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**DEPARTMENT OF ONCOLOGY**



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MD, prof. Bashtan V.P.

**METHODICAL POINTING  
FOR INDEPENDENT WORK OF STUDENTS  
DURING PREPARATION TO PRACTICAL EMPLOYMENT**

<i>Educational discipline</i>	<i>Palliative help</i>
<i>Module №</i>	<i>I</i>
<i>Rich in content module №</i>	<i>I</i>
<i>Theme of employment</i>	<b>Lung cancer</b>
<i>Course</i>	<i>VI</i>
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MD, prof. Sheleshko P.V.

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# LUNG CANCER

## Small cell lung cancer

Lung cancer is the second most common malignancy after prostate cancer in men and breast cancer in women, and is the leading cause of smoking- and cancer-related mortality in both sexes. Most lung carcinomas are diagnosed at an advanced stage, conferring a poor prognosis. The most common cause of the advanced lung cancer is the inadequate onco- suspicion and qualification of the physicians. The need to diagnose lung cancer at an early and potentially curable stage is obvious. In addition, most patients, who develop lung cancer, smoke and have smoking-related damage to the heart and lungs, making aggressive surgical or multimodality therapies less viable options.

## Epidemiology

***Incidence.*** Average incidence rate of lung cancer in the industrialized countries is about 50 per 100,000 population, with an estimated 1.04 million new cases each year worldwide. Fifty-eight percent of new lung cancer cases occur in the developing world. Lung cancer incidence is increased in urban areas (especially in industrial centers, and areas with transportation paper, chemical, and petroleum industries).

However there are essential incidence differences between male- female, and in the various countries of the World. Globally, lung cancer is the most frequent malignancy in males, while it is the fifth most common cancer in females. So, the highest incidence in male is in Scotland (109.6), USA (71.6) and in Poland (68.4 per 100,000 population). The lowest incidence in male is in Syria (2.1), Salvador (2.2) and in Thailand (2.6). The highest incidence in female is in Scotland (28.1) too, in Hungary (12.8), and in USA (11.4). The lowest incidence in female is in Syria (0.7), Salvador (2.2) and in Thailand (2.4) too.

**Death rate.** Lung cancer is the cause of 921,000 deaths each year worldwide, accounting for 17.8% of cancer-related deaths. The highest death rate in male is in Scotland (105.2), Belgium (104.1), and in Netherlands (103.8), and the lowest is in Peru (7.3), Martinique (12.2), and in Surinam (15.9). In female the highest death rate is in Singapore (33.2), Hong Kong (32.1), USA (26.2), and the lowest is in Barbados (2.5), Peru (3.2), and in Ecuador (4.2 per 100,000 population).

**Sex.** Lung cancer is more common in men than in women. In the United States, northern Europe and western Europe, the prevalence of lung cancer has been decreasing in men. Most Western countries have encountered a disturbing trend of increasing prevalence in women and younger patients. The incidence of lung cancer started to decline among males in the early 1980s and has continued to do so over past 20 years. By contrast, the incidence in women started to increase in the late 1970s and only recently reached a plateau.

**Age.** The probabilities of developing lung cancer among males are Lung cancer is the second most common malignancy after prostate cancer in men and breast cancer in women, and is the leading cause of smoking- and cancer-related mortality in both sexes. Most lung carcinomas are diagnosed at an advanced stage, conferring a poor prognosis. The most common cause of the advanced lung cancer is the inadequate onco- suspicion and qualification of the physicians. The need to diagnose lung cancer at an early and potentially curable stage is obvious. In addition, most patients, who develop lung cancer, smoke and have smoking-related damage to the heart and lungs, making aggressive surgical or multimodality therapies less viable options. the following: 0.04% from birth to 39 years; 1.24% - to 40-59 years; 6.29% - to 60-79 years; and 8.09% from birth to death. Among females, the probabilities are as follows: 0.03% from birth to 39 years; 0.92% - to 40-59 years; 4.04% - to 60-79 years; and from birth to death -5.78%.

**Race.** Among men, the age-adjusted incidence of lung cancer (per 100,000) ranges from 14 in Native Americans, 42-53 for Hispanic and Chinese Americans, 71-89 for Vietnamese and whites, to 117 among black Americans. Among women, the age-adjusted incidence of lung cancer ranges from 15 among Japanese, 16-25

among Hispanics and Chinese, SI- 44 among Vietnamese and black Americans, to 51 among Alaskan natives.

There are two most common different morphological and clinical forms of lung cancer:

- Non-Small-Cell Lung Cancer (NSCLC);
- Small Cell Lung Cancer (SCLC).

## **Small Cell lung Cancer**

Small cell lung cancer (SCLC) is considered distinct from the other lung cancers, called non-small-cell lung cancers (NSCLCs), because of their clinical and biological characteristics. SCLC exhibits aggressive behavior, with rapid growth, early spread to distant sites, exquisite sensitivity to chemotherapy and radiation, and frequent association with distinct paraneoplastic syndromes. Approximately 65-70% of patients with SCLC have disseminated disease at presentation. Surgery usually plays no role in its management, except in rare situations (<5% of patients) in which it presents at a very early stage as a solitary pulmonary nodule. Even then, adjuvant chemotherapy after surgical resection is recommended, since SCLC always should be considered a systemic disease.

***Frequency.*** Small cell carcinomas account for approximately 20-25% of all lung cancers.

## **Etiology and Pathogenesis**

***Causes.*** The predominant cause of SCLC, as of NSCLC, is tobacco smoking.

***Uranium miners.*** All types of lung cancers occur with increased frequency in uranium miners, but SCLC is most common. The incidence is increased further in smokers.

***Radon.*** Exposure to radon, which is an inert gas developing from the decay of uranium, also has been reported to cause SCLC.

## **Pathophysiology**

Small cell carcinomas arise in peribronchial locations and infiltrate the

bronchial submucosa. Widespread metastases occur early in the course of the disease, with common spread to mediastinal lymph nodes, liver, bones, adrenal glands, and brain. In addition, production of a variety of peptide hormones leads to a wide range of paraneoplastic syndromes. The most common paraneoplastic syndromes are the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and the syndrome of actopic adrenocorticotrophic hormone (ACTH) production. In addition, autoimmune phenomena may lead to various neurological syndromes.

## The Pathologic Evaluation

**Histopathology.** Approximately 5% of SCLCs exhibit features of mixed small cell and large cell components and, less frequently, may exhibit mixed small cell and squamous cell components. There are 3 subcategories of SCLCs: oat cell carcinoma, intermediate cell type, and combined oat cell carcinoma. SCLCs typically are centrally located, arising in peribronchial locations. They are thought to arise from Kulchitsky cells.

**Site.** Small cell carcinomas are usually centrally located. In other words, SCLC is most frequently considered to be central lung cancer.

### Staging

The staging system has failed to provide important prognostic information in patients with SCLC (Table 3.1)

**Table 3.1.**

#### **Staging of Small Cell Lung Cancer**

Stage	Description
Limited stage	Disease confined to one hemithorax; includes involvement of mediastinal, contralateral hilar, and/or supraclavicular and scalene lymph
Extensive stage	Disease has spread beyond the definition of limited stage, or malignant pleural effusion is

## Clinical Manifestation

SCLC typically presents with a relatively short duration of symptoms. The onset of symptoms usually is within 8-12 weeks prior to presentation. Symptoms include the following:

*Constitutional symptoms:* fatigue, anorexia, weight loss.

Symptoms due to primary tumor: *cough, dyspnea, hemoptysis.*

*Symptoms due to intrathoracic spread:* superior vena cava obstruction, hoarseness (ie, palsy of the recurrent laryngeal nerve), phrenic nerve palsy, dysphagia (ie, compression of esophagus), stridor (ie, compression of the trachea mainstem bronchus).

*Symptoms due to distant spread:* neurological dysfunction (ie, brain metastasis, spinal cord compression), bone pain (bone metastasis), abdominal/right upper quadrant pain (ie, liver metastasis).

The symptoms can result from local tumor growth, intrathoracic spread, distant spread, and/or paraneoplastic syndromes.

***Local tumor growth.*** Small cell carcinomas usually may cause irritation and/or obstruction of the major airway. Common symptoms resulting from local tumor growth include cough, dyspnea, and hemoptysis. Patients give a short history of symptoms of recent onset, with rapid worsening. Rapid tumor growth may lead to obstruction of major airways, with distal collapse and consequent post-obstructive pneumonitis. Fever may result from infections distal to obstruction or from the tumor itself.

***Intrathoracic spread,*** Small cell carcinomas grow in size rapidly and metastasize to the mediastinal lymph nodes relatively early in the course of the disease. At presentation, patients may have a very large intrathoracic tumor, and distinguishing primary tumor from lymph node metastasis may be impossible. Pressure on mediastinal structures can cause a variety of symptoms.

*Superior vena cava obstruction.* Malignancy is the most common cause of superior vena cava (SVC) obstruction, and lung cancer accounts for the overwhelming majority of cases (60-90%). SCLC causes SVC

obstruction more often than other lung cancers do. Patients have facial edema, dusky skin coloration, and, possibly, conjunctival edema. Edema of the upper extremities and prominent veins on the upper thoracic wall with retrograde flow may be present. Headache, dizziness, and other neurological symptoms are late occurrences.

*Paralysis of the recurrent laryngeal nerve.* The recurrent laryngeal nerve may be compressed by a mediastinal mass (ie, primary tumor or lymph node metastasis) as it traverses up on the left to supply the vocal cords. Patients complain of hoarseness of recent onset.

*Phrenic nerve palsy.* Compression of the phrenic nerve causes paralysis of the ipsilateral hemidiaphragm, contributing to respiratory symptoms.

*Esophageal compression.* Compression of the esophagus can lead to dysphagia and odynophagia.

*Tracheal compression.* Compression of the mainstem bronchi and trachea can cause severe shortness of breath and stridor.

*Symptoms from distant spread.* These symptoms depend upon the site of spread (Table 3.2). Common sites of spread include brain, bones, liver, adrenals, and bone marrow.

*Symptoms.* Physical findings in SCLC depend upon the extent of local and distant spread and the organ system involved.

*Respiratory system.* Patients usually complain of shortness of breath, and examination may reveal use of accessory muscles of respiration (scalene muscles, intercostal muscles, flaring of alae of nose). In addition, by virtue of central tumor location, patients may develop distal atelectasis and post-obstructive pneumonia. With pleural effusion, examination reveals dullness to percussion and decreased or absent breath sounds on the side of the effusion.

**Table 3.2.**

***Paraneoplastic Syndromes***

<b>Organ/</b>	<b>Syndrome</b>	<b>Mechanism</b>	<b>Frequen</b>
Endocrin e	SIADH	Antidiuretic	5-10%
	Ectopic secretion of Atrial natriuretic	Adrenocorticotro	5%
Neurolog ical	Eaton-Lambert		5-6%
	Subacute cerebellar		
	Subacute sensory		
	Limbic	Anti-Hu, Anti-Yo	

**Table 3. 7.**

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	Subacute cerebellar		
	Subacute sensory		
	Limbic	Anti-Hu, Anti-Vo	

**Cardiovascular system.** SCLC may cause pericardial effusion and is the malignancy most often causing obstruction of the SVC. Patients usually are short of breath. Heart sounds may be distant on auscultation. Jugular venous pulsation is elevated; paradoxically, it rises with inspiration. Pulsus paradoxus is a classic sign

of pericardial tamponade. Tamponade is an emergency and requires immediate decompression of the pericardium.

**Central nervous system.** Patients with SCLC may have asymptomatic brain metastasis in 5-10% of cases, which may be picked up on staging workup. Patients with symptomatic brain metastases may have raised intracranial pressure secondary to mass lesions, as well as surrounding brain edema, and may complain of headache (usually worse early in the morning), blurring of vision, photophobia, nausea, vomiting, and various localizing symptoms, eg, weakness of an extremity. The physical findings again are dependent upon the site of the brain lesions.

**Vertebral and paraspinal metastases.** The importance of early recognition of these metastasis is due to their close proximity to the spinal cord (spinal cord compression), potentially leading to permanent loss of neuro

logical function if diagnosis is delayed. The initial symptom usually is back pain, with or without neurological dysfunction.

**Gastrointestinal system.** The liver is the common site of spread, and physical examination may reveal icterus (secondary to widespread liver metastasis or obstruction of biliary outflow) or hepatomegaly.

**Lymphatic system.** Lymph node examination should be carried out carefully. Currently, enlarged ipsilateral supraclavicular lymph nodes are included in limited stage, but enlarged axillary lymph nodes upstage the diagnosis to extensive-stage disease.

**Extremities.** Examination of the extremities may reveal clubbing, cyanosis, or edema. In the presence of SVC obstruction, the right upper extremity usually is edematous.

## Diagnostics

1. Investigations are performed to establish the diagnosis of lung cancer. Procedures include the following:

**History and physical examination.** A thorough history and physical examination usually provide clues to the organ systems involved and are used to

guide further workup.

**Chest X-ray (CXR).** Good posteroanterior and lateral radiographs are useful in identifying the primary tumor as well as concurrent parenchymal abnormalities. Mediastinal widening may be noticed as well. Chest radiographs may show unilateral hilar enlargement, increased hilar opacity, a (H'rihilar mass, mediastinal mass, or a combination of these. Less commonly, SCLC may appear as a solitary pulmonary nodule (fig. 3,1). Compression of the bronchi is relatively common in SCLC because of the central location of the tumor in most cases. About 30-50% of SCLCs show evidence of obstructive pneumonitis (fig. 3,2) on the initial presentation. SCLC can appear as segmental or lobar atelectasis with or without an obvious hilar mass.

**Sputum cytology** is a noninvasive test, and, if positive, usually allows more invasive diagnostic tests to be averted. The highest yield of this test is with large, central tumors.

**Bronchoscopy.** SCLC usually is centrally located and can be approached directly with a bronchoscope. The advantage of endoscopy is direct visualization of the tumor, allowing direct biopsy as well as cytologic examination of bronchial washings.

**CTscans.** The patient in whom lung cancer is suspected or diagnosed should undergo imaging of the thorax (fig. 3,j3) and all common sites of metastasis to adequately stage the disease. In the United States, CT scans of the chest and upper abdomen to include the liver and adrenal glands, are standard.

**Transthoracicpercutaneous fine-needle aspiration.** For accessible tumors this test is less invasive than bronchoscopy and is carried out under (T scan guidance.

**Complete blood cell (CBC) count.** In 5-10% of patients, the disease may have spread to bone marrow at presentation. Bone marrow examination is not performed routinely unless abnormalities are identified in the CBC count

or peripheral smear examination, raising the possibility of bone marrow spread. These may include variable degrees of cytopenias; the presence of immature white and red blood cells (a leukoerythroblastic blood picture) raises the

possibility of myelophthisic anemia. Additionally, the absolute neutrophil count should be  $>1000 \times 10^3/\text{mL}$ , hemoglobin  $>10 \text{ g/dL}$ , and platelet count  $>100 \times 10^3/\text{mL}$  before instituting initial full- *dose* combination chemotherapy.

**Strum chemistry.** Elevated serum calcium and alkaline phosphatase mls<sup>1</sup> the suspicion of bone metastasis, and bone scan should be ordered r-vt\*n in the absence of symptoms. Serum electrolytes should be obtained to look for paraneoplastic syndromes, as already discussed. The presence of hyponatremia is considered an adverse prognostic indicator. Elevated •st?rum lactate dehydrogenase (LDH) indicates increased tumor mass and cell turnover and is an adverse prognostic indicator. Abnormal liver function findings raise the possibility of hepatic metastasis and may provide a

clue to the cause (eg, biliary outflow obstruction versus parenchymal liver metastasis).

## 2. Staging workup of SCLC.

Investigations are performed to identify limited-stage disease (ie, potentially curable and requiring the addition of radiotherapy to its management), as well as to assess organ function before starting therapy. The purpose of the staging workup is to determine the prognosis and management of SCLC. Staging workup of SCLC is as follows:

- - Complete history and physical examination
- -Chest x-ray
- - CT scans of chest and abdomen. Evaluation via CT scan of thorax (lungs and mediastinum) and commonly involved abdominal viscera (ie, liver, adrenals) is the minimum requirement in standard staging workup of SCLC.
- - CT/MRI scan of brain. Brain metastasis may be present in as many as 10% of patients at diagnosis and may be occult in 5% of patients. Even though obtaining imaging scans of brain in all patients with controversial diagnosis, the policy of most authors is to obtain a scan of the brain for adequate staging.
- - Positron emission tomography (PET) scanning still is under evaluation for lung cancers and, to date, has had its greatest application in NSCLC, in which it

is used to more accurately stage patients prior to anticipated surgery.

- - *Bone scan. Bone is a common site of metastasis for SCLC, and a radionuclide bone scan should be obtained to identify bone metastases. Since some benign etiologies also can cause abnormalities on bone scan, obtaining plain radiographs of abnormal areas for radiographic correlation is important. Bone metastases from SCLC are predominantly osteoblastic, and a bone scan is superior to plain radiographs in detecting osteoblastic lesions. Bone scans should be obtained in all patients with SCLC at diagnosis or during follow-up if new bone symptoms develop or if serum calcium or alkaline phosphatase level is elevated.*
- - MRI scans are not part of the routine staging workup of SCLC, even though they have been shown to detect abnormal bone marrow signal in patients with bone marrow metastasis. MRI scans have an increased ability to detect disease in proximity to neurovascular structures. MRI examination is considered standard in the workup of patients in whom spinal cord compression is suspected.
- - Thoracentesis. The presence of malignant pleural effusion upstages the disease to extensive stage, For adequate staging, pleural effusions should be aspirated and examined for malignant cells if no other sites of distant spread are identified. If a large symptomatic pleural effusion Is present, therapeutic thoracentesis provides symptomatic relief. In patients with resistant, relapsed, or non-responding disease, thoracentesis can be combined with pleurodesisto prevent recurrence. The preferred agent currently is sterilized talc, which can be instilled either as a slurry or as a powder during pleuroscopy.
- - Bone marrow aspiration and biopsy if there are abnormalities in CBC or peripheral smear. Bone marrow examination is necessary in patients in whom myelophthisic anemia (leukoerythroblastic peripheral blood) is suspected.
- - CBC with differential serum electrolytes (including calcium), renal function studies, and liver function tests all are part of the routine staging workup, and in some cases they may identify the site of metastasis, eg, elevated serum calcium

level with bone metastasis. These tests also are important to assess organ function prior to starting therapy.

- Serum LDH and sodium levels also provide prognostic information. Increased uric acid levels may indicate the possibility of rapid tumor lysis syndrome with therapy.

### ***Differential diagnosis***

The major differential diagnoses of SCLC are Bronchogenic cyst, Neurogenic tumors, Teratodermoid tumor, Thymoma, Vascular aneurysm, Esophageal lesions, and other causes of mediastinal and hilar masses. Other causes of mediastinal mass include the following: (1) Lymphadenopathy from other malignant lesions (Lymphoma, Leukemia, Metastasis from other cancers), and (2) Benign lymphadenopathy (Inflammatory processes such as tuberculosis, fungal infections, Sarcoidosis).

## **Treatment**

Patients with limited-stage disease are offered combined chemoradiotherapy, while those with extensive-stage disease usually are treated with chemotherapy alone.

**Surgery** plays little, if any, role in the management of SCLC, except in a small minority of patients who present with very early stage disease confined to lung parenchyma. If the diagnosis of SCLC is established before resection by nonsurgical means, ie, sputum cytology, bronchoscopy, or intrathoracic percutaneous needle biopsy, these patients should be offered chemotherapy and radiation as opposed to primary surgical resection.

Management of SCLC limited-stage involves combination chemotherapy, usually with a platinum-containing regimen, and thoracic radiation therapy. If the patient achieves a complete remission, he or she may be offered prophylactic cranial irradiation.

SCLC extensive-stage remains incurable with current management options, and patients are treated with combination chemotherapy. Several chemotherapy

combinations are active in SCLC, but usually a platinum- containing regimen is chosen.

***Single-agent chemotherapy.*** Currently cisplatin, etoposide, vincristine, doxorubicin, and cyclophosphamide are the agents most commonly employed to treat previously untreated patients with SCLC. Scheduling of etoposide has been demonstrated to be important in achieving a higher response rate, and currently etoposide is given over 3 days. Protracted oral administration of etoposide has been an acceptable initial therapy in elderly patients with extensive-stage SCLC, especially in those with poor performance status, but recent studies suggest combination chemotherapy may be better than single-agent oral etoposide in those with good performance status.

More recently, the taxanes (paclitaxel) and topotecan have emerged as active agents in previously untreated patients with SCLC.

***Combination chemotherapy.*** Combination chemotherapy is accepted widely as being associated with superior response rates and survival. The combination of cisplatin and etoposide (PE), or the combination of cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV) currently is the most widely used regimen in both limited- and extensive-stage SCLC.

***High-dose chemotherapy with bone marrow or stem cell transplantation.*** The available data do not support the use of such an approach because it has not yielded better survival rates than standard management and is associated with greater immediate and delayed toxicity.

***Radiation therapy*** is used only to palliate symptoms, if required (eg, for painful bone metastases). Response rates are excellent, but patients invariably relapse. Prophylactic cranial irradiation is used more frequently. Until recently, the use of prophylactic cranial irradiation (PCI) was controversial. Several randomized trials showed a decrease in CNS relapse rate with PCI but no survival advantage. Additionally, patients receiving PCI had a higher incidence of neuropsychiatric dysfunction than those who did not receive PCI. Arriagada et al recently reported a meta-analysis of randomized trials of PCI in limited-stage SCLC and showed a



5% overall survival advantage in those receiving PCI. Even though such an analysis has inherent limitations, PCI currently is offered to patients with limited-stage SCLC who have achieved complete remission after having completed the full chemoradiotherapy regimen.

***Surgical care.*** Most patients with SCLC are treated nonsurgically. The exceptions are the relatively small number of patients (<5%) who present with very early stage disease confined to the lung without any lymph node involvement. Such patients usually undergo resection of lung tumors as the initial diagnostic procedure. Even in these patients, surgery alone is not considered curative, and they should be offered adjuvant chemotherapy.

## **Prognosis**

Extensive-stage SCLCs are incurable, and patients with extensive disease have a median survival duration of less than 1 year. Even patients presenting with localized disease (ie, limited stage) have a median survival duration of less than 2 years. The 5-year survival rate for SCLC is less than **20%**.

## ***Questions for self control***

1. What place does lung cancer take in the structure of oncological diseases? Give a characteristic of it.
2. Name two main morphological forms of lung cancer.
3. Enumerate the most often paraneoplastic syndromes at the small-cell lung cancer.
4. Enumerate the symptoms related to intrathoracic spread of the tumor at the small-cell lung cancer.
5. Give a characteristic of the limited-stage of the small-cell lung cancer.
6. Give a characteristic of the extensive-stage of the small-cell lung cancer.
7. What method of treatment is the main at the small-cell lung cancer?

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**LUNG CANCER (NON-SMALL CELL LUNG CANCER)**Non-small cell lung cancer (NSCLC) accounts for approximately 75-80% of rill lung cancers.

## **Etiology**

The predominant cause of NSCLC, as of SCLC, is *tobacco smoking*.

Unlike many other malignancies, whose causes are largely unknown, I he cause of lung cancer is tobacco smoking in as many as 90% of patients (78% in men, 90% in women). For a person who currently smokes, the risk of developing lung cancer is 13.3 times; but who had begun smoking being 15 years old the risk is 24 times that of a person who has never smoked. **riu>** risk also varies with the number of cigarettes smoked. The risk ranges from 10 times higher than controls for those smoking 20 or fewer cigarettes per day to 20 times higher than controls for those smoking more than 20 cigarettes per day. Once a person quits smoking, the risk of lung cancer increases for the first 2 years and then gradually decreases, but it npver returns to the same level as that of a person who has never smoked. As many as 15% of the lungcancers in persons who do not smoke are believed to be caused by secondhand smoke (passive smoking).

Because not all persons who smoke develop lung cancer and because not all patients with lung cancer have a history of smoking, other factors, Including genetic susceptibility, also play role.

***History of interstitial lung disease.*** The presence of concomitant chronic obstructive bronchitis and tuberculosis is a risk factor for lung cancer. As many as 6-12% of patients with pneumosclerosis and pneumoconiosis develop bronchogenic carcinoma (adenocarcinoma).

***Asbestos.*** Asbestos exposure has been shown to be strongly associated With the causation of lung cancer, malignant pleural mesothelioma, and pulmonary fibrosis. The silicate type of asbestos fibeI is an important carcinogen. Asbestos exposure increases the risk of developing lung cancer liy <is much as 5 times. Tobacco smoke and asbestos exposure act synergistically, and the risk of developing lung

cancer for persons who currently smoke tobacco and have a history of asbestos exposure approaches 80-90 times that of control population.

**Radon.** Radon is an inert gas produced as a result of uranium decay. Radon exposure is a well-established risk factor for lung cancer in uranium miners. Approximately 2-3% of lung cancers annually are estimated to be caused by radon exposure.

**Other environmental agents.** Aromatic polycyclic hydrocarbons, beryllium, nickel, copper, chromium, cadmium, and diesel exhaust all have been implicated in causing lung cancer. Dietary fiber and vegetables have been suggested as a protective barrier from lung cancer.

## **Pathophysiology**

The base of pathogenesis of central lung cancer is the metaplasia of bronchial epithelium due to irritant actions caused by smoking (N-nitro- amines and aromatic polycyclic hydrocarbons, which act as carcinogens), and chronic inflammatory processes. The base of peripheral lung cancer is the scars on the lung parenchyma caused by tuberculosis and/or fibrosis.

## **The Pathologic evaluation**

**Histologic findings.** The origin of lung cancer is the basal cells of bronchial epithelium. NSCLC includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Sometimes lung cancers can exhibit 2 or more histologic patterns. **Adenocarcinoma** is the most common type of NSCLC, representing 35-40% of all lung cancers, usually occurring in a peripheral location within the lung and arising from bronchial mucosal glands. Adenocarcinoma manifests itself as a scar carcinoma. This is the lung cancer histological type observed most commonly in persons who do not smoke. Adenocarcinoma appears to be increasing in incidence, especially in women, compared with squamous cell carcinoma, which was previously the most common type of NSCLC. Histologically, adenocarcinomas form glands and produce mucin.

The World Health Organization classification *of* lung cancer divides adenocarcinomas into (1) acinar, (2) papillary, (3) bronchoalveolar, and (4) mucus-secreting. Bronchoalveolar carcinoma is a distinct clinicopathologic entity that appears to arise from type II pneumocytes, grows along alveolar septa, and may manifest as a solitary peripheral nodule, multifocal disease, or a pneumonic form, which can spread rapidly from one lobe to another.

Advanced stages of adenocarcinomas are associated with worse prognoses than squamous cell carcinomas, with the exception of T1 N0 M0 tumors.

***Squamous cell carcinoma*** accounts for 25-30% of all lung cancers. Squamous cell carcinoma has a distinct dose-response relationship to tobacco smoking and usually develops in proximal airways, progressing through stages of squamous metaplasia to carcinoma in situ. Well-differentiated squamous cell carcinomas contain keratin pearls, while poorly differentiated squamous cell carcinomas may stain positive for keratin.

***Large cell carcinoma*** is the least common of all NSCLCs, and accounts for 10-15% of lung cancers. Histologically, this type has sheets of highly atypical cells with focal necrosis, with no evidence of keratinization (typical of squamous cell carcinoma) or gland formation (typical of adenocarcinomas). It is composed of large cells with prominent nucleoli, and no mucin production or intercellular bridging is identified.

A variant of ***large cell carcinoma*** has been identified; it contains **neuroendocrine** features and is called large cell neuroendocrine carcinoma, large cell neuroendocrine carcinomas are associated with a worse prognosis than large cell carcinomas.

**Site.** The relative frequency of lung cancer is 3:2 in the right compared **With** the left lung and in the upper lobe compared with the lower lobe. Lung cancer is divided further into central and peripheral forms. Determination of central or peripheral forms is due to the size of the affected bronchial tube.

Central lung cancer affects main bronchus and has the following anatomical forms: ***endobronchial, peribronchial nodal, and peribronchial ramified forms.***

Squamous cell carcinomas occur predominantly in a central location, whereas adenocarcinoma presents in approximately 50% of patients as a peripheral lesion.

Peripheral tumors arising endobronchially are located in segmental or lobar bronchi.

Fewer than 4% of cancers arise in the apex of the upper lobes, and fewer than 1% arise from the trachea.

## **Staging and TNM classification**

The staging of all NSCLC follows the TNM system. The TNM system is used for all lung carcinomas except small cell lung carcinomas.

### ***Primary tumor (T)***

***TX*** — Positive malignant cytology results, no lesion seen ***T1*** —

Diameter smaller than or equal to 3 cm

***T2*** — Diameter larger than 3 cm — Extension to pleura, chest wall, diaphragm, pericardium, within 2 cm of carina, or total atelectasis

***T3*** — Invasion of mediastinal organs (eg, esophagus, trachea, great vessels, heart), malignant pleural effusion, or satellite nodules within the ***primary lobe***.

### ***Regional lymph nodes (N)***

***N0*** — No lymph nodes involved

***N1*** — Ipsilateral bronchopulmonary or hilar nodes involved

***N2*** — Ipsilateral mediastinal or subcarinal nodes

***N3*** — Contralateral mediastinal, hilar, any supraclavicular nodes involved

### ***Distant Metastasis (M)***

***M0*** — No metastases

***M1*** — Metastases present

For TNM staging NSCLC is divided into 4 stages, with further subdivision of stages I-III into A and B subtypes. These stages have important therapeutic and prognostic implications, which are discussed later. The current TNM staging system came into effect in 1997 after revision for stage groupings for stages I,

II, and III (table 4.1).

**Table 4.1.**

***Stage grouping for non-small cell Lung Cancer***

<b>Stage</b>	<b>TNM</b>
<b>IA</b>	<b>T1N0M0</b>
<b>IB</b>	<b>T2N0M0</b>
<b>IIA</b>	<b>T1N1M0</b>
<b>IIB</b>	<b>T2N1M0orT3N0M0</b>
<b>IIIA</b>	<b>T1-</b>
<b>IIIB</b>	<b>T4orTany N3M0</b>
<b>IY</b>	<b>AnyTanyNMI</b>

***Clinical Manifestation***

Approximately 90% of lung cancers manifest with symptoms produced by:

1. the primary tumor;
2. locoregional spread;
3. metastatic disease;
4. ectopic hormone production.

But, there are no pathognomonic symptoms associated with lung cancer.

1) The symptoms and signs produced by the primary tumor depend on its location (ie, central, peripheral, or Pancoast tumor).

**Central tumors** are diagnosed in 70-85% of all NSCLC- They produce symptoms of cough, dyspnea, atelectasis, postobstructive pneumonia, wheezing, and hemoptysis. Centrally located obstructing tumors can

c. cause collapse of the entire lung with an absence of breath sounds on the side of the lesion. It is the type most often associated with hypercalcemia.

**Peripheral tumors** are diagnosed in 15-30% of all NSCLC. Most peripheral tumors are adenocarcinomas or large cell carcinomas. Adenocarcinoma may

manifest as multifocal tumors in a bronchoalveolar form, and, in addition to *t* causing cough and dyspnea, can cause symptoms due to pleural effusion and severe pain as a result of infiltration of parietal pleura and the chest wall.

Peripheral lesions can cause individual segments or lobes to collapse, leading to findings of dullness to percussion and/or decreased breath sounds. *Pleural effusions give rise to* characteristic findings of dullness and decreased breath sounds, depending on the size. Bronchoalveolar carcinoma is a distinct subtype of adenocarcinoma with the classic manifestation as an interstitial lung disease. This subtype may manifest as a solitary peripheral nodule, multifocal disease, or a rapidly progressing pneumonic form. A characteristic finding in persons with advanced disease is voluminous watery sputum.

Large cell carcinoma of lung typically manifests itself as a large peripheral mass on a CXR. Patients with large cell carcinoma are more likely to develop gynecomastia and galactorrhea.

A **Pancoast tumor** (superior sulcus tumor) is a rare form (1%) of broncho- yonic carcinoma that arises in the superior sulcus of the lung apex. The most common tissue type is squamous cell carcinoma, but adenocarcinoma also may occur at this site. These tumors often lead to invasion of the pleura and rib, producing shoulder pain that is often treated as musculoskeletal pain. Involvement of the lower roots of brachial plexus causes arm pain and paresthesias in ulnar nerve distribution. The tumor may spread to the sympathetic ganglion, leading to Horner syndrome, which manifests as ipsilateral enophthalmos, miosis, partial ptosis, and anhidrosis. Symptoms due to locoregional spread. These symptoms can include superior vena cava obstruction, paralysis of the recurrent laryngeal nerve, and phrenic nerve palsy, causing hoarseness and paralysis of the diaphragm; pressure on the sympathetic\* plexus, causing Horner syndrome (**Pancoast** tumor); dysphagia resulting from esophageal compression; **and** pericardial effusion. Superior vena cava (CVC) obstruction syndrome is **commonly** i .used by small cell carcinomas, but any centrally located tumor **or** mediastinal spread can give rise to superior vena cava syndrome. This results from obstruction of blood flow to the heart from



the head and neck regions and upper extremities due to tumor compression of the superior vena cava.

*Superior sulcus tumors* (Pancoast tumor) can cause compression of the brachial (the cervical sympathetic) plexus roots as they exit the neural foramina, resulting in intense, radiating neuropathic pain in the ipsilateral upper extremity. Superior sulcus tumors are located at the apex of the lung, and can compress the cervical sympathetic plexus, causing classic Horner syndrome. Findings include ipsilateral ptosis, miosis, and anhidrosis (ie, lack of sweating).

2) Symptoms of metastatic disease depend on location of metastases.

3) Paraneoplastic syndromes caused by ectopic hormone production.

Squamous cell carcinomas are more likely to be associated with hypercalcemia due to parathyroidlike hormone production. Clubbing and hypertrophic pulmonary osteoarthropathy and the Trousseau syndrome of hypercoagulability are caused more frequently by adenocarcinomas.

## **Diagnostics**

In diagnostics of lung cancer there is the following strategy: apart from a handful of asymptomatic patients, in whom lung cancer is diagnosed incidentally, virtually all patients with lung cancer are symptomatic at presentation.

**Chest X-ray (CXR).** A chest radiograph is usually the first test ordered in patients in whom a lung malignancy is suggested. If the tumor is clearly visible and measurable, a CXR can sometimes be used to monitor response to therapy. The most common findings are described below.

1. CXR findings in central form of lung cancer.

A. *Bronchial stenosis.* Bronchial stenosis and poststenotic changes are common because most non-small cell carcinomas demonstrate intraluminal growth. Narrowing of the main bronchi or a complete cutoff can be identified on chest radiographs. Development of the main X-ray symptoms is connected with disturbance of the lung ventilation. Exophytic endobronchial lesion

commonly leads to partial (fig. 4.1) or complete (fig. 4.2) atelectasis and is the most common sign of bronchogenic carcinoma. Complete endobronchial obstruction can sometimes produce distal mucoid impaction, which may be visible on plain radiographs as a tubular or branching opacity.

- B. Radiographic *signs* include patchy irregular or homogeneous opacities in a lobar or segmental distribution. A loss of lung volume may be seen, as well as displacement of interlobar fissures, mediastinum, diaphragm, and the ribs.
- D.C *Postobstructive pneumonia* may be identified in a segmental or lobar distribution. In patients with recurrent pneumonia, bronchogenic carcinoma is suggested unless proven otherwise. Regional hyperlucency. Partial stenosis of segmental bronchus leads to hypoventilation of corresponding lung segment. An endobronchial lesion reduces the ventilation despite normal or increased air volume. As a result, hypoxic vasoconstriction reduces perfusion, and attenuation is seen as hyperlucency on chest radiography.
- E. *Hilar mass*. Central bronchogenic carcinomas manifest added opacity in the hilar region. In the early stage, the tumor may fill the lateral concavity of the hilar shadow, and in the advanced stage, all hilar structures are obliterated. Infiltration of lymphatics with bronchogenic carcinomas may be demonstrated as linear opacities radiating from the hilar mass into the lung periphery.

## 2, CXR findings in peripheral *form* of lung cancer.

Peripheral form has the following clinico-anatomical types:

- solitary round pulmonary nodule;
- similar pneumonia type;
- Pancoast tumor.

The main X-ray symptom is the ***solitary round pulmonary nodule*** (fig. 4.3). But a solitary pulmonary nodule is benign in as many as 60% of patients in some cases. In these cases solitary pulmonary nodule may be relatively well margined and appears as a rounded lung opacity. All patterns of calcification except eccentric or scattered punctate (stippled) calcification are associated with a

benign lesion. Procuring and identifying the lesion on previous chest radiographs is extremely important. This may help establish the doubling time interval for the nodule. A doubling time of 30-365 d.iys commonly is associated with a malignancy.

Other possible signs of peripheral lung cancer include the following: tumor diameter more than 3cm, Rigler notch sign (a notch on the nodu- It\* corresponding to the vascular supply), radial striated markings at the nodular margin (termed corona radiata), thick-walled cavity, eccentric cal- i fication.

The CXR sings of nonresolving pneumonia may occur both in central and peripheral forms of lung cancer. An ill-defined homogeneous or patchy consolidation in a segmental or non-segmental distribution may lie\* an indication of bronchogenic carcinoma. Patients with these findings of ten are treated initially for pneumonia; the lack of response to antibiotic therapy suggests the diagnosis of a malignancy. The opacity may contain air bronchograms and air alveolograms. This presentation is often seen with adenocarcinoma and bronchoalveolar carcinoma.

3. Mediastinal lymph node enlargement. Metastases to paratracheal, tracheobronchial, peribronchial, aortopulmonary, and subcarinal lymph nodes may be identified on chest radiographs. The radiographic signs include a widened mediastinum, an increase in the right paratracheal stripe, a convex margin of the mediastinum, an absence of concavity in the aortopulmonary window, and splaying of carina.

***Sputum cytologic studies.*** Centrally located endobronchial tumors exfoliate malignant cells into sputum. Therefore, sputum cytology can be a quick and inexpensive diagnostic test, if results are positive. Sputum cytologic studies in the suspicion of lung cancer can be performed as obligatory method. A positive finding for malignancy from a cytologic specimen is accurate in as many as 90% of cases, but any distinction between different histologic subtypes is not accurate.

***Bronchoscopy.*** When a central lung cancer is suggested, bronchoscopy provides a means for direct visualization of the tumor, allows determination of the

extent of airway obstruction, and allows collection of pathologic material under direct visualization. Fiberoptic bronchoscopy has the advantage of providing direct visualization of the bronchial tree. Diagnostic material can be obtained with direct biopsy of the visualized tumor, bronchial brushings and washing, and transbronchial biopsies.

***Biopsy.*** This procedure is preferred for tumors located in the periphery of the lungs because peripheral tumors may not be accessible through a bronchoscope. Diagnostic material can also be obtained from other abnormal sites (eg, enlarged palpable lymph nodes, liver, pleural and pericardial effusions).

***Serum chemistries.*** The most informative test for the lung cancer diagnosis is the establishment of the increased level of CA-19-9.

***A complete staging workup for NSCLC*** should evaluate the extent of disease.

***Staging work-up for NSCLC.***

*Complete history and physical examination.*

*Ultrasound or Computer Tomography (CT) scan.* Because common sites of spread of a NSCLC include the liver and adrenals, an ultrasound scan of the upper abdomen is the minimum standard for a staging workup for a person newly diagnosed with NSCLC.

*Complete blood cell counts.* This should be obtained in every patient, especially before instituting chemotherapy.

*Liver and kidney functions tests* by electrolytes and renal function studies. Because of the propensity of lung cancers to cause paraneoplastic syndromes, serum electrolyte levels are evaluated.

*A CT scan or MRI of the brain* may be required if neurological symptoms or signs are present. Most thoracic surgeons perform imaging of the brain before attempting definitive resection of a lung malignancy.

*Bone scintigraphy.* The skeletal system is another common site of metastases for lung cancers. If patients report bone pain or if their serumcalcium and/or alkaline phosphatase levels are elevated, a bone scan should be obtained to search for bone metastases.

*Positron emission tomography (PET)* scanning is approved for the workup of solitary lung nodules. PET scanning is useful for searching for systemic spread, if other diagnostic modalities cannot clarify an abnormality that (may change the treatment of the patient's condition.

*MRI* is most useful when evaluating a patient in whom spinal cord compression is suggested. In addition, brain MR! has a greater sensitivity than C T scan for detection of central nervous system metastasis.

Information obtained from these tests can then be used to guide further testing (eg, imaging studies): invasive staging procedures such as mediastinoscopy and mediastinotomy may be required to assess mediastinal lymph nodes In patients who are candidates for potentially curative surgical resection.

*Mediastinoscopy* is usually performed to evaluate the status of enlarged mediastinal lymph nodes (seen on CT, X-ray or ultrasound scan) before attempting definitive surgical resection of lung cancer. *Thoracoscopy* is usually reserved for tumors that remain undiagnosed *after* bronchoscopy or biopsy. Thoracoscopy is also an important tool in the management of malignant pleural effusions.

#### ***Complications of lung cancer:***

- Bleeding from destroyed tumor of large bronchus.
- Spinal cord compression.
- Metabolic complications. The most common metabolic complication associated with NSCLC is hypercalcemia, which is usually associated with squamous cell carcinoma. Other findings can include hyponatremia, and syndrome of inappropriate secretion of antidiuretic hormone and they should be considered.

#### **Treatment**

All share similar treatment approaches and prognoses but have distinct histologic (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) and clinical (tumor location) characteristics.

The radical method of lung cancer treatment is surgery. But, because most lung

cancers cannot be cured with currently available therapeutic modalities, the appropriate application of skilled palliative care is an important part of the treatment of patients with NSCLC.

***Surgical care.*** Surgical resection provides the best chance of long-term disease-free survival and possibility of a cure. In stages I and II NSCLC, surgical resection is almost always possible unless comorbid medical conditions are present or the patient's respiratory reserve is so low that the intended resection will leave the patient with crippling respiratory dysfunction. The role of surgery for stage III disease is controversial. Patients with completely resectable primary tumors (ie, T4N0) have a much better prognosis than those with spread to ipsilateral mediastinal or subcarinal lymph nodes (ie, N2), signifying that spread beyond the primary tumor is associated with a poor prognosis. Patients with stage IIIB or IV tumors are generally not surgical candidates.

***Surgical procedures.*** The standard surgical procedures for lung cancer include lobectomy (in *peripheral tumors without lymph node metastases*), lobectomy with mediastinal lymph nodes dissection (in *peripheral tumors with lymph node metastases*), or pneumonectomy (in *central lung cancer*). Wedge resections are associated with an increased risk of local recurrence and a poorer outcome.

Unresectable NSCLC is treated with chemotherapy or a combination of chemotherapy and radiation therapy.

***Chemotherapy.*** Only 30-35% of patients with NSCLC present with sufficiently localized disease at diagnosis to attempt curative surgical resection (stages IA and IB, IIA and IIB, and IIIA). Approximately 50% of patients who undergo surgical resection experience local or systemic relapse; thus, approximately 80% of all patients with lung cancer are considered for chemotherapy at some point during the course of their illness.

Chemotherapy may be considered as part of multimodality therapy for locally advanced NSCLC and is used alone in the palliative treatment of stage IIIB NSCLC (owing to malignant pleural effusion) and stage IV NSCLC.

Patients with good performance status and less than 10% body weight loss are

good candidates for chemotherapy. In such patients, platinum-based chemotherapy provides better palliative benefits than the best supportive care and may provide a modest survival advantage. Commonly used regimens include carboplatin-paclitaxel, cisplatin-gemcitabine, and cisplatin-vinorelbine, all of which achieve similar results.

**Biologic therapy.** With the increased understanding of molecular abnormalities in lung cancer, recent research efforts have focused heavily on identifying molecular targets and using this knowledge to develop molecular-targeted therapies. One such abnormality, which is common in NSCLC, is overexpression of the epidermal growth factor receptor (EGFR). Gefitinib ("Iressa") is one such approach and represents a class of EGFR pathway inhibitors that act intracellularly to block activation of EGFR pathway.

**Radiation therapy.** Radiation therapy alone used as local therapy has been associated with **5-year** survival rates of 12-16% in early-stage NSCLC (Ie, T1 and T2 disease).

In the treatment of stage I and stage IIA NSCLC, radiation therapy alone is considered only when surgical resection is not possible because of limited pulmonary reserve or the presence of comorbid conditions. The role of radiation therapy as surgical adjuvant therapy after resection of the primary tumor is controversial. Radiation therapy reduces local failures in completely resected (stages IIB and IIIA) NSCLC but has not been shown to improve overall survival rates.

**Combined chemoradiotherapy.** The current standard of care in the management of good-risk (ie, Karnofsky performance score of 70-100, minimal weight loss) patients with locally advanced NSCLC is combined-modality therapy consisting of platinum-based chemotherapy and radiation. This results in statistically significant improvement in both disease-free and overall survival rates compared with either modality used alone.

Current research efforts focus on the use of chemotherapy (with or without radiation therapy) in the neoadjuvant setting to try to improve resectability.

## **Prognosis**

Estimated 5-year survival rates are as follows: Stage IA -75%; Stage IB -55%; Stage IIA -50%; Stage IIB -40%; Stage IIIA-10-35%; Stage IIIB — Less than 5%; Stage IV — Less than 5%. The main cause of death of patients after radical treatment at long-term period is distant metastases.

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