WHO CLASSIFICATION OF TUMOURS OF ENDOCRINE ORGANS Textbook

WHO classification of tumours of endocrine organs is a comprehensive system developed by the World Health Organization to categorize and diagnose tumors originating from endocrine glands. This classification provides a standardized framework that aids pathologists, endocrinologists, and oncologists in understanding the nature, prognosis, and appropriate treatment strategies for these tumors. Given the complexity and diversity of endocrine tumors, the WHO classification has evolved over the years to incorporate advances in molecular pathology, histopathology, and clinical research.

Introduction to Endocrine Tumors and Their Significance

Endocrine tumors are neoplasms arising from endocrine glands such as the thyroid, parathyroid, adrenal glands, pituitary, and neuroendocrine cells scattered throughout various organs. These tumors can be benign or malignant and often produce hormones, leading to diverse clinical syndromes. Accurate classification is vital for prognosis determination, therapeutic decision-making, and research.

Historical Development of WHO Classification of Endocrine Tumors

The WHO classification was first introduced in 2004 and has undergone multiple updates, notably in 2017. These revisions reflect new insights from molecular genetics, immunohistochemistry, and clinical behavior patterns. The current system emphasizes a combined approach that considers morphology, immunophenotype, and molecular features, facilitating precise diagnosis and personalized medicine.

Major Categories in WHO Classification of Endocrine Tumours

The WHO classification divides endocrine tumors primarily based on the organ of origin and tumor behavior. The main categories include:

- Thyroid tumors
- Adrenal tumors
- Parathyroid tumors
- Pituitary tumors
- Neuroendocrine tumors of other organs

Each category comprises benign, uncertain malignant potential, and malignant tumors, with specific subtypes and grading systems.

Thyroid Tumours

Thyroid tumors are among the most common endocrine neoplasms. They are classified into several categories:

Differentiated Thyroid Carcinomas

These tumors retain some features of normal thyroid tissue and are generally associated with a better prognosis.

- **Papillary Thyroid Carcinoma (PTC):** The most common type, characterized by papillary structures and nuclear features such as clearing and grooves.
- **Follicular Thyroid Carcinoma (FTC):** Comprises follicular structures; invasion through the capsule or blood vessels signifies malignancy.
- **Hürthle Cell Carcinoma:** A variant of FTC with oncocytic features.

Medullary Thyroid Carcinoma (MTC)

Arises from parafollicular C cells and secretes calcitonin. It has familial and sporadic forms and is associated with RET mutations.

Anaplastic Thyroid Carcinoma

A highly aggressive undifferentiated carcinoma with poor prognosis.

Other Thyroid Tumors

Includes tumors such as diffuse sclerosing carcinoma and benign adenomas.

Adrenal Tumours

Adrenal tumors originate from the cortex or medulla, with distinct classifications.

Adrenocortical Tumors

These include benign adenomas and malignant carcinomas.

- **Adrenocortical Carcinoma (ACC):** Malignant, often secreting hormones like cortisol, and associated with poor prognosis.
- **Adrenocortical Adenoma:** Usually benign and hormonally active or inactive.

Pheochromocytoma and Paragangliomas

Arise from chromaffin cells in the adrenal medulla or paraganglia.

- **Pheochromocytoma:** Located in adrenal medulla; secretes catecholamines.
- **Paraganglioma:** Extra-adrenal; can be sympathetic or parasympathetic.

Other Adrenal Tumors

Rare tumors include myelolipomas and metastases.

Parathyroid Tumours

The most common parathyroid tumor is the parathyroid adenoma, which causes primary hyperparathyroidism.

Benign Parathyroid Tumors

- Parathyroid adenoma: The majority of cases.

Parathyroid Carcinoma

A rare but aggressive malignant tumor requiring surgical excision.

Pituitary Tumours

Pituitary tumors are classified based on size, hormone secretion, and histology.

Adenomas

Most common, benign tumors classified by the hormone they produce:

- Prolactinomas
- Somatotroph adenomas (growth hormone-secreting)

- Corticotroph adenomas (ACTH-secreting)
- Other hormone-secreting adenomas

Pituitary Carcinomas

Extremely rare malignant tumors with metastatic potential.

Others

Include Rathke cleft cysts and craniopharyngiomas, which are non-neoplastic lesions.

Neuroendocrine Tumours of Other Organs

Neuroendocrine tumors (NETs) are a diverse group originating from neuroendocrine cells in various tissues, including the pancreas, lungs, and gastrointestinal tract.

Pancreatic Neuroendocrine Tumours (PanNETs)

Classified based on differentiation, hormonal activity, and grading.

- Well-differentiated neuroendocrine tumors (NETs)
- Neuroendocrine carcinomas (NECs)

Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs)

Includes tumors of the stomach, small intestine, colon, and rectum.

Lung Neuroendocrine Tumors

Divided into typical carcinoids, atypical carcinoids, large cell neuroendocrine carcinomas, and small cell lung carcinomas.

Grading and Staging in WHO Classification

The WHO system incorporates grading based on mitotic activity, Ki-67 proliferation index, and histological features to predict tumor behavior. Staging follows the TNM system, considering tumor size, lymph node involvement, and metastasis.

Molecular Pathology and Its Role in Classification

Recent updates emphasize molecular alterations, such as mutations in RET, RAS, TP53, and others, which refine diagnosis and enable targeted therapy. For example:

- RET mutations are prominent in medullary thyroid carcinoma.
- BRAF mutations are common in papillary thyroid carcinoma.
- MDM2 amplification may suggest certain adrenal tumors.

Molecular testing complements histopathology, especially in ambiguous cases.

Clinical Implications of WHO Classification

Accurate classification influences treatment choices, prognosis, and follow-up strategies. For example:

- Benign tumors may require surgical excision with curative intent.
- Malignant tumors often need multimodal therapy, including surgery, radiotherapy, and targeted agents.
- Understanding tumor subtype informs prognosis and genetic counseling, especially in familial syndromes like MEN (Multiple Endocrine Neoplasia).

Conclusion

The WHO classification of tumours of endocrine organs provides a vital framework that integrates morphological, immunohistochemical, and molecular features to deliver precise diagnoses. As research advances, this classification continues to evolve, reflecting our growing understanding of the pathogenesis and behavior of endocrine tumors. Clinicians and pathologists must stay updated with these revisions to optimize patient care, facilitate research, and improve outcomes for individuals affected by these diverse neoplasms.

Keywords: WHO classification, endocrine tumors, thyroid neoplasms, adrenal tumors, parathyroid tumors, pituitary tumors, neuroendocrine tumors, tumor grading, molecular pathology

WHO classification of tumours of endocrine organs is an essential framework that provides a standardized approach to diagnosing, categorizing, and understanding tumors arising from endocrine tissues. These classifications are integral for pathologists, endocrinologists, oncologists, and researchers alike, as they guide clinical management, prognostication, and research directions. Since the World Health Organization?s (WHO) first publication on this topic, the classification system has undergone multiple updates to incorporate advances in molecular biology, histopathology, and clinical outcomes. This review aims to provide a comprehensive overview of the

WHO classification of endocrine tumors, discussing its structure, key categories, updates, strengths, limitations, and clinical implications.

Introduction to WHO Classification of Endocrine Tumours

The WHO classification of tumours of endocrine organs is a globally recognized system that categorizes tumors based on histological features, immunohistochemical profiles, molecular genetics, and clinical behavior. It serves as an authoritative reference for tumor diagnosis and classification, promoting consistency and comparability across different institutions and studies. The latest edition, published in 2022, reflects significant advances in understanding the molecular underpinnings of endocrine tumors, which have led to refinements in classification criteria.

The classification encompasses tumors originating from various endocrine organs, including the thyroid, parathyroid, adrenal glands, pituitary, neuroendocrine neoplasms of the pancreas, and other neuroendocrine tumors (NETs). It distinguishes benign from malignant lesions, identifies variants with distinct behavior, and integrates molecular insights for a more precise categorization.

Structure of the WHO Classification System

The WHO classification is organized by organ system, with each chapter dedicated to a specific endocrine organ. Within each chapter, tumors are classified into categories based on their histogenesis, differentiation, and aggressiveness. The key elements include:

- Benign tumors: e.g., adenomas
- Borderline or uncertain malignant potential: e.g., certain tumors with atypical features
- Malignant tumors: e.g., carcinomas, neuroendocrine carcinomas

The classification also incorporates:

- Grading: based on proliferative activity
- Staging: for clinical prognosis
- Molecular features: genetic mutations associated with tumor types

This systematic approach enhances diagnostic accuracy and informs prognosis and management strategies.

Thyroid Tumours

The thyroid gland harbors a variety of neoplasms, with papillary thyroid carcinoma (PTC) being the

most common.

Benign Thyroid Tumours

- Follicular adenoma: encapsulated, benign tumor of follicular cells.
- Features:
- Well-circumscribed, non-invasive
- No capsular or vascular invasion

Thyroid Carcinomas

- Papillary thyroid carcinoma (PTC):
- Most common thyroid malignancy
- Characterized by papillary structures, nuclear features like grooves and inclusions
- Molecular hallmark: BRAF mutations, RET/PTC rearrangements
- Follicular thyroid carcinoma:
- Invades capsule or blood vessels
- Molecular features: RAS mutations, PAX8-PPAR? rearrangements
- Medullary thyroid carcinoma (MTC):
- Arises from parafollicular C cells
- Associated with RET mutations, MEN syndromes
- Anaplastic thyroid carcinoma:
- Highly aggressive, undifferentiated tumor
- Poor prognosis

Features & Pros/Cons:

| Feature | Pros | Cons |

|---|---|---|

| Molecular profiling | Guides targeted therapies | Not always available in resource-limited settings |

| Histological classification | Standardized diagnosis | Overlap in some subtypes complicates diagnosis |

Parathyroid Tumours

Most parathyroid tumors are benign adenomas responsible for primary hyperparathyroidism.

Benign Parathyroid Tumours

- Parathyroid adenoma:
- Encapsulated, monoclonal proliferation
- Features: Chief cell proliferation, sometimes with oxyphil cells
- Features & Considerations:
- Usually solitary
- Can be distinguished from hyperplasia by histology

Malignant Parathyroid Tumours

- Very rare
- Parathyroid carcinoma:
- Invasive growth, potential metastasis
- Features: Trabecular growth, capsular invasion, mitoses

Features & Pros/Cons:

| Feature | Pros | Cons |

|---|---|---|

| Histology | Helps differentiate benign from malignant | Limited by overlapping features and rarity of carcinomas |

Adrenal Gland Tumours

Adrenal tumors include benign adenomas, malignant carcinomas, and neuroendocrine tumors.

Adrenal Cortical Tumours

- Adenomas: benign, non-functional or functional
- Carcinomas: aggressive, associated with hormonal syndromes
- WHO criteria: Weiss score assesses malignancy potential

Pheochromocytomas and Paragangliomas

- Neuroendocrine tumors arising from chromaffin cells
- Features:
- Pheochromocytomas are adrenal
- Paragangliomas are extra-adrenal
- Genetic mutations: SDHx, RET, VHL, NF1

Features & Pros/Cons:

| Feature | Pros | Cons |

|---|---|---|

| Molecular genetics | Allows targeted therapy and risk stratification | Requires advanced testing infrastructure |

Pituitary Tumours

Most are benign adenomas, with a few aggressive or malignant variants.

Types of Pituitary Tumours

- Lactotroph adenomas: prolactin-secreting
- Somatotroph adenomas: growth hormone-secreting
- Corticotroph adenomas: ACTH-secreting, causing Cushing's disease
- Non-functioning adenomas: do not secrete hormones

Features & Pros/Cons:

| Feature | Pros | Cons |

|---|---|---|

| Immunohistochemistry | Helps identify tumor subtype | Hormone levels often guide diagnosis more directly |

Neuroendocrine Tumours of the Pancreas and Other Sites

This includes pancreatic neuroendocrine tumors (PNETs) and other neuroendocrine neoplasms.

Classification of PNETs

- Well-differentiated tumors:
- Functioning (insulinoma, gastrinoma, etc.)
- Non-functioning
- Graded based on proliferative index (Ki-67) and mitotic rate
- Poorly differentiated neuroendocrine carcinomas:
- High-grade, aggressive tumors
- Features: high mitotic rate, necrosis

Features & Pros/Cons:

| Feature | Pros | Cons |

|---|---|---|

| WHO grading | Provides prognostic information | Requires precise proliferation assessment |

Advantages of the WHO Classification

- Standardization: Ensures consistent terminology across institutions.
- Integration of Molecular Data: Reflects current understanding of tumor genetics.
- Prognostication: Helps predict clinical behavior based on histology and molecular features.
- Guides Treatment: Facilitates tailored therapeutic approaches, including targeted therapies.
- Research Facilitation: Provides a framework for clinical and translational research.

Limitations and Challenges

- Complexity: The detailed molecular classifications can be resource-intensive.
- Variability in Access: Not all centers have access to advanced molecular diagnostics.
- Evolving Nature: Rapid advances mean classifications need frequent updates.
- Overlap in Features: Some tumors display overlapping histological and molecular features, complicating diagnosis.
- Prognostic Uncertainty: Some tumors with similar histology behave differently clinically.

Clinical Implications of WHO Classification

The WHO classification influences various aspects of patient care:

- Diagnosis: Accurate tumor typing determines prognosis and management.

- Treatment Planning: Molecular insights enable targeted therapy and personalized medicine.
- Follow-Up: Grading and staging inform surveillance strategies.
- Research and Trials: Uniform classification allows for better patient stratification in clinical trials.

Conclusion

The WHO classification of tumours of endocrine organs represents a cornerstone in endocrine pathology, integrating histopathological features with molecular genetics to refine tumor diagnosis, prognostication, and treatment. While it offers numerous advantages, ongoing updates and integration of novel molecular techniques are necessary to overcome current limitations. As our understanding of tumor biology deepens, future iterations will likely become even more precise, facilitating personalized approaches that improve patient outcomes. Ultimately, the WHO classification remains a dynamic and vital tool in the management of endocrine neoplasms, reflecting the evolving landscape of tumor biology and clinical practice.

QuestionAnswer What is the WHO classification of tumors of endocrine organs based on? The WHO classification of tumors of endocrine organs is based on histopathological features, including cell type, differentiation, molecular characteristics, and tumor behavior, to provide a standardized framework for diagnosis and prognosis. How are neuroendocrine tumors of the pancreas categorized in the WHO classification? In the WHO classification, pancreatic neuroendocrine tumors are categorized into well-differentiated neuroendocrine tumors (NETs) grades 1 and 2, poorly differentiated neuroendocrine carcinomas (NECs), and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs), based on differentiation and proliferative activity. What are the key features used to differentiate benign from malignant endocrine tumors in WHO classification? Key features include tumor size, invasion into surrounding tissues, mitotic rate, Ki-67 proliferation index, presence of metastasis, and cellular atypia, which help determine whether an endocrine tumor is benign or malignant. How does the WHO classify medullary thyroid carcinoma? The WHO classifies medullary thyroid carcinoma as a malignant tumor arising from parafollicular C cells, characterized by amyloid stroma and calcitonin production, and distinguishes it from other thyroid neoplasms based on histology and immunohistochemistry. What is the significance of molecular markers in the WHO classification of endocrine tumors? Molecular markers such as MEN1, DAXX, ATRX, and RET mutations are increasingly incorporated into the WHO classification to improve diagnostic accuracy, predict behavior, and guide targeted therapies for endocrine tumors.

Related keywords: endocrine tumors, WHO tumor classification, endocrine neoplasms, endocrine gland tumors, neuroendocrine tumors, endocrine pathology, tumor grading, tumor staging, endocrine tumor types, tumor histology

WHO CLASSIFICATION OF TUMOURS OF THE LUNG PLEURA

WHO classification of tumours of the lung pleura

The World Health Organization (WHO) classification of tumours of the lung and pleura provides a comprehensive framework for diagnosing, categorizing, and understanding the diverse neoplasms that originate in these regions. This classification is pivotal for clinicians, pathologists, and researchers because it standardizes terminology, facilitates accurate diagnosis, guides treatment strategies, and aids in prognostication. This article delves into the detailed WHO classification of lung and pleural tumours, exploring the various tumour types, their histopathological features, clinical relevance, and updates from the latest WHO editions.

Overview of WHO Classification of Lung and Pleural Tumours

The WHO classification system for lung and pleural tumours was first established to address the heterogeneity of neoplasms arising within these thoracic structures. It is periodically updated to incorporate advances in pathology, molecular biology, and clinical insights. The latest WHO classification categorizes tumours into benign, borderline, and malignant entities, based on histological features, behaviour, and molecular characteristics.

The classification encompasses tumours originating from:

- Lung parenchyma (primarily epithelial tumours)
- Pleura (mesothelial tumours)
- Other rare tumours of the lung and pleura

Understanding these categories is essential for accurate diagnosis and appropriate management.

Classification of Tumours of the Lung

Lung tumours are predominantly epithelial in origin, with non-small cell lung carcinomas (NSCLCs) being the most common, followed by small cell lung carcinomas (SCLCs). The WHO classification emphasizes histological subtypes, molecular alterations, and clinical implications.

Benign Lung Tumours

Benign lung tumours are rare and usually asymptomatic. They are often discovered incidentally during imaging studies. Main benign tumours include:

- Bronchial adenomas (now termed neuroendocrine tumors of low malignant potential)
- Hamartomas

- Leiomyomas
- Hemangiomas

Malignant Lung Tumours

Malignant tumours are classified primarily based on histological features into non-small cell lung carcinomas and small cell lung carcinomas.

Non-Small Cell Lung Carcinomas (NSCLCs)

This group includes the most prevalent lung cancers and is subdivided into:

- adenocarcinoma
- squamous cell carcinoma
- large cell carcinoma

Adenocarcinoma: The most common type, especially among non-smokers. It originates from glandular epithelium and often occurs peripherally.

Squamous cell carcinoma: Typically arises centrally within the bronchi and is strongly associated with smoking.

Large cell carcinoma: A diagnosis of exclusion characterized by undifferentiated malignant cells without glandular or squamous differentiation.

Small Cell Lung Carcinoma (SCLC)

SCLC accounts for approximately 15% of lung cancers. It is characterized by small, round to oval cells with neuroendocrine features, high mitotic rate, and aggressive behavior. It often presents with extensive disease at diagnosis and responds initially to chemotherapy and radiotherapy.

Other Rare Lung Tumours

The WHO also recognizes rare tumours such as carcinoid tumours, sarcomatoid carcinomas, and lymphomas involving the lung.

Classification of Tumours of the Pleura

Pleural tumours primarily originate from mesothelial cells lining the pleura. The WHO classification emphasizes mesothelial tumours, their benign, borderline, and malignant categories.

Benign Pleural Tumours

The most common benign pleural tumour is:

- Localized fibrous tumour of the pleura (also called solitary fibrous tumour)

These are usually asymptomatic, slow-growing, and incidentally found.

Borderline and Intermediate Tumours

This category includes tumours with uncertain malignant potential, though they are less well-defined compared to malignant tumours.

Diffuse Mesothelioma of the Pleura

While classified as malignant, mesotheliomas are a distinct entity with unique pathological features.

Malignant Pleural Tumours

The most significant malignant pleural tumour is:

- Malignant mesothelioma

This tumour arises from mesothelial cells and is strongly associated with asbestos exposure.

WHO Classification of Mesothelial Tumours

Mesothelial tumours are categorized based on histological subtypes, differentiation, and cellular features:

- Epithelioid mesothelioma: The most common form, characterized by epithelial-like cells.

- Sarcomatoid mesothelioma: Composed of spindle-shaped cells resembling sarcomas.

- Biphasic (mixed) mesothelioma: Contains both epithelioid and sarcomatoid components.

Additional features include the grading of cellular atypia, mitotic activity, and invasion patterns, which influence prognosis.

Key Features and Diagnostic Criteria in WHO Classification

The WHO classification emphasizes several diagnostic criteria:

- Histopathological features: Cell morphology, growth patterns, invasion depth.

- Immunohistochemistry: Markers such as calretinin, WT-1, cytokeratin 5/6 for mesothelial origin; TTF-1, Napsin A for adenocarcinomas; p40, p63 for squamous cell carcinomas.

- Molecular features: Genetic alterations, e.g., EGFR mutations in adenocarcinoma, BRAF, KRAS mutations, and PD-L1 expression relevant for targeted therapy.

Importance of WHO Classification in Clinical Practice

The WHO classification guides clinicians by:

- Providing a standardized terminology for diagnosis and communication.

- Informing prognosis; for example, adenocarcinomas generally have better outcomes compared to small cell carcinomas.

- Influencing treatment decisions; targeted therapies depend on molecular subtypes.

- Facilitating research and epidemiological studies through consistent categorization.

Updates in the Latest WHO Classifications

The WHO periodically revises its classification to incorporate advances in pathology and molecular biology. Notable updates include:

- Recognition of new subtypes of lung adenocarcinoma (e.g., lepidic, acinar, papillary).

- Inclusion of molecular markers as diagnostic criteria.

- Clarification of borderline and pre-invasive lesions.

- Better characterization of mesothelial tumours, including epithelioid, sarcomatoid, and biphasic variants.

Conclusion

The WHO classification of tumours of the lung and pleura remains a cornerstone in thoracic pathology, fostering precise diagnosis, guiding treatment, and improving understanding of tumour biology. Its systematic approach to categorizing benign, borderline, and malignant neoplasms based on histological, immunohistochemical, and molecular features ensures consistency across institutions and enhances patient care. Staying updated with WHO revisions is essential for healthcare professionals involved in the management of thoracic tumours, ultimately leading to better outcomes for patients.

Keywords: WHO classification, lung tumours, pleural tumours, mesothelioma, lung carcinoma, benign lung tumours, malignant lung tumours, thoracic pathology, tumour histology, thoracic neoplasms

WHO Classification of Tumours of the Lung Pleura

The World Health Organization (WHO) classification of tumours of the lung and pleura represents a comprehensive framework that guides pathologists, oncologists, and researchers in diagnosing, categorizing, and managing thoracic neoplasms. This classification system, regularly updated to incorporate advances in molecular pathology and histopathology, provides a standardized language that enhances clinical decision-making and facilitates epidemiological studies. In this review, we explore the detailed taxonomy of pleural tumours as outlined by the WHO, emphasizing their histopathological features, molecular characteristics, and clinical implications.

Introduction

The pleura, a vital serous membrane enveloping the lungs and lining the thoracic cavity, is a site for a diverse array of benign and malignant tumours. Malignant pleural mesothelioma (MPM) is the most notorious primary neoplasm arising from the mesothelial cells, but secondary tumours such as

metastases from lung, breast, and other carcinomas also involve the pleura. The WHO classification provides a structured approach to distinguish these entities, primarily focusing on mesothelial neoplasms, fibrous tumours, and other rare variants.

Understanding the WHO classification is essential for accurate diagnosis, prognostication, and therapeutic planning, especially given the heterogeneity of pleural tumours and the evolving landscape of molecular diagnostics.

Primary Tumours of the Pleura

Primary tumours originate from the mesothelial lining or associated stromal components. They are classified based on histopathological features, immunohistochemical profiles, and molecular alterations.

Mesothelial Tumours

Mesothelial neoplasms are the most common primary pleural tumours and encompass benign, borderline, and malignant categories.

Benign Mesothelial Tumours

- Localized Mesothelial Hyperplasia: Reactive proliferation of mesothelial cells often associated with inflammation or trauma.
- Well-Differentiated Papillary Mesothelial Tumour (WDPMT): A rare benign entity characterized by papillary proliferation of mesothelial cells with minimal atypia and no invasion.

Malignant Mesothelial Tumours

- Malignant Mesothelioma (MM): The most significant primary malignant tumour of the pleura, with distinct histological subtypes and molecular features.

Malignant Mesothelioma Subtypes

The WHO recognizes three main histological subtypes, each with differing prognosis and therapeutic responses:

- Epithelioid Mesothelioma
- Sarcomatoid Mesothelioma

- Biphasic (Mixed) Mesothelioma

Epithelioid Mesothelioma:

Most common (~60-70%), characterized by polygonal cells forming tubules, papillae, or solid sheets. Frequently exhibits a prominent fibrous stroma and tends to have a better prognosis.

Sarcomatoid Mesothelioma:

Less common (~10-20%), composed of spindle-shaped cells resembling sarcoma. These tumours are often more aggressive and less responsive to therapy.

Biphasic Mesothelioma:

Contains both epithelioid and sarcomatoid components, with prognosis depending on the proportion of each.

Molecular and Immunohistochemical Features of Mesothelioma

- Key Immunohistochemical Markers:

- Positive: Calretinin, WT1, D2-40 (podoplanin), Cytokeratin 5/6, Mesothelin
- Negative: Carcinoma markers such as TTF-1, CEA, Ber-EP4

- Molecular Alterations:

- Loss of BAP1 expression
- CDKN2A (p16) deletion detectable via FISH
- Rare mutations in BRAF, NRAS

Other Mesothelial Tumours

- Localized Malignant Mesothelioma: Rare, similar to diffuse but confined to localized areas.
- Multicystic Mesothelioma: Generally benign, presenting as multicystic lesions.

Fibrous and Other Tumours of the Pleura

Aside from mesothelial origins, the pleura can host fibrous and miscellaneous tumours.

Solitary Fibrous Tumour (SFT)

- Originates from fibroblastic mesenchymal cells.
- Usually benign but can be malignant.
- Features: Well-circumscribed, spindle cells with high vascularity, "patternless" pattern, and CD34 positivity.
- Malignant SFTs show increased cellularity, atypia, mitoses, necrosis.
- Molecular hallmark: NAB2-STAT6 gene fusion detectable via immunohistochemistry (STAT6 nuclear positivity).

Fibrosarcoma and Other Sarcomas

Rare; includes fibrosarcoma, malignant peripheral nerve sheath tumour, and angiosarcoma. These are generally distinguished through histomorphology and immunoprofile.

Mesenchymal Tumours with Other Differentiations

- Lipomas and Liposarcomas
- Hemangiopericytoma

Secondary Tumours of the Pleura

Metastatic involvement of the pleura is common, especially from lung, breast, and other carcinomas.

Common Metastases

- Lung Carcinomas: Adenocarcinoma, squamous cell carcinoma
- Breast Carcinoma
- Gastrointestinal Tumours
- Lymphomas and Leukemias

Immunohistochemistry and molecular studies help determine the primary site, especially in poorly differentiated tumours.

Rare and Unusual Pleural Tumours

- Mesenchymal chondrosarcoma
- Malignant fibrous histiocytoma
- Synovial sarcoma

These are exceedingly rare but are recognized within the WHO framework based on histopathology and molecular features.

Diagnostic Challenges and Advances

Accurate classification relies on a combination of histopathology, immunohistochemistry, and increasingly, molecular diagnostics.

Role of Molecular Diagnostics

- Detection of BAP1 loss and CDKN2A deletions for mesothelioma
- Identification of NAB2-STAT6 fusion in SFT
- Next-generation sequencing panels for rare entities

Diagnostic Algorithms

- Use of panel immunohistochemistry to differentiate mesothelioma from metastatic carcinoma
- Employing molecular markers for ambiguous cases

Clinical Implications of WHO Classification

The WHO classification informs prognosis and guides management strategies:

- Benign vs. Malignant: Surgery for benign tumours; multimodal therapy for mesothelioma.
- Histological Subtypes: Epithelioid mesotheliomas have better outcomes.
- Molecular Features: Potential targets for novel therapies.

Conclusion

The WHO classification of tumours of the lung and pleura offers a detailed and nuanced taxonomy that reflects advances in our understanding of thoracic neoplasms. It emphasizes the importance of integrating histopathological, immunohistochemical, and molecular data to achieve accurate diagnosis. As research continues to evolve, especially in molecular genetics and targeted therapies, this classification will likely undergo further refinements, ultimately improving patient outcomes

through tailored treatment approaches.

Understanding the diverse spectrum of pleural tumours aids clinicians and pathologists in making precise diagnoses, prognostic assessments, and guiding appropriate management. The ongoing evolution of the WHO classification underscores the importance of multidisciplinary collaboration in thoracic oncology.

QuestionAnswer What is the WHO classification of tumors of the lung and pleura? The WHO classification of tumors of the lung and pleura is a standardized system that categorizes benign and malignant tumors based on histological features, genetic profiles, and clinical behavior to guide diagnosis and treatment. How are mesotheliomas classified in the WHO system? In the WHO classification, mesotheliomas are categorized into epithelioid, sarcomatoid, biphasic (mixed), and rare variants, based on their cellular morphology and immunohistochemical profiles. What are the main types of primary lung carcinomas according to WHO? The main types include non-small cell lung carcinomas (adenocarcinoma, squamous cell carcinoma, large cell carcinoma) and small cell lung carcinoma, each with distinct histological and molecular features. How does the WHO classify benign tumors of the lung and pleura? Benign tumors are classified as hamartomas, papillomas, lipomas, and other rare benign neoplasms, characterized by their benign histological appearance and non-invasive behavior. What is the significance of the WHO classification in clinical management? The WHO classification helps in accurate diagnosis, prognosis, and selection of appropriate treatment strategies by providing a standardized framework for tumor categorization. Are genetic features incorporated into the WHO classification of lung and pleural tumors? Yes, the WHO classification increasingly incorporates molecular and genetic markers that aid in subclassification, prognosis, and targeted therapy options. How are metastatic tumors to the lung and pleura classified in the WHO system? Metastatic tumors are classified based on their primary origin and histological similarity, with common types including metastases from breast, colon, and other cancers, but they are not part of the primary WHO tumor classification. What updates have recent WHO classifications introduced for lung and pleural tumors? Recent updates include enhanced molecular characterization, recognition of new tumor variants, and refined criteria for differentiating benign from malignant lesions to improve diagnostic accuracy. How does the WHO classification address rare tumors of the lung and pleura? The WHO classification provides specific categories for rare tumors such as solitary fibrous tumors, carcinoids, and other uncommon neoplasms, facilitating their recognition and management. Why is the WHO classification important for pathologists and clinicians? It ensures consistent diagnosis, informs prognosis, guides treatment decisions, and fosters research by providing a comprehensive, evidence-based framework for tumor categorization.

Related keywords: lung tumors, pleural tumors, WHO classification, thoracic oncology, mesothelioma, lung cancer types, pleural mesothelioma, malignant pleural effusion, tumor histology, lung neoplasms

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