Thymomas II

A Clinicopathologic Correlation of 250 Cases With a Proposed Staging System With Emphasis on Pathologic Assessment

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Key Words: Thymoma; Thymus; Staging; Thorax

Abstract

We present 250 cases of thymomas with emphasis on their clinical staging and follow-up. The patients were 120 males and 130 females between the ages of 13 and 92 years. Surgical resection was performed and histopathologic material evaluated in every case. Grossly, the tumors resected varied in size from 3 to 20 cm in greatest diameter. According to our proposed staging system, 31 cases were stage 0, 128 were stage I, 70 stage II, and 21 stage III at the time of resection. Histologically, approximately 53% of thymomas were of mixed histologic types. Follow-up information ranging from 1 to 16 years was obtained, showing significant statistical P values of .044 and .016 for overall and recurrence-free survival, respectively. We consider that our proposed staging system offers better stratification of cases and improved histologic definitions for proper staging of cases of thymoma.

During the last decade, the subject of thymic epithelial neoplasms, mainly thymomas, has become a topic of interest in terms of histopathologic diagnosis, treatment, and prognosis. One important topic that has generated great controversy has been the histopathologic assessment of these tumors, with some proponents believing that histologic typing has a central role in a patient’s prognosis and others believing that proper staging is of utmost importance. Some of these issues have been presented in the literature.1-9

In contrast, one of the most overlooked topics during the last decades has been the necessity to reevaluate the staging of thymomas. Even though there have been several proposals,10-15 some of these schemas have been modifications to the Masaoka staging system of 1981.11 As much more knowledge regarding thymomas has been gained during these last decades, the need for a more critical and modern appraisal of thymoma staging is long overdue. Therefore, the study herein presented attempts to propose a novel staging system for these tumors that can be translated into better stratification for patients who may need additional treatment.

Materials and Methods

We identified 250 cases of thymomas from the files of the Department of Pathology, M.D. Anderson Cancer Center, Houston, TX, during a period from 1980 to 2009.

Materials

Specific requirements were established for inclusion: (1) histopathologic evaluation in every case; (2) a minimum requirement of 5 sections of tumor for histologic evaluation and proper subclassification of the tumor; and (3) surgical resection (biopsy material not included in this study).
The number of histologic sections in the evaluation of these tumors varied from 5 to 30 per case. Even though immunohistochemical stains were available in some cases, they were evaluated only in the context of their use for diagnostic purposes. The clinical records of each patient were reviewed and entered in a data bank for further analysis.

Methods

A clinical staging scheme was discussed between surgeons and pathologists with the development of the following:

- Stage 0: All encapsulated thymomas without macroscopic or microscopic evidence of invasion
  - Image 1.
- Stage I: Invasive thymomas, histologically proven, in which the invasion is into the perithymic adipose tissue
  - Image 2.
- Stage II: Direct invasion Image 3, Image 4, and Image 5.
  - A. Invasive thymoma:
    - Innominate vein
    - Mediastinal pleura
    - Lung
  - B. Invasive thymoma:
    - Pericardium
  - C. Invasive thymoma:
    - Great vessels (aorta, superior vena cava)
    - Heart
- Stage III: Metastatic disease Image 6.
  - A. Intrathoracic structures:
    - Diaphragm (so-called drop metastases)
    - Lymph nodes
  - B. Extrathoracic

Definitions

Stage 0: Encapsulated thymoma in which the tumor is confined within a fibroconnective tissue “capsule.” The capsular integrity is preserved. In some cases, one can observe the presence of tumor within the capsule, but the tumor does not breach the fibroconnective tissue capsule. Thus, these cases also fall into the category of encapsulated thymomas (noninvasive tumor), or stage 0 (Image 1).

Stage I: The tumor has breached the fibroconnective tissue capsule (the capsular integrity is not preserved). Thus, the tumor penetrates into perithymic adipose tissue but does not involve any neighboring anatomic structures such as pleura, pericardium, or great vessels (Image 2).

Stage II includes 3 stratifications.

IIA: Tumors that involve innominate vein, pleura, or lung parenchyma. The identification of the innominate vein may not be apparent and requires that the surgeon, at the time of the resection, provide a mark for that structure. Once the vessel is identified, the tumor may be found wrapping the wall of the vessel or within the vessel itself. Regarding lung, the tumor must involve alveolated lung parenchyma (Image 3A). On the other hand, the issue of pleural involvement is the one that may pose more difficulties for pathologists assessing involvement of tumor. We consider pleural involvement when the submesothelial fibrous layer is involved. This particular feature is illustrated in Image 7 (Image 4A).

IIB: Tumor involving pericardium. Similar to pleural involvement, the issue of pericardial involvement may pose difficulties for pathologists attempting to demonstrate invasion in the pericardium. The involvement of the submesothelial fibrous layer should be considered positive involvement (Image 7). However, in some unusual cases, this issue may

Image 1 A, Schematic presentation of thymoma, stage 0 (encapsulated tumor). B, Histologic features of a well-encapsulated thymoma. Note the dense fibroconnective tissue separating the tumor from adipose tissue (H&E, ×10).
A, Schematic presentation of invasive thymoma, stage I (invasion into perithymic adipose tissue). Histologic features of an invasive thymoma, stage I. B, The tumor has breached the capsule (H&E, ×10). C, The tumor is into perithymic adipose tissue (H&E, ×10).

Image 3 A. Schematic presentation of invasive thymoma, stage IIA (continuous invasion into mediastinal pleura, lung, and/or innominate vein). B, Histologic features of invasive thymoma involving lung parenchyma (H&E, ×20).
not be a problem, as the tumor may be present in the mediastinal aspect and in the cardiac aspect of the pericardium, as illustrated in Image 4.

IIC: Invasion of great vessels and heart may not be as problematic owing to the size of both structures. The tumor may involve any large vessels by continuity into the wall of the vessel (Image 5), or the tumor may penetrate directly into the vessel. Also, the tumor may directly extend into the heart muscle.

Stage III includes 2 stratifications.

IIIA: Contrary to the direct extension of the tumor present in stages I and II, the tumor may invade the diaphragm not by direct extension. This is the so-called drop metastasis, and the tumors should involve skeletal muscle (Image 6).

IIIB: The tumor extends below the diaphragm or above the thoracic inlet. Tumor involvement of any structure beyond those confines is considered stage IIIB.

Statistical Analysis

This analysis was performed by using Statistica software, version 6 (StatSoft, Tulsa, OK). The Fisher exact test and survival analysis were performed using the Kaplan-Meier method. Statistical significance was defined as a $P$ value of less than .05.
Results

Clinical Features

Our patient population included 120 males and 130 females between the ages of 13 and 92 years, with the great majority of cases occurring in the fifth, sixth, and seventh decades of life. The patients had diverse symptoms including chest pain, cough, and dyspnea. None of the patients had a history of myasthenia gravis. Of the patients, 6 had a history of malignancy: breast carcinoma, 2; prostatic carcinoma, 1; colonic adenocarcinoma, 2; and papillary thyroid carcinoma, 1. All patients underwent surgical resection of the mediastinal mass. Some of the most relevant clinical features and their statistical significance are given in Table 1. The median age was estimated at 57 years, and, when compared with the total number of cases, a significant P value was obtained (P < .0001). However, sex was not found to show statistical significance (P < .4954).

Pathologic Features

Grossly, tumor sizes varied from 3 to 20 cm in greatest diameter, with about 80% of the tumors 5 cm or more, with a median size of 7 cm. Tumor size, however, did not correlate with any particular stage. A nonsignificant statistical P value of .0702 was obtained (Table 1). Histologically, the tumors were divided according to their morphologic features following the grouping proposed by the World Health Organization. Type A thymoma represented 21.6% of the cases (54 cases), while thymomas B1, B2, and B3 represented 13.2%, 3.2%, and 9.2%, respectively. Approximately 53% of the tumors showed different morphologic growth patterns with combinations of types A, B1, B2, and B3. In addition, no statistically significant value was obtained by correlating histologic type with invasive or encapsulated tumors (P = .4074; Table 1). Table 2 depicts all histologic growth patterns that may be seen in thymomas in relation to the proposed staging system. These results support the concept that histologic type alone is not a predictor of clinical behavior.

Staging

At the time of diagnosis, according to our proposed staging system, 31 thymomas were stage 0 (encapsulated tumors), and 219 thymomas were invasive. Of the invasive
thymomas, 128 tumors were stage I, 70 stage II (54, IIA; 14, IIB; 2, IIC), and 21 stage III (19, IIIA; 2, IIIB). By stratifying cases in these staging categories, we were able to obtain statistically significant overall survival curves with a $P$ value of .044 [Figure 1], while the recurrence-free survival $P$ value was .015 [Figure 2]. Although we further stratified cases in stage II into A, B, and C, we did not obtain any statistically significant values among these categories. Similarly, we were not able to obtain a statistically significant $P$ value between stage IIIA and IIIB. This latter issue may have been due to the lower number of cases among those categories. It is important to highlight that the overall survival and recurrence, based on our statistical analysis, are determined by the extent of infiltration. Patients with tumors with limited disease to the mediastinum (stages 0 and I) definitely fare much better than patients with tumors invading neighboring organs (stages II and III). Table 3 depicts the recurrence rate of these tumors with our proposed staging system and highlights that once the tumor invades adjacent structures, the chances of recurrence are higher than with tumors limited to the thymus. Also important to note is that once the tumor invades adjacent mediastinal structures, regardless of the structure affected, it is more likely that overall survival will be affected, as will
appropriate subclassifications but also in addressing the staging of these tumors. Owing to their rarity, it is difficult to accumulate enough cases to properly address the important issues that may provide meaningful insights into these problems, as most studies have found a lack of statistical correlation in sex, age, clinical manifestations, size of tumor, and even the association of myasthenia gravis with the prognosis of thymomas.16-29

The 2 most important parameters that have been mentioned in the literature in the prognosis of thymomas are staging and histologic typing. Several attempts at staging have been presented in the literature, with one of the earliest by Bergh et al.10 who studied 43 cases and staged them in three categories: stage I, intact capsule or growth within the capsule; stage II, pericapsular growth into the mediastinal fat tissue; and stage III, invasive growth into the surrounding organs, intrathoracic metastases, or both. Clinical follow-up information that was provided showed that not one of the patients with tumors in stages I and II had a fatal outcome.

Discussion

Thymomas represent a morphologically heterogeneous group of tumors, which, throughout their history, have remained difficult to categorize by conventional histologic findings. Confusion continues to exist about the value of histopathologic subclassification of these tumors in relation to their clinical behavior. It is worth mentioning that the issue of finding prognostic factors in thymomas is nothing new, as several parameters have been presented in the literature as possible predictors of clinical behavior, including histologic typing, grading, and staging. Currently, with the advancement in different treatment protocols, there is considerable interest not only in refining the diagnosis of thymomas with appropriate subclassifications but also in addressing the staging of these tumors. Owing to their rarity, it is difficult to accumulate enough cases to properly address the important issues that may provide meaningful insights into these problems, as most studies have found a lack of statistical correlation in sex, age, clinical manifestations, size of tumor, and even the association of myasthenia gravis with the prognosis of thymomas.16-29

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In 1981, Masaoka et al11 presented a novel staging system based on the study of 96 cases. In this study, the authors

**Table 3**

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Cases</th>
<th>No. (%) of Recurrences</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30</td>
<td>0 (0)</td>
<td>Alive 1-10 y; mean 3.49 y</td>
</tr>
<tr>
<td>I</td>
<td>115</td>
<td>7 (6.1)</td>
<td>Alive 1-16 y; mean 3.49 y</td>
</tr>
<tr>
<td>II</td>
<td>66</td>
<td>15 (22.7)</td>
<td>Alive 1-16 y; mean 3.49 y</td>
</tr>
<tr>
<td>III</td>
<td>20</td>
<td>4 (20)</td>
<td>9 died, 1-12 y; mean 3.49 y</td>
</tr>
</tbody>
</table>

**Figure 1** Prognosis analyzed by proposed stages 0-I vs II-III. Overall survival curve showing a statistically significant difference ($P = .044$) Kaplan-Meier analysis; cumulative proportion surviving, $n = 231$.

**Figure 2** Recurrence-free survival curve showing a statistically significant difference ($P = .016$). Kaplan-Meier analysis; cumulative proportion surviving, $n = 231$. 

**Figure 3** Clinical Follow-up of Patients With Recurrent Thymoma and Our Proposed Staging System

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Moran et al / Staging of Thymomas

Table 4
Comparison of Staging Systems

<table>
<thead>
<tr>
<th>Stage</th>
<th>Bergh et al10</th>
<th>Masaoka et al11</th>
<th>Koga et al14</th>
<th>Curran et al12</th>
<th>GETT13</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Intact capsule or growth within the capsule</td>
<td>Macroscopically completely encapsulated and microscopically no capsular invasion</td>
<td>Grossly and microscopically completely encapsulated</td>
<td>Macroscopic complete encapsulation; microscopic invasion into, but not through the capsule</td>
<td>A. Encapsulated, noninvasive; total excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B. Localized invasion to mediastinal structures; total excision</td>
</tr>
<tr>
<td>II</td>
<td>Pericapsular growth into mediastinal fat tissue</td>
<td>1. Macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or 2. Microscopic invasion into capsule</td>
<td>1. Microscopic transcapsular invasion 2. Macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent to but not breaking through mediastinal pleura or pericardium</td>
<td>Macroscopic invasion into surrounding fatty tissues or mediastinal pleura or microscopic invasion through the capsule</td>
<td>A. Invasive growth into surrounding organs; total excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B. Invasive growth into surrounding organs; biopsy of the tumor</td>
</tr>
<tr>
<td>III</td>
<td>Invasive growth into the surrounding organs, intrathoracic metastases, or both</td>
<td>Macroscopic invasion into neighboring organ, ie, pericardium, great vessels, or lung</td>
<td>Macroscopic invasion of neighboring organ, ie, pericardium, great vessel, or lung</td>
<td>Macroscopic invasion into neighboring structure, ie, pericardium, great vessels, or lung</td>
<td>A. Invasive growth into surrounding organs; incomplete excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B. Invasive growth into surrounding organs; biopsy of the tumor</td>
</tr>
<tr>
<td>IV</td>
<td>—</td>
<td>A. Pleural or pericardial dissemination B. Lymphogenous or hematogenous metastasis</td>
<td>A. Pleural or pericardial dissemination B. Lymphatic or hematogenous metastasis</td>
<td>Pleural or pericardial dissemination or metastases</td>
<td>A. Largely invading tumor cells with clavicular lymph nodes or pleural or pulmonary grafts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B. Hematogenous metastasis (≥1)</td>
</tr>
</tbody>
</table>

GETT, French Groupe d’Etudes des Tumeurs Thymiques.

Separated cases into 4 stages depending on macroscopic and microscopic evaluation. Stage I included the encapsulated thymoma, and stage IVB, tumors with hematogenous metastases. However, on critical review of the definitions of these stages, one can find that stage II-1, defined as macroscopic invasion into surrounding fatty tissue or mediastinal pleura, may not be so simple to address, as some cases of invasive thymoma can breach the capsule only focally, a feature that may not be so readily appreciated on macroscopic examination. On the other hand, stage II-2 was defined as microscopic invasion into the capsule. That feature, for most pathologists, is not a feature of invasive tumors, which requires the presence of a tumor breaching the capsule, or, in other words, “the capsular integrity is violated.” Histologic evidence of “invasion into the capsule” should not be considered a feature of invasive thymoma. In addition, stage III was defined as macroscopic invasion into neighboring organs, ie, pericardium, great vessels, or lung, and stage IVA was defined as pleural or pericardial dissemination. The line separating those 2 definitions is, at best, ambiguous, as a tumor can infiltrate the pericardium and pleura and can be placed in either of those stages. Nevertheless, the authors provided a survival rate that ranged from 92% for stage I to 50% for stage IV at 5 years.

In 1994, Koga et al14 modified the Masaoka staging system mainly by adding more appropriate definitions, such as for stage II-1, “microscopic transcapsular invasion,” but overall kept the same approach of macroscopic and microscopic evaluation. Two additional proposals are worth mentioning, even though they represent modifications to the Masaoka staging system. Curran et al12 in 1988 presented a study of 117 cases that were stratified into 4 stages: stage I for encapsulated tumors, stage II for invasive tumors into the perithymic adipose tissue, stage III for invasion into adjacent organs, and stage IV for thoracic dissemination of the tumor or metastases. Gamondes et al13 reported 65 cases staged in 4 similar categories: I, encapsulated tumor or tumors with local invasion; II, invasive tumors into surrounding organs; III, differs from stage II in terms of complete vs incomplete excision; and IV, tumor with hematogenous metastases or tumor invading lymph nodes, pleura, or lung. In a different approach, Yamakawa et al15 using the TNM classification for thymoma, found that in a study of 207 cases of thymoma, only 7 had metastatic disease in lymph nodes, thus making such an approach impractical.
Currently, the Masaoka staging system modified by Koga et al\textsuperscript{14} seems to be the most commonly used as a predictor of clinical behavior. In that regard, it is important to evaluate previous studies in which reasonably large numbers of cases have been reported and in which the Masaoka staging or the other modified systems have been used. There were about 13 studies of thymomas \textbf{Table 5} in a period of 23 years (1973-1996) in which similar general information was provided and the clinical behavior of approximately 1,900 cases was reported. As a group, the survival rates at 5, 10, and 15 years were approximately 75%, 60%, and 47%, respectively. However, when taken in isolation, the survival rates in cases of encapsulated tumors improved to 83%, 75%, and 50%, respectively, while the survival rates in cases of invasive tumors were 49%, 30%, and 12%, respectively.

It is interesting that when stages I and II of the Masaoka system are compared, survival does not seem to be dramatically different when compared with stages III and IV. In these 13 studies with 1,921 total cases, if one isolates Masaoka stages I and II the percentage of cases is approximately 52% with a recurrence rate varying from 0% to 7% and with an approximate survival of 83% at 10 years. In our proposed scheme, we found that the recurrence rate for stage I was approximately 6%. However, the recurrence for other stages was more than 20%. Similar conclusions were drawn by Gupta et al,\textsuperscript{30} who reported a meta-analysis of thymomas and stated that transcapsular invasion is not a significant prognostic factor because they found no significant difference in disease-free survival for patients with stages I and II tumors. Based on this collective evidence, it is clear that there is a need to reevaluate the current staging system, which may not provide the information required for today’s treatment protocols.

The study herein presented conceptualizes a different staging schema in which the encapsulated tumor represents what in other anatomic areas is considered in situ malignancy or premalignant neoplasm but in which, after complete surgical resection, the possibilities of recurrence or metastases are limited and one that most likely can be controlled by complete surgical resection alone, thus the concept of stage 0. However, it is important to recognize that the occurrence of recurrent tumors that are otherwise encapsulated has been recorded in the literature.\textsuperscript{31} In our proposed staging \textbf{Table 6} (comparison with Masaoka system), only invasive tumors are assigned a staging number as the tumor invades the different anatomic compartments.

Also worth highlighting in our staging system is the possible stratification for patients who may benefit from additional therapy vs patients in whom complete surgical resection may be the treatment of choice (stages 0 and I). We also found no significant difference by comparing stages 0 and I in our proposed scheme. However, when we compared stages 0 and I with stages II and III, we observed differences that were statistically significant. Even though we provide stratification for stage II, depending on the different thoracic structures that may be involved, we were not able to establish any significant statistical differences in stages IIA, IIB, and IIC. However, we consider that such stratification is important for the possibility of additional therapy. Perhaps with a larger number of cases in these different stage groups, one may be able to determine more important differences. Furthermore, we consider that our staging system should be easy to follow not only for pathologists but also for surgeons and oncologists because the definitions are clear and reproducible.

One important pathologic aspect that we encountered in our cases was the fact that in 80% of our cases the tumor was 5 cm or larger with a median size of 7 cm. Nevertheless, we were not able to establish any statistically significant difference by comparing size and stage of the disease. However, it

\textbf{Table 5}

\begin{tabular}{lllll}
Reference & No. of Cases & Masaoka Stage I & Recurrence & Follow-up \\
& & (Some Stage II) & & \\
Gamondes et al\textsuperscript{13} & 65 & 38 & NA & A/W, 96%; 5 y \\
Bernatz et al\textsuperscript{16} & 181 & 66 & NA & A/W, 47%; 15 y \\
Verley and Hollman\textsuperscript{17} & 200 & 133 & NA & A/W, 80%; 10 y \\
Lewis et al\textsuperscript{18} & 283 & 47 & 4 & A/W, 67%; 5 y \\
Nahahara et al\textsuperscript{19} & 141 & 78 & NA & A/W, 97%; 5 y \\
Pescarmona et al\textsuperscript{20} & 83 & 49 & NA & A/W, 100%; 5 y \\
Witkins et al\textsuperscript{22} & 89 & 68 & NA & A/W, 75%; 10 y \\
Pan et al\textsuperscript{24} & 112 & 73 & NA & A/W, 90%; 5 y \\
Blumberg et al\textsuperscript{25} & 118 & 25 & 4% & A/W, 95%; 5 y \\
Regnard et al\textsuperscript{26} & 307 & 205 & 3%-7% & A/W, 75%; 10 y \\
Quintanilla-Martinez et al\textsuperscript{27} & 116 & 84 & 4 & A/W, 95%; 5 y \\
Salyer and Eggleston\textsuperscript{29} & 65 & 37 & NA & A/W, 85%; 5 y \\
Maggi et al\textsuperscript{21} & 165 & 106 & NA & A/W, 85%; 5 y \\
Total & 1,921 & 1,009 (52.5%) & 0%-7% & A/W, 83%; 10 y (average) \\
\end{tabular}

A/W, alive and well; NA, not available.
would be logical to suggest that larger tumors are most likely to belong in advanced stages. This should not be surprising, as one can conceptualize that the larger the tumor, the more likely it is to compromise adjacent structures.

In short, we have presented a new, practical, and reproducible staging system for thymomas, which we consider can be easily translated into clinical practice not only by pathologists but also by oncologists, surgeons, and interventional radiation oncologists. This stratification of cases should provide the most important information that is needed to pursue, if clinically indicated, additional therapy for the patients.

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