

## Lung Cancer: Invasion and Metastasis, Paraneoplastic Syndromes and Treatment of Mesothelioma, Small-cell Lung Carcinoma (SCLC) and Non-small Cell Lung Cancer (NSCLC)

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**Lung cancer is notoriously one of the most common lethal tumors in the medical world. It is essential to be accustomed to the basic details about this disease. In this article, you will gain all exam-relevant information about the epidemiology, pathogenesis and clinical recognition of lung cancer.**



### Overview

It is important that one is familiar with the following sets of tumors encountered in the lung:

Type	Explanation
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<a href="#">Lung cancer</a>	Malignant cancers arising from respiratory tract epithelium
Lung metastases	Malignant cancers arising outside of the lung that have spread to affect the lung
Mesothelioma	Primary malignant cancer of the mesothelium
Rarer lung tumors	Unusual benign/ malignant cancers of the lung

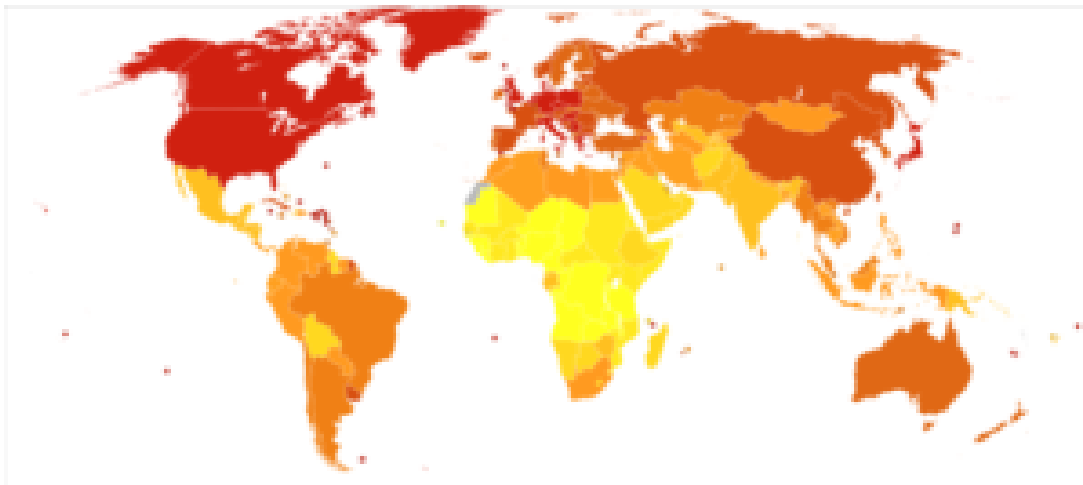
Lung cancer is divided into two types: non- small cell and small cell lung cancers based on histological constitution.

## Epidemiology of Lung Cancer

Lung cancer is the commonest fatal cancer. It accounts for 13 % of all cancers, but 90% of cases are fatal. The incidence increases with age and lung cancer are rare before 50 years of age. The peak incidence age is about 75-79 years. The incidence of lung cancer in males is about 500/100,000 per year; while in females it has substantially increased to about 400/100,000 per year.

97 % of lung cancers are carcinoma of the lung that arises from uncontrolled growth of epithelial cells. 80-85 % of lung cancers are non-small cell lung cancer.

The increase in lung cancer incidence in females in the recent past has been attributed to the escalated smoking tendency in this population. In the UK the lifetime risk of an individual developing lung cancer is about 1 in 14 in men and about 1 in 19 in women.



[Image](#): "Trachea, bronchus, lung cancers world map-Deaths per million persons-WHO2012" by Chris55. License: [CC BY-SA 4.0](#)

## Histological Types of Lung Cancer

The various histological types of lung cancer can be mentioned as follows::

### Non-small cell lung cancer

80% of cases are non-small cell lung cancers. There are 3 predominant histological types. **Squamous cell carcinoma** contributes to about 30% of all patients with lung cancer; squamous cell carcinoma is mainly a disease of the central airways. These tumors arise from the respiratory epithelium in the central region of the lungs most commonly in proximal bronchus.

**Adenocarcinoma** is responsible for about 40% of all lung cancer patients; these are peripheral tumors. They arise from the mucosal glands in a peripheral location in the lung. It is seen mostly in persons who are nonsmokers. **Large cell cancer** contributes to about 10% of all cases of lung cancer. They inflict the peripheral lung and are histologically varied in nature atypical cells that have focal necrosis.

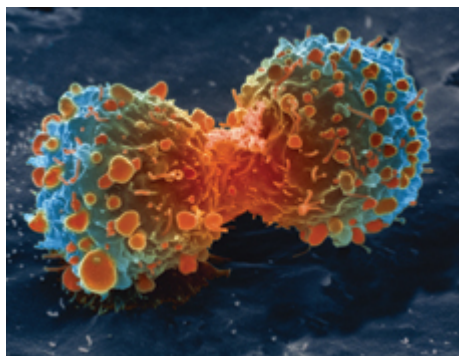
## Small cell lung cancer

Small cell lung cancer claims about 1/5<sup>th</sup> of all cases of lung cancer. These are **centrally placed and arise from the peribronchial epithelium**. They are ill famous for their rapid growth and early metastasis to mediastinal lymph nodes, bones, adrenal glands, liver, and brain. Small cell lung carcinoma is sensitive to chemotherapy. Surgery is not curative in these patients.

## Pathogenesis of Lung Cancer

Sequential acquisition of [multiple mutations and gene duplications](#) affecting the tumor suppressor genes and the oncogenes such as **p53, K-ras, and EGFR** ultimately culminates into lung cancer. About 90% of cases are due to cigarette smoking. Also, asbestos exposure works in synergy with smoking.

**Other risk factors which act as harbingers of lung carcinoma are mentioned as follows:**



[Image](#): "Lung cancer cell during cell division" by the United States: National Institutes of Health. License: Public Domain

- Radon gas exposure
- Uranium exposure
- Radiotherapy to the lungs
- [Family history](#)
- Chemical exposure such as diesel exhaust

Intriguingly, the incidence of lung cancer in patients with [COPD](#) is increased over and above the effects of smoking. It is of great significance to note that not all lung cancers are due to smoking alone. Adenocarcinoma; for instance, is seen in non-smoking middle-aged women.

## Clinical Recognition of Lung Cancer

By United Kingdom standards; the model age group is 75 to 79 years with incidence more in males as already mentioned above. In this scenario; current or previous smoking

clubbed with the following factors with radiological evidence of a patch in the left upper part of the lung is potential lung cancer. Multiple different clinical symptoms can present to different specialties.

**The same is mentioned below:**

- Aged over 50 years
- Lung mass on an X-ray
- Bone pain
- Weight loss, cachexia, anorexia, neurologic dysfunction, and fatigue

A few weeks history of tumor symptoms such as lung symptoms, those due to local invasion, distal metastases and paraneoplastic symptoms. The primary lung disease usually presents with a short history of a few weeks duration.

**The most frequent modes of presentation of the primary disease can be briefly touched upon as follows:**

Symptom	Explanation
New cough	Most frequent local symptom
Haemoptysis	<ul style="list-style-type: none"> <li>• Associated with central tumors of airway origin</li> <li>• Massive and occasionally fatal in nature</li> </ul>
Asymptomatic lung mass	<ul style="list-style-type: none"> <li>• More likely to be adenocarcinoma</li> <li>• Squamous cell carcinoma usually presents as a central mass; while a central mass with large nodes is more typical of small cell lung cancer(SCLC)</li> </ul>
<a href="#">Shortness of breath</a>	<ul style="list-style-type: none"> <li>• Slow insidious progressive shortness of breath over weeks is a feature of obstruction of large airways by the tumor either by infiltration or by compression</li> <li>• Associated clinical signs are fixed monophonic wheeze, lobar or total lung collapse, and distal pneumonia</li> </ul>
Systemic symptoms	<ul style="list-style-type: none"> <li>• Classic systemic symptoms of malignancy: weight loss, anorexia, fatigue, and malaise can appear within a few weeks of presentation</li> <li>• Eventually; a very morbid doomed cachexic appearance sets in</li> </ul>
Clubbing	This clinical sign may or may not be present.

There is a subtle but definite clinical-radiological association. Classic presentation if present; more often than not; the tumor can be localized to a particular part of the lung.

**Simple such instances can be mentioned as follows:**

Radiological feature	Clinical co-relation
Right upper lobe Collapse	Mostly secondary to central tumor blocking the right upper lobe bronchus. This leads to cough with occasional hemoptysis
Right apical mass	Presents with pain in arm and cough
Small right lung lesion	Often seen as an incidental finding; it is helpful if one gets a previous radiological image to compare the same. A new onset lesion along with a history of smoking is potentially a cancer lesion unless proved otherwise

Once the tumor leaves the lung borders; local invasion affects the lymph nodes first. Hilar and mediastinal lymph nodes by obstruction secondary to compression or infiltration can affect the surrounding vital neurovascular structures leading to respective pressure manifestations.

**A brief mention of the various modes in which local invasion can manifest is as follows:**

Structure affected	Manifestations
None	Asymptomatic masses
Superior vena cava obstruction in right-sided tumors	Arm and face edema with a headache, fixed engorged JVP and dilated superficial chest wall veins are the manifestations
Recurrent laryngeal nerve palsy on the left side	A hoarse voice is seen with <b>“bovine”</b> cough
Phrenic nerve palsy	Raised hemidiaphragm is present as seen on chest skiagram
Oesophageal obstruction	This results in dysphagia and higher frequency of aspiration
Tracheal or major bronchial obstruction	Dyspnoea with the collapsed lung is seen in patients with airway obstruction

Local invasion infrequently involves chest wall infiltration. Chest wall invasion is associated with excruciating pain radiating from shoulder to ulnar aspect of the arm to hand, rib destruction, and palpable firm non-tender mass. Invasion of the chest wall in cases of apical tumors results in a constellation of symptoms with the tumor being then called as the **“Pancoast’s tumor”**. They are basically squamous cell carcinomas or adenocarcinomas.

**The salient features of Pancoast’s tumor can be mentioned as follows:**

- Invasion of the [brachial plexus](#)
- Pain in the arm (T1 root)
- Wasting of the hand small muscles
- Horner’s syndrome (partial ptosis, meiosis, and enophthalmos)

Lung cancer can spread to a multitude of varied organs. Its tendency for early and wise metastasis is a significant quality which accelerates its lethal nature. While liver and brain metastasis are very frequently encountered; adrenal glands, bone, and cervical lymph nodes are also known to be affected occasionally.

**A short description of distal metastases is as follows:**

Organ with distal metastasis	Manifestations
<b>Brain</b>	Present as a space-occupying lesion, the symptoms are congruent with those secondary to raised intracranial pressure such as vomiting, nausea, headache, focal neurological signs, mental state changes and seizures
<b>Bone</b>	Bone metastasis is characterized by unbearable night pains, pathological fractures and cord compression in case of vertebral body involvement with an elevation of alkaline phosphatase
<b>Liver</b>	Hepatomegaly with pain, weight loss, anorexia, and nausea are encountered
<b>Cervical nodes</b>	Palpable hard mass in the neck may be the only complaint
<b>Lungs</b>	Lung parenchymal involvement may be seen on CT scan. It is not always associated with symptoms
<b>Pleura</b>	Effusion with dyspnea is seen
<b>Adrenal glands</b>	Usually asymptomatic; adrenal metastasis is a CT scan based diagnosis

## Paraneoplastic syndromes

Non-metastatic distal effects of cancer secondary to ectopic hormones and autoantibodies collectively constitute paraneoplastic syndromes. The significant

paraneoplastic syndromes associated with lung cancer and are induced by an alteration in the immune system responding to neoplasm and their clinical features can be mentioned as follows:

Cancer type	Paraneoplastic syndrome	Clinical features
All	<ul style="list-style-type: none"> <li>• Systemic disturbance</li> <li>• Hypercoagulability</li> <li>• Anemia of chronic disease</li> <li>• Dermatological</li> </ul>	<ul style="list-style-type: none"> <li>• Cachexia, anorexia, malaise, fatigue</li> <li>• DVT, PE, thrombocytosis</li> <li>• Low Hb</li> <li>• Gynaecomastia, acanthosis nigricans, dermatomyositis</li> </ul>
SCLC	<b>SIADH</b>	<ul style="list-style-type: none"> <li>• Hyponatremia</li> <li>• Confusion</li> <li>• seizures</li> <li>• coma</li> </ul>
	<b>Cushing's syndrome</b>	Cushingoid appearance, weakness, hypokalemia
	<b>Eaton Lambert syndrome</b>	Muscle weakness
	<b>Neurological</b>	Neuropathies, cerebellar syndromes, cognitive dysfunction
NSCLC	<b>Hypertrophic pulmonary osteoarthropathy</b>  <b>Hypercalcemia</b>	Clubbing, painful and tender wrists and ankles Polyuria, polydipsia, confusion, and hyperreflexia

## Differential Diagnosis of Suspected Lung Cancer

There are many conditions which can mimic lung cancer. The important differentials of lung masses are summarized as follows:

Differential	Example
Lung metastases from another type of cancer	<ul style="list-style-type: none"> <li>• Breast cancer</li> <li>• Prostate cancer</li> </ul>
Less common tumors of the lung	Carcinoid
Lung infection	<ul style="list-style-type: none"> <li>• TB: active disease or healed granulomas</li> <li>• Lung abscess</li> <li>• Fungal/ parasite infections</li> </ul>
Benign masses	<ul style="list-style-type: none"> <li>• Lung sequestration</li> <li>• Enfolded lung</li> <li>• Parenchymal scar</li> </ul>
Lung inflammatory conditions	<ul style="list-style-type: none"> <li>• Sarcoid</li> <li>• Vasculitis</li> </ul>

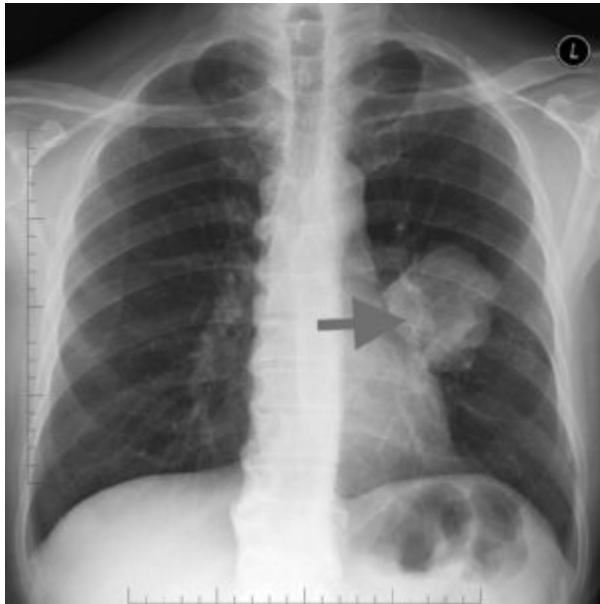
## Management and Treatment of Lung Cancer

3 important questions need to be addressed before one can start treating lung cancer. These questions are focused to determine the stage and histology of the disease to ultimately fathom the fact that whether the tumor is curable or not.

## Diagnosis

There is a multitude of diverse tests available to determine the stage of the disease. All patients with lung cancer should have a [chest X-ray](#) and CT of the chest, liver, and adrenals. One should look for size and local invasion extent, the presence of hilar and mediastinal nodes, lung and pleural metastases; and liver or adrenal gland metastases.

Blood tests are also required like Fbc, U+E, and LFT. One should look for raised ALP to rule out liver and bone metastases. Paraneoplastic syndromes and fitness for therapy are also related to these tests.



**Image:** "60-year-old male a chronic smoker presented with blood in sputum and breathlessness. Chest Xray showed a mass in the left lung and biopsy confirmed to be cancer" by Dr manikandan d. License: [CC BY-SA 3.0](#)

Selected patients according to the clinical presentation should have a neck USG. It has a role in case of palpable cervical nodes. A bone scan helps in identifying bone metastases and during a Spinal MRI, one should be wary of vertebral metastases or potential cord lesion to evaluate spinal cord compression. Also, a PET scan helps in the pre-operative assessment. A Pleural tap helps in evaluating pleural effusion.

To obtain a histological diagnosis; there are many methods of biopsy available. One tends to use the least invasive and maximally safe option. Often distal and safer lesions outside lung are typically biopsied. Mediastinal nodes are important for deciding on whether curative treatment is possible.

**The potential biopsy methods depending on the target lesion can be summarized as follows:**

Location of the lesion	Available biopsy techniques
Peripheral lung lesion	Ct guided percutaneous biopsy, surgical excision, sputum cytology, and bronchial washings
Proximal lung lesion	Bronchoscopy with bronchial biopsy, brushings, and washings for sputum cytology
Mediastinal lymph nodes	Endobronchial ultrasound-guided biopsy(EBUS) or surgical biopsy by mediastinotomy or mediastinoscopy
Cervical nodes	Ultrasound-guided percutaneous biopsy

Bone	CT guided percutaneous biopsy
Pleura	Pleural tap for cytology, CT or ultrasound-guided percutaneous biopsy of pleura
Adrenal	CT guided percutaneous biopsy
Liver	CT or ultrasound-guided percutaneous

Lung cancer staging is important as one can identify potentially curable disease through the stages. A simplified version of the complex TNM staging is as follows:

Score	1er Tumor size	Nodal involvement	Metastases
0	-	None	None
1	< 3 cm diameter	Ipsilateral hilar nodes	Any
2	3 to 7 cm diameter	Ipsilateral mediastinal nodes	-
3	> 7 cm diameter	Contralateral/extrathoracic nodes	-
4	Invading trachea, vessels, mediastinum, or spine		-

Functional capacity is also measured to select patients who can tolerate resection of lung

- 0: Fully active, able to carry on regular activity without restriction
- 1: cannot perform the physically strenuous activity but ambulatory and able to perform light or sedentary work (e.g., light housework, office work)
- 2: Ambulatory and can take self-care but unable to carry out any work activities in more than 50% of waking hours
- 3: Capable of performing only limited self-care, confined to a bed or chair more than 50% of waking hours
- 4: Completely disabled, totally dependent on others, incapable of performing self-care activities, totally confined to a bed or chair
- 5: Dead

**Potentially curable disease**

Only about 15% of patients with lung cancer achieve 70% 5-year survival if the tumor is resected.

Treatment for curable NSCLC in Stage I, II and III involves surgery followed by postoperative chemotherapy or radiotherapy. Stage I and II involves minimal surgical invasive approach. If a tumor is confined to one lobe; lobectomy is offered. If the tumor has crossed the oblique fissure; one thinks of pneumonectomy. If not fit for surgery; radical radiotherapy is used.

Treatment for incurable NSCLC involves palliative chemotherapy with a modest increase in life expectancy by about 6 months and dismal prognosis of less than 5 % 5-year survival.

**Palliative radiotherapy has a definite role in the treatment of incurable NSCLC in Stage IV in the following circumstances :**

- Pain due to local invasion
- Bronchial obstruction (can also be treated endobronchially)
- Haemoptysis
- Bone and brain metastases

**Other relevant treatment options in incurable NSCLC can be mentioned as follows:**

Treatment modality	Explanation
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High dose corticosteroids	Brain metastases and/or bronchial obstruction call for use of steroids
Targeted <a href="#">chemotherapy</a>	Newer targeted chemotherapy drugs such as EGFR inhibitors are very effective for selected patients

SCLC is a high volume disease often with metastases at presentation. SCLC is sensitive to chemotherapy and therefore not suitable for surgical resection. Treatment involves chemotherapy unless a patient has a poor performance status. Radiotherapy helps if the disease is restricted to one hemithorax. SCLC is known to relapse in a few months and median survival is around 15 months. Palliative treatment regime is the same as NSCLC.

## End of Life Care

About 90% of patients with lung cancer die due to cancer. As a consequence; end of life care is mandatory for almost all the patients. A multidisciplinary dedicated team works the best; inclusive of palliative care physician, lung cancer nurse specialist, community palliative care nurse, and respiratory physician and oncologist. Pain control is an important aspect of end of life care.

### **Few salient features of pain control can be mentioned as follows:**

- Initially short-acting agents such as Oramorph
- Titrate up until the pain is controlled
- Then swap with long-acting agents such as MST
- End-stage may need subcutaneous opiate pumps

## Mesothelioma

Mesothelioma denotes primary malignant tumor of the mesothelium. It is an aggressive tumor fatal to patients. It has a very poor prognosis. It typically affects middle-aged men with a history of asbestos exposure and has a lag phase from exposure to the disease of about 20-40 years. The risk of developing mesothelioma increases proportionately to the amount of inhaled asbestos fibers. Few professions ill-famous for asbestos exposure are dockers, engineers, shipbuilders, boilermakers; and those in building trades such as plumbers, carpenters, and electricians.

Early on; mesotheliomas present with exudative pleural effusion. Chest wall pain, weight loss, anemia, and malaise follow. Distinctive radiological features can be appreciated only at later stages

### **The same can be mentioned as follows:**

- Circumferential irregular pleural thickening with or without effusion
- Mediastinal surface involvement
- Marked loss of volume of affected lung

Pleural effusion in a patient with asbestos exposure is potentially mesothelioma unless proven otherwise. Diagnosis requires pleural biopsies; CT guided or thoracoscopic and often need repeating. Mesotheliomas are almost impossible to cure. With a median survival of 8 to 14 months; palliative radiotherapy and chemotherapy with opiate painkillers and occasional pleurodesis to prevent recurrent effusions are most of all that can be offered.

# Summary

Lung cancer, malignant cancer arising from the respiratory epithelium; is the **most fatal cancer of all times**. With an incidence of about 13 % of all cancers; it claims life in almost 90% of the cases. The incidence in females reflects a rising trend.

The major histological types of lung cancer are small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) NSCLC comprises 3 major groups:

- Squamous cell carcinomas
- Adenocarcinoma
- Large cell tumors

About 90% of cases are due to smoking.

Lung cancer symptoms include local symptoms such as a cough and breathlessness; and systemic features such as weight loss, malaise, neurological dysfunctions, and fatigue. Radiological features vary depending on the location of the tumor. Once the tumor trespasses the lung border; it invades the hilar and mediastinal lymph nodes first and then can cause pressure symptoms either by compression or by infiltration in surrounding structures such as the esophagus, superior vena cava, and the recurrent laryngeal nerve.

Invasion of the chest wall in cases of apical tumors results in a constellation of symptoms with the tumor being then called as the "[Pancoast's tumor](#)". Symptoms include pain in arm, hands and Horner's syndrome. Distal metastases can occur in diverse organs such as liver, brain, bone, and adrenals.

Non-metastatic distal effects of cancer secondary to ectopic hormones and autoantibodies collectively constitute paraneoplastic syndromes. Confirmation of histological grade, clinical assessment of the patient and ultimate understanding of the fact that whether or not the patient is curable is essential for comprehensive and holistic management of the patient.

Treatment for curable NSCLC involves surgery followed by postoperative chemotherapy or radiotherapy. SCLC responds to chemotherapy, assessed by functional capacity criteria and stages of cancer but it typically relapses and has a dismal prognosis. Mesothelioma is a malignant primary tumor of the mesothelium. Related to asbestos exposure; mesothelioma is almost impossible to cure and treatment is analogous to palliative care with chemoradiation.

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