Resection of thymoma should include nodal sampling

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Objective: Thymoma is best treated by surgical resection; however, no clear guidelines have been created regarding lymph node sampling at the time of resection. Additionally, the prognostic implications of nodal metastases are unclear. The aim of this study was to analyze the prognostic implications of nodal metastases in thymoma.

Methods: The Surveillance, Epidemiology, and End Results database was queried for patients who underwent surgical resection of thymoma with documented pathologic examination of lymph nodes. The impact of nodal status on survival and thymoma staging was examined.

Results: We identified 442 patients who underwent thymoma resection with pathologic evaluation of 1 or more lymph nodes. A median of 2 nodes were sampled per patient. Fifty-nine patients (59 of 442, 13.3%) had $\geq$1 positive node. Patients with positive nodes were younger and had smaller tumors than node-negative patients. Median survival in the node-positive patients was 98 months, compared with 144 months in node-negative patients ($P = .013$). In multivariable analysis, the presence of positive nodes had a significant, independent, adverse impact on survival (hazard ratio 1.945, 95% confidence interval 1.296-2.919, $P = .001$). The presence of nodal metastases resulted in a change in classification to a higher stage in 80% of patients, the majority from Masaoka-Koga stage III to stage IV.

Conclusions: Nodal status seems to be an important prognostic factor in patients with thymoma. Until the prognostic significance of nodal metastases is better understood, surgical therapy for thymoma should include sampling of regional lymph nodes. (J Thorac Cardiovasc Surg 2015;149:737-42)

See related commentary on pages 743-4.

Thymoma is a rare tumor of the anterior mediastinum with an incidence of 0.15 per 100,000 person-years.[1] The most commonly accepted staging system for thymomas is the modification of the Masaoka classification by Koga and colleagues,[2] which classifies tumors according to invasion of adjacent organs. In this classification, thymoma with nodal metastases is classified as stage IVB. Kondo and Monden[3,4] compiled a database of 1320 patients with thymic epithelial tumors and found a 1.8% incidence of nodal metastases in patients with thymoma. Most metastases were to anterior mediastinal lymph nodes, and there was no significant difference in survival between patients with stage IVA thymoma (pleural/pericardial spread) and patients with stage IVB thymoma (nodal or hematogenous metastases). To our knowledge, Kondo and Monden's work is the only publication to date reporting on the incidence and prognostic relevance of nodal metastases in patients with thymoma. The goals of the present study were to identify the incidence and prognostic significance of nodal metastases in patients with thymoma in a large database of patients in the United States.

METHODS

The Surveillance, Epidemiology, and End Results (SEER) database is sponsored by the National Cancer Institute and has been used to track cancer incidence and patient survival since 1973. The SEER database currently covers approximately 28% of the US population and captures 98% of all cancer cases within the surveyed geographic areas. We used the SEER 18 Registry, including the Hurricane Katrina Impacted Louisiana Cases, for this analysis (SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2010 Sub (1973-2007 varying) National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011, based on the November 2010 submission).

This SEER database was queried for all cases of thymoma from January 1, 1988 to December 31, 2009 using the International Classification of Diseases–03 codes for thymoma (8580, 8581, 8582, 8583, 8584, and 8585). Specific fields for number of lymph nodes examined and number of positive nodes were created in 1988. Patients with thymic carcinoma were not included in this analysis. We included only patients who had resection of the thymus and had at least 1 lymph node analyzed pathologically, and who survived for more than 30 days after resection. SEER*Stat software (seer.cancer.gov/seerstat) version 6.6.2 was used for data mining. Using available data, patients were staged according to the

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Abbreviations and Acronyms

CI = confidence interval
ITMIG = International Thymic Malignancy Interest Group
SEER = Surveillance, Epidemiology, and End Results
TNM = tumor, node, metastases
WHO = World Health Organization

Masaoka-Koga classification. Stage I (no transcapsular invasion) and stage IIa (microscopic transcapsular invasion) thymomas could not be separated using the available data and were therefore analyzed together.

Data are presented as median, and 25th and 75th percentile. Survival is presented in months and with a 95% confidence interval (CI). Continuous data variables were analyzed using Student *t* test. Nominal data were analyzed utilizing crosstabs and Pearson χ^2 statistic. Kaplan–Meier survival curves were constructed and compared using the log-rank test.

A Cox proportional hazard model was used to identify the relevant variables that affected overall survival. Only variables that significantly affected survival in univariable analysis were included in the Cox model. The proportionality of hazards was evaluated using the Cox regression analysis with time-dependent covariables. The assumption of proportionality of hazards was tested and was not broken in any of the Cox regression models. Statistical analysis was performed with SPSS statistical software package version 19.0 (SPSS, Inc, Chicago, Ill). Significance was set at $P < .05$. This study was approved by the University of Pittsburgh Institutional Review Board, and the requirement for informed consent was waived.

RESULTS

From 1988 to 2009, a total of 2227 patients with thymoma were entered into the SEER database. Of these, 442 patients (19.8%) had undergone thymoma resection, with pathologic analysis of the lymph nodes, and therefore qualified for the study. The majority of patients were white males, with a median age of 58 years. Most tumors were Masaoka-Koga stage III, and the median number of lymph nodes analyzed was 2. There were 59 (13.3%) patients with involved lymph nodes (node positive), and 383 patients whose nodes were not involved (node negative). Patients with positive nodes were younger (53 years vs 58 years) and had smaller tumors (37 mm vs 50 mm) than patients with node-negative thymoma (Table 1). The median number of positive nodes per patient was 1. Forty-seven patients had 1 positive lymph node, 8 had 2 positive nodes, 1 patient had 3 positive nodes, 1 patient had 4, and 2 patients had 5 positive lymph nodes.

Lymph Node Assessment and Thymoma Staging

Changes to thymoma staging as a result of the identification of involved nodes could be assessed in 56 of the 59 node-positive patients. The presence of nodal metastases led to the thymoma being classified as a higher stage in a significant number of patients. If the positive nodes were discounted, 4 of 56 (7.1%) would have been classified as Masaoka-Koga stage I/IIA, 9 of 56 (16.1%) as stage IIB, and 32 of 56 (57.1%) as stage III. The remaining patients (11 of 56, 19.6%) were already classified as stage IV, and therefore, the stage could not be increased. Effectively, the presence of positive nodes led to reclassification at a higher stage in 80% of patients who would not have been classified as having stage IV thymoma based on other morphological features of the tumor.

Survival

Overall median survival for the full cohort was 139 months. Five-year survival for the whole cohort was 77%, and 10-year survival was 29%. Node-negative patients had a median survival of 144 months, and a 5- and 10-year survival of 79% and 32%, respectively. In contrast, node-positive patients had a median survival of 98 months, and a 5- and 10-year survival of 66% and 16%, respectively, which differed significantly from that seen in patients with node-negative thymoma ($P = .013$; Figure 1). Over the 21-year study period, a total of 106 patients without nodal metastases died; 32 patients who had nodal metastases died. Node-negative patients had a mean disease-specific survival of 205 months (5-year: 94%; 10-year: 74%), compared with 152 months (5-year: 77%; 10-year: 48%) in node-positive patients ($P < .001$; Figure 2).

In univariable analysis (Table 2), older age at diagnosis ($P < .001$); Masaoka-Koga stage I/IIA versus IV ($P = .027$); Masaoka-Koga stage IIB versus IV ($P = .006$); and positive lymph nodes ($P = .019$) were significant variables affecting survival. Because of the strong correlation between nodal status and Masaoka-Koga classification (all patients with positive nodes are classified as Masaoka-Koga stage IV), we could use only one of these variables at a time in the Cox model used to calculate the hazard ratio. In a first model, being older than 58 years at diagnosis ($P < .001$); Masaoka-Koga stage I/IIA versus IV ($P = .016$); and Masoka-Koga stage IIB versus IV ($P = .004$) were significant factors affecting survival. In a second model, older age at diagnosis ($P < .001$) and positive lymph nodes ($P = .001$) were the only factors affecting survival (Table 3).

In node-positive patients, data on adjuvant radiation therapy were available in 56 of 59 patients; 39 of 56 (69.6%) patients received adjuvant radiation therapy, and 17 of 56 (30.4%) did not. Survival in node-positive patients who received adjuvant radiation was 145 months, compared with 62 months in patients who did not receive adjuvant therapy, but this difference was not significant ($P = .317$).

DISCUSSION

In the present study, we used a large database to identify a cohort of patients with thymoma who had at least 1 lymph node analyzed pathologically. We found that among