CHAPTER

10 Tumors of the Lower Respiratory Tract

LUNG CANCER

Incidence

Lung cancer is the most common cancer in the world with about 1.1 million new cases every year. It contributes to 13% of total cancers in both sexes, ranking the first in males and the fourth in females. More than half (55%) of the cases occur in the developing world. Lung cancer is also a leading cause of death, being responsible for 25% of all cancer mortality, the first rank in males and the second in females.

The median age is 60 years with a male predominance of 3:1. However, lung cancer rates in women have been rising dramatically because of the increased numbers of young women who smoke. Thus, the male predominance is only 2:1 in patients below the age of 45 years and 4:1 in patients over the age of 45. The frequency of histologic types of carcinoma is affected by age. Thus, adenocarcinoma is the most common type in young patients and squamous cell carcinoma in older age group.

Etiology

The vast majority of lung cancers are due to chronic cigarette smoking (80%), as well as passive smoking (5%). Other etiologic factors include: air pollution (car exhaust), industrial exposure such as asbestos, chloromethyl ether, arsenic, nickel, polycyclic aromatic hydrocarbons and chromium. Tobacco smoking is thought to be synergistic with these elements. Acquired and inherited genetic defects in the somatic cells may increase the risk for lung cancer upon exposure to even low doses of tobacco smoke or other carcinogens. Radiation may also play a role e.g. radium miners, radon gas and survivors of Hiroshima bomb. Chronic inflammation and chronic obstructive pulmonary disease are associated with an increased risk for lung cancer. Dietary deficiency in antioxidants (e.g. vitamins C, A, E and selenium) is a contributing factor.

Pathogenesis

The multicellular model (Pearse, 1969) which considered small cell carcinoma to be of neural crest (neuroectodermal) origin and other carcinomas of endodermal origin is not currently accepted.

The unicellular model (Gazdar, 1981) is supported by studies demonstrating correlations between human lung tumor gene signatures and signatures of normal lung development. These studies propose that all types of carcinomas arise from a single *multipotent stem cell* which under the control of gene transcriptional activation and/or repression events is capable of expressing a variety of phenotypes including: columnar, reserve cells, pneumocytes and neuroendocrine cells (Fig 10-1). Squamous cell carcinoma arises on top of a series of morphologically distinct changes in bronchial epithelium mostly in central bronchi, namely hyperplasia, squamous metaplasia, dysplasia, and carcinoma in situ.

Molecular Oncogenesis

Genetic susceptibility factors associated with carcinogen metabolism, DNA damage repair, and cell cycle control play an important role in the determination of the response to the injury caused by dozens of carcinogens contained in tobacco smoke exposure. Field cancerization with associated alterations in the DNA of the bronchial epithelium leads to multihit proto-oncogene activation and loss of suppressor gene action.

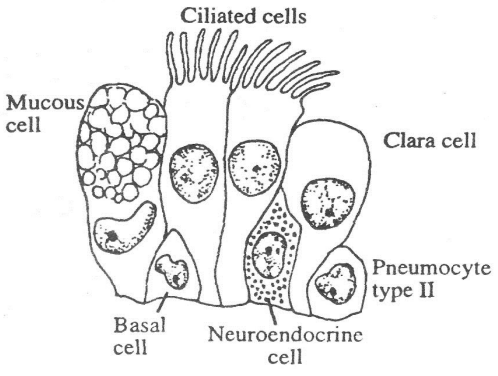

Fig 10-1 *Types of bronchopulmonary epithelium*

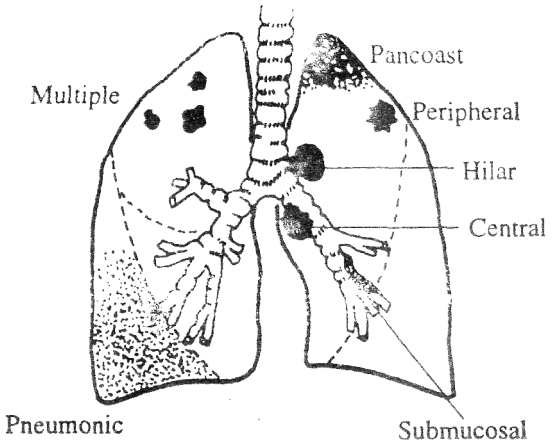

Fig 10-2 *Macroscopic types of lung cancer*

Mutations in the tumor suppressor gene TP53 and chromosome 3p allele loss are common findings in all types of lung carcinoma. KRAS mutations are common in adenocarcinoma but rare in other types. The molecular profile of small cell lung cancer (SCLC) is different from non-small cell lung cancer (NSCLC). Thus, in SCLC, TP53 and Rb gene mutations as well as, telomerase, c-kit and Bcl-2 expression are common, but, K-ras and p16 and cox-2 mutations are rare. In NSCLG, 25% of cases are associated with EGFR mutations and 75% of cases with EGFR overexpression.

MACROSCOPY

Seven gross types are recognized (Fig 10-2). The *central type* involves a major bronchus and is commonly observed with squamous carcinoma or small cell carcinoma. It appears as a solid nodule (80%) or may show central cavitation (20%) as a result of tumor necrosis (P 10-1). The *hilar type* presents as lymphadenopathy from an occult carcinoma usually small cell type. The *peripheral type* common with adenocarcinoma and large cell undifferentiated carcinoma, appears as a subpleural nodule. *Pancoast tumor*, a variant of peripheral type, arises from the apex of the lung and invades the sympathetic nerves, hence, resulting in Horner's syndrome (enophthalmos, ptosis, miosis and anhydrosis). The carcinoma may be present as an invasive submucosal lesion, particularly in small cell cancer. *Multiple tumors* may be due to multifocal origin (3%) or represent satellite tumors spreading from the main carcinoma. The diffuse *pneumonic type*, common with bronchiolo-alveolar carcinoma, appears as consolidation of a segment or lobe of lung (P 10-2).

CLASSIFICATION

Over 95% of lung cancers are epithelial in origin (carcinomas), comprising four main types: squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma. Through the 1960s, squamous cell carcinoma was the predominant histologic type, however, in recent years adenocarcinoma has increased in both relative and absolute incidence. This phenomenon was attributed to changes in tobacco blends and the use of filters on cigarettes.

The classification of lung cancer into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) is a clinical one to help allocate patients to different treatment protocols. The WHO histological classification of tumors is generally adopted (Table 10-1). A comparison of the different pathobiologic features of SCLC and NSCLC are outlined in (Table 10-2).

Table 10-1 WHO Histologic Classification of Lung Cancer

Histologic type	%
Non-small lung cancer (NSLC)	
Adenocarcinoma (including Bronchiolo-alveolar)*	40
Squamous cell carcinoma	30
Large cell carcinoma	10
Clear cell type	
Large neuroendocrine	
Basaloid	
Small cell carcinoma (SCLC)	20
Neuroendocrine (Carcinoid)	
Other lung cancer	
Salivary type carcinomas	
MALT Lymphoma	
Mesenchymal tumors	
Mixed tumors including:	
Adenosquamous carcinomas	
Carcinosarcoma	
Combined SCLC and NSCLC and pulmonary blastoma	

(Travis et al, 2004 / DeVita et al , 2011)
* Bronchiolo-alveolar carcinoma <3 cm without stromal invasion is recently considered carcinoma in situ (Travis et al., 2011

Non-Small Cell Lung Cancer (NSCLC)

This is the most common group, comprising 75% of lung cancers. They are subdivided into three subtypes: squamous cell carcinoma (P 10-3), adenocarcinoma (P 10-4) and large cell carcinoma. The bronchiolo-alveolar carcinoma (BAC) is a subtype of well-differentiated adenocarcinoma constituting 5% of cases (P 10-5). Like bronchial carcinoid, BAC is not etiologically related to cigarette smoking. They are thought to arise from Clara cells or type II pneumocytes. Thyroid transcription factor 1 (TTF-1) is expressed by adenocarcinoma and large cell carcinoma but usually not by squamous cell carcinoma. Adenocarcinomas also have a distinct cytokeratin (CK) profile from squamous cell carcinoma; CK5/6 - / CK7+ in adenocarcinoma and CK5/6+/CK7- in squamous cell carcinoma. A carcinoma showing components of both squamous cell carcinoma and adenocarcinoma with each comprising at least 10% of the tumor is designated as adenosquamous carcinoma (P 10-6). Large cell undifferentiated carcinoma is characterized by large cells with vesicular nuclei, prominent nucleoli, abundant cytoplasm and absence of squamous or glandular differentiation (P 10-7).

Small-Cell Lung Cancer (SCLC)

Small-cell lung cancer represents 25% of all lung cancers. It is extremely aggressive, highly disseminative and has the poorest prognosis. Histologically, it is characterized by small cells, with scanty cytoplasm and fine chromatin (P 10-8). Nuclear moulding is a prominent feature as a result of cellular mutual compression. The neuroendocrine nature of this tumor is confirmed by immunopathologic and electron microscopic (EM) studies. Immunohistochemistry demonstrates the presence of neuron-specific enolase (NSE), chromogranin and synaptophysin. Also, EM demonstrates dense-core neurosecretory granules. Such studies are helpful tools in the diagnosis of SCLC. Small cell carcinoma is also usually positive for TTF-1.

Table 10-2 Comparison of Small-cell and Non-Small-Cell Lung Carcinomas

	SCLC	**NSCLC**
Markers of neuroendocrine differentiation	70%	20%
Neuron specific enolase (NSE)		
Chromogranin		
Synaptophysin		
Neural cell adhesion molecule (NCAM, CD56)		
Leu-7 (CD57)		
Kinetic parameters		
Thymidine kinase	High	Low
Growth Fraction	High	Low
Tumor doubling time	30 days	120 days
Proto-oncogene activation		
KRAS	Absent	Present
EGFR	High	Present
Oncosuppressor gene inactivation		
p53	80%	50%
Rb	90%	15%
Dissemination	Early (70%)	Late
Paraneoplastic syndromes	Various	Restricted
Preferred therapy	Chemo-radiotherapy	Multimodality
5-year survival	Limited stage 7%	Resectable 30%
	Extensive stage 1 %	Overall 10%

(Modified from DeVita, 1997 and 2011)

DIFFERENTIAL DIAGNOSIS

1. Squamous dysplasia and carcinoma in situ: Bronchial dysplasia usually presents as non-specific mucosal swelling or thickening at a bronchial bifurcation. These lesions represent a continuum of atypical cytologic and histologic changes in bronchial epithelium, but unlike squamous cell carcinoma, they do not invade the stroma (P10-9A).

2. Atypical adenomatous hyperplasia (atypical alveolar hyperplasia): usually less than 5 mm in diameter and generally in the absence of a mass lesion. These features help differentiation bronchiolo-alveolar carcinoma (P10-9B).

3. Tumorlet: Minute (<5 mm) benign carcinoid tumors which, unlike central carcinoid, occur in the peripheral lung (P10-9C).

4. Carcinoid tumors: contrary to SCLC the mitotic rate is <10/10 hpf.

Paraneoplastic syndromes

Lung cancer is often associated with paraneoplastic syndromes caused by ectopic production of polypeptide hormones by the tumor. The syndromes associated with SCLC are variable, whereas, those associated with NSLC are more restricted. Thus, SCLC may be associated with hyponatremia, Cushing, myasthenia, hyperpigmentation or hypocalcemia. Conversely, in NSCLC: (1) squamous cell carcinoma is associated with hypercalcemia, (2) adenocarcinoma is associated with periosteitis (hypertrophic pulmonary osteoarthropathy) and (3) large cell undifferentiated carcinoma is associated with gynecomastia and galactorrhea.

SPREAD

Lung cancer spreads by four main routes: (l) *local:* to trachea, esophagus, mediastinum, pleura, diaphragm or chest wall, (2) *lymphatic:* to regional lymph nodes (Fig 10-3); intrapulmonary, subcarinal, mediastinal, or to supraclavicular lymph nodes (3) *air-borne metastases:* satellite nodules, (4) *hematogenous:* to bone, liver, brain and adrenals. About 25% of bone metastases are osteosclerotic, especially after chemotherapy.

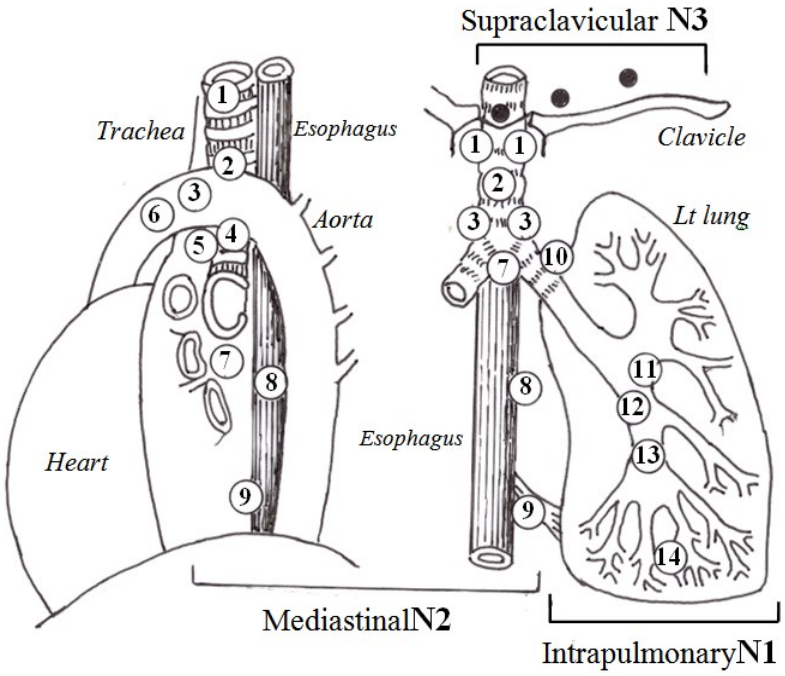

Fig 10-3 *The regional lymph nodes of lung (Naruke classification 2000) and their corresponding updated TNM categories (Edge et al, 2010). N1 Intrapulmonary: (10) hilar (11) interlobar (12) lobar (13) segmental (14) subsegmental. N2 Mediastinal: (1) superior (2) paratracheal (3) pretracheal (4) tracheobronchial (5) subaortic (6) paraaortic (7) subcarinal (8) paraesophageal (9) pulmonary ligament. N3 Supraclavicular (including sternal notch and scalene node).*

Staging

The TNM staging system is used for NSCLC (Table 10-3 and 10-4). For small cell lung cancer (SCLC), the simple and practical VA staging system (Veterans Administration, 1973) groups the patients into only two categories, namely: limited stage and extensive stages (Table 10-5).

Prognostic Factors

Lung cancer generally has a very poor prognosis, with overall 5-year survival below 10% (a higher survival of 15% was reported by Abraham et al, 2010). The survival, however, depends on the histologic type and clinical stage.

Table 10-3 Simplified TNM Staging of NSCLC for Non meta-static Disease

Stage	N0	N2	N2	N3
T1	IA	IIA	IIIA	IIIB
T2	IB	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIB
T4	IIIB	IIIB	IIIB	IIIB

(Travis et al, 2004). The stage is obtained by matching T and N categories.

Table 10-4 Descriptive TNM staging of lung

Stage	Features
I	Tumor confined to bronchus or lung (A) <3 cm and (B) >3 cm
II	Limited regional disease (A) Intrapulmonary or hilar node metastases (NI) (B) Invasion of chest wall
III	Extensive regional disease (A) Ipsilateral mediastinal or subcarinal node metastases (N2) (B) Contralateral mediastinal or supraclavicular node metastases (N3) or mediastinal invasion.
IV	Distant metastases or bilateral lung carcinomas

(Edge et al, 2010)

The prognostic factors of SCLC and NSCLC will be discussed separately for obvious pathobiologic differences. The unfavorable prognostic factors in SCLC include: extensive stage, poor performance status, high alkaline phosphatase and lactic dehydrogenase (LDH). For the potentially resectable NSCLC localized disease (TNM stage I), the various unfavorable prognostic factors are presented in (Table 10-6).

Prevention

Lung cancer is very easy to prevent but most difficult to cure. Quitting smoking is the main step towards primary prevention of lung cancer. However, by discontinuing smoking, it takes almost 20 years before the risk of lung cancer approaches that of non-smokers. Also, patients with lung cancer are more liable to develop a second primary in the lung. Thus, if a patient survives the initial cancer, the risk of subsequent lung cancer is about 5% per year. Hence, close follow up is essential for these patients. Chemoprevention by retinoids and antioxidants is another potential approach of primary prevention in these patients.

In lung cancer, there is a poor impact of early detection on survival, and this is mainly due to dismal results of current therapy (overall 5-year survival below 10%). For this reason, screening programs with regular check up are not advisable.

Other Tumors of the Lung

Salivary gland tumors

They arise from submucous bronchial glands. Mostly located centrally and include: *(1) Adenoid cystic carcinoma:* Most common type with frequent regional lymph nodes involvement and (2) *Mucoepidermoid carcinoma:* May arise in children. It is locally invasive with low malignant potential. High grade tumors with poor prognosis are better classified as adenosquamous carcinoma arising from surface epithelium.

Table 10-5 Staging of SCLC

I. LIMITED STAGE DISEASE (30%)
Primary and its lymph nodes are confined to one hemithorax

II. EXTENSIVE STAGE (70%)
Spread beyond one hemithorax to invade other side or distant sites

(VA System, 1973)

Table 10-6 Unfavorable Prognostic Factors of NSCLC, Localized Disease

1. Large cell type, adenocarcinoma, neuroendocrine differentiation
2. Expression of ras, c-erb B-2, or p53
3. High alkaline phosphatase or LDH
4. Aneuploidy
5. High S-phase > 12%
6. Ki-67, PI > 3.5
7. TLI > 2.9
8. High microvessel count
9. Established cell lines

(Strauss, 1995)

Mesenchymal tumors

1. Angiosarcoma and hemangioendothelioma: Derived from endothelial cells. The epithelioid hemangioendothelioma is more common, occurring mostly in young adult females, typically appears with multiple nodules. The tumor grows slowly but progressively. The differential diagnosis includes epithelioid hemangioendothelioma metastatic to the lung, adenocarcinoma (both primary and metastatic) as well as mesothelioma (if it involves the pleura).

2. Inflammatory myofibroblastic tumor (P 10-10)*:* A subgroup of the category of "inflammatory pseudotumors" derived from myofibroblasts and showing clonal changes in 2/3 of cases involving chromosome 2 at the 2p23 location of the ALK gene. It presents as a localized mass, often locally infiltrative, in children and young adults. Chest wall invasion, recurrence, and metastases are rare.

3. Pleuropulmonary blastoma (P 10-11)*:* a rare malignant tumor of infancy and early childhood that arises in the lung or parietal pleura. Cell of origin is unknown. It is formed of a cystic and/ or solid admixture of primitive blastemal and sarcomatous elements. Tumors with a solid component recur locally and have a predilection for metastases.

4. Synovial sarcoma: Derived from a totipotent mesenchymal stem cell. It has to be differentiated from metastases from a synovial sarcoma arising elsewhere. Differential diagnosis also includes other primary sarcomas, spindle cell carcinoma, mesothelioma, and Ewing sarcoma/PNET. In difficult cases by morphology and immune-histochemistry, the detection of specific cytogenetic/ molecular abnormality might be useful.

Carcinoid

Pulmonary carcinoid tumors are malignant tumors derived from neuroendocrine cells known to exist in normal airways. Most are non-functioning. Central (intrabronchial) and peripheral (often subpleural) carcinoids show well-differentiated neuroendocrine architecture with immunohistochemical and ultrastructural phenoltype. *Typical* carcinoids (P 10-12) are low grade and have 5 and 10 year survival rates up to 95%. *Atypical* carcinoids (P 10-13) have higher nuclear grade with mitoses of 2 to 10 per 10 HPF and necrosis. The 5 year survival in atypical carcinoids is 60-70%.

MALT lymphoma
Plasmacytoma

Presenting primarily in the lungs (P 10-14 and P 10-15), with or without hilar node involvement but without clinical evidence of disease elsewhere. They constitute about 0.5% of all primary lung tumors mostly presenting in patients above the age of 40. The imaging findings may simulate sarcoidosis, bronchiolo-alveolar cell carcinoma, or infections.

MESOTHELIOMA

Incidence

Diffuse malignant mesothelioma affects men 50 -70 years old and develops commonly in the pleura, but rarely other serosal surfaces, such as the peritoneum, pericardium and tunica vaginalis of the testis (adanomatoid tumor). The cell of origin is a submesothelial mesenchymal stem cell.

History of occupational or environmental exposure to asbestos (industries such as construction materials, ship building, insulation, as well as, paper and textile industries) can be elicited in most of the patients. Tumor usually develop 15-20 years after exposure. The male to female ratio is 3 to 5:1.

Etiology

Asbestos is considered as a complete carcinogen in the induction of mesothelioma, with initiating DNA damaging effect and promotor

effect causing inflammatory and cell proliferation processes. However, the cellular and molecular mechanisms involved in the evolution of asbestos-induced mesothelioma are still under study.

Allelic loss of the chromosome 22 is a common alteration in mesothelioma. Less frequent alterations are deletions in the short (p) arm of chromosomes 1, 3, and 9 and in the long (q) arm of chromosome 6.

Macroscopy

Mesothelioma presents as multiple small nodules on the parietal and sometimes visceral pleura. With progression the nodules become confluent with resulting fusion of the visceral and parietal pleurae and encasement and contraction of the lung. The CT chest usually features a pleural -based mass encasing the lung (Fig 10-4).

Classification

Four histological variants are observed (P 10-16 to P 10-22): monophasic epithelial (50%), monophasic sarcomatous (20%), biphasic (25%), and a less common desmoplastic variant (5%). The non-epithelioid histology is considered as a poor prognostic factor.

Spread

Mesothelioma spreads rapidly over the pleura and encases the lung with parenchymal invasion of the lung. Multifocal pleural nodules are common. Distant metastases are not common due to the aggressive nature of the local disease leading to shortened survival. In the event of metastases, mediastinal and hilar lymph nodes and the peritoneal cavity are usually involved. Liver, bone, and brain are rare sites of metastases.

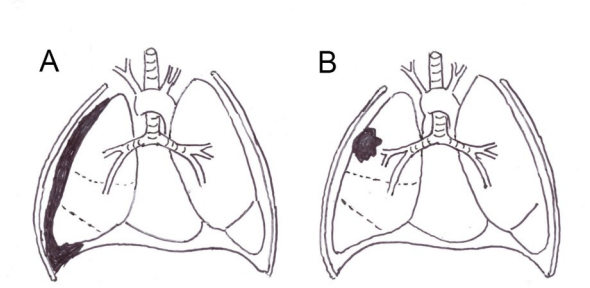

Fig 10-4 *Comparison of CT picture of (A) mesothelioma: a surface pleural-based mass lesion and (B) lung parenchymal mass in lung carcinoma.*

Staging

The TNM staging system recognizes four stages. *Stage I* tumor is confined to pleura where (A) only parietal pleura is infiltrated and (B) there is visceral pleural involvement, *Stage II* with lung or diaphragm invasion, *Stage III* describes locally advanced but resectable tumor or metastases in ipsilateral lymph nodes, whereas, *Stage IV* describes unresectable locally-advanced tumor or metastases in contralateral lymph nodes or distant metastases.

Differential Diagnosis

1. Atypical Mesothelial Hyperplasia: Such lesions lack CT evidence of pleural mass (P 10-20).

2. Primary Adenocarcinoma of the lung: The diffuse involvement whether by radiographs or specimen examination suggests mesothelioma but is not conclusive. At least 2 positive and 2 negative immunohistochemical markers for mesothelioma should be available to make the diagnosis (Table 10-7). Immunohistochemical results must be interpreted in the context of the histopathology and CT scans. Cytopathology is suggestive, but inconclusive of malignancy phenotyp (P 10-22).

3. Metastatic Adenocarcinoma: Usually a primary tumor can be outlined by radiographic studies. It is also negative for mesothelial markers. Mucin production as detected by periodic acid-Schiff (PAS) stain and absent hyaluronic acid production by alcian blue is more in favor of adenocarcinoma. By electron-microscopy mesothelioma shows very long surface microvilli and absent secretory granules.

4. Diffuse Pleural Sarcoma: Such as epithelioid hemangioendothelioma and synovial sarcoma. Cyokeratin positive immunostaining can help in the diagnosis of mesothelioma in such cases, however it can also be positive in both epithelioid hemangioendothelioma and synovial sarcoma. The negative endothelial cell markers (usually positive in epithelioid hemangioendothelioma) and the absence of X:18 translocation (usually positive in synovial sarcoma) are helpful in the diagnosis.

LOCALIZED PRIMARY PLEURAL TUMORS

1. Solitary Fibrous Tumor (P 10-23)*:* Benign tumor, considered of mesenchymal cell origin.

Table 10-7 Immunohistochemical Markers in Epithelioid Mesothelioma and Pulmonary Adenocarcinoma

Marker	Epithelioid Mesothelioma (%)	Pulmonary Adenocarcinoma (%)
Leu-M1 (CD15)	5	85
CEA	5	82
TTF-1	5	75
CK5/6	90	6
Calretinin	86	10
WT1	78	10

(Hammar, 2006)

Table 10-8 Malignant Pleural Effusion and Frequency of Primary

Cancer	Frequency (%)
Bronchogenic carcinoma	40
Breast carcinoma	25
Mesothelioma	10
Lymphoma	10
Ovarian carcinoma	5
Gastric Carcinoma	5
Unknown Primary	5

(Devita et al, 2011)

The main sites are the pleura and retroperitoneum. It shows fibrous and more cellular areas of pericytoma pattern. It is negative for cytokeratin and positive for CD34 and CD99. About 15% of the tumors are aggressive.

2. Well-differentiated Papillary Mesothelioma: A rare tumor of borderline malignancy with a papillary architecture, bland cytologic features and a tendency toward superficial spread without invasion. Multifocal tumors need to be differentiated from diffuse malignant mesothelioma

3. Adenomatoid Tumor: A rare solitary small pleural tumor with histological features identical to those seen in adenomatoid tumors of the testis.

4. Localized Malignant Mesothelioma: A rare tumor that grossly appears as a distinctly localized nodular lesion without gross or microscopic evidence of diffuse pleural spread, but with the microscopic, histochemical, immunohistochemical and ultrastructural features of diffuse malignant mesothelioma.

PLEURAL EFFUSION

Pulmonary cytology has sensitivity and specificity ranging from 60% to 90%. False-positive diagnoses tend to be more common than false-negative diagnoses. However, the incidence of false-negatives is higher in pleural effusions than in sputum or FNA cytology. Knowledge of complete clinical history and radiological findings and awareness of the common sources of misinterpretation can minimize errors. Pleural effusion may be classified on etiologic basis into: non-malignant, paramalignant, and malignant.

1. Non-malignant effusion includes transudates and inflammatory conditions (pleuritis).

2. Paramalignant effusion is associated with malignant disease but the effusion is negative for malignant cells. It may present reactive mesothelial hyperplasia, chylous effusion due to lymphatic obstruction, or a complication of chemotherapy.

3. Malignant effusions contain malignant cells in the effusion indicating spread of cancer cells to surface mesothelium. The relative frequency of cancers encountered in clinical practice is listed in Table 10-8.

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