Small-Cell Lung Cancer
From Natural History to Chemotherapy

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1. INTRODUCTION

Small-cell lung cancer (SCLC) represents a distinct clinicopathologic entity that is biologically and clinically distinct from non-small-cell lung cancer (NSCLC). It is distinguished by its rapid growth characteristics, accompanied by the early development of widespread metastases. Although SCLC is also extremely sensitive to both chemotherapy and radiotherapy, relapse usually occurs, despite treatment within 2 yr. Overall long-term survival continues to be dismal, with poor 5-yr survival rates of approx 3–8% (1).
2. ETIOLOGY AND EPIDEMIOLOGY

There will be 164,000 new cases of lung cancer in the United States diagnosed annually, of which SCLC represents 20–25% of cases (2). Of the 160,000 deaths caused annually by lung cancer, about 40,000 are estimated to be the result of SCLC. Historically, lung cancer was predominantly diagnosed in men, but the increase in smoking among women has resulted in an estimated male-to-female prevalence ratio of 1.2:1.0. (3)

Cigarette smoking is the primary risk factor for SCLC, accounting for more than 90% of cases (4). In one series, only 2% of 500 SCLC patients had no smoking history (5). SCLC is also the most common histologic subtype among uranium miners, probably because of exposure to radioactive radon, which is a byproduct of uranium decay (6).

3. PATHOLOGY

The majority of SCLCs are centrally located, presenting in the main stem or lobar bronchii. They arise in the peribronchial tissues and infiltrate the bronchial submucosa. They are believed to arise from basal neuroendocrine or Kulchitsky cells, which are relatively rare in the adult lung, but commonly found in the fetal lung. SCLC is characterized by the proliferation of highly malignant cells of small size (2–3 times the size of mature lymphocytes). They contain heterochromatic nuclei, with finely dispersed chromatin, indistinct nucleoli, and scanty cytoplasm. The nucleus of these cells conforms to the cytoplasm of adjacent cells in well-preserved specimens. However, there is often extensive smearing of the fine chromatin of these delicate cells, producing a characteristic “crush” artifact in poorly preserved specimens. Mitotic figures are common, and the tumor grows in sheets without a specific pattern.

3.1. Pathologic Classification

The World Health Organization Classification divides SCLC into classic “oat cell,” intermediate cell, and combined (SCLC with squamous or adenocarcinoma) subtypes (7). The oat-cell type consists of uniform small cells with dense round or oval nuclei, diffuse chromatin, indistinct nucleoli, and sparse cytoplasm, growing in sheets or nests in a sparse connective-tissue stroma. The intermediate cell type comprises less uniform polygonal or fusiform cells, which are larger in size, possess more cytoplasm, and display rosette formation. Mixtures of oat cells and intermediate cells are frequently present in the same tumor. Current studies indicate that there are no differences between oat-cell and intermediate-cell subtype with regard to disease stage, metastatic potential, response to therapy, or survival (6,8–10).

The lack of significant clinical, biologic, or ultrastructural differences between the oat-cell and intermediate-cell subtype differentiation led to the proposal of