THYMIC EPITHELIAL NEOPLASMS

Cesar A. Moran, MD

Director of Thoracic Pathology
Tenured Professor in the Department of Pathology
The University of Texas M.D. Anderson Cancer Center
Houston, Texas, USA

Primary thymic epithelial neoplasms have long been a source of controversy in pathology due to their wide spectrum of histologic appearances, biologic behavior, and clinical manifestations. In fact, such variability has been responsible for difficulties in the classification and prognostication of these tumors. This has led to a proliferation of classification systems in recent years and conflicting views on the best approach to the evaluation of these lesions by pathologists. The pathology of thymomas has thus turned into a complex and controversial issue that has generated much confusion for practicing pathologists.

Historical Considerations

The term thymoma, as currently defined, refers to a neoplastic proliferation of thymic epithelial cells. Throughout the years, numerous attempts at classification of these tumors have been presented in the literature. The most widely accepted classification scheme in the Unites States was the one proposed by Dr. Barnatz et al from the Mayo Clinic, which classified thymomas according to their relative proportion of lymphocytes and the shape of the neoplastic epithelial cells into predominantly lymphocytic, predominantly epithelial, mixed, and predominantly spindle cell type (Table I). Numerous clinicopathologic studies of thymoma in large series of patients utilizing this histologic approach, however, failed to find any statistically significant correlation between the morphology and the clinical behavior of these tumors.

Despite the apparent unreliability of the various morphological classifications of thymoma for predicting biologic behavior in these tumors, it was soon appreciated by several investigators that clinical staging of the lesions based on their status of capsular integrity afforded a better means for assessing their biologic behavior. For this reason, Levine and Rosai in 1978 introduced the concept of defining thymomas on the basis of their capsular status into benign and malignant, depending on whether the tumor was encapsulated or invasive (Table I). In their classification, Levine and Rosai additionally espoused the concept that invasive tumors displaying overt cytologic features of malignancy should be regarded as equivalent with thymic carcinoma (so-called malignant thymoma type-II) (Table I).

More recently, interest in the morphological classification of thymoma was revived by the studies of Marino and Muller-Hermelink, who presented a novel histologic classification of these tumors based on histogenetic considerations. These investigators proposed that thymomas could be divided on the basis of their cytological features into those derived from the cortical or from the medullary epithelium of the thymus into “cortical” and “medullary” thymomas. Cases that contained features of both were regarded as “mixed”. The authors subsequently modified their approach by adding two additional categories, the

predominantly cortical or "organoid" thymoma, and a fifth category designated as "well-differentiated thymic carcinoma" (Table I).

TABLE I: Review of Major Classifications of Thymoma (1961-1989)

Barnatz et al (1961)	***Levine & Rosai (1978)***	***Muller-Hermelink et al (1989)***
Predominantly epithelial	***Benign thymoma***	***Medullary thymoma***
Predominantly lymphocytic	***- Encapsulated***	***Cortical thymoma***
Mixed	***Malignant thymoma***	***Mixed thymoma***
Spindle cell thymoma	***- Type I (invasive)***	***Predominantly cortical***
	- Type II (thymic carcinoma)	***Well-differentiated thymic carcinoma***

Many studies have been presented in the literature that would appear to validate the clinical use of the Muller-Hermelink classification. The proponents of such classification have claimed that the various morphologic subtypes directly correlate with the probability of invasiveness for these tumors, and that histologic subtyping according to this classification is predictive of clinical behavior independent of stage. Despite the undoubted wide appeal of the Muller-Hermelink classification, major objections have been voiced by experts in the field concerning its applicability for clinical practice. Most of the criticism of the studies supporting the Marino & Muller-Hermelink classification has been centered around issues of inadequate sampling, reproducibility, and reliability for accurately predicting the prognosis of these tumors, particularly when dealing with limited biopsy samples (i.e., endoscopic biopsies of large mediastinal masses).

Given this controversy, a number of new classification schemes have been proposed by different investigators for these tumors in recent years. In the new AFIP Fascicle on Tumors of the Mediastinum, Drs. Shimosato and Mukai propose a complex classification scheme that takes into consideration the extent, histology, cell type and degree of atypia of the neoplastic cells, and incorporates terminology from various other existing classifications (Table II). The most recent classification scheme presented by Dr. Kuo from Taiwan proposes that thymomas be classified according to their cytokeratin expression profiles. Based on a study of 34 immunostained thymomas, and an additional 113 thymomas without the stains, the author proposed that his approach provided a useful method for the clinical evaluation of thymomas (Table II).

Table II: Recent Additional Classifications of Thymoma

Shimosato & Mukai (1997)	***Kuo (2000)***
By extent:	***Spindle cell thymoma***
-Circumscribed	***Small polygonal***
-Invasive	***Mixed***
-With implants or metastasis	***Organoid***
By histology:	***Large polygonal cell***
-Lymphocytic, mixed, epithelial	***Squamoid thymoma***
By cell type:	
-Spindle, polygonal, polygonal-oval	
By cell atypia:	
-Absent, slight, moderate, marked	

Given the controversy and lack of consensus regarding thymoma classification, the WHO organization commissioned Dr. Juan Rosai to establish a panel for the study of this topic. After many years of deliberation, a compromise, "non-committal" formula was devised by the WHO panel for the classification of thymic epithelial neoplasms. The new WHO classification schema did not introduce a new terminology but simply assigned a combination of letters and numbers to the various histologic types in the existing classifications of thymoma (Table III). The letters A and B represent thymomas predominantly composed of either spindle or round cells, respectively. Type AB is composed of both spindle and round cells; and type C is reserved for those showing overt features of carcinoma (i.e., thymic carcinoma). In their WHO monograph, the authors state that this schema is *not intended as a new histologic classification* of thymoma nor is it meant to replace any previous terminology, but rather should be employed as a means for facilitating comparison among the various terms from the existing classifications.

Table III: Comparison of WHO Schema With Other Classifications

WHO Schema	***Barnatz et al***	***Muller-Hermelink et al***
Type A	***Spindle cell***	***Medullary thymoma***
Type AB	***---***	***Mixed thymoma***
Type B1	***Lymphocyte rich***	***Predominantly cortical***
Type B2	***Mixed***	***Cortical thymoma***
Type B3	***Epithelial rich***	***Well-differentiated thymic carcinoma***
Type C	***Thymic carcinoma***	***---***

Although the recently introduced WHO schema does not settle the issue of thymoma classification, the WHO monograph is of importance because it supported and stressed certain valuable concepts that were agreed upon by all the panel members in that publication: 1) no histogenetic basis has yet been conclusively demonstrated between the normal anatomic compartments of the thymus and any of the different histologic types for any of the existing classifications; 2) thymic epithelial neoplasms represent a spectrum of lesions that may range from histologically benign to malignant, hence the inclusion of thymic carcinoma as "thymoma type C"; and 3) the degree of invasiveness relates more closely to recurrence and outcome than the cytoarchitectural features, to the point of markedly reducing the independent prognostic value of the latter.

It follows from review of the above that markedly different opinions continue to exist regarding the issue of thymoma classification and that a widely agreed upon classification remains to be devised. Moreover, it has become increasingly obvious to workers in this field that the complexity of thymoma classification continues to increase with every new proposal and with the introduction of new and increasingly complex (albeit colorful) terms.

New Concepts

Current opinions appear to continue to be divided between those who contend that histologic classification provides a reliable means for assessing prognosis of thymic epithelial neoplasms, and those who claim that staging represents the best if not the only valid parameter for the evaluation of thymoma. We believe the truth probably lies somewhere in-between, and that proper evaluation of these lesions would benefit from an approach that incorporates, as in other tumor systems throughout the body, a combination of histologic grading and clinical staging of the lesions.

In a recent review (Am J Clin Pathol, Vol.111:826-833,1999) we presented a novel conceptual approach to primary thymic epithelial neoplasms that is based on a combination of grading and staging of these tumors. In traditional pathology, most tumor systems follow a stepwise progression in their histologic evolution leading to progressive loss of differentiation of the tumor cells. Thus, for most epithelial tumor systems, the first step in this progression is represented by carcinoma in-situ, followed by well-differentiated (usually invasive) carcinoma, moderately differentiated carcinoma, and finally poorly differentiated carcinoma. The equivalent of such a spectrum has not been yet recognized in the thymus. One of the reasons for this is the tremendous histological variability that these tumors can display. The other reason is the traditional belief that malignancy in thymoma cannot be predicted based on features of differentiation and atypia because of the overwhelmingly "bland" appearance of the majority of such tumors. Thymic epithelial neoplasms characterized by overt cytologic evidence of malignancy (i.e., thymic carcinoma) have thus been traditionally separated from conventional thymomas and felt to represent a totally different and unrelated entity.

Careful study of our cases and review of the literature have led us to believe otherwise, and have demonstrated that the lesions which we call thymic carcinoma and thymoma are closely related entities that most likely represent opposite ends of a single spectrum of differentiation. In a recent study we were able to document the existence of tumors demonstrating direct transitions between areas showing the classical features of thymoma and areas showing unequivocal features of thymic carcinoma. Moreover, in several of these cases, we were able to identify different areas within the same tumor showing a spectrum of differentiation that ranged from classical thymic epithelial cells with round to oval, vesicular nuclei with small nucleoli and abundant rim of eosinophilic cytoplasm, to larger cells with well-demarcated cell borders and features of atypical keratinizing epithelium. These observations have led us to believe that thymic epithelial neoplasms form part of a spectrum of closely related lesions that may display varying histological appearances depending on their degrees of differentiation.

Unlike other epithelial tumor systems in which a progression from well differentiated through poorly differentiated carcinoma can be easily determined, thymomas have not lent themselves easily to such categorization because of their great variability in cytological composition and architectural growth patterns. Another difficulty involved in establishing the degree of differentiation in these tumors is the fact that the "normal" thymus can differ dramatically in appearance depending on the age of the individual. Thus, the normal *mature* thymus of a child will look quite different from the normal but *involuted* thymus in the adult. The mature thymus in childhood and adolescence will show the prototypical features of this organ characterized by a sharp demarcation between the cortex and the medulla and the admixture of thymic lymphocytes with large, round epithelial cells containing vesicular nuclei and indistinct cell borders with abundant amphophilic cytoplasm. The normal involuted thymus of older adults, on the other hand, will often be characterized by a paucity of lymphocytes and the epithelial cells will frequently adopt the shape of small, oval to spindle cells with scant cytoplasm and inconspicuous nucleoli. Although these contrasting appearances are an expression of the functional (i.e., active *vs.* inactive) state of the organ, they

both represent the normal status of this organ at different stages in its evolution. Tumors displaying features that closely resemble these two "normal" appearances of the thymus could therefore be regarded as showing a high degree of differentiation.

Commonly accepted features of organotypical differentiation in thymomas on routine microscopy include: 1) a well-developed lobular architecture on scanning magnification; 2) dual cell population (neoplastic thymic epithelial cells and thymic lymphocytes) admixed in various proportions; 3) distended perivascular spaces; 4) areas of "medullary" differentiation characterized by discrete rounded foci predominantly composed of epithelial cells surrounded by a population of cells that resembles the normal cortex; and 5) the bland appearance of the epithelial cells, which lack overt cytological features of malignancy. To the above features we would also add the presence of a bland-appearing spindle cell proliferation with scant lymphocytes, cystic and glandular formations, and rosette-like epithelial structures, which are features that are commonly encountered in the regressed thymus of older adults (Table IV).

Table IV: Organotypical Features of Thymic Differentiation

Normal Mature Thymus of Childhood or Adolescence	**Normal Mature Thymus of the Adult**
-Low-power lobulation	***-Bland spindle cell population with scant lymphocytes***
-Dual (epithelial/lymphoid) cell population	***-Cystic and glandular formations***
-Distended perivascular spaces	***-Rosette-like epithelial structures***
-Areas of "medullary" differentiation	
-Lack of cytological features of malignancy	

Applying the above parameters, tumors that exhibit most or all of the above features could be categorized as well differentiated, whereas tumors displaying total loss of these organotypical features would be classed as poorly differentiated neoplasms. Fortunately, the vast majority of thymic epithelial neoplasms will generally fall within the first group, i.e., that of well-differentiated tumors displaying most of the organotypical features of the normal thymus. Such tumors have been designated by convention as thymoma. Thymic epithelial neoplasms in which most or all of the organotypical features of differentiation

of the normal thymus have been lost and the tumor cells already display overt cytological features of malignancy would correspond to those traditionally designated in the literature as thymic carcinoma. There exists a third, smaller group of primary thymic epithelial neoplasms that displays features intermediate between thymoma and thymic carcinoma. Such tumors are characterized by the presence of cytological atypia of the tumor cells, yet they still retain many if not most of the organotypical features of differentiation of the normal thymus. These tumors can be regarded as representing an intermediate stage in the spectrum of differentiation of thymic epithelial neoplasms (i.e., moderately-differentiated tumors). On the basis of the cytological features of atypia displayed by their tumor cells, we have proposed the designation of atypical thymoma for these tumors.

Based on the above considerations, we currently believe that thymic epithelial neoplasms can be reliably classified into three simple categories: well-differentiated thymoma, moderately differentiated or atypical thymoma, and poorly differentiated tumors (i.e., thymic carcinoma) (Table V). Assigning a given lesion to any of these various categories does not depend on any purported histogenetic considerations, does not require the use of special stains or advanced techniques not readily available to general pathologists in community practice, and simply requires basic familiarity with the organotypical features of differentiation of the normal thymus and attention to the degree of cytological atypia displayed by the neoplastic epithelial cells on routine microscopy.

Table V: Classification of Thymic Epithelial Neoplasms According to Grades of Differentiation

Type	Grading	Histological Criteria
Thymoma	*Well-differentiated*	*-Preservation of organotypical features of differentiation* *-No cytological evidence of atypia*
Atypical thymoma	*Moderately-differentiated*	*-Preservation of organotypical featured of differentiation* *-Mild to moderate cytological atypia*
Thymic carcinoma	*Poorly-differentiated*	*-Loss of organotypical features of thymic differentiation* *-Presence of overt cytological evidence of malignancy*

Prognostic Features

The evaluation of prognosis in thymoma remains a controversial issue. Most studies seem to indicate that staging represents the most important parameter for assessing the clinical behavior of these

tumors. Many of the proponents of some of the more recent morphologic classifications, however, contend that histologic subclassification of well-differentiated thymoma represent a valuable independent prognostic criterion for determining clinical behavior and guiding therapy in these tumors. Studies using special techniques, such as determination of ploidy by flow cytometry, immunohistochemical determination of proliferative index, assessment of p53 protein expression, etc., have so far yielded conflicting and inconclusive results.

The proponents of the Muller-Hermelink classification have maintained that the different histologic types of their histogenetic classification directly correlate with invasiveness, and therefore can be reliably utilized to predict the biologic behavior of the lesions. The majority of such studies, however, have failed to demonstrate any correlation with mortality and survival on long-term follow-up. The fact that certain histologic subtypes (such the predominantly epithelial thymoma) were associated with increased invasive properties, and that others (such as spindle cell thymoma) were more often associated with indolent clinical behavior has been well-recognized in several studies predating the histogenetic classification of Muller-Hermelink and colleagues. The same studies, however, also demonstrated that when stratified according to staging, all the different histologic subtypes ultimately behaved in a similar manner.

This begs the question: is histologic subclassification of thymoma, particularly the well-differentiated variants, necessary? We believe the answer to this question is that subtyping of well-differentiated thymic epithelial neoplasms offers no distinct advantage for prognostication, and that determination of the status of capsular integrity constitutes the most important step in the evaluation of these tumors. Another factor that renders subclassification of well-differentiated thymoma nearly irrelevant is the fact that these tumors tend to display marked morphologic heterogeneity, with frequent admixtures of different histologic growth patterns and cells types often being observed within the same tumor mass. In a recent study of 630 consecutive thymomas, we compared the final histologic classification of the tumors with the number of sections examined per case. It was found that when the number of sections examined per case increased, more cases were included in the “mixed” category, and fewer cases could be assigned to either the pure “cortical” or “medullary” types. These findings suggest that histologic subclassification of thymoma, although of academic interest, may be of limited practical relevance for the assessment of prognosis, particularly in limited biopsy tissue samples.

Staging of thymic epithelial neoplasms also remains a controversial subject. The most popular staging system for these tumors was introduced in 1981 by Masaoka et al, in a study in which statistically significant differences in survival could be appreciated for the different groups of patients depending on the gross and microscopic status of the capsule, spread into adjacent structures, and presence or absence of metastases. Since then, several refinements and modifications to this staging scheme have been introduced by other investigators. A TNM staging system was also introduced by Masaoka in 1991 for thymic carcinoma, but has been felt to be impractical for the well-differentiated variants of thymoma. The most recent staging proposal was presented in the WHO monograph on the Histologic Typing of Tumors of the

Thymus (Table VI). We believe until more extensive data becomes available on the discriminatory value for prognosis of these various schemas, a more simplified approach should be favored that basically addresses the distinction between encapsulated (non-invasive), locally invasive, widely invasive, and metastatic tumors.

In summary, classification of thymoma need not be a cumbersome task for general pathologists and can be readily accomplished by most experienced surgical pathologists in clinical practice. Given the relative rarity of these tumors and the questionable role that complex substratification by histologic type plays in prognostication and treatment of these tumors, we favor a simplified approach that combines histologic grading (based on organotypical features of differentiation of the thymus and cytologic atypia) with staging (status of capsular integrity/presence or absence of metastasis). It is our contention that this simplified approach affords an equal opportunity for proper management of these patients as the more sophisticated systems currently in existence, which generally will require review of the case by an expert in the field for proper typing and categorization.

Table VI: Comparison of various staging schemes for thymoma

Masaoka et al (1981)	*WHO (1999)*	*Suster & Moran (1999)*
Stage I: Encapsulated	***Encapsulated***	***Encapsulated***
Stage II: Invasion of capsule and/or perithymic fat	***Minimally invasive***	***Locally invasive***
Stage III: Gross invasion of adjacent organs	***Widely invasive***	***Widely invasive with or without implants***
Stage IVA: Implants	***With implants***	***Metastatic***
Stage IVB: Metastases	***Lymph node mets***	***With distant metastases***

Select Bibliography

- Suster S, Moran CA. Primary thymic epithelial neoplasms: current concepts and controversies, in: Fechner RE, Rosen PP (Eds), Anatomic Pathology, 1997, Vol.2, Chicago, ASCP Press, pp.1-19.
- Suster S, Moran CA. Thymoma, atypical thymoma, and thymic carcinoma. A novel conceptual approach to the classification of thymic epithelial neoplasms. Am J Clin Pathol 1999; 111:826-833.
- Suster S, Moran CA. Primary thymic epithelial neoplasms: spectrum of differentiation and histological features. Semin Diagn Pathol 1999; 16:2-18.
- Shimosato Y, Mukai K. Tumors of the mediastinum, Fascicle 21, in: Atlas of Tumor Pathology, 3rd. series, Washington, D.C., Armed Forces Institute of Pathology, 1997, pp.33-157.
- Bernatz PE, Khonsari S, Harrisson EG Jr, Taylor WF. Thymoma: factors influencing prognosis. Surg Clin N Am 1973; 53:885-902.
- Lattes R. Thymoma and other tumors of the thymus: an analysis of 107 cases. Cancer 1962; 15:1224-1260.
- Salyer WF, Eggleston JC. Thymoma: a clinical and pathological study of 65 cases. Cancer 1976; 37:229-235.
- Bernatz PE, Harrison EG, Clagett OT. Thymoma: a clinicopathologic study. J Thorac Cardiovasc Surg 1961; 42:424-444.
- Masaoka A, Monden Y, Nakahara Z, Tanioka T. Follow-up studies of thymomas with special reference to their clinical stages. Cancer 1981; 48:2485-2492.
- Levine GD, Rosai J. Thymic hyperplasia and neoplasia. A review of current concepts. Hum Pathol 1978; 9:495-515.
- Marino M, Muller-Hermelink HK. Thymoma and thymic carcinoma: relation of thymoma epithelial cells to the cortical and medullary differentiation of the thymus. Virchows Arch A (Pathol Anat) 1985; 407:119-149.
- Kirschner T, Muller-Hermelink HK. New approaches to the diagnosis of thymic epithelial tumors. Prog Surg Pathol 1989; 10:167-189.
- Ho FCS, Fu KH, Lam SY. Evaluation of a histogenetic classification for thymic epithelial tumors. Histopathology 1994; 25:21-29.
- Quintanilla-Martinez L, Wilkins EW, Choi N et al. Thymoma: histologic subclassification is an independent prognostic factor. Cancer 1994; 74:606-617.
- Kuo T-T, Lo S-K, Thymoma: a study of the pathologic classification of 71 cases with evaluation of the Muller-Hermelink system. Hum Pathol 1993; 24:766-771.
- Kornstein MJ, Curran WJ, Turrisi AT III, Brooks JJ. Cortical vs. medullary thymoma: a useful morphologic distinction? Hum Pathol 1988; 19:1335-1339.

- Wick MR. Assessing the prognosis of thymomas. Ann Thorac Surg 1990; 50:521-522.
- Pan C-C, Wu H-P, Yang C-F. The clinicopathological correlation of epithelial subtyping in thymoma: a clinicopathological study of 112 cases. Hum Pathol 1994; 25:893-899.
- Shimosato Y. Controversies surrounding the subclassification of thymoma. Cancer 1994; 74:542-544.
- Dawson A, Ibrahim NBN, Gibbs AR. Observer variation in the histopathological classification of thymoma: correlation with prognosis. J Clin Pathol 1994; 47:519-523.
- Moran CA, Suster S. Current status of the histologic classification of thymoma. Int J Surg Pathol 1995; 3:67-72.
- Kuo T-T. Cytokeratin profiles of the thymus and thymomas: histogenetic correlations and proposal for a histological classification of thymomas. Histopathology 2000; 36:403-414.
- Rosai J. Histological typing of tumors of the thymus. In: World Health Organization International Histological Classification of Tumors. Second edition. Springer Verlag, Berlin, 1999.
- Suster S, Moran CA. Primary thymic epithelial neoplasms displaying combined features of thymoma and thymic carcinoma: a clinicopathologic study of 22 cases. Am J Surg Pathol 1996; 20:1469-1480.
- Moran CA, Suster S. On the histologic heterogeneity of thymoma: impact of sampling in subtyping and classification. Mod Pathol 2000; 13:214A.
- Moran CA, Suster S. On the histologic heterogeneity of thymoma: impact of sampling in subtyping and classification. Am J Clin Pathol 2000; 114:760-766.