

Lung: small cell cancer

Classification

Note Although it is possible to distinguish a number of different histological sub-classes of lung cancer by light microscopy, the most important current clinical distinction is between small cell lung cancer (SCLC) and [non-small cell lung cancer \(NSCLC\)](#). Based primarily on its clinical behaviour, SCLC, a neuroendocrine lesion, is considered as a separate entity to the non-small cell carcinomas. The disease has a particularly aggressive clinical course with widespread early metastasis and somewhat in contrast to NSCLC, tumours will frequently show a short term response to cytotoxic chemotherapy and radiotherapy. As SCLC is almost always overtly metastatic at presentation, surgical resection is rare.

Clinics and Pathology

Note Small cell carcinomas tend to be centrally located, arising in a large bronchus, with only a small number presenting as peripheral lesions. The tumours generally grow around the bronchus, invading surrounding structures. They may obstruct the airway, but this is generally through circumferential compression rather than luminal invasion. Extensive necrosis and lymph node metastases are common.

SCLC cells are small and round to fusiform with scant cytoplasm. The relatively large round, oval or fusiform nucleus contains finely stippled chromatin and nucleoli may be inconspicuous or absent. The tumour cells, which have a high mitotic index, often grow in sheets but they may be arranged in ribbons or rosettes. Small cell carcinomas frequently express markers of neuroendocrine differentiation such as creatine kinase-BB, chromogranin and neuron specific enolase. They may also express small peptide hormones such as gastrin-releasing peptide, calcitonin and serotonin. As significant differences exist in the treatment of SCLC and NSCLC, the distinction of SCLC from other neuroendocrine lesions (such as large cell neuroendocrine carcinoma) is important. No pre-malignant states have been identified for small cell tumours.

Although in the future, gene expression profiling is likely to define new disease subdivisions with variable drug sensitivities and outcomes, only two subtypes of SCLC are currently discriminated:

small cell carcinoma (about 90%);

combined small cell carcinoma (about 10%)

It is not clear whether this division is clinically significant, but it may be taken into account when therapy is considered. In the combined tumour, SCLC may be mixed with a second histological component of NSCLC (large cell, adenocarcinoma or squamous

cell) and the relative balance of the subtypes within the tumour may shift after chemotherapy. Such observations lend weight to the argument for a common stem cell origin of lung tumours, a hypothesis supported by microarray data which suggest that small cell tumour gene expression patterns are closely related to those of bronchial epithelial cells.

Staging

Using molecular analyses, malignant cells can be demonstrated at distant sites in all cases of diagnosed SCLC and patients should therefore receive combination chemotherapy as part of their treatment. Staging of the disease, although not carried out in order to identify a subset of patients who might be treated with local therapy, is nevertheless useful to direct treatment and predict prognosis. Bronchoscopy usually allows biopsy of the primary tumour which defines the diagnosis but if malignant small cells are detected cytologically in the sputum, this may be unnecessary.

Appropriate subsequent investigations include: clinical examination, blood analyses including haemoglobin, leukocyte, thrombocyte counts, assessment of liver and kidney function and measurement of electrolytes (sodium, calcium), uric acid, alkaline phosphatase, and lactate dehydrogenase (LDH).

Further investigations may include: bone scan (if there are bone pains, elevated calcium or alkaline phosphatase), thoracic and abdominal CT scan and in the case of a pathological neurological status, an MRI or CT scan of the brain. Nowadays, bone marrow punctures are indicated in rare situations only. These examinations allow a two stage classification of limited versus extensive disease. Limited disease is defined as a tumour confined to the hemithorax of origin and regional lymph nodes that can be encompassed in a tolerable radiation therapy port (20-30% of patients). Beyond this, the tumour is classified as an extensive disease (60-70% of patients).

The most important prognostic factors are tumour extent (extensive disease), performance status, elevated LDH and alkaline phosphatase, and decreased sodium level (Manchester Score). Cure is rare even in limited disease (10%); disease-free survivals at 2 years are 30% and 3% for limited and extensive disease, respectively.

Treatment SCLC is highly sensitive to chemotherapy. Response rates vary between 50-90% depending on the stage of disease and the patient's tolerance of the chemotherapy. Survival and quality of life are generally highly improved. In extensive disease, several (up to six) cycles of a platinum containing combination therapy is usually administered. In case of relapse further chemotherapy is given with less success, but even in this situation, quality of life might be improved. In limited disease, combination chemotherapy concomitantly with radiotherapy is the cornerstone of management. In the case of complete remission, initial therapy is completed by a prophylactic cranial irradiation.

Cytogenetics

Note As surgical resection is rare, and although some primary tumour karyotypes have been reported, much of the information on cytogenetic abnormalities in SCLC is based on the analysis of short term cultures and cell lines. Chromosomal changes are usually fairly extensive. Although no characteristic balanced translocations have been identified, breakpoints tend to cluster on chromosomes 1, 3, 5 and 17. Losses of the short arms of chromosome 3 and 17 and the long arm of 5 are seen consistently.

In addition to these changes, extra-chromosomal double minutes and intra-chromosomal homogeneously staining regions have sometimes been observed, especially in SCLC cell lines and especially in tumours from chemotherapy-treated patients. These characteristic structures, indicative of somatic gene amplification, generally encode multiple copies of MYC family genes.

Comparative genomic hybridisation (CGH) has been used to extend conventional karyotypic analysis in SCLC. Prominent imbalances seen in several studies include losses of chromosomes 3, 4, 5, 8, 10, 13 and 17 with the most frequently implicated regions being 3p13-14, 4q32-35, 5q32-35, 8p21-22, 10q25, 13q13-14 and 17p12-13. Common gains include 3q, 5p, 8q and 19q with the most commonly involved sub-regions being 3q26-29, 5p12-13, 8q23-24 and 19q13.1.

Using molecular probes, the loss of material from the short arm of chromosome 3 has been shown to occur in almost 100% of SCLCs. This striking loss may occur in the earliest stages of malignancy: in histologically normal and pre-neoplastic smoking damaged epithelia. A number of different regions of 3p have subsequently been highlighted by high density allelotyping leading to the hypothesis that multiple tumour suppressor genes involved in lung cancer pathogenesis may be localised to 3p. Whilst many candidates have been considered (including [FHIT](#), [RASSF1](#) and [FUS1](#)) none show consistent coding sequence mutation in SCLC. However, a number of these candidate sequences show epigenetic differences between tumour and normal cells which may implicate them pathologically.

Genes involved and Proteins

Gene Name [TP53](#)

Note Consistent somatic mutation of coding sequence in primary tumours is strong evidence that a particular gene has been or is involved in the development of a neoplastic phenotype. In common with many tumour types, mutation of the [TP53](#) gene is frequent in SCLC, occurring in ~80% of primary lesions.

Gene Name [PTEN](#)

Note Chromosomal loss involving 10q24-26 is commonly seen in SCLC which suggests that this region may contain a disease-relevant tumour suppressor. Alterations (point mutations, small deletions) of the [PTEN](#) gene, located at 10q23.3, were observed in 18% of SCLC cell lines and 10% of primary tumours. PTEN encodes a lipid phosphatase which

influences cell survival through signalling down the phosphoinositol-3-kinase/Akt pathway.

Gene Name MYC family

Note Amplification of chromosomal bands 1p32, 2p23 and 8q24.1, regions encoding respectively [MYCL](#), [MYCN](#) and [MYC](#) has been observed by CGH. The tendency for these genes to be amplified in SCLC has been confirmed through the use of gene-specific probes. The consistent involvement of these related but geographically disseminated sequences suggests that deregulation of some aspect of MYC function is important in SCLC pathogenesis and/or drug resistance. The MYC gene encodes a transcription factor which promotes cell proliferation by inducing the activation of growth-promoting genes and perhaps by inducing the repression of growth-suppressing sequences.

Gene Name [RB1](#)

Note Abnormal expression and/or mutation of the genes controlling progression through the G1 phase of the cell cycle occurs in many tumours. Two genes which negatively regulate this progression are RB1 and [CDKN2A](#). In almost all cases of SCLC, the product of RB1 (the retinoblastoma protein, pRB) is not expressed as a consequence of deletion, mutation, chromosomal loss or other mechanisms. Conversely, and somewhat in contrast to NSCLC, the expression of the product of CDKN2A, the cyclin dependent kinase inhibitor p16, is generally retained in the tumour cells. The p16 protein negatively regulates cell cycle progression by blocking the phosphorylation of pRB by cyclin dependent kinases 4 and 6. The lack of a functional pRB protein in SCLC cells probably explains the lack of mutational and epigenetic inactivation of p16 in those cells.

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