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Small Cell Lung Carcinoma (SCLC)

A Clinicopathologic Study of 100 Cases With Surgical Specimens

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Separation of small cell lung carcinoma (SCLC) from nonsmall cell lung carcinoma (NSCLC) is a critical distinction to be made in the diagnosis of lung cancer. However, the diagnosis of SCLC is most commonly made on small biopsies and cytologic specimens, and practicing pathologists may not be familiar with all its morphologic guises and frequent combination with NSCLC elements, which may be seen in larger specimens. Following the most recent WHO classification of lung tumors and with the hope of identifying prognostic markers, we examined in detail the histology of 100 surgical biopsies or resections with a diagnosis of SCLC from the AFIP and pathology panel of the International Association for the Study of Lung Cancer (IASLC). Multiple clinical and histologic features were studied by Kaplan-Meier analysis. Neuroendocrine architectural patterns, including nested and trabecular growth, with peripheral palisading and rosette formation were common in SCLC. Necrosis and apoptotic debris was prominent in all cases, but crush artifact was infrequent. Cell size in surgical biopsy specimens appears larger than in bronchoscopic biopsy specimens and occasional cells may show prominent nucleoli and vesicular nuclear chromatin, but this does not preclude the diagnosis of SCLC. A high percentage of cases (28%) showed combinations with NSCLC, with large cell carcinoma the most common, followed by adenocarcinoma and squamous cell carcinoma. Because of the frequency of a few scattered large cells in SCLC, we arbitrarily recommend that at least 10% of the tumor show large cell carcinoma before subclassification as combined SC/LC. However, combined SCLC is easily recognized if the additional component consists of other NSCLC subtypes such as adenocarcinoma or squamous cell carcinoma, so no percentage requirement is needed. Stage remained the only predictor of prognosis.

Key Words: Small cell lung carcinoma—Pathology—Histology—Morphology—Carcinoid—Atypical carcinoid—Large cell neuroendocrine carcinoma—Pulmonary—Neuroendocrine.

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Small cell lung carcinoma (SCLC) currently accounts for 15% to 25% of invasive lung cancer worldwide, and approximately 45,000 new cases are diagnosed annually in the United States alone.[24] SCLC is separated from all other types of lung cancer by a clinical and histopathologic profile that is distinctive from all other cell types, which are collectively called nonsmall cell carcinoma (NSCLC). SCLC is found almost exclusively in smokers.[42] It has a rapid doubling time,[54] pursues a more aggressive clinical course than NSCLC,[49,62] and is often disseminated at presentation.[2,62] It is associated more frequently with particular endocrine and neurologic paraneoplastic syndromes (syndrome of inappropriate antidiuretic hormone secretion, Cushing's syndrome, and Eaton Lambert syndrome).[12] SCLC is not usually amenable to surgical management[32,34,40] and has a staging system that differs from NSCLC and is based on the concept of limited or extensive disease.[13] SCLC is, however, chemosensitive and, unlike NSCLC, chemotherapy currently forms the cornerstone of treatment with high response rates that allow extension of survival.[1,5,25]

SCLC is a member of the quartet of neuroendocrine (NE) lung tumors that includes the typical carcinoid tumor (TC), atypical carcinoid (AC), and large cell neuroendocrine carcinoma (LCNEC).[5,50,53] SCLC was one of

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the earliest pulmonary neuroendocrine tumors to be identified dating back to Barnard's seminal description of "oat celled sarcoma" in 1926.[7] Although SCLC by definition is composed of small cells, Barnard acknowledged that there is cytologic heterogeneity within SCLC, stating, "in all these tumors, cells other than small 'oat' cells could be found."[7] This heterogeneity has been addressed in a series of histologic classifications of SCLC beginning in 1962[31] when a two-part classification, including oat and polygonal cell types, was introduced by Dr. L. Kreyberg (Table 1).[31] The first WHO classification of SCLC, published in 1967, was based on Barnard's original morphologic description and incorporated four subtypes, including lymphocyte-like, polygonal, fusiform, and other.[59] Modifications set forth by the Working Party for Therapy of Lung Cancer (WP-L) in 1973,[39] were incorporated into the second WHO classification published in 1981 (Table 1).[60] Under the 1981 classification, the lymphocyte-like term was changed to "oat-cell," and polygonal, fusiform, and mixed types were subsumed under the heading "intermediate." The "other" category was renamed "combined" to indicate combinations of malignant squamous and glandular elements. In 1988 the IASLC proposed a further modification by collapsing oat and intermediate cell subtypes into a pure small cell category (Table 1).[21] Furthermore, it was proposed that SCLC admixed with large cells be defined as a separate category of mixed SCLC, whereas combined SCLC should contain components of squamous cell and/or adenocarcinoma. These earlier classifications generated much controversy and debate, but lack of reproducibility confounded pathologists, as various studies failed to demonstrate a consistent relationship between the histologic subtype and patient outcome.[10,22,23,43,45] The most recent 1999 WHO/IASLC classification of lung tumors collapses "mixed" and "combined" subtypes into one (Table 1). SCLC is now defined as pure or combined with nonsmall cell elements (adenocarcinoma, squamous cell, large cell, spindle, or giant cell carcinoma).

Most patents with SCLC have greater than stage I disease and are not surgical candidates,[34] and in over 90% of cases the diagnosis is reliably established based on small biopsy or cytologic specimens.[15,41,46,56] As a result, the surgical pathologist rarely sees SCLC in a large biopsy or a tumor resection and may not appreciate that the histologic appearance of SCLC in such specimens can be quite different. Few papers address the histologic features of SCLC based on surgical biopsy or resected tumors,[26] and much of what has been written about SCLC histology has been gleaned from small biopsy and autopsy material.[47] Given the prognostic and therapeutic implications of this diagnosis, the surgical pathologist may face a daunting task distinguishing SCLC from NSCLC in a small biopsy. Moreover, SCLC may be difficult to recognize if seen in the unfamiliar context of a large, well-preserved biopsy.

The aim of the current study was to examine the histology of a large number of surgical biopsies of SCLC to document and illustrate the spectrum of architectural and cytologic features, evaluate immunohistochemical staining patterns, and perform survival analysis to identify potential prognostic indicators.

METHODS

Case Selection and Clinical Features

Seventy-two surgical biopsy specimens of SCLC were retrieved from the consultation files of the Armed Forces Institute of Pathology (AFIP) in Washington, DC, and 28 from the pathology panel of the IASLC. The cases included were initially reviewed by two of the authors (S.N., W.D.T.) and a consensus diagnosis was reached. Any disagreements were resolved by third person review (M.B.B.). Cases included were accessioned between 1975 and 1997 but fulfilled the histologic criteria of the 1999 WHO/IASLC classification of lung and pleural tumors and clinical follow-up information was available. Clinical features, including the age, sex, race, history of cigarette smoking, referring diagnoses, tumor size, location, stage, surgical procedure, details of adjuvant therapy, and survival data were gleaned from the surgical pathology reports, referring pathologists, and the national death index in the United States.

Pathologic Features

The macroscopic descriptions were extracted from surgical pathology reports. The light microscopic features were assessed by examination of hematoxylin and eosin (H&E)-stained sections prepared at the AFIP. Architectural and cytologic features were both examined. Accepted neuroendocrine morphologic traits, including nested and trabecular patterns of growth, rosettes, and peripheral palisading were assessed, in addition to the features such as solid sheet-like growth and necrosis. The percentage contribution of each of these patterns was assessed in a semiquantitative fashion and graded as absent (0), <5% (1), 5%–25% (2), 26%–50% (3), 51%–75% (4), or 76%–100% (5). Aerogenous and/or interstitial spread, vascular invasion, tumor necrosis, stromal response, tumor vascularity, crush artifact, and "Azzopardi effect" were assessed. The airways adjacent to the tumor were assessed for the presence of preinvasive lesions.

The presence and degree of pleomorphism was evaluated; the percentage of spindle-shaped cells was noted. Mitoses were counted on an Olympus BX40 microscope at 40× magnification using a specially manufactured reti-

cule so that 10 HPF equaled 2 mm^2.[53] The cytoplasmic features assessed included the amount, clear-cell change, and the presence of mucin.

Combined SCLC

The presence of NSCLC elements was evaluated. When adenocarcinoma and squamous cell carcinoma are found in combination with SCLC, their presence was documented regardless of the amount. However, for combined small cell/large cell carcinoma (SC/LC), we arbitrarily chose to require at least 10% large cell carcinoma for the diagnosis of combined SC/LC.

Immunohistochemistry

Immunohistochemical staining performed at the AFIP was evaluated. The markers included pancytokeratin (n = 70) (AE1/3LP34, 200:40, Boehringer/Dako) and the neuroendocrine markers chromogranin (n = 80; Chromogranin AB, 1:100, Sanbio), synaptophysin (n = 72; synaptophysin, 1:1, Ventana), and Leu-7 (n = 64; HNK-1, 1:20, Becton-Dickinson). When present, the percentage and intensity of tumor cell staining was assessed. Distribution was graded in quartiles: 1%–25%, 26%–50%, 51%–75%, and 76%–100%. The intensity of staining was graded as absent (0), weak (1), moderate (2), or strong (3).

Statistical Analysis

Statistical analysis of all factors examined (see Tables 2 and 3) was performed using the χ^2 and Fisher exact tests. Survival analysis was performed using the Kaplan-Meier and Cox regression methods. Results were regarded as significant if $p < 0.05$.

RESULTS

Clinical Features

The clinical and gross pathologic findings are summarized in Table 2. Of 100 cases of SCLC, 67 occurred in men and 33 in women, at a mean age of 64 years (range, 30–87 yr). A documented smoking history was available in 43 cases with 41 smokers (pack-year range of 25–160) and 2 reported nonsmokers. The contributor's diagnosis was correct made in only 40% of the 55 cases with referral diagnoses available (Table 2).

Tumor location, known for 81 cases, was equally divided between the right (n = 40) and left lung (n = 38); 3 patients had mediastinal masses. The specific location of the tumors is summarized in Table 2. Tumor size ranged from 0.5 to 9 cm with a mean of 3.0 cm. Staging information in 99 patients was: 45 stage I, 20 stage II, 21 stage III, and 13 stage IV tumors. One patient developed the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, paraneoplastic encephalitis was reported in another, and one patient had Pancoast syndrome. Information regarding adjuvant therapy was available in only a small group of patients (Table 2). Eighteen patients were alive at the time of follow-up (length of follow-up: 0.71–6.5 yr, mean 2.52 yr), whereas 82 were deceased.

Gross Pathologic Features

The macroscopic appearance was recorded for 63 tumors (Table 2). Forty-six were described as well-circumscribed, often lobulated; 9 were described as endobronchial, somewhat polypoid lesions; 5 were described as subpleural in location; and the patient with Pancoast syndrome had an apical tumor. The cut surface was reported variously as soft, rubbery, firm, wooden, and gritty. The description of color varied also, from white to tan, to yellow, and to gray with anthracotic stippling. In only seven cases was grossly apparent necrosis recorded. Cavitation and cystic degeneration was described in two tumors. Hemorrhagic discoloration of three tumors was described.

Light Microscopic Features

Between 1 and 17 hematoxylin and eosin-stained sections were examined in each case with a mean of 3. The results are summarized in Table 3. All tumors conform to the 1999 WHO/IASLC light microscopic criteria for SCLC, consisting of small, round, ovoid, and spindle-shaped cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or

TABLE 1. *Classification of small cell lung carcinoma*

Kreyberg[31] 1962	WHO[59] 1967	1973 WP-L WHO[60] 1981	IASLC[21] 1998	WHO/IASLC[50] 1999
Oat cell	Lymphocyte-like	Oat cell	Pure SCLC	SCLC
Polygonal	Polygonal	Intermediate		
	Fusiform		Mixed (with large cells)	
	Other (containing squamous and glandular foci)	Combined	Combined	Combined SCLC (containing any other NSCLC component)

WHO, World Health Organization; IASLC, International Association for the Study of Lung Cancer; WP-L, Working Party for Therapy of Lung Cancer.

TABLE 2. *Clinical features*

	No.	
Age	100	Range = 30–87 Mean = 64
Gender	100	Male = 67 Female = 33
Race	32	White = 27 Black = 4 Hispanic = 1
Tobacco smoking	43	Yes = 41 No = 2 Pack year range (25–160)
Referral diagnosis	55	SCLC = 22 AC = 10 LCNEC = 6 NE Carcinoma, nos = 5 PD Carcinoma, nos = 12
Surgical procedure	82	Lobectomy = 49 Pneumonectomy = 11 Wedge excision = 13 Lymph node biopsy = 9
Chemotherapy	29	Yes = 23 No = 6
Radiation	19	Yes = 19
Length of follow-up	100	Range = 0.71–6.5 years Mean = 2.5 years
Tumor size	65	Range = 0.5–0.9 cm Mean = 3.0 cm
Tumor location	77	Central = 40 Peripheral = 37
Tumor distribution	81	RUL = 14; RML = 8; RLL = 10; R hilum = 7; RML = 1; LUL = 21; LLL = 13; L, NOS = 4 Mediastinum = 3
Stage	99	I = 45; II = 20; III = 21; IV = 13
Survival	100	Dead of disease = 82 Alive = 18
2-year survival by stage	99	Stage I & II = 50%, Stage III & IV = 7%
5-year survival by stage	99	Stage I & II = 14%, Stage III & IV = 7%
Macroscopic description	63	Well-circumscribed = 46 Endobronchial = 9 Subpleural = 5 Apical = 1 Cavitation/cystic degeneration = 2

n, number of patients with information available; UL, upper lobe; ML, middle lobe; LL, lower lobe.

inconspicuous nucleoli (Fig 1A, B). The appreciation of this histology depended greatly, however, on the quality, thickness, and staining of the hematoxylin and eosin-stained section examined. There were 72 "pure" and 28 combined SCLC. The combined forms consisted of SCLC combined with LCC (n = 16), adenocarcinoma (n = 9), and squamous cell carcinoma (n = 3). One SCLC combined with squamous cell carcinoma also included spindle cell carcinoma.

Growth Patterns

A striking feature was the predominance of a neuroendocrine morphologic pattern in most of our resected tumors. The nested or organoid pattern (Fig. 2) was the most common (94%) and peripheral palisading of tumor cell nests was seen in 72% of cases (Fig. 2). Sheet-like growth was a dominant pattern in only 34% of cases. In two cases, there was such marked cellular dyscohesion that lymphoma was included in the differential diagnosis (Fig. 3). However, this was felt to be an artifact of poor fixation and cell preservation rather than a true reflection of the tumor morphology. Other markers of neuroendocrine morphology, including trabecular growth (Fig. 4A) and rosette formation (Fig. 4B), were seen in 46% and 36% of cases, respectively. Most cases demonstrated a combination of patterns with variable distribution. In one case a pseudopapillary pattern was seen (Fig. 5). Crush artifact was prominent in 14 cases, present but minimal in a further 17, but absent from the majority (69) of cases. When present, crush artifact was largely confined to the periphery of the tumor (Fig. 6). Large areas of necrosis were present in 56 cases, including 2 cases with infarct-like areas. The Azzopardi effect, encrustation of DNA around blood vessel walls within an area of necrosis, was noted in 8 cases (Fig. 7). Smaller areas and punctate foci of necrosis were identified in 22 and 9 cases, respectively. Single cell necrosis or apoptosis was prominent in all cases. Examination of the tumor periphery showed aerogenous spread in 59 cases, whereas interstitial spread was seen in only 12 cases. In regard to preinvasive lesions, undermining of normal ciliated bronchial epithelium by pagetoid spread of SCLC (Fig. 8) was noted in 4 cases, mild squamous dysplasia was noted in one case, and invasive squamous cell carcinoma was seen arising within bronchial epithelium in a com-

TABLE 3. *Light microscopic features*

	Histologic feature	Percent of cases
No. of slides examined in each case		Range = 1–17 Mean = 3
Growth pattern	Nested/organoid	94
	Peripheral palisading	72
	Sheet-like	34
	Trabecular	46
	Rosettes	36
Crush artifact	Present	14
	Minimal	7
	Absent	69
Necrosis	Extensive	78
	Punctate foci	9
	Inconspicuous	10
Azzopardi effect		8
Apoptosis		100
Tumor stroma	Fine septa	50
	Broad fibrous bands	43
	Primitive myxoid stroma	1
	Granulomas	5
	Calcification	5
	Metaplastic bone	1
Vascular invasion		42

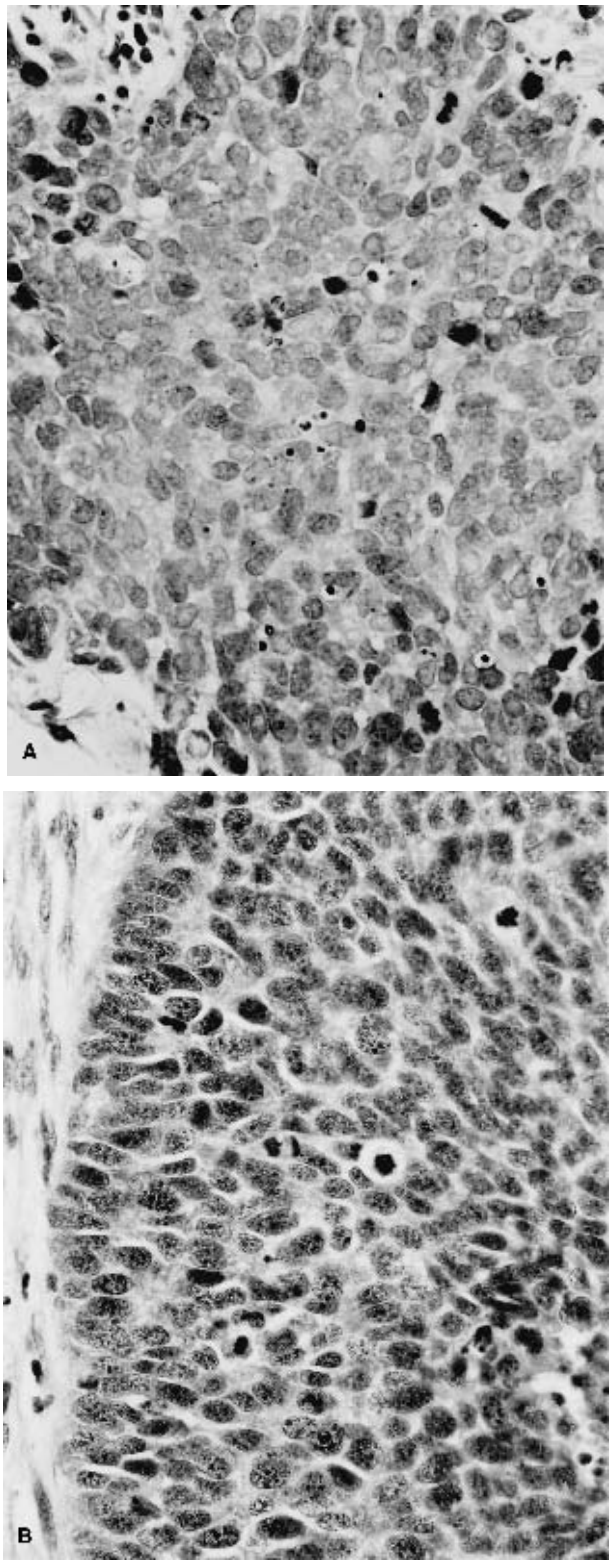

FIG. 1. (**A** and **B**) The "classic" appearance of SCLC consisting of small, round, ovoid, and spindle-shaped cells with finely granular nuclear chromatin, absent or inconspicuous nucleoli, scant cytoplasm, and ill-defined cell borders. Numerous mitotic figures and apoptotic debris is seen. A tumor cell nest has a peripheral palisade (**B**, left).

bined SCLC and squamous cell carcinoma. Other neuroendocrine proliferations such as TC or tumorlets were not seen.

The tumor stroma consisted of fine fibrous septa in 50 cases, a desmoplastic response in 43 cases (Fig. 9), and a very primitive myxoid stroma in one case. Granulomas were part of the stromal response in 5 cases. Tumor vascularity took the form of fine capillaries similar to other neuroendocrine neoplasms. Vascular invasion into arterioles, venules, or lymphatics was seen in 42 cases. Calcification was noted within 5 cases and metaplastic bone formation within one. Mucin was present in 9 cases. Four of these represented SCLC combined with adenocarcinoma, the mucin being confined to the glandular component. In 5 cases, mucin was noted focally in pure SCLC in the form of cytoplasmic or luminal droplets.

Cytologic Features

The diameter of the tumor cells was typically less than the diameter of three small resting lymphocytes. However, the cell size often appeared larger than typically seen in SCLC from bronchoscopic biopsy specimens (Fig. 10). Moderate amounts of eosinophilic cytoplasm were present in 18 cases. Clear cytoplasm was noted in 15 tumors, focally in 11, and diffusely in 4. This was

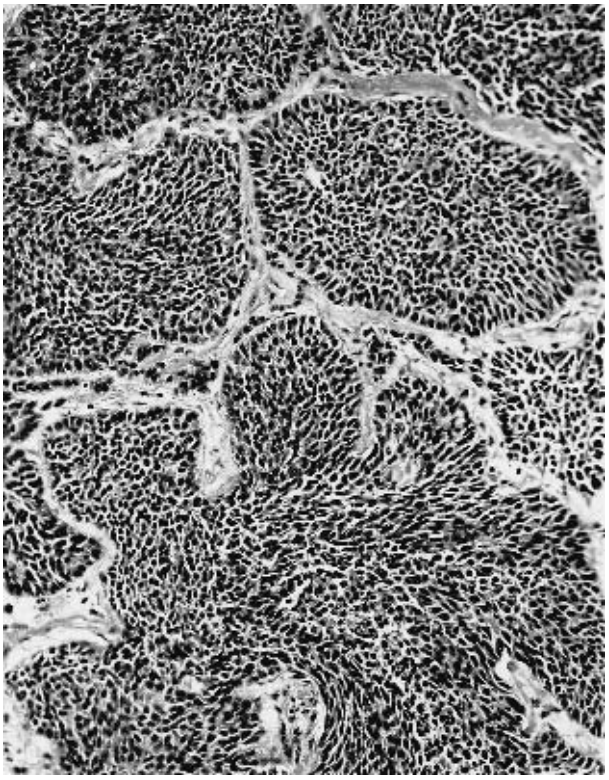

FIG. 2. Packeting of tumor in nests shows peripheral palisading.

interpreted as an artifactual change (Fig. 11). In some tumors, distinct cell boundaries could be seen. Nuclear molding was commonly present. Spindle-shaped cells were identified in 39 cases. Mitotic counts ranged from 18 to 286/2 mm^2, with a mean of 97. The majority of tumor cells had finely to coarsely granular chromatin, but admixtures of cells with pale chromatin were also seen. In rare cases, the nuclear chromatin on submitted slides appeared diffusely vesicular but this was interpreted as artifactual because it usually disappeared on H&Es performed at the AFIP.

Nucleoli were absent, or at best inconspicuous, in virtually all of the tumor cells in 71 cases. In 29 cases, a varying percentage of cells demonstrated nucleoli that were conspicuous but small. Once tumor cells with conspicuous nucleoli were identified, these were interpreted as large cell carcinoma elements. When these constituted 10% or more of the tumor volume, we characterized the tumor as combined SC/LC.

While absent in the majority of cases, 23 tumors displayed cytologic pleomorphism in the form of scattered or clustered multinucleated tumor giant cells. These cells were included in the percentage of large cells used to reach the 10% criteria of SC/LC. However, if the large cell component did not reach 10%, the tumor was regarded as pure SCLC.

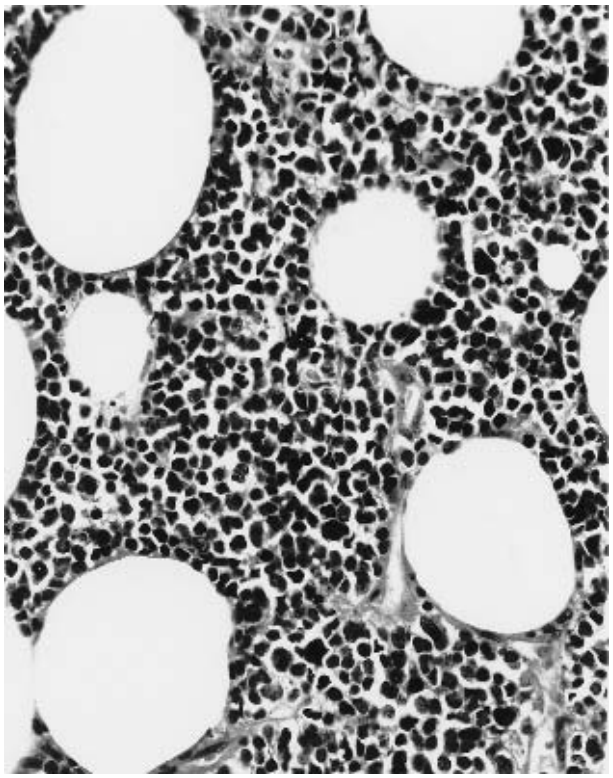

FIG. 3. Infiltration of fat by a dyscohesive sheet of tumor cells mimics malignant lymphoma.

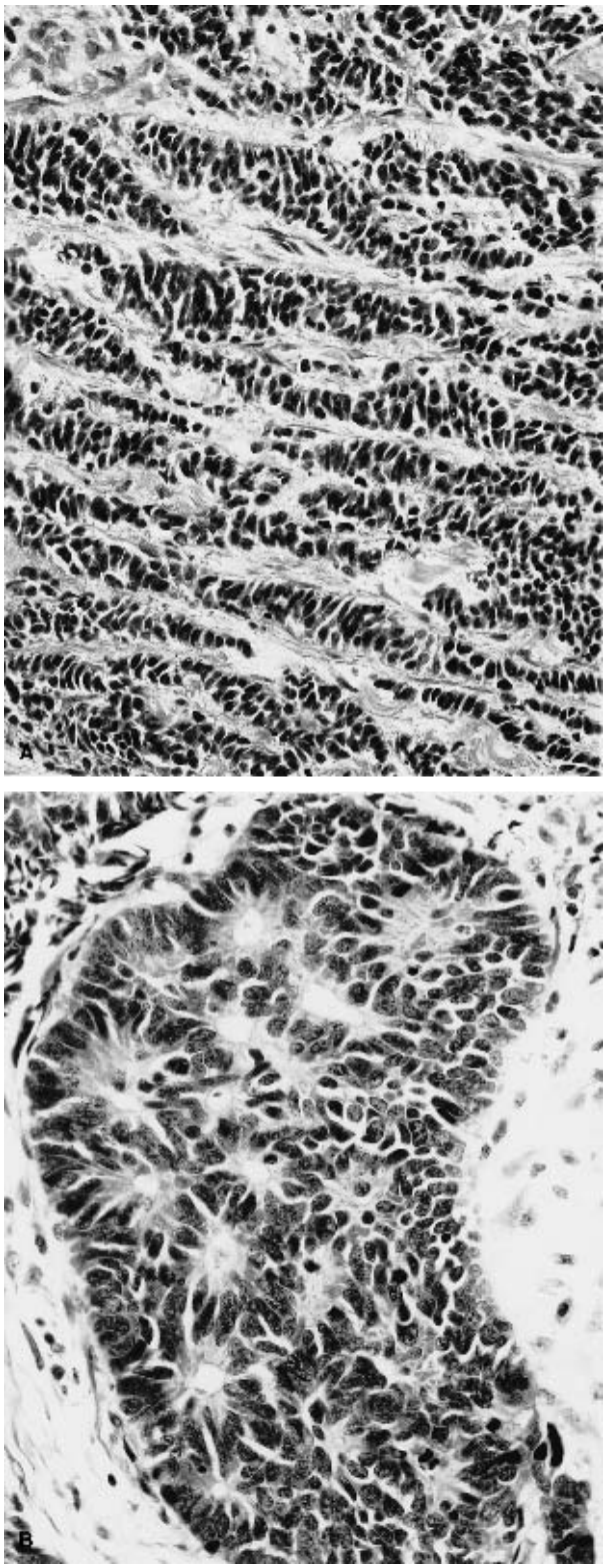

FIG. 4. (**A**) Ribbons of tumor cells characterize the trabecular pattern. (**B**) Rosette formation in SCLC.

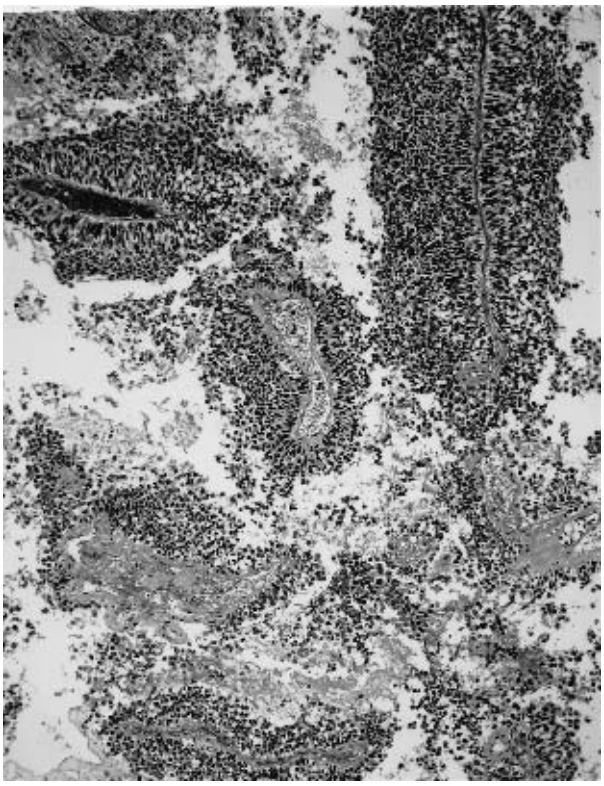

FIG. 5. Pseudopapillary growth pattern. In this tumor, there is necrosis with preservation of tumor cells surrounding blood vessels giving a pseudopapillary pattern.

Combinations With NSCLC

A small component of squamous cell carcinoma was found in combination with SCLC in three cases. Squamous cell carcinoma formed a minor component, comprising approximately 5% of the overall tumor volume. A population of large cells, clearly distinct from SCLC, with coarse or vesicular chromatin, prominent nucleoli, abundant dense eosinophilic cytoplasm, or intercellular bridges, distinguished the squamous cell component (Fig. 12). One case showed keratinization. The third case also demonstrated areas of spindle cell carcinoma, which were embedded in a distinctly myxoid stroma. The majority of the 9 combined SCLC and adenocarcinoma showed an intimate admixture of small cell and adenocarcinoma components, although in one case there was an obvious demarcation of SCLC from adenocarcinoma with acinar and papillary features and psammoma body formation (Fig. 13). The designation of adenocarcinoma was based on overt acinar or papillary architecture rather than the presence of mucin. In 2 cases, significant cytologic pleomorphism coexisted in both the adenocarcinoma and small cell components. In the 16 combined SC/LC, the large cell component was recognized based on larger cell size, nuclear chromatin characteristics, and assessment of nucleolar prominence (Fig. 14). In the majority of combined SC/LC cases, there was a continuum rather than a sharp divide between the different elements. The large cell carcinoma component in these cases usually showed neuroendocrine morphology, including nesting, peripheral palisading, and rosette formation, with acquisition of more vesicular chromatin and prominent nucleoli. In 2 cases, the large cell component did not retain neuroendocrine architectural characteristics and was regarded as large cell carcinoma, not otherwise specified.

Histochemistry and Immunohistochemistry

Information on mucin staining was available for 47 cases only. Intracytoplasmic mucin was identified in 5 cases of pure SCLC and in the adenocarcinoma component alone of 4 combined SCLC.

Immunohistochemical study information was available for 80 cases (Table 5). Pancytokeratin studies were performed on 70 cases, all of which demonstrated positive staining with varying distribution (Table 5) with the majority of cases staining strongly and diffusely throughout. Forty-six cases (58%) were positive for chromogranin, predominantly focal in distribution but strong in stain intensity (Table 5). Forty-one cases (57%) were positive for synaptophysin with a wider distribution but generally less intense staining. Seventeen (27%) cases were positive for Leu-7. All three neuroendocrine markers were

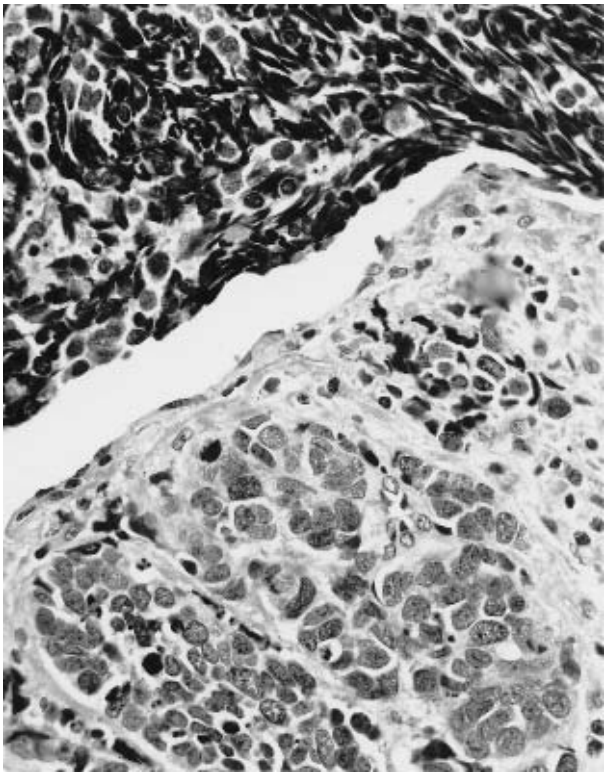

FIG. 6. Crush artifact is seen on the top with well-preserved tumor cells on the bottom.

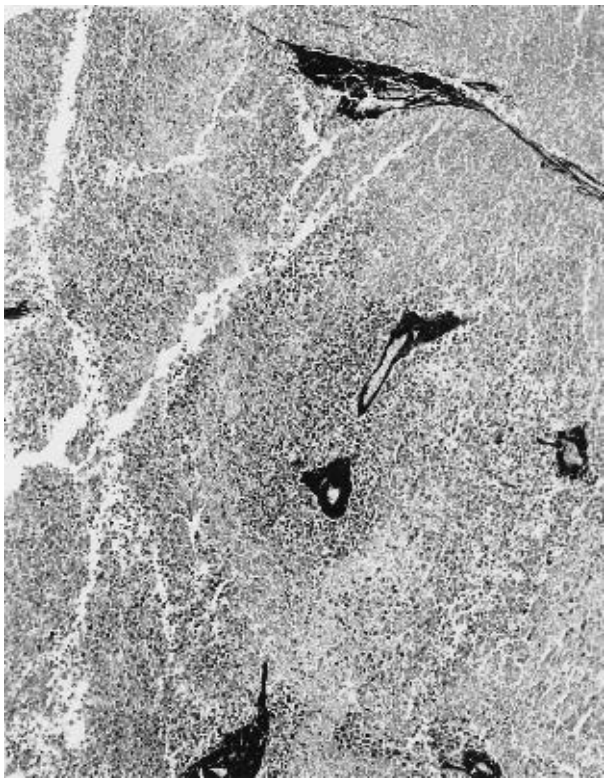

FIG. 7. The Azzopardi effect: encrustation of basophilic DNA around blood vessel walls in an area of extensive necrosis.

negative in 9 of the 61 (15%) cases in which all three stains were available.

Attempts to examine the pattern of immunohistochemical marking of combined small and large cell carcinomas were hampered both by the quality of the material and difficulty in distinguishing discrete small and large

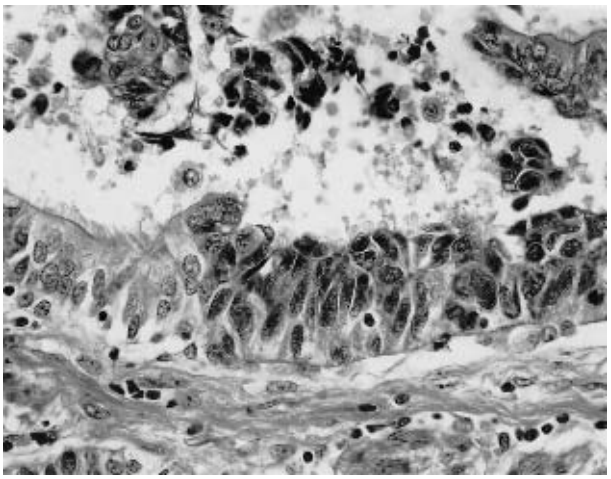

FIG. 8. In a bronchiole, there is ciliated pseudostratified respiratory epithelium on the left, which is undermined by SCLC on the right, but retains apical cilia along the surface.

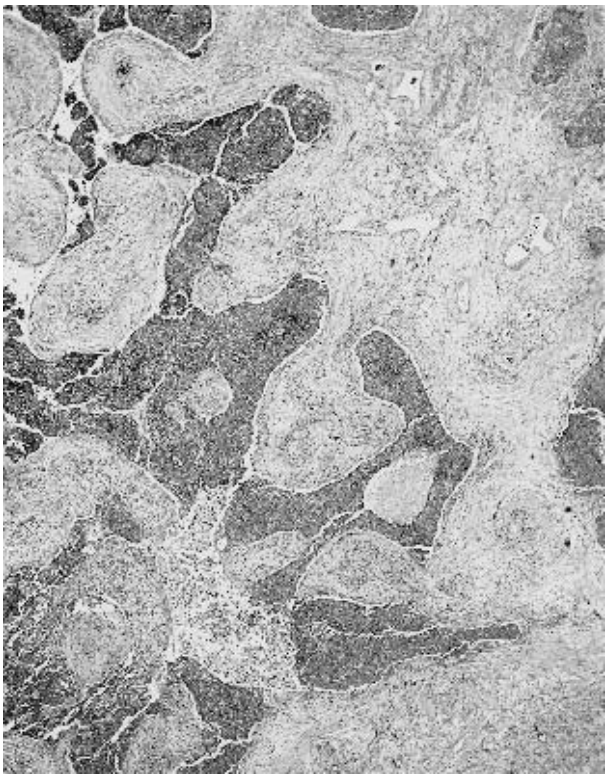

FIG. 9. Islands of tumor infiltrating desmoplastic stroma.

cell areas on the immunohistochemical stains. Of 16 cases, immunohistochemical studies on representative sections were available for 10 cases. In 6 cases, staining for neuroendocrine markers chromogranin and synaptophysin was noted in both components and the diagnosis of combined SC/LCNEC could be made. The cases in which either immunohistochemistry was negative or not available in the large cell component, we classified as combined SC and LCC with neuroendocrine morphology (LCNEM). In the two combined large cell carcinomas, not otherwise specified, reactivity for chromogranin and synaptophysin was restricted to the SCLC component only.

Survival Analysis

Despite exhaustive survival analysis, the only variable that showed prognostic significance was stage. Stages I and II were combined, as were stages III and IV, to reflect the clinical concept of limited and extensive disease. Although there was a significant difference in survival at 2 years, the 5-year survival figures were similar. The 2- and 5-year survival for stages I and II combined was 50% and 14%, whereas that of stages III and IV was 7 and 7%, respectively ($p = 0.0017$). No statistically significant histologic (Table 3) or immunohistologic (Table 4) predictors of prognosis were identified. There was no difference in survival between patients with com-

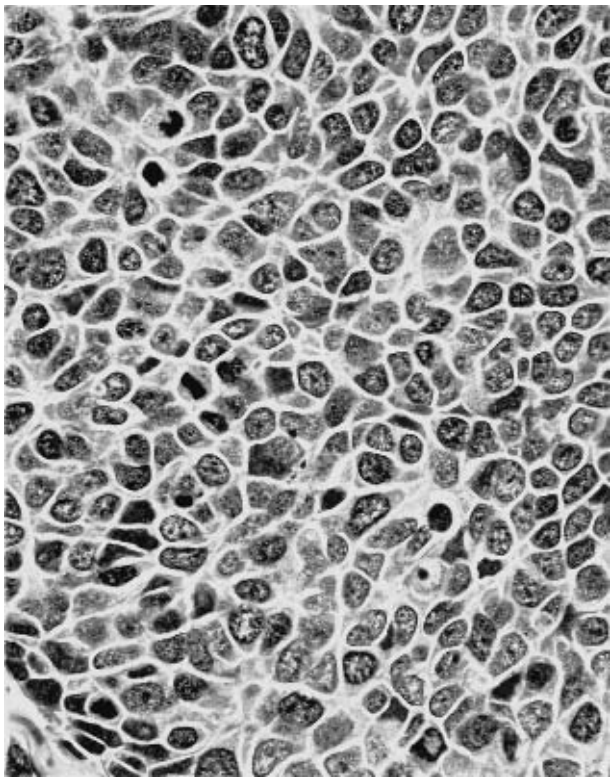

FIG. 10. In resected tumors, cell size appears larger, small amounts of cytoplasm may be seen, and cell boundaries are occasionally visible. Rosette-like structures are present. Vesicular chromatin and nucleoli are seen in a minority (less than 10%) of the tumor cells.

bined SCLC versus pure SCLC. Furthermore, age, gender, tumor size, and tumor location were not found to be significant predictors of prognosis.

DISCUSSION

Despite the exhaustive search for immunohistochemical and molecular markers specific for the diagnosis of SCLC, the final diagnosis is based on light microscopy and immunohistochemistry may be more confusing than helpful in the distinction of SCLC from NSCLC.[50] In the pathologic diagnosis of lung cancer, the most important decision hinges on whether a tumor is SCLC or NSCLC. It is essential for pathologists to be familiar with the spectrum of pathologic manifestations of SCLC. The therapeutic and prognostic implications of this diagnosis are so profound, that distinction of SCLC in all its guises, from NSCLC and from other neuroendocrine tumors, is of the utmost importance. Because of unfamiliarity with the morphologic appearance, we have observed that resected SCLC is easily misinterpreted as a lower-grade neuroendocrine pulmonary tumor (TC or AC), as NSCLC, including LCNEC or recognized as neuroendocrine but not classified further. Twenty-eight percent of cases in this study were misdiagnosed by the referring hospital.

A major finding in our study was the presence of striking NE morphologic patterns often regarded as characteristic of the better-differentiated TC and AC. In recent years, the introduction of strict diagnostic criteria has simplified the separation of the low-grade TC and AC from each other, and from the high-grade SCLC and LCNEC, on the basis of mitotic counts and the presence of necrosis.[8,53] Once a pulmonary tumor is recognized as a high-grade neuroendocrine carcinoma, the differential diagnosis narrows to SCLC and LCNEC. In our study we found that neuroendocrine architectural patterns are common in SCLC. Combinations of nested and trabecular growth patterns with rosette formation and peripheral palisading of tumor cell nests, heretofore associated with other neuroendocrine tumors, do not preclude the diagnosis of SCLC. Thus, a high-grade pulmonary NE tumor still should be classified as either a SCLC or LCNEC, rather than TC or AC.[50]

The cytologic features of resected SCLC conform largely to the classic descriptions. However, in resected specimens, the cell size appears larger in which there is less crush, greater preservation of cytoplasm and occasionally better-defined cell boundaries. The nuclear:cytoplasmic ratio is correspondingly lowered, but recognition of this fact should avert misdiagnosis as NSCLC.

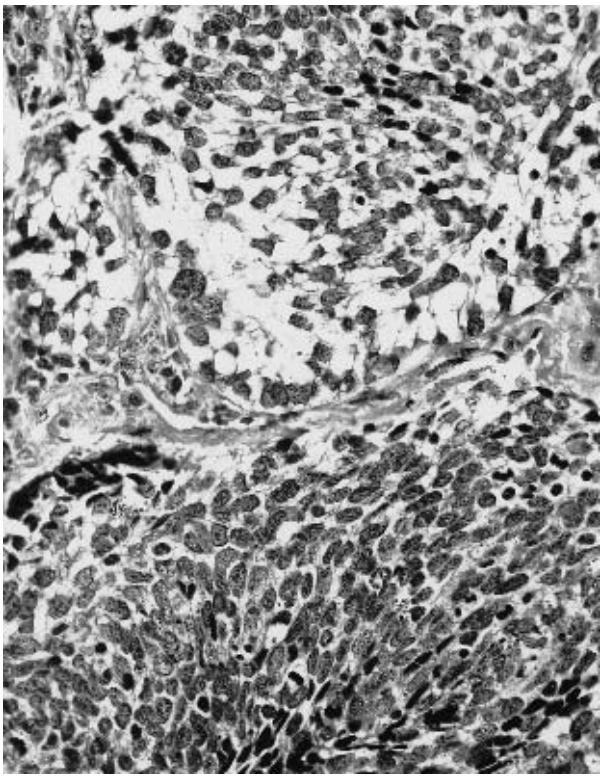

FIG. 11. Well-preserved SCLC is seen on the left, but the adjacent tumor cell nest has artifactually clear cytoplasm.

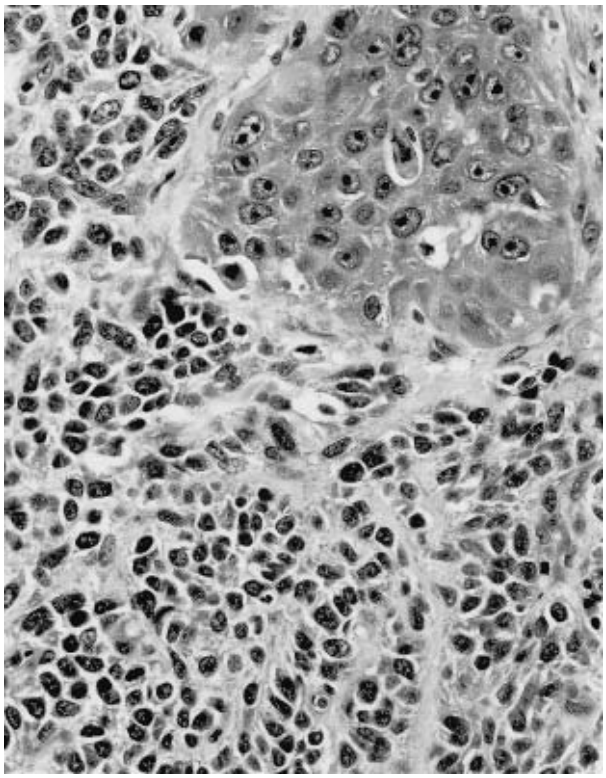

FIG. 12. Combined squamous cell and SCLC. Squamous cell carcinoma on the top right is distinguished from SCLC by polygonal cells with intercellular bridges, vesicular nuclear chromatin, prominent nucleoli, and abundant cytoplasm with keratinization at the center of the tumor cell nest.

Previous studies have shown, using morphometric analysis, that there is a continuous spectrum of cell size from small to LCC and that cases falling in the middle are difficult to categorize.[56] Moreover, nucleolated cells representing a sprinkling of NSCLC elements may be seen frequently in resected specimens of SCLC. However, if the dominant cell population is that of SCLC, one should not diagnose NSCLC based on the presence of a few scattered, larger cells with nucleoli. Nuclear chromatin can vary from coarse to finely granular to pale and focally vesicular, and there may be some overlap in nuclear features with some LCNEC (Table 6).[52] It should also be recognized that droplets of mucin are found occasionally within SCLC. This is not a new observation, having been noted in an early paper by Azzopardi, who cautioned against the erroneous diagnosis of this as poorly differentiated adenocarcinoma.[6] In difficult cases, the distinction of SCLC from LCNEC must rest on the constellation of histologic findings and possibly the consensus opinion of several pathologists.

A recent study examined cell size by morphometry in a group of surgically resected SCLC and LCNEC, demonstrating an overlap in cell size among these categories.[38] For some reason no cases in this study were classified as combined SC/LC, although the morphometry data would suggest that such cases were included.[38] While the authors used this data to propose that SCLC and LCNEC should be combined into a single group of high-grade neuroendocrine carcinoma, they did not report any difficulty reaching a consensus about the diagnosis of SCLC and LCNEC used in this study.[38] In contrast to the authors' conclusions,[38] the results of this study emphasize previous data and recommendations that cell size alone is insufficient as a criteria for establishing the diagnosis of SCLC, and a constellation of histologic criteria must be applied.[11,52,55]

Several studies have shown that approximately 5% of cases present difficulty even to experienced pulmonary pathologists.[46,56] This occurs as a result of a variety of reasons, including the continuum of cell size and morphology between SC and LC,[35,36,38,55] the cytologic heterogeneity within SCLC, as well as poor sampling and tissue artifacts. Artifacts and difficulties in interpretation may arise from inadequate fixation, suboptimal processing, "bubbling," crush, dyscohesion, and necrosis. These alter nuclear and/or cytoplasmic features complicating separation of SCLC from NSCLC. In addition, thickly cut sections and overstaining with hematoxylin may obscure conspicuous nucleoli and truly vesicular chroma-

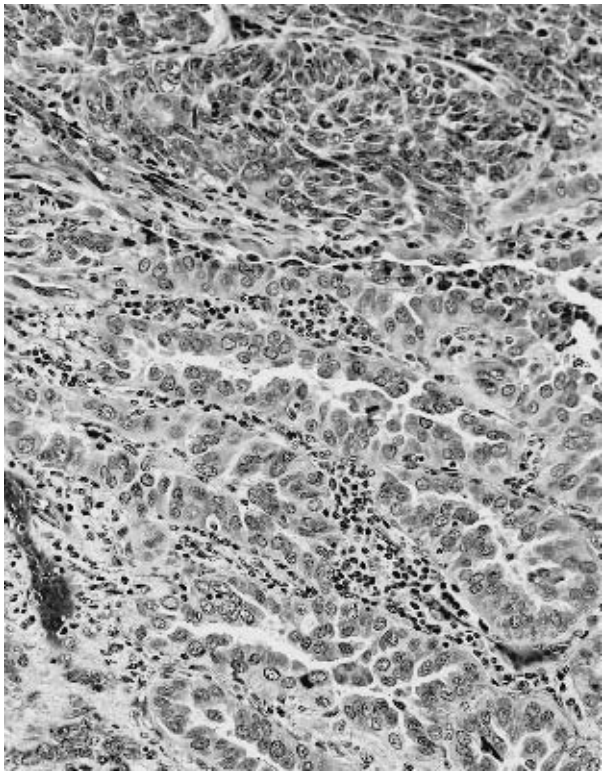

FIG. 13. Combined adenocarcinoma and SCLC. Adenocarcinoma (bottom) is distinguished from SCLC (top) by nonsmall cell morphology and the formation of glandular structures.

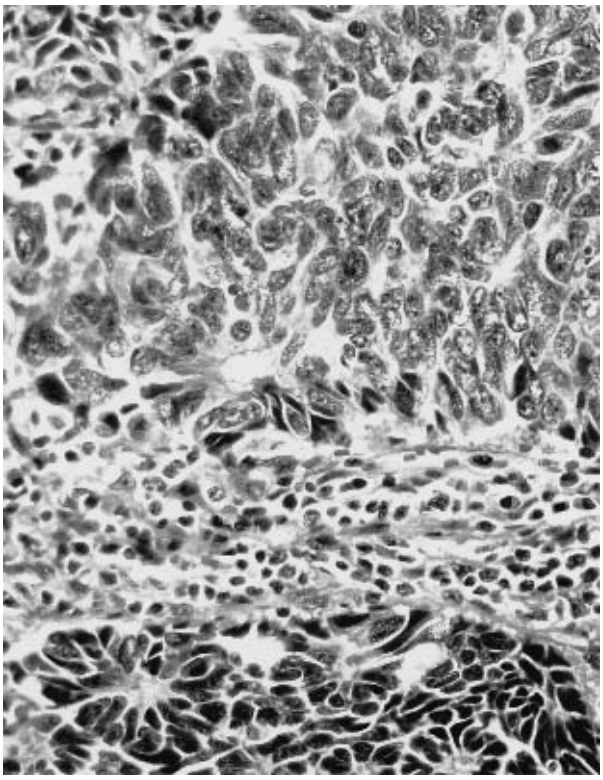

FIG. 14. Combined SC/LC. The large cell component (top) shows vesicular chromatin, nucleoli, and a rosette formation. SCLC (bottom) also shows rosette formation.

tin, and in this situation NSCLC is easily misinterpreted as SCLC. We consider that the evaluation of well-prepared hematoxylin and eosin sections is essential in the distinction of SCLC from NSCLC.

The diagnosis of combined SC/LC presents a diagnostic challenge because the percent of large cells required for this diagnosis is not clearly defined. Barnard recognized the presence of "large polygonal cells indistinguishable from cells of epithelial origin" within SCLC as early as 1926.[7] The category of mixed SC/LC defined by Radice and Matthews as "distinct areas of SCLC intermixed with clusters of large neoplastic cells with abundant cytoplasm and prominent nucleoli."[45] In some cases the two distinct cell populations may not be clearly defined and exist rather as a continuous spectrum.[21] A further definition proposed that large cells must comprise 1% of the total population.[17] If one adopts this latter definition, then the majority of resected SCLC might fall into this category. When SCLC is found in combination with other NSCLC types such as adenocarcinoma or squamous cell carcinoma, a minimum percentage of this component is not necessary. However, given the frequency of scattered large cells in our surgically resected SCLC, we propose that at least 10% of the tumor is large cell carcinoma to classify a tumor as a combined SC/LC. This figure is somewhat arbitrary, but it has been used for other histologically heterogenous lung carcinomas, including pleomorphic carcinoma and adenosquamous carcinoma. Because we did not observe any difference in survival between SCLC and combined SC/LC, this distinction is probably not clinically important. The identification of 16 combined SC/LC in the current study is in general agreement with previous studies, derived from biopsy and autopsy material, which reported 4% to 14% of SCLC as mixed SC/LC.[17,23] These earlier studies detected no difference in outcome, and no prognostic significance was attributed to mixed versus pure SCLC.[4,9]

There has been a recent proposal that the term high-grade (or grade III) neuroendocrine carcinoma should be used to lump SCLC and LCNEC together.[38,57,58] It is possible that in the future this approach could be used, but it is premature. Studies such as ours that evaluate surgically resected specimens[38,51] provide a skewed perspective of SCLC emphasizing some of the more difficult diagnostic problems. It is important not to forget that over 90% of SCLC are readily diagnosed on small biopsy or cytology specimens.[15,41,46,56] While it is important to be honest when dealing with very difficult cases and to inform clinicians when there is uncertainty, this is so rare a situation that such a significant change in terminology is not warranted. The clinical behavior of LCNEC is also not well defined, and there is no definitive data whether it is chemosensitive like SCLC. Because of the rarity of LCNEC, the answer to this information awaits a prospective multicenter clinical trial. Therefore, at the present time, there is no sound basis for using the term of high-grade neuroendocrine carcinoma for all SCLC and LCNEC, and it is better to draw a distinction between these two categories of high-grade neuroendocrine carcinoma using traditional terms.

TABLE 5. *Immunohistochemistry results*

			Distribution of staining				Intensity of staining		
Stain	No.	Total Positive (%)	<25% Positive	26–50% Positive	51–75% Positive	76–100% Positive	Weak (1+)	Moderate (2+)	Strong (3+)
Cytokeratin	70	70 (100)	7	6	13	44	2	22	46
Chromogranin	80	46 (58)	16	13	11	6	4	16	25
Synaptophysin	72	41 (57)	7	5	17	12	10	18	13
Leu 7	64	17 (27)	8	4	3	2	3	5	9

no. = number of cases stained.

TABLE 6. *Histologic criteria for distinction of SCLC from LCNEC**

Histologic feature	Small cell carcinoma	Large cell carcinoma
Cell size	Smaller (<3 resting small lymphocytes)	Larger
Nuclear:cytoplasmic ratio	Higher	Lower
Nuclear chromatin	Finely granular, uniform	Coarsely granular or vesicular, less uniform
Nucleoli	Absent or inconspicuous	Often (not always) present, may be prominent or faint
Nuclear molding	Characteristic	Uncharacteristic
Fusiform shape	Common	Uncommon
Polygonal shape with ample pink cytoplasm	Uncharacteristic	Characteristic
Nuclear smear	Frequent	Uncommon
Basophilic staining of vessels and stroma	Occasional	Rare

* Adapted from reference 52.

The current study identified 12 cases of SCLC combined with adenocarcinoma (n = 9) and squamous cell carcinoma (n = 3). This correlates well with previous studies of lung cancer heterogeneity, in which one group found that half of their cases of SCLC include major or minor elements of NSCLC.[46] An autopsy-based study of SCLC found 13% NSCLC in at least one site.[47] Other studies have yielded smaller percentages of NSCLC, ranging from <1% to 3.2%,[17] but again it must be emphasized that these older studies are based on small biopsies and the examiners did not have the opportunity to study the tumors in their entirety.

There is no recognized preinvasive lesion for pulmonary SCLC unlike squamous cell carcinoma and adenocarcinoma.[50] In contrast to a previous biopsy-based study[61] that identified atypical squamous metaplasia and squamous cell carcinoma-in-situ in 9% and 5% of cases, respectively, we rarely found preneoplastic changes within bronchial epithelium in our surgically resected specimens. However, pagetoid spread of SCLC undermined normal respiratory epithelium in a small number of cases. Whether the tumor had obliterated the evidence of airway dysplastic changes in our cases or perhaps what was described as in-situ carcinoma was in fact pagetoid spread are possible explanations for the discrepancy. The absence of tumorlets in our cases distinguishes SCLC from the low-grade TC and AC, in which multiple tumorlets may be found.[18] Tumorlets are minute neuroendocrine cell proliferations (<0.5 cm).[11,50]

A stromal response is not usually appreciable in bronchoscopic biopsies, and SCLC is therefore not commonly associated with a fibroinflammatory stroma. However, we identified a desmoplastic response in approximately half of these resected tumors. Therefore, a desmoplastic stromal response does not exclude SCLC. We also observed a granulomatous response to tumor, which has been reported previously in occasional cases.[27,30]

Although SCLC is a light microscopic diagnosis and immunohistochemistry is not necessary for the diagnosis, a number of markers are useful in the study of SCLC and can serve to distinguish it from other small cell tumors that occasionally enter the differential diagnosis, such as lymphoma, lymphoid infiltrates resulting from chronic inflammation, or less commonly primitive neuroectodermal tumor (PNET). Lymphoid lesions are typically keratin-negative and -positive for lymphoid markers in contrast to SCLC. PNET is usually negative or only focally positive for keratin and often stains strongly for MIC-2 in contrast to SCLC.[14,20,37] In our study, pancytokeratin was positive in 100% of the 70 SCLC studied.[19,48] In our study the common neuroendocrine markers chromogranin and synaptophysin stained 58% and 57% of the cases studied, respectively. Staining was patchy and of varying intensity. Chromogranin showed a tendency toward more focal but intense staining, whereas synaptophysin was more widely distributed but fainter in intensity. The frequent absence of staining for neuroendocrine markers in small biopsy specimens is easily understood, given the very focal staining observed in many tumor sections. These findings are in broad agreement with previous immunohistochemical studies of SCLC, although staining for synaptophysin was seen in a greater percentage of cases than we previously reported.[19] No correlation was found between survival and either positivity or distribution and intensity of staining for these markers. Because most of these cases were seen before 1998, immunohistochemistry for NCAM (CD56)[29,33] and TTF-1,[3,16,28] both recently recognized useful markers for SCLC, were not investigated in this series.

To date, the only proven predictors of survival in SCLC are extent of disease and performance status.[44] We did not have sufficient information regarding chemotherapy to evaluate the effect it may have had on prognosis within the staging groups. Despite an extensive analysis of many histologic factors, we could not identify any significant predictor of survival. The presence of rosettes suggested a poorer prognosis but this trend did not reach statistical significance. These findings support the fact that SCLC is an entity of aggressive biologic behavior, despite the presence of conspicuous organoid or neuroendocrine morphology in some cases. Similarly, prognostic subsets were not identified within the range of mitotic rates counted for these tumors, un-

like that recently observed within AC.[8] The short survival of patients limited the analysis of predictors of survival. Although the majority of patients reportedly had stage I and II disease, an element of understaging may be present given that the cases were gathered from diverse, remote institutions.

In summary, the current pathologic study of 100 resected SCLC focuses on the architectural and cytologic features and concludes that prominent neuroendocrine morphologic patterns, relatively large cell size, and frequent combination with NSCLC are sources of considerable diagnostic difficulty. A well-fixed specimen, optimally cut and properly hematoxylin and eosin-stained section, is essential to see the cytologic detail of the tumor cells and to make an accurate diagnosis of SCLC. We propose arbitrarily that at least 10% of tumor volume be composed of large cells before subclassifying a SCLC as a combined SC/LC, although this group of patients does not appear to have a different prognosis compared with those with pure SCLC. No predictors of survival other than stage were identified in the statistical analysis of this study cohort. This detailed review of the pathologic features of SCLC in surgically resected specimens will hopefully provide useful information in the morphologic distinction between SCLC and NSCLC. □

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