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Review Article

Pathology Section

An Update on WHO Classification of Thoracic Tumours 2021- Newly Described Entities and Terminologies

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ABSTRACT

The 5th edition of the World Health Organisation (WHO) "Classification of Thoracic Tumours" replaces the previous edition from 2015, which was released in 2021. The new edition includes specific diagnostic criteria for each entity and lays a stronger emphasis on diagnostic molecular pathology. Immunohistochemistry (IHC) was heavily promoted in 2015, as a way to improve classification precision. The book places more attention on molecular pathology developments for all tumour types in 2021. Classification based on microscopic biopsy samples of the characteristics of lung cancer is an alternative to resection-based categorisation. A grading system for invasive non mucinous adenocarcinomas has been developed, using the percentage of distinctive histological patterns found inside each tumour. Lung adenocarcinoma is also predisposed by Tumour Spread Through Air Spaces (STAS). A basaloid variety of Squamous Cell Carcinoma (SCC) and lymphoepithelial carcinoma was added to the SCC group. The ciliated muconodular papillary tumour and thoracic SMARCA4-deficient undifferentiated carcinoma are recent inclusions. Therefore, the following new terms and entities have been added to the WHO classification of 2021: (1) Thoracic SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (SMARCA4)-deficient undifferentiated tumour; (2) Bronchiolar adenoma/ciliated muconodular papillary tumour; (3) Primary pulmonary hyalinising clear cell carcinoma of lung; (4) Lypmphoepithelial carcinoma; (5) STAS.

Keywords: Bronchiolar adenoma, Ciliated muconodular papillary tumour, Squamous cell carcinoma, World health organisation

INTRODUCTION

The previous edition from 2015, was replaced by the WHO classification of thoracic tumours, 5th edition, which was released in 2021. The classification of many thoracic tumours hasn't changed, but, the new edition places more emphasis on diagnostic molecular pathology and offers distinct, desirable diagnostic criteria for each entity [1]. The fundamentals of classifying thoracic tumours remain the same: morphology comes first, then IHC, and finally molecular methods [2]. In 2015, a lot of emphasis was placed on using IHC to enhance classification accuracy [3]. The book places more attention on developments in molecular pathology for all tumour types in 2021. Along with classification based on resections, classification based on small biopsy samples of particular lung cancers is also possible. Based on the proportion of various histological patterns discovered inside each tumour, a grading system for invasive non mucinous adenocarcinomas has been created. STAS is a predictive marker for lung cancer [4].

Lymphoepithelial like carcinoma nomenclature changed to Lymphoepithelial carcinoma and has been introduced to the group of SCCs, and have been reclassified to include a basaloid variant. The latest additions are thoracic SMARCA4-deficient undifferentiated carcinoma and bronchiolar adenoma/ciliated muconodular papillary tumour. In the 2021 WHO classification, the following new terms and entities have been added: 1) Thoracic SMARCA4-deficient undifferentiated tumour; 2) Bronchiolar adenoma/ciliated muconodular papillary tumour; 3) Primary pulmonary hyalinising clear cell carcinoma of lung; 4) Lypmphoepithelial carcinoma; 5) STAS [Table/Fig-1,2] [2].

The newly described entity in the recent classification

The following new entities are added to the 2021 WHO classification of thoracic tumour:

Thoracic tumours with International Classification of Diseases for Oncology (ICD-O) codes
Epithelial tumours
Papillomas Squamous cell papilloma, NOS Squamous cell papilloma, inverted Glandular papilloma Mixed squamous cell and glandular papilloma
Adenomas Sclerosing pneumocytoma Alveolar adenoma Papillary adenoma Bronchiolar adenoma/ciliated muconodular papillary tumoura Mucinous cystadenoma Mucous gland adenoma
Precursor glandular lesions Atypical adenomatous hyperplasia Adenocarcinoma in-situ Adenocarcinoma in-situ, non mucinous Adenocarcinoma in-situ, mucinous
Adenocarcinomas Minimally invasive adenocarcinoma Minimally invasive adenocarcinoma, non mucinous Minimally invasive adenocarcinoma, mucinous Invasive non mucinous adenocarcinoma Lepidic adenocarcinoma Acinar adenocarcinoma Papillary adenocarcinoma Micropapillary adenocarcinoma Solid adenocarcinoma Invasive mucinous adenocarcinoma Mixed invasive mucinous and non mucinous adenocarcinoma
Colloid adenocarcinoma Foetal adenocarcinoma Adenocarcinoma, enteric type Adenocarcinoma, NOS
Squamous precursor lesions Squamous cell carcinoma in-situ Mild squamous dysplasia Moderate squamous dysplasia Severe squamous dysplasia

Squamous cell carcinomas Squamous cell carcinoma, keratinising Squamous cell carcinoma, non keratinising Basaloid squamous cell carcinoma
Lymphoepithelial carcinoma Large cell carcinomas Adenosquamous carcinomas Sarcomatoid carcinomas
Pleomorphic carcinoma Giant cell carcinoma Spindle cell carcinoma Pulmonary blastoma Carcinosarcoma Other epithelial tumour NUT carcinoma 8023/3 Thoracic SMARCA4-deficient undifferentiated tumour Salivary gland-type tumours Pleomorphic adenoma Adenoid cystic carcinoma Epithelial-myoepithelial carcinoma Mucoepidermoid carcinoma Hyalinising clear cell carcinoma Myoepithelioma Myoepithelial carcinoma
Lung neuroendocrine neoplasms precursor lesion Diffuse idiopathic neuroendocrine cell hyperplasia
Neuroendocrine tumours Carcinoid tumour, NOS/neuroendocrine tumour, NOS Typical carcinoid/neuroendocrine tumour, grade 1 Atypical carcinoid/neuroendocrine tumour, grade 2
Neuroendocrine carcinomas Small cell carcinoma Combined small cell carcinoma Large cell neuroendocrine carcinoma Combined large cell neuroendocrine carcinoma
Tumours of ectopic tissues Melanoma Meningioma Mesenchymal tumours specific to the lung Pulmonary hamartoma Chondroma Diffuse lymphangiomatosis Pleuropulmonary blastoma Intimal sarcoma Congenital peribronchial myofibroblastic tumour
Pulmonary myxoid sarcoma with EWSR1-CREB1 fusion PEComatous tumours Lymphangioleiomyomatosis PEComa, benign PEComa, malignant Haematolymphoid tumours MALT lymphoma Diffuse large B-cell lymphoma, NOS
Lymphomatoid granulomatosis, NOS Lymphomatoid granulomatosis, grade 1 Lymphomatoid granulomatosis, grade 2 Lymphomatoid granulomatosis, grade 3
Intravascular large B-cell lymphoma Langerhans cell histiocytosis Erdheim-Chester disease

[Table/Fig-1]: WHO classification of thoracic tumours 2021 [2].
ICD-O: International classification of diseases for oncology; NOS: Not otherwise specified; NUT: Nuclear protein in testis; EWSR1: Ewing sarcoma breakpoint region 1; CREB1: cAMP responsive element binding protein 1; PE: Perivascular epithelioid; MALT: Mucosa-associated lymphoid tissue

WHO 2015	Entity name (changed or new nomenclature)	WHO 2021
	Bronchiolar adenoma/ciliated muconodular papillary tumour	New entity in 2021 WHO classification under the category of adenoma
	Thoracic SMARCA4-deficient undifferentiated tumour	New entity in 2021 WHO classification
	Primary pulmonary hyalinising clear cell carcinoma	New entity in 2021 WHO classification under the category of salivary gland tumour
Lymphoepithelial like carcinoma	Lymphoepithelial carcinoma	Change in nomenclature and catagorise under squamous cell carcinoma
	Spread through the airspaces (STAS)	New term added in WHO 2021 classification

[Table/Fig-2]: The following new entities are added to the 2021 WHO classification of thoracic tumour.

Bronchial Adenoma/Ciliated Muconodular Pulmonary Tumour (BA/CMPT): The WHO classifies lung adenomas as of 2015, as sclerosing pneumocytoma, alveolar adenoma, papillary adenoma, mucinous cystadenoma, and mucous gland adenoma [3]. Adenomas formed by the bronchiolar epithelium are poorly understood. Adenomas, that develop in tandem with the range of the lung airway epithelium include mucous gland adenomas and peripheral alveolar structures (alveolar adenoma). According to a recent theory, CMPT may stand for mucinous/papillary morphology prominent, bronchiolar difference across lesions with a wider range of morphologies, prompting the creation of a BA umbrella name to capture all lesions with this feature. CMPT refers to a collection of lesions with conventional morphology [4]. One of the distinguishing features of BA/CMPT is the proliferation of non pleomorphic double layered bronchiolar type epithelium along the alveolar lung parenchyma, with luminal cells layer surrounded by basal cell [5]. Luminal cells with several ciliated and/or mucin-filled cells can be categorised as proximal or distal airways [5]. Older persons are primarily impacted by CMPT. This tumour has no connection to smoking history and can affect either sex [6]. Mild atypia and a low proliferation index in CMPT support the benign nature of the tumour. Thyroid transcription factor 1 (TTF-1), Cytokeratin 7 (CK7) and carcinoembryonic antigen are thought to be CMPT specific markers, however, CK20 is negative [7].

The molecular changes in both, distal and proximal BAs (the latter corresponding to the conventional CMPT) is frequently identical and show mutation in proto-oncogene B-Raf (BRAF) V600E. Ki-ras2 Kirsten Rat Sarcoma viral oncogene homolog (KRAS), Harvey Rat Sarcoma virus (HRAS), Anaplastic Lymphoma Kinase (ALK), and Ak Strain Transforming (ATK) alterations, as well as, mutations in Epidermal Growth Factor Receptors (EGFR) have all been reported [5,8-11]. On imaging, BA/CMPT has solid or ground glass appearance with or without cavity formation. The lesions typically have a diameter of between 0.5 and 1.5 cm. There is no preference for one sex over the other and patients range in age 6th to 7th decade. As of right now, no BA/CMPT patients, who had surgical resection have developed any new symptoms [5,12,13]. The most crucial differential diagnosis for BA/CMPT is adenocarcinoma. Ischaemia-modified Albumin (IMA) is one of the possible diagnoses for peripheral skin lesions and substantial mucinous features in proximal-type BA/CMPT [5,14,15]. The only difference between proximal-type BA/CMPT and glandular/mixed papillomas, in terms of their physical characteristics, is that, the former are found in the alveolar lung parenchyma, whereas, the latter are found in the endobronchial space [10,11].

SMARCA4-Deficient undifferentiated thoracic tumour: The new edition now includes a highly aggressive tumour lacking SMARCA4 {also known as Brahma-related Gene-1 (BRG1)} and with an undifferentiated or rhabdoid phenotype. The condition was formerly referred to as "SMARCA4-deficient thoracic sarcoma [16-18]". There is biallelic inactivation of SMARCA4 without any germline SMARCA4 mutation, and Tumor Protein 53 (TP53) mutation occurs in roughly 69% of cases. SMARCA4 (BRG1) is a member of chromatin remodelling complex, regulates transcription and promotes cell differentiation. The majority of cases are now being categorised as dedifferentiated/undifferentiated lung carcinoma due to recent molecular research showing that, it has a tight genomic relationship to smoking related Non Small Cell Lung Cancer (NSCLC) [19].

Due to the fact that, it possesses properties that distinguish it from typical NSCLC with SMARCA4 deficit, the WHO recognises SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4- Undifferentiated Tumour (SMARCA4-UT) as a distinct entity from the latter. These hypercalcaemic variant of small cell ovarian carcinoma and malignant rhabdoid tumours share transcriptomic similarities with these SMARCA4-deficient thoracic sarcomas, but they differ from them in terms of genomic instability,

frequent TP53 mutations, higher tumour mutation burdens, and the absence of germline SMARCA4 alterations [18]. Young to middle aged male with history of heavy and chronic smoking are usually affected. Clinical correlation is necessary because similar cancer can metastasize to the thorax, and SMARCA4-UT tumours in the lungs are extremely aggressive, with survival of only four to seven months [16-19]. Histopathology reveals, sheets of round to oval shaped discohesive epithelioid cells with monomorphic nuclei, minor nuclear pleomorphism and conspicuous nucleoli, which are the hallmarks of the SMARCA4 defective tumour. The malignant rhabdoid tumour morphologic range in youngsters is similar overall. Except in rare mixed cases, when normal NSCLC is juxtaposed, clear epithelial architecture should be lacking. Rhabdoid cell differentiation may be present, but not required for diagnosis. These tumours are also frequently positive for Sex determining region Y-box 2 (Sox2), Cluster of Differentiation 34 (CD34), and Sal-like protein 4 (SALL4) On IHC, there is a reduction of expression of SMARCA4 (BRG1) by the tumour cells; occasionally, the expression is not totally lost but, there is a considerable decrease in BRG1 expression [16,19].

Lymphoepithelioma-like Carcinoma (LELC) (lymphoepithelial carcinoma): In 1987, Begin LR et al., identified a lung cancer called LELC in a 40-year-old non smoking Southeast Asian woman [20]. Serum antibodies against Epstein-Barr Virus (EBV) capsid antigens were found to be quite elevated, and the scientists noted a possible link between the two. Further research using in-situ hybridisation to detect EBV-encoded small nuclear Ribonucleic Acid (RNA) in tumour cell nuclei provided further evidence of the connection [21]. While lymphoepithelial carcinoma was included in the large cell carcinoma subtype in the 2004 WHO classification, it is now classed as "other and unclassified carcinomas" in the 2015 WHO classification [22] because, CK and Epithelial Membrane Antigen (EMA) are typically expressed by the tumour cells of lymphoepithelial carcinoma. Furthermore, CK 5/6, p63, and p409 is also positive, indicating squamous cell lineage [23,24]. As a result, LELC, which was listed under "other and unclassified carcinomas" in the fourth edition, has been renamed lymphoepithelial carcinoma and is now regarded as a subtype of SCC.

STAS (Spread Through Air Space): New term added to the 2021 classification, in which tumour cells lies in air gaps beyond the main tumour's border. It can be seen in approximately 15%-50% of NSCL can also be found in small cell carcinoma. Micropapillary formations, solid nests of malignant cells, and single discohesive cells are examples of patterns. In lung adenocarcinomas, STAS is now included in the WHO classification of thoracic tumour 2021. If STAS is discovered in sublobar resection, it may indicate that, lobectomy is needed later. If STAS is detected in limited resections, it may have a higher recurrence risk than lobectomy [3,25,26].

Primary pulmonary Hyalinising Clear Cell Carcinoma (HCCC) of lung: The 2021 WHO classification of lung malignancies now includes this new category [27]. Primary pulmonary salivary gland-type malignancies account for about 1% of all thoracic tumours. The diagnostic challenge can be significant, when it occurs in unusual places, like the bronchus or nasopharynx. Hyalinising clear cell carcinoma frequently affects small salivary glands of the palate and oral base [28]. The tumour cells display immunoreactivity for CK7 and also for p40 and p63 [29]. The tumour is comprises of abnormally small to medium sized epithelioid cells with round to oval nuclei, barely perceptible nucleoli, eosinophilic to clear cytoplasm, and very low mitotic figures. Correct diagnosis is aided by knowledge of the important immunohistochemical and molecular testing along with the fundamental morphologic aspects of pulmonary HCCC, as it is challenging to diagnose primary pulmonary HCCC from a small sample [29].

Nomenclature in small biopsy

If the distinction between adenocarcinoma and SCC on the basis of morphology is not clear and there is a requirement of IHC, then the term Non Small Cell Carcinoma (NSCC)- favouring adenocarcinoma or SCC should be used. Since, no invasion is seen in the lepidic growth pattern and this pattern can be seen in the above mentioned entity, it should be reported as adenocarcinoma with lepidic pattern and distinction between minimally invasive adenocarcinoma, adenocarcinoma in-situ, and invasive adenocarcinoma required a resected specimen should be noted in the comment section. Similar to small biopsy or cytology specimens, large cell carcinoma should not be diagnosed and should only be utilised in resection specimens, if the tumour has been thoroughly evaluated to rule out a differentiated component [1]. Use the term small cell carcinoma, if it has the characteristic features; if the features are similar to those of a large cell neuroendocrine carcinoma, it should be classified as a NSCC with neuroendocrine morphology. Similarly, the term NSSC-NOS specified is indicated when both an adenocarcinoma and SCC component present, or it can't be subtyped further [1,2].

Small biopsies tissue preservation

Efforts must be made to maximum preservation of the tissue which allows the examination of different biomarkers and they may be eligible for immunotherapy or targeted therapy. IHC should only be performed if the morphology requires it, and double IHC, such as TTF-1 and p40, should be used whenever possible, because both are nuclear stains, so different chromogen used to differentiate them. The p40 protein could be combined with Napsin [1].

Molecular updates of thoracic tumours

Adenocarcinoma molecular abnormalities were included in the "Somatic genetics" part of the 2015 WHO classification [3]. As of the 2021 WHO classification, molecular abnormalities are classified under "Aetiology", "Pathogenesis," and "Diagnostic molecular pathology." Adenocarcinoma is characterised by numerous molecular alterations that have been linked to its development, progression, and most importantly treatment. [Table/Fig-3] discusses the changes that have been made to the lung tumour classification over the years from 2015 to 2022 [30-40]. These changes are briefly explained below.

Molecular markers as per 2015 WHO	Author's name, year, reference number	Inference of the study
EGFR	Cortes-Funes H et al., 2005 [30] Tokumo M et al., 2005 [31]	EGFR mutations were found in 10 of 83 (12%) of patients EGFR mutations were present in 38 cases out of 120 (32%) and the majority of mutations were in-frame deletions of exon 19 (19 cases) and a missense mutation in exon 21 (18 cases).
ALK	Kwak EL 2010 [32]	Identified 82 patients with advanced ALK-positive disease
ROS1	Bergethon K 2012 [33]	A total of 1,073 tumours screened, 18 (1.7%) were ROS1 rearranged by FISH, and 31 (2.9%) were ALK rearranged
RET rearrangement	Wang R et al., 2012 [34] Saito M et al., 2014 [35]	A total of 936 patients with NSCLC, the RET fusion gene was exclusively detected in 13 patients Results suggest that the RET fusion functions as a driver for the development of thoracic tumours, whose growth is inhibited by RET tyrosine kinase inhibitors
RET rearrangement	Wang R et al., 2012 [34] Saito M et al., 2014 [35]	A total of 936 patients with NSCLC, the RET fusion gene was exclusively detected in 13 patients Results suggest that, the RET fusion functions as a driver for the development of thoracic tumours, whose growth is inhibited by RET tyrosine kinase inhibitors

MET Exon 14 mutations	Awad MM et al., 2016 [36] Schrock AB et al., 2016 [37]	MET exon 14 mutations were identified in 28 of 933 non squamous NSCLCs (3.0%) A total of 11,205 lung cancers profiled by comprehensive genomic profiling, 298 (2.7%) carcinomas harbored alterations predicted to cause METex14
ERBB2-HER2	Mazières J et al., 2013 [38] Arcila ME et al., 2012 [39]	HER2 mutation was identified in 65 (1.7%) of 3,800 patients tested and was almost an exclusive driver, except for one single case with a concomitant KRAS mutation Identified 25 cases with HER2 mutations, representing 6% of EGFR/KRAS/ALK-negative specimens.
BRAF mutations	Barlesi F et al., 2016 [40]	EGFR mutations were reported in 1947 (11%) of 17,706 analyses for which data were available, HER2 mutations in 98 (1%) of 11,723, KRAS mutations in 4894 (29%) of 17,001, BRAF mutations in 262 (2%) of 13,906, and PIK3CA mutations in 252 (2%) of 10,678; ALK rearrangements were reported in 388 (5%) of 8134 analyses

[Table/Fig-3]: Molecular updates on thoracic tumours [30-40].
ROS1: c-ros oncogene 1; RET: Rearranged during transfection; FISH: Fluorescence in-situ hybridization; MET: Mesenchymal epithelial transition; HER2: Human epidermal growth factor receptor 2; PIK3CA: Phosphatidylinositol-bisphosphate 3-kinase catalytic subunit alpha

An imbalance between oncogenes and tumour suppressor genes causes lung carcinogenesis, which manifests as a tumour composed of malignant cells, that have taken on the phenotypic "hallmarks of cancer" [41]. Prior to a few years ago, advanced NSCLC had a grim prognosis. Nevertheless, the discovery of oncogene addiction sparked the development of targeted therapies against driver mutations, which produced outstanding response rates and survival outcomes [42]. Mutations in the EGFR gene, that increase susceptibility to the disease occur in 30-40% of Asian patients and 10-12% of non Asian patients. They're linked to being a non smoker, having adenocarcinoma, and being of the female sex [30,31]. Since, the identification of the driving oncogene for the EGFR and the tyrosine kinase inhibitors that target it, individualised genomic-driven management decisions have been accepted as the gold standard of care in NSCLC [43]. The most frequent driver modifications in NSCLC are KRAS mutations, which are virtually exclusively found in adenocarcinomas [44]. They impact 25% of patients and are linked to smoking and a reduced life expectancy [45]. A 5% of NSCLC patients had ALK gene rearrangements, primarily in adenocarcinoma and non/light smokers [32]. Patients with ALK rearrangements are more likely to be male and younger than EGFR-mutant individuals [46]. Some changes, such as TP53, NRAS, and Mitogen-activated Protein Kinase 11 (MAP2K11), are more prevalent among smokers [47-49]. In the untreated context, oncogenic drivers are often mutually exclusive within a specific tumour. It is hypothesised that, when these drivers are mutually exclusive, they constitute early events in tumour formation; these modifications are detected in early lesions, including atypical adenomatous hyperplasia and Adenocarcinoma In-situ (AIS), supporting this hypothesis [50] The ALK gene on chromosome 2 encodes ALK, a protein that belongs to the family of insulin-receptor tyrosine kinases. A 3%-5% of NSCLC patients experience ALK rearrangements, which are more prevalent in younger individuals, those with a light smoking history, adenocarcinoma histology, and tumours with wild-type EGFR and KRAS [32,51]. Lung cancer treatment focuses on ROS1 only recently. ROS1 fusion has been identified as a driving mutation in NSCLC cell lines and primary tumours [52]. A small percentage, 1%-2%, of NSCLCs has ROS1 rearrangement. There is a lot of similarity between the ROS1-kinase domain and the ALK-kinase domain. Patients who test positive for ROS1 are similar to those, who test positive for ALK in several respects, including their shared adenocarcinoma histology, histomorphology, younger age, and high incidence of non smokers [33].

Emerging Molecular Targets: The RET is capable of oncogenic activation via mutation or rearrangement. Rearranged RET occurs in 1%-2% of unselected instances of NSCLC. These mutations are frequently observed in non smokers' adenocarcinomas [34]. When it comes to NSCLC, Kinesin Family Member 5B (KIF5B) is RET's upstream fusion partner of choice [35]. In 3% of non squamous NSCLC, MET exon 14 mutations are another emerging target genetic change. These mutations are more likely to be found in non smokers, and clinical trials are necessary to evaluate how well MET inhibitors work, because only a small number of case reports and restricted series have shown positive results [35,37].

CONCLUSION(S)

The 5th WHO classification of thoracic tumour includes specific diagnostic criteria for each entity and lays a stronger emphasis on diagnostic molecular pathology. Classification based on microscopic biopsy samples of the characteristics of thoracic cancer is an alternative to resection-based categorisation. A grading system for invasive non mucinous adenocarcinomas has been proposed and lung adenocarcinoma is also predisposed by STAS. A basaloid variety of SCC was added, and lymphoepithelial carcinoma was added to the SCC group. The ciliated muconodular papillary tumour, thoracic SMARCA4-deficient undifferentiated carcinoma and primary pulmonary HCCC are the recent inclusions. Beside this, a lot of emphasis has been placed on the molecular basis and precise nomenclature used for small biopsy samples, because these factors determine which clinician will be in charge of the patient's future treatment.

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