The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors?

Alexander Marx, MD,[a,*] John K. C. Chan, MD,[b] Lara Chalabreysse, MD,[c] Sanja Dacic, MD, PhD,[d] Frank Detterbeck, MD,[e] Christopher A. French, MD,[f] Jason L. Hornick, MD, PhD,[g] Hiroshi Inagaki, MD, PhD,[h] Deepali Jain, MD,[i] Alexander J. Lazar, MD, PhD,[j] Mirella Marino, MD,[k] Edith M. Marom, MD,[l] Andre L. Moreira, MD, PhD,[m] Andrew G. Nicholson, MD,[n] Masayuki Noguchi, MD,[o] Daisuke Nonaka, MD,[p] Mauro G. Papotti, MD,[q] Stefan Porubsky, MD,[r] Lynette M. Sholl, MD,[s] Hisashi Tateyama, MD,[t] Vincent Thomas de Montpréville, MD,[u] William D. Travis, MD,[v] Arun Rajan, MD,[w] Anja C. Roden, MD,[x] Philipp Ströbel, MD[y]

[a]*Institute of Pathology, University Medical Centre Mannheim, Heidelberg University, Mannheim, Germany*
[b]*Department of Pathology, Queen Elizabeth Hospital, Kowloon, Hong Kong SAR, People's Republic of China*
[c]*Department of Pathology, Groupement Hospitalier Est, Bron Cedex Lyon, France*
[d]*Department of Pathology, University Pittsburgh Medical Center, Pittsburgh, Pennsylvania*
[e]*Department of Surgery, Yale University School of Medicine, New Haven, Connecticut*
[f]*Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*
[g]*Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*
[h]*Department of Pathology and Molecular Diagnostics, Nagoya City University, Nagoya, Japan*
[i]*Department of Pathology, All India Institute of Medical Sciences, New Delhi, India*
[j]*Department of Pathology and Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[k]*Department of Pathology, Istituto di Ricovero e Cura a Carattere Scientifico Regina Elena National Cancer Institute, Rome, Italy*
[l]*Department of Diagnostic Imaging, Chaim Sheba Medical Center, affiliated with Tel Aviv University, Ramat Gan, Israel*
[m]*Department of Pathology, New York University Langone Health, New York, New York*
[n]*Department of Histopathology, Royal Brompton and Harefield Hospitals and National Heart and Lung Institute, Imperial College, London, United Kingdom*
[o]*Department of Diagnostic Pathology, University of Tsukuba, Tsukuba-shi, Japan*
[p]*Department of Cellular Pathology, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, United Kingdom*
[q]*Department of Oncology, University of Torino, Turin, Italy*
[r]*Department of Pathology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*
[s]*Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts*
[t]*Department of Pathology, Kasugai Municipal Hospital, Kasugai, Japan*
[u]*Department of Pathology, Marie Lannelongue Hospital, Le Plessis-Robinson, France*
[v]*Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York*
[w]*Thoracic and Gastrointestinal Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*
[x]*Department of Laboratory Medicine and Pathology, Mayo Clinic Rochester, Rochester, Minnesota*
[y]*Institute of Pathology, University Medical Center Göttingen, Göttingen, Germany*

Received 28 August 2021; revised 6 October 2021; accepted 7 October 2021
Available online - 22 October 2021

*Corresponding author.

Disclosure: Dr. Dacic reports receiving personal fees from AstraZeneca, Takeda, and Janssen, outside the submitted work. Dr. French reports receiving grants from Boehringer Ingelheim, personal fees from Boehringer Ingelheim, and other support from Epigenetix, outside the submitted work. Dr. Hornick reports receiving personal fees from Aadi Biosciences and Tracon Pharmaceuticals, outside the submitted work. Dr. Nicholson reports receiving grants and personal fees from Pfizer and personal fees from Merck, Boehringer Ingelheim, Novartis, AstraZeneca, Bristol Myers Squibb, Roche, AbbVie, Oncologica, UpToDate, European Society of Oncology, and Liberum, outside the submitted work. Dr. Papotti reports receiving personal fees from Pfizer, Eli Lilly, and AAA/Novartis, outside the submitted work. Dr. Sholl reports receiving grants from Genentech and Eli Lilly and personal fees from GV20 Therapeutics. The remaining authors declare no conflict of interest.

Address for correspondence: Alexander Marx, MD, Institute of Pathology, University Medical Centre Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. E-mail: alexander.marx@umm.de

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2021.10.010

ABSTRACT

This overview of the fifth edition of the WHO classification of thymic epithelial tumors (including thymomas, thymic carcinomas, and thymic neuroendocrine tumors [NETs]), mediastinal germ cell tumors, and mesenchymal neoplasms aims to (1) list established and new tumor entities and subtypes and (2) focus on diagnostic, molecular, and conceptual advances since publication of the fourth edition in 2015. Diagnostic advances are best exemplified by the immunohistochemical characterization of adenocarcinomas and the recognition of genetic translocations in metaplastic thymomas, rare B2 and B3 thymomas, and hyalinizing clear cell carcinomas. Advancements at the molecular and tumor biological levels of utmost oncological relevance are the findings that thymomas and most thymic carcinomas lack currently targetable mutations, have an extraordinarily low tumor mutational burden, but typically have a programmed death-ligand 1^{high} phenotype. Finally, data underpinning a conceptual advance are illustrated for the future classification of thymic NETs that may fit into the classification scheme of extrathoracic NETs. Endowed with updated clinical information and state-of-the-art positron emission tomography and computed tomography images, the fifth edition of the WHO classification of thymic epithelial tumors, germ cell tumors, and mesenchymal neoplasms with its wealth of new diagnostic and molecular insights will be a valuable source for pathologists, radiologists, surgeons, and oncologists alike. Therapeutic perspectives and research challenges will be addressed as well.

Keywords: Thymoma; Thymic carcinoma; Thymic neuroendocrine tumor; NET G3; Germ cell tumor; WHO classification

Introduction

The fifth edition of the "WHO Classification of Thoracic Tumours"[1] is largely a revision of the fourth edition that was entitled "WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart" and published in 2015 under the editorship of William D. Travis, Elizabeth Brambilla, Allen Burke, Alexander Marx, and Andrew Nicholson.[2] Similar to the fourth edition, the fifth edition continues (1) to use the unique, globally accepted "type A, AB, B1-B3 thymoma" nomenclature originally introduced by the late Dr. Juan Rosai for the major thymoma types in the second edition of the WHO Classification in 1999; (2) to cover all tumor types together with clinical, pathologic, and genetic data in one book (introduced in the third edition); and (3) to stress the interdisciplinary "tumor board approach" in mediastinal oncology that has been prominently advocated and promoted by the International Thymic Malignancy Interest Group (ITMIG)[3] and led to the involvement of clinical experts from radiology, thoracic surgery, and oncology as co-authors in the fourth edition. Along these lines, the incorporation of state-of-the-art computed tomography and positron emission tomography/computed tomography images and cytology has since been maintained. Furthermore, the broad, interdisciplinary and international consensus that underlies the fifth edition is reflected by a change in editorship: instead of five editors who were in charge of the third and fourth editions owing to their expertise in the fields of pulmonary, pleural, thymic, and cardiac pathology, the fifth edition is under the auspices of an editorial board comprising 16 experts from North America, Europe, and Asia with expertise in pathology, surgery, radiology, and oncology.

The time period since the publication of the fourth edition has seen highly dynamic new developments in the fields of pathology, tumor biology, and medical oncology related to thymic epithelial tumors (TETs) and left their imprints on the fifth edition: First, a TNM staging system for thymomas, thymic carcinomas (TCs), and thymic neuroendocrine tumors (NETs) was approved and published by the Union for International Cancer Control (previously International Union Against Cancer)[4] in 2017 on the basis of joint data from the International Association for the Study of Lung Cancer and ITMIG,[5] prompting the editors of the fifth edition to adopt the TNM system as obligatory and the modified Masaoka-Koga system as optional for the staging of TETs.[6] Second, thymomas and TCs were the last cancer group investigated by the multiomics-based The Cancer Genome Atlas (TCGA) project, explaining why groundbreaking new insights were mainly achieved in thymomas and TC, including the realization that they exhibit an extreme paucity of targetable mutations.[7,8] Third, immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein-1 or programmed death-ligand 1 (PD-L1), approved for treatment of several cancers since 2014,[9] have attracted the interest of medical oncologists and pathologists given the frequent expression of PD-L1 by TETs,[10,11] resulting in initiation of clinical trials to evaluate ICIs for treatment of advanced TETs.[12–14] The results, in turn, have sparked interest in paraneoplastic autoimmunity and biomarkers, because the occurrence of severe immune-related adverse events remains a major challenge.[15]

In the chapters on germ cell tumors (GCTs) and soft tissue neoplasms, there are no changes in the concept or diagnostic criteria in the fifth compared with the fourth edition. Minor revisions concern new adaptation of nomenclature and definitions to the fifth WHO

Classifications of Tumours—Soft Tissue and Bone Tumours[16] and Tumours of the Urinary System and Male Genital Organs.[17] "New" diagnostic pitfalls owing to overlapping immunohistochemical features between SMARCA4 thoracic tumors, NUT carcinomas, and GCTs are also mentioned.

The subsequent review focuses on the differences between the fourth and fifth editions of the WHO classification of solid tumors of the thymus and mediastinum rather than providing comprehensive description of the tumors.

Thymoma

Features Maintained

The concept of the classification, nomenclature, diagnostic criteria, and reporting strategies for thymomas and their interpretation as malignant tumors (except for micronodular thymoma with lymphoid stroma) have been maintained (Table 1).[18] Thymomas are classified as type A thymoma (including an atypical variant), AB thymoma, type B thymoma (separated into B1, B2, and B3 thymomas), micronodular thymoma with lymphoid stroma, and metaplastic thymoma by histologic features and, rarely, immunohistochemistry, such as immature T cell content. The high frequency of the *GTF2I* (p.L424H) mutation in type A and AB thymomas[8] was confirmed,[7] although the low prevalence in type B thymomas and TCs is less consistently reported.[7,8,19]

What Is New?

A formal new feature throughout the book is the introduction of paragraphs termed "essential and desirable diagnostic criteria" where obligatory and optional morphologic and molecular features of a given tumor entity are listed as exemplified for each TET in the Supplementary Table 1.

Two lesions previously listed as thymoma types are no longer included in the fifth edition: Microscopic thymomas are now considered nodular epithelial hyperplasias because of persistent lack of evidence for their progressive potential, and sclerosing thymomas are now considered to represent conventional thymomas with regressive changes.

The classification of thymomas and TCs is strongly reinforced by new molecular findings. First, the TCGA study[7] revealed that type A and AB thymomas on one hand and B1 to B3 thymomas on the other hand each belong to a spectrum of tumors, with minimal overlap between them. Both groups were genomically completely distinct from TCs (Fig. 1). Second, gain-of-function mutations of *HRAS*, such as the oncogenic *GTF2I* mutation, segregated with type A and AB thymomas, but loss-of-function mutations of *TP53* were typical of type B thymomas (and TCs).[7] Third, chromosomal translocations (gene fusions) have been newly recognized in thymomas: metaplastic thymomas had a unique *YAP1-MAML2* translocation,[20] whereas novel *KMT2A-MAML2* translocations were restricted to 6% of pretreated aggressive types B2 and B3 and a combined TC and B3 thymoma, but were not found in other thymomas and "pure" TCs.[21] Both translocations are thought to be oncogenic drivers. Together with the well-established *MAML2* translocation of thymic mucoepidermoid carcinomas, there are now three different TET types implicating oncogenic involvement of the *MAML2* gene, suggesting the possibility that the thymic niche could be conducive to growth of clones harboring fusions involving the *MAML2* gene. Fourth, micro-RNA profiles (including overexpression of the micro-RNA cluster miC19MC on chromosome 19) sharply separate type A and AB thymomas from type B thymomas and TCs.[22,23]

With respect to the enigmatic triggering factors of thymomas, the observation of an enrichment of C>T mutations within CpG di-nucleotides is the first hint to an aging-related pathogenesis.[7]

Unexpectedly, the TCGA study on thymomas did not reveal oncogenic driver mutations amenable to currently available targeted therapies.[7] Nevertheless, the small molecule inhibitor, everolimus, is clinically active and used for treatment of recurrent thymomas.[24] Furthermore, thymomas were found to exhibit the lowest tumor mutational burden among all adult human cancers, which might limit the value of currently available ICIs.[7] Nevertheless, thymomas count among human cancers to have the highest prevalence of extensive and strong PD-L1 expression in tumor cells[10,11] (Fig. 2*A* and *B*), a predictive biomarker of response to ICIs. It is the high frequency of ICI-induced severe immune-mediated toxicity that currently prohibits adoption of immunotherapy, including ICIs for the management of thymomas.[15] Whether aneuploidy and particular transcriptomic profiles that were found to be associated with the presence of autoimmune myasthenia gravis in thymomas[7,25] may serve as predictive biomarkers of immune-mediated adverse events associated with ICI-based interventions has not been evaluated.

Reporting of Heterogeneous TETs. Although thymomas composed of more than one histologic type are common, other combinations of TETs are rare.[26] Examples include combined thymic squamous cell carcinoma and type B2 or B3 thymoma, combined TC and micronodular thymoma with lymphoid stroma, combined low-grade papillary adenocarcinoma and type A or AB thymoma, combined sarcomatoid carcinoma and type A or metaplastic thymoma, combined small cell carcinoma

Table 1. WHO Classification of Thymic Epithelial Tumors, Including Thymomas, Thymic Carcinomas, and Neuroendocrine Tumors

ICD-O Morphology and Behavior Codes	
Epithelial tumors	
Thymomas	
8580/3	Thymoma, NOS
8581/3	Thymoma, type A[a]
8582/3	Thymoma, type AB
8583/3	Thymoma, type B1
8584/3	Thymoma, type B2
8585/3	Thymoma, type B3
8580/1	Micronodular thymoma with lymphoid stroma
8580/3	Metaplastic thymoma
9010/0	Lipofibroadenoma
Squamous carcinomas	
8070/3	Squamous cell carcinoma, NOS
8123/3	Basaloid carcinoma
8082/3	Lymphoepithelial carcinoma[b]
Adenocarcinomas	
8140/3	Adenocarcinoma, NOS
8260/3	Low-grade papillary adenocarcinoma[c]
8200/3	Thymic carcinoma with adenoid cystic carcinoma-like features
8144/3	Adenocarcinoma, enteric type[d]
Adenosquamous carcinomas	
8560/3	Adenosquamous carcinoma
NUT carcinomas	
8023/3	NUT carcinoma
Salivary gland-like carcinomas	
8430/3	Mucoepidermoid carcinoma
8310/3	Clear cell carcinoma[e]
8033/3	Sarcomatoid carcinoma
8980/3	Carcinosarcoma[f]
Undifferentiated carcinomas	
8020/3	Carcinoma, undifferentiated, NOS
Thymic carcinomas	
8586/3	Thymic carcinoma, NOS[g]
Thymic neuroendocrine neoplasms	
Neuroendocrine tumors	
8240/3	Carcinoid tumor, NOS/neuroendocrine tumor, NOS
8240/3	Typical carcinoid/neuroendocrine tumor, grade 1
8249/3	Atypical carcinoid/neuroendocrine tumor, grade 2
Neuroendocrine carcinomas	
8041/3	Small cell carcinoma
8045/3	Combined small cell carcinoma
8013/3	Large cell neuroendocrine carcinoma

Note: These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2) (IACR, 2019).[18] Behavior is coded /0 for benign tumors; /1 for unspecified, borderline, or uncertain behavior; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumors, primary site; and /6 for malignant tumors, metastatic site. Behavior code /6 is not generally used by cancer registries. This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

[a]Including atypical variant.

[b]Previously labeled lymphoepithelioma-like carcinoma.

[c]Previously labeled papillary adenocarcinoma.

[d]Newly delineated mucinous or nonmucinous adenocarcinoma with expression of at least one intestinal marker, CK20, CDX2, or MUC2.

[e]Including hyalinizing clear cell carcinoma.

[f]Subtype of sarcomatoid carcinoma.

[g]Including hepatoid carcinoma, rhabdoid carcinoma, undifferentiated large cell carcinoma associated with Castleman disease-like reaction, and sebaceous carcinoma.

IACR, International Association of Cancer Registries; NOS, not otherwise specified. Reprinted from WHO Classification of Tumours Editorial Board. Thoracic Tumours. Lyon, France: International Agency for Research on Cancer; 2021 (WHO Classification of Tumours Series, 5th ed.; vol. 5, page 7, Copyright; 2021).

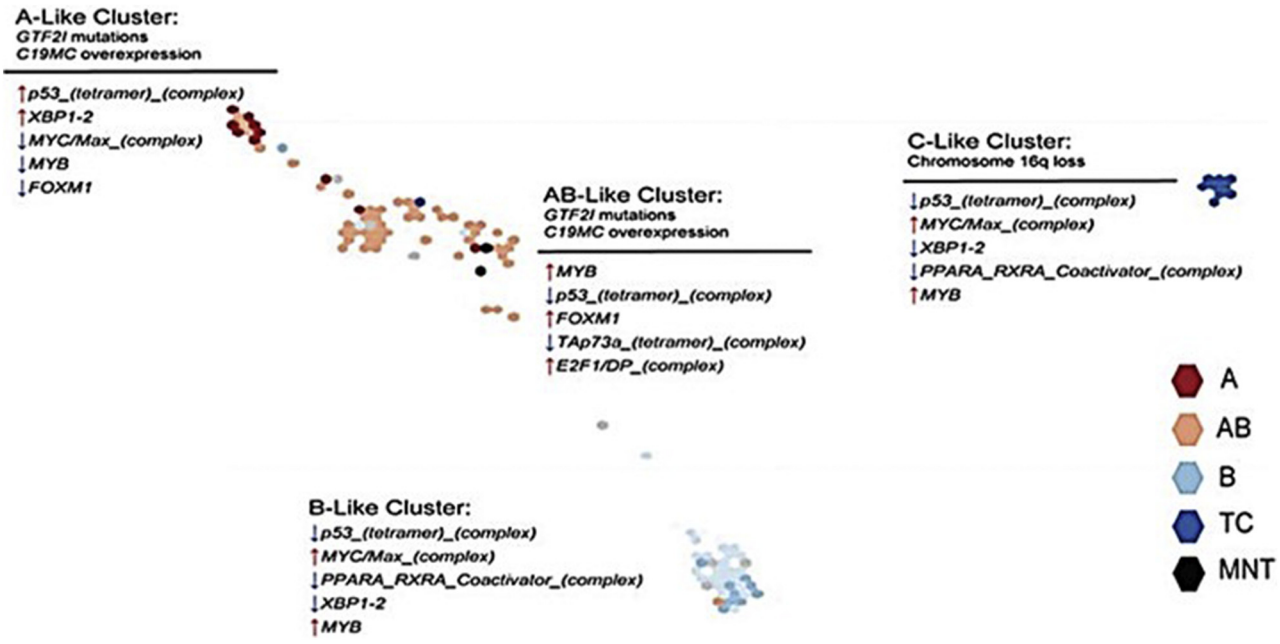

Figure 1. Molecular thymoma subtypes (A-like, AB-like, B-like, and "C-like" TCs) derived from integrative unsupervised clustering based on five data platforms largely reflect WHO histotypes.[7] Key features derived from single platforms (e.g., the overexpressed C19MC micro-RNA cluster in the A-like and AB-like cluster) are listed above the thin line, whereas results of multiplatform analysis that integrate copy number alteration and RNA expression profiles are listed below the thin line. MNT, micronodular thymoma with lymphoid stroma; TC, thymic carcinoma. Reproduced from Fig. 3 of Ref. 7 with permission from *Cancer Cell*.

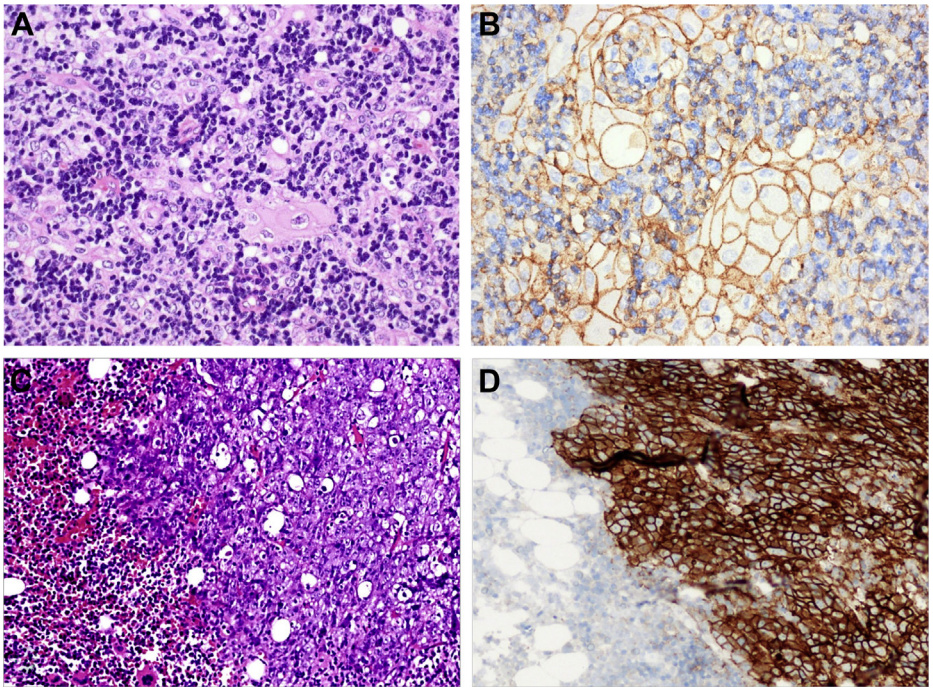

Figure 2. PD-L1 expression in neoplastic epithelial cells of a type B3 thymoma (*A* and *B*) and undifferentiated thymic carcinoma (*C* and *D*). (*A*) Conventional histologic features of type B3 thymoma. (*B*) Strong, membranous PD-L1 expression in type B3 thymoma (IHC). (*C*) Bone metastasis of an undifferentiated thymic carcinoma. (*D*) Strong, membranous PD-L1 expression in apparently all tumors cells (IHC, TPS 100%). IHC, immunohistochemistry, using immunoperoxidase; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

and thymoma, and combined small cell carcinoma and TC. The combinations usually occur not as random events but are likely clonally related, owing to transformation of a lower-grade neoplasm to a more aggressive neoplasm or bidirectional differentiation of the neoplasm. In the fifth edition of the WHO Classification of Thoracic Tumours, the nomenclature is more streamlined (Fig. 3). Whereas the reporting of heterogeneous thymomas is exclusively based on the prevalence of the different thymoma components, the reporting of other combined TETs takes the aggressiveness of the various components into account, when applicable.

Open questions are addressed in the subsequent texts together with those related to TCs.

Thymic Carcinoma

Features Maintained

The nomenclature and diagnostic criteria of most TCs have remained unchanged. Nevertheless, changes concern not only molecular aspects but also new histologic types and subtypes (Table 1 and Supplementary Table 1), diagnostic refinement through new immunohistologic criteria, and new names for old entities to better convey tumor biology or streamline nomenclature across thoracic cancers.[26]

What Is New?

The group of TCs now includes several new subtypes (Table 1), which are as follows: (1) micronodular TC with lymphoid hyperplasia is an apparently less aggressive subtype of thymic squamous cell carcinoma with "non-organotypic" lymphoid stroma that otherwise mimics "micronodular thymoma with lymphoid stroma"[27] (Fig. 4*A–C*), (2) hyalinizing clear cell carcinoma that resembles its salivary gland analogue in terms of histologic featues and *EWSR1* rearrangement[28] (Fig. 4*D–F*), and (3) thymic sebaceous carcinoma (Fig. 4*G–I*) that mimics its cutaneous counterpart[29] and is currently grouped with other rare TCs among the new, heterogeneous group of "Thymic carcinoma NOS."

New nomenclature and refined immunohistologic criteria concern "papillary adenocarcinoma" that is now labeled "low-grade papillary adenocarcinoma" to convey its bland histologic features and mostly indolent clinical course. High-grade adenocarcinomas with papillary features are classified as "adenocarcinomas NOS" instead. There have also been changes in nomenclature to align with lung cancers, with the renaming of "lymphoepithelioma-like carcinoma" as "lymphoepithelial carcinoma." "Mucinous adenocarcinomas" are now either reclassified as "enteric-type adenocarcinomas"[30] if there

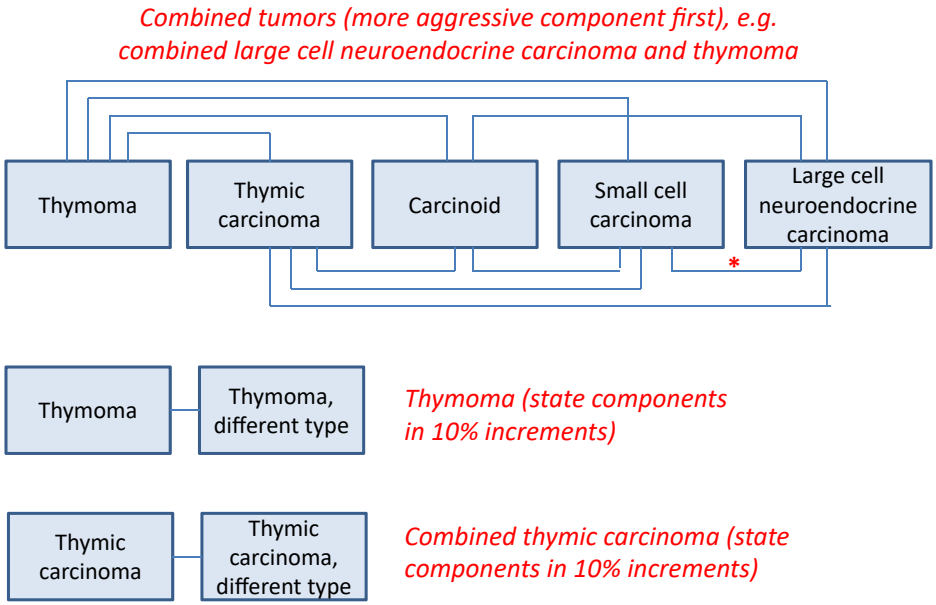

Figure 3. Reporting scheme for thymic epithelial tumors with heterogeneous components. Top: Any combinations of thymoma, thymic carcinoma, carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma can occur, as indicated by the connecting lines. Such tumors are termed "combined tumor 1 and tumor 2," with the more aggressive component being listed first. *In line with the nomenclature of pulmonary neuroendocrine neoplasms, small cell carcinoma combined with more than or equal to 10% large cell neuroendocrine carcinoma is termed "combined small cell carcinoma and large cell neuroendocrine carcinoma," whereas the combined tumor is only termed "small cell carcinoma" if the large cell neuroendocrine carcinoma component is less than 10%. Middle: Thymoma composed of two or more types are termed "thymoma," with listing of the components in 10% increments. Bottom: Thymic carcinomas composed of two different types are termed "combined thymic carcinoma," with the components listed in 10% increments.

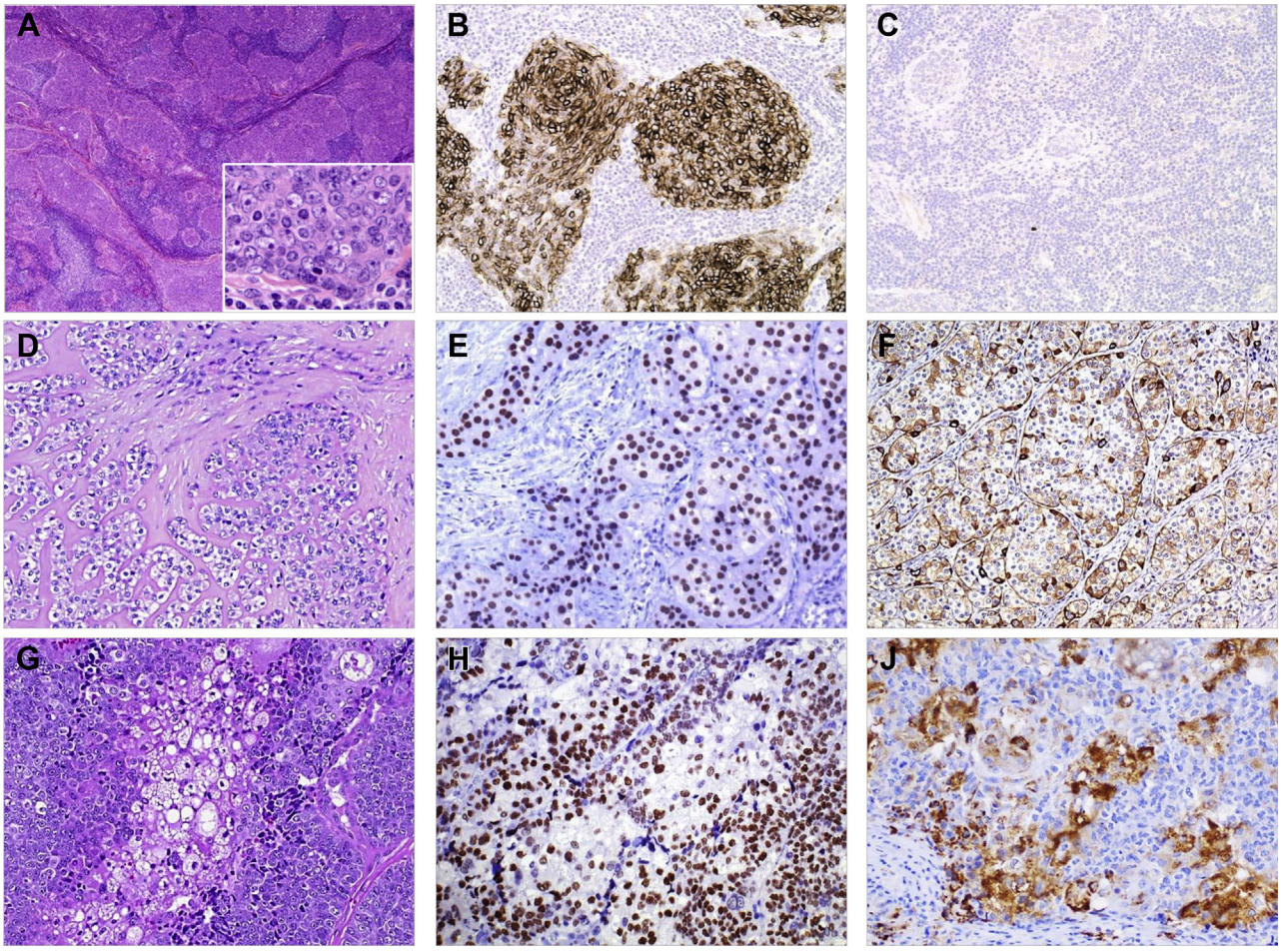

Figure 4. New thymic carcinoma (sub)types in the new WHO classification. (*A-C*) Micronodular thymic carcinoma with lymphoid hyperplasia revealing islands of cohesive, atypical epithelial cells in a lymphoid stroma without desmoplasia; inset highlights cytologic atypia of tumor cells. (*B*) Expression of CD117 (also called KIT) is common (IHC). (*C*) Absence of TdT(+) immature T cells on IHC is distinctive compared with micronodular thymoma with lymphoid stroma (IHC). (*D-F*) Hyalinizing clear cell carcinoma of the thymus: single or grouped clear cells in a collagen-rich stroma. (*E*) Diffuse p40 expression (IHC). (*F*) Labeling of CK5/6(+) basal cells in the periphery of clear tumor cell groups (IHC). (*G-I*) Sebaceous carcinoma of the thymus revealing multivacuolated clear cells (sebocytes) associated with basophilic squamoid cells and focal calcification. (*H*) Nuclear expression of androgen receptor (IHC). (*I*) Adipophilin expression in "sebocytes." IHC, immunohistochemistry using immunoperoxidase.

is expression of one or more enteric markers, CK20, CDX2, or MUC2, or are assigned to the new, morphologically heterogeneous group of "adenocarcinomas NOS." Of note, enteric-type adenocarcinomas can also be nonmucinous.

The TCGA study has revealed molecular pathogenesis of TCs distinct from thymomas.[7] The identification of only two combined TCs and B3 thymomas in an independent cohort of more than 600 type B2 and B3 thymomas and TCs[21] supports this conclusion. Furthermore, the most common abnormality identified in TCs, loss of chromosome 16q, was absent from thymomas, and the tumor mutational burden was higher in TCs, particularly in the rare TC case with an inactivating *MLH1* mutation and mismatch repair deficiency (microsatellite instability).[7] Another novel disease mechanism in TETs, chromoplexy, a single "catastrophic event" resulting in multiple rearrangements, has been discovered to result in formation of NUT-fusion oncoproteins, the sole drivers of NUT carcinoma growth.[31] Nevertheless, apart from long-known rare actionable *KIT* mutations, TCs, such as thymomas, lack recurrently mutated genes that are currently targetable.[7] Nevertheless, phase 2 clinical trials have revealed the efficacy of the targeted therapies, sunitinib, lenvatinib, and everolimus against some recurrent TCs.[24,32,33] The underlying mechanisms of action of these drugs remain to be clarified.

It seems promising that TCs have strong PD-L1 expression in tumor cells (Fig. 2*C* and *D*) almost as often as in thymomas.[11,34] Indeed, early clinical trials have revealed a correlation between PD-L1 expression in TCs and the response to the ICI, pembrolizumab.[13,14]

Nevertheless, severe ICI-induced immune-mediated toxicity can occur quite often (~20%), even though TCs are far less susceptible to develop paraneoplastic autoimmunity compared with thymomas.[15]

Open Questions in Relation to Thymomas and TCs

The pathogenesis of most thymomas and TC remains unknown, largely precluding targeted interventions. Epigenetic, noncoding RNA-related and metabolic mechanisms need further elucidation.[22,23,35,36] No biomarkers are available to predict the response to chemotherapy or kinase inhibitors except for rare *KIT*, and even rarer *PI3K* mutations.[37] A key challenge in drug development for TETs is the paucity of thymoma and TC cell lines[38,39] and unavailability of more representative preclinical models (e.g., xenografts or organoids) for functional studies and high-throughput screens. To better exploit the strong expression of PD-L1 in TCs, new biomarkers are needed to better predict both the response to ICIs and the risk for development of severe immune-mediated toxicity, including strategies to mitigate ICI toxicity while maintaining therapeutic efficacy.

Thymic Neuroendocrine Neoplasms

Features Maintained

The nomenclature and diagnostic criteria of NETs of the thymus (TNETs) and lung have remained unchanged (Table 1 and Supplementary Table 1). TNETs are classified into typical carcinoids, atypical carcinoids (ACs), large cell neuroendocrine carcinomas (LCNECs), and small cell carcinomas (SCCs). The separation of these tumors is based on morphologic features, presence of necrosis, and mitotic counts. Although the proliferation marker Ki67 is very useful to exclude LCNEC or SCC in crushed samples,[40] it is unsuitable for the distinction between typical carcinoid and AC (Fig. 5).

What Is New?

Emerging data reveal that pulmonary and thymic NETs fit into the common classification framework of neuroendocrine neoplasms elsewhere in the body[41] and fall into two main groups—low-grade (typical carcinoid, AC) and high-grade (LCNEC, SCC) tumors. Similar to grade 3 NET in the pancreas, recent data convincingly reveal the existence of a group of thymic tumors with carcinoid morphologic features and elevated mitotic counts and Ki67 index.[42] Although these tumors are designated as LCNEC

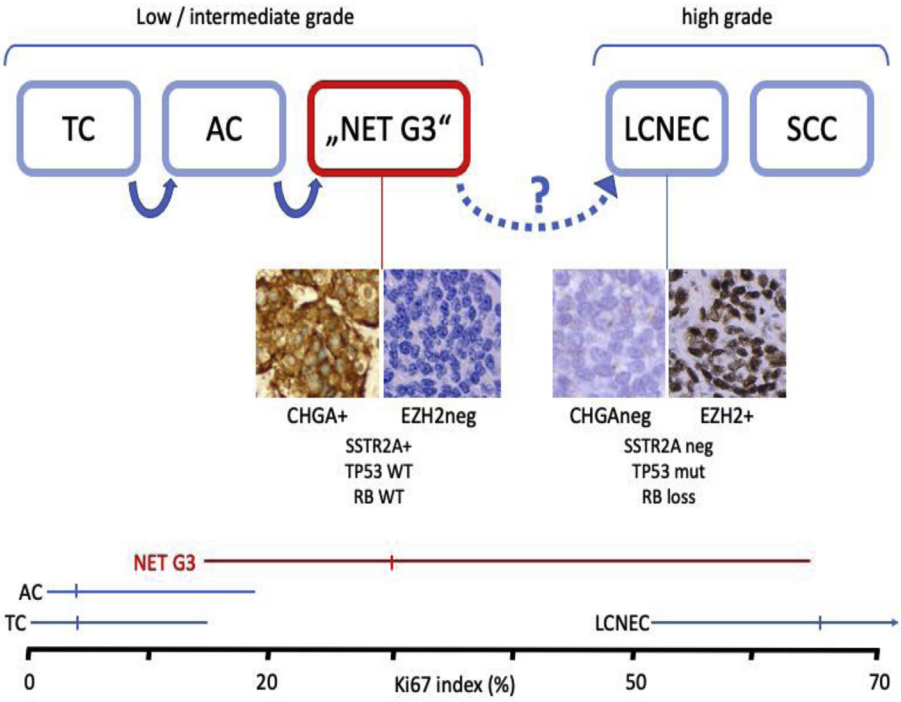

Figure 5. The group of atypical carcinoids with elevated mitotic counts ("NET G3") shares morphologic, immunohistochemical, and molecular features with TC and ACs and cases with relapses or metastases revealed that these tumors form a continuum, whereas it remains to be found if such tumors can progress further to high-grade carcinomas (LCNEC and SCC). NET G3 and LCNEC can be discriminated using a panel of immunohistochemical markers, notably chromogranin A and EZH2. Ki67 staining is not helpful in individual cases owing to large overlap between the single entities (horizontal lines: range; vertical lines: mean). AC, atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; mut, mutated; neg, negative; SCC, small cell carcinoma; TC, typical carcinoid; WT, wild-type. Adapted from Dinter et al.[42]

according to current WHO criteria by virtue of high mitotic activity, they seem more closely aligned with the low-grade group of tumors, that is, typical carcinoid and AC. Such "NET G3" tumors can be separated from true LCNEC by a panel of immunohistochemical markers, including chromogranin, EZH2, TP53, RB, and SSTR2A (Fig. 5).

Open Questions in Relation to NETs

Although the WHO classification of TNETs has revealed prognostic relevance,[43] it is currently unknown which of the findings mentioned previously should have an impact on clinical management. For example, it is not known whether an "NET G3" with a Ki67 index of 45% should be treated differently from a true high-grade LCNEC with a Ki67 index of 55%. Despite significant molecular overlap between low- and high-grade NETs, the current paradigm remains that low-grade TNETs generally do not progress to high-grade TNETs. It is unclear which molecular pathways drive (and separate) these two tumor groups and whether the essential oncogenic drivers in TNETs are different from NETs of the lung. It is also currently not possible to discriminate between primary TNETs and pulmonary NETs metastatic to the mediastinum by immunohistochemistry.

Need for Global Cooperation to Resolve Open Questions in Thymomas, TCs, and Thymic NETs

Research to identify molecular biomarkers, especially those with therapeutic impact, has been hampered by the paucity of TETs[1] with current evidence mostly arising from limited, single-institutional studies. Multi-institutional investigations driven by international organizations such as International Association for the Study of Lung Cancer and ITMIG were invaluable in building a staging system[3–6] and uncovering molecular properties of TETs.[7] In the future, more global collaborations are warranted to collect sufficient samples to further improve tumor classification (e.g., in TNETs) and discover clinically actionable biomarkers.

Mediastinal GCTs

Features Maintained

The concepts, nomenclature, histologic, and immunohistologic criteria defining the main GCT categories are maintained in the fifth edition of the WHO classification (Table 2).[18]

What Is New?

The term "endodermal sinus tumor" has been discontinued and is not recommended as a synonym for yolk sac tumor.

New insights have been gained into the pathogenesis of mediastinal GCTs: type I GCTs encompass infantile teratomas and yolk sac tumors.[44] Somatic mutations are usually not identified in type I teratomas. Type II GCTs are malignant, include seminomas and non-seminomatous GCT, occur in adolescents and adult men, and characteristically have gain of chromosome 12p, most often as an isochromosome. A recent study further suggests that mediastinal teratomas possibly develop through two different pathways.[45] Teratomas in children, women, and a subset of men may arise from a benign pluripotent cell, lack 12p copy number alterations and cytologic atypia, often have organoid morphologic features, and behave in a benign manner. Pure teratomas resected in a subset of postpubertal men after chemotherapy for mixed GCTs may derive from a malignantly transformed precursor cell, most often harbor 12p copy number gains and cytologic atypia, only

Table 2. 2021 WHO Classification of Mediastinal GCTs

ICD-O Morphology and Behavior Codes	
9061/3	Seminoma
9070/3	Embryonal carcinoma
9071/3	Yolk sac tumor
9100/3	Choriocarcinoma
9080/0	Mature teratoma
9080/1	Immature teratoma
9085/3	Mixed germ cell tumor
9084/3	Teratoma with somatic-type malignancies
9086/3	Germ cell tumor with associated hematological malignancy

Note: These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2) (IACR, 2019).[18] Behavior is coded /0 for benign tumors; /1 for unspecified, borderline, or uncertain behavior; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumors, primary site.

GCT, germ cell tumors; IACR, International Association of Cancer Registries.

rarely exhibit organoid morphologic features, and behave in a malignant fashion. The latter teratoma likely develops through differentiation from a malignant component of a mixed GCT. After chemotherapy that eradicates the primitive GCT component, persistence of the teratoma component as malignant teratoma will result. Although one study failed to confirm 12p copy number gains in mature teratomas of postpubertal men,[46] none of these patients underwent presurgical chemotherapy.

Some caveats are worth mentioning in connection with "old" immunohistochemical GCT markers: thoracic SMARCA4-deficient undifferentiated tumors[47,48] that most often invade the mediastinum often have SALL4, SOX2, and vimentin expression, may or may not have keratin positivity and, therefore, may be confused with GCTs. Another pitfall is misinterpretation of SALL4- and AFP-expressing NUT carcinomas as genuine GCTs,[49] and conversely, the frequent expression of wild-type NUT protein in GCTs that can lead to the misdiagnosis of NUT carcinoma.[50]

Open Questions

An unresolved problem is lack of an official, meaningful staging system for primary mediastinal GCTs.

Mesenchymal Tumors of the Mediastinum

Features Maintained

Nomenclature and diagnostic criteria of all entities are largely maintained (Table 3).[18] The molecular pathology of mediastinal mesenchymal tumors corresponds to those occurring elsewhere. The current edition re-emphasizes the importance of immunohistochemical and molecular testing in establishing the correct diagnosis. No conceptual, diagnostic, or molecular changes have been published on desmoid fibromatosis and most lipomatous and malignant vascular tumors.

What Is New?

In contrast to the previous WHO classification of thoracic tumors, the fifth edition discusses only the most common mesenchymal tumors and those characteristically encountered in the thorax (Table 3). Thymolipoma as the only thymus-specific mesenchymal tumor is included in this section. The full repertoire of soft tissue tumors is covered in the WHO classification of soft tissue and bone tumor volume.[16]

Lipomas and all types of liposarcoma have been reported in the mediastinum and can occur in all mediastinal compartments, particularly in the anterior (prevascular) and posterior (paravertebral) compartments. MDM2 and CDK4 nuclear expression or evidence of *MDM2* gene (12p15) amplification is desirable diagnostic criterion for well-differentiated and dedifferentiated liposarcomas. In myxoid liposarcoma, DDIT3 immunohistochemistry is a new option,[51,52] and confirmation of *DDIT3* gene rearrangement or detection of specific *FUS-DDIT3* or EWSR1-DDIT3 gene fusion is desirable criterion in selected cases.

Solitary fibrous tumor can rarely occur in the mediastinum. Immunohistochemistry to reveal nuclear STAT6 resulting from a NAB2-STAT6 gene fusion is most helpful in establishing the diagnosis.[53] Rather than classifying solitary fibrous tumor as benign, malignant, or of uncertain malignant potential, the fifth edition recommends reporting the risk according to the proposed three- and four-variable risk stratification models[54,55] (Table 4).

Primary intrathoracic synovial sarcoma is uncommon, and its diagnosis is facilitated by the demonstration of one of the characteristic *SS18-SSX* fusions. A novel antibody against the SS18-SSX fusion protein, not available at the time of publication of the WHO classification blue book, is a welcome addition to aid in routine diagnosis of synovial sarcoma owing to its high sensitivity and specificity.[56,57] Nevertheless, rare cases stain negative and may still need *SS18-SSX* translocation analysis and exclusion of mediastinal spindle cell tumor mimics through immunohistochemistry and molecular testing (Supplementary Table 2).

Benign vascular tumors such as hemangiomas occur in the thymus and slightly more often in the anterior rather than the posterior mediastinum. Many lesions previously described as cavernous or venous hemangiomas are now considered to be venous malformations as defined by the classification of the International Society for the Study of Vascular Anomalies.[58]

Peripheral neuroblastic tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma) occur in the posterior mediastinum. Rarely, neuroblastoma and ganglioneuroma occur in the thymus of adults presenting with the syndrome of inappropriate secretion of antidiuretic hormone or with a thymic cyst. It is desirable to perform molecular testing for *MYCN*, *ALK*, *TERT*, and *ATRX* status, DNA index and segmental chromosomal aberrations for predicting clinical behavior.[59]

Relevant Findings Since the Publication of the WHO Classification

Frequent expression of cancer testis antigens, specifically MAGE-A, MAGE-C1, NY-ESO-1, SAGE, and GAGE7, was described in up to 43% of thymomas and TCs, and expression of SAGE and GAGE7 was associated with a poor prognosis in type B2 and B3 thymomas.[60] In TCs, higher expression of GAD1 in relation to *GAD1* hypermethylation was associated with an adverse clinical course.[35] These findings might have an

Table 3. 2021 WHO Classification of Mesenchymal Tumors of the Thorax

ICD-O Morphology and Behavior Codes	
Adipocytic tumors	
8850/0	Lipoma, NOS[a]
8850/0	Thymolipoma[a]
8850/3	Liposarcoma, NOS
8851/3	Liposarcoma, well-differentiated[a]
8852/3	Myxoid liposarcoma[a]
8854/3	Pleomorphic liposarcoma[a]
8858/3	Dedifferentiated liposarcoma[a]
Fibroblastic and myofibroblastic tumors	
8821/1	Desmoid-type fibromatosis[a]
8815/1	Solitary fibrous tumor, NOS[a]
8817/0	Calcifying fibrous tumor
8825/1	Inflammatory myofibroblastic tumor
8811/3	Myxofibrosarcoma
Vascular tumors	
9120/0	Hemangioma, NOS
9121/0	Cavernous hemangioma
9122/0	Venous hemangioma
9132/0	Intramuscular hemangioma
9123/0	Arteriovenous hemangioma[a]
9170/0	Lymphangioma, NOS
9173/0	Cystic lymphangioma
9133/3	Epithelioid hemangioendothelioma
9120/3	Angiosarcoma[a]
Skeletal muscle tumors	
8900/3	Rhabdomyosarcoma, NOS
8910/3	Embryonal rhabdomyosarcoma
8912/3	Spindle cell rhabdomyosarcoma
8920/3	Alveolar rhabdomyosarcoma
8901/3	Pleomorphic rhabdomyosarcoma
Peripheral nerve sheath and neural tumors	
8693/3	Extra-adrenal paraganglioma
9580/0	Granular cell tumor
9580/3	Granular cell tumor, malignant
9560/0	Schwannoma
9540/3	Malignant peripheral nerve sheath tumor
9490/0	Ganglioneuroma[a]
9490/3	Ganglioneuroblastoma[a]
9500/3	Neuroblastoma[a]
Tumors of uncertain differentiation	
9040/3	Synovial sarcoma, NOS
9041/3	Synovial sarcoma, spindle cell
9042/3	Synovial sarcoma, epithelioid cell
9043/3	Synovial sarcoma, biphasic
9364/3	Ewing sarcoma
9367/3[b]	*CIC*-rearranged sarcomal
9368/3[b]	Sarcoma with *BCOR* genetic alterations
9366/3[b]	Round cell sarcoma with *EWSR1*-non-ETS fusions

Note: These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2) (IACR, 2019).[18] Behavior is coded /0 for benign tumors; /1 for unspecified, borderline, or uncertain behavior; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumors, primary site.

[a]Tumors that most often occur in the mediastinum are labeled ([a]). Mesenchymal tumors that are specific for the lung and heart are described separately in the respective sections.

[b]Codes marked with an ([b]) were approved by the International Agency for Research on Cancer/WHO Committee for ICD-O at its meeting in October 2020.

IACR, International Associaton of Cancer Registries; NOS, not otherwise specified.

Table 4. Solitary Fibrous Tumor: New Four-Variable Risk Model for the Prediction of Metastatic Risk[3]

Risk Factor	Cutoff Value	Points Assigned
Age (y)	<55	0
	>55	1
Mitoses/2 mm^2	0	0
	1-3	1
	≥4	2
Tumor size (mm)	0-49	0
	50-99	1
	100-149	2
	>150	3
Tumor necrosis	<10%	0
	>10%	1
Risk	Low	0-2 points
	Intermediate	3-4 points
	High	5-6 points

Note: Compared with the historic three-variable model, the new model takes necrosis into account.

immunotherapeutic perspective. Finally, 80% of thymic squamous cell carcinomas, including all KIT(+) cases, were just described as POU2F3-positive "tuft cell-like cancers," which share a unique gene expression profile not only with normal chemosensory tuft cells[36] but also with 20% of small cell lung cancers[61] and smaller subset of NSCLC.[36] Because almost all "tuft cell-like cancers" lack targetable mutations, this hints to a currently unknown carcinogenic mechanism in tuft cell-like cancers, including thymic squamous cell carcinomas.[36]

CRediT Authorship Contribution Statement

The authors are "responsible authors" of chapters that deal with thymic epithelial tumors, mediastinal germ cell tumors, and mediastinal mesenchymal neoplasms in the "WHO Classification of Tumours Editorial Board. Thoracic Tumours. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours, fifth ed.; vol. 5)." Specific contributions were as follows:

Alexander Marx: Conceptualization, Original draft preparation, Visualization (submission of images for figure preparation), and Reviewing and editing.

John K.C. Chan: Conceptualization, Original draft preparation, Visualization, and Reviewing and editing.

Lara Chalabreysse, Frank Detterbeck, Christopher A. French, Jason L. Hornick, Hiroshi Inagaki, Deepali Jain, Alexander J. Lazar, Mirella Marino, Andre L. Moreira, Andrew G. Nicholson, Masayuki Noguchi, Daisuke Nonaka, Mauro G. Papotti, Lynette M. Sholl, Hisashi Tateyama, Vincent Thomas de Montpréville: Reviewing and editing.

Sanja Dacic, Edith M. Marom, Arun Rajan, Anja C. Roden: Original draft preparation, Reviewing and editing.

Stefan Porubsky: Visualization, Reviewing and editing.

William D. Travis: Conceptualization, Visualization, Reviewing and editing.

Philipp Ströbel: Original draft preparation, Visualization, Reviewing and editing.

Acknowledgments

We wish to thank Professor Ian Cree (Editorial Board Chair), all members of the Editorial Board for the Thoracic Tumor Book, and staffs from the International Agency for Research on Cancer involved in the WHO Classification of Tumours, fifth edition series, for their contribution to the completion of the fifth edition book.

Tables 1 to 3 are reprinted with permission from WHO Classification of Tumours Editorial Board. Thoracic Tumours. Lyon, France: International Agency for Research on Cancer; 2021. (WHO Classification of Tumours series, fifth ed.; vol. 5). In addition, with permission, Supplementary Table 1 summarizing the essential and diagnostic criteria is listed from this same WHO classification. Figure 1 is reprinted with permission from Cancer Cell.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.10.010.

References

1. WHO Classification of Tumours Editorial Board. *Thoracic tumours*. In: *WHO Classification of Tumours*. 5th ed 5. Lyon, France: International Agency for Research on Cancer; 2021.
2. Travis WD, Brambilla E, Burke AP, et al. *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*. In:

WHO Classification of Tumours. 4th ed. 7. Lyon, France: International Agency for Research on Cancer; 2015.
3. Huang J, Ahmad U, Antonicelli A, et al. Development of the international thymic malignancy interest group international database: an unprecedented resource for the study of a rare group of tumors. *J Thorac Oncol*. 2014;9:1573–1578.
4. Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*. Chichester, United Kingdom: John Wiley & Sons, Ltd; 2017.
5. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9(suppl 2):S65–S72.
6. Ruffini E, Fang W, Guerrera F, et al. The International Association for the Study of Lung Cancer thymic tumors staging project: the impact of the eighth edition of the Union for International Cancer Control and American Joint Committee on Cancer TNM stage classification of thymic tumors. *J Thorac Oncol*. 2020;15:436–447.
7. Radovich M, Pickering CR, Felau I, et al. The integrated genomic landscape of thymic epithelial tumors. *Cancer Cell*. 2018;33:244–258.e10.
8. Petrini I, Meltzer PS, Kim IK, et al. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. *Nat Genet*. 2014;46:844–849.
9. Dobosz P, Dzieciątkowski T. The intriguing history of cancer immunotherapy. *Front Immunol*. 2019;10:2965.
10. Inaguma S, Wang Z, Lasota J, et al. Comprehensive immunohistochemical study of programmed cell death ligand 1 (PD-L1): analysis in 5536 cases revealed consistent expression in trophoblastic tumors. *Am J Surg Pathol*. 2016;40:1133–1142.
11. Padda SK, Riess JW, Schwartz EJ, et al. Diffuse high intensity PD-L1 staining in thymic epithelial tumors. *J Thorac Oncol*. 2015;10:500–508.
12. Rajan A, Heery CR, Thomas A, et al. Efficacy and tolerability of anti-programmed death-ligand 1 (PD-L1) antibody (avelumab) treatment in advanced thymoma. *J Immunother Cancer*. 2019;7:269.
13. Cho J, Kim HS, Ku BM, et al. Pembrolizumab for patients with refractory or relapsed thymic epithelial tumor: an open-label phase II trial. *J Clin Oncol*. 2019;37:2162–2170.
14. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *Lancet Oncol*. 2018;19:347–355.
15. Zhao C, Rajan A. Immune checkpoint inhibitors for treatment of thymic epithelial tumors: how to maximize benefit and optimize risk? *Mediastinum*. 2019;3:35.
16. WHO Classification of Tumours Editorial Board. *Soft tissue and bone tumours*. In: *WHO Classification of Tumours*. 5th ed 3. Lyon, France: International Agency for Research on Cancer; 2020.
17. Moch H, Humphrey PA, Ulbright TM, Reuter VE, eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs. WHO Classification of Tumours*. 4th ed. 8. Lyon, France: International Agency for Research on Cancer; 2016.
18. International Association of Cancer Registries (IACR) [Internet]. Lyon (France): International Agency for Research on Cancer; 2019. ICD-O-3. 2. http://www.iacr.com.fr/index.php?option=com_content&view=article&id=149:icd-o-3-2&catid=80&ltemid=545. Accessed April 23, 2019.
19. Higuchi R, Goto T, Hirotsu Y, et al. Primary driver mutations in GTF2I specific to the development of thymomas. *Cancers*. 2020;12:2032.
20. Vivero M, Davineni P, Nardi V, Chan JKC, Sholl LM. Metaplastic thymoma: a distinctive thymic neoplasm characterized by YAP1-MAML2 gene fusions. *Mod Pathol*. 2020;33:560–565.
21. Massoth LR, Hung YP, Dias-Santagata D, et al. Pan-Cancer landscape analysis reveals recurrent KMT2A-MAML2 gene fusion in aggressive histologic subtypes of thymoma. *JCO Precis Oncol*. 2020;4:109–115
22. Enkner F, Pichlhöfer B, Zaharie AT, et al. Molecular profiling of thymoma and thymic carcinoma: genetic differences and potential novel therapeutic targets. *Pathol Oncol Res*. 2017;23:551–564.
23. Radovich M, Solzak JP, Hancock BA, et al. A large microRNA cluster on chromosome 19 is a transcriptional hallmark of WHO type A and AB thymomas. *Br J Cancer*. 2016;114:477–484.
24. Zucali PA, De Pas T, Palmieri G, et al. Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy. *J Clin Oncol*. 2018;36:342–349.
25. Yamada Y, Weis CA, Thelen J, et al. Thymoma associated myasthenia gravis (TAMG): differential expression of functional pathways in relation to MG status in different thymoma histotypes. *Front Immunol*. 2020;11:664.
26. Chan JKC, Detterbeck F, Marino M, et al. Thymic carcinoma: introduction. In: Board E, ed. *WHO Classification of Tumours Editorial Board Thoracic Tumours*. 5. Lyon (France): International Agency for Research on Cancer (IARC); 2021:351–353.
27. Weissferdt A, Moran CA. Micronodular thymic carcinoma with lymphoid hyperplasia: a clinicopathological and immunohistochemical study of five cases. *Mod Pathol*. 2012;25:993–999.
28. Porubsky S, Rudolph B, Rückert JC, et al. EWSR1 translocation in primary hyalinising clear cell carcinoma of the thymus. *Histopathology*. 2019;75:431–436.
29. Porubsky S, Jessup P, Kee D, et al. Potentially actionable FGFR2 high-level amplification in thymic sebaceous carcinoma. *Virchows Arch*. 2020;476:323–327.
30. Moser B, Schiefer AI, Janik S, et al. Adenocarcinoma of the thymus, enteric type: report of 2 cases, and proposal for a novel subtype of thymic carcinoma. *Am J Surg Pathol*. 2015;39:541–548.
31. Lee JK, Louzada S, An Y, et al. Complex chromosomal rearrangements by single catastrophic pathogenesis in NUT midline carcinoma. *Ann Oncol*. 2017;28:890–897.
32. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. *Lancet Oncol*. 2015;16:177–186.

33. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. *Lancet Oncol*. 2020;21:843–850.
34. Sakane T, Murase T, Okuda K, et al. A comparative study of PD-L1 immunohistochemical assays with four reliable antibodies in thymic carcinoma. *Oncotarget*. 2018;9:6993–7009.
35. Soejima S, Kondo K, Tsuboi M, et al. GAD1 expression and its methylation as indicators of malignant behavior in thymic epithelial tumors. *Oncol Lett*. 2021;21:483.
36. Yamada Y, Simon-Keller K, Belharazem-Vitacolonnna D, et al. A tuft cell-like signature is highly prevalent in thymic squamous cell carcinoma and delineates new molecular subsets among the major lung cancer histotypes. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer*. 2021;16:1003–1016.
37. Alberobello AT, Wang Y, Beerkens FJ, et al. PI3K as a potential therapeutic target in thymic epithelial tumors. *J Thorac Oncol*. 2016;11:1345–1356.
38. Gökmen-Polar Y, Sanders KL, Goswami CP, et al. Establishment and characterization of a novel cell line derived from human thymoma AB tumor. *Lab Investig*. 2012;92:1564–1573.
39. Ehemann V, Kern MA, Breinig M, et al. Establishment, characterization and drug sensitivity testing in primary cultures of human thymoma and thymic carcinoma. *Int J Cancer*. 2008;122:2719–2725.
40. Pelosi G, Rodriguez J, Viale G, Rosai J. Typical and atypical pulmonary carcinoid tumor overdiagnosed as small-cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. *Am J Surg Pathol*. 2005;29:179–187.
41. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018;31:1770–1786.
42. Dinter H, Bohnenberger H, Beck J, et al. Molecular classification of neuroendocrine tumors of the thymus. *J Thorac Oncol*. 2019;14:1472–1483.
43. Ströbel P, Zettl A, Shilo K, et al. Tumor genetics and survival of thymic neuroendocrine neoplasms: a multiinstitutional clinicopathologic study. *Genes Chromosomes Cancer*. 2014;53:738–749.
44. Oosterhuis JW, Looijenga LHJ. Germ cell tumors from a developmental perspective: cells of origin, pathogenesis, and molecular biology (emerging pattern). In: Nogales FF, Jimenez RE, eds. *Pathology and Biology of Human Germ Cell Tumors*. 201. Berlin, Germany: Springer; 2017:23–129.
45. Kao CS, Bangs CD, Aldrete G, Cherry AM, Ulbright TM. A clinicopathologic and molecular analysis of 34 mediastinal germ cell tumors suggesting different modes of teratoma development. *Am J Surg Pathol*. 2018;42:1662–1673.
46. Lee T, Seo Y, Han J, Kwon GY. Analysis of chromosome 12p over-representation and clinicopathological features in mediastinal teratomas. *Pathology*. 2019;51:62–66.
47. Rekhtman N, Montecalvo J, Chang JC, et al. SMARCA4-deficient thoracic sarcomatoid tumors represent primarily smoking-related undifferentiated carcinomas rather than primary thoracic sarcomas. *J Thorac Oncol*. 2020;15:231–247.
48. Le Loarer F, Watson S, Pierron G, et al. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. *Nat Genet*. 2015;47:1200–1205.
49. Agaimy A, Haller F, Renner A, Niedermeyer J, Hartmann A, French CA. Misleading germ cell phenotype in pulmonary NUT carcinoma harboring the ZNF532-NUTM1 fusion [e-pub ahead of print]. *Am J Surg Pathol*. https://doi.org/10.1097/PAS.0000000000001774. Accessed July 8, 2021.
50. Haack H, Johnson LA, Fry CJ, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. *Am J Surg Pathol*. 2009;33:984–991.
51. Baranov E, Black MA, Fletcher CDM, Charville GW, Hornick JL. Nuclear expression of DDIT3 distinguishes high-grade myxoid liposarcoma from other round cell sarcomas. *Mod Pathol*. 2021;34:1367–1372.
52. Scapa JV, Cloutier JM, Raghavan SS, Peters-Schulze G, Varma S, Charville GW. DDIT3 immunohistochemistry is a useful tool for the diagnosis of myxoid liposarcoma. *Am J Surg Pathol*. 2021;45:230–239.
53. Robinson DR, Wu YM, Kalyana-Sundaram S, et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. *Nat Genet*. 2013;45:180–185.
54. Demicco EG, Wagner MJ, Maki RG, et al. Risk assessment in solitary fibrous tumors: validation and refinement of a risk stratification model. *Mod Pathol*. 2017;30:1433–1442.
55. Demicco EG, Park MS, Araujo DM, et al. Solitary fibrous tumor: a clinicopathological study of 110 cases and proposed risk assessment model. *Mod Pathol*. 2012;25:1298–1306.
56. Baranov E, McBride MJ, Bellizzi AM, et al. A novel SS18-SSX fusion-specific antibody for the diagnosis of synovial sarcoma. *Am J Surg Pathol*. 2020;44:922–933.
57. Perret R, Velasco V, Le Guellec S, Coindre JM, Le Loarer F. The SS18-SSX antibody has perfect specificity for the SS18-SSX fusion protein: a validation study of 609 neoplasms including 2 unclassified tumors with SS18-non-SSX fusions. *Am J Surg Pathol*. 2021;45:582–584.
58. Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: recommendations from the International Society for the study of vascular anomalies. *Pediatrics*. 2015;136:e203–e214.
59. Peifer M, Hertwig F, Roels F, et al. Telomerase activation by genomic rearrangements in high-risk neuroblastoma. *Nature*. 2015;526:700–704.
60. Sakane T, Murase T, Okuda K, Masaki A, Nakanishi R, Inagaki H. Expression of cancer testis antigens in thymic epithelial tumors. *Pathol Int*. 2021;71:471–479.
61. Huang YH, Klingbeil O, He XY, et al. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. *Genes Dev*. 2018;32:915–928.