Development of the International Thymic Malignancy Interest Group International Database: An Unprecedented Resource for the Study of a Rare Group of Tumors

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Background: Our knowledge of thymic malignancies has largely been derived from small, single-institution series. Recognition of the need for broad collaboration led to the creation of the International Thymic Malignancy Interest Group (ITMIG) and the development of a large, centralized database to advance knowledge of these rare tumors.

Methods: A multidisciplinary Database Committee was convened to define a common set of data elements a priori. Retrospective data were solicited from ITMIG members and collated using standardized fields. Patients with thymoma, thymic carcinoma, or thymic carcinoid were included.

Results: Over a 6-month period, 47 institutions spanning 15 countries contributed a total of 6097 cases (mean, 129 [range, 10–1209]). The sex distribution was equal for thymomas, but there was a greater proportion of men with thymic carcinoma and thymic carcinoid ($p < 0.0001$). Nearly all cases (99%) were treated surgically. WHO type B2 was the most frequent histologic classification among thymomas, whereas squamous was the most common among thymic carcinomas. In total, 38% of patients with thymoma had myasthenia gravis compared with less than or equal to 5% for thymic carcinoma and thymic carcinoid. Median overall survival was 18.9 years (95% confidence interval [CI], 17.4–20.3) for thymoma, 6.8 years (95% CI, 5.5–7.9) for thymic carcinoma, and 7.5 years (95% CI, 6.5–8.5) for thymic carcinoid.

Conclusions: The rapid creation of the ITMIG database demonstrates the feasibility of international collaboration for this rare set of malignancies and attests to the engagement of its membership. This database represents the largest collective data set ever assembled and provides an unprecedented resource for research of these tumors.

Key Words: Thymoma, Thymic carcinoma, Thymic carcinoid, Database, Thymic malignancies.

(*J Thorac Oncol*. 2014;9: 1573–1578)

Thymic malignancies are uncommon tumors whose unusual behavior and association with immunologic derangements have long captivated clinicians. Few prospective studies have been conducted, and our knowledge is largely derived from small, dated series. The seminal report by Masaoka et al.,[1] whose eponymous classification was based on only 96 patients, appeared more than three decades ago. Given the rarity of these malignancies, meaningful advancement requires international collaboration.[2]

The International Thymic Malignancy Interest Group (ITMIG) arose from the recognition of this need.[3] One of its central priorities was the collection of worldwide data and the development of a centralized database. The precedent of the International Association for the Staging of Lung Cancer staging project provided a model for collaboration,[4] and the need for more data to inform the development of a formal staging classification served as a major driver for this project.[5]

This database was also intended as a resource for the investigation of clinical issues, including histology, treatment, prognosis, autoimmune disease, and second malignancies. Existing population-based registries are limited in their utility for addressing these specific questions,[6] and this effort was aimed at enriching data collection with greater detail. This article provides an overview of the ITMIG database, its contents, and the process behind its creation.

PATIENTS AND METHODS

The ITMIG Database Committee has broad representation, including surgery, medical oncology, radiation oncology,

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†††A list of the contributors is given in Appendix 1.

Disclosure: The authors declare no conflict of interest.

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DOI: 10.1097/JTO.0000000000000269

ISSN: 1556-0864/14/0910-1573

radiology, pathology, and information technology across North America, Europe, and Asia. The committee was assigned the tasks of defining the relevant data elements and identifying a suitable provider to create the data infrastructure.

A collaboration between ITMIG and Purdue University created the data structure, using the HUBzero platform and the Purdue Cancer Center Engineering project.[7] This created an open-source, Health Insurance Portability and Accountability Act-compliant infrastructure with flexibility for future expansion as a centralized hub for scientific discourse among ITMIG members.

Existing retrospective data were collected from established institutional databases worldwide. A common set of data elements was defined in collaboration with the Japanese Association for Research of the Thymus, the European Society of Thoracic Surgeons, and the Chinese Association for Research of the Thymus (Supplemental Appendix 1, Supplemental Digital Content, http://links.lww.com/JTO/A637). The database includes patients diagnosed with thymoma, thymic carcinoma, or thymic carcinoid. To achieve consistency, the data elements build on the standard definitions developed by ITMIG,[8] the Masaoka or Masaoka-Koga stage classification systems,[1,9] the World Health Organization histologic classification,[10] and the Myasthenia Gravis Foundation of America classification of myasthenia gravis severity.[11]

Patient characteristics were compared using two-tailed *t* tests for continuous variables and χ^2 and Fisher's exact tests for categorical variables. Survival was measured from the first date of treatment to the date of death or last follow-up, and curves were generated using the Kaplan-Meier method.

RESULTS

From September 2012 to February 2013, a total of 6097 cases were submitted from 47 institutions across 15 countries spanning North America, South America, Europe, and Asia. The tasks of cleaning, standardization, clarification of missing or nonsensical entries, and aggregation of data were completed by August 2013. The contributing centers are listed in Table 1 and Figure 1. Institutions contributed a mean of 129 cases (range, 10–1209). Basic demographic characteristics are listed in Table 2. Most of the cases were diagnosed between 2000 and 2010. The mean age was similar among patients with thymoma, thymic carcinoma, and thymic carcinoid; however, whereas sex distribution was equal among patients with thymoma, there was a greater proportion of men among those with thymic carcinoma ($p < 0.0001$) and thymic carcinoid ($p < 0.0001$).

Histologic Classification

The histologic distribution is listed in Table 3; B2 was the most common histologic classification reported. Among patients with thymic carcinoma, squamous was the most common histologic classification reported. The distribution of Masaoka stage is listed in Table 4. In some cases, Masaoka (or Masaoka-Koga) stage was provided without further subdivision into A or B subcategories (stages II and IV). A majority had early-stage tumors (Masaoka I or II), but a substantial number of stage III ($n = 1167$) and IV ($n = 673$) cases were also captured.

TABLE 1. Contributing Institutions by Country

Country	Institution(s)
Argentina	Alexander Fleming Institute, Maria Ferrer Institute
Belgium	Antwerp University, University Hospitals Leuven
China	Beijing Cancer Hospital, Henan Cancer Hospital, Shanghai Chest Hospital, Shanghai Pulmonary Disease Hospital, Sichuan Cancer Hospital, Tianjin Cancer Hospital
Denmark	Rigshospitalet University Hospital
France	Louis Pradel Hospital
Germany	Klinik Schillerhoehe, Mannheim University
Greece	AHEPA University
Italy	Hospital Riuniti, Ancona; Regina Elena National Cancer Institute, Rome; S. Croce e Carle Hospital, Cuneo; University of Catania; University of Napoli Federico II; University of Padua; University of Pisa; University of Torino
Korea	Gangnam Severance Hospital, Seoul National Hospital, Severance Hospital
Netherlands	Maastricht University
Romania	Fundeni Clinical Institute Bucharest
Spain	Hospital Mutua de Terrassa
Turkey	Istanbul Medical University
United Kingdom	Birmingham Heartlands Hospital, Guy's and St. Thomas Hospital, Royal Brompton & Harefield
United States	Fox Chase, Hackensack University Medical Center, Indiana University, Massachusetts General Hospital, Mayo Clinic, MD Anderson Cancer Center, Memorial Sloan Kettering, Oregon Health and Science University, Penn Presbyterian Medical Center, Stanford University, Swedish Medical Center, University of Chicago, Yale University

Autoimmune Disease

Autoimmune disease was reported in one-third of all patients with thymic malignancies and was primarily limited to patients with thymoma (Table 5). In total, nearly 38% of patients with thymoma had myasthenia gravis. Other paraneoplastic syndromes, such as hypogammaglobulinemia and red cell aplasia, were exceedingly rare, with each representing less than 1% of thymoma cases. Autoimmune disease was also rare among patients with thymic carcinoma and thymic carcinoid, with nearly all involving myasthenia gravis ($n = 36$).

Treatment

The vast majority of submitted cases were treated at initial diagnosis with surgery as primary therapy (Fig. 2). Adjuvant radiotherapy was administered to 1664 patients (42%), and a minority of patients received neoadjuvant therapy, either chemotherapy (11%) or radiotherapy (2%). Less than 1% of cases received palliative chemotherapy ($n = 27$) or radiotherapy ($n = 7$) only.

Outcomes

Vital status was available for 4821 cases (79%), with 904 deaths (19%). Recurrence status was available for 4101 cases (67%), 715 of whom experienced relapse (17%). Information on cause of death was available for 526 cases: 325 (62%) died