Thymic carcinoma outcomes and prognosis: Results of an international analysis

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Objectives: The objectives of this collaborative study were to characterize patients with thymic carcinoma, their treatment patterns, and association with overall survival (OS) and recurrence-free survival (RFS).

Methods: Clinical, pathologic, treatment, and follow-up information were analyzed. OS and RFS were the primary outcome measures.

Results: In 1042 cases of thymic carcinoma, 42 (5%) patients had pathologic Masaoka stage I, 138 (17%) had stage II, 370 (45%) had stage III, and 274 (33%) had stage IV disease. Overall, 166 patients (22%) underwent induction chemotherapy and 48 (6%) had preoperative radiation therapy. An R0 resection was performed in 447 cases (61%), R1 in 102 cases (14%), and R2 in 184 cases (25%). Squamous cell carcinoma was the predominant histologic subtype (n = 560; 79%). Adjuvant chemotherapy was administered to 237 (31%) patients, and 449 (60%) received adjuvant radiation therapy. The median OS was 6.6 years (95% confidence interval [CI], 5.8-8.3) and the cumulative incidence of recurrence at 5 years was 35% (95% CI, 30%-40%). In univariate analysis, early Masaoka stage, R0 resection, chemotherapy, and radiation therapy were associated with OS. Early Masaoka stage and R0 resection were also associated with RFS. On multivariable analysis, R0 resection and radiation therapy were associated with prolonged OS. Radiation therapy and male gender were associated with prolonged RFS.

Conclusions: R0 resection and radiation therapy are associated with improved OS, whereas radiation therapy and male gender are associated with longer RFS. (J Thorac Cardiovasc Surg 2015;149:95-101)

See related commentary on pages 101-2.

Supplemental material is available online.

Thymic carcinomas are rare thymic neoplasms.[1,2] Our knowledge of treatment and prognostic factors is limited to small retrospective series. Only 2 multicenter studies have been reported so far, including a review of 186 patients from 115 centers in Japan,[3] and an analysis of 290 cases in the Surveillance, Epidemiology, and End Results (SEER) registry.[4]

In order to study these tumors in a large international sample, the International Thymic Malignancy Interest Group (ITMIG) and the European Society of Thoracic Surgeons (ESTS) created a combined database of all thymic malignancies.[5-7] Here, we report the first analysis from this combined database of patients with thymic carcinomas, which is the largest analysis of this rare disease to date. The objective of this study was to identify the prognostic, patient, tumor, and treatment characteristics that are associated with overall survival (OS) and recurrence-free survival (RFS) in patients with thymic carcinoma.

METHODS

Approval for this study was granted by the Yale University Institutional review board (#1307012419).

Patients

The ITMIG database was launched in September 2012; further details are described elsewhere.[6] Cases of thymic carcinoma from 67 participating institutions were included in this analysis. Participating institutions are listed in Appendix E1. The ESTS database was populated in parallel by other participating centers (Appendix E2). The ITMIG and ESTS databases collected limited datasets from which deidentified data were extracted.

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Abbreviations and Acronyms

CIR = cumulative incidence of recurrence
ESTS = European Society of Thoracic Surgeons
IASLC = International Association for the Study of Lung Cancer
ITMIG = International Thymic Malignancy Interest Group
OS = overall survival
RFS = recurrence-free survival
SEER = Surveillance, Epidemiology, and End Results

Multiple rounds of requests for missing data were performed in order to obtain a dataset that was as complete as possible. Despite this effort and the standardization of variables across databases, not all data were retrievable. Therefore the number of cases that could be analyzed for each variable and test are reported.

Clinicopathologic Variables and Outcomes

Data regarding demographic and clinical characteristics, histology, tumor size and invasion, staging, surgery, chemotherapy, and radiation therapy were collected. Data on recurrence and survival was also collected. For the purpose of this report, only the first recurrence and the associated recurrence-free interval were included.

Time intervals were calculated according to the following descriptions.

Overall survival. OS was determined as the time interval between date of surgery, or the last day of therapy if no surgery, and the date of death or the date when last known alive.

Recurrence-free survival. RFS was determined as the time interval between date of surgery or the last day of therapy if no surgery, and the date when recurrence was noted or the date of last follow-up without recurrence.

Staging system. Various centers reported tumor stage using either the Masaoka[8] or Masaoka-Koga[9] systems. Initial analyses revealed a lack of difference in outcomes between stages I and II and the ITMIG/International Association for the Study of Lung Cancer (IASLC) staging system. The Prognostic Factors Committee of ITMIG also found no difference in outcomes between stages I and II.[10] Therefore, cases with stages I and II (II, IIa, IIb) were pooled and analyzed together, and cases staged using the Masaoka and Masaoka-Koga staging systems were combined.

In this cohort, lymph node involvement was reported in only 20 patients. The role of lymph node involvement could not be studied because of the small number of patients with positive nodes and because there is no consistent practice of lymphadenectomy or lymph node sampling. Data on the presence of distant metastases were reported and incorporated into the Masaoka stage.

Statistical Analysis

A core statistical team of ITMIG investigators (X.Y. and Y.Z.) performed all analyses with SAS 9.3 and R. OS and RFS were the primary outcomes. The association of OS with clinical and prognostic factors was tested using the log-rank test. Prognostic factors that were significantly associated with survival on univariate analysis and clinically relevant factors were included in a Cox proportional hazards model for multivariate analysis.

The cumulative incidence of recurrence (CIR) was assessed using competing risk analysis, with death included as the competing event (curves of death were not shown in cumulative incidence plots). The effect of clinical factors on freedom from recurrence was assessed using Gray's test. The Cox proportional hazards model was used for multivariate analysis.

RESULTS

Fourteen percent of all thymic tumors in the ITMIG database were thymic carcinomas. A total of 1042 cases of thymic carcinoma were identified for analysis. There was no geographic predominance, and most cases were diagnosed and treated between 2001 and 2010 (Table 1).

The clinical characteristics are described in Table 1. A pretreatment biopsy was performed in 57% of cases (needle biopsy, 19%; core biopsy, 10%; surgical biopsy, 20%). Two hundred fifty-one (35%) cases were assigned a stage using the Masaoka system and 297 (41%) using the Masaoka-Koga system. A large proportion of patients were upstaged (Table E1). Squamous cell carcinoma was by far the most common histologic subtype (79%) followed by lymphoepithelioma-like and basaloid histologies (Table 1). There was no significant association between stage at presentation and histologic subtype ($P = .4$). Surgery, radiation, and chemotherapy treatment details are shown in Tables 2 and E2. Seven hundred thirty-three patients (70%) had resection status data available and 447 (61%) had R0 resections (Table 2). Four hundred ninety-four patients (65%) received neoadjuvant or adjuvant chemotherapy. Radiation treatment was administered to 545 patients (72%) and 449 patients (82%) received it in the adjuvant setting. Only 48 patients (9%) had radiation as neoadjuvant treatment.

Survival and Recurrence

Median follow-up in the overall cohort was 4.4 years. Vital status was known for 836 patients (80%). Of these, 303 patients (36%) had died. The cause of death was available for 224 patients (74%): 164 deaths (74%) were associated with thymic carcinoma, 4% with treatment complications, and 13% were attributed to other causes. The median OS for all cases of thymic carcinoma was 6.6 years (95% confidence interval, 5.8-8.3). The overall 5-year survival was 60% and 10-year survival was 40%. The overall CIR was 35% at 5 years and 40% at 10 years.

Prognostic Factors

Masaoka stage was significantly associated with OS ($P < .0001$; Figure 1, *A*). The 5-year OS by stage was 80% for stage I/II, 63% for stage III, 42% for stage IVa, and 30% for stage IVb. The 10-year OS was 60% for stage I/II, 42% for stage III, 28% for stage IVa, and 13% for stage IVb.

Masaoka stage was also significantly associated with CIR ($P = .0005$; Figure 1, *B*). The CIR for stages I and II was 15% at both 5 and 10 years, but for stage III, the CIR was

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