Lung cancer: diagnosis, staging and treatment

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Abstract

Lung cancer is the most common malignancy worldwide and carries a high mortality rate. The risk of developing lung cancer is strongly associated with smoking. The predominant subtypes of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC forms the majority of cases while SCLC makes up a smaller proportion. Patients with symptoms and signs suggestive of lung cancer are managed by a multi-disciplinary team approach in order to diagnose and stage the disease. The type and stage of lung cancer guides further management. Early stage lung cancer should be treated aggressively; with the most appropriate modality which may include surgery, chemotherapy and radiotherapy, or a combination of these various modalities.

Keywords Lung cancer; non-small cell lung cancer; surgery; targeted therapy

Epidemiology and aetiology

Until the 1930s, primary lung cancer was a rare condition. Today, worldwide, lung cancer is the most common cancer, with 1.61 million cases diagnosed in 2008. The highest incidence occurs in Europe and North America, with parts of Africa having the lowest incidence. In the UK, lung cancer is the second most common cancer in men and third most common cancer in women. It is the leading cause of cancer death in women. There are more than 39,000 new cases of lung cancer in the UK each year with more than 35,000 deaths annually.

Lung cancer is rare example of a tumour with known carcinogens. This was elucidated by epidemiological studies by Doll and Hill in the 1950s. They observed that doctors who smoked had a relative risk of 12.7 of dying from lung cancer compared to doctors who did not smoke. Between 85% and 90% of patients with lung cancer have a positive smoking history, although only 15% of smokers go on to develop lung cancer. The risk of developing a smoking-related lung cancer is proportional to the number of cigarettes smoked and length of smoking history. Other risk factors that may increase the risk of developing lung cancer are passive smoking, radon exposure, occupational exposure to asbestos, silica and uranium, previous radiotherapy to the lungs, decreased fruit and vegetable consumption, extreme air pollution such as intense indoor exposure to smoky coal and genetic and familial factors. The 15q24-25 chromosome region encodes for nicotinic acetylcholine receptor subunit genes that play a role in nicotine addiction. Whilst nicotine does not induce cancer, its promotion of proliferation and growth of cancer cells may support tumour growth.

Pathogenesis

Polycyclic aromatic hydrocarbons from tars are thought to be the main carcinogens in lung cancer. Various mechanisms are thought to play a role in the development of primary lung cancer:

- tumour suppressor gene inactivation
  - the absence or inactivation of wild-type p53 has been identified in up to 70% of lung cancers. Mutation results in the loss of normal repair and apoptotic mechanisms that help to protect against tumour development.
- oncogene activation
- activation of proliferation
- evasion of apoptosis, angiogenesis
- suppression of immune response

The identification of genetic mutations in primary lung cancer has facilitated an era of targeted therapy in the management of advanced lung cancer. Where present, 95% of these mutations are mutually exclusive.

- Epidermal growth factor receptor protein (EGFR) gene occurs in around one-quarter of adenocarcinomas and is more frequent in non-smokers, females and Asians.
- Kirsten rat sarcoma viral oncogene (KRAS) protein stimulated pathways are downstream from EGFR and stimulate cell growth. KRAS mutation is seen in 25% of adenocarcinoma, 5% of squamous carcinoma and are more common in smokers and males.
- Anaplastic lymphoma kinase (ALK) mutations are associated with abnormal cell proliferation and occur in 6% of adenocarcinoma and are more common in non-smokers and younger patients. They confer sensitivity to crizotinib in locally advanced and metastatic disease and resistance to EGFR tyrosine-kinase inhibitors.
- BRAF mutation is responsible for triggering MAPK pathway involved in cell division and differentiation. It is more common in smokers and is seen in 3% of adenocarcinomas.
- MET amplifications are seen in 5% of NSCLC and 2% of adenocarcinomas and are commoner in male smokers.

Pathology

Lung cancer is broadly divided into small cell (SCLC) (18% of lung cancer) and non-small cell lung cancer (NSCLC) (78% of lung cancer). The main subtypes of NSCLC are adenocarcinoma (40% of lung cancers), squamous cell carcinoma (25% of lung cancers) and large cell carcinoma (10% of lung cancers) (Table 1).

Adenocarcinomas are usually peripheral lesions. Recent reclassification has unified terminology and diagnostic criteria, and consequently the terms bronchioloalveolar carcinoma and mixed subtype adenocarcinoma have been discontinued. Adenocarcinoma subtypes include:

- preinvasive lesions (atypical adenomatous hyperplasia, AAH and adenocarcinoma in-situ $\leq$3 cm)

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WHO classification of non-small cell lung cancer

- Squamous cell carcinoma
  - Papillary
  - Clear cell
  - Small cell
  - Basaloid
- Adenocarcinoma
- Large cell carcinoma
  - Large cell neuroendocrine carcinoma
    - Combined large cell neuroendocrine carcinoma
  - Basaloid carcinoma
  - Lymphoepithelioma-like carcinoma
  - Clear cell carcinoma
  - Large cell carcinoma with rhabdoid phenotype
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
  - Pleomarphic carcinomas with spindle and/or giant cells
  - Spindle cell carcinoma
  - Giant cell carcinoma
  - Carcinosarcoma
  - Pulmonary blastoma
- Carcinoid tumour
  - Typical carcinoid
  - Atypical carcinoid
- Carcinomas of salivary gland type
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Epithelial-myoepithelial carcinoma
- Unclassified carcinoma

Table 1

- minimally invasive adenocarcinoma
- invasive adenocarcinoma (which includes lepidic pattern predominant, acinar pattern predominant, papillary pattern predominant, micropapillary predominant and solid pattern predominant).

Immunohistochemistry staining of adenocarcinoma shows thyroid transcription factor-1 (TTF-1) positive in 89%, p63 in 32%, cytokeratin 5/6 in 18% and 34βE12 in 82%.

Squamous cell carcinomas (SCCs) are often central, arising in large central airways that are proximal to segmental bronchi. SCC normally has an irregular, grey-white cut surface, commonly showing an area of central necrosis, with or without cavitation. The surrounding parenchyma is often tethered to the tumour, giving rise to a spiculated appearance on imaging. Microscopically, SCC is defined by stratified squamous epithelium of the upper airway with disordered architectural and cytologic maturation. Immunohistochemistry, in contrast to adenocarcinomas, are negative for TTF-1 with diffuse p63.

Large cell carcinomas are characterized by the absence of morphological characteristics that would diagnose the tumour as another histological subtype. The histologic features of large cell carcinoma are similar to those of small cell lung cancer. Large cell carcinoma is differentiated from small cell carcinoma by the larger size of cell, a lower nuclear:cytoplasm ratio and coarser chromatin.

Diagnosis

Presentation may be due to incidental finding or due to symptoms or signs relating to the primary tumour, metastatic disease or secondary to paraneoplastic syndromes. As with all tumours presentation may be due to general, nonspecific symptoms.

The symptoms and signs of lung cancer that arise from the effects of primary tumour within the chest include cough, dyspnoea, wheeze, haemoptysis and chest pain. Cough is a result of bronchial irritation or compression and is the most common symptom, occurring in about 75% of patients. Dyspnoea may result from partial or complete airway obstruction from central tumours. Haemoptysis usually presents as streaks of blood in the sputum and is frequently associated with central tumours that are degenerating or tumours that invade and ulcerate surrounding bronchial tissue. These symptoms often give rise to the impression of a non-resolving chest infection. Invasion of tumour into the chest wall may result in chest pain. The presence or absence of chest pain has a 90% predictive value for chest wall invasion. Superior sulcus tumours result is a syndrome of shoulder or arm pain, Horner's syndrome and atrophy of small muscles of the hand.

Manifestations of metastasis within the chest include dyspnoea and wheeze secondary to extrinsic compression of airway due to lymph node metastases, superior vena cava obstruction (SVCO), breathlessness secondary to pleural or pericardial effusions and hoarse voice due to recurrent laryngeal nerve invasion.

Distant metastasis of lung cancer produces non-pulmonary manifestations. The most common site of distant metastasis is the brain, causing headaches, seizures, symptoms of raised intracranial pressure, localizing neurological signs, cerebellar signs or papilloedema. Bone metastases result in pain and tenderness in the back, ribs or long bones. Other possible sites of distant metastasis are liver, adrenal glands and lung.

Paraneoplastic syndromes occur in about 13% of NSCLC. The mechanisms for these syndromes are not known but may be secondary to neurological, vascular and hormonal pathways. Hypertrophic pulmonary osteoarthropathy (HPOA) is defined by digital clubbing and distal periostitis of long bones. The periostitis leads to tenderness and swelling and the symptoms can respond well to non-steroidal anti-inflammatory agents. Resection of the primary tumour usually results in complete resolution of the symptoms. HPOA is usually associated with adenocarcinoma.

Syndrome of inappropriate anti-diuretic hormone secretion (SIADH) is commonly associated with SCLC. It leads to hyponatraemia, anorexia, nausea, vomiting and increased neurologic dysfunction such as confusion, lethargy and seizures. The primary treatment is chemotherapy and response of tumour is associated with resolution of symptoms. However, symptomatic control of SIADH can be achieved with hypertonic saline infusion combined with diuretics or treatment with democycline, an antibiotic that blocks the action of ADH on the renal tubules.

Staging

Lung cancer is staged according to the Union for International Cancer Control (UICC) American Joint Cancer Committee (AJCC) 7th edition of TNM staging based on International Association for the Study of Lung Cancer (IASLC) (Tables 2 and 3). Accurate