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Small Cell Carcinoma

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Small cell carcinoma of the lung (SCCL) is a common tumor, accounting for 20% to 25% of the approximately 170,000 lung cancers detected each year in the United States.[1–5] Although 75% occur in patients between 50 and 70 years of age, the relative frequency of this tumor compared with other tumor types is similar among younger persons.[1] For many years, SCCL has been regarded as a male-dominated tumor, with retrospective studies from the 1960s reporting male-female ratios of 11:1 to 19:1.[6] The incidence of SCCL in women is steadily rising, with reports of male-female ratios as low as 3.67:1 and 1.9:1.[3,7–9] In one study of 1745 patients conducted between 1972 and 1986, the percentage of women with SCCL increased from 21% to 35%.[10]

SCCL is characterized by a rapid clinical course, reflecting the short doubling time and high DNA-labeling index of this neoplasm.[11,12] Recent advances in radiographic detection and chemotherapy have resulted in significant palliation and prolonged survival. Complete therapeutic responses with relatively long-term survival (*i.e.*, >2 years) are being observed for some patients with limited disease. Despite these and other advances, early detection of primary or recurrent SCCL remains difficult because of the tumor's penchant for rapid dissemination. Clinical trials investigating new treatment modalities and biologic markers of tumor progression are ongoing.

HISTOGENESIS AND THE DIFFUSE NEUROENDOCRINE SYSTEM

In 1938, Feyrter observed clear cells within the gastrointestinal tract, which he thought represented the local component of a "diffuse epithelial endocrine organ."[13] He postulated that these cells would exert their effects only on neighboring cells, rather than on distant organs, and designated this mode of action as "paracrine."[13] The discovery of similar cells in the lung and elsewhere led to the introduction of the amine precursor uptake and decarboxylation (APUD) concept by Pearse in 1966.[14–17] The APUD concept was modified several times since its inception but essentially stated that all endocrine and paraendocrine cells were derived from the neural crest.[18,19] The APUD concept was quickly disproved by the experiments of Fontaine and LeDouarin.[20] Using quail-chick chimeras, the researchers showed that, despite ablation of the neural crest early in embryogenesis, Kulchitsky cells (*i.e.*, K cells) still appeared within the colonic endoderm, but the neural crest–derived myenteric plexus structures were absent. Additional experiments by Pictet and colleagues confirmed that the endocrine cells of the gastrointestinal tract and pancreatic islets were of endodermal derivation.[21]

Pearse and Takor-Takor subsequently proposed the revised concept of a diffuse neuroendocrine system (DNES) composed of 40 individual cell types with common characteristics but different embryologic origins.[22] The DNES concept is important in cell biology, but the origin of these cells remains unsettled. Gould emphasizes that, regardless of embryologic origin, all cell types within the DNES share a common neuroendocrine program to produce and use various peptides and biogenic amines found within the nervous and endocrine systems.[23,24]

The precise origin and histogenesis of SCCL are still controversial. The bronchial mucosa is lined by basal reserve cells, some of which are argyrophilic and contain intracytoplasmic neurosecretory-type granules.[14,15,25] These cells are relatively numerous in the human fetus and neonate but are rarely found in the adult. The cells can metabolize precursor amine substances into polypeptide hormones and are thought to represent the pulmonary neuroendocrine equivalent of the DNES, similar to islet cells of the pancreas, C cells of the thyroid, and K cells of the gastrointestinal tract.[14,15,25]

K cells in the lung were first described in 1949 by Froelich, who speculated that the cells functioned as chemoreceptors and may represent the progenitor cell of bronchial carcinoids.[26] The ultrastructural presence of neurosecretory granules within the bronchial clear (*i.e.*, Kulchitsky) cells was described in 1965.[14,15] Speculation soon followed that the neurosecretory granules in

SCCL and bronchial carcinoid tumors indicated the tumors were closely related and probably Kulchitsky cell derived.[27,28] Most SCCL are submucosal tumors, providing additional evidence for a reserve cell origin.

In 1972, Lauweryns and colleagues described aggregates of clear, argyrophilic cells in human bronchial mucosa with neurosecretory-type granules, which they designated as neuroepithelial bodies (NEBs).[29,30] The NEBs are distinct from the individual argyrophilic basal cells and appear to be innervated and associated with vessels, consistent with a chemoreceptor function. NEBs and isolated neuroendocrine cells are more readily identified in the lungs of children than adults, but the cells often require immunohistochemical staining for identification.

Although the precise cell of origin for SCCL is unknown, most investigators favor the tumor derived from similar neuroendocrine precursors or another endodermally derived pulmonary epithelial cell that is capable of neuroendocrine differentiation.[31] Neuroendocrine features are found in other histologic types of lung cancer, raising the possibility that a common stem cell exists with the capability for multidirectional differentiation.[32]

PATHOLOGY

Pathogenesis

The central location of many SCCL implies a chronic mucosal irritation mechanism after absorption of airborne carcinogens, particularly at points of bronchial bifurcation. There is a strong association of SCCL with several environmental carcinogens, including cigarette smoke, radiation, and chloromethyl methyl ether.[2,33–35] These associations have not been demonstrated with bronchial carcinoids.

The strongest association has been found with cigarette smoking, and a linear dose-response association between cigarette consumption and the incidence of pulmonary SCCL has been reported.[35] SCCL occur more often in heavy smokers and in those who began smoking at an early age than in light smokers who begin smoking later in life.[2,36] In several large SCCL series, virtually all patients have been smokers.

Pulmonary SCCL is the most common cancer in uranium miners, and accounts for 66% of all lung tumors in this occupational group.[37] A synergistic association between radon exposure and cigarette smoking has been proposed.[37–39] Whole-body irradiation increases the relative risk of lung cancer in all groups but does so to a lesser extent in uranium miners.[40] SCCL also accounts for almost 70% of lung tumors associated with chloromethyl methyl ether exposure.[41]

Histologic Subtypes

In 1958, the World Health Organization (WHO) formulated a tentative classification for lung cancer under the direction of Kreyberg (Table 49-1).[42] Intended to standardize international nomenclature and encourage cooperative data analysis, the system recognized two subtypes of SCCL: the oat cell (*i.e.*, 21) and the polygonal cell (*i.e.*, 22). The WHO classification was adapted by the Veterans Administration Lung Cancer Study Group (VALCG), who concluded that recognition of the oat cell type posed little difficulty.[5] Diagnosis of the polygonal cell type was less reliable, with unanimity reported in only 34% of cases.[5]

The WHO published its first official lung cancer classification in 1967.[43] In a departure from the earlier, tentative system, SCCL was divided into four subtypes: lymphocytelike, polygonal, fusiform, and other. The lymphocytelike type, essentially identical to the earlier oat cell type, designated SCCL with ovoid, hyperchromatic cells, smudged chromatin, and little to no visible cytoplasm. The polygonal and fusiform cell types, both previously designated as polygonal, included tumors with oval or round and fusiform neoplastic cells, finely granular chromatin, and scant cytoplasm. The "other" category included SCCL with squamous or glandular foci and rosettes.

In 1973, the Working Party for Therapy of Lung Cancer (WP-L) proposed a modified system to improve consistency and reliability in diagnosis.[44] Similar to the VALCG, the WP-L concluded that the lymphocytelike variant presented minimal diagnostic difficulty and its designation was retained. The polygonal and fusiform subdivision was considered unnecessary, and both types, in addition to those in the "other" category, were grouped under the designation of intermediate cell.[44]

The WHO lung cancer classification was revised in 1977 under the direction of Yesner, although formal publication did not take place until 1981.[45] In this system, lymphocytelike was replaced with oat cell, and the intermediate subtype was retained

TABLE 49-1
Evolution of Small Cell Lung Cancer Classification

Kreyburg (1962)[42]; VALG (1965)[5]	WHO (1967)[43]	WP-L (1973)[44]	WHO (1977)[45]	NCI-VA (1978)[48,49]	IASLC (1985)[50]
Oat cell	Lymphocytelike	Lymphocytelike	Oat cell	Lymphocytelike	Small cell
Polygonal cell	Polygonal cell Fusiform cell Others	Intermediate cell	Intermediate cell Combined	Intermediate cell Mixed small cell and large cell Combined	Mixed small cell and large cell Combined

IASLC, Pathology Committee of the International Association for the Study of Lung Cancer; NCI-VA, National Cancer Institute—Veterans Administration, Medical Oncology Branch; VALG, VA Lung Cancer Study Group; WHO, World Health Organization; WP-L, Working Party for Therapy of Lung Cancer.

for the polygonal and fusiform subtypes. The "other" category for SCCL with squamous or glandular areas was replaced with the designation of combined oat cell carcinoma. The system recommended that tumors showing mixtures of oat cells and intermediate cells be categorized as oat cell, but neoplasms composed of intermediate and large anaplastic cells should be designated as intermediate.[45]

Despite these and other revisions, substantial variation in diagnosis was still found for the morphologic subtypes other than oat cell, primarily because of difficulties in criteria interpretation.[46] In 1982, Vollmer stated that tumor cell size in pulmonary SCCL partially depended on the size of the biopsy specimen and that subclassification according to cell type was spurious.[47]

In 1978, the National Cancer Institute—Veterans Administration Medical Oncology Branch supported the revised WHO classification but advocated that mixed small cell and large cell carcinoma, previously contained in the intermediate category, be separately designated as "22/40" tumors (*i.e.*, their respective 1967 WHO classification numeric designations) because of their poorer prognosis and relative unresponsiveness to therapy.[48,49]

In 1985, the Pathology Committee of the International Association for the Study of Lung Cancer found no significant clinicopathologic differences between the oat cell and intermediate cell types and recommended that both terms be discarded for the encompassing term "small cell carcinoma."[50] Only two subtypes were recognized: mixed small cell and large cell carcinoma for tumors containing areas of large cell undifferentiated carcinoma (*i.e.*, 22/40 tumors) and combined small cell carcinoma for SCCL with areas of squamous or glandular differentiation. This system was published in a more detailed format in 1988 and is the most widely used classification for SCCL.[51]

Gross Pathology

SCCL of the lung arise centrally in more than 90% of patients. Tumors usually circumferentially involve large bronchi, producing luminal stenosis and submucosal peripheral extension. Rare cases with intraluminal exophytic growth have been reported, including one case with multiple tracheal and bronchial tumors resembling tracheobronchial papillomatosis.[52,53] On cut section, a pulmonary SCCL is usually gray-white and has areas of hemorrhage and necrosis. Tumors are usually soft, reflecting the absence of a desmoplastic response within the neoplasm or surrounding tissue. Unlike squamous cell carcinoma, central liquefaction and cavitation are rare. Compression or frank invasion of the adjacent vasculature (*e.g.*, the inferior vena cava, pulmonary arteries, veins) is common (Fig. 49-1). SCCL metastases are often massive and appear grossly similar to the primary lung tumor (Fig. 49-2).

Microscopic Pathology

Endoscopic biopsies of SCCL often show considerable fragmentation and crush artifact because of the marked fragility of the neoplastic cells. Intact, well-preserved neoplastic cells may be difficult or impossible to identify (Fig. 49-3). Well-preserved, undistorted tissue is important for proper interpretation and may require repeated biopsies. Nonetheless, crush artifact is distinctly uncommon in non-SCCL pulmonary tumors, and although it may be seen in lymphoid infiltrates, its presence should prompt a strong suspicion of SCCL.

Most SCCL, regardless of histologic subtype, lack a defined architectural pattern. Sheets of haphazardly arranged tumor cells partitioned by thin fibrous septa are commonly seen; cell nests, ribbons, and peripheral palisading may be observed in some tumors (Figs. 49-4 and 49-5). Necrosis is invariably found, and it may be extensive (Fig. 49-6). The virtual absence of a desmoplastic or lymphocytic host response is common, even in areas of tumor necrosis. Basophilic deposition of tumoral DNA within blood vessel walls, referred to as nuclear encrustation or the Azzopardi phenomenon, is common in SCCL but rarely seen in other pulmonary tumor types (Fig. 49-7). Rare SCCL also have foci of rosette formation (Fig. 49-8). The bronchial epithelium is usually separated from the tumor by an attenuated zone of uninvolved submucosa; pagetoid invasion of the overlying epithelium by tumor cells is uncommon.

The classic oat cell and intermediate cell types probably represent phenotypic variation of a single cell type. The tumor cells are two to three times the size of a resting lymphocyte and may appear round or oval, fusiform, or spindled (Figs. 49-9 through 49-11). Nuclear pleomorphism is often pronounced, and mitotic figures

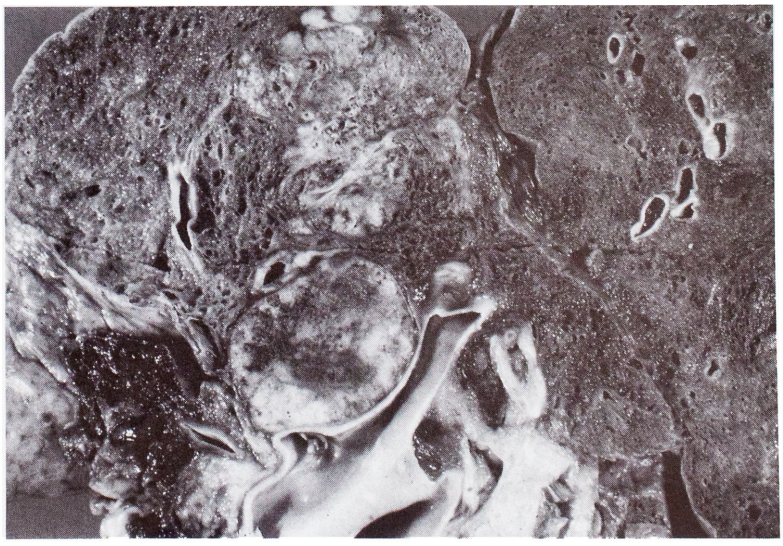

FIGURE 49-1. Small cell carcinomas of the lung are typically centrally located, well circumscribed, and have a variegated gross appearance with areas of hemorrhage and necrosis. This tumor is compressing an adjacent pulmonary artery, and there is a distal, wedge-shaped area of obstructive pneumonia.

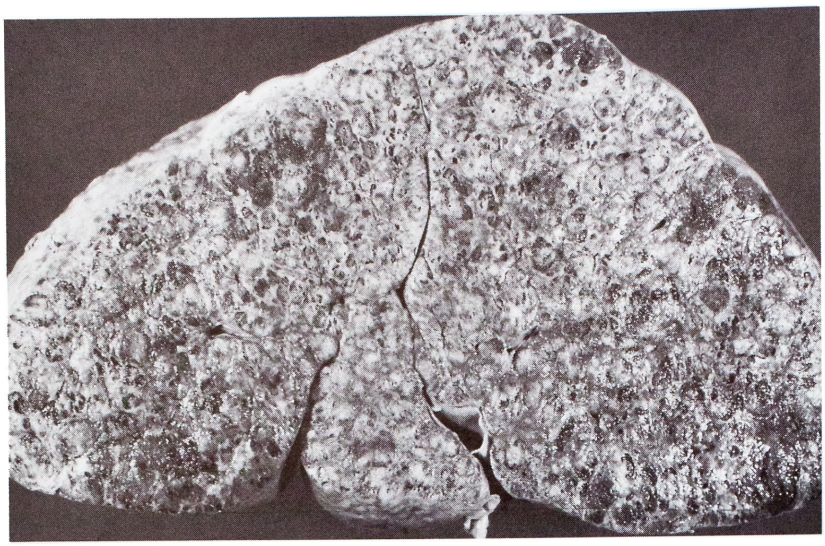

FIGURE 49-2. Some patients with small cell carcinoma of the lung present with hepatic failure due to massive liver metastases.

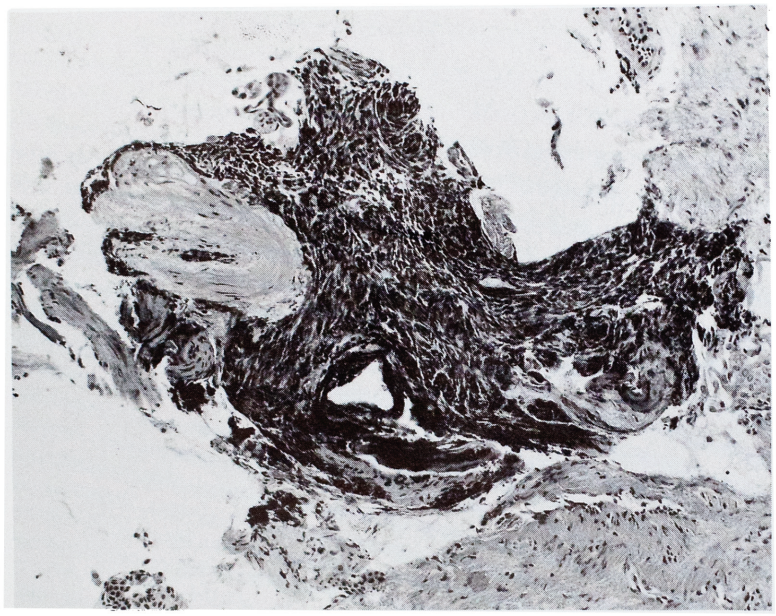

FIGURE 49-3. Transbronchial biopsies of pulmonary small cell carcinomas often show an extensive crush artifact, which obscures histologic detail and prevents a definitive diagnosis. (H & E stain; low magnification.)

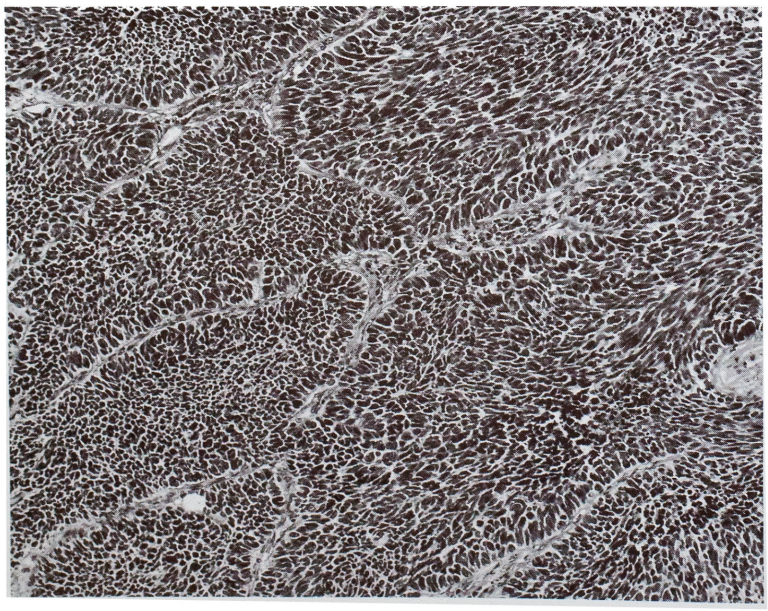

FIGURE 49-4. Small cell carcinomas of the lung typically form sheets of haphazardly arranged cells separated by delicate, fibrous septa. The closely opposed tumor cells create a hyperchromatic appearance. Notice the areas of peripheral pallisading. (H & E stain; low magnification.)

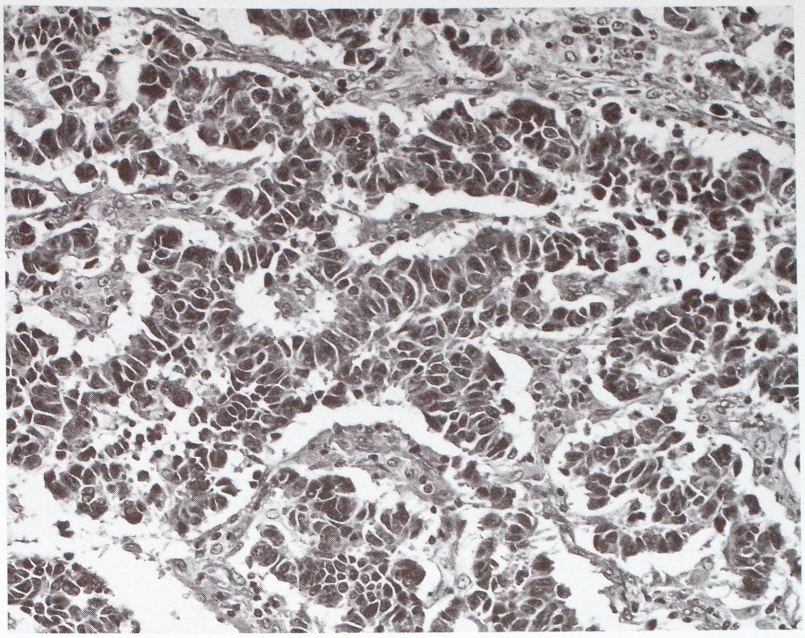

FIGURE 49-5. Some small cell carcinomas have cells arranged in cords and trabeculae, reminiscent of an atypical carcinoid tumor. (H & E stain; intermediate magnification.)

are abundant. In poorly preserved tissue or small biopsies, the tumor cells often appear smaller and more hyperchromatic, with smudged, dark nuclei and inapparent cytoplasm (*i.e.*, oat cells). In well-preserved tissue, the tumor cells are larger, with finely granular nuclear chromatin, inconspicuous nucleoli, and scant or moderate amounts of basophilic cytoplasm (*i.e.*, intermediate cells). In both cell types, the nuclei are closely apposed, giving the tumor a characteristic hyperchromatic or blue cell appearance at low magnification. Cell molding is frequently observed, and giant cells may be seen, particularly after treatment.

Two uncommon variants of pulmonary SCCL are mixed small cell and large cell carcinomas and combined tumors, accounting for approximately 10% to 15% and fewer than 1% of pulmonary SCCL, respectively.[54–56] Mixed small cell and large cell carcinomas contain a subpopulation of large, undifferentiated cells occurring singly or in small clusters and intimately admixed with the small cell component (Fig. 49-12). The nuclei are oval or elongated and irregular, with cleared chromatin and prominent eosinophilic nucleoli. The large cells contain various amounts of amphophilic or lightly eosinophilic cytoplasm with indistinct cytoplasmic borders. The nuclear diameter of the large cells may not exceed that of well-preserved SCCL cells, nor are two distinct cell populations necessarily apparent. A continuum of cell types is usually seen, ranging from typical SCCL cells to the large cells.

Combined SCCL with squamous carcinoma or adenocarcinoma are rare at initial presentation and more commonly encountered at autopsy in SCCL patients after intensive therapy. These tumors are composed of a predominant SCCL population with areas of mature glandular or squamous differentiation (Fig. 49-13). The glandular or squamous foci may be intermixed with

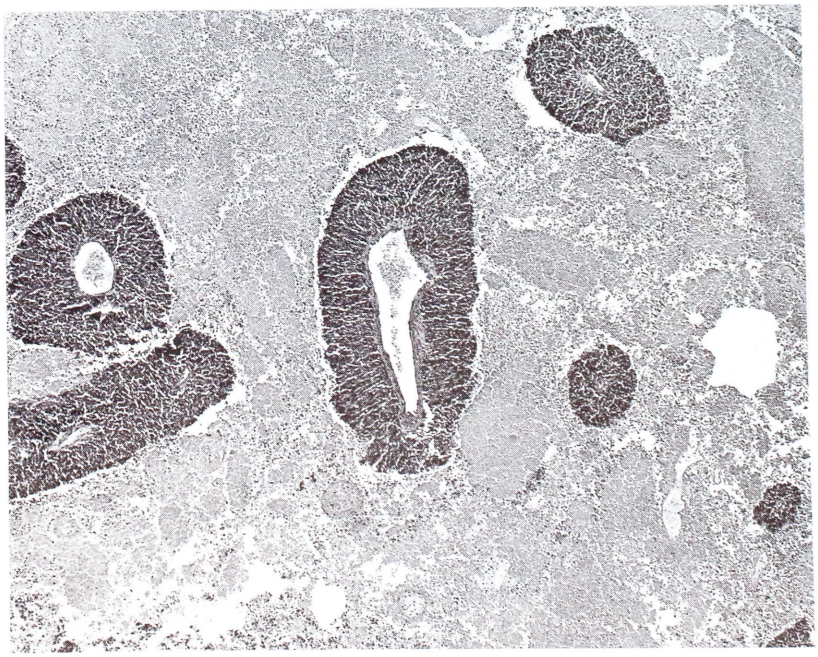

FIGURE 49-6. Some small cell carcinomas of the lung are predominantly necrotic. Notice the perivascular aggregation of tumor cells. (H & E stain; low magnification.)

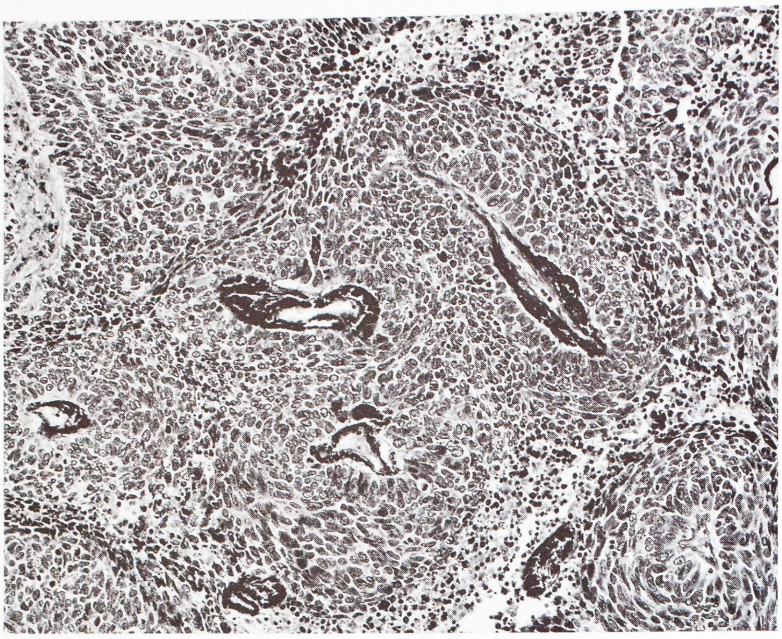

FIGURE 49-7. Some small cell carcinomas show basophilic deposition of tumoral DNA within vessel walls; this is also called the Azzopardi phenomenon. (H & E stain; low magnification.)

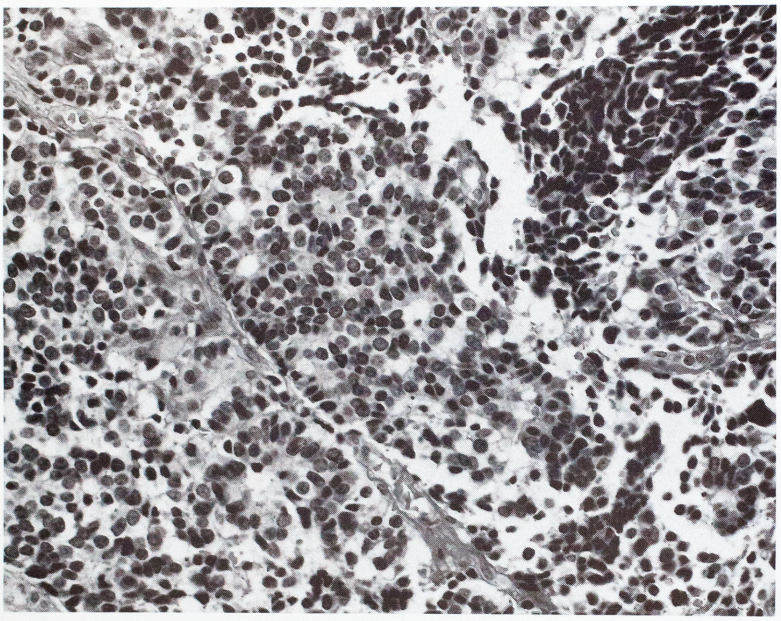

FIGURE 49-8. Rarely, small cell carcinomas show areas of rosette formation. This tumor has Flexner-type rosettes in which the tumor cells surround a definite central lumen. (H & E stain; intermediate magnification.)

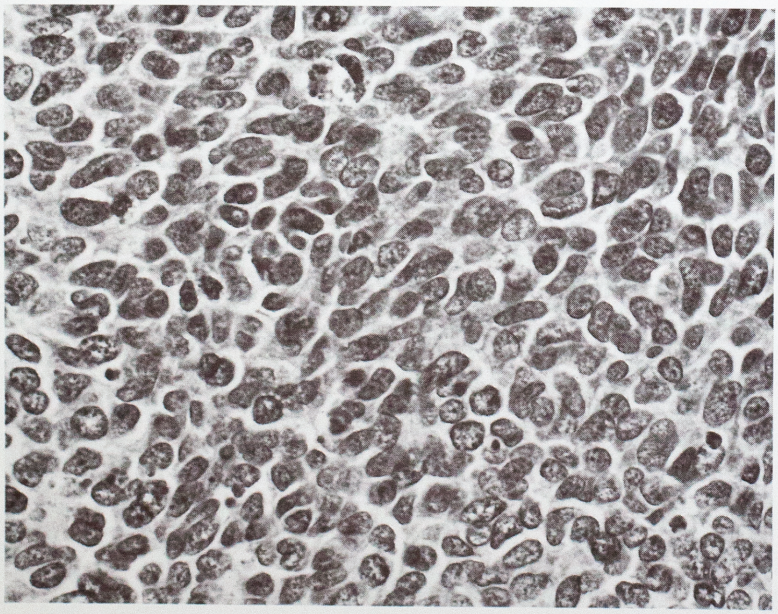

FIGURE 49-9. This small cell carcinoma is composed predominantly of oval-to-polygonal tumor cells. The clumped chromatin pattern, mildly irregular nuclear outlines, and inconspicuous amounts of cytoplasm are characteristic. (H & E stain; high magnification.)

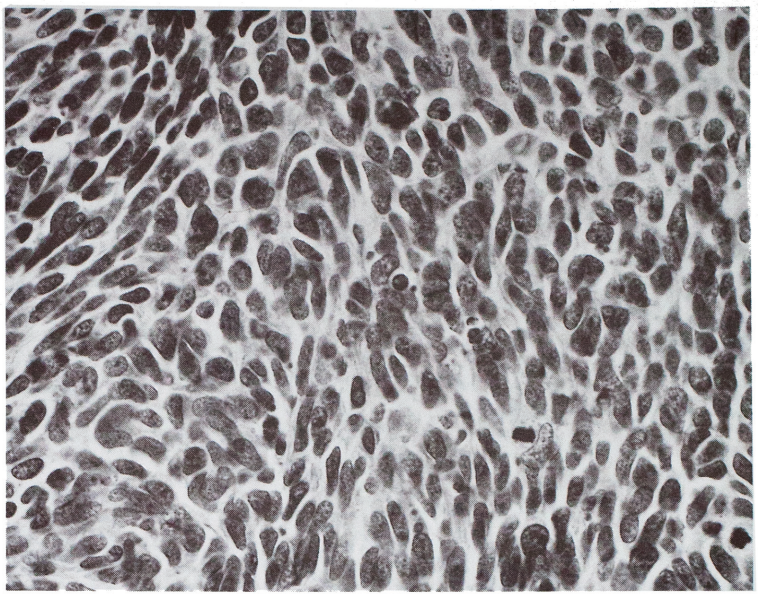

FIGURE 49-10. This small cell carcinoma of the lung is composed of ovoid-to-fusiform tumor cells. (H & E stain; high magnification.)

the predominant SCCL component, but more often, the two components are categorically distinct, and the appearance resembles a collision tumor.

IMMUNOHISTOCHEMISTRY

As with bronchial carcinoids and neuroendocrine tumors of other sites, pulmonary SCCL are neuroendocrine epithelial tumors characterized by cytoskeletal intermediate filaments and the production of various hormones and bioactive amines. The immunohistochemical findings are not specific for pulmonary SCCL and must be interpreted in concert with the tumor's morphologic appearance. Non-small cell pulmonary carcinomas may also express neuroendocrine features, but they are usually easily separated by conventional histologic means.

The precise intermediate filament composition of these tumors was once a controversial topic, because preliminary studies reported that pulmonary SCCL were immunohistochemically negative for cytokeratin and positive for neurofilament.[57,58] Subsequent studies using appropriate monoclonal antibodies and preliminary enzymatic digestion showed that virtually all pulmonary SCCL express low-molecular-weight cytokeratins (Fig. 49-14).[59–62] Two-dimensional electrophoresis studies have shown that pulmonary SCCL specifically express cytokeratin polypeptides 8, 18, and 19.[59] Neurofilaments are rarely found in pulmonary SCCL and are not considered diagnostically useful.[63] Other intermediate filament types, such as vimentin, desmin, and glial filament protein, are not routinely detected.[59,60,64]

Other markers commonly found in pulmonary SCCL include desmoplakins, epithelial membrane antigen, and neuron-specific enolase (NSE).[59,61,65] NSE, an enolase isoenzyme normally present in neurons and neuroendocrine cells, was once considered a relatively specific marker of neural and neuroendocrine differen-

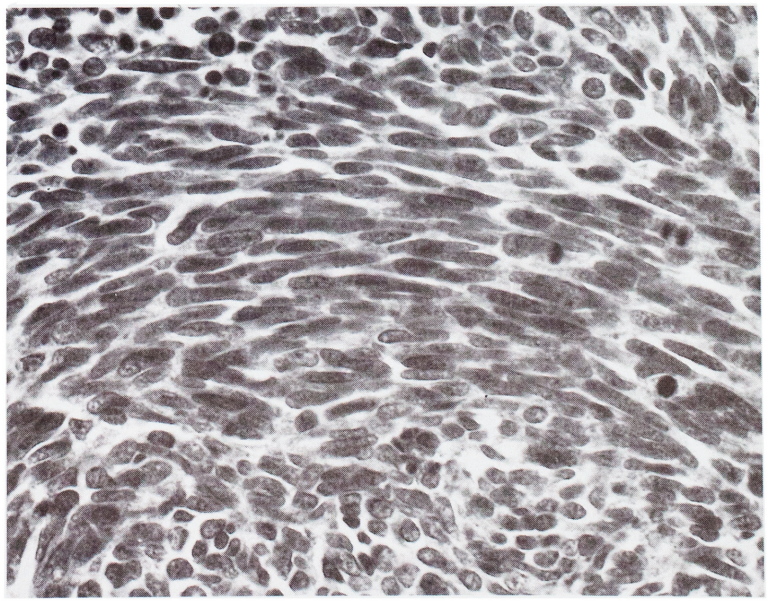

FIGURE 49-11. This small cell carcinoma has focal areas composed mostly of spindled cells with numerous mitoses. (H & E stain; high magnification.)

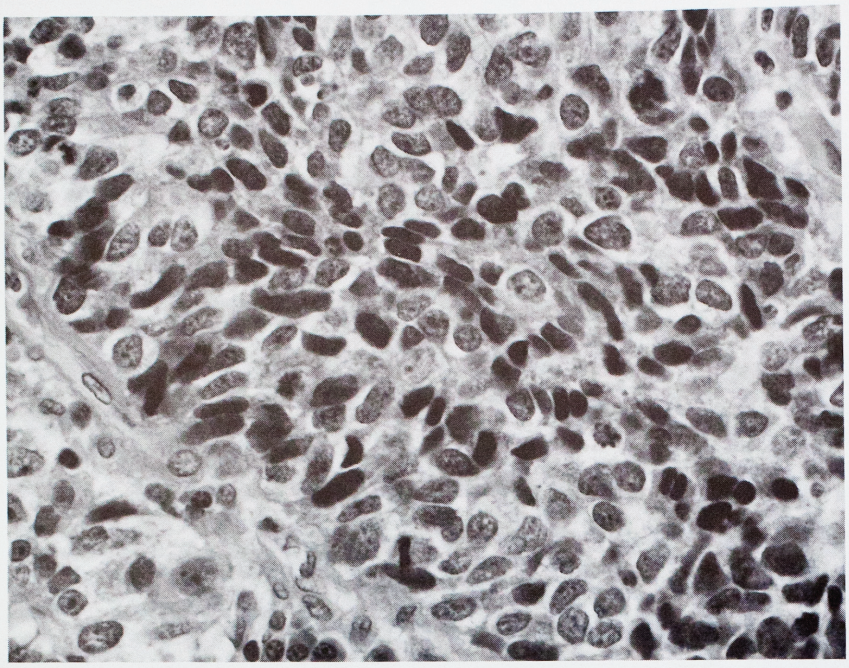

FIGURE 49-12. A mixed small cell–large cell undifferentiated carcinoma consists of small fusiform cells with molded, hyperchromatic nuclei intermixed with larger cells that have more prominent cytoplasm and vesicular nuclei. (H & E stain; high magnification.)

tiation. Immunoreactivity with the polyclonal and, to a lesser extent, monoclonal anti-NSE preparations have been documented in many other nonendocrine tissues and tumors.[66–68] Several studies reported diffuse cytoplasmic immunoreactivity for NSE in approximately one half of the SCCL studied, but because of its varied distribution, immunopositivity for NSE cannot be used to reliably differentiate SCCL from other, non-SCCL tumor types.[65,67,68]

The chromogranin-secretogranin polypeptides comprise a family of acidic proteins found in mammalian and nonmammalian species.[69] Two chromogranins designated A and B are recognized; both form a major portion of the soluble proteins in endocrine secretory granules.[69] Pulmonary SCCL contain abundant chromogranin A mRNA but little stored chromogranin A protein, consistent with the low number of neuroendocrine granules in these tumors.[69–71] Pulmonary SCCL stain focally or often not at all with antichromogranin monoclonal antibody LK2H10 (Fig. 49-15).[63,65,72] Although one study found chromogranin immunopositivity in 18 (56%) of 32 SCCL samples, in our experience, definitive, punctate cytoplasmic positivity for chromogranin A in SCCL is an unusual event.[63]

Synaptophysin, a 38-kd membrane glycoprotein isolated from presynaptic vesicles of bovine brain neurons, is a highly sensitive and specific marker of neuronal and neuroendocrine differentiation.[73,60,62,64] A monoclonal antibody raised against synaptophysin (*i.e.*, SY38) labels the vesicles of neuronal and neuroendocrine tissues and neoplasms in a granular, peripheral cytoplasmic distribution. The immunohistochemical expression of synaptophysin is often masked on formalin-fixed, paraffin-embedded tissue.[74] For optimal results, the use of cryostat sections, ethanol-fixed sections, or tissues fixed for 2 to 4 hours in Bouin solution has been advocated.[74] Even in studies using optimal

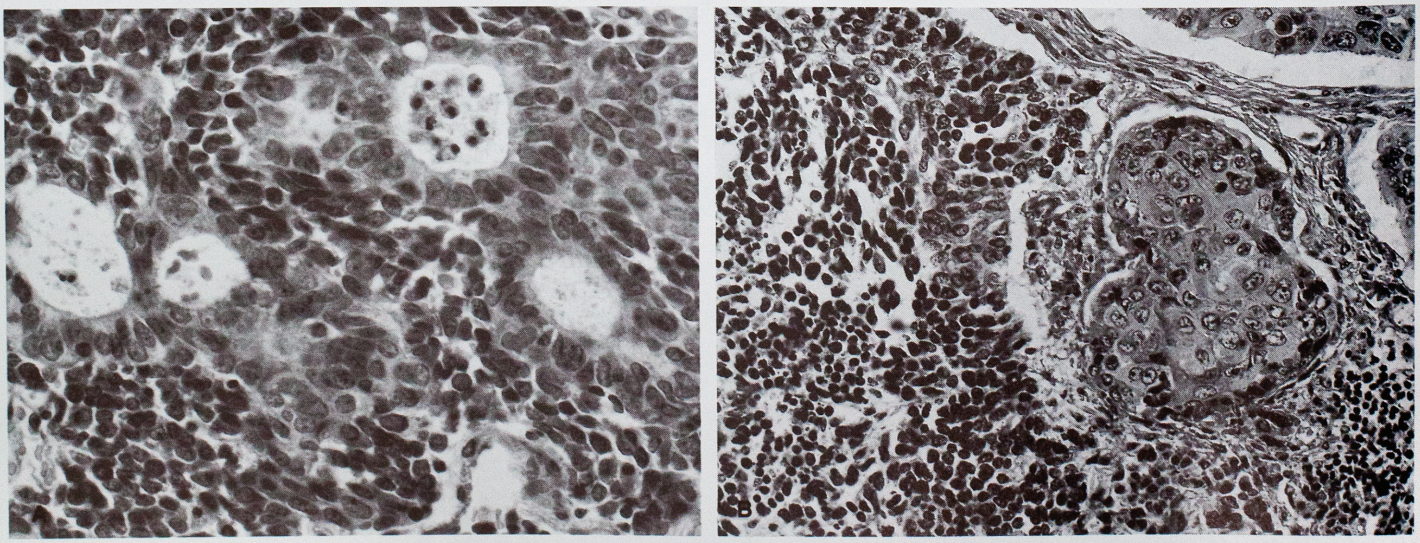

FIGURE 49-13. A combined small cell carcinoma has areas of (**A**) glandular and (**B**) squamous differentiation. (H & E stain; [**A**] high and [**B**] intermediate magnifications.)

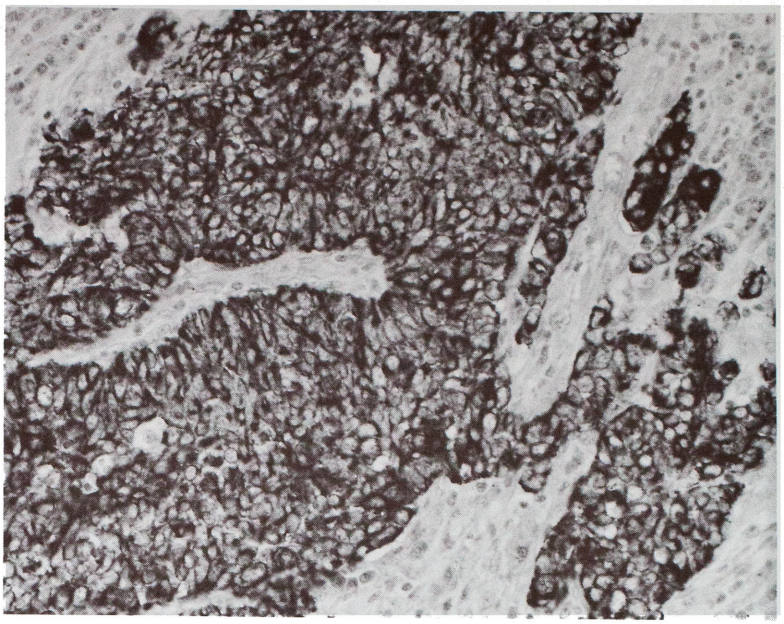

FIGURE 49-14. Virtually all small cell carcinomas of the lung immunostain for low-molecular-weight cytokeratins using the appropriate antibodies and preliminary enzymatic digestion. (Immunoperoxidase stain for keratin; intermediate magnification.)

fixation techniques, synaptophysin immunoreactivity is usually observed in only a portion of the pulmonary SCCL.[75,62,64] Gould and associates reported synaptophysin positivity in 2 of 10 SCCL on cryostat section and in 6 (43%) of 14 SCCL on Bouin-fixed tissue.[60] Kayser and colleagues observed SY38 reactivity in 49 (79%) of 68 SCCL samples and in 6 (8%) of 74 non-SCCL samples.[75]

Pulmonary SCCL react with various hormonal peptides and biogenic amines, including bombesin, calcitonin, ACTH, leu-enkephalin, gastrin, serotonin, somatostatin, vasoactive intestinal peptide, glucagon, insulin, and substance P.[59,76] Immunoreactivity for bombesin and probombesin has been reported in as many as 69% of pulmonary SCCL, but it may also be found in rare cases of non-SCCL.[63,65,75,77] Hamid and associates reported immunoreactivity for the C-terminal peptide of human bombesin in 175 (70%) of 250 pulmonary SCCL and in 31 (63%) of 49 atypical carcinoids but in only 10 (16%) of 62 of carcinoids.[78] Patients with tumors immunoreactive for the C terminal fragment had significantly shorter survival times than those without the fragment, leading the researchers to propose the C-terminal peptide as a useful marker for diagnosis and predicting the course of disease.[78]

The monoclonal antibody, HNK-1, directed against the Leu-7 antigen originally described on human natural killer cells has been proposed as useful in the diagnosis of SCCL.[63] The HNK antibody reacts with a 75-kd protein within the matrix of the chromaffin granule, and Leu-7 immunopositivity has been described in many neuroendocrine tumors, including islet cell tumors, carcinoids, and pheochromocytomas.[79,80] The HNK antibody reacted with 18 (56%) of 32 samples of pulmonary SCCL by Linnolia and colleagues, but it also labeled 17 (22%) of 77 of non-SCCL.[63] Because of its relatively poor sensitivity and specificity, most investigators do not advocate the routine use of Leu-7 immunohistochemistry in the diagnosis of pulmonary SCCL.

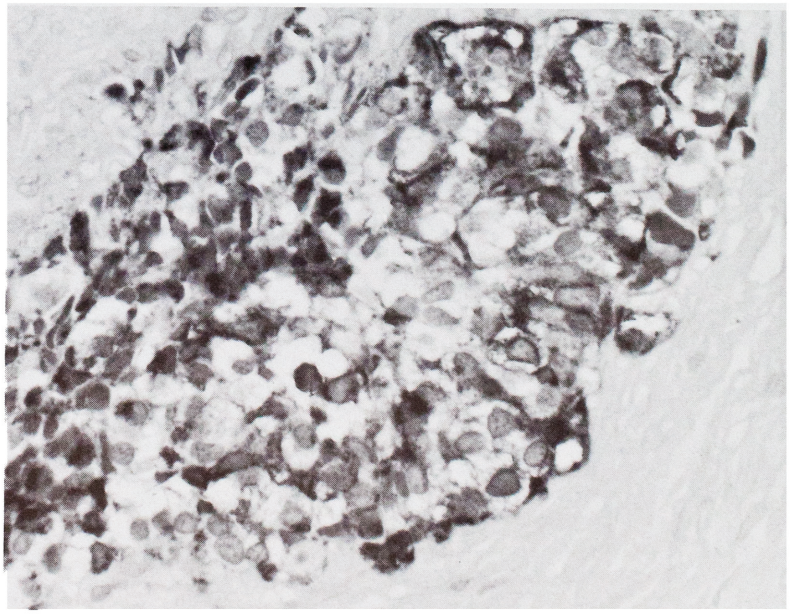

FIGURE 49-15. Rarely, small cell carcinomas immunostain for chromogranin in a granular, cytoplasmic distribution. (Immunoperoxidase stain; high magnification.)

ELECTRON MICROSCOPY

Well-preserved, nondistorted material is always desirable in an ultrastructural examination, but careful specimen sampling and thick-section screening is vitally important in the ultrastructural examination of pulmonary SCCL because of the large areas of necrosis and crush artifact in these tumors.

Ultrastructurally, a SCCL is composed of round or oval cells with complex, interlacing cytoplasmic processes connected by primitive cell junctions or, less often, well-formed desmosomes. The nuclei are typically angular and mildly irregular, with focally clumped chromatin and occasional nucleoli (Fig. 49-16). Nuclei are typically closely apposed, with such small amounts of cytoplasm that the shape of the cell usually parallels that of the nucleus.

Neurosecretory-type granules that are 80 to 150 nm in diameter are found in most, but not all, SCCL (Fig. 49-17).[15,81–83] Elema and Keuning were unable to locate dense core granules in 7 (16%) of 43 pulmonary SCCL studied.[81] This is also our experience and that of other investigators.[84,85] The granules are spherical, uniform, typically 80 and 150 nm in diameter, and demarcated by a limiting membrane separated from the granular substance by a halo. Granules may be seen throughout the cytoplasm but tend to aggregate within the dendritic processes. The cytoplasm is typically sparse and contains a few bundles of intermediate filaments and scattered microtubules. Unlike non-small cell pulmonary carcinomas, there is a marked paucity of cytoplasmic organelles in SCCL.

Distorted tumor cells with dark, irregular nuclei, coarse chromatin clumping, and dark cytoplasm packed with mitochondria and other organelles may be seen.[81] Cell borders are indistinct, and the general appearance is that of tumor degeneration. These areas are considered secondary to tumor anoxia or crush artifact and probably correspond to the oat cell phenotype seen histologically.[81]

Pulmonary SCCL may mimic many other poorly differentiated metastatic tumors, including lymphoma, small cell melanoma, rhabdomyosarcoma, Ewing sarcoma, and olfactory neuroblastoma. In selected cases, confirmatory studies may be helpful. In our experience, the immunohistochemical demonstration of neuroendocrine epithelial differentiation, in combination with the morphologic features described, are sufficient to confirm the diagnosis in most cases. The situations for which electron microscopy would be required for diagnosis are rare, and most would involve examination of poorly preserved or suboptimally fixed tissue in which immunohistochemical examination proved unsatisfactory.

DNA PLOIDY AND CYTOGENETICS

Relatively few studies have analyzed the ploidy (*i.e.*, DNA content) of pulmonary SCCL by flow cytometry or other means. Vindelov and associates analyzed 38 SCCL, 74% of which were aneuploid and 26% of which were diploid.[86] Of the aneuploid specimens, 73% were hypotetraploid or near-tetraploid, 15% were hypodiploid, and 12% were hypotriploid.[86] The researchers also detected two or more cell clones with different ploidy measurements in 21% of the tumors overall.[86] Bunn and colleagues studied 87 SCCL; 83% were aneuploid, and 17% were near-diploid.[87] Most of these were hypotriploid, with a tetraploid or greater DNA index observed in 7 tumors (8%). In this study, the mean DNA index was 1.42 ± 0.37, with a median of 1.43. Compared with the findings of Vindelov, there was a much smaller prevalence of clonal heterogeneity, with multiple cell clones detected in 9 (9%) of 99 tumor samples.[86,87] Other investigators have found DNA aneuploidy in approximately 75% of SCCL studied.[76,88] Aneuploidy in SCCL has not been found to be an independent prognosticator of patient survival, tumor recurrence, or progression.[86–88]

Cytogenetic investigations have shown a relatively specific chromosomal abnormality in SCCL: deletion of part of the short arm of chromosome 3. The size of the deletion varies, but most cases show a deletion in the 3p14-p23 region.[89–97] Karyotypic

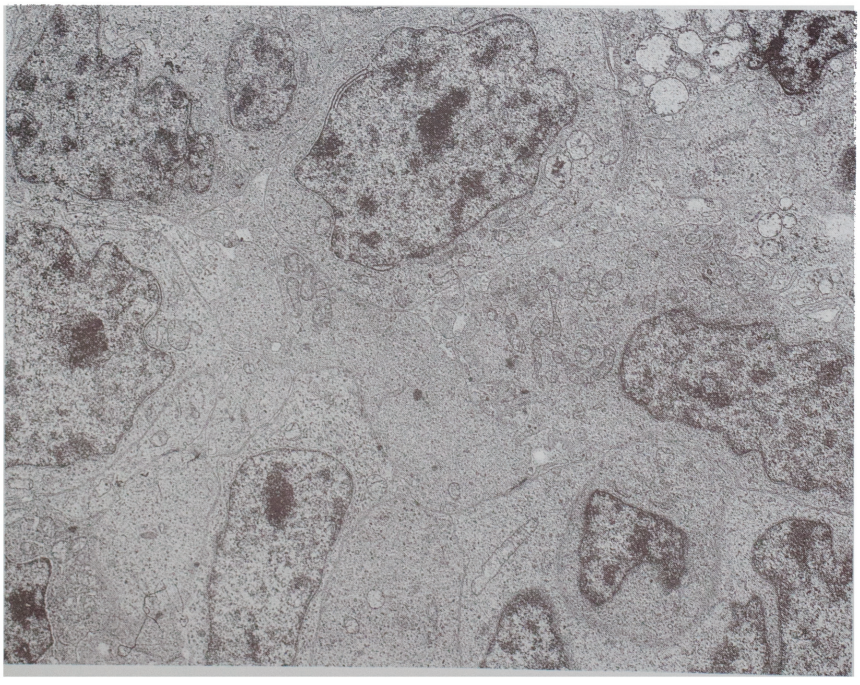

FIGURE 49-16. A small cell carcinoma of the lung has a typical ultrastructural appearance. The neoplastic cells have mildly irregular, closely opposed nuclei with rare nucleoli. The cellular organelles are characteristically scant. (Original magnification ×7000.)

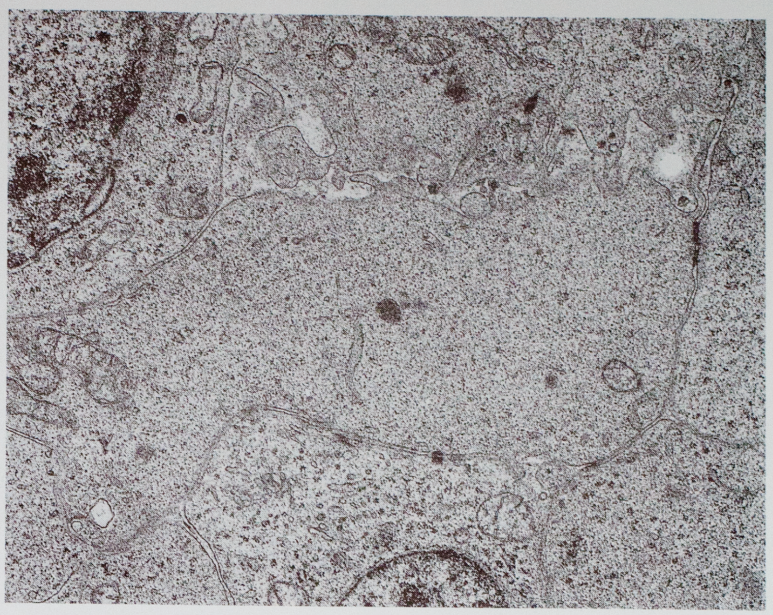

FIGURE 49-17. Intertwining cellular processes joined by primitive cellular junctions are often observed in small cell carcinomas. Notice the single, dense-core, neurosecretory-type granule. (Original magnification ×18,000.)

analyses have identified this deletion in about 85% of SCCL (range, 21%–100%). These results led to the conclusion that inactivation of one or more genes within the 3p14-23 region may be an early, essential step in SCCL carcinogenesis. However, many of these studies were conducted on cell lines derived from treated patients and maintained in culture for 4 to 96 months rather than on primary tumor tissue. Abnormalities of the short arm of chromosome 3 also occur in most pulmonary carcinoids and in as many as 25% of non-SCCL tumors.[93,98,99]

Pulmonary SCCL cell lines have frequent structural aberrations of chromosomes 1, 2, 9, 10, 14, and the X chromosome; aberrations of the remaining chromosomes, with the sole exception of chromosome 18, have been found in at least one SCCL cell line.[97] Using restriction fragment length polymorphism technology, Yokota and associates reported the loss of heterozygosity on chromosome 3p in 7 of 7 patients, 13q in 10 of 11 patients, and 17p in 5 of 5 patients.[100]

Structural abnormalities have been observed within the 13q14 retinoblastoma gene; Harbour and colleagues reported 13q14 anomalies in 1 (12%) of 8 primary SCCL tumors, in 4 (18%) of 22 SCCL cell lines, and in 1 of 4 pulmonary carcinoid cell lines.[101] Harbour and associates also reported an absence of retinoblastoma gene mRNA expression in 60% of the SCCL cell lines, including all samples with structural abnormalities.[101] In contrast, retinoblastoma gene mRNA was found in 90% of non-SCCL cell lines and in normal lung tissue. These findings suggest that inactivation or loss of the retinoblastoma gene may be important in the development of pulmonary neuroendocrine tumors.

Some pulmonary SCCL may appear as different histologic types at autopsy, presumably because of the clonal heterogeneity and genetic instability inherent in these tumors. Yesner examined 205 biopsy-diagnosed SCCL treated with adjuvant chemotherapy or placebo; overall, 82% were histologically unchanged at autopsy, 8% were diagnosed as combined SCCL, and 10% were interpreted as non-SCCL.[102] Continuous cell lines established from patients with pure SCCL may also convert into large cell carcinomas.[103] Other human SCCL cell lines have developed several variant morphologic and biochemical characteristics, such as accelerated growth and cloning efficiency, radiation resistance, and morphologic characteristics of mixed small and large cell or large cell carcinomas.[103–106]

Numerous DNA abnormalities and examples of genetic instability have been identified in primary SCCL tumors and cell lines, corresponding to the high incidence of aneuploidy in these tumors. None of the aberrations identified are entirely sensitive or specific for the disease, nor do they seem to be prognostically useful.

CLINICAL MANIFESTATIONS

Because of the rapid clinical progression of SCCL, most patients are symptomatic at the time of presentation. Except for the various paraneoplastic syndromes, the symptoms are nonspecific. Complaints secondary to regional or metastatic disease are relatively frequent. The duration of symptoms is usually shorter than in other lung carcinoma types; more than 80% of SCCL patients typically have symptoms for 3 months or less.[6,48]

Patients usually present with airway irritation because of the central location of most SCCL. Cough is by far the most common complaint (75%), followed by chest pain from regional nerve involvement (36%), and dyspnea secondary to bronchial obstruction (20%–35%).[48,107] The usual submucosal location of the tumor may account for a lower frequency of hemoptysis (10%–15%) than with other lung cancer types.[48]

Regional extension of the tumor into the mediastinum almost always occurs, accounting for the frequent occurrence of the superior vena cava syndrome, hoarseness from recurrent laryngeal nerve involvement, and dysphagia secondary to extrinsic esophageal compression.[108–110] Signs and symptoms of pericardial involvement are uncommon at presentation but develop during the clinical course of disease in as many as 25% of patients.[111]

Because of rapid tumor growth, systemic metastases appear earlier and more frequently in SCCL than in other lung cancer types.[112,113] Patients presenting with liver failure, bone marrow failure, or central nervous system (CNS) symptoms secondary to

metastatic tumor are common. As many as 67% of patients have clinical evidence of metastatic disease at presentation. The most common sites of extrathoracic disease detected during pretreatment staging include bone (38%), liver (22%–28%), bone marrow (17%–23%), and the CNS (8%–14%).[114–116] At autopsy, virtually all patients had hilar and mediastinal node involvement, and 50% had metastases to bone, liver, adrenal, pancreas, contralateral lung, abdominal lymph nodes, and CNS sites.[48,117] SCCL may also metastasize to relatively unusual sites, such as the heart, bowel, and testis.[118–120]

CNS involvement is more common in SCCL than in other types of lung cancer, and prophylactic irradiation is frequently included in many treatment protocols.[113,121–123] Most chemotherapeutic agents poorly penetrate the blood-brain barrier, leaving the brain as a relatively protected reservoir for metastases. Without prophylaxis, the incidence of CNS dissemination appears to be increasing with lengthened survival, and as many as 50% of patients develop brain metastases during the course of disease.[122–127] Metastases to the CNS are classified in three groups: intracranial, spinal epidural with spinal cord compression, and leptomeningeal with carcinomatous meningitis.[128–130] Intracranial metastases are the most common, occurring in about 42% of patients with CNS dissemination. Spinal and leptomeningeal metastases each occur in approximately 15% of patients, and pituitary dissemination has been observed in 0% to 21% of patients with CNS spread.[2,113,123] Most intracranial metastases are cerebral and multiple.

Elevated concentrations of polypeptide hormones produced ectopically are common in pulmonary SCCL, but clinical paraneoplastic syndromes are relatively infrequent.[131–133] Inappropriate antidiuretic hormone (*i.e.*, vasopressin) secretion (SIADH) and Cushing syndrome are strongly associated with pulmonary SCCL. Bondy and Gilby evaluated 106 patients with pulmonary SCCL before therapy; 47% showed abnormal adrenocortical hormone secretion, 38% had SIADH, but only two patients had clinical Cushing syndrome.[134] Eagan and colleagues studied 37 patients with SCCL and found evidence of 13 ectopic hormonal syndromes in 11 patients, including 5 with SIADH and 3 with Cushing syndrome.[127] Gropp and associates detected elevated levels of ACTH in 15 (30%) of 50 SCCL patients before therapy, although only 2 had Cushing syndrome.[131] Calcitonin levels are also frequently increased, with elevated levels detected in as many as 48% of patients. Hansen and colleagues reported elevated calcitonin in 48 (64%) of 75 SCCL patients, 33% of whom also had SIADH.[133] Elevations in human chorionic gonadotropin and parathormone levels may also be seen, and parathyroid hormone mRNA has been demonstrated in a SCCL by Northern blot analysis.[127,131,135,136]

The Eaton-Lambert (*i.e.*, myasthenic) syndrome occurs almost exclusively in patients with SCCL.[127,137,138] Of 40 patients with this syndrome evaluated at the Mayo Clinic, 28 had malignant neoplasms, and 20 of these had pulmonary SCCL.[139] The pathogenetic mechanism for the impairment of neuromuscular transmission is uncertain, but the syndrome is often reversed with effective chemotherapy.[140,141]

STAGING

Two principal staging systems are used for patients with pulmonary SCCL: the TNM system advocated by the American Joint Committee (AJC) for Cancer Staging and End Results Reporting and the limited and extensive disease system of the VALCG.[5,142] Mountain and associates reviewed 268 pulmonary SCCL patients with the AJC staging system and found that, in contrast with other types of lung cancer, the prognosis for SCCL was independent of more than 40 tumor characteristics, including stage, tumor size, and anatomic location.[143] Because the TNM system did not appear to have prognostic significance for SCCL patients treated with surgery or radiation therapy, the AJC initially recommended its use for reference purposes only. However, recognition that some pulmonary SCCL are surgically resectable has revived the use of TNM staging, primarily for identifying potential surgical candidates.[144]

For most patients who do not undergo surgical resection, virtually all investigators have adopted the two-stage VALCG system. In this two-stage system, limited disease is defined as that confined to one hemithorax and regional lymph nodes, including the mediastinal, contralateral hilar, and ipsilateral supraclavicular nodes, and extensive disease is defined as that beyond the limited area, including distant nodal, cranial, and soft tissue metastases. The system was designed primarily to determine whether the known tumor could be encompassed within a tolerable radiation port. Its significance today is less evident, because systemic multiagent chemotherapy is the accepted treatment for most SCCL patients. Ipsilateral pleural effusion and mediastinal extension with recurrent laryngeal nerve involvement and superior vena cava obstruction has been considered consistent with limited or extensive disease by different researchers, but neither factor appears to influence survival.[115]

CLINICAL COURSE AND TREATMENT

Dramatic, albeit short-term, results have been achieved in recent years with the use of multiagent chemotherapy.[112,145,146] Current treatment modalities include multiagent chemotherapy, with or without radiation therapy, and surgical resection in selected cases. Patients presenting with resectable SCCL confined to the lung have been shown in some studies to benefit from resection coupled with adjuvant chemotherapy or irradiation.[145]

SCCL is exquisitely radiosensitive, and external beam irradiation is often used for emergent management of obstructive complications. Because of dissemination of disease, most patients cannot be adequately treated by irradiation alone, and irradiation is rarely used as the only therapeutic modality. The role of radiation therapy in patients with limited-stage disease remains controversial.

Because most SCCL are locally unresectable and are often complicated with distant metastases, multiagent chemotherapy is the best primary treatment modality in most cases. One preliminary study comparing cyclophosphamide with no treatment showed a nearly threefold increase in survival in treated patients.[147] Eagan and colleagues reported a partial response rate of 85% using cyclophosphamide, vincristine, and methotrexate combined with irradiation.[127] Most programs use various combinations of cyclophosphamide, doxorubicin, vincristine, methotrexate, lomustine, and etoposide.

In patients with pure SCCL and limited-stage disease, combination chemotherapy results in a complete response rate of about 60% with a median survival of 15 months. In patients with pure SCCL and extensive disease, the complete response rate drops to approximately 20%, with a median survival of 8 months. In general, relapses occur within 6 months of initial therapy and

respond poorly to second-line chemotherapy. Prophylactic cranial irradiation has been shown to reduce the incidence of cranial metastases by as much as 20%, but it has not resulted in increased median or disease-free survival.[148] Intellectual deficits are being reported in long-term survivors with increasing frequency.

Cell subtype in SCCL appears to have minimal effect on patient prognosis. Most studies investigating the prognostic significance of morphologic subtyping have reported no differences in survival or response to therapy between the oat cell and intermediate cell variants.[55,56,149,150] To our knowledge, published cases of combined SCCL with foci of squamous or glandular differentiation are rare enough to preclude meaningful survival comparisons with the other cellular types.

Mixed large cell and small cell SCCL (*i.e.*, 22/40 tumor) appears to have a poorer survival and lower response rate than typical SCCL.[55,56] Radice and associates found that the differences remained significant after adjusting for disease extent, although there were too few mixed large cell and small cell patients with limited disease for meaningful comparison; among patients with extensive disease, the mixed subtype retained a significant survival disadvantage.[56] In a study of 249 SCCL patients, including 13 mixed large cell and small cell tumors, Bepler and colleagues found no significant survival differences among the different subtypes.[149] The degree to which intraobserver diagnostic variation contributed to these differences is unknown but cannot be ignored. In our opinion, the evidence that mixed large cell and small cell tumors have a worse prognosis than typical SCCL is suggestive but inconclusive.

The prognosis of previously untreated patients with pulmonary SCCL primarily depends on disease stage and patient performance. The importance of stage was demonstrated in a VALCG study, which reported median survival times in 118 untreated patients with limited and extensive pulmonary SCCL as 3.1 and 1.4 months, respectively.[147,151] In chemotherapeutic trials with or without irradiation, patients with limited disease had a 60% complete response rate and a median survival of 51 weeks, compared with a 25% complete response rate and a 33-week median survival for patients with extensive disease.[112] Limited-disease patients with surgically resected tumors subsequently treated with adjuvant chemotherapy, irradiation, or both have an especially favorable prognosis.[152]

Some studies have reported considerable prognostic variation within the category of extensive disease, depending on the extent and distribution of tumor involvement. In one study of 106 patients, those with extensive disease and a single metastatic site had survival rates statistically indistinguishable from patients with limited disease, but liver, CNS, or multiple soft tissue metastases conferred an especially poor prognosis.[115] In another study of more than 800 patients, multivariate analysis revealed that specific sites of metastatic involvement were not prognostically independent of disease stage, performance status, and various markers of tumor burden.[152]

Initial performance status strongly influences survival of untreated patients and those receiving adjuvant therapy.[115,142] Within either stage, performance status is the single most important prognostic variable.[115,153] That favorable performance status is more common among limited-stage patients and poor performance is more common among extensive-disease patients correlates with increasing numbers of metastases, suggesting that the prognostic effect of performance may be related to overall tumor burden.[115]

Other tumor- and host-related factors have been proposed as prognostically important in pulmonary SCCL, including weight loss, impaired immune status, gender, age, and time since cessation of smoking.

REFERENCES

1. Antkowiak JG, Regal AM, Takita H. Bronchogenic carcinoma in patients under age forty. Ann Thorac Surg 1989;47:391.
2. Auerbach O, Garfinkel L, Parks VR. Histologic type of lung cancer in relation to smoking habits, year of diagnosis and sites of metastases. Chest 1975;67:382.
3. Johnson WW. Histologic and cytologic patterns of lung cancer in 2,580 men and women over a 15-year period. Acta Cytol 1988; 32:163.
4. Minna JD, Higgins GA, Glatstein EJ. Cancer of the lung. In: DeVita VT, Hellman S, Rosenberg SA, eds. Principles and practice of oncology. Philadelphia: JB Lippincott, 1985:507.
5. Yesner R, Gerstl LB, Auerbach O. Application of the World Health Organization classification of lung carcinoma to biopsy material. Ann Thorac Surg 1965;1:33.
6. Kato Y, Ferguson TB, Bennett DE, Burford TH. Oat cell carcinoma of the lung. A review of 138 cases. Cancer 1969;23:517.
7. Meigs JW. Epidemic lung cancer in women. JAMA 1977;238:1055.
8. Godwin JD II, Brown CC. Comparative epidemiology of carcinoid tumors and oat cell carcinoma of the lung. Cancer 1977;40:1671.
9. Choi NC, Carey RW, Kaulman SD, Grillo HC, Younger J, Wilkins EW. Small cell carcinoma of the lung. A progress report of 15 years' experience. Cancer 1987;59:6.
10. Spiegelman D, Maurer LH, Ware JH, et al. Prognostic factors in small cell carcinoma of the lung. An analysis of 1,521 patients. J Clin Oncol 1989;7:344.
11. Hainau B, Dombernowsky P, Hansen HH, et al. Cell proliferation and histologic classification of bronchogenic carcinoma. J Natl Cancer Inst 1977;59:1113.
12. Muggia FM, Krezoski SK, Hansen HH. Cell kinetics studies in patients with small cell carcinoma of the lung. Cancer 1974;34:1683.
13. Feyrter F. Ueber diffuse endokrine epitheliale Organe. Leipzig: JA Barth, 1938.
14. Bensch KG, Gordon GB, Miller LR. Studies on the bronchial counterpart of the Kulchitsky (argentaffin) cell and innervation of bronchial glands. J Ultrastruct Res 1965;12:668.
15. Bensch KG, Gordon GB, Miller LR. Electron microscopic and biochemical studies on the bronchial carcinoid tumor. Cancer 1965; 18:592.
16. Feyrter F. Zur Pathologie des argyrophilen Helle-Zellen Organes im Bronchialbaum des Menschen. Virchows Arch [A] 1954;325:723.
17. Pearse AGE. Common cytochemical properties of cells producing polypeptide hormones, with particular reference to calcitonin and the thyroid C cells. Vet Rec 1966;79:587.
18. Pearse AGE. The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. J Histochem Cytochem 1969;17:303.
19. Pearse AGE, Polak JM. Neural crest origin of the endocrine polypeptide (APUD) cells of the gastrointestinal tract and pancreas. Gut 1971;12:783.
20. Fontaine J, LeDouarin NM. Analysis of endoderm formation in the avian blastoderm by the use of quail-chick chimeras. J Embryol Exp Morphol 1977;4:209.
21. Pictet RL, Rall LB, Phelps P, Rutter WJ. The neural crest and the origin of the insulin-producing and other gastrointestinal hormone producing cells. Science 1976;191:191.
22. Pearse AGE, Takor-Takor T. Embryology of the diffuse neuroendocrine system and its relationship to the common peptides. Fed Proc 1979;38:2288.
23. Gould VE, Linnoila I, Memoli VA, Warren WH. Biology of disease:

neuroendocrine components of the bronchopulmonary tract: hyperplasias, dysplasias, and neoplasms. Lab Invest 1983;49:519.
24. Gould VE, Linnoila RI, Memoli VA, Warren WH. Neuroendocrine cells and neuroendocrine neoplasms of the lung. Pathol Annu 1983; 18:287.
25. Tateishi R. Distribution of argyrophilic cells in human adult lungs. Arch Pathol 1973;96:198.
26. Froelilch F. Die "Helle-Zelle" der Bronchialschleimhaut und ihre Beziehungen zum Problem des Chemorezeptoren. Frankf Z Pathol 1949;60:517.
27. Bensch KG, Corrin B, Pariente R, Spencer H. Oat-cell carcinoma of the lung. Its origin and relationship to bronchial carcinoid. Cancer 1968;22:1163.
28. Hattori S, Matsuda M, Tateishi R, Nishihara H, Horai T. Oat-cell carcinoma of the lung. Clinical and morphological studies in relation to its histogenesis. Cancer 1972;30:1014.
29. Lauweryns JM, Cokelaere M, Theunynck P. Neuroepithelial bodies in the respiratory mucosa of various mammals: a light optical, histochemical, and ultrastructural investigation. Z Zellforsch Mikrosk Anat 1972;135:569.
30. Lauweryns JM, Peuskens JC. Neuroepithelial bodies (neuroreceptor or secretory organ?) in human infant bronchial and bronchiolar epithelium. Anat Rec 1972;172:471.
31. Hashimoto T, Fukuoka M, Nagasawa S, et al. Small cell carcinoma of the lung and its histological origin. Report of a case. Am J Surg Pathol 1979;3:343.
32. Baylin SB, Gazdar AF. Endocrine biochemistry in the spectrum of human lung cancer: implications for the cellular origin of small cell carcinoma. In: Greco FA, Oldham RK, Bunn PA Jr, eds. Small cell lung cancer. Orlando: Grune & Stratton, 1981:123.
33. Watson WL, Berg JW. Oat cell lung cancer. Cancer 1962;15:759.
34. Weiss W, Boucot KR, Seidman H, et al. Risk of lung cancer according to histologic type and cigarette dosage. JAMA 1972; 222:799.
35. Yesner R, Gelfman NA, Feinstein AR. A reappraisal of histopathology in lung cancer and correlation of cell types with antecedent cigarette smoking. Am Rev Respir Dis 1973;107:790.
36. Huhti E, Sutisen S, Reinlia A, et al. Lung cancer in a defined geographical area: history and histological types. Thorax 1980; 35:660.
37. Saccomanno G, Archer VE, Auerbach O, et al. Histologic types of lung cancer among uranium miners. Cancer 1971;27:515.
38. Auerbach O, Saccamanno G, Kuschner M, et al. Histologic findings in the tracheobronchial tree of uranium miners and non-miners with lung cancer. Cancer 1978;42:483.
39. Saccomanno G, Huth GC, Auerbach O, et al. Relationship of radioactive radon daughters and cigarette smoking in the genesis of lung cancer in uranium miners. Cancer 1988;62:1402.
40. Weiss W. Small cell carcinoma of the lung: epidemiology and etiology. In: Greco FA, Oldham RK, Bunn PA Jr, eds. Small cell lung cancer. Orlando: Grune & Stratton, 1981:1.
41. Weiss W, Moser RL, Auerbach O. Lung cancer in chloromethyl ether workers. Am Rev Respir Dis 1979;120:1031.
42. Kreyberg L. Histological lung cancer types. Acta Pathol Microbiol Scand 1962;157(Suppl):14.
43. Kreyberg L, Liebow AA, Uehlinger EA. Histologic typing of lung tumors. In: International histologic classification of tumors. no. 1. Geneva: World Health Organization, 1967:1.
44. Matthews MJ. Panel report: morphologic classification of bronchogenic carcinoma, part 3. Cancer Chemother Rep 1973;4:299.
45. Histological typing of lung tumors. In: International histological classification of tumors. no. 1. 2nd ed. Geneva: World Health Organization, 1981:19.
46. Hirsch FR, Matthews MJ, Yesner R. Histopathologic classification of small cell carcinoma of the lung. Comments based on an interobserver examination. Cancer 1982;50:1360.
47. Vollmer RT. The effect of cell size on the pathologic diagnosis of small and large cell carcinomas of the lung. Cancer 1982;50:1380.
48. Cohen MH, Matthews MJ. Small cell bronchogenic carcinoma: a distinct clinicopathologic entity. Semin Oncol 1978;5:234.
49. Minna JD, Matthews MJ, Ihde DC, et al. Identification and combination chemotherapy of mixed histology large cell-small cell (WPL #40/22) lung cancer (abstract). Proc AACR ASCO 1978;19:397.
50. Yesner R. Classification of lung cancer: histology. N Engl J Med 1985;312:652.
51. Hirsch FR, Matthews MJ, Aisner S, et al. Histopathologic classification of small cell lung cancer. Changing concepts and terminology. Cancer 1988;62:973.
52. Blackman F, Chung HR, McDonald RJ, et al. Oat cell carcinoma with multiple tracheobronchial papillomatous tumors. Chest 1983; 83:817.
53. Watkin SW, Soorae AJ, Green JA. Bronchoscopic "resection" of small cell carcinoma. Endoscopy 1989;21:186.
54. Adelstein DJ, Tomashefski JF, Snow NJ, Horrigan TP, Hines JD. Mixed small cell and nonsmall cell lung cancer. Chest 1986;89:699.
55. Hirsch FR, Osterlind K, Hansen HH. The prognostic significance of histopathologic subtyping of small cell carcinoma of the lung according to the classification of the World Health Organization. A study of 375 consecutive patients. Cancer 1983;52:2144.
56. Radice PA, Matthews MJ, Inde DC, et al. The clinical behavior of "mixed" small cell/large cell bronchogenic carcinoma compared to "pure" small cell subtypes. Cancer 1982;50:2894.
57. Lehto V-P, Stenman S, Miettinen M, et al. Expression of a neural type of intermediate filament as a distinguishing feature between oat cell carcinoma and other lung cancers. Am J Pathol 1983;110:113.
58. Ramaekers FCS, Puts JJG, Moesker O, et al. Antibodies to intermediate filament proteins in the immunohistochemical identification of human tumors: an overview. Histochem J 1983;15:691.
59. Blobel GA, Gould VE, Moll R, et al. Coexpression of neuroendocrine markers and epithelial cytoskeletal proteins in bronchopulmonary neuroendocrine neoplasms. Lab Invest 1985;52:39.
60. Gould VE, Wiedenmann B, Lee I, et al. Synaptophysin expression in neuroendocrine neoplasms as determined by immunocytochemistry. Am J Pathol 1987;126:243.
61. Thomas P, Battifora H. Keratins versus epithelial membrane antigen in tumor diagnosis: an immunohistochemical comparison of five monoclonal antibodies. Hum Pathol 1987;18:728.
62. Wiedenmann B, Franke WW, Kuhn C, Moll R, Gould VE. Synaptophysin: a marker protein for neuroendocrine cells and neoplasms. Proc Natl Acad Sci USA 1986;83:3500.
63. Linnoila RI, Mulshine JL, Steinberg SM, et al. Neuroendocrine differentiation in endocrine and nonendocrine lung carcinomas. Am J Clin Pathol 1988;90:641.
64. Miettinen M. Synaptophysin and neurofilament proteins as markers for neuroendocrine tumors. Arch Pathol Lab Med 1987;111:813.
65. Said JW, Vinadalal S, Nash G, et al. Immunoreactive neuron-specific enolase, bombesin, and chromogranin as markers for neuroendocrine lung tumors. Hum Pathol 1985;16:236.
66. Pahlman S, Esscher T, Nilsson K. Expression of (gamma)-subunit of enolase, neuron specific enolase, in human non-neuroendocrine tumors and derived cell lines. Lab Invest 1986;54:554.
67. Thomas P, Battifora H, Manderino GL, Patrick J. A monoclonal antibody against neuron-specific enolase. Immunohistochemical comparison with a polyclonal antiserum. Am J Clin Pathol 1987; 88:146.
68. Vinores SA, Bonnin JM, Rubinstein LJ, et al. Immunohistochemical demonstration of neuron-specific enolase in neoplasms of the CNS and other tissues. Arch Pathol Lab Med 1984;108:536.
69. Lloyd RV, Jin L, Kulig E, Fields K. Molecular approaches for the analysis of chromogranins and secretogranins. Diagn Mol Pathol 1991;1:2.
70. Hamid QA, Corrin B, Sheppard MN, Huttner WB, Polak JM.

Expression of chromogranin A mRNA in small cell carcinoma of the lung. J Pathol 1991;163:293.
71. Lloyd RV, Jin L, Fields K. Detection of chromogranins A and B in endocrine tissues with radioactive and biotinylated oligonucleotide probes. Am J Surg Pathol 1990;14:35.
72. Wilson BS, Lloyd RV. Detection of chromogranin in neuroendocrine cells with a monoclonal antibody. Am J Pathol 1984;115:458.
73. Gould VE, Lee I, Wiedenmann B, et al. Synaptophysin: a novel marker for neurons, certain neuroendocrine cells, and their neoplasms. Hum Pathol 1986;17:979.
74. Hoog A, Gould VE, Grimelius L, et al. Tissue fixation methods alter the immunohistochemical demonstrability of synaptophysin. Ultrastruct Pathol 1988;12:673.
75. Kayser K, Schmid W, Elbert W, et al. Expression of neuroendocrine markers (neuron specific enolase, synaptophysin and bombesin) in carcinoma of the lung. Pathol Res Pract 1988;183:412.
76. Travis WD, Linnoila RL, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol 1991;15:529.
77. Addis BJ, Hamid Q, Ibrahim NB, et al. Immunohistochemical markers of small cell carcinoma and related neuroendocrine tumors of the lung. J Pathol 1987;153:137.
78. Hamid QA, Addis BJ, Springall DR, et al. Expression of the C-terminal peptide of human pro-bombesin in 361 lung endocrine tumors, a reliable marker and possible prognostic indicator for small cell carcinoma. Virchows Arch [A] 1987;411:185.
79. Shioda Y, Nagura H, Tsutsumi Y, et al. Distribution of Leu-7 (HNK-1) antigen in human digestive organs: an immunohistochemical study with monoclonal antibody. Histochem J 1986; 16:843.
80. Tischler AS. Small cell carcinoma of the lung: cellular origin and relationship to other neoplasms. Semin Oncol 1978;5:244.
81. Elema JD, Keuning HM. The ultrastructure of small cell lung carcinoma in bronchial biopsy specimens. Hum Pathol 1985;16:1133.
82. Fisher ER, Palekar A, Paulson JD. Comparative histopathologic, histochemical, electron microscopic, and tissue culture studies of bronchial carcinoids and oat cell carcinomas of the lung. Am J Clin Pathol 1978;69:165.
83. Sidhu GS. The ultrastructure of malignant epithelial neoplasms of the lung, part 1. Pathol Annu 1982;:235.
84. Hammar SP, Brockus D, Remington F, et al. Small cell undifferentiated carcinomas of the lung with nonneuroendocrine features. Ultrastruct Pathol 1988;9:319.
85. Vollmer RT, Shelburne JD, Iglehart JD. Intercellular junctions and tumor stage in small cell carcinoma of the lung. Hum Pathol 1987; 18:22.
86. Vindelov LL, Hansen HH, Christensen IJ, et al. Clonal heterogeneity of small cell anaplastic carcinoma of the lung demonstrated by flow-cytometric DNA analysis. Cancer Res 1980;40:4295.
87. Bunn PA, Carney DN, Gazdar AF, Whang-Peng J, Matthews MJ. Diagnostic and biological implications of flow cytometric DNA content analysis in lung cancer. Cancer Res 1983;43:5026.
88. Johnson TS, Katz RL, Pershouse M. Flow cytometric applications in cytopathology. Anal Quant Cytol Histol 1988;10:423.
89. Bepler G, Jacques G, Koehler A, et al. Markers and characteristics of human SCLC cell lines: neuroendocrine markers, classic tumor markers, and chromosomal characteristics of permanent human small cell lung cancer cell lines. J Cancer Res Clin Oncol 1987; 113:253.
90. DeFusco PA, Frytak S, Dahl RJ, et al. Cytogenetic studies in 11 patients with small cell carcinoma of the lung. Mayo Clin Proc 1989;64:168.
91. Falor WH, Ward-Skinner R, Wegryn S. A 3p deletion in small cell lung carcinoma. Cancer Genet Cytogenet 1985;16:175.
92. Johnson BE, Sakaguchi AY, Gazdar AF, et al. Restriction fragment polymorphism studies show consistent loss of chromosome 3p alleles in small cell lung cancer patients' tumors. J Clin Invest 1988; 82:502.
93. Kok K, Osinga J, Carritt B, et al. Deletion of a DNA sequence at the chromosomal region 3p21 in all major types of lung cancer. Nature 1987;330:578.
94. Morstyn G, Brown J, Novak U, et al. Heterogeneous cytogenetic abnormalities in small cell lung cancer lines. Cancer Res 1987; 47:3322.
95. Naylor SL, Johnson BE, Minna JD, et al. Loss of heterozygosity of chromosome 3p markers in small cell lung cancer. Nature 1987; 329:451.
96. Whang-Peng J, Bunn PA, Kao-Shan CS, et al. A nonrandom chromosomal abnormality, del 3p(14-23) in human small cell lung cancer (SCLC). Cancer Genet Cytogenet 1984;6:119.
97. Whang-Peng J, Kao-Shan CS, Lee EC, et al. Specific chromosome defect associated with human small cell lung cancer: deletion 3p(14-23). Science 1982;215:181.
98. Rey JA, Bello MJ, de Campos JM, et al. Deletion 3p in two lung adenocarcinomas metastatic to the brain. Cancer Genet Cytogenet 1987;25:355.
99. Zech L, Bergh J, Nilsson K. Karyotypic characterization of established cell lines in short-term cultures of human lung cancers. Cancer Genet Cytogenet 1985;15:335.
100. Yokota J, Wada M, Shimosato Y, et al. Loss of heterozygosity on chromosome 3, 13, and 17 in small-cell carcinoma and on chromosome 3 in adenocarcinoma of the lung. Proc Natl Acad Sci USA 1987;84:9252.
101. Harbour JW, Lai S-L, Whang-Peng J, et al. Abnormalities in structure and expression of the human retinoblastoma gene in SCLC. Science 1988;241:353.
102. Yesner R. Small cell tumors of the lung. Am J Surg Pathol 1983; 7:775.
103. Gazdar AF, Carney DN, Nau MM, et al. Characterization of variant subclasses of cell lines derived from small cell lung cancer having distinctive biochemical, morphological, and growth properties. Cancer Res 1985;45:2923.
104. Bepler G, Jacques G, Havemann K, et al. Characterization of two cell lines with distinct phenotypes established from a patient with small cell lung cancer. Cancer Res 1987;47:1883.
105. Carney DN, Gazdar AF, Bepler G, et al. Establishment and identification of small cell lung cancer lines having classic and variant features. Cancer Res 1985;45:2913.
106. Goodwin G, Baylin SB. Relationships between neuroendocrine differentiation and sensitivity to gamma radiation in culture line OH-1 of human small cell lung carcinoma. Cancer Res 1982;42:1361.
107. Dombernowsky P, Hirsch F, Hansen HH, et al. Peritoneoscopy in staging of 190 patients with small-cell anaplastic carcinoma of the lung with special reference to subtyping. Cancer 1978;41:2008.
108. Ahmann FR. A reassessment of the clinical implications of the superior vena caval syndrome. J Clin Oncol 1984;2:961.
109. Maddox A-M, Valdivieso M, Lukeman JM, et al. Superior vena cava obstruction in small cell bronchogenic carcinoma: clinical parameters and survival. Cancer 1983;52:2165.
110. Sculier JP, Evans WK, Feld R, et al. Superior vena caval obstruction syndrome in small cell lung cancer. Cancer 1986;57:847.
111. Strauss BL, Matthews MJ, Cohen MH, et al. Cardiac metastases in lung cancer. Chest 1977;71:607.
112. Bunn PA, Cohen MH, Ihde DC, et al. Advances in small cell bronchogenic carcinoma. Cancer Treat Rep 1977;61:333.
113. Bunn PA, Nugent JL, Matthews MJ. Central nervous system metastases in small cell bronchogenic carcinoma. Semin Oncol 1978; 5:314.
114. Elliot JA, Osterlind K, Hirsch FR, et al. Metastatic patterns in small cell lung cancer: correlation of autopsy findings with clinical parameters in 537 patients. J Clin Oncol 1987;5:246.

115. Ihde DC, Makuch RW, Carney DN, et al. Prognostic implications of stage of disease and sites of metastases in patients with small cell carcinoma of the lung treated with intensive chemotherapy. Am Rev Respir Dis 1981;123:500.
116. Levenson RM, Ihde DC, Matthews MJ, et al. Small cell carcinoma presenting as an extrapulmonary neoplasm: sites of origin and response to chemotherapy. J Natl Cancer Inst 1981;67:607.
117. Matthews MJ. Problems in morphology and behavior of bronchopulmonary malignant disease. In: Israel L, Chahinian AP, eds. Lung cancer: natural history, prognosis, and therapy. Orlando: Academic Press, 1976:23.
118. McNeill PM, Wagman LD, Neifeld JP. Small bowel metastases from primary carcinoma of the lung. Cancer 1987;59:1486.
119. Wegener M, Borsch G, Reitemeyer E, et al. Metastasis to colon from primary bronchogenic carcinoma presenting as occult gastrointestinal bleeding: report of a case. Gastroenterology 1988;26:358.
120. Stein A, Sova Y, Lurie M, et al. Bilateral testicular metastases of pulmonary small cell carcinoma: a rare incidental finding following orchiectomy for prostatic carcinoma. Br J Urol 1989;63:552.
121. Doyle TJ. Brain metastases in the natural history of small cell lung cancer 1972-1979. Cancer 1982;50:752.
122. Newman SJ, Hansen HH. Frequency, diagnosis, and treatment of brain metastases in 247 consecutive patients with bronchogenic carcinoma. Cancer 1974;33:492.
123. Nugent JL, Bunn PA, Matthews MJ, et al. CNS metastases in small cell bronchogenic carcinoma: increasing frequency and changing pattern with lengthening survival. Cancer 1979;44:1885.
124. Aisner J, Aisner SC, Ostrow S, et al. Meningeal carcinomatosis from small cell carcinoma of the lung: consequences of improved survival. Acta Cytol 1979;23:292.
125. Aroney RS, Dalley DN, Chan WK, et al. Meningeal carcinomatosis in small cell carcinoma of the lung. Am J Med 1981;71:26.
126. Brereton HD, O'Donnell JF, Kent CH, et al. Spinal meningeal carcinomatosis in small cell carcinoma of lung. Ann Intern Med 1978;88:517.
127. Eagan RT, Maurer LH, Forcier RJ, Tulloh M. Small cell carcinoma of the lung: staging, paraneoplastic syndromes, treatment, and survival. Cancer 1974;33:527.
128. Murphy KC, Feld R, Evans WK, et al. Intramedullary spinal cord metastases from small cell carcinoma of the lung. J Clin Oncol 1983;1:99.
129. Pedersen AG, Bach F, Melgaard B. Frequency, diagnosis, and prognosis of spinal cord compression in small cell bronchogenic carcinoma: a review of 817 consecutive patients. Cancer 1985;55:1818.
130. Rosen ST, Aisner J, Makuch RW, et al. Carcinomatous leptomeningitis in small cell lung cancer: a clinicopathologic review of the National Cancer Institute experience. Medicine (Baltimore) 1982;61:45.
131. Gropp C, Havemann K, Scheuer A. Ectopic hormones in lung cancer patients at diagnosis and during therapy. Cancer 1980;46:347.
132. Hansen M, Hammer M, Hummer L. Diagnostic and therapeutic implications of ectopic hormone production in small cell carcinoma of the lung. Thorax 1980;35:101.
133. Hansen M, Hansen HH, Hirsch FR, et al. Hormonal polypeptides and amine metabolites in small cell carcinoma of the lung, with special reference to stage and subtypes. Cancer 1980;45:1432.
134. Bondy PK, Gilby ED. Endocrine function in small cell undifferentiated carcinoma of the lung. Cancer 1982;50:2147.
135. Hayward ML, Howell DA, O'Donnell JF, Maurer LH. Hypercalcemia complicating small-cell carcinoma. Cancer 1981;48:1643.
136. Yoshimoto K, Yamasaki R, Sakai H, et al. Ectopic production of parathyroid hormone by small cell lung cancer in a patient with hypercalcemia. J Clin Endocrinol Metab 1989;68:976.
137. Lambert EH, Rooke ED. Myasthenic state and lung cancer. In: Brain WR, Norris FH, eds. The remote effects of cancer on the nervous system. New York: Grune & Stratton, 1965:67.
138. Sculier JP, Feld R, Evans WK, et al. Neurologic disorders in patients with small cell lung cancer. Cancer 1987;60:2275.
139. Elmquist D, Lambert EH. Detailed analysis of neuromuscular transmission in a patient with myasthenic syndrome associated with bronchogenic carcinoma. Mayo Clin Proc 1968;43:689.
140. Clamon GH, Evans WK, Shepard FA, Humphrey JG. Myasthenic syndrome and small cell cancer of the lung. Variable response to antineoplastic therapy. Arch Intern Med 1984;144:999.
141. Kalter S, Dhingra HM, Farha P. Primary therapy for small cell lung cancer reversing the Eaton-Lambert syndrome. Southern Med J 1985;78:197.
142. Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 1973;4(Suppl):31.
143. Mountain CF, Carr DT, Anderson WAD. A system for the clinical staging of lung cancer. Am J Roentgenol 1974;120:130.
144. Meyer JA. Effect of histologically verified TNM stage on disease control in treated small cell carcinoma of the lung. Cancer 1985;55:1747.
145. Bunn PA, Cohen MH, Lichter A, et al. Randomized trial of chemotherapy versus chemotherapy plus radiotherapy in limited stage small cell lung cancer. Proc Am Soc Clin Oncol 1983;2:200.
146. Weiss RB. Small cell carcinoma of the lung: therapeutic management. Ann Intern Med 1978;88:522.
147. Green RA, Humphrey E, Close H, et al. Alkylating agents in bronchogenic carcinoma. Am J Med 1969;46:516.
148. Bleehen NM, Bunn PA, Cox JD, et al. Role of radiation therapy in small cell anaplastic carcinoma of the lung. Cancer Treat Rep 1983;67:11.
149. Bepler G, Neumann K, Holle R, Havemann K, Kalbfleisch H. Clinical relevance of histologic subtyping in small cell lung cancer. Cancer 1989;64:74.
150. Vollmer RT, Birch R, Ogden L, Crissman JD. Subclassification of small cell carcinoma of the lung. The Southeastern Cancer Study Group Experience. Hum Pathol 1985;16:247.
151. Roswitt B, Patno ME, Rapp R. The survival of patients with inoperable lung cancer: a large-scale randomized study of radiation therapy versus placebo. Radiology 1968;90:688.
152. Osterlind K, Hansen HH, Hansen M, et al. Treatment policy of surgery in small cell carcinoma of the lung: retrospective analysis of a series of 874 consecutive patients. Thorax 1985;40:272.
153. Livingston BR, Moore TN, Heilbrun L, et al. Small cell carcinoma of the lung: combined chemotherapy and radiation. Ann Intern Med 1978;88:194.