Impact of Positive Nodal Metastases in Patients with Thymic Carcinoma and Thymic Neuroendocrine Tumors

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Introduction: Thymic carcinomas and thymic neuroendocrine tumors are rare diseases often treated with surgical resection. Currently, there are no guidelines regarding nodal dissection at the time of tumor resection. Moreover, the prognostic significance of nodal metastases is unclear. The goal of this study was to define the incidence and prognostic relevance of nodal metastases in patients with thymic carcinoma and thymic neuroendocrine tumors.

Methods: The Surveillance, Epidemiology and End Results database was queried for patients who underwent surgical resection of thymic carcinoma or a thymic neuroendocrine tumor with documented pathological examination of lymph nodes. The incidence of nodal metastases and the impact on survival were examined.

Results: We identified 176 patients with thymic carcinoma and 53 with thymic neuroendocrine tumors. A median of three lymph nodes was sampled per patient. Positive metastasis to at least one lymph node was identified in 92 patients (40.2%). Nodal metastasis was more common in patients with thymic neuroendocrine tumors than in patients with thymic carcinoma (62.3% versus 33.5%). In multivariate analysis, nodal metastasis was more likely in patients with thymic neuroendocrine tumors and with more advanced tumors. The presence of nodal metastases had significant, independent, adverse impact on survival (hazard ratio, 2.933, 95% confidence interval, 1.903–4.521, $p = 0.001$). Median survival was 47 months in patients with nodal metastasis and 124 months in patients without nodal metastases ($p < 0.001$).

Conclusions: Nodal status seems to be an important prognostic factor in patients with thymic carcinoma and thymic neuroendocrine tumors. Nodal sampling should be performed during resection of these thymic malignancies.

Key Words: Thymic tumors, Thymic carcinoma, Thymic neuroendocrine tumors, Lymph node metastases, SEER registry.

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Thymic carcinomas used to be defined by World Health Organization (WHO) classifications as a heterogeneous group of tumors that include adenocarcinoma of the thymus, squamous cell carcinoma of the thymus, and neuroendocrine tumors, among others.[1] The recent WHO classification[2] clearly distinguishes thymic carcinomas from thymic neuroendocrine tumors. Thymic carcinomas are very rare tumors, and historically, they have not been well studied because of the difficulty in acquiring sufficient cases for analysis.[3] We and others have retrospectively analyzed large databases to circumvent this limitation. We previously used the Surveillance, Epidemiology, and End Results (SEER) database to analyze prognostic variables in a cohort of 290 patients with thymic carcinoma.[4] In early 2015, two large retrospective database studies were published that assessed stage at presentation, survival, and recurrence in patients with thymic carcinoma and thymic neuroendocrine tumors.[5,6]

Although most previous studies on thymic epithelial tumors easily defined the tumor and metastases, very few studies have addressed the incidence and prognostic significance of the lymph nodal status in patients with thymic carcinoma or thymic neuroendocrine tumors. Our knowledge of nodal status in patients with thymic epithelial tumors comes mostly from a study by Kondo et al.,[7] who compiled a database of 1320 patients with thymic epithelial tumors including 183 patients with thymic carcinoma and 40 patients with thymic carcinoid tumors. The incidence of nodal metastases in these patients was 26.8% and 27.5%, respectively. A smaller study by Park et al.[8] analyzed nodal metastases in 29 patients with thymic carcinoma who underwent nodal dissection and found that 20.8% of patients had pathologically confirmed nodal metastases.

This study was designed to further define the incidence of nodal metastases in patients with thymic carcinoma and thymic neuroendocrine tumors and assess the prognostic significance of nodal metastases.

MATERIALS AND METHODS

Database and Query Criteria

The 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 U.S. 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

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Impacted Louisiana Cases, November 2010 Sub [1973–2011 varying], National Cancer Institute, Surveillance Research Program, Cancer Statistics Branch, released April 2014 based on the November 2013 submission). Specific fields for number of lymph nodes examined and number of positive nodes were created in 1988. SEER*Stat software (seer.cancer.gov/seerstat) version 8.2.1 was used for data mining.

The SEER 18 database was queried for all cases of thymic carcinoma and thymic neuroendocrine tumors from January 1, 1988 to December 31, 2011 using the ICD-03 codes 8002, 8010, 8012, 8013, 8020, 8021, 8070–8072, 8074, 8140, 8240, 8243, 8246, 8586, 8588, and 8589. We included patients with the primary site labeled as C37.9 (thymus). We further refined the patient cohort to include only patients who had resection or debulking of the thymus, had at least one lymph node analyzed pathologically, and who survived for more than 30 days after resection. Patients with thymoma were not included in the analysis. Using available data, patients were staged according to the Masaoka-Koga classification.[9] Stage I (no transcapsular invasion) and stage IIa (microscopic transcapsular invasion) could not be differentiated from one another using the available data and were analyzed together. The University of Tennessee Health Science Center Institutional Review Board approved this study, and the requirement for informed consent was waived.

Statistical Analysis

Continuous data variables were analyzed using Student's *t* test. Nominal data were analyzed using crosstabs and Pearson's χ^2 test. To identify variables that could predict the presence of nodal metastases, univariate binary logistic regression was performed, followed by a multivariate analysis including only variables that had a *p* value less than 0.10 in the univariate analysis. Kaplan–Meier survival curves were constructed and compared using the log-rank test. To assess variables that impacted overall survival, univariate analysis was performed using the Cox univariate model and calculating the hazard ratio and 95% confidence interval. Multivariate analysis was performed using a Cox proportional hazard model, again including only variables that had a *p* value less than 0.10 in univariate analysis. The proportionality of hazards was evaluated using 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 21.0 (SPSS inc., Chicago, IL). Significance was set at *p* value less than 0.05.

RESULTS

We identified 229 patients in the SEER database eligible for this analysis (Table 1). The majority of patients were male (56.8%) and white (79.0%) with a median age of 59 years (range 47–70 years). There were 176 patients (76.9%) with thymic carcinoma and 53 (23.1%) with thymic neuroendocrine tumors. Excluding the upstaging from nodal sampling, there were 62 (27.1%) classified as Masaoka-Koga stage I/IIA; 25 (10.9%) classified as stage IIB; 120 (52.4%) as stage III; and 20 (8.8%) as stage IV. There were two (0.8%) patients who could not be staged without the nodal sampling. The median number of lymph nodes sampled per patient was three (median, 6; interquartile range [IQR], 1–43) and did not differ between patients with nodal metastasis (node positive) and patients without nodal metastasis (node negative). There were also no difference in number of sampled nodes between patients with thymic carcinoma and thymic neuroendocrine tumors ($p = 0.590$). Positive metastasis in at least one lymph node was identified in 92 patients (40.2%), and node-positive patients had a median of one positive node (IQR, 1–26).

TABLE 1. Patient Demographics

	Full Cohort	Node Negative	Node Positive	*P*
n (%)	229 (100)	137 (59.8)	92 (40.2)	
Sex, n (%)				0.122
Male	130 (56.8)	73 (53.3)	57 (62.0)	
Female	99 (43.2)	64 (46.7)	35 (38.0)	
Median age, yr (IQR)	59 (48, 69)	58 (49, 68)	59 (47, 70)	0.415
White, n (%)	181 (79.0)	102 (75.0)	79 (85.9)	0.066
Tumor type, n (%)				<0.001
Thymic carcinoma	176 (76.9)	117 (85.4)	59 (64.1)	
Neuroendocrine tumor	53 (23.1)	20 (14.6)	33 (35.9)	
Tumor size, mm (IQR)	67 (48, 90)	65 (48, 86)	70 (49, 100)	0.069
Masaoka-Koga stage, n (%)				<0.001
Stage I/IIA	46 (20.1)	46 (33.6)	0	
Stage IIB	16 (7.0)	16 (11.7)	0	
Stage III	68 (29.7)	68 (49.6)	0	
Stage IV	98 (42.8)	6 (4.4)	92 (100)[a]	
Stage unknown	1 (0.4)	1 (0.7)		
Lymph nodes analyzed, median (IQR)	3 (1, 6)	2 (1, 6)	4 (1, 7)	0.338
Surgery, n (%)				0.436
Resection	213 (93.0)	129 (94.2)	84 (91.3)	
Debulking	16 (7.0)	8 (5.8)	8 (8.3)	
Radiation therapy, n (%)				0.299
Preoperative	14 (6.1)	8 (5.8)	6 (6.5)	
Postoperative	126 (55.0)	69 (50.4)	57 (62.0)	
None	86 (37.6)	57 (41.6)	29 (31.5)	
Unknown	3 (1.3)	3 (2.2)	0 (0)	

[a]By definition the presence of positive lymph nodes dictates classification as stage IV.
IQR, interquartile range.

There were a higher proportion of node-positive patients with thymic neuroendocrine tumors than with thymic carcinoma. Nodal metastasis was present in 33 of 53 patients (62.3%) with thymic neuroendocrine tumors when compared with only 59 of 176 patients (33.5%) with thymic carcinoma ($p < 0.001$). Similarly, patients with thymic neuroendocrine tumors had a significantly more positive nodes per patient (median, 2; IQR, 1–26) than patients with thymic carcinoma (median, 1; IQR, 1–9, $p = 0.031$). There were no significant differences in surgical treatment or radiation therapy between node-positive and node-negative patients (Table 1).

Identification of positive nodes resulted in significant changes to Masaoka-Koga staging that could be evaluated in

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