Review Article

Carcinoma lung: Clinical presentation, diagnosis, and its surgical management

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Abstract

The aim of this article is to review the surgical management of lung carcinoma. Lung cancer is the most common cancer in the world, and a leading cause of death in men and women. By any conventional measure, the enormity of this global problem is immense. In some countries incidence and mortality rates have peaked and are beginning to decline. In many developing nations, the burden of disease is rising and will continue to rise because of aggressive tobacco industry marketing which is leading to a growing prevalence of cigarette smoking. This is also one of the major causes of cancer deaths in our Kashmir valley. The method of literature search was from articles published in PubMed and Google Scholar.

Key words: Carcinoma, clinical presentation, lobectomy, lung, surgical management

INTRODUCTION

Lung cancer is the most common cancer in the world, and a leading cause of death in men and second most common cause in women.[1,2] It is responsible for 1.3 million deaths worldwide.[3] It accounts for nearly 13% of all new cancer diagnoses in both sexes combined.[4]

The implications of these incidence and mortality trends are staggering in their own right, but perhaps even more so because of decades of confirmed epidemiologic evidence linking prolonged exposure to tobacco smoke as prime etiologic agent associated with lung cancer. Peto *et al.*, reported a 16-fold increase in cumulative lung cancer risk in persistent smokers.[5] World Health Organization (WHO) estimates that by year 2025 tobacco-related deaths worldwide will exceed 10 million annually, with lung cancer expected to contribute at least 30% of that total. Though rates of lung cancer in males are decreasing, there is a continuous increase in females. Even more disturbing is a recent increased incidence of non-small cell lung cancer in relatively young nonsmoking females.

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Lung carcinogenesis is known to occur from an accumulation of several genetic alterations, most commonly with p53 mutations and deletions on chromosomes 3p, 5q, 9p, 11p, and 17p. The frequency of these alterations is more common in smokers than in nonsmokers. Patients with a history of lung cancer are at increased risk for a second lung cancer at a rate of 1-2% per year. This rate is increased for those survivors who continue to smoke. Other agents found in the industrial environment, such as asbestos, coal tar fumes, nickel, chromium, arsenic, diesel exhaust, indoor radon, and radioactive materials, have also been related to the development of lung cancer. Zinc copper and selenium intake appear to be associated with decreased risk of lung cancer.[6]

Presentation: The presentation in lung cancer may be in the form of:

- Manifestation of a local disease
- Manifestation of a locally advanced disease
- Manifestation of extra thoracic spread
- Paraneoplastic syndrome.

MANIFESTATIONS OF LOCAL DISEASE

Asymptomatic

In its early stages, lung cancer is asymptomatic. The lung parenchyma is not generously supplied with pain fibers, and primary lung cancers can reach considerable size without causing any symptoms. It is particularly true for more peripheral lesions. Less than 5% of lung cancers are discovered in patients who have no symptoms of the disease. These lesions are often discovered during the investigation of an unrelated complaint, or on a chest radiograph done as part of a preoperative evaluation or as part of an extended physical examination.

Cough (70-90%)

Cough is an early symptom due to bronchial irritation. It may be produced by small tumor acting as a foreign body interfering with bronchial peristalsis or by ulceration of bronchial mucosa. Prolonged cigarette smoking produces paralysis of tracheobronchial cilia causing interference with bronchial peristalsis and with cleansing of the tracheobronchial tree. Cigarette smoking also produces bronchorrhea and excessive mucus. Cough and sputum are nonspecific, and their duration may vary from days to years. Sputum may become mucopurulent with secondary infection. In occasional cases, nonproductive cough may be due to invasion of the carina. Peripheral tumors arising from small bronchi and bronchioles may attain large size without producing cough. Cough with or without sputum occurs in between 70 and 90% of patients during the course of bronchogenic carcinoma.[5] Severe bout of cough may cause pneumothorax due to rupture of an emphysematous bleb, fainting (cough syncope), or even rib fracture.

Hemoptysis (25-40%)

Hemoptysis is coughing out of frank blood/blood clot or sputum tinged with blood. Blood streaking is due to ulceration of the bronchial mucosa by tumor and usually is rather minimal in degree. However, some patients report significant hemoptysis of 25-200 ml, related to rupture of bronchial veins or venules. Blood streaked sputum may vary in amount, frequency, and duration. Prompt diagnostic studies, including bronchoscopy, chest X-ray, and sputum studies for tumor cells are indicated. Hemoptysis may also occur with tuberculosis, coccidioidomycosis, pulmonary infarction, bronchiectasis, bronchial adenoma, or lung abscess.[4]

Dyspnea (breathlessness 58%)

Dyspnea has been reported as an early symptom in 58% of patients. It is usually disproportionate to radiological findings and exaggerated because of associated underlying smoke-related lung changes. Sometimes dyspnea is positional and is due to obstruction by endobronchial tumor. Dyspnea may also be related to pulmonary emphysema, congestive heart failure, extension of tumor to the trachea, coincidental pneumonia, pleural effusion, atelectasis, or bronchopulmonary infection.[5]

Wheezing (2-10%)

Wheezing, stridor, or sudden increase in breathlessness is highly suggestive of a partial bronchial obstruction. It results due to pressure and narrowing of large bronchus or trachea. It occurs in about 2-10% of patients and is especially meaningful when unilateral or of recent origin. This is more likely to occur with a hilar tumor which produces narrowing of a large bronchus; or rarely, of the trachea.[3]

Chest pain

Chest pain is a common symptom in early stage lung cancer, and it is often present without frank evidence of invasion of the pleura, chest wall, or mediastinum. Because the lung parenchyma is not well-supplied with pain fibers, the origin of this type of pain is not clear. This pain is not a poor prognostic sign and it typically responds well to management of the underlying tumor. Severe chest pain requiring narcotics is almost always caused by pleural metastasis. Superior sulcus tumor often produces constant pain involving the shoulder and arm because of invasion of brachial plexus. Other signs found are weakness of the hand and Horner's syndrome. Persistent chest pain with destruction of a person's bony thorax is most often caused by squamous cell carcinoma.[5]

Weight loss

It is a common symptom of lung cancer at presentation, but it is not necessarily a sign of advanced disease. Among those with squamous cell carcinoma, approximately one-third of early stage patients report weight loss of 10 pounds or more.

MANIFESTATION OF LOCALLY ADVANCED DISEASE

Hoarseness of voice

Hoarseness in association with lung cancer is almost always caused by involvement of the left recurrent laryngeal nerve. Hoarseness occasionally improves with treatment of the causative malignancy, but most often it persists because of either inadequate control of the tumor or irreversible damage to the nerve.

Phrenic nerve paralysis

The phrenic nerve courses along the pericardium bilaterally and is subject to injury caused by invasion by primary

tumor or bulky adenopathy. The left phrenic nerve is more commonly affected than the right.

Dysphagia

Dysphagia can result from esophageal obstruction by bulky mediastinal adenopathy. Although bulky adenopathy is a relatively common occurrence, this symptom is surprisingly uncommon. Another potential cause of dysphagia is recurrent laryngeal nerve injury.

Stridor

Stridor results from compromise of the lumen of the trachea. It can be caused by invasion of the trachea by tumor, or bilateral vocal cord paralysis. An aggressive approach to the management of stridor is necessary because this problem is life-threatening and extremely distressing.

Superior vena cava syndrome

Superior vena cava syndrome is a relatively common complication of lung cancer. It is generally a consequence of obstruction of superior vena cava by right upper lobe tumor. The syndrome is characterized by: Facial swelling, flushing, cough, and neck and chest wall vein distention. The extent and severity of symptoms greatly depends on how rapidly the obstruction progresses and on the speed and extent of the development of collateral circulation.

Pleural effusion

Approximately 15-20% of lung cancer patients present with pleural effusion. Although most of these effusions are ultimately determined to be malignant, about one-half is initially cytologically negative.

Pericardial effusion

Pericardial effusion develops in 5-10% of patients with lung cancer and typically occurs in the setting of progressive locally advanced disease.

Pancoast syndrome

It is the occurrence of shoulder and upper chest wall pain caused by the presence of a tumor in the apex of lung with the invasion of adjacent structures. It can be accompanied by Horner's syndrome, brachial plexopathy, and reflex sympathetic dystrophy.

MANIFESTATION OF EXTRA THORACIC SPREAD

Brain metastasis

Lung cancer is the most common cause of brain metastasis. The manifestations of brain metastasis are variable and depend on the location of the lesion and the amount of the associated edema or hemorrhage. Patient may present with focal weakness, generalized or focal seizures, confusion or dementia, dysphasia, visual disturbances, or ataxia. Leptomeningeal disease may present as cranial nerve palsies or cauda equine syndrome.

Bone metastasis

Bone is a common site of metastatic involvement by lung cancer. These patients may present with bone pain which may be controlled by significant doses of narcotics.

Liver and adrenal metastasis

Lung cancer commonly spreads to the liver and adrenal glands in addition to the brain and skeletal system.

PARANEOPLASTIC SYNDROME

Carcinoma of the lung most often present with the symptoms related to the locoregional effects of the primary tumor or to the manifestation of extrathoracic spread. However, remote effects of the primary cancer, termed as paraneoplastic syndromes, result in organ dysfunction. The paraneoplastic manifestations commonly seen in lung cancer are enlisted in Table 1.

Staging of lung cancer

Tumor, Node, Metastasis (TNM) Staging System for Lung Cancer; including revised staging system [Table 2].

Primary tumor

TX Positive malignant cell; no lesion seen
T1 Tumor <3 cm diameter

Table 1: Paraneoplastic manifestations in lung cancer

Endocrinological	Hematological/vascular
Hypercalcemia (PTH-RP)	Anemia
Hyponatremia (SIADH)	Autoimmune hemolytic anemia
Cushing's syndrome (ACTH)	Leukocytosis
Gynecomastia (beta hCG)	Eosinophilia
Galactorrhea (prolactin)	Monocytosis
Hypoglycemia	Thrombocytosis
Acromegaly	Idiopathic thrombocytopenic purpura
Nonbacterial thrombotic endocarditis	Trousseau's syndrome
Vasculitis	
Neurologic	Miscellaneous
Peripheral neuropathy	Fever
Cerebellar degeneration	Renin hypertension
Encephalomyelitis	Membranous nephropathy
Lambert-Eaton syndrome	Hyperuricemia/hypouricemia
Musculoskeletal/dermatological	
Clubbing	
Hypertrophic pulmonary osteoarthropathy	
Dermatomyositis	
Polymyositis	

PTH-RP: Parathyroid hormone related peptide, SIADH: Syndrome of inappropriate antidiuretic hormone hypersecretion, ACTH: Adenocorticotropic hormone, hCG: Human chorionic gonadotropin

T2 Tumor >3 cm diameter; distal atelectasis
T3 Extension to pleura, chest wall diaphragm, or pericardium; <2 cm from carina or total atelectasis
T4 Invasion of mediastinal organs.

Regional lymph-node involvement

N0 No nodal involvement
N1 Ipsilateral bronchopulmonary nodes
N2 Ipsilateral or subcarinal mediastinal; ipsilateral supraclavicular nodes
N3 Contralateral mediastinal hilum or supraclavicular nodes.

Metastatic involvement

M0 No metastasis
M1 Metastasis present [Table 2].

DIAGNOSTIC WORK-UP

Radiological examination

Chest radiography

A chest radiograph will detect most lung cancers, but some particularly early curable tumors, are hidden by other structures. Secondary effects such as pleural effusion, distal collapse, and raised hemidiaphragm may be evident.

Computerized Tomography

This is the first investigation in suspected lung cancer. The surgeon needs to know if primary is resectable (T stage) and which if any lymph nodes are involved (N stage). Lymph nodes of more than 2 cm in diameter are likely to be involved in the disease (70%) and those less than 1 cm in diameter are very unlikely to be involved.

Pulmonary function tests

Before pulmonary resection, patients are evaluated by a combination of pulmonary function tests, including spirometry. Each of these tests measure a specific component of patient's pulmonary function and in some cases, measures the combined function of both the heart and the lungs. Spirometry measures the lung volumes and mechanical properties of lung elasticity, recoil, and compliance. Pulmonary function testing also evaluates gas exchange functions. Occasionally, this combined measurement of cardiorespiratory axis serves as a more appropriate study to assess the patient's physical reserve.[7] The predicted forced expiratory volume in 1 second (FEV_1) is the most commonly used predictor of postoperative pulmonary reserve. Typically this is greater than 0.8 liter. The FEV_1 second to forced vital capacity ratio (FEV_1/FVC) describes the relationship between the FEV_1 and total lung volume. This ratio is low in obstructive disease and is about normal in restrictive diseases.

Table 2: Revised staging system

Stage	TNM	5 year survival rate (%)
IA	T1, N0, M0	>70
IB	T2, N0, M0	60
IIA	T1, N1, M0	50
IIB	T2, N1, M0	30
	T3, N0-1, M0	40
IIIA	T1-3, N2, M0	10-30
IIIB	Any T4, any N3, M0	<10
IV	Any M1	<5

TNM: Tumor, node, metastasis

Sputum cytology

Cytological analysis of exfoliated cells in the sputum is a rapid, relatively inexpensive means to establish a tissue diagnosis in an individual with an apparent pulmonary carcinoma. Previous reports have indicated that the sensitivity of the sputum cytology is 65% (range 22-98%) in the setting of established cancer. The diagnostic yield of sputum cytology is enhanced in the context of centrally located lesions, squamous cell carcinomas, and large tumors, particularly if multiple sputum samples are examined.[8]

Bronchoscopy

In patients with lung cancer, 59-74% of lesions are seen through the fiberoptic bronchoscope; biopsy and brushing give a true positive diagnosis in 86-96% of patients. The combination of bronchial brushings and biopsy yield an overall accuracy of 79% including 66-78% in peripheral lesions and 86% in central lesions.

Percutaneous fine needle aspiration

It is an excellent method for establishing tissue diagnosis. This can be performed using fluoroscopic or CT-guided techniques. The positive yield in experienced hands exceeds 95% even if lesions are less than 1 cm in diameter. However, it cannot rule out malignancy unless a true positive benign diagnosis (i.e., hematoma or infectious process) is definitively established.

Mediastinoscopy

Mediastinoscopy remains the most accurate technique to assess paratracheal (station 2, 3, and 4), proximal peribronchial (station 10) and subcarinal (station 7) lymph nodes in lung cancer patient. It is indicated in patients suspected of having locally advanced disease on the basis of direct tumor extension to the medistinum, enlarged lymph nodes on CT scan, or mediastinal uptake on positron emission tomography (PET).

Radioisotope procedure

PET scan has emerged as a valuable tool for diagnostic staging and therapeutic treatment planning for non-small cell cancer. PET is an analytic imaging technology

developed to use compounds labeled with positron emitting radioisotopes as molecular probes to image and measure biologic processes using a biologically active molecule, such as 2-fluorodeoxy-2-glucose (FDG).

In non-small cell carcinoma, PET mainly has been used for the evaluation of pulmonary nodules and for staging the mediastinum. FDG-PET is more sensitive and specific than CT in detecting metastatic disease in normal sized lymph nodes and in the differentiation of enlarged benign nodes from enlarged nodal metastasis. Other studies suggest additional value for FDG-PET to detect occult extra thoracic metastasis with a frequency of 11-20%.

TREATMENT OF LUNG CANCER

Treatment options include surgery for localized disease, chemotherapy for metastatic disease, and radiation therapy for local control in patients whose condition is not amenable to surgery. Radiation therapy and chemotherapy together are better than chemotherapy or radiation therapy alone for primary treatment of advanced-stage lung cancer. Protocols evaluating chemotherapy, radiation, and surgery for advanced-stage lung cancer are ongoing.

Small cell lung cancer is frequently disseminated at diagnosis. Surgery is not the primary treatment for small cell carcinoma unless it mimics stage I non-small cell cancer at clinical staging presentation. Chemotherapy can provide patients with a survival advantage over no treatment. In patients with a solitary pulmonary nodule and no evidence of metastatic disease, resection (with wedge resection and frozen section) may reveal cancer. Lobectomy would be appropriate along with mediastinal lymph node dissection. If a wedge resection cannot be performed because of location in a patient with a suspicious nodule (speculated, PET positive, and greater than 1 cm), lobectomy for diagnosis would be appropriate in a physiologically fit individual. Survival depends on the cumulative mechanical and biological effects of that treatment on the primary tumor and micrometastasis. Even in earlier-stage cases, that is, stages IB, IIA, and IIB; 5-year survival may only reach 55, 50, and 40%, respectively.[9]

SURGICAL MANAGEMENT

The principal of surgery is to remove all cancer but to conserve as much lung as possible. This is usually done by lobectomy, but there is evidence that small peripheral lesions have as good an outcome if subjected to segmentectomy or simple wedge excision as lobectomy.

Pneumonectomy is removal of the whole lung. This is a major undertaking and has a high mortality rate (5%). The surgeon must be satisfied that the patient is fit enough to tolerate this procedure from the preoperative work-up. This procedure is reserved for either centrally placed tumor involving the main bronchus or those that straddle the fissure. The objective is to keep this to minimum, but extensive conservation would deny the patient a chance of cure.[10]

SELECTION OF THE SURGICAL CANDIDATES

Operative mortality rates for resection of lung cancer averages 4%, with lobectomy having a mortality of 3% and pneumonectomy a mortality of 7-9%. The most common causes of death include pneumonia/acute respiratory distress syndrome (36%, $n = 21$), bronchopleural fistula (BPF)/empyema (33%, $n = 19$), cerebrovascular accident (10%, $n = 6$), cardiac-related events (7%, $n = 4$), and others (14%, $n = 8$).[11] Surgical selection should not be defined by chronological age, but by compulsive functional correlation of the cardiopulmonary reserve with the age of patient. In a recent review of literature, the mortality of pulmonary resection for lung cancer in patients 70-79 years or 80 years or greater was 6 and 8%, respectively. Massard *et al.*, reported mortality rate for lobectomy to be 6.6 and 10% for pneumonectomy in patients aged 70 years and more.[12] These rates are obviously higher for younger patients and are more a function of comorbidity than of age alone. Accordingly, in all ages of patients selected for pulmonary resection, thorough preoperative functional assessment should be done.

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