Role of Endobronchial Ultrasound in Diagnosis of Peripheral Lung Shadows

Thesis
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Introduction

The diagnostic yield in the case of peripheral tumours beyond bronchoscopic vision is bound to be lower and more variable. Factors that influence yield include the skill and experience of the bronchoscopist, the time available for the procedure, the availability of supporting fluoroscopic facilities and their competent operation, the size of the lesion and whether it is a primary or secondary deposit, the yield has also been noted to be lower if the lesion has a sharp rather than an irregular border ***(Chechani, 1996).***

Previous bronchoscopic experience has been shown to influence the rate of positivity following biopsy of visible endobronchial tumor and it can therefore be inferred that same factor is likely to operate at least as strongly in the technically more difficult biopsy of peripheral lesions ***(Douglas, 2000).***

In order to save patient's unnecessary surgery and to improve the diagnostic yield of endoscopic procedures, new imaging and guidance technology is needed. Endobronchial ultrasound (EBUS)-guided transbronchial biopsy is feasible. It appears to beat least equivalent to fluoroscopy without the accompanying radiation exposure ***(Becker et al., 2002).***

EBUS is a diagnostic technique for visualizing the tracheobronchial wall and the immediate surrounding structures ultrasound waves are transmitted to anatomical structures, and the reflected achos are transformed into electrical signals. EBUS is used to evaluate the regional extension of lymph node involvement in bronchogenic carcinoma (staging), to identify and localize solid mediastinal structures adjacent to the airways (mediastinal tumors, heart, great vessels and esophagus) before diagnostic or therapeutic interventions, to localize solid structures in the lung tissue for bioptic procedures, and to stage the depth of tumor invasion in the bronchial wall ***(Bolliger et al., 2002).***

Aim of the Work

Evaluation of the role of endobronchial ultrasound in the diagnosis of peripheral lung shadow.

Peripheral Pulmonary Lesions

Peripheral pulmonary lesions are mostly detected accidentally on chest radiographs. Although there is high chance that lesions>2cm in diameter are of malignant origin, nodules < 2cm in diameter are often but not always benign ***(Libby et al., 1995),*** and a histologic diagnosis is warranted in order to offer a chance of cure in case of malignancy. Peripheral pulmonary lesions are, by definition, not visible endoscopically.

1.NEOPLASMS;

1) BENIGN

Frequency: Benign tumors make up 2-5% of all primary lung tumors. The exact incidence is not known because these tumors are often asymptomatic and are only detected during autopsy. Reported series suggest that benign lung tumors affect men more frequently than women (adenoma and hamartoma). The age range of patients affected is 17-77 years, with a mean age of 56.2 years for all types.

a) Hamartoma

Pulmonary hamartoma is a benign lung neoplasm that occurs most frequently in middle-aged or elderly adults, and the peak incidence is in the sixth or seventh decade of life. Younger patients and even neonate have been reported in other series. A greater prevalence been reported in other series. A greater prevalence of male patients was found in most studies, with a variation in preponderance 2:1 to 3:1. Pulmonary hamartomas can be seen in all parts of the lung, but most often in the periphery and rarely near the hilar parts. Histologically, hamartomas generally consist of epithelial tissue and other tissues such as fat and cartilage. Hamartomas can be easily enucleated, but wedge resection is also appropriate .Most of the patients with pulmonary hamartoma are free of symptoms, and tumor is found incidentally on chest X-ray examination. It is difficult to determine if the symptoms were related to the tumors. However, pulmonary hamartomas with bronchial compression or intraluminal growth can lead to atelectasis, infections, pyrexia and perhaps bleeding ***(Gjevre et al., 1996).***

CT criteria for hamartoma included a diameter of 2.5 cm or less, a smooth edge, and focal collections of fat or fat alternating with areas of calcification. No case of cancer (n = 283) or metastatic disease fulfilled these criteria. Seventeen hamartomas with no detectable calcium or fat were not diagnosed by means of CT. Two other lesions contained

diffuse calcium deposits. In 28 lesions, a CT diagnosis of hamartoma was based on the detection of fat or calcium plus fat ***(Gjevre et al., 1996)***.

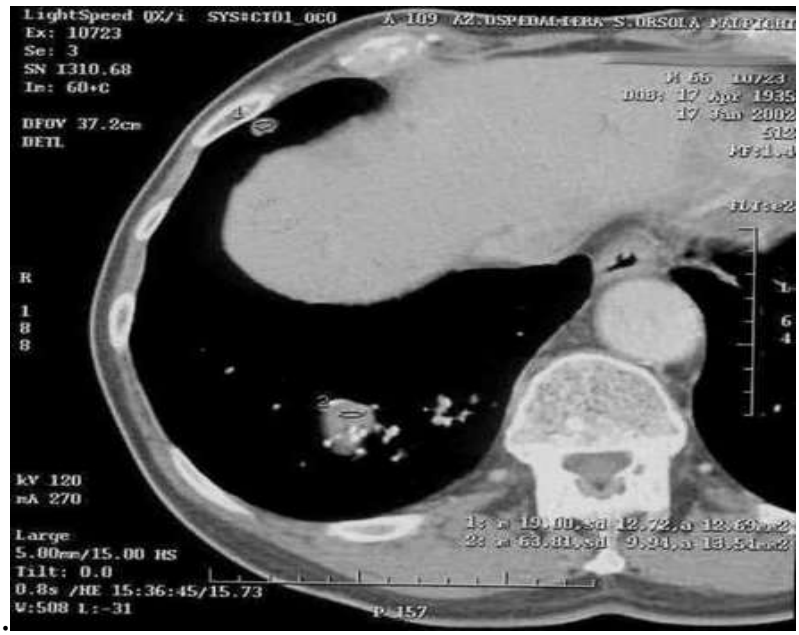

Figure (1): CT of the chest showing hamartoma

b) Endometrioma :

Occasionally endometrial-like tissue implants in the thorax, either as parenchymal or endobronchial masses. It is uncertain whether the tissue is deposited via hematogenous spread or arises from coelomic metaplasia. In the few cases reported, the masses appear radiographically as a solitary pulmonary nodule up 4 cm in diameter. Most often there is history of recurrent pneumothoraces or hemoptysis during menses ***(Gjevre et al., 1996).***

c- Neurogenic tumors:

Neurogenic tumors most commonly occur in posterior mediastinum, but neurofibromas and neurolemoma may rarely occur as solitary pulmonary nodules, usually located in the peripheral lung. Pulmonary neurofibroma, especially if multiple may be associated with neurofibromatosis ***(Harry et al.., 1987).***

d- Hemangioma:

Hemangioma is a benign tumor consisting of a mass of thin walled vessels and a variable amount of intervening stroma. The connective tissue stroma may hyalanize as a product of aging, so sometimes called selerosing hemangioma ***(Liebow and Hubbell, 1956).***

The tumor is more common in women in the fourth and fifth decades. Hemangiomas usually develop in the subpleural lung periphery and thus appear radiographically as sharply circumscribed, lobulated nodules averaging 3 cm in diameter. They may enlarge slowly. There is

a preference for the right lung and especially the right lower lobe. Hemoptysis occurs frequently due to prominent vascularity ***(Arean and Wheat, 1962).***

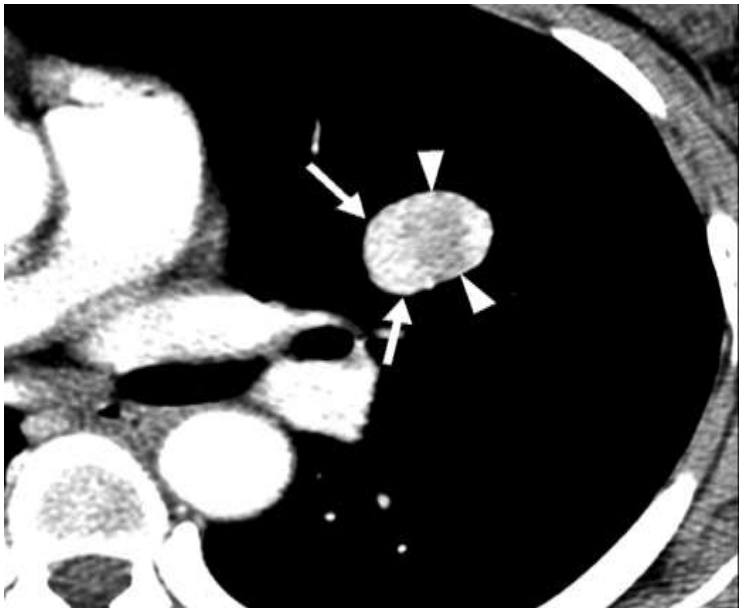

Figure (2): CT of the chest showing hemangioma

e- Fibroma:

Fibroma is a mesenchymal soft tissue tumor that may arise as a peripheral or endobronchial mass. Endobronchial tumors may be sessile or polypoid. The peripheral lesion may be solitary, well circumscribed and located preferentially in a lower lobe ***(Harry et al., 1987).***

f- Lipoma:

Lipoma may arise from the chest wall, mediastinum, subpleural region or endobronchial surface. Endobronchial lipomas comprise about 80 % of intrathoracic lipomas. Pulmonary parenchymal lipomas are less common than the endobronchial variety and most are subpleural in location, many are pedunculated or dumbbell in shape. The mass may change in shape during respiration. Being flattened against the chest wall on deep inspiration and rounded on expiration. Some lipomas arise from the extrapleural region and grow secondarily into the lung ***(Harry et al.., 1987).***

2) Malignant

a- Lung Cancer:

The lung is a major site of cancer in the world today. In 1990, the estimated new cases worldwide were 1.04 million representing 12.8% of all new cancers and the number is increasing at the rate of about 3% year. Lung cancer is responsible for 28% of all deaths related to cancer

and is the most frequently diagnosed major cancer worldwide. About 42% of cases occur in developing countries. The disease is more common in men than women although this difference has become smaller; a decade ago male to female ratio was 10:1, but is now 2:1 ***(Skuladottir and Oslen, 2001).***

In Egypt, it was the seventh most common tumor in 1991, representing 2.8% of all cancers presenting to National cancer institute in Cairo ***(El Bolkiny, 1991)***. There is rapidly increasing rate in recent years and the dimensions of disease are approaching an epidemic proportion as stressed by ***Gad El Mawla et al., (1986), Madkour (1991), Nayel et al., (1995) and Salem et al., (1995).***

The mortality rate from bronchogenic carcinoma in Egypt has been reported to be increasing. There is more than three times increase in the period between 1952 and 1975 from 0.36 to 1.91/100,000 ***(Madkour, 1980). Madkour and Nabil (1985)*** on evaluating bronchogenic carcinoma, reviewed the material available in Egyptian literature in period between 1974 and 1979, found that more than 87% of cases were above the age of 40 years and the maximum age distribution is in the 5th decade. The disease was mainly in males; males to females ration 9:1. They added that, the incidence in females is rising recently with the practice of smoking among females.

It is clear that the predominant risk factor is cigarette smoking. The rapid increase in lung cancer occurrence in most areas of the world is following about 20-30 years after parallel trend in cigarette smoking. Most developing countries have still not experienced the worst consequences of the tobacco epidemic, as cigarette only become widespread during last 30 years ***(Skuladottir and Oslen, 2001).*** Approximately 85% of lung cancer occurs in smokers or former smoker and about half of all regular smokers are eventually killed by their habit ***(Midthun and Jett, 1999)***.

In Egypt, cigarette smoking is also the predominant risk factor. Astonishingly, tobacco consumption is much higher than the national increase of population and the total tobacco consumption become doubled every 7-10 years; predicting a future lung cancer burden. There is also positive correlation between cigarette production and mortality rate from lung cancer ***(Madkour, 1980)***.

At the time lung cancer is detected, usually the disease is in the advanced stage, where the options for treatment are only palliative. Approximately 85% of patients diagnosed will die from it and only 15% of them will be alive at 5 years. There is a great need for prevention and effective treatment ***(Lam and Becker, 1996).***

The failure rate of lung cancer surgical resection alone is 50-60%. The main cause of failure is the persistence of occult disease not previously discovered by current diagnostic tools leading to local and /or distant spread ***(Rocmans, 2001).***

Early detection of cancer offers greater hope for successful intervention and cure. The treatment of early lung cancer is quite effective, the five-year survival of stage I lung cancer is in the range of 70% ***(Flehinger, et al., 1992)***.

Recently, new technologies for screening of early lung cancer and local staging have been developed and seem to be capable for shifting forward the detection, localization and treatment of early lung cancer. They are currently under prospective investigations ***(Herth and Becker, 2001-b).***

Clinical presentations of lung cancer

Patients with lung cancer can present in many different ways ***(Fergusson, 2000)***. Some of the clinical manifestations of bronchogenic carcinoma depend on the cell type. Small cell lung cacer (SCLC) has a very aggressive behavior with significant mediastinal and early extrathoracic spreading. Conversely, patients with squamous cell carcinoma usually have local symptoms because these tumors invade locally prior to systemic spread. Patients with adenocarcinoma and large cell carcinoma tend to have systemic manifestations relatively early in their course ***(Dweik and Arrologia, 1999)***.

1. Asymptomatic presentation

One fourth of patients who have lung cancer present with no symptoms at the time of diagnosis. A nodule or mass may be identified on a chest radiograph carried out as part of a preoperative evaluation for unrelated surgery or may be noted on imaging carried out in pursuit of other concerns ***(Midthun and Jett, 1999)***.

2. Symptomatic presentation

Approximately three fourths of patients who have lung cancer present with symptoms at the time of diagnosis ***(Midthun and Jett, 1999).***

The clinical features manifested by patients suffering from lung cancer depend on the location of the primary tumor, its locoregional spread, metastases and its systemic manifestations caused by non-metastatic (paraneoplastic) syndromes ***(Ginsberg et al., 1997).***

I. Local manifestations and intrathoracic spread: (table 1).

(a) Clinical manifestations secondary to central growth of the primary tumor:

Three-quarters of patients with lung cancer have their primary disease in the central airway. This is especially true in squamous and small cell carcinoma. The commonest symptoms at presentation are cough, haemoptysis, dyspnoea and chest pain, either alone or in combination ***(Fergusson, 2000)***.

Cough is the most common presenting symptom of lung cancer. Patients who have a persistent cough or a change in cough should have a chest radiograph especially if they are smokers and aged over 40 yr. Lung cancers occurring in central airways can lead to post-obstructive pneumonia. Failure of acute exacerbation of chronic bronchitis to clear within a few weeks should raise the suspicion of a neoplasm.

Hemoptysis is a common presenting symptom. It is rarely severe and is usually only streaking of blood in the sputum. The chest radiograph is usually abnormal, but if normal in a heavy smoker aged over 40 yr, the yield of endobronchial tumors at fiberoptic bronchoscope (FOB) is less than 5%. Dyspnoea develops early in up to 60% of patients. It is usually associated with increasing cough and sputum. If the tumor is occluding a major airway, it may be associated with a unilateral wheeze. Chest discomfort is common and occurs in up to 60% of patients at diagnosis. This is often of an ill-defined nature, intermittent and aching in quality. Definite pleuritic pain may occur as a result of infection or direct spread of the tumor to the pleural surface, although this can also be painless ***(American Thoracic Society/European Respiratory Society, 1997).***

(b) Clinical manifestations secondary to peripheral growth of the primary tumor:

Peripheral tumors, commonly adenocarcinomas or large cell types, often have a different mode of presentation. They may be asymptomatic; cough and hemoptysis are less common than central lesions.

Bronchorrhea or cough that is productive of large volumes of thin mucoid secretions may be a feature of bronchioloalveolar carcinoma (BAC) described in 10% of cases although this is unusual symptom. Dyspnoea is also less common and if present it is likely to be due to either pleural involvement with tumor or blockage of lymphatics in lymphangitis carcinomatosa. Pain from pleural or chest wall involvement can be also a presenting symptom ***(Ginsberg et al., 1997)***.

(c) Regional spread:

Depending on the location of the primary tumor, adjacent structures, such as the chest wall or the mediastinum, may ultimately become involved by direct spread. Shoulder pain, often radiating down the upper inner arm, can be caused by a tumor in the apex of the lung or superior sulcus (Pancoast's tumor). Involvement of the last cervical and first thoracic segments of the sympathetic trunk produces Horner's syndrome. Hoarseness secondary to entrapment of the left recurrent laryngeal nerve is a frequent presenting symptom. Invasion of ribs or vertebrae will cause continuous localized aching pain. Superior vena caval (SVC) obstruction is due to either occlusion of the vena cava by tumor or thrombosis from tumor breaching and damaging the luminal surface. Dysphagia results from esophageal compression by enlarged metastatic mediastinal LNs and less commonly from direct tumor invasion. Cardiac metastases are rare and occur late because the pericardium appears to be an efficient natural barrier. However, pericarditis does occur and occasionally an effusion may cause classic symptoms of tamponade. Tumors invading or involving LNs in the mediastinum may interfere with the phrenic, vagus or recurrent laryngeal nerves, resulting in e.g. hoarseness or cricopharyngeal dysphagia and they are uncommon presenting symptoms. Pleural invasion ultimately can result in pleural seeding. Pleuritic pain or increasing shortness of breath due to massive pleural effusion can ensue. Of patients who have lung cancer, <10% have pleural involvement at presentation. Presence of carcinoma cells in the pleural fluid establishes the lung cancer as unresectable. Pleural effusion may result from lymphatic obstruction, postobstructive pneumonitis, or atelectasis. The presence of pleural metastasis needs to be confirmed so that a chance or curative resection is not overlooked ***(American Thoracic Society/ European Respiratory Society, 1997).***

Table (1): Summary of local and intrathoracic manifestations **of lung cancer ***

#Cough 45-75%	Pneumotharx
Excessive sputum	Plueral effusion
Persistent infection	Horner's syndrome
#Haemoptysis 29-35%	Elevation of a hemidiaphragm
#Dyspnoea 40-60%	#Hoarsness of voice 7-21%
#Chest discomfort or pain 30-50%	#Superior vena cava obstruction 4%
#Wheezes/Stridor 2-23%	#Dysphagia 2-9%

 # Appropriate frequency at time of presentation

****(Spiro and Fabrizio, 2001)***

II. Extrathoracic manifestations:

About one third of patients present with symptoms as a result of distant metastases. Supraclavicular and anterior cervical nodes are enlarged in 15-30% patients during the course of their illness. Bone pain is present in up to 20% of all patients at presentation. Liver metastases occur with lung cancer; however, liver function tests are seldom abnormal until the metastases are numerous and large. Adrenal lesions and para-aortic LNs metastases may occur and are most commonly seen with SCLC. Intracranial metastases occur in 10% of patients at presentation. Spinal cord metastases are less common but tend to occur in patients with cerebral metastases ***(American Thoracic Society/ European Respiratory Society, 1997).***

III. Paraneoplastic syndromes:

Paraneoplastic syndromes occur in approximately 10-20% of patients with lung carcinoma. A variety of remote effects of lung cancer may occur that are unrelated to direct invasion, obstruction, or metastatic effects ***(American Thoracic Society/European Respiratory Society, 1997).***

Pathological Diagnosis of Lung Cancer:

The pathologic diagnosis of lung cancer can be established either - on cytologic or histological biopsy specimens or both ***(Colby et al., 1995).***

The certainty of the diagnosis may depend on the quantity and quality of viable tumor cells in the specimen. One of the most important issues in the approach to lung cancer diagnosis is communication between pathologist and clinician ***(American Thoracic Society / European Respiratory Society, 1997).***

The newly revised updated World health oganisation (WHO) histological classification in (1999) is the most widely accepted lung tumor classification schema (Table 2) ***(Travis et al., 1999)***. The histopathological classification of lung cancer is expected to continue to change as clinical practice and biological understanding of these tumors change ***(Franklin, 2000).***

1. Histological classification of lung cancer:

The histopathological appearance of lung carcinoma remains an important guide to prognosis and treatment. Histologic biopsy specimens can be obtained endobronchial, transbronchial, transthoracic or open biopsy procedures. Small tissue cores can be obtained for histologic material with transbronchial or transthoracic needle biopsy

(***American Thoracic Society / European Respiratory Society, 1997)***. The histological typing of specimens obtained may be normal, inflammatory, hyperplasia, mild dysplasia, moderate-severe dysplasia, carcinoma in situ, microinvasive carcinoma, invasive carcinoma or unsatisfactory specimens ***(WHO, 1981).*** The major histologic subtypes of lung cancer include squamous cell carcinoma, adenocarcinoma, SCLC, and large-cell carcinoma ***(WHO, 1981).***

Neoplastic versus non-neoplastic conditions:

Distinction between reactive and neoplastic process is usually straightforward, but diagnostic difficulties may arise in the case of inadequate or poorly prepared histologic material to evaluate the presence of cytological atypia in epithelium stimulated by inflammation, viral infection, radiation, or chemotherapy. Immunohistochemical stains are usually of no help in this circumstance. Diagnostic distinction between atypical reactive epithelium and well differentiated carcinoma, especially adenocarcinoma, must ultimately rest on the subtle morphological clues, such as degree of nuclear atypia, numbers of atypical cells, clustering pattern of suspicious cells, and extent of inflammatory reaction in relation to the amount and degree of epithelial atypia ***(Franklin, 2000).***

Table (2): WHO Histologic Classification of Lung and Pleural Tumors*

1. Epithelial tumors
1.1 Benign
1.1.1 Papillomas
1.1.1.1 Squamous cell papilloma
1.1.1.1.1 Exophytic
1.1.1.1.2 Inverted
1.1.1.2 Glandular papilloma
1.1.1.3 Mixed squamous cell and glandular papilloma
1.1.2 Adenomas
1.1.2.1 Alveolar adenoma
1.1.2.2 Papillary adenoma
1.1.2.3 Adenomas of salivary gland type
1.1.2.3.1 Mucous gland adenoma
1.1.2.3.2 Pleomorphic adenoma
1.1.2.3.3 Others
1.1.2.4 Mucinous cystadenoma
1.1.2.5 Others
1.2 Preinvasive lesions
1.2.1 Squamous dysplasia/carcinoma *in situ*
1.2.2 Atypical adenomatous hyperplasia
1.2.3 Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
1.3 Invasive malignant
1.3.1 Squamous cell carcinoma
Variants:
1.3.1.1 Papillary
1.3.1.2 Clear cell
1.3.1.3 Small cell
1.3.1.4 Basaloid
1.3.2 Small cell carcinoma
Variant:
1.3.2.1 Combined small cell carcinoma
1.3.3 Adenocarcinoma
1.3.3.1 Acinar
1.3.3.2 Papillary
1.3.3.3 Bronchioloalveolar carcinoma
1.3.3.3.1 Non-mucinous(Clara cell/type II pneumocyte type)
1.3.3.3.2 Mucinous (goblet cell type)
1.3.3.3.3 Mixed mucinous and nonmucinous (Claracell/type II pneumocyte and goblet cell type) or indetermi nate
1.3.3.4 Solid adenocarcinoma with mucin formation
1.3.3.5 Mixed
1.3.3.6 Variants:
1.3.3.6.1 Well-differentiated fetal adenocarcinoma
1.3.3.6.2 Mucinous ("colloid")
1.3.3.6.3 Mucinous cystadenocarcinoma
1.3.3.6.4 Signet ring
1.3.3.6.5 Clear cell
1.3.4 Large cell carcinoma
Variants:
1.3.4.1 Large cell neuroendocrine carcinoma
1.3.4.1.1 Combined large cell neuroendocrine carcinoma
1.3.4.2 Basaloid carcinoma
1.3.4.3 Lymphoepithelioma-like carcinoma
1.3.4.4 Clear cell carcinoma
1.3.4.5 Large cell carcinoma with rhabdoid phenotype
1.3.5 Adenosquamous carcinoma
1.3.6 Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements 1.3.6.1 Carcinomas with spindle and/or giant cells
1.3.6.1.1 Pleomorphic carcinoma
1.3.6.1.2 Spindle cell carcinoma
1.3.6.1.3 Giant cell carcinoma
1.3.6.2 Carcinosarcoma
1.3.6.3 Blastoma (pulmonary blastoma)
1.3.6.4 Others
1.3.7 Carcinoid tumor
1.3.7.1 Typical carcinoid
1.3.7.2 Atypical carcinoid
1.3.8 Carcinomas of salivary gland type
1.3.8.1 Mucoepidermoid carcinoma
1.3.8.2 Adenoid cystic carcinoma
1.3.8.3 Others
1.3.9 Unclassified carcinoma
2. Soft tissue tumors
2.1 Localized fibrous tumor
2.2 Epithelioid hemangioendothelomia
2.3 Pleuropulmonary blastoma
2.4 Chondroma
2.5 Calcifying fibrous pseudotumor of the pleura
2.6 Congenital periobronchial myofibroblastic tumor
2.7 Diffuse pulmonary lymphangiomatosis
2.8 Desmoplastic small round cell tumor
2.9 Other
3. Mesothelial tumors
3.1 Benign
3.1.1 Adenomatoid tumor
3.2 Malignant
3.2.1 Epithelioid mesothelioma
3.2.2 Sarcomatoid mesothelioma
Desmoplastic mesothelioma
3.2.3 Biphasic mesothelioma
3.3 Other
4. Miscellaneous tumors
4.1 Hamartoma

Table (3): WHO Histologic Classification of Lung and Pleural Tumors*

4.2 Sclerosing hemangioma 4.3 Clear cell tumor 4.4 Germ cell neoplasms 4.4.1 Teratoma, mature 4.4.2 Teratoma, immature 4.4.3 Other germ cell tumors 4.5 Thymoma 4.6 Melanoma 4.7 Others 5. Lymphoproliferative diseases 5.1 Lymphoid interstitial pneumonia 5.2 Nodular lymphoid hyperplasia 5.3 Low-grade marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue 5.4 Lymphomatoid granulomatosis 6. Secondary tumors 7. Unclassified tumors	8. Tumor-like lesions 8.1 Tumorlet 8.2 Multiple meningotheloid nodules 8.3 Langerhans' cell histiocytosis 8.4 Inflammatory pseudotumor (inflammatory myofibroblastic tumor) 8.5 Organizing pneumonia 8.6 Amyloid tumor 8.7 Hyalinizing granuloma 8.8 Lymphangioleiomyomatosis 8.9 Multifocal micronodular pneumocyte hyperplasia 8.10 Endometriosis 8.11 Bronchial inflammatory polyp 8.12 Others

(Travis et al., 1999)

Early lung cancer, carcinoma in situ (CIS) and invasive tumors:

Definition of early lung cancer: The limitation of the local infiltrating growth of tumor to the different layers of the bronchial wall, which means that the tumor tissue must not exceed the outer tunica fibrocartilaginea and the adjacent lung tissue must not be infiltrated ***(Brockmann and Müller, 1986).***

Definition of CIS: This includes cellular changes in the full thickness of the mucosa but with intact basement membrane. CIS is usually squamous carcinoma ***(Colby et al, 1994).***

Microinvasive carcinoma: Is described as few millimeters of basement membrane invasion but involving the muscle or cartilage ***(Colby et al, 1994).***

The concept of a progressive sequence of dysplasia, carcinoma in situ, and invasive carcinoma is generally accepted for squamous cell carcinoma but not for other histologic types of lung carcinoma ***(Colby et al., 1995).***

With increasing reliance on smaller quantities of tissue, diagnostic decisions are made on ever-smaller amounts of tissue. This can be hazardous when attempting to distinguish between invasive non-small cell lung carcinoma (NSCLC) and epithelial dysplasia or carcinoma in situ. At present time, the only certain way to diagnose invasive NSCLC is to specifically identify stromal invasion in tissue sections. An extreme degree of cytologic atypia may suggest invasive carcinoma and warrant the procurement of additional tissue to confirm the diagnosis of invasive tumor ***(Franklin, 2000).***

Small cell versus non-small cell tumors:

Since there are major differences in the therapeutic approach to patients with SCLC and NSCLC, pathologic differentiation between the two types is critical. The distinction of NSCLC from SCLC should not rest on a single criterion.

It should be emphasized that diagnosis of small cell carcinoma is made on the basis of nuclear details, including high mitotic rate and inconspicuous of nuclei, and finely granular ('salt and pepper') nuclei, as well as on the overall cell size. Apparent cell size and the nuclear details are dependent on the state of preservation of the specimen, and severe crush artifact that frequently affects the fragile tumor cells of small cell carcinoma may render diagnosis difficult ***(Franklin, 2000).***

In some cases, comparison with cytology specimens taken at the time of bronchoscopy will provide the definitive diagnosis. Lymphoid infiltrates, whether due to small lymphocytic lymphoma or chronic inflammation, can be distinguished from SCLC by their dyscohesive pattern of growth, contrasting with the epithelial clustering and nuclear molding of SCLC ***(American Thoracic Society / European Respiratory Society, 1997).***

In most cases, SCLC strongly expresses the neuroendocrine marker, neural cell adhesion molecule (NCAM), and this can be demonstrated by a simple immunohistochemical stain of a paraffin section using the monoclonal antibody 123c3; on the other hand NSCLC typically expresses epidermal growth factor receptor (EGFR). These two markers can sometimes be useful in confirming the diagnosis ***(Franklin, 2000).***

Disagreement among expert lung cancer pathologists between SCLC and NSCLC may occur in up to 5-7% of cases ***(American Thoracic Society / European Respiratory Society, 1997).***

Differential diagnosis of NSCLC:

Distinction among the different types of NSCLC can sometimes prove difficult. Squamous cell carcinoma is recognized by the histologic features of intercellular bridging, squamous pearl formation, and individual cell keratinization. Adenocarcinomas may take the form of several histologic subtypes as acinar (gland forming), papillary, bronchioloalveolar, solid with mucin formation or mixed. Cases with mixed adeno- and squamous differentiation are called adenosquamous carcinoma ***(Association of Directors of Anatomic and Surgical Pathology, 1995).***

Large-cell carcinoma is a poorly differentiated NSCLC. It is a diagnosis of exclusion made after ruling out the presence of adenocarcinomatous or squamous differentiation. Large-cell carcinoma