OCCUPATIONAL RESPIRATORY DISEASES

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

September 1986

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DHHS (NIOSH) Publication No. 86-102

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

PATHOLOGY OF OCCUPATIONAL LUNG CANCER

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The association of environmental factors with lung cancer is well recognized. Among these factors cigarette smoking, air pollution, and occupational exposures to specific industrial agents such as asbestos, arsenic, uranium, chromium, nickel, and chloromethyl ether are considered paramount. Unfortunately for epidemiological purposes, the majority of industrial workers smoke and many live in polluted urban environments; thus separation of risk factors is difficult. The issue is complicated further by synergistic and additive effects between risk factors. Two examples of the former are seen with cigarette smoke and asbestos (35) and cigarette smoke and uranium (6).

The overwhelming majority of lung cancers occur in smokers, and in the United States squamous cell carcinoma is known to be the most prevalent histological type of tumor in males (13)(23)(46) followed by adenocarcinoma, oat cell carcinoma, and large cell carcinoma, respectively (49). The existence of four major histological types of lung cancer is useful as it can be evaluated by pathologists to study the possible influence of smoking, occupational, and other factors on the histogenesis of pulmonary neoplasms. In addition to histological type, the lobe of origin and its position within the lobe (central or peripheral) may also be important.

The majority of studies reporting the distribution of lung cancer by histological type have used the WHO histological classification of lung tumors (24) and its revisions (41)(53).

Histologically, lung cancers can be divided into four major categories: *squamous cell carcinoma, small cell carcinoma, adenocarcinoma,* and *large cell carcinoma.* From the clinical standpoint separation into distinct types is important in view of their different natural histories (28) and responsiveness to therapy (12). These four types together account for approximately 85% of all primary malignant neoplasms of the lung. Lung cancer can be further subdivided into subtypes based on distinct morphological characteristics (53). Subtypes and degree of differentiation may also be important in relation to occupational exposures (29). Other primary malignant tumors of the lung include mixed combined tumors showing features of two or more major types, bronchial gland tumors, carcinoid tumors, carcino-sarcomas, sarcomas, and other rare tumors (Table VIII-15). An association between benign lung tumors and occupational exposure has not been demonstrated; therefore, these will not be considered further. The relationship between malignant tumors of the pleura (mesotheliomas) and occupation are addressed elsewhere.

Grossly, lung cancers may be classified as hilar types (presumed origin within a bronchial wall) or peripheral types (presumed origin in small airways or pulmonary parenchyma).

The majority of *squamous cell carcinomas* are of the hilar type, arising from the major to segmental bronchi. Multicentric origin is also common. These are thought to originate in areas of metaplasia or dysplasia, though this is not always the case (42). Squamous cancers can be further subdivided into: 1) polypoid type, 2) nodular infiltrating type, 3) superficial infiltrating type, and 4) combinations of 1, 2, and 3 (37). The tumors are usually large, pale yellow in color and may show areas of central necrosis. Histologically, the tumors are classified into well, moderately, or poorly differentiated depending on the degree to which they exhibit keratinization and/or intercellular bridges. Hypercalcemia is the most important paraneoplastic syndrome of squamous cell tumors (37).

Small cell carcinomas arise in both major bronchi and in the lung periphery. They typically spread beneath the mucosa to produce raised

Table VIII-15

HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS

I. Epithelial Tumors

A. Benign

1. Papillomas
   a. Squamous cell papilloma
   b. "Transitional" papilloma
2. Adenomas
   a. Pleomorphic adenoma ("mixed" tumor)
   b. Monomorphic adenoma
   c. Others

B. Dysplasia, Carcinoma *In Situ*

C. Malignant

1. Squamous cell carcinoma (epidermoid carcinoma)
   Variant:
   a. Spindle cell (squamous) carcinoma
2. Small cell carcinoma
   a. Oat cell carcinoma
   b. Intermediate cell type
   c. Combined oat cell carcinoma
3. Adenocarcinoma
   a. Acinar adenocarcinoma
   b. Papillary adenocarcinoma
   c. Bronchiolo-alveolar carcinoma
   d. Solid carcinoma with mucus formation
4. Large cell carcinoma
   Variants:
   a. Giant cell carcinoma
   b. Clear cell carcinoma
5. Adenosquamous carcinoma
6. Carcinoid tumour
7. Bronchial gland carcinomas
   a. Adenoid cystic carcinoma
   b. Mucoepidermoid carcinoma
   c. Others
8. Others

Table VIII-15
HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS (Continued)

II. Soft Tissue Tumors

III. Mesothelial Tumors

A. Benign mesothelioma

B. Malignant mesothelioma

1. Epithelial
2. Fibrous (spindle-cell)
3. Biphasic

IV. Miscellaneous Tumors

A. Benign

B. Malignant

1. Carcinosarcoma
2. Pulmonary blastoma
3. Malignant melanoma
4. Malignant lymphomas
5. Others

V. Secondary Tumors

VI. Unclassified Tumors

VII. Tumor-like Lesions

A. Hamartoma

B. Lymphoproliferative Lesions

C. Tumorlet

D. Eosinophilic granuloma

E. "Sclerosing haemangioma"

F. Inflammatory pseudotumor

G. Others

Source: (53)

longitudinal folds (37). The primary tumor may be exceedingly small and the first clinical indication may result from entrathoracic metastases. Necrosis is less frequently seen in small cell carcinomas than in squamous cell carcinomas and cavity formation is rare. Microscopically, the tumors may be divided into oat cell, intermediate cell and combined oat cell carcinoma (53). The oat cell type is characterized by small cells with round or oval hyperchromatic granular nuclei, ill defined borders, and scanty cytoplasm. The cells tend to form trabeculae and rosettes. The intermediate cell type is similar to the oat cell type but has more abundant cytoplasm and distinct cell borders. The combined type is composed of areas of definite oat cell carcinoma with adjacent areas of either squamous cell carcinoma and/or adenocarcinoma. At the ultrastructual level small cell carcinomas can be distinguished from the other types of carcinoma by the presence of dense neurosecretory type granules with limiting membranes. Small cell carcinomas frequently produce polypeptide and biogenic amine hormones which give rise to a number of clinically important syndromes (21).

Adenocarcinomas may arise in the hilar or

peripheral regions of the lung; the majority arise in the latter location. The peripheral type is thought to arise from cells lying distal to the terminal bronchioles. Well differentiated tumors tend to have poorly defined borders whereas the poorly differentiated tumors may secrete copious mucus which may grossly resemble Klebsiella pneumonia (28). Their occurrence in fibrotic lung disease has led to speculation that these tumors arise in areas of cubodial metaplasia adjacent to scars. This theory is difficult to prove, however, as adenocarcinomas may provoke a marked desmoplastic fibrous stromal response. Minute, presumably early, adenocarcinomas have also been demonstrated in areas devoid of fibrosis (37)(38). Because the most common type of metastatic carcinoma to the lungs is adenocarcinoma, it is important to exclude other possible primary sites of origin before a definitive diagnosis is made. Inclusion of metastatic tumors would tend to increase the frequency of adenocarcinomas. Although it is rare, adenocarcinomas can secrete a salivary gland type amylase (1). Histologically, they may be grouped into acinar, papillary, bronchiolo-alveolar, and solid carcinomas with mucus formation. The first two are further classified into well, moderately, and poorly differentiated adenocarcinoma.

Large cell carcinomas are composed of undifferentiated malignant cells showing no features of the other histological types. They are thus diagnosed by exclusion. Included in this category are tumors showing clear cells or giant cells. On the basis of electron microscopical studies the majority of these tumors probably represent poorly differentiated squamous or adenocarcinomas (37). The frequency distribution of histologic types is probably related to the size of the biopsy available for study. The larger the sample the greater the chance of the tumor showing areas of squamous or adeno differentiation. Large cell carcinomas tend to arise from more distal bronchi, have well defined rounded borders, and show hemorrhage and necrosis on cut section. An inflammatory cellular reaction is frequently seen with the giant cell type. Human gonadotrophic hormone production has been described in association with the large cell variant (17).

Several studies have reported the relative frequencies of the different histological types of lung cancer in the general population and these have largely formed the basis for comparison with occupational groups. Determining the true prevalence of the different histologic types in occupational cohorts has proven difficult due to numerous confounding variables. Some of these will be considered briefly. First, in most studies the occupational histories of the comparison population are not known or are incomplete, thus biases due to occupation may remain undetected. Second, as mentioned earlier, the vast majority of lung cancer cases occur in smokers, thus occupational effects on lung cancer histogenesis are superimposed on the already existing effects of smoking. In many studies smoking histories are incomplete and in most, cumulative exposures are not known. Both of these factors influence cell type frequencies. All types of lung tumor show a dose-response relationship with cigarette smoking. Several studies indicate that this effect is greatest for squamous cell carcinomas (8)(25)(47); other studies indicate oat cell tumors are more responsive (4)(55). Third, it has been shown that the frequency distribution of histological type is dependent on the method of diagnosis. For example, centrally located tumors, which tend to be squamous cell carcinomas, are more easily accessible to bronchoscopy, whereas peripheral tumors, which tend to be adenocarcinomas, are more likely to be diagnosed at autopsy (19). Thus studies based on autopsy material will differ from biopsy based studies. Fourth, the frequency distribution of lung cancer by cell type appears to be changing. In particular, there is evidence that the proportion of adenocarcinomas and possibly squamous cell carcinomas in the general population is increasing (5)(45). While part of this trend may reflect changes in diagnostic criteria, there is also evidence that this is a real phenomena. Fifth, there is considerable inter and intra observer variability in tumor classification by pathologists, particularly for the less well differentiated types (16). Sixth, age at diagnosis appears to influence the frequency distribution of different histological types (48), with a greater proportion of squamous cell carcinomas appearing in the older groups. Finally, there are distinct sex differences with relatively more adenocarcinomas in women (7).

Studies showing the distribution of lung cancer by histological type in the general population categorized by sex and smoking status are summarized in Tables VIII-16-VIII-22. These indicate that in male cigarette smokers (Table VIII-16), the predominant cell type is squamous

with lesser frequencies of adenocarcinoma, small cell undifferentiated carcinoma, and large cell undifferentiated tumors in that order. In female smokers adenocarcinomas predominate (Table VIII-17).

Very few studies of histological type of lung cancer have been reported for nonsmokers. For both males and females, adenocarcinoma appears to be the most common type, although the number of cases is too small to draw a definite conclusion (Tables VIII-18 and VIII-19). In studies in which smoking status is not specified, squamous cell carcinoma is the most frequent tumor type for males whereas in females, adenocarcinoma predominates (Tables VIII-20 and VIII-21). This distribution of types is similar to that seen in smoking populations—suggesting that the majority of these cases are in fact smokers. Table VIII-22 shows the data from studies in which both sex and smoking status were unspecified. These show an excess of squamous cell carcinomas, which probably reflects the proportion of male smokers in these groups.

It is clear from the foregoing that interpretation of studies relating histological type to occupation is difficult without information on sex and smoking status. However, despite these limitations certain occupational exposures do appear to exert an influence on the histogenesis of lung cancer.

Data relating cell type of lung cancer to occupation is shown in Table VIII-23. The pathology of lung cancer in cases with asbestos exposure and/or asbestosis has been studied (22) (52). These investigations indicate a relative increase in the number of adenocarcinomas. Asbestos associated tumors also tend to arise in areas of the lung most affected by asbestosis, i.e., peripherally in the lower zones (22) (39). Although a peripheral, lower lobe adenocarcinoma arising in an area of fibrosis may be considered to be a typical asbestos-associated lung cancer, the majority do not fall into this pattern. Thus in an individual case, knowledge of location or cell type has limited etiologic or medico-legal significance.

Several studies have shown a link between ionizing radiation, such as occurs in uranium miners and an increased frequency of small cell carcinomas (2)(33). Moreover, the relative frequency of this type of tumor increased with increased cumulative exposure to radiation (3)(33). The lungs of uranium miners also showed a slight excess of severe atypia and early primary invasive carcinoma of the bronchial mucosa as compared to matched controls, although the prevalence of carcinoma *in situ* was approximately the same for the two groups (6).

An increase in small cell undifferentiated carcinomas in iron-ore miners (9)(15)(31) may also be due to moderate, but raised levels of radon within the mines, rather than the promoter effect of iron oxides on polycylic aromatic hydrocarbons (34). A similar pronounced excess of small cell carcinomas has been observed in workers exposed to chloromethyl ether (50). There is also a dose-response effect. The authors concluded that small cell carcinoma was a specific response to chloromethyl ether exposure.

Significant but less impressive relationships have been observed in other occupations. Copper smelter workers exposed to arsenic appear to have a relative increase in adenocarcinomas as compared to the general population (51). In another group of copper smelter workers, an excess of poorly differentiated squamous cell carcinomas was observed (29).

Data for coal miners is conflicting: one study indicates almost equal proportions of the three major types of tumor (44) and another indicates an excess of squamous cell tumors (36). The populations were drawn from different geographic regions with either predominantly hard coal (anthracite) exposure (36) or predominantly soft coal (bituminous) exposure (44), and this may account for the differences observed.

There is no evidence to date to suggest that exposure to silica (32) or beryllium (40) exerts an influence on the histogenesis of lung cancer.

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Table VIII-16

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
830	53	10			37	1956-65	U.S.A.	Autopsy	Weiss et al., 1977 (Cancer)
662	35	25	25	14	1	1955-72	U.S.A.	Autopsy	Auerbach et al., 1975 (Chest)
138	60	12	15		13	1955-70	U.S.A.	Autopsy	Saccomanno et al., 1971 (Cancer)
121	59	13	14	13	1	1955-70	U.S.A.	Autopsy	Archer et al., 1974 (Cancer)
1237	65	10			25	1957-63	U.S.A.	Autopsy	Cooper et al., 1968

Table VIII-17

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
46	54	26			20	1953-55	U.S.A.	Autopsy	Wynder et al., 1956
163	12	50	10		28	1947-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
72	31	21			48	1957-63	U.S.A.	Autopsy	Cooper et al., 1968

Table VIII-18

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
6		100				1955-72	U.S.A.	Autopsy	Auerbach et al., 1975
13	0	85			15	1957-63	U.S.A.	Autopsy	Cooper et al, 1968

Table VIII-19

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
50	32	58			10	1957-63	U.S.A.	Autopsy	Cooper et al., 1968
59	27	49			24	1953-55	U.S.A.	Autopsy	Wynder et al., 1956

Table VIII-20

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
1228	52	11			37	1956-65	U.S.A.	Autopsy	Weiss et al., 1977
94	52	22	16	5	5	1956-65	U.S.A.	Autopsy	Weiss and Boucot, 1977
1186	37	25	21	16	1	1955-75	U.S.A.	Autopsy	Auerbach et al., 1979
152	75	9	9	7	0	1963-77	Irish Republic	Surgical	Healey, 1980
50	24	18	28	16	14	1954-71	U.S.A.	Autopsy & Surgical	Kannerstein and Churg, 1972
45	60	7	24	7	2	1954-72	U.S.A.	Autopsy & Surgical	Newman et al, 1976
42	47	12	14	19	7	1950-74	U.S.A.	Autopsy & Surgical	Wicks et al, 1981
1140	60	19			21	1941-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
1017	33	28	22		17	1958-77	U.S.A.	Autopsy & Surgical	Cox and Yesner, 1979
902	38	7			55	1933-48	England	Autopsy & Surgical	Mason, 1949
916	52	4	33		11	1948-52	England	Autopsy	Doll and Bradford, 1952
1404	42	24	18	9	8	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-21

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
98	11	13			76	193 -48	England	Autopsy & Surgical	Mason et al., 1949
79	23	13	48		16	1948-52	England	Autopsy	Doll and Bradford, 1952
164	26	38			36	1955-57	U.S.A.	Autopsy & Surgical	Haenszel et al., 1958
163	22	50			28	1947-63	U.S.A.	Autopsy & Surgical	Vincent et al., 1965
201	16	31	12	22	19	1957-72	U.S.A.	Autopsy & Surgical	Beamis et al., 1975
278	20	38	24	12	6	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-22

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION AND SMOKING STATUS UNSPECIFIED

#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Method of Diagnosis	Reference
231	42	20			38	1938-44	U.S.A.		Hollingsworth, 1947
1000	35	7			58	1933-48	England	Autopsy & Surgical	Mason, 1949
351	43	11	14		27	1942-51	U.S.A.		Collins, 1958
849	38	13	9		40	-48	U.S.A.	Autopsy & Surgical	McDonald et al., 1951
199	62	12	8		15	1933-58	U.S.A.	Biopsy & Surgical	Reinhoff et al., 1965
1309	63	11			27	1957-63	U.S.A.	Autopsy	Cooper et al., 1968
81	32	27	27	14	0	1963-77	Irish Republic	Autopsy	Healey, 1980
219	26	39	16		11	1963-76	U.S.A.	Autopsy & Surgical	Valaitis et al., 1981
1682	38	27	19	9	7	1962-75	U.S.A.	Autopsy & Surgical	Vincent et al., 1977

Table VIII-23

HISTOLOGICAL TYPE OF LUNG CANCER IN MALES (%): OCCUPATION SPECIFIED

Occupation/ Exposure	#N	Squamous	Adeno & BA	Small Cell	Large Cell	Other	Year of Diagnosis	Country	Smoking Status	Method of Diagnosis	Reference
Iron Ore Miners/Radon	69			37			1948-67	U.K.	NK	Autopsy	Boyd et al., 1970
Iron Ore Miners/Radon				44				France	NK	Autopsy	Roussel et al., 1964
Coal Miners (Anthracite)	165	79	10				1957-68	U.S.A.	I	Autopsy & Surgical	Scarano et al., 1972
Coal Miners (Bituminous)	202	24	31	28	9	8	1972-77	U.S.A.	S	Autopsy	Vallyathan et al., 1980
Free Silica	16	63	1	18			1960-67	Switzer-land	NS	Autopsy	Ruttner and Heer, 1969
Beryllium Workers	25	20	32	36	12	0	NK	U.S.A.	I	Autopsy & Surgical	Smith and Suzuki, 1980
Copper Smelter Workers/Arsenic	42	31	38	24	7	0	1950-74	U.S.A.	I	Autopsy & Surgical	Wicks et al., 1981
Copper Smelter Workers/Arsenic	25	56	12	28	4		1954-72	U.S.A.	I	Autopsy & Surgical	Newman et al., 1976
Copper Mine Workers	54	61	9	20	9	0	1954-72	U.S.A.	I	Autopsy & Surgical	Newman et al., 1976
Chloromethyl Ether Workers	28	3	18	68	7	3	1960-75	U.S.A.	S	Autopsy & Surgical	Weiss et al., 1979
Asbestos Workers	88	22	34	26	14	5	1962-72	U.K.	S	Autopsy & Surgical	Whitwell et al., 1974
Asbestos Workers	50	22	22	22	12	22	NK	U.S.A.	I	Autopsy & Surgical	Kannerstein and Churg, 1972
Uranium Workers	107	23	7	69		1	1950-70	U.S.A.	S	Autopsy	Archer et al., 1974
Uranium Workers	121	26		61		13	1950-	U.S.A.	S	Autopsy	Saccomanno et al., 1971

BA Bronchioloalveolar
NK Not Known
I Incomplete
NS Nonsmokers
S Smokers

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CLINICAL PRESENTATION

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The clinical presentation of primary lung cancer due to either occupational or non-occupational causes is varied and depends on numerous factors including cell type, location and extent of tumor, and poorly defined host-tumor interactions. Some patients with lung cancer detected by routine chest radiographs will have no signs or symptoms. In other cases, particularly those with more central lesions, cough, hemoptysis, bronchial obstruction with secondary pneumonia, or other localized findings will be apparent. Intrathoracic spread may involve any structure, causing such symptoms as dyspnea due to pericardial or large pleural effusions, dysphagia due to esophageal compression or invasion, or hoarseness due to invasion of the recurrent laryngeal nerve. Metastasis outside the chest may involve any organ or structure with the most common sites being brain, liver, and bone. Alternatively, patients may present with nonspecific constitutional complaints as anorexia, weight loss, fatigue or weakness. Finally, primary lung cancers (particularly small cell carcinoma) may produce a number of paraneoplastic syndromes such as Cushing's syndrome, cerebellar degeneration, migratory thrombophlebitis, and nonbacterial thrombotic endocarditis.

DIAGNOSIS

The diagnosis of bronchogenic carcinoma usually centers around abnormalities seen on the chest radiograph. Special radiographic exams such as tomograms as well as old x-rays are often helpful in this clinical assessment. In general, cytologic or tissue diagnosis is obtained to confirm the clinical impression. Staging of the tumor is then necessary to determine the appropriate therapy. Interested readers are referred to the following excellent sources of comprehensive discussions of cancer staging:

American Joint Committee for Cancer Staging and End Results Reporting. "Staging of Lung Cancer, 1979." Chicago, Illinois.

D. T. Carr: Diagnosis and Staging. In: Lung Cancer, 1980. II World Conference, Copenhagen, Editors H. H. Hansen and M. Rorth. Excerpta Medica, Amsterdam, pp. 49-70.

Mountain, C. F., Carr, D. T., and Anderson, W. A. D. A System for the clinical staging of lung cancer. Am J. Roent. *120:*130-38, 1974.

Numerous approaches and procedures have been used in the diagnostic evaluation of bronchogenic carcinoma, and each patient must be individualized. The underlying plan in all cases, however, is first to establish the diagnosis, then to determine the tumor's resectability (the chance that it can be totally removed surgically), and if resectible, to determine the patient's operability (the chance that he could survive post-resection cardiopulmonary function). Although the finding of small cell carcinoma is generally considered a contraindication to surgery, staging of this tumor can be useful in determining therapy and prognosis.

THERAPY

The primary mode of treatment of non-small cell bronchogenic carcinoma is surgical resection. Unfortunately, most patients are either unresectable or inoperable at the time of presentation. "Curative" radiotherapy has had some success in limited studies, but for the most part radiotherapy is used for palliation. It may relieve hemoptysis, superior vena cava obstruction, or brain or bone metastases. To date chemotherapy has had little permanent benefit. Combination therapy approaches have been and continue to be tried, including those using immunotherapy, but most well controlled studies again show little benefit.

Although the most lethal, small cell carcinoma is also the bronchogenic cancer most sensi-