Clinical Characteristics and Outcomes for Patients With Thymic Carcinoma

Evaluation of Masaoka Staging

Anya M. Litvak, MD, Kaitlin Woo, MS,† Sara Hayes, MD,‡ James Huang, MD,§ Andreas Rimner, MD,‖ Camelia S. Sima, MD, MS,† Andre L. Moreira, MD, PhD,¶ Maria Tsukazan, MD,§ and Gregory J. Riely, MD, PhD**

Background: Thymic carcinomas are rare cancers with limited data regarding outcomes, particularly for those patients with advanced disease.

Methods: We identified patients with thymic carcinomas diagnosed between 1993 and 2012. Patient characteristics, recurrence-free survival (RFS), and overall survival (OS) were analyzed.

Results: One hundred twenty-one patients with thymic carcinomas were identified. Higher Masaoka stage was associated with worse OS and RFS (5-year OS of 100%, 81%, 51%, 24%, and 17% for stage I, II, III, IVa, and IVb respectively, $p < 0.001$ and 5-year RFS of 80%, 28%, and 7% for stage I/II, III, and IV respectively, $p < 0.001$). Patients with stage IVb lymph node (LN) only disease had a better 5-year OS as compared with patients with distant metastasis (24% versus 7%, $p = 0.025$). Of the 61 patients with stage IVb disease, 22 of 29 patients (76%) with LN-only disease underwent curative intent resection versus 3 of 32 patients (9%) with distant metastasis. Twenty-two patients with LN involvement were treated with multimodality therapy. Three (14%) remain free of disease with long-term follow-up (range, 3.4+ years– to 6.8+ years).

Conclusions: We describe the clinical features of a large series of patients with thymic carcinoma in North America. The Masaoka staging system effectively prognosticated OS and RFS. Patients with stage IVb LN-only disease had significantly better OS as compared with patients with distant metastasis with a subset of patients sustaining long-term RFS with multimodality therapy. If validated, these data would support a revised staging system with subclassification of stage IVb disease into two groups.

Key Words: Thymic carcinoma, Masaoka staging.

(*J Thorac Oncol.* 2014;9: 1810–1815)

*Department of Medicine, Thoracic Oncology Service, Division of Solid Tumor Oncology, and Departments of †Epidemiology and Biostatistics, ‡Radiology, §Surgery, ‖Radiation Oncology, ¶Pathology, Memorial Sloan Kettering Cancer Center, New York, and Weill Cornell Medical College, New York, New York.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Gregory J. Riely, MD, PhD, Memorial Sloan Kettering Cancer Center, 300 East 66th New York, NY 10065. E-mail: rielyg@mskcc.org

DOI: 10.1097/JTO.0000000000000363

ISSN: 1556-0864/14/0912-1810

Thymic carcinomas are rare tumors, representing only 15% to 20% of all thymic neoplasms with fewer than 500 cases diagnosed in the United States per year.[1,2] As such, most of the literature on thymic carcinomas comes from retrospective reviews of surgical series, often from countries in Asia, where thymic carcinoma appears to be more prevalent.[3–16] Data is limited regarding the clinical characteristics and clinical behavior in a Western population, particularly in patients with advanced disease who are not surgical candidates.

Because of the rarity of the disease and absence of prospective data, there is no overall consensus about the ideal staging system for thymic carcinomas. The Masaoka staging system is widely used to stage thymomas as it can predict for overall survival (OS) in this disease. However, several groups have reported that similar results are not seen in thymic carcinomas.[6,13,15,17–19] These authors evaluated mostly small surgical series and showed that survival differences were observed only when comparing early versus advanced Masaoka stage or when other anatomical factors, such as involvement of the great vessels, were taken into account.[6,18–21] Ruffini et al.[22] recently showed good prognostic stratification among Masaoka staging, although stages I and II were again grouped together because of a similar survival. A tumor, node, metastasis (TNM) based staging system has been proposed for thymic carcinomas—however this staging system has thus far failed to show significant survival differences in several studies.[23,24]

In this study, we describe our experience in the management of 121 surgical and nonsurgical cases of thymic carcinomas evaluated at Memorial Sloan Kettering Cancer Center over a 20 year period. The aim of this study was to describe the clinical characteristics of patients with thymic carcinoma and to identify prognostic factors of survival. Based on a preview of our institutional experience, we hypothesized that the Masaoka staging system can effectively prognosticate overall and recurrence-free survival and that those patients with stage IVb lymph node only disease would have longer survival as compared with patients with distant metastasis.

PATIENTS AND METHODS

Patient Selection

We identified all consecutive patients diagnosed with thymic carcinoma between January 1, 1993 and December 31,

2012 at Memorial Sloan Kettering Cancer Center (MSKCC). Patients with thymomas, well differentiated thymic carcinomas (type B3 thymomas), thymic carcinoid tumors, or thymic small- or large-cell neuroendocrine carcinomas were excluded from this analysis. This cohort of patients includes the 23 patients described by Huang et al.[9] and Bott et al.[25] All pathology specimens were reviewed at MSKCC to confirm the diagnosis. Approval for this retrospective chart review was obtained from the institutional review board at MSKCC.

Data Collection

Patient characteristics and outcomes including age, race, sex, smoking history, evidence of paraneoplastic syndromes, stage, treatment details including use of chemotherapy, surgery, and/or radiation, recurrence data, and the last date of follow-up/date of death were abstracted from medical records manually and analyzed retrospectively. Preoperative imaging was regularly performed with a computed tomography scan of the chest, abdomen, and pelvis. The staging was characterized according to Masaoka staging.[26] Total thymectomy, with or without en bloc resection of adjacent structures performed through a median sternotomy, was the standard procedure for resection of thymic carcinoma during the study period. The lymph nodes were staged using N0 and N1 categories as extensive nodal dissections were not routinely performed in a systematic manner. Resection status was evaluated using operative and pathology reports. Resection status was characterized as R0 if all the margins were microscopically negative, R1 if the margins were microscopically positive, or R2 if grossly incomplete resection was performed. Follow-up status was obtained from institutional records and verified by the Social Security Death Index. Recurrence was defined as clinical appearance of new disease by imaging and/or pathology after curative intent resection. Type of recurrence, either local (mediastinal), intrathoracic (lung/pleura), or distal (extrathoracic) was recorded.

Statistical Analysis

Two endpoints were investigated: OS in the full cohort and time to recurrence in the subset of patients who had a curative intent surgery. Both the endpoints were estimated by the Kaplan-Meier method, and univariate associations between patient, disease or treatment factors and survival were analyzed using the log-rank test. OS was defined as the time from pathologic diagnosis until death by any cause. The time to recurrence was defined as the time from surgical resection until the date of imaging confirming recurrence of disease. In each analysis, patients who did not experience the event of interest during the study time were censored at the date of the last available follow-up. All statistical tests were two-sided and used a 5% significance level. Statistical analyses were performed using R (version 3.0.1; R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria), including the "survival" and "survcomp" packages.

RESULTS

Patient Characteristics

One hundred twenty-one patients were diagnosed with thymic carcinoma during the study period. Patient characteristics are summarized in Table 1. The majority of patients with thymic carcinoma presented with locally advanced (III, IVa) or metastatic disease at diagnosis, with squamous cell carcinoma as the most common histologic subtype. Three patients developed concurrent dermatomyositis and one patient developed limbic encephalitis with positive anti-voltage-gated potassium channel antibodies during their clinical course. Myasthenia gravis was not seen in any patients. On univariate analyses, age, sex, smoking history, and the presence of a paraneoplastic syndrome were not associated with OS.

OS by Stage

Stage at initial diagnosis was associated with OS ($p < 0.001$, Fig. 1). Five-year OS was 100%, 81%, 51%, 24%, and 17% for stage I, II, III, IVa, and IVb, respectively.

OS Based on Type of Resection

Of the 121 patients analyzed, 77 patients underwent resection with curative intent. Two patients had surgical

TABLE 1. Patient Demographics ($n = 121$)

Age at Diagnosis (years)	58 (12–84)
Women	52 (43%)
Race	
White	91 (75%)
Asian	14 (12%)
Black	11 (9%)
Hispanic	3 (2%)
Other	2 (2%)
Smoking status	
Never smokers	74 (61%)
Light smokers (≤15 pack years)	16 (13%)
Heavy smokers (>15 pack years)	31 (26%)
Masaoka stage at diagnosis	
Stage I	7 (6%)
Stage II	13 (11%)
Stage III	25 (21%)
Stage IVa	13 (11%)
Stage IVb	61(50%)
Undeterminate stage	2 (2%)
Paraneoplastic syndrome	
Dermatomyositis	3 (3%)
Anti-voltage-gated potassium channel antibodies	1 (1%)
Myasthenia gravis	0 (0%)
Histologic subtype	
Squamous cell carcinoma	65 (54%)
Undifferentiated carcinoma	32 (27%)
Lymphoepithelioma-like carcinoma	9 (7%)
Basaloid carcinoma	7 (6%)
Mucoepidermoid carcinoma	1 (1%)
Sarcomatoid carcinoma	1 (1%)
Clear cell carcinoma	2 (2%)
Carcinoma with neuroendocrine features	4 (3%)
C- kit mutation	3/19 (16%)

