Clinical Characteristics and Outcomes for Patients With Thymic Carcinoma

Evaluation of Masaoka Staging

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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)

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Disclosure: The authors declare no conflicts of interest.

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DOI: 10.1097/JTO.0000000000000363
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ISSN: 1556-0864/14/0912-1810
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 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 surgery, 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), intra-thoracic (lung/pleura), or distal (extrathoracic) was recorded.

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), intra-thoracic (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...
resections outside of MSKCC and the details of the resection could not be assessed. Complete tumor resection with pathologically confirmed negative resection margins (R0) was achieved in 35 (47%) patients. Twenty-two (29%) patients had microscopic residual disease (R1), and 18 (24%) patients had gross residual disease (R2). 48% of the patients with an R0 resection underwent adjuvant mediastinal radiation as compared with 94% and 88% for R1 and R2 resections, respectively. OS was significantly improved for patients who had a R0 or R1 resection versus a R2 resection ($p = 0.018$, Fig. 2). For R0, R1, and R2 resection, the 5-year OS was 60%, 49%, and 32%, respectively.

**OS Based on Distant Metastasis Versus Lymph Node Only Involvement**

Sixty-one patients were diagnosed with stage IVb disease at initial diagnosis. Twenty-nine patients had lymph node involvement without distant metastasis. Of the 29 patients, 14 patients had preoperative findings of enlarged lymph nodes by imaging and 15 patients were diagnosed with positive lymph nodes after pathology review of the resected specimen. Thirty-two patients had distant metastatic disease (69% had lung metastasis, 41% had bone metastasis, and 31% of the patients had liver metastasis involvement at presentation). Of the 61 patients with stage IVb disease, 22 of 29 patients (76%) with lymph node only involvement underwent resection as compared with 3 of 32 patients (9%) with distant metastasis ($p < 0.001$). Stage IVb patients with lymph node involvement had a better 5-year OS as compared with patients with distant metastasis (24% versus 7%, $p = 0.025$, Fig. 3).

**Management of Early Stage Disease.**

Our series included seven patients with stage I disease and 13 patients with stage II disease. All the patients with stage I and stage II disease were treated with resection. All the patients with stage I disease had an R0 resection as compared with 69% of the patients with stage II disease. None of the stage I patients received additional perioperative chemotherapy or radiation therapy. Nine of the 13 patients with stage II disease received adjuvant mediastinal radiation, including all patients with a R1 resection. Five-year OS was 100% and 81% for stage I and II disease, respectively.
Management of Locally Advanced, Resectable Disease and Role of Neoadjuvant Chemotherapy

We assessed outcomes in locally advanced disease, including all stage III patients and selected patients with stage IVa–IVb disease with intrathoracic involvement that were treated with curative intent resection. This included a total of 54 patients. Thirty-seven patients received neoadjuvant chemotherapy before surgery, whereas 17 patients received initial surgery. Of the 37 patients who received neoadjuvant chemotherapy, 39% of these patients had a R0 resection as compared with 21% of the patients with upfront surgery \((p = 0.095)\). Most neoadjuvant chemotherapy administered was platinum based.

Management of Unresectable Locally Advanced or Metastatic Disease

Forty-four patients including four patients with stage III disease, three patients with stage IVa disease, and 37 patients with stage IVb disease were felt to be unresectable. Of these 44 patients, 13 received chemoradiation, 20 received palliative chemotherapy, two received palliative radiation and nine were lost to follow-up and/or received no further treatment. The median OS for these patients was 19 months (95% confidence interval [CI], 15–31).

Recurrence

Of the 74 evaluable patients who had potentially curative resection and recurrence data available, 40 patients (53%) had recurrence or disease progression. The stage at initial diagnosis was significantly associated with the rate of recurrence \((p < 0.001\), Fig. 4). Four of the 20 patients (20%) with initial stage I/II disease recurred as compared with 36 of the 54 patients (67%) with locally advanced disease (stage III, IVa, or IVb disease). The median time to recurrence was 11 months (range, 2–108 months). In the mediastinum 13% of the patients recurred, 48% of the patients recurred in the thorax (pleura and lung), and 39% recurred distally. The distant sites included lung, bone, and liver. Brain metastases were identified in two patients.

Multimodality Therapy in Stage IVb Disease with Lymph Node Involvement

Twenty-two patients with stage IVb disease received multimodal therapy including curative-intent resection, mediastinal radiation, and/or chemotherapy. Thirteen of these 22 patients received neoadjuvant chemotherapy with postoperative mediastinal radiation, six received adjuvant chemotherapy and postoperative mediastinal radiation, and three patients received postoperative mediastinal radiation without chemotherapy. Of these patients, 3 of 22 (14%) are currently free of disease with long-term follow-up (Table 2). One patient had a local recurrence 16 months after definitive resection, had the recurrence resected, and has been free of disease for over 4.9 years.

DISCUSSION

Our study represents one of the largest reported series of patients with localized and advanced, unresectable disease treated in North America. The results of our study indicate several important findings: (1) The Masaoka staging system predicts likelihood of overall and recurrence-free survival; (2) patients with stage IVb lymph node-only disease have a better OS as compared with patients with distant metastasis; and (3) for a subset of patients with stage IVb lymph node only disease, treatment with multimodality therapy including surgery, chemotherapy, and radiation can result in a long-term recurrence-free survival. These data should prompt consideration of a revised Masaoka staging system with subclassification of stage IVb disease into two groups if supported by data in the International Thymic Malignancies Interest Group staging database.

For patients who undergo surgical resection, our data support the importance of an R0 resection. Specifically, we showed that a R0 or R1 resection is associated with improved OS, as compared with an R2 debulking procedure. The similar survival curves for R0 and R1 resections could be explained...
by the fact that most patients with a R1 resection received adjuvant radiation therapy.

For patients with advanced disease, a multidisciplinary approach, including the collaboration of radiation oncologists, medical oncologists, oncologic surgeons, pathologists, and radiologists may be considered in the comprehensive management of these complicated patients. We showed that platinum-based neoadjuvant chemotherapy can potentially improve the rates of R0 resection, although a randomized clinical trial would need to be performed to confirm these results.

Finally, our results demonstrate that myasthenia gravis is an incredibly rare event in thymic carcinoma. Although myasthenia gravis is diagnosed in up to 50% of the patients with thymomas, this autoimmune paraneoplastic disorder was not detected in any of the 121 patients with thymic carcinomas evaluated. Others report that patients with thymic carcinoma can present with myasthenia gravis. However, we believe that when this autoimmune phenomenon is present, the diagnosis of thymic carcinoma needs to be reconfirmed and thymoma ruled out.

Our study has several strengths and limitations. The main strength of this study is that it represents one of the largest series of patients with localized and advanced, unresectable disease treated in North America. Furthermore, all biopsies and surgical specimens obtained were reviewed by expert pathologists in one center. It is well known that there is significant interobserver variation in the classification of thymic tumors making central pathology review essential for accuracy. In addition, patients with thymomas and well differentiated thymic carcinomas (B3 thymomas) were excluded from the analysis. Many studies have grouped thymic carcinomas and thymomas in the same analysis based on past histologic classifications. However, the latest World Health Organization histologic classification observes that thymic carcinomas are a distinct group of thymic malignancies and recommends that they be analyzed separately.

Finally, as data was collected from one center, information regarding clinical characteristics, recurrences, resection status, and chemotherapy responses were readily available for most patients. As with previously reported reviews of thymic carcinoma, our study is limited by the retrospective nature of the data collection and heterogeneity of treatments. Furthermore, our median follow-up time was 24 months, and a longer follow-up may provide more data regarding late recurrences.

In conclusion, our results demonstrate that the Masaoka staging system can prognosticate overall and recurrence-free

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Pack (years)</th>
<th>Race</th>
<th>Histology Type</th>
<th>Masaoka Stage at Diagnosis</th>
<th>Treatment</th>
<th>Areas of Metastasis</th>
<th>Recurrence</th>
<th>Disease-Free Survival since resection</th>
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<tr>
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<td>F</td>
<td>12</td>
<td>Asian</td>
<td>Squamous</td>
<td>IVb</td>
<td>Resection/XRT/neoadjuvant chemotherapy</td>
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<td>No</td>
<td>6.8 years+</td>
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<td>0.6</td>
<td>White</td>
<td>Lympho-epithelioma-like carcinoma</td>
<td>IVb</td>
<td>Resection/XRT/neoadjuvant chemotherapy</td>
<td>Lymph node (no visceral metastasis)</td>
<td>No</td>
<td>3.4 years+</td>
</tr>
<tr>
<td>3</td>
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<td>M</td>
<td>0</td>
<td>White</td>
<td>Lympho-epithelioma-like carcinoma</td>
<td>IVb</td>
<td>Resection/XRT/neoadjuvant chemotherapy</td>
<td>Lymph node (no visceral metastasis)</td>
<td>Yes: local recurrence to mediastinum. Pt treated with resection.</td>
<td>4.9 years+</td>
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survival. Our data suggests that patients with stage IVb lymph node disease may have a better OS as compared with patients with distant metastasis and can achieve long-term disease-free survival with multimodality therapy. The rates of recurrence are high at all stages of the disease, with distant disease in the liver, bone, and lungs usually seen. Thus, prospective trials and collaborative efforts are necessary in the future to evaluate and compare therapies to improve outcomes in this rare disease.

ACKNOWLEDGMENTS

This study was supported by Biostatistics Core grant (P30 CA08748).

REFERENCES