Multimodality therapy for locally advanced thymomas: A propensity score–matched cohort study from the European Society of Thoracic Surgeons Database

Giovanni Leuzzi, MD,[a] Gaetano Rocco, PhD,[b] Enrico Ruffini, PhD,[c] Isabella Sperduti, MS,[d] Frank Detterbeck, PhD,[e] Walter Weder, MD,[f] Federico Venuta, PhD,[g] Dirk Van Raemdonck, PhD,[h] Pascal Thomas, PhD,[i] Francesco Facciolo, MD,[j] and the ESTS Thymic Working Group

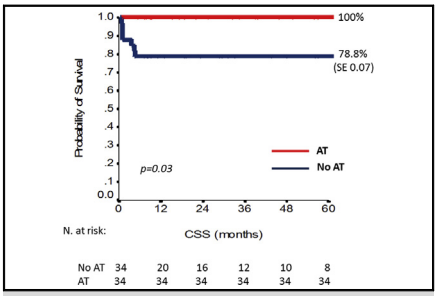
ABSTRACT

Objective: This study investigated the prognostic impact of multimodality therapies in locally advanced thymomas.

Methods: From January 1990 to January 2010, clinicopathological, surgical, and oncological features were retrospectively reviewed in a cohort of 370 Masaoka-Koga stage III thymomas (World Health Organization classification A to B3) collected from 37 institutions. A multivariate Cox proportional hazard model was created to identify independent predictors of overall, cancer-specific (CSS), and relapse-free survivals. Furthermore, a propensity score–matching analysis for exposure to adjuvant (AT) therapy was generated.

Results: Induction therapy and AT were administered to 88 (24.9%) and 245 (69.4%) patients, respectively. Overall, 5- and 10-year overall survival, CSS, and relapse-free survivals were 82.8%, 88.4%, and 80.0%, and 68.9%, 83.3%, and 71.5%, respectively. At multivariable analysis performed in the matched cohort, AT was confirmed as the strongest predictive factor for overall survival (hazard ratio, 2.83; 95% confidence interval, 0.88-9.12; $P = .08$) and CSS (hazard ratio, 4.70; 95% confidence interval, 1.00-22.2; $P = .05$). Pathologic T classification (according to International Association for the Study of Lung Cancer and International Thymic Malignancy Interest Group TNM staging proposal) was an independent factor for relapse (hazard ratio, 8.69; 95% confidence interval, 1.08-70.04; $P = .04$). When CSS was adjusted for T classification, AT confirmed a significant survival advantage for pT3 tumors ($P = .04$). On the other hand, for thymomas larger than 5 cm, stratifying for tumor size and AT did not affect 5-year CSS ($P = .17$).

Conclusions: Our results indicate that AT is beneficial for locally advanced thymomas, mainly for specific pathologic features (pT3 or tumor size smaller than 5 cm). Further larger studies are needed to confirm these data. (J Thorac Cardiovasc Surg 2016;151:47-57)



Cancer-specific survival according to the use of adjuvant therapy in stage III thymomas.

Central Message

Adjuvant therapy should be administered in locally advanced thymomas with specific pathologic features (pT3 or tumor size <5 cm).

Perspective

Given the heterogeneity of stage III tumors, we assessed the effect of adjuvant therapy on outcome according to specific pathologic features (pT and tumor size) that may play a role postoperatively in the decision-making process on either adjuvant therapy or surveillance as well. These data may be considered for development of future trials on adjuvant therapy.

See Editorial Commentary page 58.

See Editorial page 20.

From the [a]Thoracic Surgery Unit, IRCCS Istituto Nazionale dei Tumori Foundation, Milan, Italy; the [b]Department of Thoracic Surgery, Istituto Nazionale Tumori, IRCCS, Fondazione Pascale, Naples, Italy; the [c]Department of Surgery, Section of Thoracic Surgery, University of Torino, Torino, Italy; [d]Scientific Direction, Regina Elena National Cancer Institute–IFO, Rome, Italy; the [e]Department of Surgery, Section of Thoracic Surgery, Yale University, New Haven, Conn; the [f]Department of Thoracic Surgery, University Hospital, Zurich, Switzerland; the [g]Department of Thoracic Surgery, University of Rome SAPIENZA, Policlinico Umberto I, Fondazione Eleonora Lorilard Spencer Cenci, Rome, Italy; the [h]Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium; the [i]Department of Thoracic Surgery, Aix-Marseille University, Marseille, France; and the [j]Department of Surgical Oncology, Thoracic Surgery Unit, Regina Elena National Cancer Institute–IFO, Rome, Italy.

Read at the 95th Annual Meeting of The American Association for Thoracic Surgery, Seattle, Washington, April 25-29, 2015.

Received for publication April 4, 2015; revisions received June 17, 2015; accepted for publication Aug 10, 2015; available ahead of print Sept 21, 2015.

Address for reprints: Giovanni Leuzzi, MD, Thoracic Surgery Unit, IRCCS Istituto Nazionale dei Tumori Foundation, Milan, Italy (E-mail: gio.leuzzi@yahoo.it).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2015.08.034

GTS

Abbreviations and Acronyms:

TT = thymic tumor
OS = overall survival
LAT = locally-advanced thymoma
IT = induction therapy
AT = adjuvant therapy
ESTS = European Society of Thoracic Surgeons
pT = Pathologic tumor invasion according to the proposed International Association for the Study of Lung Cancer and International Thymic Malignancy Interest Group TNM staging system
HR = hazard ratio
CI = confidence interval
CSS = cancer-specific survival
RFS = recurrence-free survival

Supplemental material is available online.

Thymic tumors (TTs) are rare mediastinal malignancies accounting for 0.2% to 1.5% of all tumors and arising in approximately 1-5 patients/million population/y.[1] Thymoma represents the most common histologic type, occurring in about 90% of the overall resected TTs.[2] Specifically, patients with advanced-stage disease, occurring in 20% to 29% of all surgically treated thymomas,[2,3] are likely to be subjected to a different range of radical resections (50%-78% in the major surgical series[2-4]). Furthermore, a significant proportion (as great as 50%) of patients with stage III thymomas have recurrence after surgery[5-7]; in these patients the pleura, lung, diaphragm, and tumor primary site are the most common sites of relapse.[3,8] These data are significant if one takes into account that overall survival (OS) decreases with higher stage (III-IV) and after incomplete resection, whereas recurrence rate increases with greater tumor size, stages III and IV, and more aggressive histologic features.[2,5]

Reportedly, controversy still exists concerning the oncologic management of locally advanced thymomas (LATs). Although TTs have been documented to be chemoresponsive and radioresponsive, arguable and limited results have been reported when analyzing the outcome after induction therapy (IT).[9,10] Similarly, adjuvant therapy (AT) has been associated with variable survival after thymectomy.[2,8]

In this setting, the aim of this study was to investigate the prognostic indicators in the specific subset of stage III thymomas with a large multicenter TT database. Furthermore, we explored the impact of different multimodality treatments on survival.

MATERIALS AND METHODS

The European Society of Thoracic Surgeons (ESTS) thymic database project includes patients with TTs who underwent surgery from 1990 to 2010. Overall, 37 institutions joined the project: 29 from Europe, 5 from the United States and Canada, and 3 from Asia. Institutional review board approvals were obtained from each institution.

Among 2317 patients with TTs, we identified 370 cases with Masaoka-Koga stage III thymoma (World Health Organization [WHO] histologic type from A to B3). Thymic carcinomas and neuroendocrine TTs were excluded from the analysis.

The recorded data included demographic characteristics, presence of paraneoplastic syndromes, histologic type, 2004 WHO classification,[1] tumor size, Masaoka-Koga staging system,[11] year of surgery, type and extension of surgical procedure, completeness of resection, classification according to the International Association for the Study of Lung Cancer and International/Thymic Malignancy Interest Group TNM staging proposal (pT),[12] administration of IT or AT, cause of death, and recurrence.

Preoperative staging was performed by computed tomographic scan in all cases, positron emission tomographic scan in most centers, and magnetic resonance imaging in selected cases mainly to asses major vascular involvement.

Histologic specimens were evaluated by pathologists experienced in mediastinal tumors. Patients undergoing surgery in or before 2004 has reclassification at each institution in accordance with the latest WHO histologic classification.[1]

Indications for IT and AT depended on the experience of each center and the multidisciplinary team evaluation. In particular, IT was administered mainly to those patients deemed to have potentially unresectable disease at preoperative workup. Chemotherapy for IT or AT varied according to different institutional treatment trials; as a rule, cisplatin-based regimens (mostly the combination of cisplatin, doxorubicin, and cyclophosphamide or the combination of cisplatin, doxorubicin, cyclophosphamide, and vincristine) were administered. In general, adjuvant radiotherapy was administered to a total dose of 40 to 60 Gy.

Most institutions adopted a surveillance protocol that was based on a 3- to 6-month computed tomographic scan for the first 2 years, followed by lifelong annual scans. With respect to clinical outcome, the follow-up data were collected from hospital medical notes and from interviews with patients, their next of kin, and their general practitioners. Surveillance information was available for 352 cases (95.1%), with a median follow-up of 60 months (range 1-248 months).

Statistical Analysis

Descriptive statistics were used to summarize pertinent study information. Cutoffs of continuous variables were determined by performing the analysis by means of maximally selected log-rank statistics. The associations between variables were tested according to χ^2, Student t, and Mann-Whitney (nonparametric) tests when appropriate. The hazard ratio (HR) and the confidence intervals (CI) were estimated for each variable by means of the Cox univariate model. A multivariate Cox proportional hazard model was also developed with stepwise regression (forward selection) by selecting those variables that were significant on univariate analysis. Entry and removal limits were $P = .10$ and $P = .15$, respectively. Survival was calculated by the Kaplan-Meier product-limit method from the date of surgery until the time of death from cancer (cancer-specific survival [CSS]), death from any cause (OS), or recurrence (recurrence-free survival [RFS]) at last follow-up. The log-rank test was used to assess differences between subgroups.

The effect of AT on survival has been explored in patients with R0 resection. To reduce the selection biases related to a nonrandomized cohort,