

Pathology of Thymic Tumors

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As the thymus is composed of heterogeneous admixture of lymphoid and epithelial elements, tumors originating in the thymus may be of varied histologic types. Thymomas are the most common thymic tumor in adults. Thymoma classification has historically been controversial, but a system put forth by the World Health Organization (WHO) in 2004 has been generally accepted as a reproducible and clinically relevant classification. In addition to histologic subtype, tumor stage and resection status are important factors in determining outcome in thymomas. Thymic lymphomas typically occur in younger patients than thymomas. The most common thymic lymphomas are precursor T-lymphoblastic lymphoma, Hodgkin lymphoma, and primary mediastinal large B-cell lymphoma. Thorough histologic sampling and, in some cases, the appropriate use of ancillary studies such as immunohistochemistry, flow cytometry, and molecular studies, are important in proper pathologic evaluation of thymic tumors. *Semin Thorac Cardiovasc Surg* 17:2-11 © 2005 Elsevier Inc. All rights reserved.

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Normal Thymus

The thymus is a complex organ with epithelial and lymphoid elements (thymocytes) and represents the main site of T-cell maturation. It derives from the third pharyngeal pouch and becomes populated by lymphoid progenitor cells originating from the bone marrow. The organ is distinctly lobulated both on gross examination and microscopically. On histology, the *cortex*, located at the periphery of the lobules, appears dark due to closely packed immature small T-cells with relatively fewer epithelial cells. The more mature T-cells of the central *medulla* are admixed with numerous epithelial cells and some B-cells, imparting a paler appearance (Fig. 1A). The epithelial cells of the cortex contain markedly elongated cytoplasmic processes forming a reticular network which enmeshes the cortical lymphocytes.¹ The thymic medullary epithelial cells have fewer processes and undergo a terminal keratinization which forms pink, concentrically whorled keratinized structures called Hassall's corpuscles (Fig. 1B). These structures may undergo calcification or cystic change spontaneously or as a result of inflammation. The maximal thymic weight of approximately 35 g is achieved at puberty, after which the thymus undergoes a slow, progres-

sive involution.² The involution is due to predominantly to reduced numbers of lymphocytes with relative preservation of epithelial elements, eventually resulting in small islands of predominantly spindled epithelial cells with sparse lymphocytes in a background of adipose tissue.^{3,4}

Thymic Neoplasms: General Considerations

The term 'thymoma' refers to a neoplasm derived from thymic epithelium. These represent the most common thymic tumors in adults. Thymic carcinomas are distinguished from thymomas by their overt cytologic malignancy. However, this distinction should not be considered analogous to the 'adenoma-carcinoma' model in other organ sites, because thymomas may recur and metastasize even without overt cytologic features of malignancy. The recognition that certain histologic types of thymomas behave more aggressively provided the rationale to devise clinically useful histologic classification schemes for thymomas. Given the critical role of surgery in the clinical management of thymomas in particular (as opposed to thymic lymphomas), this article will focus mainly on these thymic epithelial tumors.

Lymphomas are far more common than thymomas in children and adolescents. These derive from the lymphoid cells of the thymus. As the thymus is the normal site of early T-cell maturation, it is not surprising that one of the most common lymphoid neoplasms to involve the thymus is precursor T-lymphoblastic lymphoma. In contrast to the epithelial-de-

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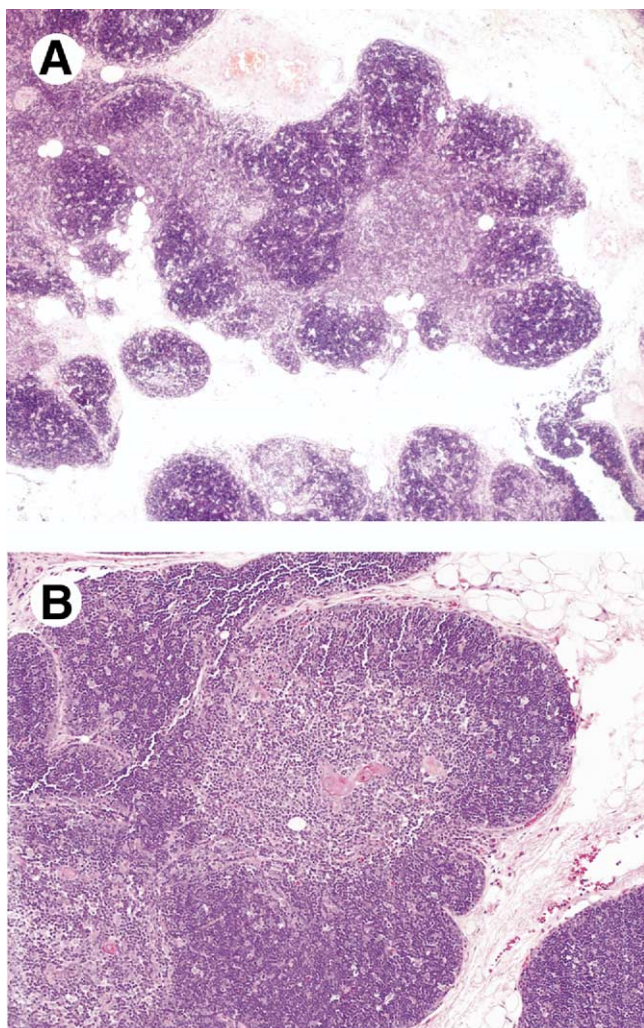


Figure 1 Normal thymus. (A) Low-power view of normal thymus demonstrates lobulated parenchyma with a thin fibrous capsule and surrounding mediastinal fat. The dark blue-staining cortex surrounds the pale medulla, located at the central aspect of the lobules. (B) Eosinophilic, whorled Hassall's corpuscles are located in the medulla. (Color version of figure is available online at <http://www3.us.elsevierhealth.com/semtcv/s/>.)

rived thymomas, cytokeratin-positive thymic epithelial cells are rare or absent in lymphoblastic lymphomas and primary mediastinal B-cell lymphomas; pseudoepithelial hyperplasia of medullary type epithelium may however accompany thymic nodular sclerosis Hodgkin lymphoma.

Mesenchymal and germ cell tumors of the thymus are uncommon tumors of uncertain histogenesis. Teratomas are the most common germ cell tumor, but seminomas and nonseminomatous germ cell tumors also occur in the thymus, almost exclusively in men.⁵ The thymus can rarely be a site of metastasis.

History of Thymoma Classifications Before the WHO Classification

A distinction of thymomas from thymic carcinomas and sarcomas was originally suggested in 1913 and 1916 by Sim-

monds and Ewing, respectively^{6,7} while Bell, in 1917, proposed for the first time that thymomas may be tumors derived from the thymic epithelium.⁸ This proposal remained controversial throughout decades,⁹ until Rosai and Levine in 1976 suggested that “the definition of thymoma should be restricted to neoplasms of the thymic epithelial cells, regardless of the presence or absence of a lymphoid component or the abundance of the latter.”¹⁰ This view has been generally accepted since then, but uncertainties about thymus physiology and histogenesis have fueled long lasting controversies about the most appropriate classification and nomenclature for thymomas.¹¹⁻¹⁶

The first widely used *histological* thymoma classification proposed by Bernatz¹⁷ and its modifications^{18,19} were “descriptive,” distinguishing “predominantly lymphocytic,” “predominantly epithelial,” “predominantly mixed,” and “predominantly spindle cell type” thymomas. Other authors suggested definitions based on the combined consideration of tumor cell morphology (spindle, polygonal, mixed) and lymphocyte content.^{15,20} These classifications distinguished thymic carcinomas from thymomas. As far as thymomas were concerned, however, these classifications were of limited clinical value.^{18,19}

To overcome this flaw, Levine and Rosai in 1978 proposed a classification¹⁰ that proved to be of high clinical relevance.^{19,20} That was not too surprising since both clinical stage and the degree of cellular atypia were taken into account, distinguishing benign (noninvasive) from malignant (invasive) thymomas. Malignant thymomas were further subdivided into category I (with no or minimal atypia) and category II (showing moderate to marked atypia). Category II thymomas were considered as equivalent to thymic carcinomas. Of note, a histological terminology was applied only to the group of thymic carcinomas, using terms of general tumor pathology. Thus, for benign and category I malignant thymomas, the “Levine and Rosai classification” was clinicopathological rather than histological.

In an attempt to define clinically relevant *histological* thymoma subtypes as an adjunct to clinical staging, Müller-Hermelink and coworkers have suggested a “histogenetic” thymoma classification since 1985.^{11,16} This classification included terms (medullary, cortical) that reflected the normal differentiation of the major functional and anatomic compartments of the thymus. It proved to be of independent prognostic value^{21,22} and was reasonably reproducible.²³ However, although supported by the bulk of morphological, immunological and genetic data,²⁴⁻²⁶ the histogenetic concept and suggested nomenclature have not been generally accepted.^{12,14,20}

Basis of the WHO Histologic Classification of Thymomas

Therefore, a WHO committee in 1999 proposed a noncommittal classification using letters and numbers.¹⁴ This classification was largely confirmed and supplemented with a few

new entities in 2003²⁷ and is based on the following major criteria and suggestions:

1. There are two major types of thymoma depending on whether the neoplastic epithelial cells and their nuclei have a spindle or oval shape (Type A thymoma) or whether the cells have a dendritic or epithelioid appearance (Type B thymoma).¹⁴
2. Type B thymomas are further subdivided on the basis of the proportional increase (in relation to the lymphocytes) and emergence of atypia of the neoplastic epithelial cells into three subtypes B1 (richest in lymphocytes), B2, and B3 (richest in epithelial cells).
3. Thymomas combining Type A with B1-like or (rarely) B2-like features are designated as Type AB.
4. Thymic carcinomas are named according to their differentiation (e.g., as squamous cell, mucoepidermoid, etc.). In contrast to the 1999 edition, the 2004 edition of the WHO classification encompasses neuroendocrine carcinomas (including carcinoids) among the thymic carcinomas, due to their overlapping morphological²⁸ and genetic features.²⁹ The term WHO type C thymoma is the “headline designation” to stress the thymic epithelial cell origin of these carcinomas.
5. Combined thymomas are specified by the WHO histology (A-C) and approximate percentage of each component.

Although the “WHO labels” may not be very intuitive, the “WHO classification” has been widely accepted and shown to be relevant in clinical, immunological and genetic studies [26,30 to 33]. Therefore, it is highly recommended for the sake of comparability that the WHO labels (Table 1) be used in clinical trials and pathology reports.

This recommendation also extends to the clinico-pathological evaluation of alternative proposals and new hypothetical concepts.^{13,34} It is anticipated that recent breakthroughs in thymus embryology³⁵ and the identification of thymic epithelial stem cells^{36,37} will help to elaborate a thymoma nomenclature that is both scientifically sound and morphologically intuitive.

Thymoma Pathology

Gross Pathology

Thymomas are typically encapsulated tumors, which have a grossly lobulated appearance. Although most tumors are solid, some may contain cystic cavities and rarely the tumor may be predominantly cystic (Fig. 2A). Penetration of the capsule, defining a more advanced tumor stage, may be suggested by extensions of unencapsulated tumor beyond the confines of the main tumor mass; the pathologist should extensively sample such areas to ensure accurate tumor staging.

Microscopic Pathology: General Features

As on gross examination, a lobulated architecture is characteristically appreciated on low power microscopic examina-

Table 1 WHO Classification of Thymomas and Carcinomas Arising in the Thymus

WHO Histological Type	Synonymous Terms (Traditional Nomenclatures)
Type A	Medullary thymoma; spindle cell thymoma
Type AB	Mixed thymoma
Type B1	Predominantly cortical thymoma; organoid thymoma; lymphocyte predominant thymoma; lymphocytic thymoma
Type B2	Cortical thymoma
Type B3	Well differentiated thymic carcinoma; epithelial predominant epithelial; squamoid thymoma;
Rare other Thymomas*	
● Micronodular thymoma with lymphoid stroma	
● Biphasic metaplastic thymoma	
Type C (carcinoma, ca)	Thymic carcinoma
● Squamous cell carcinoma ¹	(identical terms as in the WHO classification)
● Basaloid carcinoma	
● Mucoepidermoid carcinoma	
● Lymphoepithelioma-like ca	
● Sarcomatoid/spindle cell ca and carcinosarcoma	
● Clear cell carcinoma	
● Papillary carcinomas and other adenocarcinomas* (e.g. hepatoid carcinoma)	
● Rare other thymic carcinomas, including undifferentiated ca and “carcinoma with t(15;19) translocation”*	
● Neuroendocrine carcinomas ²	

WHO histological types as compared to synonymous terms applied by traditional thymoma nomenclatures.^{15,16,20} Entities that were not included in the WHO classification of 1999 are asterisked (*).

¹Squamous cell carcinomas were called either keratinizing or non-keratinizing epidermoid carcinomas in the previous version of the WHO classification.¹⁰

²Neuroendocrine carcinomas (NECs): carcinoids, atypical carcinoids, large cell NECs, and small cell NECs of the thymus formed a separate group of thymic tumors distinct from thymic carcinomas in the previous version of the WHO classification.¹⁰

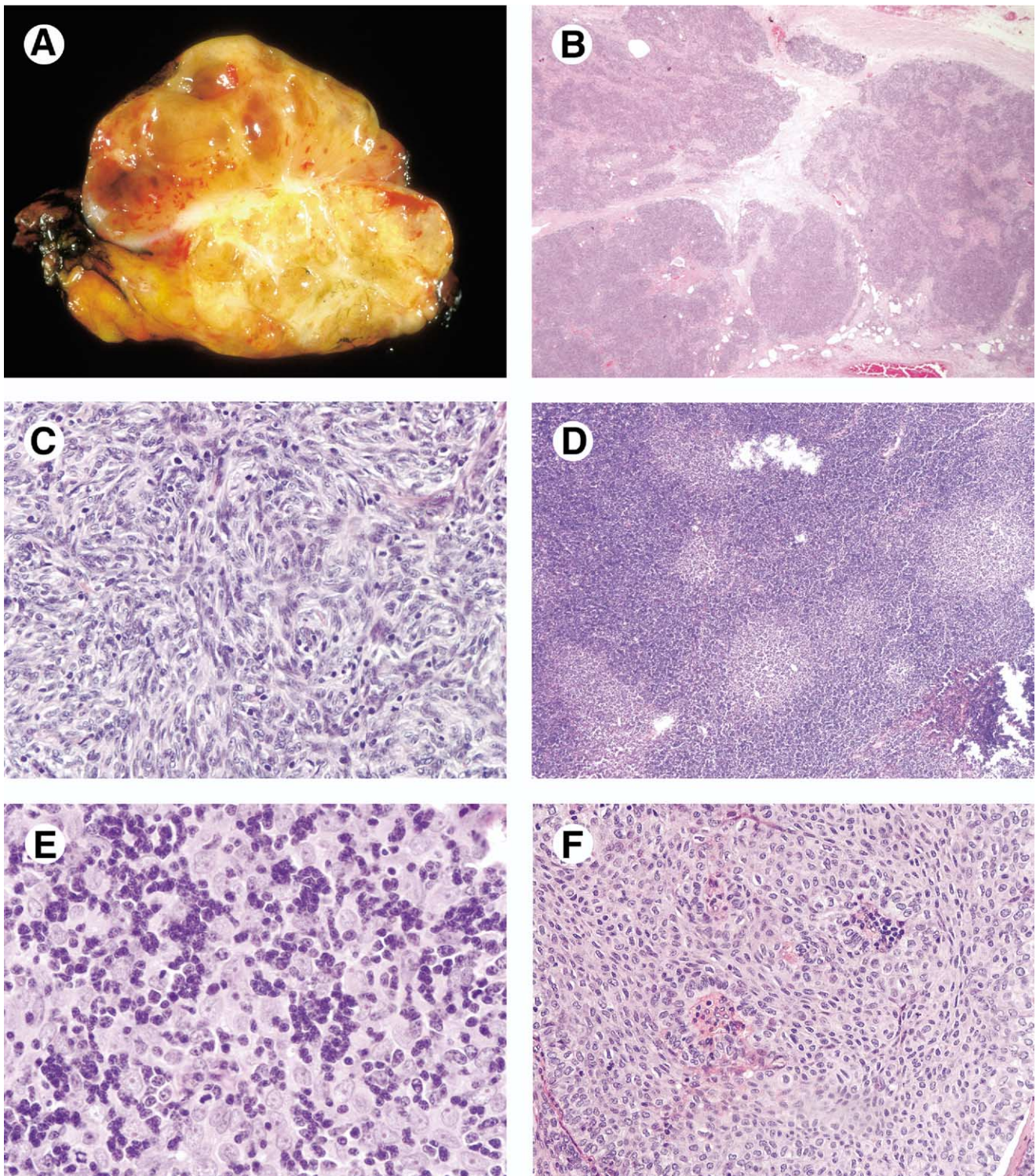


Figure 2 Thymomas. Thymomas are characteristically composed of tumor lobules separated by pink fibrous bands and with a thick fibrous capsule; this lobulated architecture is best appreciated (A) grossly and (B) microscopically at low power. (C) Thymoma Type A is composed of spindled tumor cells in sheets in a whorling or 'storiform' pattern. Lymphocytes are sparse. (D) In thymoma Type B1, lymphocytes predominate and the neoplastic epithelial cells are infrequent. Scattered pale areas represent areas of medullary differentiation; this so-called 'organoid' pattern somewhat recapitulates the normal thymic architecture. (E) In type B2 thymoma, the pale epithelial cells stand out distinctly among the small, dark blue lymphocytes. (F) Type B3 thymomas have the most abundant epithelial cells, with characteristically 'raisinoid' nuclei and sharply demarcated cytoplasmic borders. (Color version of figure is available online at <http://www3.us.elsevierhealth.com/semtevcs/>.)

tion and is helpful in distinguishing thymomas from other neoplasms (Fig. 2B). The neoplastic cells of thymomas express markers associated with epithelial differentiation such as cytokeratins and (variably) epithelial membrane antigen. Nearly all thymomas contain admixed nonneoplastic lymphocytes, which display histologic and immunophenotypic characteristics of normal thymic T-cells. Thymomas are classified according to their neoplastic (epithelial) and nonneoplastic (lymphocyte) components. It is not uncommon to have more than one histologic subtype within a single tumor, and the proportions of each subtype should be provided in the pathology report.

Type A Thymoma (Medullary Thymoma; Spindle Cell Thymoma)

In type A thymoma, the neoplastic epithelial cells assume an elongated or spindle cell appearance and are arranged in fascicles or in a whorling storiform pattern, superficially resembling a mesenchymal tumor (Fig. 2C). The spindled epithelial cells of type A thymoma may express the B-cell marker CD20, in contrast to cortical thymomas which are CD20 negative.^{38,39} Lymphocytes are typically sparse and have the phenotype of mature, medullary thymocytes (CD4+ or CD8+, CD1a-, TdT-). This quality of the admixed lymphocytes may be helpful in cases difficult to classify based on epithelial cell features alone. An unusual variant known as *micronodular thymoma* is characterized by small nodules of spindled epithelial cells in a background of predominantly B-cells with lymphoid follicles.⁴⁰ Type A thymomas are significantly more likely to be lower stage than type B thymomas.⁴¹

Type B1 Thymoma (Predominantly Cortical Thymoma)

In contrast to type A thymomas, the type B (cortical) thymomas have ovoid or polygonal epithelial cells and immature, cortical-type (double CD4+ 8+, CD1a+, TdT+) thymocytes. The latter cells are most abundant in type B1 thymoma and may obscure the rather inconspicuous, scattered epithelial cells. Cytokeratin staining often highlights more epithelial cells than is evident on routine histology. A hallmark of type B1 thymoma is the presence of focal medullary differentiation, manifested by small pale areas of somewhat more elongated epithelial cells within a background of mature, medullary-type thymocytes which is less dense than the surrounding cortical areas (Fig. 2D). Because this characteristic pattern of both cortical and medullary-like areas recapitulates normal thymic structure, this pattern is often referred to as 'organoid'. Although often large, among the cortical-type thymomas, type B1 is the most likely to be low stage.

Type B2 Thymoma (Cortical)

In contrast to Type B1 thymomas, pale areas of medullary differentiation are absent or rare in Type B2 thymomas. The epithelial cells are more numerous, larger, and have more distinct nucleoli than those of Type B1 thymoma. Lymphocytes are still frequent and have an immature, cortical thy-

mocyte phenotype. The frequent epithelial cells are readily identifiable on routine histology, and may form clusters or trabeculae (Fig. 2E). Perivascular spaces (edematous areas surrounding tumor blood vessels) are commonly seen in this type of thymoma.

Type AB Thymoma (Mixed)

Mixed thymomas include both elements of Type A thymoma and Type B thymoma in varying proportions, either as clearly defined separate areas or in a more intimate admixture. The epithelial and thymocyte features of each component resemble those of typical Type A and Type B1, or (less commonly) B2 thymomas described above.

Type B3 Thymoma (Well Differentiated Thymic Carcinoma)

Among the cortical thymomas, Type B3 has the highest ratio of epithelial cells to thymocytes. In contrast to Types B1 and B2 thymomas, the epithelial cells in this type are atypical, rounded cells with small, irregular nuclei, abundant pale cytoplasm and sharply defined cell borders (Fig. 2F). Areas of squamous differentiation and even keratinization may be present. Some cases may have a spindled appearance which may lead to confusion with the much more indolent Type A thymoma; however, the spindled epithelial cells will manifest cytologic atypia, which should not be present in Type A thymoma. Type B3 thymoma almost always has genetic abnormalities, in contrast to the typically diploid Type A and AB thymomas.^{25,42}

Type C Thymoma (Thymic Carcinoma)

Cases in which the epithelial cells exhibit cytologic features of malignancy are classified as thymic carcinomas. These tumors often lack encapsulation and may be adherent to mediastinal structures and/or metastatic to mediastinal lymph nodes at the time of resection. Thymic carcinomas often resemble malignant neoplasms from other organs (particularly lung or the upper respiratory tract) and fail to recapitulate features of normal thymus, such as medullary differentiation and an admixture of immature cortical-type thymocytes. Aside from malignant histology, the majority of thymic carcinomas express CD5, unlike Type A, AB, and B thymomas.⁴³ These tumors occur most often *de novo*, but sometimes appear to represent malignant transformation in a preexisting thymoma.⁴⁴ Subtypes include squamous cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, lymphoepithelioma-like carcinoma, sarcomatoid carcinoma, clear cell carcinoma, papillary carcinoma, neuroendocrine carcinomas, and undifferentiated carcinoma. As in other sites of the body, thymic carcinoids are now termed well-differentiated neuroendocrine carcinoma to underscore their potential for recurrence and metastasis.^{45,46} Poorly differentiated thymic neuroendocrine carcinomas histologically resemble large cell or small cell neuroendocrine carcinomas of the lung. Examples of thymic carcinomas are illustrated in Fig. 3A-C.

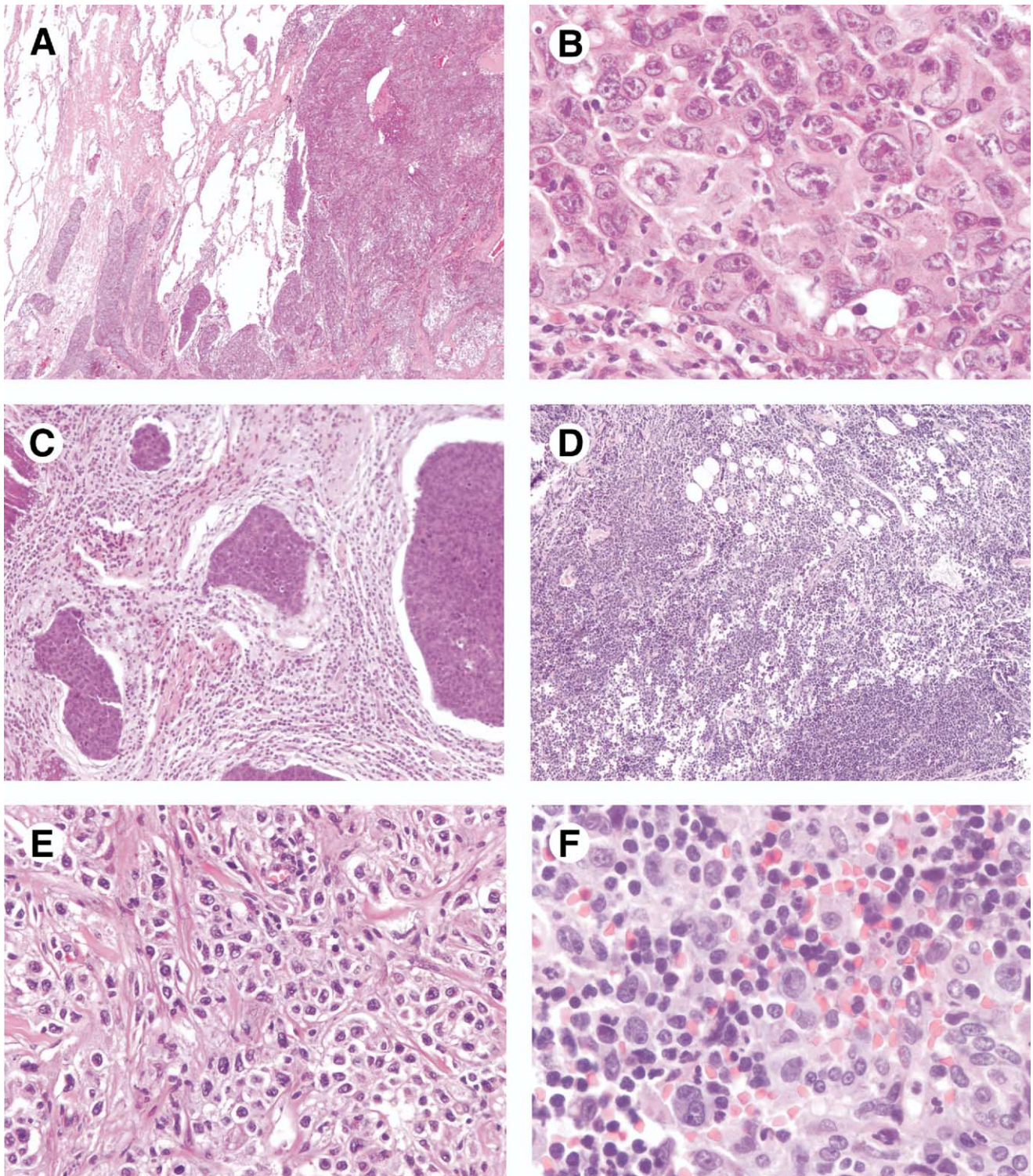


Figure 3 Thymic carcinomas and lymphomas. (A) Poorly differentiated squamous cell thymic carcinoma, invading lung at the time of resection. (B) Poorly differentiated squamous cell thymic carcinoma at high power manifests frank cytologic features of malignancy. (C) Lymphoepithelioma-like thymic carcinoma resembles lymphoepithelial carcinoma of the head and neck. The malignant epithelial cells may either be admixed with small, mature lymphocytes or may be present as lobules within a lymphoid-rich stroma, as in this example. (D) Precursor T-lymphoblastic lymphoma infiltrates the surrounding fat and lacks a capsule, unlike thymomas. Thymic epithelial cells are absent or rare. (E) Primary mediastinal large B-cell lymphoma. The tumor cells are large and exhibit a packeted configuration in a fibrous stroma with frequent small lymphocytes. (F) Thymic Hodgkin lymphoma (nodular sclerosis type). The large neoplastic Reed-Sternberg cells are in a mixed inflammatory background of small lymphocytes, neutrophils, and eosinophils. (Color version of figure is available online at <http://www3.us.elsevierhealth.com/semctcv/>.)

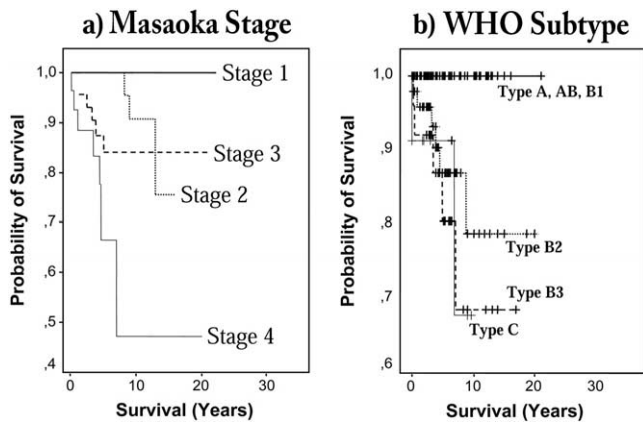


Figure 4 Correlation between (A) Masaoka tumor stage and (B) histological WHO thymoma subtype with survival.

Prevalence of Thymoma Subtypes

The predominant histological subtypes in most published series are Type B2 and AB thymomas (each 20% to 35% of all cases). Type B1 and Type A thymomas count among the rare types (5% to 10% in most studies).⁴⁷ The prevalence of Type C thymomas is 10% to 25%.^{16,32} In children, thymomas and thymic carcinomas are rare:²⁷ Type A, B1, and B2 thymomas have been observed, in addition to undifferentiated and EBV-positive lymphoepithelioma-like thymic carcinomas and the rare “carcinomas with t(15;19) translocation.”^{48,49}

Thymic Pathology in Myasthenia Gravis Patients

Thymic pathology occurs in 80% to 90% of myasthenia gravis (MG) patients.⁵⁰ In the majority of these cases, this manifests as thymic follicular hyperplasia. Thymomas are identified in only about 10% of patients. These thymomas may be microscopic, necessitating careful sampling and microscopic examination of thymectomy specimens from MG patients even in the absence of a grossly identifiable tumor mass.⁵¹ Type A, AB, and B1 to B3 thymomas are all associated with MG. In contrast, thymic carcinoma (Type C thymoma) is not associated with MG. This may reflect the partial recapitulation of normal thymus and presence of maturing T-cells in these thymomas (as opposed to thymic carcinomas), which appear to be critical for the pathogenesis of paraneoplastic MG.¹⁶

Prognostic Features and Survival in Thymomas

The most relevant prognostic factors in thymoma are tumor stage,^{20,21,30-32,52} WHO-based histologic type,³⁰⁻³³ thymoma resection status^{31,52} and tumor recurrence³¹ (Figs. 4 and 5). Thus, Type A and AB thymomas in stages I and II almost always follow a benign clinical course,^{30,32} and even at higher stages may not be fatal due to a very slowly progressive course.²⁰ Type B1 thymomas have a low malignant potential, although local recurrences or metastases

may occur more than 20 years after removal of the primary tumor. Type B2, B3, and C thymomas are clear-cut malignant tumors, with well-differentiated squamous, basaloid and mucoepidermoid carcinomas following a more favorable course than their poorly differentiated counterparts and other Type C thymomas.⁵³ The prognosis of combined thymomas is most probably determined by the most malignant component.^{31,44}

Adjuvant treatment in malignant thymomas and thymic carcinomas appeared to improve survival in some^{31,32} but not other studies.⁵⁴ Whether tumor size is a prognostic marker across the various thymomas and thymic carcinoma subtypes is not clear.^{31,52}

Paraneoplastic pure red cell aplasia, other cytopenias, and hypogammaglobulinaemia/Good’s syndrome have an adverse effect on survival.⁵⁵ By contrast, myasthenia gravis has no adverse or even a positive effect in recent clinical series, probably due to earlier thymoma detection.^{32,56}

Staging of Thymomas and Thymic Carcinomas

The Masaoka system,⁵⁷ including its slight modification²⁰ (Table 2) is the most widely used staging system for thymomas and thymic carcinomas due to its proven clinical relevance (Fig. 4A). However, its role in the staging of mediastinal neuroendocrine carcinomas (NECs, now included with the spectrum of thymic carcinomas) is less clear, due to the paucity of clinical studies and the tendency of NECs to metastasize earlier than thymomas.⁵⁸ In the WHO classification it is suggested to stage all malignant thymomas and thymic carcinomas according to a TNM scheme based on the proposal of Yamakawa⁵⁹ (Table 3). This scheme is tentative for testing (TNM-Supplement, 2nd Edition), since an authorized TNM system does not exist, due to the paucity of clinicopathological data.²⁷ In particular, it has to be determined whether the same stage grouping is reasonable for thymomas as well as neuroendocrine and other thymic carcinomas.²⁷

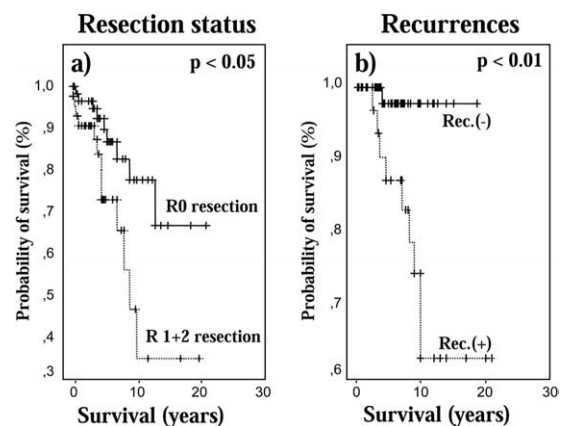


Figure 5 Correlation between (A) resection status and (B) tumor recurrence with survival (R0: complete tumor resection; R1: incomplete tumor resection by histology; R2: incomplete tumor resection by gross examination).

Table 2 Masaoka Staging System as Modified by Shimosato et al.^{20,69}

Masaoka Stage	Criteria
I	Fully encapsulated tumor*
II	Tumor infiltrates beyond the capsule into the thymus or mediastinal fat*; adhesion to the mediastinal pleura may be present
III	Tumor infiltrates through the mediastinal pleura, or infiltrates into adjacent organs (lung, pericardium, thoracic wall, diaphragm) or great vessels
IVA	Tumor dissemination (implants) in the pleural or pericardial cavity
IVB	Any tumor with lymphogeneous or hematogenous metastasis

*The original Masaoka classification^{30,57} defined thymomas with infiltration into the tumor capsule as stage II tumors. We prefer the modified definition for two reasons. First, in our experience, the diagnosis of infiltration beyond the capsule is better to reproduce. Second, with respect to clinical relevance (such as survival) the distinction between stage I and stage II appears slightly more discriminatory when applying the modified system.^{20,31,32}

Thymic Lymphomas

Lymphoblastic Lymphoma

Lymphoblastic lymphomas (LBL) are usually, and in the thymus are nearly exclusively, of T-cell lineage. The tumor cells most commonly resemble cortical thymocytes morphologically and immunophenotypically (double CD4+ 8+, CD1a+, TdT+). Unlike the cortical thymocytes of normal thymus or type B thymomas, however, the neoplastic cells of LBL infiltrate the fat and form solid sheets rather than lobules. Cytologically, the tumor cells are slightly larger than small lymphocytes with dispersed nuclear chromatin, highly irregular nuclear contours, and frequent mitotic figures (Fig. 3D). Some cases of thymic LBL represent tissue manifestations (and may in fact be the initial clinical presentation) of T-cell acute lymphoblastic leukemia.

Primary Mediastinal Large B-Cell Lymphoma

Primary mediastinal large B-cell lymphoma (MLBCL) is a type of diffuse large B-cell lymphoma of primary thymic origin, which occurs predominantly in young adults.⁶⁰ The tumor comprises large lymphoid cells with irregular, vesicular nuclei, often occurring in a sclerotic background (Fig. 3E). In contrast to the fibrous bands defining sharply demarcated large lobules in thymoma or nodules in Hodgkin lymphoma, the fibrosis of MLBCL manifests as thinner septae or bands defining smaller 'packets' of tumor cells. By definition, the tumor cells in MLBCL are positive for B-cell markers such as CD20 (although they typically lack surface immunoglobulin expression), may weakly express CD30, and are negative for cytokeratin.⁶¹ Low-grade B-cell lymphomas of the thymus

are rare. The most common of these is extranodal marginal-zone B-cell lymphoma of MALT type, which has been associated with concurrent autoimmune diseases.⁶²

Hodgkin Lymphoma

The vast majority of Hodgkin lymphomas (HL) occurring in the thymus are classical nodular sclerosis type. These cases most commonly present as a large mediastinal mass, which may have a cystic component.⁶³ The neoplastic cells are large with vesicular, often multiple nuclei and prominent nucleoli, invariably including typical Reed-Sternberg cells. Similar cells may be seen in non-Hodgkin's lymphomas (including MLBCL), but in HL there is usually a prominent mixed inflammatory background, often rich in eosinophils and neutrophils (Fig. 3F). Some cases may be impossible to distinguish from MLBCL on routine histology alone. With immunohistochemistry, the neoplastic cells in HL are CD30 and usually CD15 positive and are negative for CD45 and CD20. Rare cases may have features of both HL and MLBCL and defy definitive classification; such cases have been termed 'gray-zone' lymphomas. There is no consensus on the appropriate therapy for such 'gray-zone' lymphomas.^{64,65}

Table 3 TNM Clinical Classification (Tentative for Testing)

T—Primary Tumor			
	TX Primary tumor cannot be assessed		
	T0 No evidence of primary tumors		
	T1 Tumor completely encapsulated		
	T2 Tumor invades pericapsular connective tissue		
	T3 Tumor invades into neighbouring structures, such as pericardium, mediastinal pleura, thoracic wall, great vessels and lung		
	T4 Tumor with pleural or pericardial dissemination		
N—Regional Lymph Nodes			
	NX Regional lymph nodes cannot be assessed		
	N0 No regional lymph node metastasis		
	N1 Metastasis in anterior mediastinal lymph nodes		
	N2 Metastasis in other intrathoracic lymph nodes excluding anterior mediastinal lymph nodes		
	N3 Metastasis in scalene and/or supraclavicular lymph nodes		
M—Distant Metastasis			
	MX Distant metastasis cannot be assessed		
	M0 No distant metastasis		
	M1 Distant metastasis		
Stage Grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0, 1	M0
Stage IV	T4	Any N	M0
	Any T	N2, 3	M0
	Any T	Any N	M1

Diagnostic Approach to Thymic Tumors

Pathologists are being confronted increasingly with smaller tissue samples on which to make a diagnosis, such as material from fine needle aspiration with or without an accompanying core needle biopsy. In the case of thymic tumors, the role of such minimally invasive sampling is usually to establish a tumor as a thymic epithelial tumor and therefore a candidate for resection, as opposed to a lymphoma in which surgical resection is not indicated. Fine needle aspiration, especially if coupled with a needle biopsy and the use of immunohistochemistry, flow cytometry (to detect aberrant immunophenotypes in lymphomas), and molecular clonality studies (mainly in cases with a normal immunophenotype), usually provides accurate diagnosis of thymomas versus lymphomas.⁶⁶ However, the presence of entrapped or even hyperplastic epithelium in lymphomas or the paucity of epithelial cells in Type B1 lymphomas may lead to misclassification in limited material.^{67,68} Thus, while these minimally invasive samples provide useful guidance, close communication with the cytopathologist/pathologist is essential to determine the definitiveness of the diagnosis before treatment is instituted.

Ideally, thymic biopsy and resection specimens should be sent to the pathologist fresh to allow the possibility of special studies to help in making the diagnosis. Thymic tumors are generally classified on histologic and immunohistochemical studies, which can be done on routine sections. However, in certain cases, additional studies may be helpful or even necessary to render an accurate diagnosis. For example, flow cytometry may be useful in distinguishing low-grade B-cell lymphomas from reactive lymphoid proliferations, gene rearrangement studies on frozen tissue can help distinguishing MLBCL from Hodgkin lymphoma in difficult cases, and cytogenetics may be useful in classifying some unusual types of thymic carcinoma.⁴⁹ A frozen section taken from a portion of the fresh specimen is helpful to the pathologist in identifying cases which may require such ancillary studies and in directing which studies to send. A sample of a resected thymoma may also be frozen intraoperatively to determine tumor type and the presence of invasiveness. However as thymomas are often heterogeneous and predominantly benign-appearing tumors may harbor focal areas of carcinoma, a definitive classification can only be rendered after reviewing permanent sections taken from a thoroughly sampled tumor. Thymic cysts should also be carefully examined and sampled by the pathologist. While unilocular or multilocular thymic cysts can occur spontaneously or as a developmental abnormality, a variety of thymic tumors, such as Hodgkin lymphoma, germ cell tumors, and, rarely, thymomas and thymic carcinomas, may present as a thymic 'cyst'. The predominantly cystic nature of these tumors may obscure the diagnostic areas of tumor.

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