CHAPTER 3: LUNG CANCER OVERVIEW

INTRODUCTION

Learning about lung cancer is an important part of preparing for the decisions you will be making about your treatment and aftercare. The more you know about lung cancer, the better position you will be in to make informed decisions and advocate for your own interests. This chapter provides an overview of lung cancer topics including: lung cancer risk factors, how lung cancer develops, grows, and spreads, and types of lung cancers. The information will help you understand other chapters in this book, and your health care providers’ recommendations for your care.

WHAT IS LUNG CANCER?

Lung cancer develops when normal lung cells sustain genetic damage that eventually leads to uncontrolled cell proliferation. Like all cancers, lung cancer cells have the ability to invade neighboring tissues and spread or metastasize to distant parts of the body. Left untreated, lung cancer eventually causes death.

Lung cancer is sometimes referred to as bronchiogenic cancer or bronchiogenic carcinoma. The word bronchiogenic means originating from the bronchi, the airways of the lungs. Most lung cancers begin in the cells lining the bronchi of the lungs. There are two main types of lung cancer, and they are treated differently. Learning about your particular type of lung cancer can help you talk with your health care providers about your treatment choices. The more informed you are, the better prepared you will be to ask questions that will help you make the treatment choices that are best for you.

HOW COMMON IS LUNG CANCER?

Lung cancer is the number one cancer killer in the United States of men and women of all ethnicities. Lung cancer kills more people in the United States every year than breast, colon, and prostate cancer combined. The American Cancer Society estimates there will be 172,570
new cases of lung cancer in the United States in 2005, and 163,510 lung cancer deaths. This means that every day of the year in this country, approximately 470 people are diagnosed with lung cancer and 450 people die of the disease.

Lung cancer is the leading cause of cancer deaths not only in the United States, but worldwide. The World Health Organization (WHO) reports that over 1.1 million people die of lung cancer each year. This number increases every year. As a result, WHO has identified lung cancer as one of the major problems facing the world in this new century.¹

### Lung Cancer Trends

Lung cancer is a relatively new problem for human beings. In the early 1900’s, lung cancer was extremely rare. Although people have used tobacco for centuries, until the early 1900’s, it was most often smoked with a pipe, in a cigar form, or chewed. The machines to mass-produce cigarettes were invented in the 1880’s, but it was not until after World War I that cigarette smoking became prevalent in the United States. During the war, American soldiers were given free cigarettes donated by tobacco companies to the U.S. military. Many soldiers left the military with a lifelong addiction to the nicotine in tobacco products. At that time, the medical community did not realize the long-term impact of cigarette smoking on health.

There is usually a 20-30 year lag time between the onset of smoking and the development of lung cancer. In the 1930’s, doctors started to note a dramatic rise in the incidence of lung cancer. By 1950, several studies reported the apparent link between rising lung cancer incidence and the new wave of cigarette smoking.²⁻⁶ In 1964, Dr. Luther L. Terry released the first *Surgeon General’s Report on Smoking and Health* that definitively established the role of smoking as a contributing factor in the development of lung cancer and several other diseases.

Until recently, lung cancer was viewed primarily as a man’s disease. When lung cancer incidence first began to skyrocket, most cases were observed in men. This was because when cigarette smoking first became prevalent in this country, it was primarily among men. Over time, advertising campaigns aimed at women and other factors led to cigarette smoking eventually becoming almost as common in women as in men. The result of this unfortunate

RISK FACTORS FOR DEVELOPING LUNG CANCER

Lung cancer develops when the cells that line the lungs sustain genetic damage. Scientists have identified several different chemicals and environmental factors that are capable of causing the kind of genetic damage that can lead to lung cancer. Substances capable of producing cancerous changes in cells are called carcinogens.

The majority of lung cancers occur in people who are either current or former smokers. While the relationship between smoking and lung cancer is well-established, other factors also come into play. We know this because only about one out of every ten smokers develops lung cancer. Further, approximately one out of every six people who develops lung cancer never smoked. These statistics tell us that lung cancer development is a multifactorial process, meaning many different factors contribute to developing the disease. Known lung cancer risk factors are reviewed briefly in this section.

Smoking

More than 85% of all lung cancer cases occur among people who are either current or former tobacco smokers. The relationship between smoking and lung cancer is caused by the carcinogens present in tobacco smoke. The risk of developing lung cancer from smoking is influenced by many factors including the age at which a person began smoking. The younger a person was at the time he or she started smoking, the greater the risk of lung cancer. The effects of carcinogens accumulate over time. Therefore, a person's total lifetime exposure to cigarette smoke is considered when trying to determine his or her risk of lung cancer. Total lifetime exposure is usually expressed in pack-years. See Figure 1 for how pack-years are calculated. Recent studies suggest that women are more susceptible to the
carcinogenic effects of tobacco smoke than men are. This means that if a man and a woman have the same pack-year history of smoking, the woman is at greater risk for lung cancer than the man is.

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\text{Packs per day smoked} \times \text{Years of smoking} = \text{Pack-years}
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*Figure 1: Calculating Pack-Year Exposure to Tobacco Smoke*

Tobacco smoke is not the only type of smoke that contains carcinogens. Scientists have shown that the smoke from marijuana and crack-cocaine contain numerous carcinogens. Therefore, smoking marijuana and crack-cocaine increase a person’s risk of lung cancer.

The good news is that a smoker’s risk of developing lung cancer can be greatly reduced by quitting. Lung cancer risk does not immediately drop after smoking cessation because most lung cancers are present for several years before they become symptomatic. However, ten years after quitting, lung cancer risk drops to a level that is only 20-50% of the risk experienced by those who continue to smoke. Lung cancer risk continues to decline gradually over time. Nonetheless, a former smoker’s risk of lung cancer never drops to the same level as someone who has never smoked. A former smoker’s risk always remains higher than that of a never-smoker.

Even if you have already been diagnosed with lung cancer, there are still benefits to quitting smoking. For example, research has shown that former smokers suffer fewer complications when undergoing chest surgery than do current smokers. Another study found that people who have undergone successful therapy for small cell lung cancer and quit smoking had a much lower risk of developing another cancerous lung tumor than those who continued to smoke. A study from China found that ongoing smoking significantly reduced the chance of long-term survival from lung cancer. Other benefits of stopping smoking include: slowed progress of other lung disorders such as chronic obstructive pulmonary

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disease and emphysema, reduced risk of heart disease, and reduced risk for other smoking-related cancers such as mouth, stomach, and bladder cancer.

Smoking is not simply a bad habit. Smoking is a physical and psychological addiction to the nicotine in tobacco. Nicotine meets all the criteria of an addictive drug. Two recent reports stated nicotine is at least as addictive as heroin, and in some ways, is even more addictive than heroin or cocaine.\textsuperscript{14,15} A report issued by the Tobacco Advisory Group of Britain’s Royal College of Physicians concluded, “Most smokers do not smoke out of choice, but because they are addicted to nicotine.”\textsuperscript{16} Stopping smoking requires overcoming nicotine addiction, which is a very challenging task. Studies have conclusively shown that nicotine replacement therapy with nicotine patches, gums, or inhalers double the rates of successful smoking cessation in the first 6-12 months.\textsuperscript{16} Counseling and support are also helpful aids if you are trying to stop smoking. If you are currently smoking, talk with your health care providers about getting the help you need to stop smoking.

**Second-Hand Smoke**

The health risks of tobacco smoke are not limited to smokers. The lungs of anyone who breathes in air that contains tobacco smoke are exposed to its carcinogens. Therefore, exposure to smoky air in the home, workplace, or in public can increases a person’s risk of lung cancer. This kind of exposure is called second-hand smoke, side-stream smoke, environmental tobacco smoke, or passive smoke. The federal Environmental Protection Agency (EPA) estimates that 3,000 people in the United States die of lung cancer each year because of exposure to second-hand smoke. Children are particularly vulnerable to the health risks associated with second-hand smoke.

**Environmental Carcinogens**

Environmental carcinogens are substances in the environment capable of producing genetic damage that could contribute to the development of cancer. Following is a brief review of some of the most common, known lung carcinogens.
Asbestos
Asbestos is a fibrous mineral that has been widely used in manufacturing, construction, and industry over many years. People exposed to high amounts of asbestos are at increased risk for lung cancer and malignant pleural mesothelioma, a rare form of cancer that involves the covering of the lungs.\textsuperscript{17, 18} Although everyone has some low-level exposure to asbestos, it is usually only people who have had work-related exposure to asbestos that are at increased risk for cancer.

Radon
Radon is a naturally occurring, radioactive gas. It is odorless and tasteless. It is formed from the radioactive decay of uranium that normally takes place in the soil and deep in the earth. Exposure to high levels of radon is associated with an increased risk of lung cancer. The EPA estimates that radon causes approximately 14,000 lung cancer deaths each year in the United States.

The amount on radon in the soil varies from one location to another. Underground miners may be exposed to high levels of radon if the mine is located in a uranium-rich area. Similarly, if a home is in an area with high soil levels of uranium and radon, cracks in the basement or foundation may cause high levels of indoor radon. Testing kits to measure indoor radon levels are commercially available. Your local public health department may also have informational materials about radon levels in your area.

Arsenic
Arsenic is a naturally occurring element in the earth’s crust. Arsenic occurs in an inorganic and an organic form. The inorganic form of arsenic is a carcinogen and has been associated with increased risk for lung and other cancers. Inorganic arsenic is used in insecticides, weed killers, rat poison, fungicides, and wood preservatives. Inorganic arsenic is also used in some paints and in hide preservation in the leather industry. Workers involved in mining, copper smelting, and pesticide formulation or application are at risk for inorganic arsenic exposure.
Chromium
Chromium is a naturally occurring element found in rocks, animals, plants, and soil. Chromium is odorless and tasteless. Chromium exists in several forms. Only chromium (VI) or hexavalent chromium is carcinogenic. Studies have shown that exposure to hexavalent chromium increases risk for developing lung cancer. Chrome plating, stainless steel welding, and chromium-nickel foundry work are occupations that may put one at risk for chromium (VI) exposure.

Nickel
Nickel is a hard, silvery-white metal used to make stainless steel and other metal alloys. Workers who breathe large amounts of nickel compounds are at increased risk for lung and nasal sinus cancers. Many occupations could potentially expose a person to unsafe amounts of nickel. A partial list of these occupations includes metalworking, nickel mining and smelting, sand blasting, stainless steel manufacturing, paint and varnish manufacturing, and welding.

Polycyclic Aromatic Hydrocarbons (PAHs)
Polycyclic aromatic hydrocarbons are a group of over 100 different chemicals that are formed during the incomplete burning of coal, oil, gas, garbage, or other organic substances such as tobacco or charbroiled meat. Diesel fuel exhaust is a prevalent source of PAHs. PAHs are potent carcinogens. Tobacco smoke, wood smoke, vehicle exhausts, asphalt roads, and agricultural burn smoke all contain high levels of PAHs. PAHs are also found in coal tar, crude oil, creosote, and roofing tar. Some PAHs are used to make medicines, dyes, plastics, and pesticides.

In addition to tobacco smoke, sources of exposure to PAHs include work with coke ovens, coal gasification, petroleum refineries, creosote-soaked wood, asphalt and pavement work, roofing, aluminum production, foundry work, and others.

Other Environmental Lung Carcinogens
Known lung carcinogens not already mentioned include bis(chloromethyl)ether, chloromethyl methyl ether, ionizing radiation (x-rays), gamma radiation, mustard gas,
soots, tars, mineral oils, and vinyl chloride. Suspected lung carcinogens include acrylonitrile, cadmium, beryllium, lead, and ferric oxide dust. Many other known, suspected, and potential carcinogens could contribute to the development of lung cancer.

**Genetic Factors**

The transformation of normal cells into cancer cells is a complex, multi-step process. Everyone is exposed to lung carcinogens. While we know that the total amount of exposure is one factor that governs whether someone develops lung cancer, we also know it is not the only factor. Most lifelong smokers never develop lung cancer, and a significant number of people with no known personal or environmental risk factors develop lung cancer. These facts make it obvious that it is not only what we are exposed to, but also how our bodies handle the exposures that determine whether lung cancer develops.

Genes control how a person’s body handles carcinogens, how susceptible it is to genetic damage, and how capable it is of repairing damage that occurs. Genes also control how well the immune system detects and destroys cancer cells. Therefore, an individual’s unique genetic make-up contributes to his or her susceptibility or resistance to lung carcinogens. For example, people whose parents or siblings have had lung cancer may be at increased risk of developing lung cancer. Other people seem to be resistant to the effects of carcinogens and therefore may be less susceptible to developing cancer than most people are. Genetic susceptibility and resistance to cancer is an area of active research.

One of the most striking features of lung cancer cells is the large number of genetic changes present in them. Often 10-20 genetic mutations are found, indicating a genetic instability in lung cancer cells.

**Age**

Age itself may contribute to a person’s risk of lung cancer. Genetic damage tends to accumulate over time. Scientists currently believe that cells accumulate multiple genetic defects before becoming cancerous. Therefore, as we age, the probability of accumulating enough genetic damage to lead to cancer increases. In addition, the immune system works
less effectively as we age. This increases the likelihood that cancer cells will slip through our natural cancer surveillance system.

Lung cancer is rare among people less than 40 years of age. The vast majority of lung cancers are diagnosed in people over the age of 50. The average age of newly diagnosed lung cancer patients is around 60 years of age.

**LUNG CANCER GROWTH**

Most lung cancers are relatively slow growing. Researchers have estimated that by the time a lung tumor grows to 1 centimeter in diameter (approximately 3/8 inch), it has been present for an average of 8-15 years. However, significant variability in lung cancer growth has been reported by several researchers. Although most lung cancers are slow growing, they have the ability to metastasize or spread to other parts of the body early in their growth. This process is called *early micrometastasis*, metastasis that is not detectable by ordinary means. The high blood flow through the lungs may facilitate the metastatic process.

During the years when lung cancer is developing but is not yet detectable by x-rays or scans, microscopic and molecular changes are occurring in the cells of the bronchi. Scientists are actively researching new diagnostic techniques for earlier detection of lung cancer. Some of these techniques are discussed in *Chapter 4: Lung Cancer Diagnosis and Staging*.

**LUNG CANCER SPREAD**

The lungs are highly vascularized organs, meaning they have many blood vessels running through them. This vascularization is needed for the quick exchange of oxygen and carbon dioxide that takes place with each breath. Among people with lung cancer, these blood vessels provide many convenient routes for lung cancer cells to travel to other parts of the body. Most cancer cells that enter the bloodstream die. However, if lung cancer cells survive and begin to grow in a site distant from the lungs, they produce metastatic tumors.
The lungs also have a rich supply of lymphatic vessels. Lymphatic vessels are part of the immune system. They form a network of vessels similar to the blood vessels of the circulatory system. Lymphatic vessels contain fluid called lymph that is made up of immune cells and excess tissue fluid and proteins. Lymph is passed through a network of lymph nodes before being returned to the blood circulation. Lymph nodes are compact collections of immune cells. As lymph passes through lymph nodes, foreign particles, bacteria, and viruses are filtered out and processed by the immune system. Cancer cells can also be filtered out into lymph nodes. Cancer cells trapped in a lymph node may begin to multiply causing the node to enlarge. For this reason, a careful examination of the lymph nodes in the chest is an important part of determining whether lung cancer has spread beyond the original tumor. Cancer cells in lymph fluid that escape the lymph nodes may travel to other areas of the body and cause metastatic tumors.

The process of determining whether lung cancer has spread beyond the original tumor is called staging. Staging is necessary because the extent of spread of the disease is one of the key pieces of information that determines your treatment options. Three factors determine stage: the size and characteristics of the original or primary tumor, spread of the cancer to regional lymph nodes, and the presence or absence of distant metastases. In lung cancer, the term regional lymph nodes refers to lymph nodes that receive lymph fluid from the lungs. Examination of these lymph nodes indicates possible spread to more distant areas of the body. Chapter 4: Lung Cancer Diagnosis and Staging provides more information about lung cancer staging.

**TYPES OF LUNG CANCER**

Lung cancer arises from abnormal epithelial cells in the airways of the lungs. Epithelial cells form the covering over free surfaces in the body such as the airways. Lung cancer is divided into two main types based on how it looks under the microscope: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). In the United States, approximately 80% of lung cancers are NSCLC and 20% are SCLC. SCLC and NSCLC have different patterns of growth and spread. They are also treated differently.
In 1999, the World Health Organization and the International Association for the Study of Lung Cancer (IASLC) updated their classification system for lung tumors. The information presented here uses the terminology of the 1999 WHO/IASLC classification system. Be aware that some people and reference materials may use other terminology based on other classification systems. If you have questions about the terminology used to describe your lung cancer, ask your health care provider to explain it to you.

**Small Cell Lung Cancer**

As the name implies, the cancerous epithelial cells of SCLC are abnormally small. Their appearance led to the term *oat cell carcinoma* to describe SCLC because the cells resemble oat grains. SCLC is also sometimes called small cell undifferentiated carcinoma. *Carcinoma* is a generic term referring to any malignant tumor that comes from epithelial cells. SCLC cells are sometimes spindle-shaped or polygonal (multisided).

Some characteristics of SCLC are:

- There is a strong relationship between SCLC and tobacco smoking. Only about 1% of SCLC occurs in people who have never smoked.
- SCLC typically grows more quickly than NSCLC does. It tends to spread to lymph nodes and metastasize to other organs early in the disease process.
- SCLC tends to be initially responsive to chemotherapy and radiation therapy.
- SCLC often occurs in one of the larger airways. Therefore, SCLC tumors are often located near the center of the lung.
- Most people with SCLC have metastases at the time of diagnosis.
- Combined small cell carcinoma is a variant of SCLC.
Non-Small Cell Lung Cancer

There are three major types of NSCLC: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. NSCLCs are grouped together because they have similar growth patterns and are treated similarly. Each of the three major types of NSCLC has variants or subtypes. The names of the variants describe certain patterns of growth that are visible under the microscope. Following is a brief summary of some characteristic features of the three types of NSCLC.

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<td><img src="image3" alt="Adenocarcinoma Image" /></td>
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*Figure 3: Microscopic Views of the Three Types of Non-Small Cell Lung Cancer*

**Adenocarcinoma**

Adenocarcinoma cells have a glandular appearance. Most of these tumors produce a thick fluid called *mucin*. The incidence of adenocarcinoma has increased over the past three decades. Scientists are not certain why this has occurred, but some influences may include changes in smoking habits, dietary patterns, environmental factors, and occupational factors. Some characteristics of adenocarcinoma are listed below.

- Adenocarcinoma accounts for approximately 40% of all lung cancers in the United States, and approximately 55% of NSCLCs.
- Variants of adenocarcinoma include acinar adenocarcinoma, papillary adenocarcinoma, bronchioloalveolar adenocarcinoma, and other mixed subtypes.

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Adenocarcinoma is the most common form of lung cancer in women and people who have never smoked. This form of lung cancer is also the most common type seen in people less than age 50.

- Tumors are most often in the outer regions of the lungs.
- Adenocarcinomas are the most common form of lung cancer associated with scarring of the lung tissue.
- A subtype of adenocarcinoma called bronchioloalveolar adenocarcinoma (BAC) arises in the alveoli. BAC tends to be slow growing and seems less likely to metastasize than other forms of NSCLC. For this reason, BAC has a more favorable prognosis than other forms of NSCLC.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is also known as *epidermoid carcinoma*. This form of NSCLC has decreased in frequency over the past three decades, but is still the most common form of lung cancer among men who are current or former smokers. Squamous cells are large, flat cells. These tumors often produce a substance called keratin, which can be seen under the microscope. Some features of SCC are listed below.

- SCC accounts for approximately 25-30% of lung cancer in the United States.
- Variants of SCC include papillary SCC, clear cell SCC, small cell SCC, and basaloid SCC.
- SCC occurs most frequently in men and in people over age 65 of both sexes.
- SCC usually starts in one of the larger airways. Therefore, these tumors tend to be located in the central area of the lung.
- There is a tendency for SCC to metastasize somewhat later than other forms of NSCLC.
- SCC tumors often invade neighboring structures.
- SCC is strongly associated with tobacco smoking.

Large Cell Carcinoma

The cells of large cell carcinoma (LCC) are the largest of the various types of NSCLC. The cells are generally highly undifferentiated or immature in appearance.
Some experts believe these tumors represent adenocarcinomas or squamous cell carcinomas that are so undifferentiated as to be unrecognizable. Some characteristics of large cell carcinoma are:

- LCC accounts for 10-15% of lung cancers in the United States.
- There are several variants of large cell carcinoma including clear cell LCC, basaloid LCC, lymphoepithelioma-like carcinoma, and large cell neuroendocrine carcinoma.
- This form of NSCLC can occur in any part of the lung.
- The prognosis for large cell carcinoma is generally less favorable than for other forms of NSCLC.

OTHER CANCERS IN THE LUNGS

There are other types of non-epithelial cancers that arise in the lungs. They are all relatively uncommon compared to SCLC and NSCLC. Examples of these cancers include carcinoid tumors, malignant pleural mesotheliomas, fibrosarcomas, and leiomyosarcomas. The lungs are also a frequent location for metastatic tumors from other locations in the body. Carcinoid tumors and malignant pleural mesothelioma are briefly reviewed because they are the most common forms of these rare cancers.

Carcinoid Tumors

Carcinoid tumors are cancers that arise from neuroendocrine cells. Neuroendocrine cells are specialized nerve cells that produce hormones. They are found in many locations throughout the body. The hormones from neuroendocrine cells are released into the bloodstream and travel to target cells throughout the body. The hormones may stimulate, inhibit, or maintain the function of their target cells. Although it is uncommon, carcinoid tumors can secrete high levels of hormones, which can lead to symptoms such as bouts of diarrhea and flushing. Carcinoid tumors are divided into typical and atypical variants. Some characteristics of carcinoid tumors are:

- Carcinoids account for 1-5% of all lung tumors.
• Carcinoid tumors typically occur in people under 40 years of age. They are equally common in men and women.
• There is no known relationship between tobacco smoking and carcinoid tumors.
• The lung is the fourth most common site for primary carcinoid tumors.
• Typical carcinoid tumors tend to have a relatively benign course. They do not metastasize to distant sites for long periods, although they often spread to local lymph nodes. These tumors can often be cured by surgical removal.
• Atypical carcinoid tumors are a more aggressive variant with a greater tendency for distant metastasis and recurrence than typical carcinoid tumors.

**Malignant Pleural Mesothelioma**

Malignant pleural mesothelioma (MPM) is cancer arising from the covering of the lung and chest wall, not the lung itself. The covering on the surface of the lungs is called the *visceral pleura*. The covering on the inside of the chest wall is called the *parietal pleura*. There are other pleural surfaces in the body, but about 75% of malignant mesotheliomas occur in the pleura of the lungs. Malignant mesothelioma is a rare form of primary cancer. The pleura are much more commonly a site of metastatic cancer than of primary cancer. There are approximately 2,000-3,000 new cases of malignant mesothelioma each year in the United States.

There are three types of malignant mesotheliomas. About 50-70% of mesotheliomas are the epithelioid type; this type has the best prognosis. The other two types are sarcomatoid and mixed/biphasic mesotheliomas. Treatment options are the same for all three variants.

Asbestos is the predominant cause of MPM. The period between exposure to high levels of asbestos and the development of MPM is typically 25-45 years. There seems to be no increased risk of MPM among asbestos workers who smoke versus non-smokers. MPM is more frequently diagnosed in men than women because of the occupational link to asbestos.

Surgery is the mainstay of treatment for localized MPM. When the disease has spread, surgery, radiation therapy, and/or chemotherapy are possible treatment options.
SUMMARY

Lung cancer is the leading cancer killer of men and women in the United States and worldwide. More than 157,000 people in the United States and over 1.1 million people worldwide die of lung cancer each year. Lung cancer is a major global health concern and will remain so for many years to come.

There are two major forms of lung cancer, small cell lung cancer and non-small cell lung cancer. Both of these cancers arise from the epithelial cells that line the airways of the lungs. The vast majority of lung cancers are non-small cell lung cancers. Small cell and non-small cell lung cancer have different growth patterns and treatments. Other rare forms of cancer also occur in the lungs including carcinoid tumors and malignant pleural mesotheliomas.

Knowledge of the type of lung cancer you have will help you better understand your disease and its treatment options.