Thymoma Classification

Current Status and Future Trends

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Abstract

The classification of thymic epithelial neoplasms has been a controversial topic for many years. Recent advances in diagnostic methods and renewed interest in the biology of these tumors has led to efforts by investigators to shed new light on their biologic behavior and to offer novel perspectives on these unusual neoplasms. Several new classification schemes have been proposed, including the new World Health Organization schema for the histologic typing of tumors of the thymus. We review the current status of thymoma classification and comment on problem areas and future trends that may offer a more pragmatic approach to these tumors.

The histologic classification of primary thymic epithelial neoplasms traditionally has been the source of difficulties owing to the wide variety of morphologic appearances that these tumors can display. A number of histologic classification schemes have been proposed, none of which seems to have so far resolved the problems involved in the evaluation of these tumors. Problem areas to be discussed in this review include the approach to the histopathologic classification of thymoma, the relative value of current prognostic parameters, and ways for optimizing the evaluation of these tumors to predict clinical behavior and plan their therapy.

Historic Perspective

Historically, the morphologic classification that gained the widest acceptance during the past several decades, particularly in the United States, was the one proposed in 1961 by Bernatz et al[1] from the Mayo Clinic. These authors divided thymomas based on their relative proportion of epithelial cells to lymphocytes and on the shape of the epithelial cells. Their classification recognized 4 basic histopathologic variants: lymphocyte-predominant, epithelial-predominant, mixed (lymphoepithelial), and spindle cell thymoma. This classification essentially constituted a variation of a similar formula proposed by Lattes and Jonas[2] 4 years earlier, which also divided thymoma into predominantly lymphocytic, predominantly epithelial, and predominantly spindle cell, but that also included a category of rosette-forming thymoma. A somewhat similar schema also was adopted in Japan, with the exception that the predominantly epithelial tumors were designated as thymoma of polygonal or clear cell type.[3] The Bernatz et al[1]

classification and variants thereof have come to be known collectively as the *traditional* classification of thymoma.

Despite apparently good reproducibility among pathologists for applying the traditional histopathologic classification of thymoma, it soon became apparent that the various types did not show good correlation with the clinical behavior of the tumors and, therefore, were not very useful for prognostication. Although some studies seemed to indicate that the predominantly epithelial tumors were associated more often with an increased potential for invasiveness and recurrence, the majority of studies seemed to support that the most reliable parameter for assessing the clinical behavior of thymoma was the status of capsular integrity.[4-12] Based on this premise, Levine and Rosai,[13] in a review article on thymic hyperplasia and neoplasia published in 1978, proposed that the encapsulated tumors were benign and that all invasive tumors should be regarded as malignant. They further proposed that malignant thymoma be subclassified into type I for invasive tumors showing the same morphologic features as benign thymoma and type II for tumors displaying overt cytologic features of malignancy (also designated as thymic carcinoma). The Levine and Rosai[13] proposal gained wide acceptance, particularly in the United States, where it was used for many years, often in combination with the traditional nomenclature for the various morphologic subtypes of thymoma.

Two additional approaches to the classification of thymoma were introduced in 1985. The first was proposed by Marino and Muller-Hermelink[14] based on the premise that thymoma represents a neoplastic proliferation of cells that are derived from the cortex or the medulla of the thymus or from a combination thereof. These authors thus classified thymoma into cortical, medullary, and mixed types. This classification subsequently was modified by Kirchner and Muller-Hermelink[15] to include 2 additional categories, the predominantly cortical thymoma (later renamed *organoid*) and the well-differentiated thymic carcinoma. It was stated that the value of this new classification resided in facilitating the correlation between these various morphologic types of thymoma and invasiveness.[16-22]

The other histologic classification scheme was proposed by Verley and Hollmann[23] from France. Their schema consisted of 4 categories that included spindle cell thymoma, lymphocyte-rich thymoma, differentiated epithelial thymoma (roughly corresponding to epithelial-rich thymoma according to the traditional classification), and undifferentiated epithelial thymoma (corresponding to thymic carcinoma). The authors pointed out that although invasiveness often paralleled histologic typing, they both seemed to represent distinct and independent parameters with separate prognostic significance. The latter classification was adopted by several French investigators.

The status of thymoma classification was sufficiently confusing at this point that by 1997, when the third edition of the Armed Forces Institute of Pathology fascicle *Tumors of the Mediastinum* was published,[24] the authors did not endorse any of the schemas in existence but divided the tumors according to a complex set of criteria that included extent of invasion, histology, cell type, and cell atypia. In light of the difficulties involved in the classification of thymoma, the World Health Organization (WHO) appointed a panel of experts to devise a unified histologic classification of tumors of the thymus. After several years of deliberation, the Committee for the International Histological Classification of Thymic Neoplasms arrived at a compromise formula that assigned a combination of letters and numbers to the various existing histologic types of thymoma. The WHO schema, initially published in 1999, essentially divided thymic epithelial neoplasms into 3 categories, types A, B and C, with type B further subdivided into B1, B2, and B3.[25] According to the authors, this proposal was not meant to represent a new histologic classification for thymic epithelial neoplasms, nor was it intended to replace any previous terminology, but instead was meant to provide a universal formula that would facilitate comparison among the various terms from the already existing classifications.[25] A reiteration of this basic schema was published more recently by the WHO with some minor modifications.[26]

In 1999, shortly after the introduction of the WHO schema, we presented a novel conceptual approach to the classification of thymic epithelial neoplasms.[27] In this proposal, the histologic grading of the tumors was based on the premise that primary thymic epithelial neoplasms form part of a continuous spectrum of differentiation, which ranges from well-differentiated to moderately differentiated to poorly differentiated neoplasms. The well-differentiated tumors were designated by convention as thymoma, the poorly differentiated tumors as thymic carcinoma, and those showing intermediate differentiation as atypical thymoma. A recent large study validated this proposal and demonstrated a significant advantage for adopting this system of classification.[28] Herein, we review in more detail some of the various classifications.

Review of Current Classification Systems

Marino and Muller-Hermelink Classification (1985)

Marino and Muller-Hermelink[14] presented a novel proposal for the classification of thymic epithelial neoplasms that was based on the purported histogenetic derivation of the epithelial cells in the tumor. Based on the light microscopic characteristics of the epithelial cells, the tumors were classified into cortical, medullary, and mixed. In their retrospective study of 58 thymomas and 13 thymic carcinomas, malignant invasive character and the occurrence of myasthenia

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gravis were found to be related to the neoplastic proliferation of the cortical epithelial cells, whereas tumors composed of cells thought to be derived from the medulla or of mixed cortical-medullary type were not associated with invasion or metastases.

Cortical thymoma was composed of epithelial cells that were morphologically similar to those found in the normal cortex. These cells were characterized by large round or oval nuclei with a single prominent nucleolus and scant cytoplasm. Mitoses were observed only rarely in the epithelial cells. The lymphocytic component in these tumors resembled cortical thymocytes. In addition to small lymphocytes, medium-sized and large lymphoid cells (*lymphoblasts*) with round or convoluted nuclei were often seen, with frequent mitoses being observed.

The *medullary type* of thymoma was characterized by a predominant population of epithelial cells with few lymphocytes. The epithelial cells were spindle shaped with oval or fusiform nuclei displaying a dense, homogeneous chromatin pattern. Occasional small nucleoli could be seen, and the cell nuclei were surrounded by scant eosinophilic cytoplasm. The lymphoid cells were mostly small, with dark, round, and often pleomorphic nuclei.

The *mixed type* of thymoma was characterized by a proliferation of cortical and medullary epithelial cell types. Tumors characterized by an intimate admixture of the 2 cell types were regarded as *mixed thymoma of common type,* and tumors in which areas similar to pure cortical or pure medullary thymoma predominated (>75% of tumor area) were designated as *mixed thymoma with cortical or medullary predominance.*

Subsequently, in 1989, Kirchner and Muller-Hermelink[15] introduced a modification to this classification scheme whereby predominantly cortical thymomas were separated from the mixed category and an additional group of tumors designated as well-differentiated thymic carcinoma was added **Table 1**. The *predominantly cortical thymomas* were described as tumors showing a prevalence of cortical-type zones, but they also contained highly organoid lobular architecture with small medullary islands containing epidermoid cells or Hassall corpuscles at the base of the cortical lobules. *Well-differentiated thymic carcinoma,* on the other hand, was defined as a neoplasm showing a lobular architecture, with frequent palisading of epithelial cells around perivascular spaces and fibrous septa. The epithelial cells were tightly packed, resulting in a solid growth pattern, and showed slight to moderate atypia with occasional mitoses. The number of lymphocytes was described as low.

WHO Schema for the Classification of Thymic Epithelial Neoplasms (1999; 2004)

The WHO schema first published in 1999 was the result of extensive effort by an international panel of experts headed by Juan Rosai, MD, to develop a standard, unified classification for the histologic typing of tumors of the thymus.[25] After several years of deliberation, a compromise formula was accepted that assigned a combination of letters and numbers to the various histologic categories (Table 1). Two major types of thymoma were identified, depending on whether the neoplastic epithelial cells and their nuclei showed a spindle or oval shape (designated type A) or a round epithelioid appearance (designated type B). Tumors showing a combination of these 2 cell types were designated type AB. Type B thymomas were subdivided further on the basis of the proportional increase (in relation to the lymphocytes) and emergence of atypia of the neoplastic epithelial cells into 3 subtypes, respectively designated B1, B2, and B3. Type C thymoma was regarded as a tumor showing overt cytologic features of malignancy (ie, thymic carcinoma). Thus, the morphologic basis for this classification was essentially identical to that of the traditional classification presented more than 40 years earlier (ie, the tumors are classified in both systems according to the shape of the neoplastic epithelial cells and their relative proportion of lymphocytes).

Type A thymoma essentially was regarded as the equivalent of the spindle cell thymoma in the traditional classification and of medullary thymoma in the Marino and Muller-Hermelink[14] classification. It was defined as a tumor composed of a population of neoplastic thymic epithelial cells having

Table 1
Comparison of Major Histologic Classifications of Thymoma

Traditional (Bernatz et al, 1961[1])	Kirchner and Muller-Hermelink (1989)[15]	WHO (1999)[25]	Suster and Moran (1999)[27]
Spindle cell	Medullary	Type A	Thymoma, well-differentiated
—	Mixed	Type AB	Thymoma, well-differentiated
—	Predominantly cortical	Type B1	Thymoma, well-differentiated
Lymphocyte-rich	Cortical	Type B2	Thymoma, well-differentiated
Lymphoepithelial	Cortical	Type B2	Thymoma, well-differentiated
Epithelial-rich	Well-differentiated thymic carcinoma	Type B3	Atypical thymoma
—	High-grade thymic carcinoma	Type C	Thymic carcinoma

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spindle or oval shape, lacking nuclear atypia, and accompanied by few or no lymphocytes.

Type AB thymoma was defined as a tumor in which foci having features of type A thymoma were admixed with foci showing features of type B thymoma.

Type B1 was described as a tumor that resembled the normal functional thymus in that it combined large expanses having an appearance practically indistinguishable from the normal thymic cortex admixed with areas resembling thymic medulla. These tumors were said to correspond to lymphocyte-rich thymomas in the traditional classification and to the predominantly cortical or organoid thymoma in the Kirchner and Muller-Hermelink[15] classification.

Type B2 was a tumor in which the neoplastic epithelial component appeared as scattered large epithelial cells with vesicular nuclei and distinct nucleoli against a heavy population of lymphocytes. Perivascular spaces were common and sometimes very prominent. These tumors were said to essentially resemble B1 thymoma but without the areas of medullary differentiation. They were thought to be the equivalent of the mixed lymphoepithelial thymoma in the traditional classification and of pure cortical thymoma in the Marino and Muller-Hermelink[14] classification.

Type B3 corresponded to tumors composed predominantly of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. These tumors also contained a minor component of lymphocytes and displayed sheet-like growth of the neoplastic epithelial cells. They were regarded as equivalent to the epithelial-rich thymoma of the traditional classification and to the well-differentiated thymic carcinoma of the Kirchner and Muller-Hermelink[15] classification.

Type C thymoma was defined as a tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. They lacked immature T lymphocytes; the lymphocytes present were usually mature T or B lymphocytes and were admixed with plasma cells. Another designation for these tumors is *thymic carcinoma.* A variety of histologic types were recognized, most having their counterpart in identical tumors arising from other organs, including epidermoid, keratinizing (squamous cell) carcinoma, epidermoid nonkeratinizing carcinoma, lymphoepithelioma-like carcinoma, sarcomatoid carcinoma, clear cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, papillary carcinoma, and undifferentiated carcinoma.

In the introduction to the WHO monograph, the authors stressed the importance of independently evaluating thymic epithelial tumors on the basis of their degrees of invasiveness (using staging criteria) and their cytoarchitectural features and of using this combined approach to predict behavior.

The most recent version of the WHO classification of thymoma[26] essentially retained the same criteria and terminology as the one in the original proposal for the types A, AB, and B1 to B3 tumors. The only significant changes were the elimination of the type C thymoma from the schema, with the latter tumors being segregated into a separate and distinct category of thymic carcinoma and the introduction of various specific subtypes of unusual thymomas, including micronodular thymoma with B-cell hyperplasia, "metaplastic" thymoma, and others. The latter variants of thymoma correspond to tumors that could not be classified properly into the other categories. In the latest version of the WHO classification, the authors postulated a linear progression in terms of malignancy for these tumors, with thymoma of types A, AB, B1, B2, B3, and thymic carcinoma representing histologic subtypes showing increasing order of malignancy. The authors reiterated their belief that type A and AB thymomas behave as benign tumors, type B1 as a low-grade malignant tumor, type B2 as a slightly more aggressive tumor, and type B3 (in advanced stages) as an aggressive malignant neoplasm similar to thymic carcinoma. This claim was based on a single study of 200 cases of thymoma from China by Chen and colleagues.[29]

Suster and Moran Classification (1999)

In the same year that the first WHO monograph on the histologic typing of tumors of the thymus was published, we presented a novel conceptual approach to the classification of neoplasms of thymic epithelium.[27] In this proposal, the histologic grading of the tumors was based on the premise that primary thymic epithelial neoplasms form part of a continuous spectrum of lesions that range from well-differentiated to moderately differentiated to poorly differentiated neoplasms. In this proposal, the well-differentiated tumors corresponded to tumors designated by convention as thymoma, the poorly differentiated neoplasms were those conventionally designated as thymic carcinomas, and tumors showing intermediate features of differentiation were designated as atypical thymoma (Table 1). This approach was supported by the observation of tumor progression in thymoma, whereby tumor recurrences have shown transformation of a low-grade histologic type to that of a higher-grade histologic type,[30,31] as well as the demonstration of transitions between well-, moderately, and poorly differentiated areas within the same neoplasm.[32,33]

The determination of the degree of differentiation for any given tumor is established based on the presence or absence of the characteristic organotypical features of differentiation of the normal thymus and on the degree of cytologic atypia of the neoplastic thymic epithelial cells[33] **Table 2**. Thus, tumors displaying most or all of the organotypical features of thymic differentiation and absence of cytologic atypia are classified as well-differentiated thymic epithelial neoplasms (ie, thymoma); tumors that retain only some of the organotypical features of differentiation of the thymus but that already display mild to moderate cytologic atypia are classified as moderately

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Table 2
Organotypical Features of Differentiation of the Normal, Mature Thymus of Childhood and Adolescence and of the Involuted Thymus of the Adult

Normal mature thymus of childhood and adolescence
Lobulation and encapsulation
Dual (epithelial/lymphoid) cell population with variable numbers of immature T lymphocytes
Perivascular spaces
Areas of "medullary" differentiation
Normal involuted thymus of the adult
Spindle cell population devoid of cytologic atypia
Scant immature T lymphocytes
Rosette-like epithelial structures
Cystic and glandular structures

differentiated thymic epithelial neoplasms (ie, atypical thymoma); and tumors characterized by total absence of the organotypical features of the thymus and showing overt cytologic evidence of malignancy correspond to poorly differentiated thymic epithelial neoplasms (ie, thymic carcinoma).[27,34]

This classification is simple, easily reproducible, and does not depend on any purported histogenetic considerations or require the use of special stains or other specialized techniques. It can be applied based on the examination of routinely stained slides examined under conventional light transmission microscopy and requires only familiarity with the organotypical features of differentiation for the different stages of maturation of the normal thymus and attention to the degree of cytologic atypia displayed by the neoplastic epithelial cells.[33]

Well-differentiated thymic epithelial neoplasms (ie, thymoma) can show a wide spectrum of morphologic appearances that might vary depending on whether the neoplastic cells are attempting to recapitulate the normal, mature thymus of infancy and adolescence or whether they resemble the normal involuted thymus of the adult.[27,34]

The majority of tumors that recapitulate the normal thymus of infants and adolescents are characterized by well-developed lobules with a predominance of small lymphocytes. The lobules usually are separated by fibrous bands of variable thickness that often are angulated. Dilated perivascular spaces commonly are present in these tumors. Focal areas of medullary differentiation also can be seen. The proportion of small lymphocytes to epithelial cells can vary widely among tumors and within different areas of the same tumor. The neoplastic epithelial cells usually are in the minority and are scattered singly or in small clusters, admixed with the lymphocytes. The epithelial cells are round with large vesicular nuclei and single, small, eosinophilic nucleoli and are surrounded by abundant amphophilic cytoplasm with indistinct cell borders. The cells usually do not display any significant cytologic atypia and are devoid of mitotic activity. Mitoses often can be observed in the more immature lymphoid cell elements. These tumors are the equivalent of the lymphocyte-rich thymoma and mixed (lymphoepithelial) thymoma of the traditional classification, of the cortical and predominantly cortical thymoma of the Kirchner and Muller-Hermelink[15] classification, and of types B1 and B2 in the WHO schema.

Tumors recapitulating the features of the normal involuted thymus of the adult are characterized by a solid proliferation of oval to spindle cells with small, elongated nuclei showing a dense chromatin pattern with occasional small, inconspicuous nucleoli and surrounded by a scant rim of amphophilic cytoplasm. The cells often adopt a fascicular growth pattern but might grow as sheets admixed with variable numbers of small lymphocytes or might adopt a variety of unusual growth patterns such as the creation of rosette-like structures, a storiform pattern, a hemangiopericytic pattern, a micronodular pattern, a trabecular (adenoid) pattern, and others.[34] The epithelial tumor cells are completely devoid of cytologic atypia and mitotic activity. The tumors usually are characterized by a paucity of lymphocytes, although some cases show a significant number of T lymphocytes admixed with the epithelial cells. In some tumors, the lymphocytes display mitotic activity. These tumors correspond to the spindle cell type of thymoma in the traditional classification and to the medullary type of thymoma in the Marino and Muller-Hermelink[14] classification and are also the equivalent of type A thymoma in the WHO schema. Cases showing admixtures of spindle cell areas with round cell, lymphocyte-rich areas often are encountered and correspond to the mixed category in the Marino and Muller-Hermelink[14] classification and to type AB thymoma in the WHO schema.

Moderately differentiated thymic epithelial neoplasms (ie, atypical thymoma) are defined as tumors that still retain some of the organotypical features of differentiation of the thymus but already display some degree of cytologic atypia in the neoplastic epithelial cells. Such tumors are the equivalent of the predominantly epithelial thymomas of the traditional classification, of the well-differentiated thymic carcinoma of the Kirchner and Muller-Hermelink[15] classification, and of type B3 thymoma in the WHO schema.

The tumors are characterized histologically by sheets of large, round to polygonal epithelial cells with large, irregular, and hyperchromatic nuclei displaying occaisional prominent eosinophilic nucleoli and occasional mitotic figures. The nuclei often have irregular, raisin-like contours. The cytoplasm of the cells generally is abundant and deeply eosinophilic with very sharp cell borders often imparting the lesion with a "squamoid" appearance. Foci of early squamous differentiation can be encountered. The cells sometimes display "clear" cytoplasm and often show a tendency to palisade around vessels or perivascular spaces. The tumors often display at least some of the organotypical features of the thymus, such as lobulation, prominent dilated perivascular spaces, and

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the admixture of epithelial cells with small lymphocytes. The tumors are more often invasive than other types of thymoma and show a tendency for earlier recurrence. Atypical thymoma also can be composed of spindle to oval cells rather than round or polygonal cells. In such cases, the spindle cells will display increased nuclear size with prominent nucleoli and occasional mitotic figures.

Poorly differentiated thymic epithelial neoplasms (ie, thymic carcinoma) are characterized by the loss of the organotypical features of differentiation of the thymus and the presence of marked or overt cytologic features of malignancy. These tumors are the equivalent of thymoma type C in the initial proposal of the WHO classification, and they essentially resemble carcinomas similar to those arising in other epithelial organs. Thymic carcinoma represents a diagnosis of exclusion. Because there are no reliable, specific markers that can help determine the primary nature of these tumors, definitive diagnosis depends on the demonstration of absence of a primary tumor elsewhere by thorough clinical and radiologic studies or at the time of autopsy.[35,36] A large variety of histologic variants have been described, including keratinizing squamous cell carcinoma, nonkeratinizing poorly differentiated (lymphoepithelioma-like) squamous cell carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, basaloid carcinoma, spindle cell (sarcomatoid) carcinoma, anaplastic carcinoma, neuroendocrine carcinoma, and others.[35,36]

Critique of the Current Status of Thymoma Classification and Future Trends

It is clear that the current status of the histologic classification of thymoma has not satisfied all issues and that many questions remain unanswered. Some of the issues that still require clarification include the following:

Is the Current Terminology of Thymoma Acceptable and Scientifically Correct?

For a classification of a single family of tumors to have undergone so many permutations, it is obvious that some degree of discomfort must have existed regarding the various available designations. The purely descriptive terminology of the traditional classification, although morphologically accurate, was criticized for its inability to convey to the clinician the biologic potential of the lesion. In addition, it lacked categories for morphologic variants that did not fit into any of the 4 standard types.

The histogenetic classification later introduced by Marino and Muller-Hermelink[14] and subsequently modified by Kirchner and Muller-Hermelink[15] has been criticized (among other things) precisely for its lack of histogenetic accuracy.[25,32,37] Thus, tumors containing areas that closely recapitulate the thymic medulla are included under the category of predominantly cortical thymoma, and tumors that do not cytologically or architecturally resemble the normal medulla are designated as medullary (ie, the normal medulla is *not* composed of a solid population of small spindle cells). Tumors designated as mixed do not really represent a mixture of cortical and medullary differentiation, since a spindle phenotype is not synonymous with medullary origin or differentiation. Thus, they merely represent a mixture of the different morphologic appearances of thymic epithelial cells normally present in the different stages of maturation of the thymus (ie, round vs spindle epithelial cells).

In fact, the so-called predominantly cortical thymoma actually should be regarded as the prototypical example of a true mixed cortical and medullary thymoma according to the WHO definition because this is the only type of thymoma in which intimately admixed areas resembling the normal cortex and the normal medulla are present. Moreover, there does not seem to exist any thymic epithelial neoplasm that actually shows a strictly medullary phenotype or morphologic features (ie, one that faithfully resembles *only* the normal thymic medulla). Thus, the category of pure medullary thymoma is, strictly speaking, nonexistent. An explicit admission was made in the original WHO monograph that medullary thymoma, rather than representing a proliferation of cells showing medullary features, actually corresponds to a proliferation of "effete," nonfunctional thymic epithelial cells that recapitulate those seen in the involuted thymus of the adult.[25]

Finally, the criteria for defining the mixed category also are nebulous and confusing, and some of the tumors assigned to this category might not be displaying a mixed phenotype at all but actually might correspond to spindle cell thymomas that happen to contain an unusually heavy lymphocytic component, thus superficially resembling cortical areas.

Failure to support the histogenetic theory underlying this schema has been acknowledged by the authors of this classification and by others. Studies have found that immunostaining of thymomas with a panel of specific monoclonal antibodies (mAbs) showing selective reactivity for different types of epithelial cells of the normal thymus failed to permit clear differentiation between the tumor types.[15,19,38-40] In a study of thymoma with mAbs that exhibit selective reactivity with epithelial cells in the normal thymus, the authors of this classification themselves commented that "the immunophenotype of the neoplastic epithelial cells cannot be strictly correlated to the immunophenotypes of different epithelial cells in the normal thymus" and "using these mAbs, specific immunophenotypes of the different biological tumor types cannot be defined."[15]

It is obvious that the histogenetic approach, in general, has been unrewarding for the classification of thymic epithelial neoplasms. The histogenetic approach for these tumors

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also is dated, considering the fact that in most modern tumor classification systems, it is preferred to speak of realized lines of differentiation or phenotype rather than speculate on the "cells of origin" for any given neoplasm.

Another limitation of the histogenetic approach is that it implicitly assumes that the "normal" thymus is a static entity represented by well-defined cortical and medullary compartments. The thymus, however, is a complex lymphoepithelial organ whose morphologic appearance does not remain static over time; thus, trying to quantitate or pigeon-hole the normal appearance of the thymus can turn into an exercise in frustration because the normal (ie, nondiseased) thymus gradually changes over time. Thus, establishing the presence of *cortical* or *medullary* differentiation can become a very cumbersome and inaccurate exercise. Another criticism of this classification is that the term "well-differentiated thymic carcinoma," a relatively low-grade neoplasm compared with true thymic carcinoma, lends itself to confusion with the terminology used for more aggressive neoplasms in the other classification systems.

The terminology introduced by the WHO schema also has shown several shortcomings. One frequent criticism of the WHO schema is the use of the combination of letters and numbers to designate the various categories of thymoma, a practice that is seldom welcomed by clinicians who often prefer to deal with terms that are more intuitive and more clearly convey the nature of the lesion.

This criticism, however, should be unwarranted if we acknowledge the disclaimer made in the original monograph by the authors of the WHO schema that "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"[25] (italics added). This objective indeed has been accomplished to a great extent. One of the most significant contributions of the original WHO schema was to dispel the notion that the various competing classifications were dealing with different biologic tumor entities when in reality they were all referring to the same tumor prototypes under different designations. The WHO schema thus provided a practical and universally sanctioned means for translating and comparing results of studies from different investigators who used different terms and classifications of thymoma.

Are the Morphologic Criteria for the Histologic Typing of Thymoma Reproducible and Reliable?

One of the major criticisms leveled on the Marino and Muller-Hermelink[14] classification has been the issue of reproducibility.[28,41] In a study by Dawson et al,[41] 3 experienced thoracic pathologists evaluating a series of thymomas using the Marino and Muller-Hermelink[14] classification consistently agreed on the diagnosis in only 26 (35%) of 74 cases. In fact, reproducibility of histologic criteria for this classification has been so poor that several of the studies published in the literature based on the Marino and Muller-Hermelink[14] classification required outside review of the cases by one of the original proponents of the classification for accurate categorization.[15,18,21,22,42] Similar difficulties with reproducibility have been demonstrated for the WHO schema. In a large multicenter study by Rieker et al,[28] interobserver agreement for the subgroup of WHO type B (B1, B2, and B3) thymoma was only 0.49 using κ statistics (with a value >0.8 indicating excellent agreement and a value of ≤0.4 indicating poor agreement).

The difficulties for accurately reproducing the histopathologic criteria in the current WHO schema have been addressed.[28,43] Indeed, the morphologic criteria proposed for the WHO type AB and types B1 and B2 can show a great deal of overlap.

The round cell epithelial component in type AB thymoma is claimed to be composed of epithelial cells that are different from those seen in types B1, B2, and B3. The epithelial cells in the lymphocyte-rich areas in type AB are said to be "small and polygonal, or oval to spindle" (the latter essentially overlapping with the spindle cells in WHO type A). This claim would create a biologically untenable paradox, that of a tumor in which the neoplastic round epithelial component would not ever be expressed in pure form but only as part of an admixture with type-A elements, because it is claimed that these small polygonal cells are present only in the AB type.

We have, however, repeatedly observed examples of pure lymphocyte-rich (ie, type B1) tumors in which the thymic epithelial cells were small and had inconspicuous nucleoli such as those described for the lymphocyte-rich component in type AB, as well as cases of mixed AB thymomas in which the lymphocyte-rich areas contained epithelial cells with large, vesicular nuclei and prominent eosinophilic nucleoli essentially indistinguishable from those described for types B2 and B3 thymomas. We also have seen thymomas entirely composed of small spindle cells in which a prominent T-lymphocytic component created a close resemblance to conventional lymphocyte-rich thymoma; such tumors could easily be mistaken for the current definition of the WHO type AB thymoma.

The definition of WHO type B1 encompasses the lymphocyte-rich thymoma of Bernatz et al[1] and the predominantly cortical or organoid thymoma of Kirchner and Muller-Hermelink.[15] According to the latest WHO definition, these can vary from tumors composed predominantly of expanded areas resembling the normal cortex, with few, small round or polygonal epithelial cells scattered among a sea of lymphocytes, or they may grow displaying a lobular architecture recapitulating the normal thymic cortex separated by thick fibrous bands in which the scattered epithelial cells may be small, but also may be large with prominent nucleoli. In addition, prominent

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areas of medullary differentiation, including well-formed Hassall corpuscles, may be observed (which, when prominent, would correspond to the so-called organoid thymoma of Kirchner and Muller-Hermelink[15]).

Type B2 thymoma, on the other hand, also is listed as displaying features of lymphocyte-rich (Bernatz et al[1]) or cortical thymoma (Marino and Muller-Hermelink[14]), as well as the mixed lymphoepithelial thymoma of Bernatz et al.[1] The difference between B1 lymphocyte-rich and B2 lymphocyte-rich thymoma is said to be the size of the epithelial cells, these being "larger and more numerous," and with no areas of "medullary" differentiation.

The problem in real life is that thymomas are characterized by marked cellular heterogeneity, and the features of the tumor, including the relative size of its epithelial cells and their relative proportion of lymphocytes, can vary considerably from field to field within the same tumor, making exact categorization based on the preceding definitions a highly arbitrary exercise. Because of the frequent overlap in nuclear size and morphologic features in these tumors, rigid categorization into the WHO subtypes might be quite difficult, particularly in the type B group when numerous sections from a large resection specimen are available for review. The majority of the initial studies supporting the histogenetic classification (whose morphologic criteria closely overlap with the WHO schema) indeed were based on incompletely studied tumors for which limited biopsy samples or only a limited number of slides submitted in consultation to the authors were available for review or in which the number of sections available for review or the types of samples were not specified in the materials and methods section of their studies.[14,15,17,18,20]

The influence of tumor heterogeneity in the histopathologic classification of thymoma has been emphasized repeatedly.[7,11,44,45] In a study of 630 cases of resected thymomas, we were able to demonstrate that cellular heterogeneity can have a major role in determining the final classification of these tumors.[45] We found that the number of cases that showed mixed (AB) features was almost doubled when 5 or more histologic sections were available for review for any given tumor, as opposed to cases with fewer than 5 histologic sections. Thus, the more extensive the sampling, the more likely that morphologically heterogeneous areas will be identified within any given tumor. The rigid histologic criteria proposed by the WHO, therefore, may be reproducible and easy to apply in small core biopsy specimens or when only a limited number of histologic sections are available for review but might prove bewildering and confounding during careful examination of a properly sampled resection specimen in which an appropriate number of sections have been obtained from the resected specimen.[45,46]

Another important factor that bears on this discussion is the occurrence of unusual or rare morphologic variants of thymoma that cannot be assigned to any of the basic WHO subtypes.[31,47-49] This very problem has been acknowledged tacitly in the new WHO monograph, in which several subtypes of "unusual" thymomas have been segregated into individual categories outside the main classification scheme, including micronodular thymoma with lymphoid stroma, metaplastic thymoma, microscopic thymoma, sclerosing thymoma, and others.[26] The majority of such variants most likely represent unusual morphologic variations on the theme of thymoma, in which some of the basic elements common to these tumors (eg, location in the anterior superior mediastinum, dual cell population with admixture of epithelial cells/immature lymphocytes, lobulation, etc) are retained, but many of the other features will deviate significantly from the standard, more conventional types of thymoma. As more of these unusual variants of thymoma are recognized, how can they be reconciled with the current histopathologic classification for these tumors? What criteria are to be applied for their assessment and prognostication?

Is Subclassification of Thymoma Into Its Various Histologic Subtypes Necessary and Clinically Important?

This is another important question that has surfaced in recent years and one that merits serious consideration because of its practical implications. The plethora of terms and histologic types available for thymoma, although of academic interest, has yet to justify their existence from the viewpoint of their clinical validity.

Opinions are divided on the issue of whether histologic features alone constitute a valid predictor of outcome for these tumors or whether other factors outweigh the importance of histology. Some authors have claimed that certain histologic subtypes represent definitively benign tumors,[14,15,18,19,50] whereas others have clearly documented the potential for aggressive and malignant behavior for all histologic variants of thymoma.[3,6-9,11,20,22,24,33,43,51-53] It is our contention that histologic subclassification of thymoma, particularly for the well-differentiated variants, is of limited clinical importance. The vast majority of studies have demonstrated that for such tumors, regardless of their morphologic features, clinical staging is the most significant parameter for predicting biologic behavior.[25,27,52]

The original WHO monograph stated that, regarding the evaluation of thymoma, "the one based on the invasive/metastasizing properties of the tumor relates more closely to recurrence and outcome than the one based on cytoarchitectural features, to the point of markedly reducing the independent prognostic value of the latter."[25] In fact, a meta-analysis of some of the largest published series of thymoma during a 23-year period showed that the differences in survival for the better-differentiated variants of thymoma were not statistically significant when analyzed for histologic features alone and that significant differences were observed only when the

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patients were stratified according to clinical staging.[54] The question then arises, if the histologic features of well-differentiated, organotypical thymoma do not significantly influence prognosis, why bother subclassifying them?

The purpose of most histologic classifications, particularly as applied to neoplastic conditions, is to provide a reliable means for correlating the clinical behavior of the lesions with their morphologic features. Such a classification must be based on scientifically sound principles, should be easily reproducible and simple, and should offer a reliable correlation with clinical outcome.

So far, the majority of the proposed classifications have been very complex, often difficult to apply in clinical practice, with issues of reproducibility and interobserver variability, and with little advantage in terms of reliable prognostication for the lesions.[28,37,41,55-57] A recent study by Rieker et al[28] comparing the WHO schema with the traditional classification showed that further simplification of both systems into 3 subgroups led to classes with good discriminatory power with respect to survival. In addition, superior interobserver agreement was obtained with the simplified classification. Thus, by simplifying the WHO classification (ie, merging types A, AB, B1, and B2 into a single group, making B3 a separate group, and keeping type C as a separate group), 3 subgroups with distinct survival could be identified.[28] Similar results were observed for the Kirchner and Muller-Hermelink[15] classification in the study by Quintanilla-Martinez et al,[18] in which the authors merged the various histologic subtypes into 3 groups and found that only the well-differentiated thymic carcinoma (ie, WHO type B3) showed any significant difference in outcome from the rest.

Studies of thymoma have shown that a significant biologic breakpoint seems to occur with atypical thymoma (WHO type B3).[18,28,43] It seems that the point in the spectrum of differentiated thymomas in which histologic features become significant in predicting more aggressive behavior is when the tumor starts to show evidence of loss of functional maturity (ie, loss of immature T lymphocytes and predominance of epithelial cells) and progressive loss of the organotypical features of differentiation with the emergence of cytologic atypia in the epithelial component. This observation also is supported by recent molecular genetic studies that have shown that type B3 and type C thymomas share some genetic alterations.[58,59] Unlike the better differentiated forms of thymoma, atypical thymoma (WHO type B3) seems to be associated more often with invasion, earlier recurrence, and increased likelihood of tumor-related death.[28,33,43,60] The next significant biologic breakpoint occurs with thymic carcinoma, which follows a much more aggressive course, although some degree of overlap in clinical behavior might be seen between some well-differentiated variants of thymic carcinoma (such as well-differentiated squamous or mucoepidermoid carcinoma) and atypical thymoma.

Thus, there seems to be compelling evidence to support the adoption of a 3-tiered system for the morphologic classification of thymic epithelial neoplasms, namely one that separates low-grade from intermediate-grade from high-grade tumors. We believe the simplified classification scheme proposed previously by us fulfills this requirement,[27] as was demonstrated in the recent study by Rieker et al.[28] Assigning the various histologic variants of well-differentiated thymomas into this classification should represent a simple exercise. All that is required in this system is recognizing the organotypical features of thymic differentiation and the absence of cytologic atypia for a tumor to be classified as well-differentiated (Table 2). Establishing whether a given cell type predominates or the ratio of lymphocytes vis-à-vis epithelial cells becomes of secondary importance in this scheme, thus allowing for the inclusion of unusual combinations, rare histologic variants, and tumors with mixed or transitional features. Once a tumor has been assigned to the well-differentiated category of thymic epithelial neoplasms, prognostication can be determined by staging of the lesion.[27,34,54]

Which Are the Most Important Factors Involved in Predicting the Prognosis of Thymoma?

This represents one of the most critical questions that remain unresolved about the biology of thymoma. For many years, it was held that staging was the only reliable and critical factor for the prognostication of clinical behavior in thymoma. The trend in more recent years has been to accord histologic features an increasingly more important role in the prognostication of these tumors.[14,15,17-20] Studies of thymoma carried out mainly by French investigators, however, identified yet another significant factor affecting the prognosis of these tumors, namely the status of resectability of the tumor (ie, extent of surgery). In a large study by Regnard and associates,[53] complete surgical excision of the tumor at the time of initial surgery was the most significant independent prognostic factor in multivariate regression analysis ($P < .00001$). A meta-analysis of several large series of thymomas published during a 23-year period also found that differences in survival differed dramatically between patients who had undergone complete excision of the lesion and patients with only partial or incomplete excision.[54]

It thus becomes apparent that prognosis for thymoma is multifactorial and that at least 3 parameters might have a role in predicting the clinical behavior of these tumors to varying degrees: histologic features, staging, and status of resectability. The problem is that none of them appears to represent an absolute or totally independent parameter—they are all interdependent, and the weight that each one carries in the prognostication of these tumors might vary depending on the circumstances. We previously proposed a combined approach to the prognostication of thymoma that takes into account these

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various parameters and divides the tumors into favorable and unfavorable prognostic categories **Table 3**.[54] Although this is only a tentative schema that requires validation by clinical studies, we believe this approach provides a more pragmatic venue for the assessment of the clinical behavior of these tumors.

Future Trends and Conclusion

It is clear that much progress has been made in understanding the biology and morphology of thymoma. However, controversial issues remain, and there is still a need for a more effective approach to these tumors. The results of recent studies seem to indicate that part of the solution might lie in simplifying rather than increasing the complexity of thymoma histopathologic classification.[28] The future trend thus seems to point in the direction of a more simplified nomenclature and classification system.

Although the recognition of some of the distinctive morphologic growth patterns of thymoma can have a significant role in facilitating their histopathologic diagnosis, it has been acknowledged widely that the great variability and heterogeneity of the various cellular components in these tumors can make histologic subtyping a highly subjective and often inaccurate exercise.[11,13,32,34,45,52] Factors such as variability in staining methods, section thickness, extent of sampling, and even quantitative and qualitative overlap in morphologic criteria for defining the various subtypes can lead to significant interobserver variability.[28,41,45] In some cases, diagnostic criteria have proven so difficult to interpret that experienced pathologists have been forced to resort to the original proponents of the classification to properly classify their material.[16,18,21,22,42] Obviously, a system of classification that can be interpreted by only a few select experts eventually will be proven to be of limited practical value. Clearly, a more simplified approach that relies on easily applied morphologic criteria would lead to improved reproducibility in diagnosis for general pathologists.

Unfortunately, one of the main stumbling blocks that remains in this path is the adherence to terminology that has been time-honored or is sanctioned by members of the various schools of thought who generated the existing terms. When we proposed our histologic classification of thymoma, we also resorted to the use of time-honored terms such as *thymoma* and *thymic carcinoma,* and the only novel term we introduced was *atypical thymoma* to designate the intermediate forms representing moderately differentiated tumors in our schema.[27]

Objections, however, clearly could be raised against the use of those terms, particularly because they seem to suggest representation of separate and unrelated conditions. For example, use of the term thymic carcinoma in this context would seem to imply that the other 2 terms (thymoma and atypical thymoma) refer to benign conditions. Although the latter 2 terms indeed apply to low-grade tumors, in reality, all thymic epithelial neoplasms should be regarded as malignant neoplasms from inception with a definite potential for aggressive behavior if left untreated.[27] The terms thymoma, malignant thymoma, and thymic carcinoma, therefore, should be regarded as synonymous because they all refer to a malignant thymic epithelial neoplasm. Thus, more accurate terminology for these tumors would be that of well-, moderately, and poorly differentiated thymic carcinoma **Table 4**.

An analogous trend is being adopted for neuroendocrine neoplasms in several organ systems, whereby the old terms carcinoid, atypical carcinoid, and small cell carcinoma are being replaced by well-, moderately, and poorly differentiated neuroendocrine carcinoma.[61-63] Another alternative would be to use the designations low-grade, intermediate-grade, and high-grade thymoma for these tumors. The latter option would allow us to retain the time-honored term thymoma, with the understanding that we are referring to a malignant neoplasm, similar to the currently accepted use of the terms lymphoma and melanoma for designating malignant neoplasms of lymphocytes and melanocytes, respectively.

Because of the relatively indolent and slow growth of the majority of these tumors, the term thymoma unfortunately, in the minds of many pathologists and surgeons, is equivalent to a benign neoplasm. The fact is that if any of these tumors is left unchecked or goes untreated, it will prove in the majority

Table 3
Proposed Prognostic Categories for Thymoma, Excluding Thymic Carcinoma/WHO Type C*

Favorable prognostic categories
Group I
Encapsulated or minimally invasive thymoma
Completely excised
Equivalent to WHO histologic types A, AB, B1, B2
Group II
Encapsulated or minimally invasive thymoma
Completely excised
Equivalent to WHO histologic type B3
Group III
Widely invasive thymoma or thymoma with implants
Completely excised
All histologic types
Unfavorable prognostic categories
Group IV
Widely invasive thymoma or thymoma with implants
Incompletely excised
All histologic types
Group V
Widely invasive thymoma with or without intrathoracic metastases
Unresectable/biopsy only
All histologic types
Group VI
Widely invasive thymoma with distant metastases
Unresectable/biopsy only
All histologic types

WHO, World Health Organization.
* From Suster and Moran.[54] Reprinted by permission.

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Table 4
Proposed Terminology for the Histologic Classification of Thymic Epithelial Neoplasms and Their Equivalents in Other Systems

Proposed Terminology	Suster and Moran[27]	WHO[25]	Kirchner and Muller-Hermelink[15]	Bernatz et al[1] (Traditional)
Well-differentiated thymic carcinoma (thymoma, low-grade or grade I)	Thymoma	Types A, AB, B1, and B2	Cortical, mixed, medullary, predominantly cortical	Lymphocyte-predominant, mixed lymphoepithelial, epithelial-predominant
Moderately differentiated thymic carcinoma (thymoma, intermediate grade or grade II)	Atypical thymoma	Type B3	Well-differentiated thymic carcinoma	Epithelial-predominant with cytologic atypia
Poorly differentiated thymic carcinoma (thymoma, high grade or grade III)	Thymic carcinoma	Type C	High-grade carcinoma	—

WHO, World Health Organization.

of cases to be uniformly fatal due to uncontrolled growth and infiltration of vital structures. Because of the need for complete surgical extirpation of these tumors to obtain a good outcome and of their very real potential for aggressive and malignant behavior, acceptance of the term thymoma as synonymous with malignancy is warranted. Adoption of this approach will, of course, necessitate an active process of education of our clinical and surgical colleagues. As with any other tumor system, the term needs to be qualified to make allowances for the fact that some tumors in this family will be of very low-grade malignancy, whereas others may exhibit highly aggressive behavior.

A parallel situation applies to lymphomas and melanomas, in which indolent and low-grade tumors (eg, in situ, level I melanoma, small lymphocytic lymphoma) share the same family name with higher-grade tumors in the same group. An alternative approach would be to establish a cytologic grading system for these tumors, whereby tumors composed of cells devoid of cytologic atypia, regardless of their shape or content of lymphocytes, would correspond to a low-grade lesion (ie, thymoma, grade I); tumors with cells showing nuclear enlargement with mild to moderate cytologic atypia would correspond to intermediate-grade lesions (ie, thymoma, grade II); and tumors whose cells displayed overt cytologic features of malignancy would correspond to high-grade lesions (ie, thymoma, grade III) (Table 4).

In either case, the time seems ripe for finally leaving behind inadequate terms such as malignant thymoma (a redundant term) and the many other designations for the various histologic variants of well-differentiated or organotypical thymic epithelial neoplasms (cortical, medullary, mixed) that only further obscure our understanding of these lesions. A unifying terminology and a more rational approach to the histologic classification of these tumors might lead in turn to an improvement in our ability to diagnose them, predict their biologic behavior, further substratify meaningful prognostic categories, and offer optimum management for the patients.

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