Thymic Carcinoma: A Cohort Study of Patients from the European Society of Thoracic Surgeons Database

Enrico Ruffini, MD, Frank Detterbeck, MD,† Dirk Van Raemdonck, MD,‡ Gaetano Rocco, MD,§ Pascal Thomas, MD,‖ Walter Weder, MD,¶ Alessandro Brunelli, MD,# Francesco Guerrera, MD,* Shaf Keshavjee, MD,** Nasser Altorki, MD,†† Jan Schützner, MD,‡‡ Alex Arame, MD,§§ Lorenzo Spaggiari, MD,‖‖ Eric Lim,, MD,¶¶ Alper Toker, MD,## Federico Venuta, MD***; and the European Society of Thoracic Surgeons Thymic Working Group†††*

Introduction: Thymic carcinoma is a rare and aggressive thymic neoplasm. The European Society of Thoracic Surgeons developed a retrospective database collecting patients undergoing resection for thymic tumors from 1990 to 2010.

Methods: Of 2265 patients with thymic tumors, there were 229 thymic carcinomas. Clinicopathological characteristics were analyzed including age, associated paraneoplastic diseases, stage (Masaoka-Koga), World Health Organization histologic subtypes, type of resection (total/subtotal/biopsy/no resection), tumor size, pre/postoperative treatments, and recurrence. Outcome measures included overall survival (OS), freedom from recurrence, and cumulative incidence of recurrence.

Results: A complete resection was achieved in 140 patients (69%). Recurrence occurred in 54 patients (28%). Five- and 10-year OS rates were 0.61 and 0.37. Five- and 10-year freedom from recurrence rates were 0.60 and 0.43. Cumulative incidence of recurrence was 0.21 (3 yr), 0.27 (5 yr), and 0.32 (10 yr). Survival was better after surgical resection versus biopsy/no resection ($p < 0.001$), after complete resection versus subtotal resection ($p < 0.001$), and when using Masaoka-Koga system (stages I–II versus III versus IV) ($p < 0.001$). The use of multidisciplinary treatments resulted in a survival advantage which was significant in the surgery + radiotherapy group ($p = 0.02$). Incomplete resection ($p < 0.0001$) and advanced stage (Masaoka-Koga III–IV) ($p = 0.02$) had a negative impact on OS at multivariable analysis. Administration of adjuvant radiotherapy was beneficial in increasing OS ($p = 0.02$).

Conclusions: The results of our study indicate that patients with thymic carcinoma should undertake surgical resection whenever possible; a complete resection and early Masaoka-Koga stage are independent predictors of improved survival; our results also suggest that postoperative radiotherapy is beneficial in improving survival.

Key Words: Thymic carcinoma, Staging, Prognostic factors, Thymic tumors, Surgery.

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*Section of Thoracic Surgery, Department of Surgery, University of Torino, Torino, Italy; †Section of Thoracic Surgery, Yale University, New Haven, Connecticut; ‡Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium; §Department of Thoracic Surgery, National Cancer Institute, Pascale Foundation, Naples, Italy; ‖Department of Thoracic Surgery, Aix-Marseille University, Marseille, France; ¶Department of Thoracic Surgery, University Hospital, Zurich, Switzerland; #Division of Thoracic Surgery, St. Jame's University Hospital, Leeds, United Kingdom; **Department of Thoracic Surgery, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; ††Department of Thoracic Surgery, New York Presbyterian Hospital-Weill Cornell Medical Center, New York, New York; ‡‡3rd Department of Surgery, First Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; §§Department of thoracic surgery, Hopital Europeen Georges-Pompidou and Hopital Laennec, Paris, France; ‖‖Department of Thoracic Surgery, European Institute of Oncology, Milan, Italy; ¶¶Department of Thoracic Surgery, Royal Brompton and Harefield NHS Foundation Trust and National Heart and Lung Division, Imperial College, London, United Kingdom; ##Department of Thoracic Surgery, Istanbul University, Istanbul Medical School, Istanbul, Turkey; ***Department of Thoracic Surgery, University of Rome SAPIENZA, Policlinico Umberto I, Fondazione Eleonora Lorilard Spencer Cenci, Rome, Italy. †††The list of authors included in the European Society of Thoracic Surgeons Thymic Working Group are provided in Appendix 1.

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Address for correspondence: Enrico Ruffini, MD, Thoracic Surgery, University of Torino, 3, Via Genova 10126, Torino, Italy. E-mail: enrico.ruffini@unito.it

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Thymic tumors are rare neoplasms, although they represent the most frequent anterior mediastinal tumors. According to the latest World Health Organization (WHO) histologic classification, thymic tumors are divided in thymomas and thymic carcinomas, the latter including the rare neuroendocrine thymic tumors (NETTs). The distinction between thymomas and thymic carcinomas reflects a different histologic and molecular pattern and a different clinical and prognostic behavior. Thymic carcinomas usually present with locally advanced stages, an aggressive behavior, and a frequent incidence of lymphatic or distant metastases. As a consequence, survival rates are lower than those observed in thymomas.[1–3]

Due to the rarity of these tumors, only small series have been published so far on thymic carcinomas, with conflicting results about the prognostic factors and optimal management.

The last decade has witnessed a dramatic increase of the interest in thymic malignancies, culminated with the creation of several thymic interest groups, and the foundation of the

International Thymic Malignancies Interest Group (ITMIG) in 2010.

The European Society of Thoracic Surgeons (ESTS) thymic working group developed a retrospective database among interested centers to collect patients operated on for thymic tumors from 1990 to 2010. The aim of this study was to investigate the population of patients with thymic carcinomas submitted to surgical resection using the ESTS retrospective thymic database, to identify possible prognostic factors and to evaluate optimal therapeutic strategies.

MATERIALS AND METHODS

The ESTS enquired among its members about participation to the ESTS retrospective database thymoma project to collect patients with thymic malignancies submitted to surgery from 1990 to 2010. Follow-up data were collected until December 2011. Overall, 36 institutions replied, including 28 from Europe, five from United States/Canada, and three from Asia (Appendix 2). Institutional review board approval was obtained at each institution.

Of 2265 patients with thymic malignancies, 229 thymic carcinomas were identified. NETTs were excluded. Recording variables in the data set included demographics, the presence of associated paraneoplastic syndromes, histology, 2004 WHO classification,[4] tumor size measured as the largest diameter on the surgical specimen, tumor staging according to Masaoka-Koga,[5] completeness of resection, administration of preoperative (primary) or postoperative (adjuvant) treatment, type of surgical procedure, cause of death (when available), and recurrence. Clinical (preoperative) staging was assessed in all cases by computed tomography scan, integrated by magnetic resonance imaging to assess great vessel invasion in selected patients. Integrated positron emission tomography (PET)-computed tomography (CT) was used by most centers to exclude distant metastases. No center employed tumor, node, metastasis (TNM)-based staging systems. We had no sufficient information about the nodal status and the site of distant metastases to draw any conclusion about their role as prognostic factors. Patients operated on before 2004 were reclassified at each center using the latest WHO histologic classification. Histologic specimens were assessed in each center by pathologists experienced in thymic malignancies, and the differential diagnosis between thymic carcinoma/thymoma/lung cancer was performed in each center based on morphological evaluation and using immunohistochemistry (CD5 and KIT staining) when indicated.

Study outcomes included overall survival (OS), freedom from recurrence (FFR), and the cumulative incidence of recurrence (CIR). OS was computed from the date of surgery to the date of death (any cause). FFR was computed from the date of surgery to the date of recurrence or death (any cause). CIR was calculated from the date of surgery to the date of recurrence. Death from any cause was considered as a competing event in FFR analysis.[6] Patients alive or without recurrence were censored on the date of the last follow-up. OS was calculated on the entire population, whereas FFR and CIR were evaluated in patients receiving a complete (R0) resection and complete information on recurrence status.

Statistical Analysis

The Kaplan–Meier product-limit method was used to compute OS and FFR. The log-rank test was used to assess the differences between survival rates. The Nelson–Aalen method was used to calculate the CIR. Univariable and multivariable Cox proportional hazard models with shared frailty were employed to evaluate OS prognostic factors. Evaluated predictors included age at surgery (as continuous), sex, Masaoka-Koga stage (I–II versus III–IV), tumor size (as continuous), histology (squamous cell versus other subtypes), resection status (complete/incomplete), associated Myasthenia Gravis (MG), and administration of primary (preoperative) and adjuvant (postoperative) treatment. FFR analysis was undertaken using competing-risks regression models (Fine and Gray method), taking into account death by any causes as competing event. The missing data in the different analyses were multiple imputed; 10 imputed data sets provided the combined estimates. Chi-square test and Fisher's exact test, when appropriate, were used to evaluate the differences between groups. The statistical analysis was performed using STATA (version 12.1; StataCorp LP, College Station, TX).

RESULTS

The median contribution by institution was four patients (range, 1–28); 23 institutions (68%) provided less than five patients, seven institutions (21%) provided six to 15 patients, and four institutions (11%) contributed with more than 15 patients.

Median follow-up time was 44 months (interquartile range [IQR], 67 mo; range, 2-214).

Follow-up data were complete in 73% of the patients at the end of the follow-up period (December 31, 2011).

Figure 1 illustrates the flow of patients according to the different end points. Two hundred fifteen patients were available for OS analysis; FFR and recurrence analysis could be performed on 113 patients.

Clinical Data

The characteristics of the cohort population (n = 229) are illustrated in Table 1. Median age at surgery was 58 years, ranging from 22 to 88 years, and 58% of the patients (133 of 229) were men. Associated MG was observed in 31 of 229 patients (14%). The most frequent histologic subtypes were squamous cell carcinoma (98 of 129 patients, 76%), followed by mucoepidermoid type (10 patients, 8%). Median tumor size at surgery (largest diameter) was 5 cm (range, 1–25 cm). According to resection status, a complete (macro and microscopic) resection (R0) was achieved in 140 of 203 patients (69%); an incomplete resection was performed in 47 patients, of whom there were 23 microscopic (R1) and 24 macroscopic (R2) residuals; 16 patients received only biopsy (no resection). According to Masaoka-Koga stage, the majority of patients were at advanced stages (stages III–IV, 132 of 186, 71%). One-third of the patients (78 of 215) received preoperative (primary) therapy, mostly chemotherapy, including four patients stage I, three patients stage IIa, six patients stage IIb, 31 patients stage III, 15 patients stage IVa, and five patients stage IVb (14 patients with missing information). Indications