Reprint of “Introduction to 2021 WHO Classification of Thoracic Tumors”

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Introduction

The WHO classification system of tumors is adopted worldwide and is fundamental to how tumor or tumor-like conditions are clinically managed or treated. It is considered the international accepted standard for the diagnosis of tumors for clinical care of patients and education and research into the etiology, prevention, and treatment of cancers. The International Agency for Research on Cancer (IARC) has been responsible for the publication of the WHO classification of tumors books, often known as the Blue Book, since the third edition of the WHO Classification of Tumors of the Lung, Pleura, Thymus, and Heart was published in 2004, 1 and the fourth edition in 2015. 2

The fifth edition of the WHO Classification book on Thoracic Tumors was published in April 2021. 3 In addition to a printed book, there is an online version that includes not only text, tables, and figures, but also whole-slide images (https://tumourclassification.iarc.who.int/wELCOME/). The volume was produced in collaboration with the International Association for the Study of Lung Cancer, the International Thymic Malignancy Interest Group, and the International Mesothelioma Panel. Common to all fifth edition books, the editorial board, with Prof. Ian Cree from IARC as the board chair, included organ-specific expert members and standing members. The expert members for the Thoracic Tumor Blue Book include 18 pathologists with known expertise and publication record in the pathology, imaging, and treatment of tumors of the lung, pleura and pericardium, thymus and mediastinum, heart and genetic tumor syndromes involving the thorax.

The fifth edition Thoracic Tumor Blue Book was formulated by an international, multidisciplinary group of 217 expert authors and editors. Because the fourth edition was published only 6 years ago, few new tumor entities have been recognized and added to this fifth edition. However, a large volume of new published data and updates especially in the epidemiology, histopathology, immunohistochemistry, and molecular pathology, and diagnostics of thoracic tumors have been incorporated into this new edition.

This manuscript will briefly summarize some of the key changes and features implemented in the fifth edition of the WHO Classification of Thoracic Tumors. Separate articles focusing on tumors of the lung, pleura, and pericardium, heart, and mediastinum will be published; these will resemble those published on the fourth edition of the Thoracic WHO Blue Book. 4–7 In addition, a new article that addresses thoracic hematopoietic tumors will be published.

Key New Features in the Fifth Edition

The fifth edition has been expanded to include 10 chapters (Table 1). Tumors of the lung, tumors of the pleura and pericardium, tumors of the heart, tumors of the thymus are assigned as separate chapters. In contrast to the fourth edition, separate chapters have been created for mesenchymal tumors involving multiple organ systems in the thorax, germ cell tumors of the...
mediastinum, hematomelymphoid tumors of the mediastinum, and ectopic tumors of the thyroid and parathyroid origin. However, mesenchymal tumors that are specific to the lung are included in the chapter on tumors of the lung. Metastatic tumors were moved to a separate chapter that addresses this topic for each site. In addition, a new chapter on genetic syndromes involving the thorax has been created.

New features in the fifth edition are sections on “Diagnostic molecular pathology” and “Essential and desirable diagnostic criteria.” These highlight key clinical, pathologic, immunohistochemical, and molecular diagnostic features of an individual entity.

**Key Updates on Tumors of the Lung**

For most tumors, the diagnostic criteria remain essentially unchanged since 2015, but there is considerably more detail to reflect recent scientific advances. As approximately two-thirds of lung tumors are diagnosed at an advanced stage and, thus, the diagnoses are made on small biopsy samples, the chapter entirely dedicated to the classification of small diagnostic samples is retained. Furthermore, given advances in molecular pathology, there is an even greater emphasis on genetic testing, not just in relation to common lung cancers but also new molecular characteristics in rarer tumors. Other key updates include the following: (1) recommendation on the application of percentage of histologic patterns to a formal grading system in invasive nonmucinous adenocarcinomas, (2) recognition of spread through airspaces as a prognostically significant histologic feature, (3) simplification of classification of squamous cell carcinomas and recognition of lymphoepithelial carcinoma as a squamous cell carcinoma, (4) recognition of bronchiolar adenoma/ciliated mucocutaneous papillary tumor as a new entity within the adenoma subgroup (5) recognition of thoracic SMARCA4-deficient undifferentiated tumor, (6) recognition of hyalinizing clear cell carcinoma and myoepithelioma and myoepithelial carcinoma as new types of salivary gland-type tumors, and (7) new data to reflect evolving concepts in lung neuroendocrine neoplasm.

**Key Updates on the Tumors of the Pleura and Pericardium**

The most significant addition to the fifth edition is “mesothelioma in situ,” which has recently been recognized as a preinvasive lesion of diffuse mesothelioma.\(^{6,9}\)

The need for a multidisciplinary approach including clinical, histopathologic, and molecular features as essential diagnostic criteria for mesothelioma in situ is emphasized. For diffuse pleural and pericardial mesothelioma, the term *malignant* has been omitted, but the three subtypes (epithelioid, biphasic, and sarcomatoid) are maintained. More importantly, there is a more organized stratification of histologic features into architectural patterns and cytologic and stromal features, including “transitional” and “lymphohistiocytic,” with prognostic implications documented.\(^{10}\) A further advance is the recommendation of a grading system for epithelioid mesothelioma, which should, henceforth, be a part of diagnostic reports. Finally, there was consensus that the word “tumor” should substitute “mesothelioma” in a well-differentiated papillary mesothelial tumor as the previous terminology was inconsistent with the benign clinical course of the lesion after resection.

**Key Updates on the Tumors of the Heart**

Several nomenclatures and classification changes were made to the chapter on tumors of the heart to better reflect our contemporary understanding of lesion pathobiology and provide consistency among lesions. Molecular data were expanded for both cardiac myxoma and papillary fibroelastoma, the latter of which is now formally recognized as neoplastic on the basis of the identification of oncogenic driver mutations in these tumors.

The term histiocytoid cardiomyopathy was updated to conduction system hamartoma in recognition of its similarity pathologically and genetically with other hamartomas lesions. The list of hamartomatous lesions was also expanded to include distinctive entities.

The list of specific malignancies was condensed to reflect frequently encountered malignancies, with some tumors (e.g., myxofibrosarcoma, synovial sarcoma) being relocated to the chapter on mesenchymal tumors of the thorax given their similar presentation and implication.

**Key Updates on the Tumors of the Mediastinum**

The classification of thymic tumors has largely been maintained. Recent advances mainly concern thymic epithelial tumors—that is, thymomas, thymic carcinomas (TCs), and neuroendocrine neoplasms. These comprise rare new entities (e.g., hyalinizing clear cell carcinomas), new molecular features of well-known entities (e.g.,
MAML2 translocations in metaplastic thymomas), the refinement of diagnostic criteria (e.g., for adenocarcinomas by obligatory immunohistochemical features), and the streamlining of nomenclature, as exemplified by the term lymphoepithelial carcinoma for analogous tumors in the thymus and lung, replacing the historic “thymic lymphoepithelioma-like carcinoma.” Some new observations may even have the potential to change current therapies, including microsatellite instability in TCs11 and the delineation of molecular subgroups among neuroendocrine neoplasms12 that are, however, still classified through classical morphologic criteria as typical and atypical carcinoids, large cell neuroendocrine carcinoma, and small cell carcinoma.

On germ cell tumors of the mediastinum, the development of mediastinal teratomas along different pathways seems a major advance.13

Key Updates on Thoracic Hematolymphoid Tumors of Mediastinum

In continuity with the fourth edition, the chapter on hematolymphoid tumors of the mediastinum covers lymphomas, dendritic cell tumors, and myeloid sarcoma. If arising in mediastinal lymph nodes, virtually all lymphomas, dendritic cell tumors, and myeloid neoplasia may be encountered. Their diagnostic criteria remain unchanged.

Changes in the new edition include the following: (1) the restriction to entities with “mediastinal peculiarities” or relevant mediastinal prevalence; (2) the simplification of the nomenclature “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma” to "mediastinal gray zone lymphoma"; and (3) staging according to the Lugano classification that has been adopted from the eighth edition of the TNM classification system. For entities beyond nodular sclerosis classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, mediastinal gray zone lymphoma, T-lymphoblastic lymphoma/leukemia, mucosa-associated lymphoid tissue (MALT) lymphoma, and follicular dendritic cell sarcoma, readers are referred to the fourth edition of the WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues.14

Genetic Tumor Syndromes Involving the Thorax

A new chapter on genetic tumor syndromes was added that addresses the uncommon germline mutations among patients with lung cancer and references the many hereditary genetic disorders that have been associated with various thoracic neoplasms (Table 2). The chapter includes a more detailed discussion on three hereditary tumor syndromes. The Li-Fraumeni syndrome is caused by germline mutation involving the TP53 tumor suppressor gene, with associated thoracic malignancies including lung carcinoma, mediastinal/cardiac sarcomas, and TC. BAP1 tumor predisposition syndrome results from germline mutation involving the BAP1 gene, which predisposes the affected individual to pleural or peritoneal mesothelioma. The Carney complex includes atrial myxomas, endocrinopathy, and

### Table 2. Hereditary Genetic Disorders Associated With Familial Predisposition to Particular Thoracic Neoplasm

<table>
<thead>
<tr>
<th>Hereditary Genetic Disorder</th>
<th>Associated Thoracic Neoplasms</th>
</tr>
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<tbody>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Lung carcinoma, mediastinal/cardiac sarcomas, thymic carcinoma</td>
</tr>
<tr>
<td>BAP1 tumor predisposition syndrome</td>
<td>Mesothelioma</td>
</tr>
<tr>
<td>Carney complex</td>
<td>Atrial myxoma</td>
</tr>
<tr>
<td>DICER1 syndrome</td>
<td>Pleuropulmonary blastoma</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Lymphangioleiomyomatosis, perivascular epithelioid cell tumors (PEComas), cardiac rhabdomyomas</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>Cardiac fibromas</td>
</tr>
<tr>
<td>Gardner syndrome</td>
<td>Desmoid fibromatosis</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Malignant peripheral nerve sheath tumor, paragangliomas</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>Schwannoma</td>
</tr>
<tr>
<td>Germline SMARCB1 or LZTR1 mutations</td>
<td>Schwannomatosis</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td>Von Hippel-Lindau syndrome</td>
<td>Paraganglioma</td>
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<tr>
<td>Hereditary paraganglioma-phaeochromocytoma syndrome</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td>Carney-Stratakis syndrome</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td>Germline EGFR p.T790M</td>
<td>Lung carcinoma</td>
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<tr>
<td>ERBB2 germline mutations</td>
<td>Lung carcinoma</td>
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IARC, International Agency for Research on Cancer.
pigmented skin lesions, and is associated with germline mutation involving the PRKARIA gene, which encodes for a regulatory subunit of the protein kinase A.

Hereditary lung adenocarcinomas have been reported among family members of patients with germline EGFR T790M mutation and YAP1 R331W risk allele mutation.15 Interestingly, patients with lung adenocarcinoma and family history of lung cancer were reported at higher risk of harboring EGFR mutation in their lung cancers, albeit the mutation types are randomly distributed,16,17 suggesting that additional studies are warranted into genetic risk alleles involved in lung carcinogenesis.

Conclusion
In conclusion, the fifth edition Blue Book should serve as an important reference in the daily practice of pathologists, and others involved in the education, research, and care of patients with thoracic tumors. The editors gratefully acknowledge the wonderful scientific contributions and collegiality of each of the contributing authors and the International Association for the Study of Lung Cancer, International Thymic Malignancy Interest Group, International Mesothelioma Panel, and IARC in making publication of this book possible.

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References