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Small Cell Lung Cancer

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Introduction

Because of its rapid growth, dissemination at diagnosis, and responsiveness to both radiotherapy and chemotherapy, small cell lung cancer (SCLC) is unique among lung cancers. As a result, the other major forms of lung cancer (squamous cell, adenocarcinoma, and large cell) are grouped together as non-small cell lung cancers (NSCLC). Untreated, the accelerated growth of SCLC results in the shortest survival of any pulmonary neoplasm, with a median duration of survival from diagnosis of only two to four months.

Epidemiology

In 1993, an estimated 170,000 new cases of lung cancer will be diagnosed in the United States.[1] About 42,500 cases (25 percent) will be SCLC. If all other forms of lung cancer were excluded from these estimates, SCLC would still be the sixth most common solid tumor, trailing only cancers of the breast, prostate, colon-rectum, bladder, and uterus.[1] Although SCLC has historically been much more prevalent in males, the popularity of smoking among women has led to a predictable increase in women with the disease.

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Pathogenesis

There is a clear relationship between cigarette smoking and the development of SCLC, and the finding of SCLC in a lifelong nonsmoker should prompt review of the histologic diagnosis. Passive exposure to cigarette smoke and exposure to radon and various occupational carcinogens—such as asbestos, arsenic, chromium, and nickel—have also been associated with excess mortality from lung cancers of all histological patterns.

Increasing evidence suggests that a predisposition to lung cancer may be inherited. Carcinogenesis is thought to be a multistep process, involving the development of hyperplasia, metaplasia, dysplasia, carcinoma in situ, invasive carcinoma, and metastatic carcinoma in sequence. These steps are characterized by multiple genetic changes, including activation or overexpression of oncogenes and loss or mutation of tumor suppressor genes. Amplification of one of the *myc* family oncogenes is common in SCLC. Changes that commonly lead to loss of tumor suppressor gene function in SCLC include loss, inactivation, or mutation of genes on chromosome 3p (unknown gene or genes), 13q (retinoblastoma gene), and 17p (p53 gene).[2]

Pathology

SCLC has histologically been subdivided into lymphocyte-like and intermediate (also called fusiform or polygonal)

forms, but these forms have similar response rates and survival. The Pathology Committee of the International Association for the Study of Lung Cancer has divided SCLC into three subtypes: small cell carcinoma (about 90 percent of the total), mixed small cell/large cell, and combined small cell carcinoma (typical SCLC elements mixed with areas of differentiated squamous cell or adenocarcinoma).[3] All lung cancers are thought to arise from a common bronchial precursor cell, with differentiation then proceeding along various histologic pathways.

SCLC is considered a neuroendocrine lung carcinoma and has the poorest prognosis within this group. Other neuroendocrine lung carcinomas include bronchial carcinoid, which has an excellent prognosis after surgical resection, and the relatively newly recognized entity of well-differentiated neuroendocrine carcinoma of the lung, which was previously labelled by several terms, including malignant carcinoid, metastasizing bronchial adenoma, pleomorphic carcinoid, nonbenign carcinoid tumor, and atypical carcinoid.[4]

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Clinical Characteristics

The "typical" presentation of SCLC is a change in a cough or the development of hemoptysis in a chronic smoker with a chest x-ray demonstrating a hilar mass. The presentation of a single pulmonary nodule, or "coin" lesion, is less common (only about three percent of all SCLCs) and is usually an incidental finding upon a chest x-ray taken for other purposes.

Patients with SCLC may present with either local, regional, or metastatic disease (Table 1). The symptoms and signs of local cancer depend upon whether the tumor has a central or peripheral location. Central tumors, which are more common, may produce cough, hemoptysis, wheezing, stridor, dyspnea, and obstructive pneumonitis due to bronchial obstruction. The less common peripheral tumors also produce cough and dyspnea and may cause pain from pleural or chest wall involvement. Some of these tumors may be single pulmonary nodules.

Depending upon their location, regional lung tumors may produce the superior vena cava syndrome, recurrent laryngeal nerve paralysis with resultant hoarseness, phrenic nerve paralysis with diaphragmatic elevation and dyspnea, Horner's syndrome, Pancoast's syndrome, obstruction of the trachea or esophagus, pericardial involvement with effusion and/or tamponade, pleural effusions, and lymphangitic metastases.

Metastases may occur in multiple sites, including the adrenal glands, bone, bone marrow, liver, lungs, lymph nodes, and brain (Table 2).

Paraneoplastic syndromes as a result of SCLC include the production of ectopic adrenocorticotropic hormone (Cushing's syndrome), the syndrome of inappropriate antidiuretic hormone (hyponatremia), the Eaton-Lambert (myasthenic) syndrome, Trousseau's syndrome (migratory thrombophlebitis), and hypercalcemia. Hypercoagulable states and hypertrophic pulmonary osteoarthropathy occur most often with adenocarcinomas, and hypercalcemia occurs most commonly with squamous cell cancer.

Table 1
Disease Presentations of Small Cell Lung Cancer

Local		Regional	Distant	Paraneoplastic
Central Tumors	**Peripheral Tumors**			
Cough	Cough	Superior vena cava obstruction	Bone pain	Ectopic parathyroid hormone
Pain	Pain	Hoarseness (laryngeal nerve paralysis)	Central nervous system changes	Syndrome of inappropriate antidiuretic hormone
Hemoptysis	Dyspnea	Elevated hemidiaphragm (phrenic nerve paralysis)		Ectopic adrenocorticotropic hormone
Dyspnea		Horner's syndrome		Clubbing
Wheezing		Pancoast's syndrome		Eaton-Lambert syndrome
Pneumonia		Pleural effusion		Trousseau's syndrome
				Hypercalcemia
				Weight loss

Table 2
Metastatic Sites At Diagnosis

Site	Frequency (Percent)
Adrenal	20-40
Bone	29
Liver	28
Bone marrow	19
Brain	10

Adapted with permission from Ihde and Hansen[12]

Systemic symptoms—such as anorexia, cachexia, fatigue, and weight loss—are common, especially with advanced disease.

Screening

Although sputum cytology and chest radiographs allow for more effective treatment at earlier stages, the screening of asymptomatic smokers has not proven to be cost effective.[5]

Diagnostic Studies

Radiologic studies are essential in the diagnosis and staging of SCLC. As previously mentioned, SCLC is usually seen in the hilar or mediastinal regions, but occasionally may present as a solitary pulmonary nodule. Computed tomography (CT) with intravenous contrast has become the standard examination for the evaluation of hilar and mediastinal masses and to demonstrate abnormal masses for investigation at distal sites, including the head, liver, lymph nodes, and adrenal glands.[6] Radionuclide scans are used less frequently for detection of head and liver metastases, but remain important for the detection of bony lesions. Magnetic resonance imaging has not proven superior to CT scanning in most lung tumor applications, with the exception of patients who cannot tolerate contrast materials. Pleural effusions are detected by the radiograph, and free-flowing fluid is demonstrated by lateral decubitus films.

Spontaneously expectorating patients with central lesions can provide positive cytologic specimens in about 80 percent of cases. Cytology is also important in the evaluation of needle aspirates of peripheral nodules (obtained percutaneously or transbronchially), pleural or cerebrospinal fluid, lymph nodes, or possible metastatic sites.

Bronchoscopy is required in the diagnosis and staging of almost all bronchogenic carcinomas, including SCLC.[7] Flexible fiberoptic bronchoscopy is a well-tolerated exam, which allows examination of the bronchial tree to the sixth or seventh order. Bronchoscopy facilitates the acquisition of cytologic material by brush and collection of liquid washings and by biopsy of small specimens from endobronchial and transbronchial lesions. The diagnosis can be made with certainty from these samples in 70 to 90 percent of the cases. However, small cell carcinomas often show a characteristic "crush" artifact on these small biopsies, which can obscure or confound the diagnosis.

Table 3
Staging according to TNM Groups

Occult	Tx	N_0	M_0
Stage 0	Tis	N_0	M_0
Stage I	T_1	N_0	M_0
	T_2	N_0	M_0
Stage II	T_1	N_1	M_0
	T_2	N_1	M_0
Stage IIIa	T_3	N_0	M_0
	T_3	N_1	M_0
	T_{1-3}	N_2	M_0
Stage IIIb	Any T	N_3	M_0
	T_4	Any N	M_0
Stage IV	Any T	Any N	M_1

Tx is cancer detectable by cytology but not clinically visible; Tis is carcinoma in situ; T_1 is a primary tumor less than 3 cm without invasion; T_2 is a tumor more than 3 cm or invasive to visceral pleura or causing obstruction; T_3 is any size tumor with extension past the visceral pleura or within 2 cm of the carina. N_0 is no metastasis; N_1 is metastasis to ipsilateral hilar nodes; N_2 is metastasis to ipsilateral mediastinum; N_3 is metastasis to contralateral mediastinal or extrathoracic nodes. M_0 is no known distant metastasis; M_1 represents known distant metastasis.

Adapted with permission from Mountain[11]

Mediastinoscopy can be performed as a low-mortality procedure (0.09 percent) for the diagnosis of lesions not accessible to flexible fiberoptic bronchoscopy and for the staging of certain mediastinal lesions.[8] The left anterior mediastinotomy (Chamberlain procedure) is a modification that allows access to the aortic window and lower left hilar lesions.

Thoracentesis is used to diagnose malignant pleural effusions, with a diagnostic accuracy of about 70 percent.[9] Ultrasound guidance may be useful to detect and localize small effusions. Occasionally, pleural biopsy may be required to diagnose pleural extension of tumors, but closed biopsy has a lower yield than cytologic examination of the pleural fluid and is being supplanted by the advent of video-guided thoracoscopic techniques.[10]

Staging

The tumor-nodes-metastasis (TNM) staging system (Table 3) offered by Mountain[11] may be applied to both SCLC and NSCLC, but has more practical use with non-small cell tumors. The five stages, 0 to IV, reflect an increasing extent or spread of the cancer. Because SCLC is usually not considered a surgical

disease (see "Treatment Modalities" section), this system is usually replaced by the simpler designation of "limited" or "extensive" disease. Limited disease is defined by involvement of one lung, the mediastinum, and ipsilateral and/or contralateral supraclavicular lymph nodes (i.e., disease that can be encompassed in a single radiation therapy port). Spread beyond the lung, mediastinum, and supraclavicular lymph nodes is considered extensive disease.

SCLC is considered to be disseminated at diagnosis, and staging is aimed at the baseline determination of metastases and classification of disease into limited or extensive categories.[12] The work-up includes a CT scan of the chest through the adrenal glands (thus including the liver), a CT scan of the brain (looking for occult brain metastases), a radionuclide bone scan, and cytologic evaluation of bone marrow aspirate and bilateral biopsies. Patients with normal hematologic and biochemical profiles are unlikely to have positive bone marrow biopsies.[13] Other routine procedures include evaluation of serum lactic dehydrogenase levels, evaluation of serum chemistries to look for electrolyte abnormalities (especially hyponatremia secondary to the syndrome of inappropriate diuretic hormone), evaluation of renal and hepatic function, evaluation of hematologic profiles, and an electrocardiogram analysis.

The increased use of CT scanning in staging has identified more patients with hepatic and adrenal metastases than previously appreciated. In the 1970s, roughly one half of patients were staged as having limited disease, and one half were staged as having extensive disease. The proportions are now more commonly one-third limited and two-thirds extensive disease. An algorithm of sequential staging procedures has recently been developed and may significantly reduce the cost of an inclusive set of staging procedures.[14]

Treatment Modalities

Surgery

While NSCLC patients with early-stage disease (Stages I and II) are often candidates for curative surgical resection, most SCLC patients are not candidates for such therapy, due to either tumor extent or coexistent disease.[15] Therefore, surgery is usually considered only an adjunct to chemotherapy in SCLC. Some researchers have tried to improve local tumor control by surgical resection following chemotherapy, with or without radiotherapy. In carefully selected populations, this has led to improved long-term survival compared with historical controls. There are also a few series of patients who have had their tumors discovered at apparent Stage I or II classification and have undergone apparently successful resection.[15-17]

SCLC is usually seen in the hilar or mediastinal regions, but occasionally may present as a solitary pulmonary nodule.

Radiotherapy

SCLC is quite sensitive to radiation therapy, which, in conjunction with chemotherapy, is now routinely administered to patients with limited disease.[18,19] The radiation therapy port or field includes the tumor, the mediastinal nodes, and often the supraclavicular lymph nodes.

The role of prophylactic cranial irradiation in patients is less clear. It is usually reserved for patients who have demonstrated a complete response to therapy. It may reduce the incidence of brain metastases, but does not clearly increase survival. A recent review found that intracranial metastases from SCLC

Table 4
Active Single Agents and Combination Chemotherapy Programs

Single Agents	Combinations
Carboplatin	Doxorubicin, cyclophosphamide, etoposide
Carmustine	Cyclophosphamide, doxorubicin, vincristine
Cisplatin	Etoposide, cisplatin
Cyclophosphamide	Methotrexate, doxorubicin, lomustine
Doxorubicin	Cisplatin, doxorubicin, cyclophosphamide, etoposide
Etoposide	Vindesine, cisplatin
Ifosfamide	Vincristine, etoposide, ifosfamide, cisplatin
Lomustine	
Methotrexate	
Procarbazine	
Taxol	
Vinblastine	
Vincristine	
Vindesine	

responded to chemotherapy as readily as other metastatic sites, and the authors concluded that first-line cranial irradiation probably should be applied routinely only in cases of delayed brain metastases.[20]

Irradiation remains the cornerstone of therapy for central nervous system metastases and for the therapy of relapsed patients with the superior vena cava syndrome or spinal cord compression.

Chemotherapy

The chemotherapy of SCLC includes many active single agents and combinations (Table 4). In limited disease it is not uncommon to see response rates of greater than 80 percent to combination chemotherapy, and even in extensive disease, response rates of greater than 50 percent are common. With combination chemotherapy, complete response rates, a necessary requirement for cure, average about 50 percent for limited disease and 30 percent for extensive disease. The most commonly used agents include carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, and vincristine. Combinations of doxorubicin, cyclophosphamide, and etoposide (ACE), ACE plus cisplatin (PACE), cyclophosphamide, doxorubicin, and vincristine (CAV), or etoposide and cisplatin (EP) are currently in common use.[21] To date there is no single regimen that has proven to be superior, although etoposide-containing regimens do appear to be superior to CAV. There is also no clear evidence that alternating non-cross-resistant therapy adds to combination

therapy, although this remains an area of debate.[22-24]

The duration of therapy has evolved from treatment regimens that began at diagnosis and extended to eventual relapse to the current four to six months of chemotherapy. This is analogous to the duration of therapy for other cancers curable by chemotherapy, such as Hodgkin's disease or testicular cancer.

Because of fears of increased toxicity, some physicians are reluctant to treat elderly patients. Oral etoposide as a single agent appears to be both tolerable and effective in elderly SCLC patients, with a complete response rate of 17 percent and an overall response rate of 79 percent.[25] Others have used lower doses with less toxicity.[26]

Multimodality Therapy

For patients with limited disease, the current standard of care is chemotherapy plus thoracic radiation therapy.[18,19,27] The question of the optimal timing of the radiation therapy (early versus late) is still unsettled.[28] There are theoretical advantages to radiation therapy given early with concurrent chemotherapy. The use of both modalities dictates against the selection of chemotherapeutic drugs whose side effects are enhanced by radiation therapy (such as doxorubicin). This accounts for the current popularity of etoposide-cisplatin combinations, which can be combined with radiation therapy more safely. Although response rates are high, both acute and chronic toxicities are also enhanced. The use of prophylactic cranial irradiation is usually reserved for patients who are complete responders to therapy.

Patients with extensive disease usually receive combination chemotherapy, at least initially. Upon relapse those who remain candidates for continued therapy are candidates for investigational therapies. Radiation therapy is not used for most patients with extensive disease, since their fate is linked not only to the course of the disease in the chest but also to the distant metastases.

Prognostic factors

While extensive disease is the worst prognostic factor, other adverse prognostic factors include male sex and poor performance score (>2 on the Zubrod scale).[29] Age greater than 70 years is also associated with an adverse likelihood of survival.[30] Others have noted an interaction between age and disease extent that affected both the probability of obtaining a complete response to therapy and long-term survival.[31] Elevated serum lactic dehydrogenase levels, low serum sodium, and elevated alkaline phosphatase levels are also thought to confer a poor prognosis.[32] Prior chemotherapy is also associated with a low likelihood of response to therapy.

In spite of progress, we cannot yet add this tumor to the list of curable cancers.

Recursive partition and amalgamation algorithm analysis has been used to identify prognostic subsets of patients by using the factors identified above plus the number and sites of metastases, but the final utility of this technique has not been prospectively determined.[33,34]

Patients with mixed small cell/large cell carcinomas or combined small cell carcinomas do not do as well as those with pure small cell carcinoma.

Survival

In spite of its sensitivity to radiation therapy and chemotherapy, most patients still die of their disease. Median survival for limited-stage patients is 14 to 18 months; Median survival for patients with extensive disease is nine to 11 months. About 15 to 25 percent of limited-stage small cell patients survive two

Table 5
Future Directions of Therapy

New chemotherapeutic agents
Modulators of drug resistance
Hematopoietic growth factors
Autologous bone marrow/peripheral-blood stem-cell support
Accelerated hyperfraction radiation therapy
Interdigitation of radiation therapy and chemotherapy
Chemoprevention

years and are considered cured, although they remain at risk for the development of second lung or other primary cancers, especially if treated with both chemotherapy and radiation therapy.[35,36]

Prevention

The elimination of cigarette smoking would virtually eliminate SCLC. Efforts at smoking cessation are not only worthwhile, they should perhaps receive more attention than our attempts at therapy after the development of the tumor.

Future Directions (Table 5)

Since this is by definition a disseminated disease at presentation, the most important advance in therapy (after prevention) would be the development of additional effective chemotherapeutic agents. Promising new chemotherapeutic agents include: taxol (paclitaxel), taxotere, gemcitabine, and campothecin. Modulators of drug resistance are currently being evaluated in the clinical setting. The use of hematopoietic growth factors with autologous bone marrow or peripheral-blood stem-cell support may permit higher doses of chemotherapy and/or their safer administration, resulting in higher response rates. Modulators of acquired drug resistance may decrease the development of drug-resistant tumor cells.

New radiation schedules, such as accelerated hyperfractionation, also carry the promise of increased local control with decreased toxicity. The optimal interdigitation of radiation therapy and chemotherapy also deserves further study. Chemoprevention trials with retinoids are currently underway and offer the potential of decreasing the incidence of second malignancies. This list is reminiscent of the closing paragraphs of the last review article on small cell lung cancer in this journal, published nearly 10 years ago.[37] Clearly, in spite of progress we cannot yet add this tumor to the list of curable cancers. CA

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