Lung tumors: an overview

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Published in Atlas Database: February 2004

Online updated version: http://AtlasGeneticsOncology.org/Tumors/LungTumOverviewID5030.html

DOI: 10.4267/2042/38085

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Identity

Note
The overwhelming majority of lung tumours are carcinomas. Most commonly, they arise from the pseudo-stratified epithelial lining of the bronchial airways but they can also arise from the epithelia of the smaller terminal airways and alveoli. World-wide, lung cancer is the most common cause of cancer-related death.

Classification

Note
Lung cancer diagnosis and classification are currently based primarily on light microscopy, occasionally supplemented by immuno-histochemical assays. The use of microarray generated data in the future is likely to radically improve disease sub-classification. Lung tumours are divided into two broad categories of: small cell carcinoma (SCLC 20-25% of cases) and non-small cell lung cancer (NSCLC 70-80% of cases) based on clinical behaviour and histological appearance. Other rarer tumour types include: carcinoids (typical or atypical), carcinosarcomas, pulmonary blastomas, giant and spindle cell carcinomas. NSCLC is further divided histologically into three main disease subtypes of: squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Whilst in certain countries, adenocarcinoma is now the most common disease subtype seen, in other countries, whilst the relative frequency of adenocarcinoma is rising, squamous cell carcinoma still predominates.

Clinics and pathology

Etiology
The smoking of tobacco is the primary cause of lung cancer and patterns of occurrence are largely determined by historical exposure. In general, the contribution of genetic or other environmental factors to lung cancer risk is thought to be small but some may synergise with smoking. Such additional environmental factors include exposure to radon gas (an indoor environmental pollutant), workplace exposures to inorganic fibres (asbestos) or toxic chemical entities, air pollution and ionising radiation. As for many cancers, poor diet appears to be associated with increased disease risk.

Epidemiology
Smoking increases the risk of all histological subtypes but is most strongly associated with squamous cell and small cell disease. Adeno-carcinoma is more common in women than in men and more common in non-smokers with disease than smokers. The number of cases attributable to tobacco smoking varies between countries and regions depending on the historical levels of smoking for those regions. A recent estimate for Europe suggested that 90% of male and 60% of female lung cancers were caused by exposure to cigarette smoke.

The observation that perhaps only 1-2 of every 10 smokers develops clinical lung cancer during their lifetime has been used as an argument to suggest that some level of genetic predisposition modifies disease risk. Whilst this argument is perhaps not compelling, it
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is not unreasonable and indeed a small number of genetic polymorphisms have been associated with modest increases in lung cancer risk. As lung cancer is usually caused by a chronic exposure of the bronchial epithelium to multiple procarcinogenic (and carcinogenic) agents, it is not surprising that many of these polymorphisms lie in genes associated with the activation (cytochrome P450s) or deactivation (Glutathione S-transferases) of such entities or the repair of subsequently induced damage (TP53). In general, epidemiological analysis has not suggested the existence of highly penetrant, strongly predisposing lung cancer associated genetic variants.

**Clinics**

In the early stages of disease, lung cancer tends to be asymptomatic. Consequently, at the time of diagnosis, most tumours are overtly (stage IIIB, IV) or covertly metastatic. Resectable, localised, disease (stages I-IIIa) is identified in approximatively 20% of patients. Generally advanced stage at diagnosis and the relative resistance of the disease to currently available anti-cancer drugs leads to a high mortality rate, with 5-year survival typically between 10 and 15%. The potential benefits and costs of CT screening for the detection of early, asymptomatic lung cancer are currently being evaluated in large randomised trials in several countries.

**Pathology**

Tumours are classified primarily on their cytological appearance. The relative frequency of subtypes varies in different regions and the figures cited therefore represent broad approximations. Clinically, the most important division is between SCLC and NSCLC. Small cell tumours metastasise very early in the course of the disease but are relatively responsive to chemotherapeutic drugs: they are therefore managed in a different way to non-small cell lesions. Lung cancers are generally heterogeneous, consisting frequently of cells of different histological subtypes. Pathological classifications therefore emphasise the major cell type present in the tissue analysed and may note significant minor components. When components are roughly equal, designations such as adenosqua-mous carcinoma may be used. This common intra-tumour heterogeneity has led to the suggestion that lung carcinomas arise from a multipotent stem cell-like (or stem cell) component of the bronchial epithelium. Whilst microarray analyses have shown that gene expression can be used effectively to subdivide disease into existing or novel subtypes, it has also highlighted the similarity that lies between these subtypes at the level of gene expression. Such observations are consistent with a common stem cell progenitor.

**NSCLC**

Squamous cell lung carcinoma comprises approximately 30% of lung cancers. These tumours generally arise centrally within the lungs inside a large bronchus although they may sometimes be peripheral; Adenocarcinomas, representing perhaps 30% of invasive lesions, tend to occur in more peripheral locations arising from the smaller airways but they can be found centrally in a main bronchus;

Large cell carcinomas, 10% of lung cancers, are undifferentiated tumours which lack the diagnostic features of the other subtypes. This is therefore to some extent a default classification, made when other specific histology has been excluded.

**SCLC**

Small cell carcinomas account for 20% of lung cancers. They mostly arise centrally in a large bronchus and are highly invasive and highly metastatic.

**Treatment**

Before the appropriate treatment can be defined a careful staging of the disease must be made. The principles of therapy of NSCLC and SCLC are different. SCLC is very seldom surgically resectable, usually widespread at presentation and is generally both more chemo- and radiosensitive.

**NSCLC:**

Treatment is based on the stage of the disease at presentation (which may be assessed by thoracic CT, PET scan, brain MRI). Stage I-II are usually resected (adjuvant chemotherapy can be discussed with the patient) and locally advanced stages (III) are treated by combined modality treatments (neoadjuvant chemotherapy, resection if stage IIIA or radiotherapy). If overt distant metastases are detected, therapy is palliative and chemotherapy has been shown to improve median survival and quality of life.

**SCLC:**

If the tumour is confined to one hemithorax (limited disease), a combined modality therapy (chemo- and radiotherapy) is indicated: in more advanced disease (overt distant metastases in brain, liver, bones, surrenal glands or other organs) chemotherapy will be palliative though an excellent remission might be obtained in more than half of the patients.

New therapies based on an improved understanding of the molecular basis of the disease are currently in use or are under development. For example, Gefitinib, a tyrosine kinase inhibitor, is one such example that has been launched on the market in different countries for patients with relapsed or refractory NSCLC after chemotherapy. Further drugs with other defined molecular targets are anticipated.

**Prognosis**

Once a diagnosis of lung cancer has been made (biopsy, cytology) the disease is staged (I - IV) according to established international criteria. NSCLC
patients are divided into different groups based on the TNM classification system. This is a combined grading incorporating tumour size and location (T), lymph node involvement (N) and presence of distant metastasis (M). In general, higher stage (both overall and within each category) correlates with a poorer prognosis with a 5-year survival of 60-70% for T1-2, N0, M0 (stage I) disease and <1% for TX, NX, M1 (stage IV) disease. SCLC is classified as limited (to one hemithorax) or extensive (with distant metastasis) disease with 3-year survival being 5-10% and <1%, respectively.

**Cytogenetics**

**Note**

Lung tumours generally show complex karyotypic changes which involve multiple chromosomes. However, one of the most consistent alterations seen in both SCLC (approaching 100%) and NSCLC (approaching 90%) is a loss of coding potential from the short arm of chromosome 3. Loss of chromosome 3 sequence appears to occur frequently at the very earliest stages of neoplastic transformation, when epithelial cells may show no evidence of morphological alteration.

**Genes involved and proteins**

**Note**

The loss of p53 function, generally through mutation of the coding sequence is seen in the majority of lung carcinomas. Less dramatically, mutation of KRAS2 occurs in approximately 20% of NSCLC lesions and may indicate a poor prognosis when it is detected in small adenocarcinomas. Microarray analyses have shown that many other genes show dramatic differences in expression between lung tumours and normal lung tissue. These differences may be driven by tumour gene amplification, deletion, control region mutation or chromosomal translocation (all apparently relatively rare in primary disease) or perhaps more commonly, may be associated with changes in various types of epigenetic modification of the DNA sequence. The differential expressions may be disease-related in the sense that they are induced directly by DNA damage events in the tumour cell, or they may be only indirectly linked to the disease, in the sense that they are typical of the gene expression patterns of progenitor cells and atypical for the majority of normally differentiated lung cells.

**References**


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