005- December 2016, although these data are unpublished, they were presented at the IASLC 18th World Conference on Lung Cancer (15). In Chile, a recent study reported survival rates and basic characteristics of 65 thymic tumor patients (16), however this report does not provide information on long-term OS rates (5 or 10-year). In general, thymoma series demonstrate a predominance of females over males, and diagnosis at an early stage. Accordingly, our study found that most patients (63%) were female and early stage (50% were stage I). As expected, OS rates in our study correlated with tumor stage by Masaoka-Koga. This is also in line with published larger thymoma series (Table 2) that demonstrate lower 5 and 10-year OS at increasing tumor stages. Over the last century a variety of staging systems have been proposed for thymic tumors (3), however the Masaoka-Koga staging system remains as the preferred choice in the literature. Within this context, a recent study by Weissferdt et al. proposes a simplified staging system for thymomas, originally described by Moran et al. (7). Authors used a large cohort (n = 1,470 cases) and demonstrate a significant correlation with clinical outcomes (17). Accordingly, in our data we found a significant correlation to OS using this staging system, however this was limited to the subset of thymomas (Fig. 1E). Also as expected, the most frequent paraneoplastic symptom was MG (34%). Interestingly, our data suggest that MG + patients had better OS versus MG- counterparts (Fig. 1D). Indeed, previous studies have described a better OS in MG + thymomas (18). However, subsequent stage-adjusted studies indicated no differences in survival between MG + and MG- thymomas (8,19,20). More recently, a large retrospective study found that MG + had a slight protective effect on OS among thymoma patients. Once again, this association could not be confirmed by a multivariate analysis. Similarly, the abovementioned retrospective study in Mexico found a trend towards better OS rates in MG + that did not reach statistical significance. Although a potential link between MG + and better OS in these patients remains controversial, authors have speculated that the correlation between MG + and early Masaoka-Koga stages could explain this association (9). Furthermore, the same study also demonstrated that a higher Masaoka-Koga stage correlated with non-MG status. Evidently, our findings warrant further investigation and should be confirmed by larger series. Finally, this study has a number of limitations: first and foremost, the number of cases is relatively small compared to other published series (Table 2), this is partially explained by the total Chilean population (17.5 million) and the

low incidence rates of these tumors. Secondly, as pointed out our data were retrospectively obtained at a single institution which may represent a registration bias that may limit the scope of our findings.

Conclusion

Overall, our study confirms complete surgical resection as the standard, most effective treatment for thymic tumors. Similarly, the Masaoka-Koga staging system remains as a reliable prognostic factor for these tumors. In the same way, the Moran staging system for thymomas demonstrates a better stratification for this subset of thymic tumors, especially at 10-years and further. Our data also reports a statistically significant difference in OS regarding MG status, with better rates of OS at 5 and 10 years for MG + patients.

Declarations

Availability of data and materials

The data used and analyzed on this study are available from the corresponding author on reasonably request.

Acknowledgments

None.

Funding

No funding was received.

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Contributions

PS and MES conceived the present study. MES and MMM collected the data. MCD, MMM and MPP analyzed and interpreted the data. MPP drafted the manuscript. PS, MES, FB, CS, CI, MG, EK, FA, SM, BN, JM, JP, JV and HG critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Ethics declaration

Ethics approval and consent to participate

Study and ethics approval were obtained by the Internal Review Board and Ethics committee at the Pontificia Universidad Catolica de Chile (approval #171004005 dated on November 7th, 2017).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

TABLE 1. Demographic, pathologic and treatment management characteristics of study population (*n*=38).

Characteristics	*n*	%	Characteristics	*n*	%
Age at diagnosis			**Surgery type**		
25-49 y	18	47	Sternotomy	32	84
50-70 y	16	42	VATS	5	13
>70 y	4	11	Thoracotomy	1	3
Sex			**Surgical margins**		
Male	14	37	R0	33	87
Female	24	63	R1	2	5
Paraneoplastic symptoms			R2	3	8
Myasthenia gravis	13	34	**Resection of regional lymph nodes**		
Pure red cell aplasia	2	5	No	14	37
Nephrotic syndrome	2	5	Yes	21	55
Agranulocytosis	1	2	NA	3	8
Stage at diagnosis (Masaoka-Koga)			**Chemotherapy**		
I	19	50	No	24	63
IIa	8	21	Yes	14	37
IIb	3	8	NA	9	24
III	5	13	**Radiation therapy**		
IVa	3	8	No	22	58
Stage at diagnosis (Moran for thymoma)			Yes	8	21
0	17	53	NA	8	21
I	10	31	**WHO histologic classification**		
IIB	1	3	A	5	13
IIB	3	9	AB	5	13
IIC	1	3	B1	6	16
Stage at diagnosis (Weissferdt-Moran for thymic carcinoma)			B2	9	24
I	3	50	B3	6	16
II	3	50	C	7	18
Thymic epithelial tumor histotype					
Thymoma	31	82			
Thymic carcinoma	6	16			
Mixed†	1	2			

VATS, video-assisted thoracic surgery; *NA*, not available.
† One case evidenced both thymoma and thymic carcinoma cells during histologic analysis.

Figures

Table 2. Comparison of overall survival rates on 5 thymoma series using the Masaoka-Koga staging system.

	Salas *et al.*			Masaoka *et al.*			Mariano *et al.*			De Jong *et al.*		Zhu *et al.*	
		OS (%)			OS (%)			OS (%)			OS (%)		OS (%)
Stage	*n*	5-yr	10-yr	*n*	5-yr	10-yr	*n*	5-yr	10-yr	*n*	5-yr	*n*	5-yr
I	19	89	82	37	96	67	16	93	93	142	83	115	96
II	11	100	75	13	86	60	76	89	87	122	88	38	89
III	5	80	20	32	70	58	47	75	62	68	57	74	59
IV	3	0	0	11	50	0	32	43	29	62	56	14	50

Abbreviations: yr: year, *OS*: Overall survival.

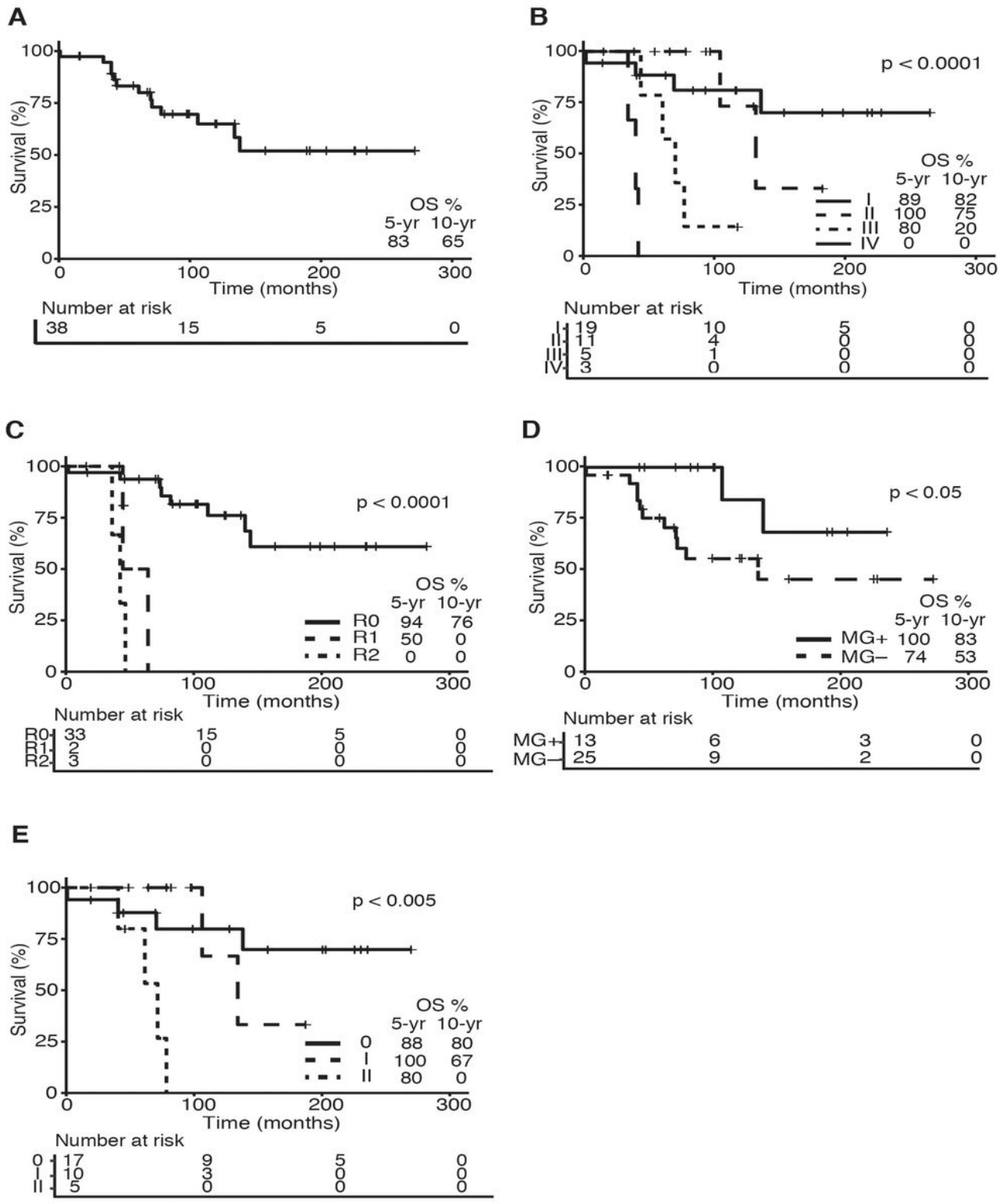

Figure 1

Survival curves in Chilean thymic tumor series. A. OS for the entire series (n=38). B. OS by Masaoka-Koga staging system at presentation. C. OS by status of surgical margins at oncological resection. D. OS by presence or absence of myasthenia gravis at diagnosis. E. OS by Moran staging at diagnosis. Abbreviations: OS overall survival, yr year; MG myasthenia gravis. PFS progression-free survival.