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Classification, Staging, and Etiology of Lung Cancer

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CLASSIFICATION

The pathologic classification of lung tumors has been the subject of several important publications. First among them is Liebow's original fascicle published in 1952.[1] An updated second edition of this fascicle by Carter and Eggleston appeared in 1979.[2] The first World Health Organization classification of lung tumors was the work of Kreyberg and colleagues and appeared in 1957.[3] An updated version of this classification, edited by Yesner and Sobin, appeared in 1982 and is presented in Display 46-1.[4] In this chapter, we follow our classification of lung cancer, which is included in Silverberg's *Principles and Practices in Surgical Pathology* and shown in Display 46-2.[5]

In our classification, malignant epithelial tumors are separated into two groups: usual tumors and rare tumors. Among the usual or group I tumors are adenocarcinoma (see Chap. 47), squamous cell carcinoma (see Chap. 48), small cell carcinoma (see Chap. 49), large cell carcinoma (see Chap. 50). Group II or rare epithelial tumors include carcinoid and other neuroendocrine tumors (see Chap. 51), submucosal bronchial gland tumors (see Chap. 52), and bronchial papillary tumors of surface epithelium (see Chap. 53).

Group III tumors are tumors combining epithelial and mesenchymal features (see Chap. 54) and include carcinosarcoma, blastoma, and teratoma. Lymphomas and other lymphoproliferative lesions (see Chap. 55) and mesenchymal (*i.e.*, soft tissue) tumors (see Chap. 56) are grouped under the designation nonepithelial tumors or Group IV tumors. Group V represents mesothelioma and other pleural tumors (see Chap. 57). Group VI or tumors of unknown histogenesis are collected under the designation of miscellaneous (see Chap. 58).

Not included in Display 46-2, but discussed elsewhere in this section, are metastatic lung cancer (see Chap. 59), pulmonary metastasis of extrapulmonary tumors (see Chap. 60), and inflammatory pseudotumors (see Chap. 61).

STAGING

TNM System

To determine operability of lung tumors, to establish prognosis, and to compare the efficacy of different treatment regimens, the physician must rely on a staging system. We follow the TNM system, in which T indicates the size of the tumor, N indicates lymph node involvement, and M indicates distant metastasis.[6,7] The following situations are considered in the TNM system:

Occult carcinoma: characterized by malignant cells in cytologic smears or bronchial secretions, but no gross evidence of tumor bronchoscopically or radiographically

Stage 0: carcinoma *in situ*

Stage I: tumor masses up to 3 cm in diameter, completely surrounded by lung tissue and visceral pleura (T1), with or without metastasis to ipsilateral peribronchial and hilar nodes (N1); tumors larger than 3 cm in diameter without nodal metastasis and tumors of any size invading visceral

DISPLAY 46-1. WORLD HEALTH ORGANIZATION HISTOLOGIC CLASSIFICATION OF LUNG TUMORS

- Epithelial tumors
  - Benign tumors
    - Papillomas
      - Squamous cell papilloma
      - Transitional papilloma
    - Adenomas
      - Pleomorphic adenoma (mixed tumor)
      - Monomorphic adenomas
      - Others
  - Dysplasia and carcinoma *in situ*
  - Malignant tumors
    - Squamous cell carcinoma (*i.e.*, epidermoid carcinoma)
      - Spindle cell carcinoma (*i.e.*, squamous carcinoma)
    - Small cell carcinoma
      - Oat cell carcinoma
      - Intermediate cell type
      - Combined oat cell carcinoma
    - Adenocarcinoma
      - Acinar adenocarcinoma
      - Papillary adenocarcinoma
      - Bronchioloalveolar
      - Solid carcinoma with mucus formation
    - Large cell carcinoma
      - Giant cell carcinoma
      - Clear cell carcinoma
    - Adenosquamous carcinoma
    - Carcinoid tumor
    - Bronchial gland carcinoma
      - Adenoid cystic carcinoma
      - Mucoepidermoid carcinoma
    - Other carcinoma
- Soft tissue tumors
- Mesothelial tumors
  - Benign mesothelioma
  - Malignant mesothelioma
    - Epithelial mesothelioma
    - Fibrous mesothelioma (*i.e.*, spindle cell mesothelioma)
    - Biphasic mesothelioma
- Miscellaneous tumors
  - Benign tumors
  - Malignant tumors
    - Carcinosarcoma
    - Pulmonary blastoma
    - Malignant melanoma
    - Malignant lymphomas
    - Other tumors
- Secondary tumors
- Unclassified tumors
- Tumorlike lesions
  - Hamartoma
  - Lymphoproliferative lesions
  - Tumorlet
  - Eosinophilic granuloma
  - Sclerosing hemangioma
  - Inflammatory pseudotumor
  - Other lesions

From World Health Organization. The World Health Organization histological typing of lung tumors, second edition. Am J Clin Pathol 1982;77:123.

pleura or a lobar bronchus more than 2.0 cm distal to the carina (T2) are also rated as stage I

Stage II: tumor classified as T2 with metastasis to ipsilateral hilar and peribronchial hilar lymph nodes (N1)

Stage III: tumors of any size with metastasis to mediastinal lymph nodes (N2) or distant metastasis (M1); tumors that invade the chest wall, diaphragm, or mediastinum (T3) are also considered stage III cancer.

International System

An International Staging System for lung cancer will soon replace the previous TNM system.[8] In the International System, stage I is characterized by the absence of lymph node metastases altogether. Stage II patients have peribronchial, hilar, or mediastinal lymph node metastases on the ipsilateral side only. In stage IIIA disease, the tumor may invade the chest wall and there may be hilar or mediastinal lymph node metastases on the ipsilateral side only. Pancoast tumors are included in stage IIIA. Patients with stage I, II, and IIIA tumors are candidates for surgical therapy.

Stage IIIB is defined by the presence of contralateral hilar, mediastinal, scalene, and supraclavicular lymph node metastases, by tumors directly invading mediastinal structures (*e.g.*, heart, great vessels, vertebrae, esophagus, trachea, carina), or by tumors with associated malignant pleural effusions. Stage IV is characterized by distant metastases (*e.g.*, brain, liver, bone, adrenals). Patients with stage IIIB and IV disease are treated with radiotherapy and chemotherapy.

Problems in Staging

Problems are bound to arise in the staging of lung cancer, as discussed by Miller and Nelems.[9]

MULTICENTRICITY

In addition to the main tumor for which surgery was performed, some specimens contain a second, radiologically inapparent tumor. Each tumor should receive independent T assessment; adequate resection of the two synchronous masses may be curative. Occasionally, the specimen shows innumerable, microscopically identical tumors in addition to the dominant lesion, which are usually well-differentiated bronchioloalveolar tumors. This type of multicentric malignancy is incurable because of the likelihood of similar lesions in the opposite lung, and the T status of these tumors is therefore undetermined (TX).

CARCINOMA IN SITU

In squamous cell carcinomas, there is frequently an *in situ* lesion extending for several centimeters as leukoplakic patches of the bronchial mucosa. Squamous carcinoma *in situ* is designated TIS disease, regardless of its extent; if there is microinvasion, the

DISPLAY 46-2. HISTOLOGIC CLASSIFICATION OF PRIMARY TUMORS OF THE LUNG

Usual epithelial tumors (90%)
- Adenocarcinoma (40%)
- Squamous cell carcinoma (25%)
- Small cell carcinoma (15%)
- Large cell carcinoma (10%)

Rare epithelial tumors (4%)
- Carcinoid and other neuroendocrine cancers (3%)
- Bronchial gland tumors (0.7%)
- Papillary tumors of surface epithelium (0.3%)

Mixed epithelial-mesenchymal tumors (1%)
- Blastoma
- Carcinosarcoma
- Teratoma

Nonepithelial tumors (2%)
- Lymphoproliferative lesions
- Mesenchymal tumors

Mesothelioma and other pleural tumors (3%)

Miscellaneous tumors (0%)

Percentages in parenthesis are estimates of prevalence based on more than 2000 cases of primary lung tumors studied by the editor in Miami, Florida, from 1977 to 1993.

tumor is considered T1 if the length of the *in situ* component is more than 3 cm.

VISCERAL PLEURAL INVASION

Tumor invasion of the mesothelial connective tissue layer, best demonstrated by elastic tissue stain (see Chaps. 1 and 75), establishes a T2 status for a tumor, regardless of size. Puckering of the pleura by itself does not necessarily mean pleural invasion. Perforation of the pleura by the tumor is worse than simple pleural invasion and has an unfavorable prognosis. Any tumor associated with malignant pleural effusion is considered inoperable. A tumor that is operable but associated with a pleural effusion that is negative for malignant cells should be classified according to the tumor, with no further consideration given to the effusion. If the parietal pleura is invaded by the tumor, the tumor status is T3, even if the invasion is only microscopic.

OBSTRUCTION

Lobar bronchus obstruction indicates a T2 lesion, regardless of size. This is a straightforward criterion for tumors of the right lung. For the left lung, the apical posterior and anterior segments are considered to be the actual left upper lobe, and the lingula is considered to be the left middle lobe containing tumor.

MEDIASTINAL INVASION

Invasion of the mediastinum by tumor indicates an unresectable lesion. Mediastinal soft tissue invasion can be mimicked by perinodal tumor spread from metastasis to mediastinal nodes containing tumor.

NODAL STATUS

In a lobectomy specimen, all intraspecimen lymph nodes are in the N1 group. In a pneumonectomy specimen, lymph nodes around the main bronchus that are outside the hilar pleural envelope are regarded as N2 nodes. If peribronchial nodes are submitted individually for assessment by the surgeon, it is important to know the location of these nodes in relation to the pleural envelope (Fig. 46-1).[10] In lung cancer, the actual node count is not as important as the presence or absence of metastasis, and all grossly negative nodes should be blocked thoroughly for this possibility.

Recently, Chen and colleagues used keratin immunoperoxidase stains for the detection of occult micrometastasis in lymph nodes of patients with non-small cell lung carcinomas, and the results were striking. They found single tumor cells and small clusters of tumor cells (*i.e.*, occult micrometastases) in 38 of 60 patients (63%) whose nodes appeared to be negative on hematoxylin-eosin—stained slides. In five patients with a diagnosis of node-positive lung cancer, five of 51 nodes (10%), judged to be metastasis-free by conventional histologic evaluation, contained tumor. Therefore, it seems clear that pathologists are presently understaging lung cancer, a fact that may provide one explanation for the frequently unpredictable clinical behavior of this disease.

ETIOLOGY

Adler observed that cancer of the lung was a rarity in the United States at the beginning of the twentieth century.[11] No one could have guessed that in the 50-year interval from the 1930s to the 1980s, cancer of the lung would show a 15-fold increase in men and a 9-fold increase in women. It is estimated that almost 175,000 new cases will occur in 1993 and that the disease will be responsible for 140,000 deaths. This sad outcome has been compared by Rosenow to "one fully loaded 747 jet crashing every day throughout the year."[12] If the prevalence trends continue to increase unabated, it is projected that close to 300,000 new cases of lung cancer will occur by the year 2000, at which time lung cancer will be responsible for two million premature deaths.[12]

The epidemic of lung cancer is by no means confined to the United States of America. With tobacco companies selling more cigarettes abroad, especially in developing countries, a worldwide epidemic is looming in the next 5 to 30 years.[12] Even if all smokers stop smoking immediately, no decline in lung cancer incidence is to be expected during the next 5 to 15 years.

In its great histologic variety, lung cancer reflects the complex structural organization of this organ, but about 94% of all lung cancers arise from the epithelial lining of the bronchial tree and submucosal glands. Unlike many other organs, malignant tumors in the lung vastly outnumber benign tumors. Another sad realization is that the 5-year survival of patients with lung cancer remains at 13% to 14%, a dismal figure that has not changed since the introduction of surgery, chemotherapy, and radiation therapy for the disease. As told by Rosenow, Everts Graham was the surgeon who performed the first pneumonectomy for squamous cell carcinoma in 1932.[12] The patient outlived Dr. Graham, who was a smoker and who died of small cell carcinoma with a doubling time of 14 days.

Although considerable advances have been made in the prevention of lung cancer, it is clear that new approaches are needed in the treatment of this disease. The new approaches can only come from a better understanding of the causes and mechanisms of the disease. In the following paragraphs, we review the most recent advances in the etiology and pathogenesis of lung cancer. For a

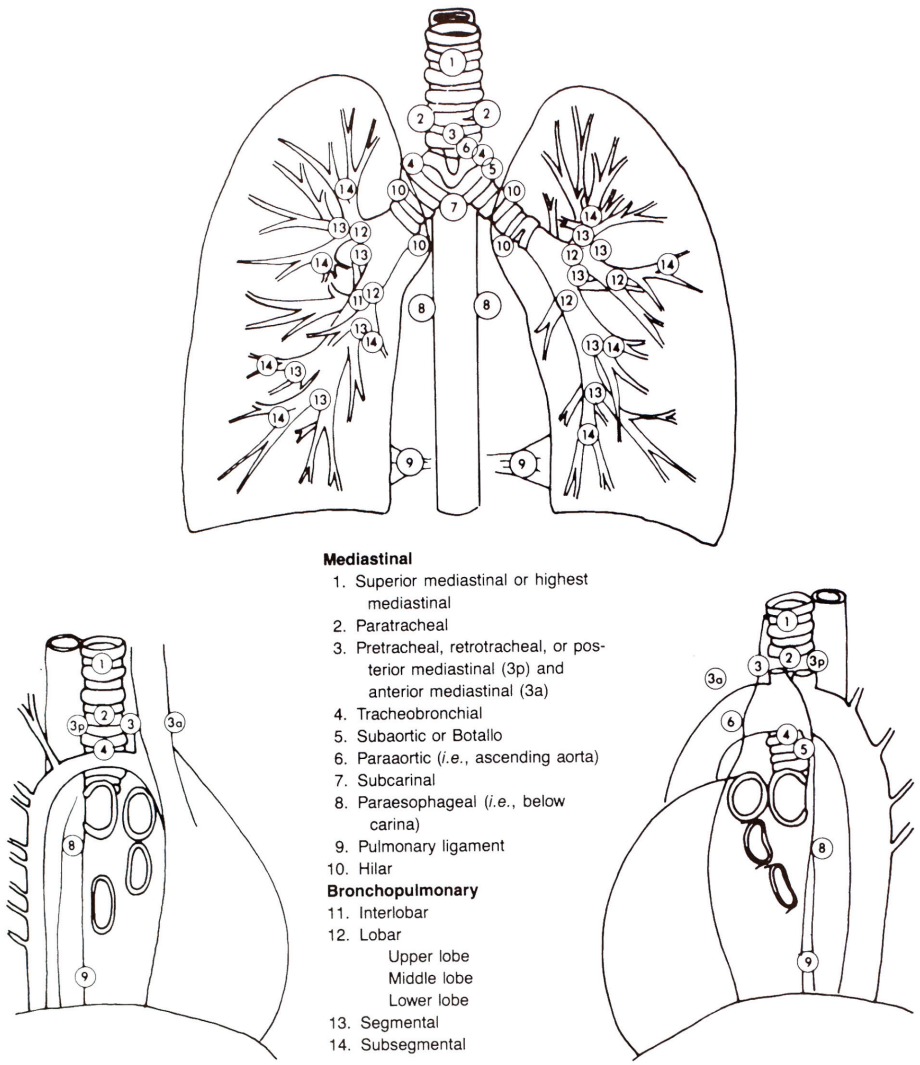

FIGURE 46-1. The distribution of lymph nodes in the lung and mediastinum is shown in Naruke's map or diagram. When surgeons and pathologists discuss metastases, it is useful to refer to a diagram like this one. (From Naruke T, Suemasu K, Ishikara S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. J Thorac Cardiovasc Surg 1978;76: 832.)

comprehensive review of this subject, the reader is referred to an article by Davila and Williams.[13]

Acquired Predisposition

CHEMICAL AGENTS

Chemicals in tobacco smoke represent the most powerful lung carcinogen. Recent results from the American Cancer Society's Prevention Study II indicate that the relative risk of lung cancer has doubled, from 11.35 to 22.36, among men and more than quadrupled, from 2.69 to 11.94, among women who smoke.[14] The results also indicate that 78% of lung cancers in women and 90% in men in 1991 were directly related to tobacco smoking.

It is agreed that the incidence of lung cancer among those who passively inhale environmental tobacco smoke is increased, although the exact level of risk is unknown. Environmental tobacco smoke represents a combination of sidestream smoke emitted by idly burning tobacco products and exhaled tobacco smoke. Sidestream smoke is the main source of environmental tobacco smoke, and in its undiluted form, it contains a higher concentration of toxins and carcinogens than mainstream (*i.e.*, exhaled) smoke.[15,16]

In one case-control study, it was suggested that 17% of the cases of lung cancer among nonsmokers can be attributed to high levels of exposure during childhood and adolescence.[17] In another large study, it was found that there was a 30% increased relative risk with exposure to environmental tobacco smoke from a spouse and a 70% increased relative risk for pulmonary adenocarcinoma from exposure to tobacco smoke for 80 or more pack-years.[18] In some reports, an increased incidence of squamous and small cell carcinoma has been observed among passive smokers, but others have not found this association.[18–22] Despite the limitations on existing studies, it is recognized that there is an increased risk of lung cancer, and estimates have ranged from 500 to 5000 lung cancer–related deaths annually from passive smoking in the United States.[23,24] Other environmental agents that increase the risk of lung cancer include asbestos (see Chap. 36), acrylonitrile, chloromethyl methyl ether, bis(chloromethyl)ether, beryllium, arsenic, cadmium, chromium, mustard gas, nickel, radon, and vinyl chloride. A review of the evidence on each of these agents is offered in a report by Whitesell and Drage.[25]

PHYSICAL AGENTS

Radon is a colorless, odorless gas produced from the decay of radium 226, which occurs naturally in soil and rock. Extensive epidemiologic studies have demonstrated a link between occupational levels of exposure to the x-ray–emitting progeny of radon in uranium mines and all types of lung cancer. The risk for cancer

mortality in nonsmoking Colorado uranium miners has been estimated to be 12-fold that of nonsmoking nonminers.[26] Smoking miners have a 10-fold higher risk of developing lung cancer than nonsmoking miners.[27,28]

Indoor exposure to radon and lung cancer risk is another matter of grave concern. Three public agencies have estimated that an indoor concentration level of 1 pCi/L of radon is associated with an excess risk of lung cancer of 0.2% to 1.2%; the risk associated with 10 pCi/L ranges from 2% to 12%. It is estimated that deaths in the United States attributable to lung cancer from more than 1 pCi/L of indoor exposure to radon ranges from 5000 to 20,000 annually.[29–31]

DIETARY FACTORS

The literature on vitamin nutritional status and lung cancer has been reviewed by Fontham.[32] The protective effects of vitamin A (*i.e.*, retinol) and foods that contain provitamin A activity in the form of β-carotene are well known. High consumption of β-carotene, which is converted to retinol in the body, has been associated with approximately a 50% reduction in risk of lung cancer compared with low consumption.[32] These nutrients particularly protect against squamous cell carcinoma and small cell carcinoma.[33]

Retinol is thought to have antineoplastic properties because of its ability to promote cellular differentiation. Carotenoids are believed to be anticarcinogenic by virtue of their antioxidant capacity to trap oxygen free radicals. Although the protective effects of carotenoids may result from conversion to retinol, the available evidence suggests that the antioxidant effect may be more important.[32]

Other substances, such as selenium, vitamin C (ascorbic acid), and vitamin E (α-tocopherol) may also reduce the risk of lung cancer through their antioxidant effects, but the results of these studies are inconclusive.[34,35]

LUNG DISEASES

There is a 14-fold increase in lung cancer among patients with diffuse pulmonary interstitial fibrosis after taking into account factors such as age, gender, and smoking.[36] An increased risk of lung cancer has also been demonstrated in patients with chronic obstructive pulmonary disease (COPD), and several studies demonstrated that emphysema and chronic bronchitis are independent risk factors after controlling for age, gender, and smoking (Fig. 46-2).[37] Poor clearance of carcinogens as a result of structural derangements in fibrosis and COPD may be implicated, but chronic oxidative exposure may also play a major role.[38]

Genetic Predisposition

Although environmental exposure may ultimately be genotoxic, there is doubtless an innate, inheritable, or genetic predisposition for lung cancer, as shown by studies on familial aggregation, genotypic associations, and phenotypic associations. Two excellent reviews on this subject were written by Law and by Amos and colleagues.[39,40]

FAMILIAL AGGREGATION

Tokuhata and Lilienfeld have found a relative risk of 2 to 2.5 for mortality due to lung cancer in cigarette smoking relatives of patients with the disease compared with smoking relatives of controls that was not accounted for by age, gender, race, or geographic location.[41] The nonsmoking relatives of patients were found to be at excess risk compared with nonsmoking relatives of control volunteers.

GENOTYPIC ASSOCIATIONS

The association of lung cancer and genes that code for naturally occurring cell surface antigens has been studied. Studies of the potential association between blood groups and lung cancer have revealed conflicting results for a deficit of group O blood type and an increased risk of lung cancer.[42,43] A greater incidence of HLA-B12 antigen has been shown in small cell carcinoma, but this finding has been contradicted by others. Lung tumors and the adjacent lung parenchyma have revealed a high incidence of genetic aberrations, especially in small cell carcinoma, on chromo-

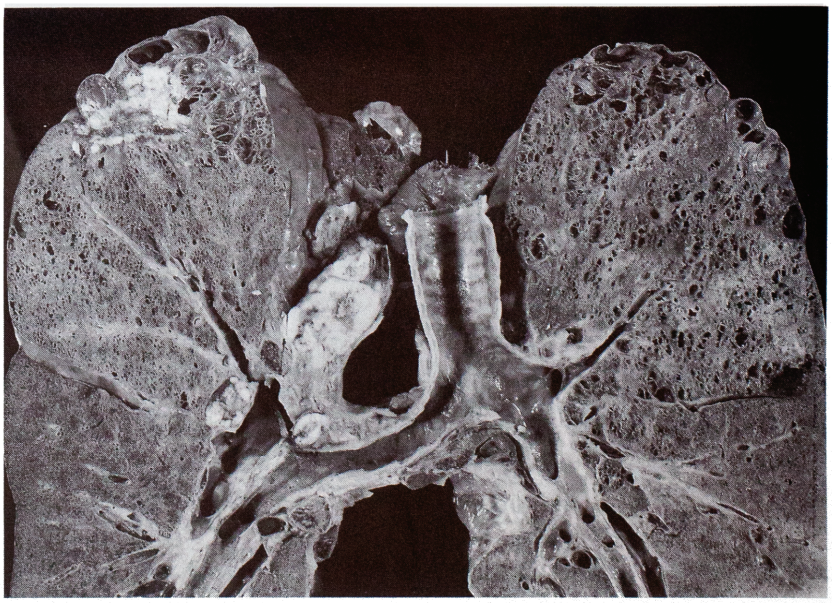

FIGURE 46-2. A set of lungs cut in the frontal plane show centrilobular emphysema with a bullous component at the apices, an adenocarcinoma arising in the left upper lobe and spreading to regional lymph nodes, and terminal bronchopneumonia extensively involving the lung tissue.

somes 3, 13, and 17.[44–46] Regions of these chromosomes that are deleted are thought to harbor the recently described recessive oncogenes *RB1*, which causes retinoblastoma, and *P53*.[47,48]

PHENOTYPIC ASSOCIATIONS

The association of increased incidence of lung cancer with certain genetically determined enzymatic phenotypes has been investigated. Attention has been focused on the cytochrome P-450 system for which cocarcinogens from tobacco combustion products, such as polycyclic aromatic hydrocarbons and nitrosamines, are known substrates. Although animal studies suggested a correlation between high aryl hydrocarbon hydroxylase activity and the development of lung cancer, the results in humans have been contradictory.[49–51]

Molecular Defects in Lung Cancer

Research on the biology of lung tumors in recent years has been dominated by the discovery of numerous cellular and molecular events in the cancer cells, including aberrant autocrine production of growth factors; several specific cytogenetic abnormalities; isolation of critically important growth-differentiating and tumor-suppressing genes in altered form; and oncogenes in various types of lung tumors (Table 46-1). A comprehensive review of this subject is provided in the papers by Davila and Williams and by Viallet and Minna.[13,48]

As reviewed by Cagle,[52] the use of molecular genetic markers to predict prognosis and response to therapy in lung cancer patients appears promising, particularly the *MYC, RAS, ERBB2, RB1,* and *P53* oncogenes. It has been shown that patients with adenocarcinomas demonstrating *KRAS* mutations have significantly shorter survival times than patients whose tumors do not demonstrate evidence of *KRAS* activation.[53] Similarly, patients with squamous cell carcinomas and adenocarcinomas that demonstrate the *RAS* oncogene protein product p21 tend to have a poorer prognosis than those who do not.

The *ERBB2* oncogene, also referred to as *HER-2/neu*, produces the protein product P185NEU, which is normally expressed in ciliated respiratory epithelial cells, type II pneumocytes, and bronchial mucosal glands. It has been shown that patients with adenocarcinomas of the lung whose tumors demonstrate the p185neu protein have significantly shorter survival times compared with patients whose tumors do not express this protein.[54]

The *MYC* family of oncogenes (*i.e., MYC, MYCN,* and *MYCL1*) are activated by overexpression through amplification. Overexpression of MYC in small cell carcinoma cell lines has been seen more frequently in chemotherapy-treated patients and has been shown to be associated with decreased survival times compared with patients whose tumors do not express this genetic marker.[55] Patients with small cell carcinoma whose tumors do not express MYCN tend to respond better to therapy, whereas those with overexpression of MYCN showed only partial or no response to chemotherapy.[55]

The *RB1* gene is a tumor-suppressor gene responsible for loss or expression of a particular function. Preliminary data suggests that early stage non-small cell carcinomas usually demonstrate RB1 expression, wherease more advanced stages do not, suggesting tumors lacking RB1 expression may have a poorer prognosis.[56]

The *P53* gene is a tumor-suppressor gene whose protein product accumulates because of decreased degradation rather than increased production. In an immunohistochemical study of P53 expression in adenocarcinomas and squamous cell carcinomas, Quinlan and colleagues found a statistically significant different in median survival times between P53-positive tumors (16.5 months) and P53-negative tumors (45.5 months).[57] The P53 protein may also be detected in dysplastic epithelia and areas of carcinoma-in-situ, suggesting its utility in detecting early lung cancer or premalignant lesions.[58]

Traditional methods of identifying molecular genetic abnormalities in a particular gene include Southern, Northern, and Western blotting, which provide information on DNA, RNA, and protein product, respectively. However, these techniques are complex and require special procurement and storage of tissue. Furthermore, there is no way to know how accurate the results are

TABLE 46-1
Cytogenetic Changes and Oncogenes in Human Lung Cancer

Oncogene or Oncogenic Locus*	Activation Mechanism	Influence	Frequency
HRAS (11p15.5), *NRAS* (1p13), *NRASL1* (9p)	Mutation	Dominant	15 of 17 NSCLC
MYCL1 (1p32), *MYCN* (2p24.1)	Amplification	Dominant	Increased copy number in 30%–50% of SCLC lines and 11%–24% SCLC tumors; overexpressed in 89% of SCLC lines, 83% of SCLC tumors, and 8% of NSCLC tumors
RB1 (13q14.2)	Mutation, deletion	Recessive	>90% of SCLC and 10%–20% of NSCLC tumors
P53 (17p12-13)	Mutation	Recessive	>50% of SCLC and NSCLC tumors
3p14-23	Mutation, deletion	Recessive	92%–100% of SCLC and 25%–50% of NSCLC tumors

* *The JUN* (1p32-p31), *RAF1* (3p25), and *CSF1R* (5q33-q35) oncogenes are also associated with lung cancer.
NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer.
Adapted from Viallet J, Minna JD. Dominant oncogenes and tumor suppressor genes in the pathogenesis of lung cancer. Am J Respir Cell Mol Biol 1990;2:225, and Harbour JV, Lai S-L, Whang-Peng J, Gazdar AF, Minna JD, Kaye FJ. Abnormalities in structure and expression of the human retinoblastoma gene in SCLC. Science 1988;241:353.

because of contamination of the tumor sample (*e.g.*, by necrosis, stroma, inflammatory cells) that is being analyzed.

It has become feasible to detect the protein products of several important oncogenes or tumor-suppressor genes by routine immunohistochemical staining of formalin-fixed, paraffin-embedded tissues using commercially available antibodies to such products.[52] This extraordinary development has the advantage over traditional molecular genetic techniques of allowing the evaluation of the molecular marker status of a tumor with the light microscope. The latter make it possible to evaluate the role of such factors as tumor volume, necrosis of tissue, and stromal and inflammatory changes.

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