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The Impact of Thymoma Histotype on Prognosis in a Worldwide Database

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Introduction: The rarity of thymomas and lack of multi-institutional studies have hampered therapeutic progress for decades. To overcome this, the members of the International Thymic Malignancy Interest Group created a worldwide retrospective database. This database was analyzed regarding the demographic and geographic distribution of thymomas and the impact of different variables on survival and recurrence.

Methods: This study analyzed 4221 thymomas diagnosed between 1983 and 2012 with World Health Organization histotype information from the International Thymic Malignancy Interest Group database. Associations to survival and recurrence were studied by univariate and multivariate analyses.

Results: Type B2 thymoma is the most common (28%) and type A the least common (12%) histotypes. They are significantly more frequent in Europe and the United States than Asia. Type A and AB occur at significantly higher age than other thymomas (64 and 57 years, respectively). There are no differences in gender distribution. Stage is lower in type A (90% in stages I–II) and AB than B1 to B3 thymomas (38% of type B3 in stage III). In univariate analysis, recurrence is significantly less frequent among stage I/II tumors, in type A and AB (recurrence rates, 1–2%) than B1 to B3 thymomas (2–7%). Multivariate analysis reveals an impact of age, stage, and resection status on survival and recurrence, whereas for histology there is only a significant impact on recurrence.

Conclusion: New findings are (1) geographic differences such as a lower incidence of type A and B2 thymoma in Asia; and (2) impact of stage and histology, the latter partially limited to early stage disease, on recurrence.

Key Words: Thymoma, International Thymic Malignancy Interest Group, World Health Organization histotype, Prognosis, Epidemiology.

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Thymomas and thymic carcinomas (TCs) are epithelial tumors of the thymus. They are the most frequent tumors of the anterior mediastinum in adults but account for less than 1% of all human neoplasms. Thymomas comprise a spectrum of unique tumors of low to moderate malignant potential that are subdivided according to the histological classification of the World Health Organization (WHO) into type A, AB, B1, B3, and B3 and rare other subtypes. By contrast, TCs resemble similarly termed carcinomas outside the mediastinum and usually follow an aggressive clinical course.[1]

The prognosis of thymomas and TCs seems to be mainly dependent on tumor stage and resection status, while the relevance of WHO defined histological subtype as an independent prognostic marker among thymomas is still controversial: some studies and meta-analyses found a more favorable outcome of patients with type A, AB, and B1 compared with B2 and B3 thymoma subtypes,[2–6] whereas others did not.[7,8] These controversies are partly due to the rarity of these histologically complex tumors, and possibly, difficulties with interobserver reproducibility involving some subtypes of the WHO classification as suggested by discrepancies between relatively small published case series from different parts of the world.[9] To overcome inherent problems of previous small and mostly single-center series, and to identify true epidemiological and clinicopathological differences between thymoma patients across the globe, the International Thymic Malignancy Interest Group (ITMIG)[10] has compiled a worldwide retrospective database of thymomas and TCs from small to large volume clinical and pathology centers in Asia, in the United States, and in Europe.[11] Furthermore, ITMIG launched a worldwide, prospective, Internet-accessible clinicopathological database in 2012 (https://ccehubg.org/itmig).[12]

An overview of the ITMIG retrospective database has been published elsewhere,[11] which includes original data from 4918 thymomas. The present article focuses on the thymoma cases in this database—specifically on those diagnosed

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between 1983 and 2012 which included data on the WHO subtype and sufficient survival and recurrence data to be germane to an analysis of the impact of the WHO histotype of thymoma. An analysis of outcomes relative to WHO histotypes was beyond the scope of the retrospective database overview.[12]

This report addresses the following issues: (1) Are there demographic and clinical differences between the different histological thymoma subtypes? (2) Is the WHO histological classification consistently applied across different geographic regions, countries, and centers? (3) Which variables (WHO histotype, stage, resection status) affect survival? and (4) Does the WHO histotype have independent impact on prognosis?

MATERIALS AND METHODS

Of the 4918 thymomas in the ITMIG retrospective database,[11] 389 lacked histotype information and 308 were excluded due to diagnosis before 1983, leaving 4221 cases (Supplementary Table S1, SDC 1, http://links.lww.com/JTO/A732). An additional 328 lacked sufficient epidemiological data and 26 were excluded due to being of tumor subtypes other than A to B3 (21 micronodular thymoma, 4 metaplastic thymoma, 1 other). The overall survival (OS) analysis involved 2891 and the recurrence analysis 2408 patients after deleting cases with missing data (resection status, intervention date, follow-up date, etc.). Clinical centers were dichotomized by geographic region into low- and high-volume centers, high-volume centers being defined as the top contributors who submitted over 50% of all cases of a particular continent. This study was approved by the Yale Institutional Review Board (HIC # 1307012419).

Thymomas were classified according to WHO criteria[13] by local surgical pathologists. Tumors other than type A, B1, B2, B3, and AB thymomas were excluded. There was no central review of slides for the purpose of this study.

Both the Masaoka et al.[14] and the Masaoka-Koga[15,16] stage classification systems were used by submitting centers. Because the Thymic domain of the Staging and Prognostic Factors Committee found no difference in outcomes between these systems[14–16] or between stages I and II,[12,17] the Masaoka and Masaoka-Koga systems and stages I and II were combined in the analysis in this article.

The ITMIG statistical core (XY, YD) performed all analyses with SAS 9.3 (SAS Institute Inc., Cary, NC) and R. The primary outcome measures OS and cumulative incidence of recurrence (CIR) were analyzed using the Kaplan–Meier method and the log-rank test. Prognostic factors that were significantly associated with survival in univariate analysis ($p < 0.05$) were included in a Cox proportional hazards model for multivariate analysis. CIR was assessed using competing risk analysis, with death included as the competing event. The effect of clinical factors on recurrence was assessed using Gray's test. All p values from pairwise comparisons were adjusted by using Bonferroni method due to multiple comparison problems. Statistical significance was set at p less than 0.05 and all tests were two-tailed.

RESULTS

Patient Characteristics and Frequencies

Characteristics of the 4221 thymoma cases are summarized in Supplementary Table S1 (SDC 1, http://links.lww.com/JTO/A732). There is no gender predilection (49% male and 51% female patients). The largest number of cases came from centers in Europe; center volume ranged from 461 to 2 patients. Demographic and clinical details specifically for each WHO histotype are shown in Table 1. There is no significant gender predilection among the five WHO types. Type A and AB patients are significantly older than B1-3 patients (median, 60 versus 52, $p < 0.0001$). Myasthenia gravis (MG) is more frequent in type B1-3 thymomas (35–49%) than in type A and AB (25–26%). There is a significant association between WHO type and stage ($p < 0.0001$, Fig. 1).

There is remarkable variability in the proportion of WHO histotypes reported from individual centers: In Figure 2*A*, the centers are ordered by center volume to assess whether this is associated with center experience; no consistent trend is apparent. The results suggested a difference according to geographic regions; to assess this further, we grouped the centers according to the region (Fig. 2*B*). The frequency of type A thymoma is similar in Europe (15%) and the United States (14%), but significantly lower in Asia (6%, adjusted $p < 0.0001$). Type AB thymoma is more frequent in Asia (27%) than Europe (23%) and the United States (18%, adjusted $p = 0.0002$). Type B2 thymoma is similar in Europe (31%) and the United States (32%), but significantly lower in Asia (20%, adjusted $p < 0.0001$). Type B3 thymoma is more frequent in Asia (32%) than Europe (15%) and the United States (16%, adjusted $p < 0.0001$). The frequencies of type B1 thymoma (16–20%) are not significantly different between geographic regions.

Survival and Recurrence

The OS probability is significantly different among the different WHO types (Supplementary Figure S1A, SDC 2, http://links.lww.com/JTO/A733, R0 resected patients, $p = 0.0165$). However, there are no significant differences except that OS was significantly lower for B3 versus B1 (adjusted $p = 0.043$). CIR among R0 resected patients, all stages, is shown in Supplementary Figure S1B (SDC 2, http://links.lww.com/JTO/A733). The 5-year recurrence rate by histotype is as follows: type A 4% (95% confidence interval [CI], 1–9%); type AB 2% (CI, 1–4%); type B1 8% (CI, 5–13%); type B2 13% (CI, 9–17%); and type B3 14% (CI, 9–17%). For CIR, the differences are statistically significant with the exceptions that A and AB are almost identical, B2 and B3 are

TABLE 1. Clinical Characteristics of Each WHO Histotype

Thymoma Histotype	*N*	% of Total	% Male	Median Age (yr)	% With MG	Median Size (cm)
A	443	11	53	64	26	6.0
AB	891	23	48	57	25	6.5
B1	663	17	45	53	35	6.0
B2	1062	28	48	52	49	6.0
B3	808	21	53	52	40	6.0

MG, myasthenia gravis; WHO, World Health Organization.