

CHAPTER 7

Lung Cancer*

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* Co-authored by Arthur L. Frank, M.D., Ph.D. and Melvin Spigelman, M.D., Departments of Neoplastic Disease and Community Medicine, Mount Sinai Medical Center.

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§ 7.00 Definition

The term lung cancer refers to one of a series of malignant diseases affecting the tissues of the lung. For the purposes of this discussion the term lung will refer to that tissue below the trachea (windpipe) from the point where it branches (the carina) into the right and left main bronchi to the farthest reaches of the alveoli, or distant air sacs. The covering of the lung, the pleura, is a separate structure and mesothelioma, the cancer which can develop there, will be discussed separately.

§ 7.10 Pathology of Lung Cancer

A majority of lung cancers affect one of the two main stem bronchi. The reason for this is poorly understood since many nests of abnormal cells, which are the precursors of cancer, can be found all along the bronchial passages, as has been shown in heavy smokers. Many more cancers than could be expected on a random basis occur at bifurcations (branchings) of the bronchial tree, related no doubt to increased deposition of foreign matter at such branchings. The lung has a very effective clearance mechanism to rid itself of foreign matter, but there is some build-up at bifurcations in the airways of the lung.

If the cancer is long standing it may be large, with yellow, necrotic, cheesy material being most often associated with squamous cell carcinoma. This is not universal and there are

no other gross characteristics that give a clue as to cell type. Lung cancers often grow along the bronchial passages, obscuring the exact site of origin. The various cell types are described in the following sections.

§ 7.11 Histopathology

The four main types of lung cancer are (1) squamous cell, (2) adenocarcinoma, (3) oat cell or small cell carcinoma, and (4) large cell carcinoma. There are a variety of other unusual types which will be described later. The classification and methods used to classify cellular types of lung cancer are under constant review by the World Health Organization, which regularly publishes in this field.

§ 7.12 Squamous Cell Carcinoma

Squamous cell carcinoma at present accounts for about 30% of all lung cancers. This is a smaller percentage than has been reported in the recent past, due in part to better methods of classification and due in part to changing patterns in lung cancer as the number of cases increases.

On microscopic investigation one uncommonly sees a well-differentiated cancer with keratinization. (Keratinization refers to the development of a horny layer of cells, a process noted in the skin, but which can also occur in any epidermoid tissue, such as the lining of the bronchial passages.) More often one sees epithelial pearl formation with intracellular bridging. The cells may be found in sheets or bundles and may have variable amounts of vascular connective tissue present. Cells are often of different sizes, but there are generally few mitoses (cells with evidence of active cellular division). There may be an appearance that mimics that of adenocarcinoma, especially if signet cells are present.

Spread of squamous cell carcinoma in the form of distant metastases occurs in less than 25% of cases. The liver and kidney are most often affected. The spread to lymph nodes, the pleura, diaphragm, and the opposite lung is much more common.

§ 7.13 Adenocarcinoma

This cell type accounts for about 30% of lung cancers at present, more than in the recent past. Microscopically this type of lung cancer is characterized by small, well-formed, irregular glandular structures in a connective tissue. If well-differentiated (closely resembling the tissue of origin) there may be a single layer of cancer cells with small, darkly staining nuclei with the cytoplasm full of mucin. If less well differentiated (looking less like the tissue of origin) the cells may have nuclei that are, in addition to darkly staining, irregular and quite variable in size, with many mitoses.

Adenocarcinomas tend to spread widely and can often be found in lymph nodes, adrenal glands, liver, bone, kidney, and the central nervous system. In one study only about 20% of adenocarcinomas had not spread beyond the chest cavity.

§ 7.14 Oat Cell (Small Cell) Carcinoma

This cell type accounts for about 25% of all lung cancers. It is more frequently found in association with some known etiologic causes, such as radiation or bis-chloromethyl ether. Under the microscope this form of lung cancer is characterized by diffuse sheets of small closely-packed cells with little cytoplasm. The nuclei are very darkly staining, often round or oval, and with frequent mitoses. If the nucleus is light-staining the nucleoli (a sub-cellular component found within the nucleus) are especially prominent.

These cancers are almost always disseminated at the time of diagnosis. Spread to lymph nodes in the opposite lung or in the abdomen is especially common, as is spread to the pancreas, liver, adrenal glands, bones, central nervous system, and other endocrine tissues. The bone marrow is involved in most cases. The particular virulence of this cell type is re-

flected in the treatment (discussed in detail in following sections).

§ 7.15 Large Cell Carcinoma

This form of lung cancer accounts for about 15% of all cases. In part the diagnosis is based on exclusion, since other forms must first be ruled out. The microscopic appearance is characterized by cells that are oval, spindled, angular or polyhedral. The cells are close together and the nuclei are often large, with nucleoli that are prominent. Staining patterns of both the nuclei and cytoplasm are variable. There is often local invasion into blood vessels and lymphatics. Spread is similar to the pattern of an adenocarcinoma with metastases often found in the lymph nodes, pleura, liver, adrenal glands and central nervous system. There is also the unusual finding of spread to the mucosa and submucosa of the gastrointestinal tract.

§ 7.16 Other Cell Types

In addition to the four major cell types noted above, other patterns are found in small numbers. There is an increasing recognition that a single cancer may have more than one malignant cell type present. These "mixed" cell types are increasingly being recognized with the additional evidence from electron microscope studies. The combination of squamous cell and adenocarcinoma is most often found.

Among the unusual cell types found are (1) carcinoid tumors, (2) cylindromas, (3) sarcomas, (4) alveolar cell carcinomas, (5) lymphomas and Hodgkin's disease, (6) embryonal cancers, and (7) hamartomas. Most of these are very rare findings. These are also types least likely to be related to known exogenous agents such as smoking, asbestos, radiation and chemicals.

Another important consideration with the finding of a nodule in the lung, and especially so with multiple nodules, is that the abnormality may not be a primary lung tumor but a

metastasis from another cancer located elsewhere in the body. The lung is a frequent site of metastatic spread of several cancers such as breast, bone, and kidney.

§ 7.17 Mesothelioma

Mesothelioma, an unusual form of cancer highly correlated with exposure to asbestos, is not a lung cancer. It is a malignancy arising in the lining of the chest, the pleura. Mesotheliomas can also arise in other lining tissue, such as the abdominal wall (in which case the cancer is called a peritoneal mesothelioma) or the outside lining of the heart (pericardial mesothelioma) or the lining of part of the male reproductive system, the tunica vaginalis.

Microscopically, mesotheliomas take three forms. There is a tubular or glandular pattern, a papillary carcinomatous pattern, and a clearly defined "mixed" pattern incorporating elements of both. Mesotheliomas can be benign growths but most often are malignant. They can spread directly, potentially enveloping the whole lung on the side of origin, or they may spread to underlying lung tissue or to the other half of the chest. Distant metastases are not common.

§ 7.18 Differential Diagnosis

When considering the diagnosis of lung cancer there are few other conditions with which it can be confused microscopically. On x-ray or clinical findings lung cancer must be differentiated from tuberculosis, pneumonia, and benign growths such as bronchial adenomas.

§ 7.20 Changes in Incidence of Lung Cancer

In the 19th century and first four decades of the 20th century lung cancer was a rare disease among the general population. Based on autopsy data, it appears that less than 0.1% of deaths were due to lung cancer. Today the rate of death from lung cancer has reached a level of enormous public health significance. Most recent data estimate about 112,000 new cases

of lung cancer in 1979 with 98,000 deaths. It is the most common cancer in males, the second most common in females (breast cancer is the most common form), and the cancer causing by far the largest number of deaths. The total number of deaths due to all forms of cancer is estimated for 1979 to be 395,000. While there has been little change in the incidence of many types of cancer and a dramatic decrease in the incidence of others, such as stomach cancer, there has been a great increase in lung cancer in the past 25 years. For males the overall change for all cancers over the past 25 years is an increase of 24.2%, mostly due to an increase of 188% in lung cancer. Among females there has been an 8.5% overall decrease, but a 236% increase in lung cancer. Most cases occur in the decade of 50 to 60. Less than 1% of cases occur before 30 years of age and about 10% occur after age 70. Among males in 1950 there was a death rate from lung cancer of 18 per 100,000, which had increased to 54 per 100,000 in 1976. The single most important factor in the increase in lung cancer deaths has been cigarette smoking.

Lung cancer had been a rare cause of death for many years. However, in retrospect it appears that certain population groups were dying from high rates of lung cancer. In 1556 a classic monograph on mining in Europe, *De Re Metallica*, was published by Georgius Agricola. In addition to describing mining and smelting operations, Agricola commented on the causes of death among miners. Prominent among the causes of death was miner's phthisis, a wasting disease characterized by abnormalities related to the lung. Undoubtedly some cases were due to tuberculosis or silicosis, but among some miners this wasting disease was due to cancer.

In 1879 the Austrian physicians Härting and Hesse described the miner's phthisis of Schneeberg as a malignant disease of the lung. They erroneously thought the process to be sarcomatous rather than carcinomatous but were correct in describing the problem as cancer. About 50 years later a similar finding was made in the mining region of Joachimsthal. The cases seen were most likely caused by the radioactive con-

tamination of the mines. It was from pitchblend obtained from the Joachimsthal mines that Marie Curie isolated radium.

Lung cancer was a rare occurrence in other groups and its incidence changed little until the habit of cigarette smoking became widespread. Tobacco was first introduced from the New World into England in 1558 and within 60 years was an important agricultural crop in Virginia. In the 1600's there was already concern about the health effects of tobacco use, but the problem did not reach important public health significance until the 20th century. Cigarette use expanded in the early part of the century due in part to the development of the mechanical cigarette making machine and the free distribution of cigarettes to American soldiers fighting in Europe during World War I. After the war there was a nucleus of cigarette smokers and the habit soon spread, primarily among males.

Given that cancer is a long term process in terms of development, it was not unexpected that the rate of lung cancer would not change for some years. It is generally understood that at least 20 years must pass after onset of exposure to a carcinogen before an increase in cancer rates can be expected in those exposed. It was not until the late 1940's and early 1950's that an increase in lung cancer rates was noticeable among males, particularly smokers. Women did not, in general, take up cigarette smoking in large numbers until World War II and the more recent increase in lung cancer rates among women reflects this later onset of smoking.

Other factors, primarily at the workplace, have been associated with increasing the risk of developing lung cancer. Although suggestions can be found in the scientific literature for the past 45 years relating certain exposures with certain diseases, it was only recently that large numbers of exposures were related to the development of lung cancer.

§ 7.30 Recognized Risk Factors for Development of Lung Cancer

The increase in lung cancer mortality can be related to smoking. Smoking, along with the effects of occupational and environmental exposure, accounts for the increase in lung cancer deaths. Smoking has the largest effect but the special susceptibility that occurs when the effects of cigarette smoking are combined with certain occupational hazards, such as asbestos or radiation, is of great importance. To date, air pollution has not been clearly shown to be an important causative factor in the development of lung cancer. If it has an effect, it is certainly very small compared to the effects of cigarette smoking or exposure to other agents.

§ 7.31 Lung Cancer and Smoking

In 1964 the first Surgeon General's report on smoking in the United States was published, clearly documenting the health hazards of smoking, and especially the risk of developing lung cancer. In the following fifteen years this association was further documented and in 1979 a new report on smoking and health was issued by the Surgeon General's office.

It is now clear that mortality is seriously affected by the habit of cigarette smoking. The following have been established:

- (1) Overall mortality ratio in male smokers is about 1.7 (70% excess).
- (2) Mortality increases with amount smoked.
- (3) Mortality is directly related to the duration of smoking.
- (4) Mortality is higher the younger one starts smoking.
- (5) Mortality declines after cessation of smoking.
- (6) Mortality increases with the "tar" and nicotine content of cigarettes.

In simple terms, a 30-year-old male smoking two packs of

cigarettes a day can be expected to shorten his life span by eight to nine years compared to a non-smoker. The major causes of increased mortality are related to cardiovascular disease, noncancerous pulmonary disease, and lung cancer.

It is now very clear that lung cancer in both men and women is related to cigarette smoking, with the ratio increasing more rapidly among women than men at this time. The risk of developing lung cancer increases with increasing amounts of smoking, and appears to decrease with the use of filtered cigarettes and low "tar" and nicotine cigarettes. Cessation of smoking reduces, over time, the risk of developing lung cancer.

§ 7.32 Interactions between Occupational Exposures and Cigarette Smoking

It is clear that certain occupational exposures act synergistically with cigarette smoking to raise the risk above that of either exposure, or even above the additive risk. This has been shown for radiation and asbestos in the production of lung cancer, and in the interaction of alcohol use and smoking in the production of oropharyngeal cancer.

§ 7.33 Occupationally Related Causes of Lung Cancer

There is a growing list of substances that have been shown to produce, or are strongly suspected of producing, lung cancer in man. For most of these substances there is experimental corroboration in laboratory animal research. A variety of known or suspected human carcinogens will be reviewed below.

(1) Arsenic

In 1820 Paris first described skin cancer related to arsenic in tin smelter workers of Cornwall, England. Saupe, in 1930, first described lung cancer in arsenic miners. Since then a variety of occupational exposures to arsenic have been associated with the development of lung cancer. These groups include miners and smelters of arsenic, fur handlers, manu-

facturers of sheep dip, and vineyard workers who use arsenical sprays on the vines. Arsenic is commonly found in the environment and can be found in air, especially near smelters, in water, food, tobacco, and drugs.

It has been reported that arsenic induced lung cancers are more common in the upper lobes, but that the cellular pattern distribution is not unusual. It is not uncommon to find multiple primary cancers after arsenic exposure, either in one organ, or in two sites such as lung and skin or liver.

At the present time there is no good laboratory model for arsenic induced cancer.

(2) Asbestos and Related Particulate Dusts

Asbestos has probably been the most studied of all occupational carcinogens. It was recognized as early as 1906 as causing asbestosis, a fibrotic condition of the lung, and in 1935 the first case of lung cancer in an asbestos worker was reported, with the suggestion that the two were related. In 1955 came definitive epidemiological proof that exposure to asbestos could lead to an increased risk of lung cancer. All commercially important forms of asbestos—chrysotile, amosite, crocidolite, and anthophyllite—have been linked to the production of lung cancer.

Lung cancer first appears as a real hazard in exposed individuals after about 20 years. There is a synergistic effect with cigarette smoking, a smoking asbestos worker having a 70-80 times greater chance of developing lung cancer than a non-smoking non-asbestos exposed individual.

In addition to causing lung cancer, asbestos exposure at the job, in contaminated homes, and in neighborhoods near plants has resulted in cases of malignant mesothelioma. Mesothelioma rates are not affected by cigarette smoking.

Other particulate dusts have been associated with the development of lung cancer or mesothelioma. In animals fibrous glass materials can produce mesotheliomas and lung cancer has resulted from exposure to talc dust, especially when contaminated by asbestos, to which it is chemically related. There

have been reports of an increased risk of lung cancer following silica exposure, but this is not proven. Exposure to zeolites, clay-like materials, has been found related to the development of mesotheliomas in some areas of Turkey where they are widely found to contaminate the environment.

(3) Beryllium

Beryllium is a widely used metal, well known for causing acute and chronic diseases of the lung. In addition to beryllium disease there is now firm animal evidence and increasingly strong human data available that beryllium may well cause lung cancer in man.

(4) Chloromethyl Ethers

The term chloromethyl ethers refers to a series of compounds, the two most important of which are chloromethyl methyl ether (CMME) and bis (chloromethyl) ether (BCME). Both were found to be animal carcinogens, BCME being most potent and contaminating CMME. In 1973 cases of lung cancer were first reported among BCME exposed workers. Soon thereafter 14 cases were described from one production facility at one chemical plant with an average age of 45 at diagnosis, with a range from 33 to 55 years of age. Of additional concern, besides the young age, was the fact that, in 12 of 13 cases for which there was tissue available, oat cell carcinoma was found, far above the expected rate.

As little as 0.1 part per million of BCME will cause lung cancer in mice. BCME forms spontaneously in moist air when the fumes of two common laboratory chemicals, formaldehyde and hydrochloric acid, mingle.

(5) Chloroprene

Chloroprene is a chemical used to make synthetic rubber. At least one epidemiologic study has shown this agent to cause lung cancer in man.

(6) Chromium

Chromium, a metal derived in large part from chromite ore, is widely used in alloys, refractories, and in the making of pigments. One form of chromate compounds, the hexavalent

form, appears to be the most toxic and capable of producing lung cancer in man, although other forms must remain suspect at this time.

Following chromate exposure there appears to be an excess of small and large cell lung cancers.

(7) Coal and Petroleum Related Compounds

Carbon containing chemicals originating from coal or petroleum abound in our modern industrial society. A general term, hydrocarbons, can be used to describe the substances of interest in this category. The first occupationally related cancer—scrotal cancer among chimney sweepers, described by Pott in 1775—was caused by hydrocarbons. This term can refer to the complex mixture of such substances as they are often found, or to one isolated substance if properly identified. Mixtures of hydrocarbons exist in many industrial settings, and occur in cigarette smoke. Industrial settings with hydrocarbon exposure include coke ovens with their emissions, chemical plants, coal gassification facilities, and refineries. Many chemicals and solvents are based on hydrocarbons, and there are a variety of reports of increased risk of lung cancer among exposed workers, such as roofers, printers, and rubber workers.

(8) Isopropyl Oil

Isopropyl oil is a hydrocarbon mixture from which isopropyl alcohol has been made. Exposure to crude isopropyl oil has been associated with an increase in lung, nasal sinus, and larynx cancer although the specific carcinogenic agent has not been identified.

(9) Mustard Gas

Mustard gas, bis (beta-chloroethyl) sulfide, is a poisonous gas which was used during World War I and manufactured, although not used, during World War II. After exposure during World War I there was the suggestion of a possible relationship with the development of lung cancer. About 15 years after the end of World War II this suggestion was proven by Japanese studies demonstrating the lung cancer potential of industrial exposure.

Of interest is that nitrogen mustards, and related compounds, have been used to treat various forms of cancer.

(10) Nickel

The relationship of the development of lung cancer and exposure to nickel was shown in the early 1930's among workers at a nickel refinery in Clydach, Wales. Of interest, engineering changes at the plant in the mid-1920's resulted in eliminating, for unknown reasons, the cancer hazard for workers beginning employment after the changes. Additional experiences in other countries have confirmed the lung cancer risk and shown that laryngeal cancer was also increased. It is not clear if the carcinogenic agent is the nickel itself or the nickel carbonyl gas made as part of the purification procedure.

(11) Radiation

Ionizing radiation, such as that received from gamma or x-rays, is found in many radioactive substances and has been shown to cause lung cancer. The experience in the mines of central Europe has been reviewed. Similar findings have been noted in other mining operations. Some mines exist for the extraction of radioactive materials, such as the uranium mines of the Colorado Plateau, but radioactive contamination can also occur in other mines, such as the fluorspar deposits of Newfoundland.

Radiation induced cancers have been reasonably well studied and several facts have become clear from these investigations. Smoking has a synergistic effect with radiation exposure, but such exposure alone can increase the risk for developing lung cancer. The cell type of lung cancer following radiation exposure is predominantly oat cell carcinoma. Cytological screening for lung cancer was extensively studied in relation to such exposure in Colorado.

(12) Smelting

The lung cancer risk associated with arsenic, chromate, and nickel exposure has been reviewed above. The smelting of other metal containing ores carries an increased risk of lung cancer. This may be due in part to the propensity of many

metal ores to contain arsenic. Increased rates for lung cancer have been found among workers at a primary cadmium smelter (cadmium has also been linked to prostatic cancer development), at a copper mining and smelter facility, and among lead smelters. Among the copper miners the distribution of all types was as expected; among the smelter workers there was a high percentage of poorly differentiated squamous cell carcinomas.

(13) Vinyl Chloride

Vinyl chloride has been proven to be a cause of a rare tumor, hemangiosarcoma of the liver, and there have also been suggestions that it may increase the risk of developing lung cancer. While not yet proven in man, this seems to be true in laboratory animals.

§ 7.40 Screening

Attempts have been made to identify those individuals in the general population who have a high probability of developing lung cancer. This process is called screening and must be differentiated from the process of diagnosing. While screening is used to define a subset of the whole population who have a high probability of having a disease, diagnosing is the act of proving a certain disease exists in an individual who usually already has a high probability of having that disease. In other words, one would first screen a group of individuals, and only after identifying those with a high likelihood of having lung cancer would one then proceed to make the diagnosis of lung cancer. The rationale for screening is that by identifying high risk individuals it may be possible to diagnose lung cancer at an early stage, and thus the mortality or death rate from the disease could be reduced.

The largest experience in screening for lung cancer has been with the use of chest x-rays. Routine chest x-rays have been done on large segments of the population to screen for lung cancer and other lung diseases. Unfortunately, there is as yet

no convincing evidence that this form of screening decreases the mortality from lung cancer.

High risk individuals, especially heavy smokers, are currently the subjects of controlled clinical trials designed to test whether chest x-rays taken periodically will permit earlier detection of lung cancer and lead to a decreased mortality from the disease. Thus far the overall consensus is that these studies have not yet shown any significant difference in mortality between the screened and the control groups.

Another method currently under investigation is the use of sputum cytology. Sputum is examined microscopically in an attempt to detect cancer cells. As with other similar cytologic tests, such as Pap smears for cervical cancer, the cells seen in a sputum cytology specimen are reported along a gradient which ranges from benign to atypical to malignant. Commonly the cytologist or specialist in interpreting the cells in a sputum collection will grade the cells from either I or 0, which is benign, to either grade IV or V, which is malignant. As with chest radiographs, there are trials presently in progress designed to determine the effect of sputum cytology screening in high risk individuals. Again, the preliminary results in these studies have not yet shown any significant benefit from this method of screening.

Screening for lung cancer has not yet been particularly fruitful. This probably relates to at least two factors. The first is that the methods available for screening can not reliably and reproducibly detect lung cancer at a very early stage. The second factor is that the treatment available for lung cancer, even when it is detected, is overall not yet very successful.

Until the value of screening for lung cancer has been demonstrated, whether in high risk groups or occupations, screening programs should probably be limited to settings in which they are being done for research purposes to document the beneficial effect of such screening. Until such evidence is

forthcoming it is difficult to justify the cost and possible risks in different screening programs.

§ 7.50 Diagnosis

The diagnosis of lung cancer can range from the obvious to the obscure. Information obtained from a patient's history, physical examination, and a wide variety of possible diagnostic procedures must all be considered in formulating both the diagnosis of lung cancer and the specific cell type.

§ 7.51 History

There are no symptoms which are specific to lung cancer. Patients may present a wide array of complaints. Some of these, such as cough, chest pain, purulent or rust-streaked sputum production, coughing up blood (hemoptysis) or shortness of breath, may be fairly specific to the chest cavity. Shoulder or arm pain or weakness may also be the first symptom of lung cancer. This usually occurs because of brachial plexus nerve involvement by the tumor. There are, moreover, a myriad of symptoms which may be produced by the so-called extrapulmonary manifestations of lung cancer. Lung cancer, as well as many other tumors, may be associated with symptoms which occur away from the primary tumor and away from the metastatic sites of involvement. These have been called "paraneoplastic" disorders and are often caused by hormone production of the tumor. The paraneoplastic syndromes associated with lung cancer may produce diverse presenting symptoms which can affect numerous organs including the skin, bones, muscles and blood, and may mimic a whole host of nonneoplastic disorders.

Symptoms caused by a paraneoplastic syndrome may occur before a lung tumor is diagnosed, occasionally even years before, or they may occur after the tumor has been diagnosed. Some of the more common paraneoplastic disorders which may be manifestations of bronchogenic carcinoma include neuropathies of both the central nervous system and periph-

eral nervous system, myopathies, coagulation disorders causing either excessive clotting or excessive bleeding, hypertrophic osteoarthropathy and skin disorders such as acanthosis nigricans, tylosis or dermatomyositis.

Finally, lung cancer can present with symptoms caused by metastases from the primary tumor. This commonly includes neurologic difficulties from brain metastases or bone pain from metastases to the bones. Common sites of lung cancer metastases include the bones, thorax, lymph nodes, adrenal glands, liver, brain and skin.

§ 7.52 Physical Examination

As with the history, there are no findings on physical examination which are specific for lung cancer. Signs of pneumonia, pleural effusions (fluid in the chest cavity) or even asthma may be the initial findings caused by the local tumor.

Disease which has spread beyond the primary tumor, but is still confined within the thoracic cavity, may also present with a myriad of physical findings. The left or right diaphragm may not move if its nerve innervation (phrenic nerve) has been compromised. Hoarseness may be noted either as a presenting complaint or as a finding on the physical exam. This should alert the physician to the possibility of involvement of the recurrent laryngeal nerve. Lung tumors may cause invasion of the lining of the heart (pericardium) or of the heart itself. This may cause a wide variety of cardiac signs including arrhythmias, congestive heart failure and cardiac tamponade (compression of the heart by accumulation of fluid within the pericardium). Lung tumors may also invade or spread to the mediastinum and cause symptoms and signs by impinging on the esophagus or even the trachea.

Physical signs caused by metastases or by paraneoplastic syndromes may also be the presenting signs. These include a wide variety of neurologic deficits, bone fractures and skin changes, to name but a few.

Since almost any organ or tissue in the body is a potential site for metastatic spread of lung cancer, the possible physical

findings which may be found when the disease has spread to distant sites are nearly innumerable. Similarly, because of the wide variety of possible paraneoplastic syndromes associated with lung cancer, the range of physical findings can include virtually any organ system or any part of the body.

Commonly however, the physical examination may be normal and not of any help in making the diagnosis.

§ 7.53 Diagnostic Procedures

Whenever there is suspicion of a lung tumor, routine chest x-rays are a vital part of the initial workup. Oftentimes specialized x-rays such as tomograms, bronchograms, angiograms, or computerized tomography may be helpful in delineating the extent or the nature of an abnormality seen on routine chest x-rays.

Occasionally cancer cells may be seen on sputum examination, but the chest x-ray and the specialized x-rays may all be normal. In that situation, bronchoscopy, usually with a flexible bronchoscope, is performed. This allows direct visualization of the trachea and several branchings of the bronchial tree. Occasionally a tumor is found by this technique even though it has not yet become visible by other tests.

Once an abnormal shadow or mass has been localized by any of the above procedures, it becomes necessary to obtain a piece of the mass or a cytologic specimen to determine its histologic or microscopic nature. In other words, to be sure one is dealing with a neoplasm, it is essential to have a biopsy. This is important not just because of the obvious implications of determining whether a growth is benign or malignant, but also to decide which cell or pathologic type a malignant tumor may be. A shadow on an x-ray may represent any of a wide variety of possible pathologies, and it is dangerous to assume a neoplasm exists without biopsy proof. Usually a bronchoscopist or a thoracic surgeon will obtain the specimen, which is then examined by the pathologist.

There are various techniques available for obtaining a biopsy. Usually the technique which is associated with the least

morbidity and still has a likelihood of success is attempted first. The possibilities include fiberoptic bronchoscopy as described above, mediastinoscopy, percutaneous lung biopsy, pleural biopsy, thoracoscopy, and thoracotomy. Mediastinoscopy is performed by insertion of a rigid tube into the center of the chest cavity through an incision in the notch of the neck. Biopsy of the tissues in that area can then be performed through the tube. A biopsy of a mass near the chest wall may sometimes be obtained through a percutaneous lung biopsy where a needle is inserted through the chest wall directly into the tumor. If a pleural effusion is present, then insertion of a needle through the chest wall to obtain a biopsy of the inner lining of the chest wall may give a diagnosis; this is a pleural biopsy. Thoracoscopy is the insertion of a tube through the chest wall through which the inner contents may actually be visualized and biopsied. Finally, a thoracotomy is an operation wherein the chest is opened and its contents are directly visible.

Treatment for lung cancer is fraught with many hazards. As described below, this treatment has many potential side effects and complications, and therefore one must be as sure as possible of the diagnosis before subjecting a patient to treatment.

§ 7.60 Staging

Deciding on optimal treatment for any given patient with lung cancer requires the determination of the stage of the disease, that is, the extent to which it has already spread. One classification commonly used to express the stage of the disease is the TNM—T for the primary tumor mass, N for lymph node involvement, and M for distant metastases (see Table 1). For example, the classification of a tumor as T1NOMO implies that the tumor is 3.0 centimeters or less in greatest diameter, surrounded by lung or the lining of the inner chest wall (visceral pleura), without evidence of invasion proximal to a lobar bronchus at bronchoscopy (T1) with no demonstrable metastasis to the regional lymph node (NO) and with no known distant metastasis (MO).

TABLE 1
TNM Classification

Primary Tumor—T

TX—Tumor proven by cytology but not visualized on x-ray or by bronchoscopy; any tumor that cannot be assessed

TO—No evidence of tumor

TIS—Carcinoma in-situ

T1—A tumor 3.0 cm or less in diameter, surrounded by lung or visceral pleura, without invasion closer than a lobar bronchus

T2—A tumor more than 3.0 cm or a tumor of any size that either invades the visceral pleura or has associated lung collapse or obstructive pneumonia. On bronchoscopy the proximal growth of the tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any pneumonia or collapse must involve less than an entire lung, and there must be no pleural effusion

T3—A tumor of any size with direct extension into an adjacent structure such as parietal pleura or chest wall, the diaphragm or mediastinum; a tumor on bronchoscopy found to be within 2.0 cm of the carina; any tumor with pneumonia or collapse of an entire lung, or any tumor with an associated pleural effusion

Involvement of Lymph Nodes—N

NO—No demonstrable growth in regional lymph nodes

N1—Growth in lymph nodes in the peribronchial or ipsilateral hilar region or both, including direct extension

N2—Growth in lymph nodes in the mediastinum

Distant Metastasis—M

MX—Not assessed

MO—No known distant metastasis

M1—Distant metastasis at a specific site. PUL-pulmonary, OSS-bone (osseus), HEP-liver (hepatic), BRA-brain, LYM-lymph nodes, MAR-bone marrow, PLE-pleura, SKI-skin, EYE-eye, OTH-other

Staging workups must be performed on patients with lung cancer to determine the extent of disease. The usual tests involved include x-ray studies of the chest to determine the size of the primary tumor. The determination of nodal involvement can usually be accomplished clinically by x-ray studies and surgically by supraclavicular node biopsy and/or mediastinoscopy. The examination of distant organs to rule out metastatic spread away from the primary tumor is usu-

ally performed by a combination of x-ray, radioisotopic studies, and bone marrow biopsies. If any of the x-ray or isotope studies indicate the possibility of metastatic disease, biopsy is oftentimes indicated to verify the spread of the tumor.

It is only when the stage or extent of spread of the tumor is known that appropriate therapy can be formulated.

§ 7.70 Therapy

There is much debate over the optimal therapy for lung cancer. This is an area of intense investigational activity with continuous accumulation of new evidence. The treatment of lung cancer should be undertaken by those expert in the field, such as medical oncologists, radiotherapists, and surgeons, usually thoracic surgeons. Medical oncologists are physicians trained in internal medicine who receive further specialized training in cancer treatment. They are usually well versed in the chemotherapy of cancer, while radiotherapists are specialists in the administration of radiotherapy. Radiotherapists are to be differentiated from radiologists, who usually do not have formal training in the administration of radiotherapy to cancer patients. Thoracic surgeons are specialists trained in the surgery of the chest cavity and will oftentimes have considerable expertise in the surgical management of lung cancer.

Factors which must be taken into consideration in determining treatment include the pathologic type of tumor, the stage of the disease, and the overall medical condition of the patient. It is often preferable to have the initial management decision for a patient with lung cancer made by a team of physicians including those described above.

The treatment modalities available include surgery, radiotherapy, chemotherapy, immunotherapy and combinations of these. Discussions of treatment of lung cancer are usually divided between treatment of small cell and non-small cell carcinoma. Surgical excision is the treatment of choice for non-small cell carcinoma if the tumor is localized, can be totally excised, and if the patient is considered able to tolerate the

surgery. A consensus is emerging, however, that there is no place for surgery as definitive treatment in small cell carcinoma of the lung. Tumors with this cell type tend to be more virulent and are usually documentably disseminated at the time of diagnosis. Thus treatment of small cell carcinoma usually consists of radiotherapy and/or chemotherapy.

There is much debate over optimal therapy for non-small cell tumors that either are not localized in one part of the lung or for other reasons are not considered potentially curable by surgery. These tumors are the subject of many ongoing studies. In general most patients with such tumors will receive both radiotherapy and chemotherapy in the course of their disease. Here one must differentiate between surgery which is performed for the sake of making the diagnosis and surgery which is undertaken as treatment.

Radiotherapy is usually very effective in relief of pain caused by tumor spread to other organs, most notably to bones. Likewise, symptoms caused by tumor spread to the brain or within the chest itself may often be palliated effectively with radiotherapy. The curative potential of radiotherapy remains a question of considerable controversy.

In general, then, for non-small cell carcinoma of the lung, surgery is the treatment of choice for patients whose disease is staged as either TONOMO or T1NOMO. Disease which is staged as either T2 or T3, with nodal status either NO, N1 or N2, and MO, would be treated by many physicians with radiotherapy alone, or sometimes surgery plus radiotherapy or radiotherapy plus chemotherapy, or occasionally with all three modalities. Others would argue that for these stages of disease, if the patient is asymptomatic and especially if the cell type is epidermoid, no treatment should be given until the patient develops symptoms. For stages which include either T3 or any distant metastases (i.e., N1) there is usually no place for surgery and treatment is oftentimes limited to chemotherapy and/or radiotherapy. As mentioned earlier, the choice of optimal treatment is very much under debate and the subject of intense investigation.

§ 7.71 Chemotherapy

There are many chemotherapeutic agents which have been shown to cause shrinkage in lung tumors in anywhere from approximately 10 to 35% of patients treated. These drugs include adriamycin, bleomycin, cis-platinum, cyclophosphamide, hexamethylmelamine, lomustine (CCNU), mechlorethamine, methotrexate, procarbazine and vincristine.

The potential side effects of some of the chemotherapeutic agents used in the treatment of lung cancer are listed in Table 2.

TABLE 2

Potential Side Effects of Chemotherapeutic Agents

Adriamycin

Hematologic

- drop in white blood cell count—leukopenia
- drop in platelet count—thrombocytopenia
- drop in red blood cell count—anemia

Gastrointestinal

- nausea
- vomiting
- diarrhea
- stomatitis—inflammation of soft tissues of mouth

Cardiac

- changes in cardiac rhythm or in electrocardiogram
- congestive heart failure—more common with higher total cumulative doses

Skin

- irritation of local tissues if injected into subcutaneous tissues rather than into vein
- alopecia—loss of hair

Bleomycin

Gastrointestinal

- nausea
- vomiting
- stomatitis

Skin

- shedding of skin
- loss of hair
- increased pigmentation
- hardening of skin at tips of fingers

Allergic Reactions

- fevers
- chills
- hypotension and possible shock

Lung

- increase in fibrous connective tissue (fibrosis)—usually occurs with high total cumulative dose

Cis-platinum

Hematologic

- leukopenia
- thrombocytopenia
- anemia

Gastrointestinal

- nausea
- vomiting

Kidney Damage

- Hearing loss, especially high frequency

Cyclophosphamide

Hematologic

- leukopenia
- thrombocytopenia
- anemia

Gastrointestinal

- nausea
- vomiting
- stomatitis

Skin

- increased pigmentation
- alopecia

- Urologic—bleeding from the bladder (hemorrhagic cystitis)

Hexamethylmelamine

Hematologic

- leukopenia
- thrombocytopenia
- anemia

Gastrointestinal

- nausea
- vomiting

Lomustine (CCNU)

Hematologic

- leukopenia
- thrombocytopenia
- anemia

Gastrointestinal

- nausea
- vomiting

Skin—alopecia

Mechlorethamine

Hematologic

- leukopenia
- thrombocytopenia
- anemia

Gastrointestinal

- nausea
- vomiting

Skin—irritation of local tissues if injected into subcutaneous tissues rather than into vein

Methotrexate

Hematologic

- leukopenia
- thrombocytopenia
- anemia

Gastrointestinal

- diarrhea
- stomatitis

Kidney damage

Skin—alopecia

Liver damage

Procarbazine

Hematologic

- leukopenia
- thrombocytopenia
- anemia

Gastrointestinal

- nausea
- vomiting
- diarrhea
- stomatitis

Neurologic

- peripheral neuropathy
- drowsiness
- depression
- convulsions
- muscle pains

Vincristine

Skin

alopecia

irritation of local tissues if injected into subcutaneous tissues rather than into vein

Neurologic

peripheral neuropathy, including involvement of cranial nerves

constipation

abdominal pain

Unfortunately, tumor regressions related to use of chemotherapeutic agents have usually been very short lived. One tumor type in which chemotherapy has had a more pronounced beneficial effect has been small cell carcinoma. Chemotherapy is now an acceptable primary treatment, often-times in conjunction with radiotherapy, in all stages of small cell carcinoma. Because of the relatively disappointing results of chemotherapy when one drug is used alone, and because of promising results in other tumors when many drugs are given simultaneously, current investigation in the chemotherapy of lung cancer mostly utilizes combination chemotherapy—that is, the simultaneous administration of more than one drug. Preliminary results appear promising.

§ 7.72 Immunotherapy

Immunotherapy is directed at altering the patient's immune system in such a way that it will cause destruction of cancer cells. The use of immunotherapy in the treatment of lung cancer is still in its infancy, with its future role or utility yet to be determined.

Some of the immunotherapeutic agents under current investigation include BCG (Bacillus Calmette Guerin), *Corynebacterium parvum*, MER (methanol-extraction residue of BCG) and levamisole. At this time, the use of immunotherapy in lung cancer should be limited to a research setting.

There is also much ongoing research utilizing various combinations of the available therapeutic modalities—combinations including surgery, radiotherapy, chemotherapy, or immunotherapy. Again, the advantages of these treatments when used together await the results of present studies.

§ 7.73 Supportive Care

The care of the patient with lung cancer must encompass not only the strictly medical component, but also the psychological and social. Lung cancer, along with all other neoplasms, can often be looked upon as a family disease since it so commonly impacts on all family members. Therefore, the involvement of vital family members in the care of the patient, and the education of both patient and family as to what is happening and what to expect are important functions of the physician or medical team. Awareness and proper utilization of support mechanisms available in the community are necessary for optimal care.

Pain control is vital and oftentimes inadequately provided, especially by the inexperienced practitioner. Virtually all analgesics are used in attempts to control pain depending on the severity or location of the pain. While giving chemotherapeutic drugs or radiotherapy that might lower the platelet counts, it is advisable to refrain from prescribing aspirin or aspirin-containing analgesics as these interfere with platelet function and may increase the risk of bleeding. Similarly, factors such as maintenance of nutritional status, especially in the face of expected side effects of chemotherapy or radiotherapy, must be considered in the care of the patient with lung cancer.

§ 7.74 Complications of Disease and Therapy

Potential complications of both the disease and the therapy are numerous. Lung cancer spread can be found in virtually any site in the body, although there is a predilection for certain organs. Serious complications which require rapid medical or surgical intervention include neurologic disturbances from brain metastases or from spinal cord compression, fractures from bone metastases, and obstruction of the superior vena cava.

Complications of the therapy for lung cancer are likewise numerous. Each of the treatment modalities have their own

side effects, some of them predictably expected and others uncommon. Thus it is predictable that blood counts will go down with many chemotherapeutic drugs and that some patients will develop either infections or bleeding. Similarly it is predictable that some patients will have tracheal or esophageal problems with certain types of radiotherapy.

The diversity of complications and side effects, both of the disease and its treatment, is another reason why the care of the patient with lung cancer should be entrusted to those specifically trained to handle the disease.

§ 7.80 Prognosis

Cancer of the lung remains a relatively lethal disease. Average overall survival is six to nine months with only 20% of all patients surviving longer than one year. Virtually the only hope for cure is in patients who have surgically resectable tumors, but even in these patients, only approximately 20% survive for 5 years. Overall, from the time of diagnosis, only 5 to 10% of the patients survive for 5 years.

The exact causes of death in patients with lung cancer are numerous. Depending on the type of therapy and the supportive facilities available for the patient's medical care, the proximate causes of death may vary considerably. The causes may be secondary to the primary tumor, to local spread, to distant metastases or to the therapy employed. Thus patients may die from pulmonary failure or from cardiac failure, either cor pulmonale or left sided failure or arrhythmic deaths. Similarly, patients may die from liver failure secondary to spread of the tumor or from brain metastases. As bronchogenic carcinoma may spread via both lymphatics and the bloodstream, as described earlier, virtually any organ may be involved and therefore the causes of death may be related to almost any organ system. The complications of therapy and disease may also be the proximate causes of death, with the most common causes being infection and bleeding. Other causes of death include pulmonary embolism and nonbacterial endocarditis.

Of all the cell types, squamous cell carcinoma of the lung has had the highest rate of resectability and of five-year survival, while small cell carcinoma has had the lowest resectability and survival rates. The five year survival rate for small cell carcinoma of the lung has been less than one percent.

Small cell carcinoma, however, appears to be the most responsive of all the cell types to chemotherapy. Response rates above 75% with median survival of greater than one year have been reported in patients with small cell carcinoma treated with chemotherapy.

The effect of chemotherapy on prognosis has not been of major significance except in small cell carcinoma. In small cell carcinoma of the lung median survivals in some studies have already been extended from approximately two months for untreated patients to over one year with chemotherapy alone.

The impact of radiotherapy on prognosis is unclear. While radiotherapy may occasionally be used in the attempted cure, it is usually employed as a palliative measure. Only in small cell carcinoma is it preferable to surgery when surgery is potentially curable and the patient is a suitable surgical risk.

Within each tumor type, the lower the stage, the better the prognosis for a longer survival. For non-small cell carcinoma of the lung, the five-year survival for stage I disease usually ranges between 30 and 50%, with that for stage II between 5 and 20%, and for stage III from one to 10%.

There is, however, some prevailing optimism that current research may yield new insight into the cure or prevention of lung cancer so that the overall poor prognosis may change.