Outcome of primary neuroendocrine tumors of the thymus: A joint analysis of the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases

Pier Luigi Filosso, MD,[a] Xiaopan Yao, PhD,[b] Usman Ahmad, MD,[c] Yilei Zhan, MS,[b] James Huang, MD,[c] Enrico Ruffini, MD,[a] William Travis, MD,[d] Marco Lucchi, MD,[e] Andreas Rimner, MD,[f] Alberto Antonicelli, MD,[g] Francesco Guerrera, MD,[a] and Frank Detterbeck, MD,[g] and the European Society of Thoracic Surgeons Thymic Group Steering Committee

Objective: Primary neuroendocrine tumors of the thymus (TNET) are exceedingly rare. We studied a large series of TNET identified through the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases.

Methods: This was a retrospective multicenter study of patients undergoing operation for TNET between 1984 and 2012. Outcome measures were: overall survival (OS) and cumulative incidence of recurrences (CIR). OS was analyzed using the Kaplan-Meier method and CIR was analyzed using competing risk analysis. Associations with clinical and prognostic factors for OS and CIR were evaluated using the log rank test and Gray test.

Results: Two hundred five patients with TNET were treated: 25 patients received induction therapy (19 chemotherapy [CT] and 6 radiotherapy [RT]). Data about resection status were available in 47% of cases: complete resection was performed in 52 patients (54%). Masaoka-Koga stages I, II, III, and IV were observed in 12, 33, 56, and 47 patients, respectively. Atypical carcinoid was the commonest histologic subtype (71 cases; 40%). One hundred one patients with TNET received adjuvant treatment; 52 patients died and 36 experienced a recurrence. The median OS was 7.5 years; 5-year OS was 68%, and 5-year CIR was 39%. OS was significantly influenced by Masaoka-Koga stage ($P = .02$) and completeness of resection ($P = .03$). CIR significantly increased in high Masaoka-Koga stages ($P = .04$). Histologic subtype was not associated with either OS or CIR.

Conclusions: Our results confirm the high biologic aggressiveness of these rare neoplasms; pathologic stage and completeness of resection were demonstrated to be strong prognostic factors, whereas histology did not influence patients outcome. (J Thorac Cardiovasc Surg 2015;149:103-9)

See related commentary on pages 110-1.

Supplemental material is available online.

From the Department of Thoracic Surgery,[a] University of Torino, Torino, Italy; Section of Medical Oncology,[b] Department of Internal Medicine and Department of Thoracic Surgery,[g] Yale University School of Medicine, New Haven, Conn; Thoracic Surgery,[c] Memorial Sloan Kettering Cancer Center, New York, NY; Department of Pathology,[d] Memorial Sloan Kettering Cancer Center, New York, NY; Division of Thoracic Surgery,[e] Cardiac and Thoracic Department, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; and Department of Radiation Oncology,[f] Memorial Sloan Kettering Cancer Center, New York, NY.

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Address for reprints: Pier Luigi Filosso, MD, Department of Thoracic Surgery, University of Torino, San Giovanni Battista Hospital, Via Genova, 3 10126 Torino, Italy (E-mail: pierluigi.filosso@unito.it).

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Primary neuroendocrine tumors of the thymus (TNET) were described for the first time by Rosai and Higa[1] in 1972. Since then, the number of cases reported in the literature is approximately 400. Moreover, the majority of these articles are case reports, and only a small number of articles contain modest single-center clinical series, and are therefore unable to provide uniform assessment and validated prognostic factors for these neoplasms.

TNET are exceedingly rare tumors, accounting for approximately 0.4% of all carcinoid tumors[2] and <5% of all anterior mediastinal neoplasms[3]; an age-adjusted incidence rate of 0.18 per 1,000,000 US population[4] has been observed. A male predominance, with a peak incidence in the fifth decade, has also been reported.[4,5]

According to the 2004 World Health Organization classification of tumors,[6] TNET are included in the thymic carcinoma group, and are classified into 4 entities in 2 major histopathologic types: well-differentiated neuroendocrine carcinomas (also called typical carcinoid and atypical carcinoid) and poorly differentiated neuroendocrine carcinomas (small-cell carcinoma and large-cell neuroendocrine carcinoma).

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Abbreviations and Acronyms

CIR = cumulative incidence of recurrences
ESTS = European Society of Thoracic Surgeons
ITMIG = International Thymic Malignancy Interest Group
OS = overall survival
R0 = complete tumor resection
R1 = microscopically residual disease
R2 = macroscopically residual disease

Almost 50% of these tumors can be complicated by endocrine disease, either due to ectopic adrenocorticotropic hormone secretion (Cushing syndrome) or because of its association with other endocrine tumors, such as in multiple endocrine neoplasia type 1 syndrome.

The prognosis of patients with TNET is poor because of the high incidence of local recurrences and distant metastases, even after a radical tumor resection: the reported overall 5-year survival rate may vary from 30% to 70%.[7-9]

Due to the fact that TNET are rare neoplasms that remain unfamiliar to the majority of practicing thoracic physicians and surgeons, the reported studies were unable to validate factors influencing long-term outcome, and there has been very limited improvement in management of these tumors, we used and analyzed the International Thymic Malignancy Interest Group (ITMIG) and the European Society of Thoracic Surgeons (ESTS) retrospective databases on thymic malignancies with the aim to evaluate factors influencing TNET patient outcomes. This article represents the first joint analysis of ITMIG and ESTS retrospective database for TNET cases.

MATERIAL AND METHODS

ESTS and ITMIG Retrospective Databases

The ESTS database project was launched in 2011 among ESTS members (Appendix E1), collecting data of surgically treated primary thymic tumors from 1990 to 2011. The ITMIG database, with similar purpose, started in 2012 with 67 participating institutions (Appendix E2).

A central data handling team and database committee overlooked the process for each dataset; details of 2 patient populations were recently described elsewhere.[10] Both datasets have similar data fields and variables, including gender, previous malignancy, TNET histology, lymph node involvement, distant metastases, clinical and pathologic Masaoka or Masaoka-Koga staging system, resection status, chemotherapy and/or radiotherapy treatment, and recurrence. Moreover, duplicate cases from ESTS centers that were already participating in ITMIG dataset have been removed for analyses.

For the purpose of our study, all TNET patients treated between 1984 and 2012 were considered, and 205 cases were identified.

Approval for this study was granted by the Yale University Institutional Review Board (No. 1307012419).

Management of Clinical Variables and Standard Outcome Measures

A dedicated staging system for TNET does not exist,[11] and different institutions worldwide used either Masaoka or Masaoka-Koga systems. In fact, these 2 classifications only differ in how stages I and II are defined.

Furthermore, as recently observed,[12] there is no difference in outcomes between stage I and II. Hence, for the purpose of our study, cases with stages I and II (II, IIa, and IIb) were joined and analyzed together, and cases staged using the Masaoka and Masaoka-Koga staging systems were combined together.

According to ITMIG standards,[13] surgery was considered radical when a complete tumor resection (R0) with negative gross and microscopic margins was accomplished, and as incomplete when there was microscopically residual disease (R1) or macroscopically residual disease (R2). Debulking surgery was also considered an R2 resection. Time intervals were calculated.

Overall survival (OS). Time interval between the date of surgery or last day of medical treatment (chemotherapy) and the date of death or the date of the last follow-up.

Cumulative incidence of recurrence (CIR). Time interval between the date of R0 surgery and the date when recurrence was diagnosed or the date of the last follow-up without recurrence.

Statistical Analysis

A core statistical team of ITMIG performed all analyses with SAS version 9.3 (SAS Institute, Inc, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria). For patient characteristics, continuous data are presented as median (range) and categorical data as frequency with percentage.

OS and CIR were the primary outcomes. OS was analyzed using the Kaplan-Meier method. The association of overall survival with clinical and prognostic factors was tested using the log-rank test. Prognostic factors that were significantly associated with survival in univariate analysis ($P < .05$) 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 freedom from recurrence was assessed using Gray test.

RESULTS

Patient Characteristics

A total of 205 TNET cases were collected for analysis after joining ITMIG and ESTS databases. A male predominance (155 patients; 77%) was observed. Median age of patients was 54 years (range, 19-82 years). No geographic predominance was observed in patient distribution.

Previous malignancies were seen in 17 cases (8.3%), the most common of which were prostate (n = 5) and skin cancer (n = 2). No data concerning endocrine related disorders was available in either database.

Typical carcinoid histology was regarded as low grade (n = 49 out of 178 patients; 28%), atypical carcinoid histology as intermediate grade (n = 71 out of 178 patients; 40%) followed by poorly differentiated carcinoma (large-cell neuroendocrine carcinoma or small cell lung carcinoma) in 49 patients (28%). A generic diagnosis of carcinoid not otherwise specified was provided in 9 cases (4%). No data concerning tumor histology occurred in 13% of cases (27 out of 205 patients).

The median tumor size was 8 cm (range, 2.1-30 cm); the majority of TNET cases presented at an advanced stages (stage III-IV n = 103; 69%). Other patient clinical characteristics are summarized in Table 1.