THYMOMA: An Update

Cesar A. Moran, MD

Thymoma

• The most common epithelial tumor of the anterior mediastinum. However, the tumor in general practice is rare.
• The classification of these tumors over the years has been controversial.
• Numerous nomenclatures or schemas have been postulated without general agreement.

Thymoma

– Important Issues
– Classification
– Sampling
– Staging

– What is the role of molecular biology?
Classifications

- ...no attempt is made in this fascicle to give special name to any particular variant.
  - Dr. Clastleman 1955

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..."A review of cases of thymoma in preparation for this fascicle strengthened our previous belief that once the term thymoma is restricted to the tumor of epithelial thymic cells, all further subdivisions are artificial. We have found that all the morphologic criteria that have been used for this purpose, such as the shape of the nucleus, the relative number of lymphocytes, etc., exhibit such a continuous range within thymomas as to prevent any rigid separation based on these criteria"......

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Bernatz et al (Mayo Clinic) 1961

- Lymphocyte-rich thymoma
- Mixed (lymphoepithelial) thymoma
- Epithelial-rich thymoma
- Spindle cell thymoma

Survival Curves by Histology and Status of Capsular Integrity (Bernatz et al; Surg Clin NA, 1973)

Levine & Rosai Classification

- Thymoma, encapsulated (benign)
- Thymoma, invasive (malignant):
  - Malignant thymoma type I
  - Malignant thymoma type II (thymic carcinoma)

Marino and Muller-Hermelink (1985) “Histogenetic” Classification

• Cortical thymoma
• Medullary thymoma
• Mixed thymoma

New Approaches to the Diagnosis of Thymic Epithelial Tumors

Thomas Kirchner
Hans Konrad Muller-Hermelink


"Using specific mAbs, specific immunophenotypes of the different histological tumor types cannot be defined. Therefore, presence or absence of reactivity with one of these mAbs does not allow a clear immunohistochemical differentiation between the different tumor types. Furthermore, the immunophenotype of the epithelial neoplastic cells cannot be strictly correlated to the immunophenotype of different epithelial cells in the normal thymus" (pp.177-178).

CIRCA 1990....

• Lymphocyte-rich
• Lymphoepithelial
• Spindle cell
• Epithelial-rich
• Invasive thymoma
• Malignant thymoma type-I
• Malignant thymoma type-II
• Thymic carcinoma
• Polygonal cell thymoma
• Differentiated thymoma
• Undifferentiated thymoma
• Cortical thymoma
• Predominantly cortical
• Organoid thymoma
• Medullary thymoma
• Well-differentiated thymic carcinoma

• Predominantly cortical
• Organoid thymoma
• Medullary thymoma
• Well-differentiated thymic carcinoma
WHO Panel, 1999

- Juan Rosai - Chairman
- Boris Elsner
- Frantisek Havlicek
- Tseng-tong Kuo
- Cesar Moran
- Kiyoshi Mukai
- H.K. Muller-Hermelink
- Giorgio Palestro
- Robert Rouse
- Mark Wick

"...the terminology chosen here is a non-committal one based on a combination of letters and numbers. It is not proposed as a new classification, but mainly to facilitate comparison among the many terms and classification schemes that have been offered over the years"...

J. Rosai – WHO Histological Typing of Tumors of the Thymus
Springer-Verlag, 1999; pp.3-4.


- No haeimogenic basis has yet been conclusively demonstrated between the normal compartments of the thymus and the various histologic variants of thymoma
- Thymic epithelial neoplasms are part of a spectrum of lesions that range from benign to malignant
- Degree of invasiveness relates more closely to clinical outcome than cytoarchitectural features, to the point of markedly reducing the independent prognostic value of the latter
WHO Schema for the Classification of Thymoma, 1999

- Type A: thymomas composed of spindle cells
- Type B: thymomas composed of round cells*
- Type AB: mixture of the above
- Type C: cytologically malignant thymoma

*B 1-2-3: refers to the progressive loss of the lymphocytic component

Comparison of WHO Schema with Traditional and Muller-Hermelink

<table>
<thead>
<tr>
<th>WHO</th>
<th>Traditional (Bernatz)</th>
<th>Histogenetic (M-H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Spindle cell</td>
<td>Medullary</td>
</tr>
<tr>
<td>AB</td>
<td>----</td>
<td>Mixed</td>
</tr>
<tr>
<td>B1</td>
<td>Lymphocytic</td>
<td>Organoid/Cortical</td>
</tr>
<tr>
<td>B2</td>
<td>Lymphoepithelial</td>
<td>Cortical</td>
</tr>
<tr>
<td>B3</td>
<td>Epithelial</td>
<td>Well-differentiated thymic carcinoma</td>
</tr>
<tr>
<td>C</td>
<td>Thymic carcinoma</td>
<td>Other thymic carcinomas</td>
</tr>
</tbody>
</table>
Issues with WHO Schema, 1999

- Only two classifications were considered out of more than 8 existing schemas.
- Sampling was never discussed.
- As the schema is presented, it appears that thymomas are homogenous tumors.
- Because it was never intended as a "classification system" there was no need of validation and reproducibility.
PROGRESS

Bernat: cell shape & proportion of lymphocytes 1961
Levine & Rosai: benign vs. malignant 1976
Muller-Hermelink: Histogenesis 1985

WHO: cell shape & proportion of lymphocytes 1999

A study of 630 cases showed that a cutoff of 5 sections of tumor provided a significant difference in sub-typing thymomas, contrary to the use of only biopsy material.
AJCP 2000; 114:760.
Classification of Thymic Epithelial Neoplasms - WHO 2004

- Thymoma type A
- Thymoma type AB
- Thymoma type B (1-2-3)
- Metaplastic thymoma
- Micronodular thymoma
- Sclerosing thymoma
- Micronodular thymoma
- Microscopic thymoma
- Thymic carcinoma

WHO Grading of Malignancy

- Type A: benign
- Type AB: benign
- Type B1: low-grade malignancy (10 yr. survival >90%)
- Type B2: "greater degree of malignancy"
- Type B3: (in advanced stages) poor prognosis equivalent to thymic carcinoma

In this study of 218 patients, survival curves for WHO types A, AB, B1 and B2 showed great overlap without any significant differences. Further simplification of both the WHO and traditional classifications into only 3 subgroups led to classes with good discriminatory power in respect to survival. In addition, very good inter-observer agreement was found in the simplified classification.

In comparison with the carcinoma group, the other subtypes showed nearly identical prognosis for survival. We therefore introduced 3 subgroups. By this simplification, subgroups with distinct survival could be identified. Therefore, our results are in favor of classifications that permit accurate allocation of these neoplasms to simple and reproducible diagnostic categories, as proposed by Suster & Moran.

**Thymoma, Atypical Thymoma, and Thymic Carcinoma**
A Novel Conceptual Approach to the Classification of Thymic Epithelial Neoplasms
Saul Suster, MD,* and Caesar A. Moran, MD†

**Key Words:** Thymoma, atypical thymoma, thymic carcinoid, thymic neoplasms, stromal tumors, B-cell lymphomas

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**Survival Curves in 218 Thymoma Patients Utilizing a 3-Tiered System**

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**WHO Grading of Malignancy**

- Type A: benign
- Type A8: benign
- Type B1: low-grade malignancy (10 yr. survival >90%)
- Type B2: "greater degree of malignancy"
- Type B3: (in advanced stages) poor prognosis equivalent to thymic carcinoma
41 cases out of 230 invasive thymomas (18%). Only cases with 5 or more sections of tumor were included.

AJCP 2010; 134:793.
### Sub-typing of Thymomas

**Thymomas**

A Clinicopathologic Correlation of 250 Cases With Emphasis on the World Health Organization Schema

Cesar A. Moran, MD,1 Avantika Wosnjerc, MD,1 Nicole Koller, MD,1 Laura M. Schu, MD,1 Carmen Behrens, MD,1 Ivan F. Witschi, MD,1 and Saul Suster, MD2

Key Words: Operable; Thymoma; histologic, Tumor, Thymus

AJCP 2012; 137:444

#### SUB-TYPING

<table>
<thead>
<tr>
<th>THYMOMA HISTOLOGIC TYPE</th>
<th>N (n=250)</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>54</td>
<td>21.6%</td>
</tr>
<tr>
<td>Type AB</td>
<td>38</td>
<td>15.2%</td>
</tr>
<tr>
<td>A+B1</td>
<td>24</td>
<td>9.6%</td>
</tr>
<tr>
<td>A+B1+B2</td>
<td>6</td>
<td>2.4%</td>
</tr>
<tr>
<td>A+B2</td>
<td>6</td>
<td>2.4%</td>
</tr>
<tr>
<td>A+B3</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td>A+B1+B2+B3</td>
<td>6</td>
<td>2.4%</td>
</tr>
<tr>
<td>Type B</td>
<td>158</td>
<td>63.2%</td>
</tr>
<tr>
<td>B1</td>
<td>33</td>
<td>13.2%</td>
</tr>
<tr>
<td>B2</td>
<td>8</td>
<td>3.2%</td>
</tr>
<tr>
<td>B3</td>
<td>23</td>
<td>9.2%</td>
</tr>
<tr>
<td>B1+B2</td>
<td>47</td>
<td>18.8%</td>
</tr>
<tr>
<td>B1+B2+B3</td>
<td>29</td>
<td>11.6%</td>
</tr>
<tr>
<td>B2+B3</td>
<td>15</td>
<td>6.0%</td>
</tr>
<tr>
<td>B1+B3</td>
<td>3</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

More than 47% of thymomas can be subtyped using WHO. More than 50% are mixed types, making the use of the WHO schema impractical.

Moran et al AJCP 2012; 137:444.
Staging

- There are at least 5 different approaches for the staging of thymomas:
  - The French approach
  - Berg’s approach
  - Masaoka’s original
  - Two modifications of the Masaoka’s Staging
Masaoka’s Staging

Stage I: Macroscopically completely encapsulated and microscopically no capsular invasion

Stage II:
1. Macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or
2. Microscopic invasion into capsule

Stage III: Macroscopic invasion into neighboring organ, i.e., pericardium, great vessels, or lung

Stage IV:
1. Pleural or pericardial dissemination
2. Lymphogenous or hematogenous metastasis

Solution
### New Proposed Staging

**Proposed Staging System**

- **Stage 0**
  - Encapsulated tumors

- **Stage I**
  - Invasion limited to the thymus

- **Stage II**
  - A: Pleura/lung/L.V; B: pericardium; C: great vessels

- **Stage III**
  - A: diaphragm (drop metastasis); B: Below diaphragm or neck invasion

Stage III-A

Figure 11: Prognosis analyzed by proposed stages G-I vs II-III. Overall survival curve showing a statistically significant difference (P = .044), Kaplan-Meier analysis; cumulative proportion surviving, n = 231.
Figure 23. Recurrence-free survival curve showing a statistically significant difference (P = .016). Kaplan-Meier analysis; cumulative proportion surviving, n = 231.
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TNM

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   TMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification
   system for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol
ITMIG 2018—Dr. Jeanne B. Ackman: TNM staging system has made huge progress in the diagnosis and treatment of thymic tumors

Editor’s note

The 9th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2018) was held from October 24th to 27th, 2018 in Seoul, Korea. The important conference highlighted the latest scientific and clinical developments related to the management of thymic malignancies and brought together established scientists and clinicians from all over the world who have interest in the field of thymic tumor research. The meeting was a great success. It was a great honor for the ITMIG President to conduct a brief summary of the meeting which shared with us the progress and the current challenges of TNM staging system for diagnosis and treatment of thymic Tumors.

Expert introduction

Jeanne B. Ackman (Figure 1), MD, FACP is Director of Thoracic MRI and Radiologist at Massachusetts General Hospital. She is an Assistant Professor at Harvard Medical School. Prior to these appointments, she performed general radiology in private practice for ten years. She

Analysis of the ITMIG database revealed an overall increased recurrence rate and death rate with increased

TNM stage. An early validation study comparing Masaoka-Koga and TNM staging systems in a cohort


The new TNM stage classification system can be used for all thymic epithelial tumors and considers not only tumor characteristics, but also lymph nodal and metastasis characteristics, unlike Masaoka-Koga. It does not distinguish between fully encapsulated tumors and those that have invaded through the capsule into adjacent thymic tissue or mediastinal fat, because analysis of the ITMIG database revealed this distinction not to be clinically relevant. In
Thymoma and thymic carcinoma: a perspective on the NCCN clinical practice guidelines in oncology

Nedra Keller, Caesar A. Moran

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Correspondence: All correspondence and design. All authors: All administrative support. Nona: (i) provision of study materials or patients; Nona: (ii) collection and assembly of data; Nona: (iii) data analysis and interpretation; All authors: (iv) manuscript writing; All authors: (v) final approval of manuscript; All authors.

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(VIII) The authors entered the newly created TNM schema based on ideals rather than hard data as there is not a single series of cases using such TNM system. However, one can argue that since this TNM proposal truly borrows from the Masaoka and Moran schemas their definitions, then there may not need to be a series of cases. On the other hand, one can argue that if that is not needed, then perhaps a TNM is the one that is not needed as the other schemas are functioning well for the most part. What we know and also acknowledged by the

<table>
<thead>
<tr>
<th>Stage</th>
<th>Masaoka/Rosai</th>
<th>Moran</th>
<th>AJCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N/A</td>
<td>Encapsulated tumor</td>
<td>N/A</td>
</tr>
<tr>
<td>I</td>
<td>Encapsulated tumor</td>
<td>Minimal invasion without pleural involvement</td>
<td>Masaoka &amp; Moran but with the possibility of mediastinal pleural involvement</td>
</tr>
</tbody>
</table>
| II    | Tumor through the capsule
| III   | Malignant invasion into
| IV    | At least one of the following: deep invasion, pleural and pericardial effusion, mediastinal lymph node involvement, extrathoracic extension |

Note: N/A: Not applicable

Malignant invasion into

At least one of the following:

- Deep invasion
- Pleural and pericardial effusion
- Mediastinal lymph node involvement
- Extrathoracic extension

Note: Malignant invasion into

At least one of the following:

- Deep invasion
- Pleural and pericardial effusion
- Mediastinal lymph node involvement
- Extrathoracic extension

Note: N/A: Not applicable
of thymoma has been proven that is meaningless. The classifications proposed by Bernatz, Marino-Muller-Hermelink, and Suster-Moran have the advantage that were real proposals based on actual review of cases and not derived from the thin air or to satisfy personal or political agendas. The introduction of a TNM schema for staging thymoma and mixing the same staging system with thymic carcinoma without hard data supporting such concept is imprecise at best. Nevertheless, it is important to mention

and Moran's schema. The use of Masaoka or Moran's proposal for staging thymomas is based on actual cases and not elaborated from the thin air. Attempting to adapt one or two schemas into a proposed TNM is not correct. All of the above brings us back to our initial assessment, and that is that unless a real panel of experts is put together to shed some light in this particular topic, the issue of thymoma will continue to be elusive and poorly understood. Guidelines
Overall Goal
“Cancer Personalized Medicine”

- Sample a patient’s tumor and perform molecular biomarker analysis
- From this profile derive information that when integrated with clinical information will determine the clinical behavior of that individual tumor:
  - Prognosis (survival and recurrence)
  - Prediction of response to specific therapies

Molecular Profiling for Personalized Cancer Approach

- Targets and Biomarkers Discovery
- Prognostic and Predictive Signatures
- In which cases?
- Selection is highly important!

Conclusions

- Staging remains the most important parameter to determine outcome in patients with thymoma.
- Sub-grouping thymic epithelial tumors into three categories – Thymoma – Atypical Thymoma – Thymic Carcinoma, appears to be the most reproducible way to classify these tumors.
- All thymomas are potentially aggressive tumors regardless of the histology that they may display.