

CHAPTER 4: LUNG CANCER DIAGNOSIS AND STAGING

INTRODUCTION

The lungs are vital organs. Working with the heart and circulatory system, they provide life-sustaining oxygen and rid the body of carbon dioxide. Normal lungs have a great reserve capacity to meet the body's need for oxygen across a wide variety of circumstances. The same is true of the heart and circulatory system. This reserve capacity permits cancerous lung *tumors* to grow for years without compromising lung function. Furthermore, the lungs do not have many nerves to transmit pain messages. Therefore, a cancerous lung tumor can grow for many years without causing any *symptoms*. Unfortunately, this means that most people are not diagnosed with lung cancer until late in the disease process. Even more unfortunate is the fact that this long period of silent growth gives the cancer time to spread before it is diagnosed. Lung cancer that has spread beyond the original tumor is difficult to cure.

Eventually, people with lung cancer do develop symptoms. Approximately 95% of people diagnosed with lung cancer have symptoms related to the disease. However, they occur late in the cancerous process. The long silent growth period of lung cancer has led to great interest in lung cancer screening, especially in recent years.

This chapter reviews how lung cancer is diagnosed, and once diagnosed, how the extent of the disease is determined. The processes involved in determining whether the cancer has spread and to what extent is called *staging*.

The information in this chapter will help familiarize you with some of the procedures you may undergo and the medical terminology you are likely to hear. The chapter begins with a discussion of lung cancer screening and early detection. Although no official screening program currently exists, it is placed at the beginning of the chapter for a reason. Currently, 95% of lung cancer patients are diagnosed because they develop symptoms, a late

occurrence in the disease process. As a result, 85% of people newly diagnosed with lung cancer already have advanced disease. Many lung cancer experts and patient advocates believe that if lung cancer screening and early detection programs were instituted, this pattern of late-stage diagnosis would change. Therefore, lung cancer screening has been placed before symptomatic lung cancer presentation.

LUNG CANCER SCREENING AND EARLY DETECTION

No discussion of lung cancer diagnosis would be complete without touching on the topic of lung cancer screening. Cancer screening is testing performed on apparently healthy people to detect unrecognized cancer. The purpose of cancer screening is to identify people with the disease so that measures can be taken to improve their prognosis. There are several familiar cancer screening programs in the United States.

- breast cancer – mammograms and monthly self-breast exams
- cervical cancer – Pap smears
- colon cancer – sigmoidoscopy and occult blood tests
- prostate cancer – prostate specific antigen (PSA) tests and physical examinations

It is notable that there are screening programs for both of the second most common causes of cancer death in the U.S. – breast cancer in women and prostate cancer in men. There are also screening guidelines for the number three cancer killer of men and women, colorectal cancer. Yet, we do not screen for the number one cancer killer of both men and women – lung cancer. Lung cancer kills more Americans every year than breast, prostate, and colon cancer combined. Why isn't there a screening program for lung cancer?

The reasons are complex and controversial. The most commonly cited reason is based on the conclusions drawn from a lung cancer screening study performed in the 1970's.¹ Many learned scientists, researchers, and doctors have debated the validity of the trial design and its conclusions. Nonetheless, based on the controversial conclusions drawn from this trial,

lung cancer screening programs are not currently supported or recommended by any official cancer or health agencies.

Despite the lack of support from public health agencies and national cancer organizations for lung cancer screening, many lung cancer advocates urge people who may be at risk for lung cancer to talk with their health care providers. People at increased risk for lung cancer due to smoking history, occupation, or family history should inform their health care providers about their risk factors and discuss appropriate testing.

The *International Conference on the Prevention and Early Diagnosis of Lung Cancer* held in Varese, Italy in December 1998 brought together lung cancer experts from around the world to discuss lung cancer screening and early detection. A consensus statement was issued by the meeting participants. Excerpts from that statement follow.

For those who develop lung cancer, outcome is dramatically better when the disease is detected at an early stage and surgically treated.... Available clinical data demonstrate that the vast majority of curable lung cancers are currently detected by chest x-rays and CT scans, although there is no proven strategy to assure early detection....

The Conference encourages national governments and public health organizations involved in cancer prevention and control to more aggressively address tobacco control and to urgently consider the issues surrounding the early detection of lung cancer....

A Program Model

We know that most lung cancers are present for many years before symptoms of the disease appear. We also know that currently, in the absence of lung cancer screening and early detection, most people with lung cancer cannot be cured because the disease is already too advanced at the time of diagnosis. Given these two known facts, it is at least theoretically possible that lung cancer screening and early detection would improve survival rates.

Proponents of lung cancer screening and early detection suggest such a program should have the following components.

- An educational component to inform the general public of lung cancer risk factors, and to be certain that those at risk understand their risk

- An assessment of risk such as a questionnaire or interview to gather information about lung cancer risk factors such as smoking history (tobacco, marijuana, crack cocaine), exposure to lung *carcinogens*, and family history of lung and other epithelial cancers
- A testing program which could have several components:
 - imaging studies of the lungs and other early detection test; possible tests that might be used include standard chest x-rays, *digital chest x-rays*, *helical/ spiral CT scans*, *tumor markers*, *sputum*-based tests, or other tests that are currently being developed
 - tests to determine genetic susceptibility to cancer; although we do not yet have such a test, this is an active area of research; such testing could identify people at risk who may need close monitoring
- Smoking cessation counseling and treatment to help those addicted to nicotine overcome their habit

There is a great deal of work to be done to develop a widely accepted, valid, and cost-effective lung cancer screening and early detection program. Many lung cancer experts believe early detection is the key to improving lung cancer survival. Recent technological advances and the call for change being voiced by lung cancer advocates worldwide have led to renewed interest in lung cancer screening policies. In September 2002, the National Cancer Institute launched the National Lung Screening Trial (NLST). Researchers intend to enroll 50,000 current and former smokers. The study will compare spiral CT scans to chest x-rays for lung cancer screening. The trial is expected to last eight years.

The hope of advocates who support lung cancer screening programs is a simple one – to diagnose people with lung cancer earlier in the disease process when there is a greater chance for cure.

LUNG CANCER PRESENTATION

In medicine, the term *presentation* refers to the *signs* and symptoms a person is experiencing that cause him or her to seek medical care and eventually lead to the diagnosis of a specific

condition. Lung cancer usually grows for many years without causing signs or symptoms. However, eventually nearly all people with lung cancer develop symptoms associated with the disease. Only 5% of people newly diagnosed with lung cancer do not have symptoms of the disease.²

The symptoms associated with lung cancer are often non-specific. Lung cancer is frequently a masquerader, meaning it can cause signs and symptoms that on the surface seem to have nothing to do with lung cancer. This lack of specificity of signs and symptoms can lead to delays in making the correct diagnosis as other more common causes of symptoms are often investigated before the diagnosis of lung cancer is considered.

The presentation of lung cancer is highly variable. Factors such as the location of the tumor, involvement of different *lymph nodes* in various locations, and involvement of a variety of distant organs can influence lung cancer presentation. Some of the possible *presenting symptoms* of lung cancer are reviewed in this section. For simplicity, the symptoms are grouped as local symptoms, locally advanced symptoms, and *metastatic* symptoms. However, there is quite a bit of overlap between these groups. For example, it is entirely possible for someone with metastatic lung cancer to have symptoms from all three categories or to have only local symptoms.

Symptoms of Localized Lung Cancer

Cough is the most common presenting symptom of lung cancer. Over 50% of people with lung cancer have a cough at the time of diagnosis. In non-smokers and long-term former smokers, the cough is usually new and persistent. In people who already have lung disease such as *chronic obstructive pulmonary disease* (COPD) or *emphysema*, it is often a change in their usual cough that heralds a diagnosis of lung cancer. Therefore, a change in a pre-existing cough should never be ignored.

I had a cough in January. Since I have had previous lung problems I went in for a chest x-ray. When nothing showed up on the x-ray, I dismissed it. Then one morning in April, I woke up and said to myself, “You idiot! You work for the American Cancer Society. You’re in charge of an educational program. You have a persistent cough, which is a sign of lung cancer!” (That’s actually the censored version of what I said.) I immediately went and got another chest x-ray. They found a nodule in my lung.

– Sandra, diagnosed with stage II NSCLC in 1998 at age 53

Some people with lung cancer cough up blood. The medical term for this symptom is *hemoptysis*. The amount of blood can range from small streaks to coughing up what appears to be pure blood, which can be a medical emergency. Although there are causes of hemoptysis other than lung cancer, anyone who coughs up blood must see a doctor to determine the cause.

Unintentional weight loss is another common symptom of lung cancer, regardless of whether it has spread beyond the original tumor. Difficult and/or painful breathing (also known as *dyspnea*), chest pain, and wheezing are also common complaints.

Symptoms of Locally Advanced Disease

The symptoms associated with locally advanced disease are due to invasion of structures in or near the lungs, or from cancerous spread to *regional lymph nodes*. New onset hoarseness that does not improve or go away can be caused by a cancerous lung tumor that involves one of the nerves controlling the vocal cords. Difficulty swallowing or *dysphagia* can be caused by regional lymph node enlargement or a lung tumor pressing against the *esophagus*, which carries food from the mouth to the stomach.

Shoulder pain, with or without arm and hand numbness and weakness, can be the presenting symptom of lung cancer in the uppermost part of the lung, the *apex*. Facial swelling and prominence of the neck and chest veins can indicate a lung cancer compressing a large vein leading to the right side of the heart. Although these symptoms are not present in most people with regionally advanced lung cancer, their presence should lead to a suspicion of lung cancer.

What [prompted me to go] to the doctor was a pain just below my rib cage that they initially thought was inflammation of the cartilage. But it turned out to be caused by a tumor in my lung.

—Ann, diagnosed with stage IIIB NSCLC in 2002 at age 54

Symptoms of Distant Lung Cancer Metastases

Lung cancer can spread to virtually any organ of the body. The most common sites of metastasis are the brain, liver, bones, and adrenal glands (see Figure 1). Early metastatic tumors may not cause symptoms because of their small size. However, as these *secondary tumors* grow they can cause a wide variety of symptoms depending on their location and size. Some of the more common symptoms associated with secondary tumors in the brain, liver,

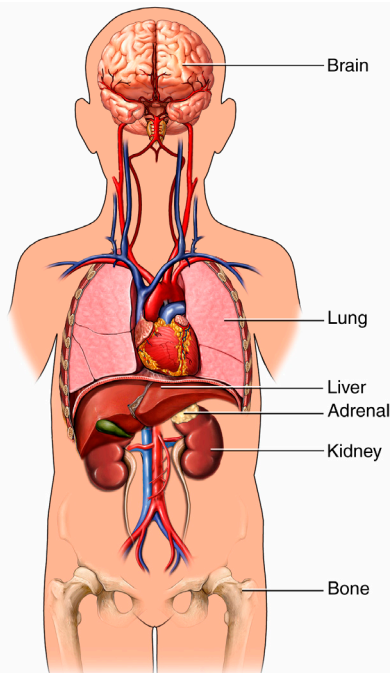


Figure 1: Common Site of Lung Metastases*

bones, and adrenal glands will be reviewed, but there are many other possible symptoms of lung cancer metastases.

Symptoms of Brain Metastases

The symptoms of lung cancer that has spread to the brain vary depending on the size, location, and number of tumors present. Severe headaches, uncontrollable vomiting, and seizures are symptoms associated with increased pressure in the brain that can be caused by a growing tumor and/or brain swelling. Weakness or paralysis that is limited to a specific area of the body may indicate a tumor in the area of the brain that controls the affected part of the body. Changes in vision, difficulty speaking or swallowing, loss of balance or coordination, and confusion are all possible symptoms associated with metastatic brain disease.

My first clue my cancer had spread was when one Sunday afternoon, a police officer drove into my driveway. I thought he was soliciting donations. However, that was not the case. He started by asking me all sorts of questions about where I had been earlier that day. Then he said, “Ma’am, you hit a car.” I said, “No I didn’t!” He asked my husband to leave us alone for a moment. I guess the officer thought I was afraid to tell the truth in front of my husband. So, I stepped outside and the officer proceeded to tell me that I did hit a car. I was almost in tears because he wouldn’t believe me that I did no such thing. Then my husband came outside and calmed the police officer and me down. It turned out, my husband knew the officer. To make a long story short it turned out that I had indeed hit this poor woman’s car.

I had an appointment with the oncologist three days later. I was so embarrassed about the [accident], I just kind of mentioned it to the doctor at the end of the appointment as he was leaving. As soon as he came back in, checked me over again, and sent me for more tests. During this time, I had also noticed my peripheral vision was deteriorating. I had told that NSCLC does not metastasize to the brain, that only small cell lung cancer does that.* So, I hadn’t really been all that worried [about my vision]. But as it turned out, I had a brain metastasis the size of a baseball. – Sue, diagnosed with stage III NSCLC at age 48

***IMPORTANT:** This information Sue was told is incorrect. Both SCLC and NSCLC frequently metastasize to the brain.

Symptoms of Bone Metastases

Pain is the most common symptom associated with bone metastases from lung cancer. The pain can range from mild to severe. Any bone in the body can be involved in lung cancer spread. Bone pain that is not associated with a recent injury or fall is particularly suggestive of possible metastatic disease. Some people are diagnosed with lung cancer after experiencing a *pathological bone fracture*. A pathological fracture is a bone break that occurs because a tumor has eroded away the involved bone. These fractures typically occur without any history of a fall or an impact, or are associated with a minor impact that would not normally cause a bone to break.

Symptoms of Liver Metastases

The liver is enclosed in a capsule that has little capacity to expand. Therefore, tumors in the liver that stretch this capsule cause pain. The pain is typically located on the right side of the body in the area below the ribs. If the tumors interfere with the function of the liver, there can be many other symptoms associated with liver metastases from primary lung cancer.

Symptoms of Adrenal Metastases

The adrenal glands are small organs that sit on top of the kidneys. The adrenal glands produce hormones that have effects throughout the body. Adrenal metastases from primary lung cancer are often silent, meaning they do not produce symptoms. The most common symptom associated with adrenal metastases is pain caused by tumor growth or sudden bleeding into the gland. The pain is typically located in the back, around waist-level, to the right or left of the spine depending upon the location of the tumor.

Other Symptoms Associated With Lung Cancer

Approximately 10-20% of people with lung cancer have *paraneoplastic syndromes*. These are signs and symptoms of the disease that are not caused by the tumors themselves, but by substances produced by the tumors. These syndromes can affect several organs of the body,

and cause a wide variety of signs and symptoms. A list of some of the many symptoms that can occur in paraneoplastic syndromes includes:

- loss of appetite and weight loss
- altered sense of taste
- fever
- *fatigue*
- muscle weakness with or without tenderness
- itchy skin or rashes
- constipation or diarrhea
- *edema* (swelling caused by fluid accumulation especially in the feet and ankles)

DIAGNOSING LUNG CANCER

Lung cancer diagnosis is a variable process. The tests used and the order in which they are done depends on numerous factors including such things as your medical history, your presenting complaints, and the findings on your physical examination. For some people, the diagnosis of lung cancer is straightforward. For other people, the process is more complex. The outcome of each step in the diagnostic process influences what the next step in the process will be.

Approximately 5% of people who are diagnosed with lung cancer have no symptoms. They are usually diagnosed because of an unexpected finding during a physical examination, an abnormality on a routine chest x-ray, or some other incidental finding. However, the vast majority of people diagnosed with lung cancer seek medical attention because they are experiencing symptoms. For the sake of simplicity, we will assume that the diagnostic process is beginning at the point of experiencing symptoms. When a person goes the doctor, he or she always begins the investigation into the source of the problem with a medical history and a physical examination.

Medical History

Your medical history gives your doctor important information that helps him or her think through possible causes of your symptoms. Pieces of information from your medical history your doctor will probably consider include:

- your personal smoking history and exposure to second-hand smoke,
- any problems you've had with your lungs in the past,
- when your current symptoms started, and how they have changed over time,
- your job history and/or exposure to potential lung carcinogens, and
- a family history of lung cancer or other *epithelial cell* cancers.

Depending on your presenting symptoms, your doctor may ask other questions about your medical history. Try to be as accurate and truthful as possible when reporting your medical history.

Physical Examination

The physical examination is a crucial part of the diagnostic process for any medical problem.

Important physical findings in someone who may have lung cancer include:

- fever
- abnormal breath sounds in the lungs
- swollen lymph nodes
- tenderness and/or enlargement of the liver
- tenderness in the flank area (over the kidney)
- swelling in the hands, feet, face, or ankles
- tenderness over any bones
- generalized or regional muscle weakness
- skin changes such as rashes, dark areas, or a blue tint of the lips and nails
- any findings that might indicate a *primary tumor* in a body organ other than the lungs

There are many other possible physical findings your doctor will consider in deciding how best to proceed.

Laboratory Testing

Laboratory testing is usually included in the diagnostic work-up of someone who may have lung cancer. The specific tests your doctor orders will depend on your medical history, presenting symptoms, and physical findings.

Sputum Cytology

A *sputum cytology* test may be performed when lung cancer is suspected (see Figure 2). A sample of sputum is collected first thing in the morning. Sputum is the thick, slippery fluid secreted by the airways; many people call sputum phlegm. The sample must come from deep in the lungs, so it must be produced by a deep cough. The sputum is placed on slides and stained in the laboratory. The slides are then examined under a microscope. The technologist examining the slides looks for cancer *cells* that may be contained in the sputum. Bacteria and other abnormal cells may also be seen. Your doctor may have you collect sputum samples on three consecutive days to increase the chances of finding cancer cells.

When cancer cells are seen in a sputum cytology specimen, it is almost certain there is cancer in the lungs. However, if cancer cells are not detected, this does not rule out the possibility of lung cancer because sputum cytology is positive in only 5-20% of people with lung cancer.^{3,4}

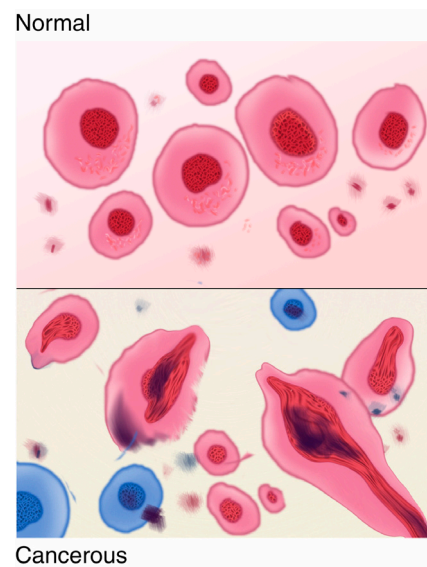


Figure 2: Microscopic Views of Sputum Cytology*

Tumor Markers

Tumor markers are substances in the blood that are found only when cancer is present, or are present in highly elevated amounts when cancer is present.

Carcinoembryonic antigen (CEA) is a tumor marker that is sometimes measured when lung cancer is suspected. However, CEA is elevated in several cancers, not just lung cancer. Therefore, an elevated CEA does not necessarily mean lung cancer is

present. The interpretation of an elevated CEA level is further complicated by the fact that smokers often have abnormally high CEA levels.

Scientists are working hard to find tumor markers for lung cancer that are both sensitive to the presence of lung cancer and are specific for lung cancer. Sensitivity is the ability of a test to detect an abnormality if one is present. Specificity is a measure of how likely it is that a test abnormality indicates a particular disease. A sensitive and specific lung cancer tumor marker could potentially be used as diagnostic tool and as a screening test for people who are at risk but have no symptoms.

Imaging Tests: Is There a Lung Tumor?

Imaging tests are performed to determine if a lung tumor is present. Some imaging studies can provide information that can help determine if a lung tumor is likely to be *benign* or *malignant*. The final determination as to whether a tumor is cancerous can only be made by examining a tissue sample under a microscope. Imaging tests are useful to look for enlargement of regional lymph nodes, which could indicate cancerous spread.

Chest X-Rays

Although studies have proven that chest x-rays miss a significant number of lung tumors, a chest x-ray is often the first imaging study performed when primary or metastatic lung cancer is suspected.⁵⁻⁷ A lung tumor can be missed on chest x-ray if it is small or hidden behind a rib, collar bone, or the breastbone. Chest x-rays can be useful for detecting abnormalities other than tumors that may be related to lung cancer. For example, chest x-rays can detect an accumulation of fluid around the lung, a condition known as *pleural effusion*. A chest x-ray may also show enlarged lymph nodes, pneumonia, or blocked airways that are preventing air from reaching part of the lung.

Even if the diagnosis of lung cancer is already clear, your doctor may want to take a chest x-ray to compare with previous and future chest x-rays. Following chest x-rays over time can help your doctors monitor the course of your disease.

Within the last few years, a new type of chest x-ray called the digital chest x-ray has been introduced. The digital chest x-ray collects the image of the chest with a computerized detector instead of on a piece of film as is done with a conventional chest x-ray. The use of the detector instead of film allows for sharper, clearer images. Researchers are also testing the use of computers to aid the reading of chest x-rays in an effort to pick up more lung tumors. This technology is called *computer-assisted diagnosis* (CAD). Early research indicates the combination of digital chest x-rays and CAD has the potential to greatly improve the efficiency and accuracy of chest x-rays in detecting lung tumors.^{8,9}

CT Scans

CT scans (computerized tomographic scans) are x-ray imaging tests that may be used in the diagnostic work-up of suspected lung cancer. CT scans are able to detect smaller tumors than chest x-rays. They are also better able to determine the size, shape, and exact location of a tumor because they collect information in three dimensions instead of two. For the

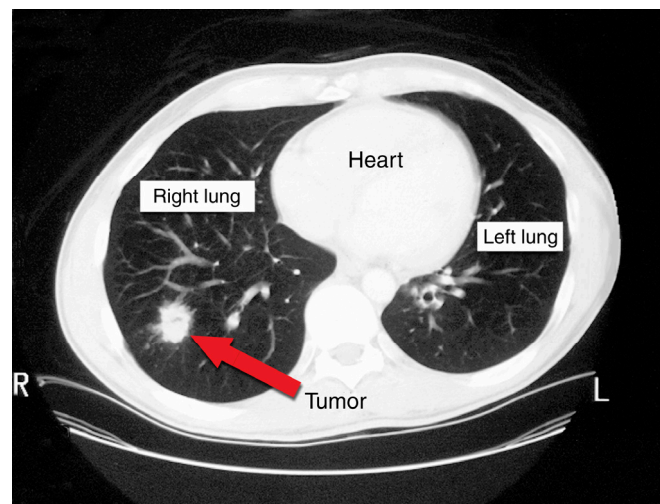


Figure 3: CT Scan of the Chest Showing a Lung Tumor*

same reasons, CT scans are better able to detect enlarged regional lymph nodes. When CT scanners were first introduced, the machines took individual x-rays of the body, which were then put together by a computer to form three-dimensional images. The scanning procedure took 15-30 minutes, and the images were affected by small movements during the study. In the early 1990's, a new type of scanner was introduced, the *spiral* or *helical CT scanner*. This scanner is able to x-ray the entire chest in 20-30 seconds while the patient holds his or her breath. The continuous nature of data collection by the computer and the reduced effects of movement make CT scans performed with helical/spiral machines clearer and better able to

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detect small tumors. In most instances, the higher quality of helical/spiral CT scans make them more desirable than CT scans performed with older scanning machines.

MRI Scans

MRI scans (magnetic resonance imaging scans) use a large magnet instead of x-rays to produce three-dimensional images. MRI is not often used in the routine work-up of suspected lung cancer. In special circumstances, MRI may be used to study a particular area that may be difficult to interpret on a CT scan such as the diaphragm or the uppermost part of the lung. However, in most instances, CT is superior to MRI for imaging the structures in the chest.

PET Scans

PET (positron emission tomography) scanning is a relatively new technology. Sugar molecules that have a radioactive component are injected into the body and then a scan is taken. The amount of radiation used for these scans is very low. Cancer cells take up more sugar than normal cells because they are growing and dividing rapidly. Therefore, areas of the body with cancer cells show up brighter on the scan than normal tissues. Primary tumors, lymph nodes containing cancer cells, and metastatic tumors all appear as bright spots on a PET scan. Substances other than radiolabeled sugar are sometimes used for PET scans, but the theory behind the scans is the same.

PET scans are not generally used as first-line diagnostic tests for lung cancer. They are sometimes used after chest x-rays or CT scans to differentiate between benign and cancerous tumors. PET scans are particularly useful for finding cancerous spread to regional lymph nodes and detecting distant metastatic tumors.¹⁰⁻¹³ However, there are conditions other than cancer that cause positive findings on PET scans. PET scan findings should be interpreted cautiously and correlated with other test results.

Tissue Diagnosis

The only way to make a certain diagnosis of lung cancer and determine the type of lung cancer present is to examine a sample of the tumor under the microscope. The process of

obtaining a tissue sample is called a *biopsy*. The method used to obtain a biopsy depends on the size and location of the tumor or lymph node being tested. Different biopsy techniques are reviewed in this section.

Bronchoscopy

Bronchoscopy is the most common technique used to biopsy a suspected lung cancer. Bronchoscopy involves putting a small, flexible tube called a bronchoscope into the larger airways of the lungs. The bronchoscope allows the doctor to see inside the airways and take tissue samples. Bronchoscopy is particularly useful for obtaining tissue samples from tumors growing in the larger airways of the *bronchial tree*, usually in the central part of the lung. Tissue samples from lymph nodes in and around the lungs can also be obtained with a bronchoscope. Bronchoscopy is generally performed as an outpatient procedure.

Autofluorescence bronchoscopy is a modified bronchoscopy procedure that uses fluorescent light to detect potentially cancerous areas of the airways. Tumors and other abnormal cells naturally glow when exposed to specific types of fluorescent light. This technique helps the doctor identify suspicious areas in the airways to sample. Autofluorescence bronchoscopy is particularly useful for people whose sputum cytology test showed cancer cells, but imaging studies failed to show a lung tumor. Autofluorescence bronchoscopy is also better than standard bronchoscopy for detecting lesions that may be progressing to lung cancer.

Mediastinoscopy

Mediastinoscopy is a surgical procedure in which a rigid instrument called an *endoscope* is inserted through a small incision at the base of the neck or near the breastbone into the central area of the chest called the *mediastinum*. The mediastinum contains the heart, the large blood vessels entering and leaving the heart, the *trachea*, the esophagus, and several lymph nodes that drain *lymph* fluid from the lungs.

Mediastinoscopy is often used for both diagnosis and staging because sampling the lymph nodes of the mediastinum is an important part of determining lung cancer stage. Mediastinoscopy is usually performed as a diagnostic test in people who have

centrally located lung tumors that can be reached from the mediastinum. Biopsies of the primary tumor and mediastinal lymph nodes are taken during the procedure. Mediastinoscopy is performed under general anesthesia and usually requires an overnight stay in the hospital.

Transthoracic Needle Biopsy

Transthoracic needle biopsies are usually reserved for people who have tumors near the surface of the lung that would be difficult to reach by bronchoscopy. Transthoracic needle biopsy is sometimes called *fine needle aspiration (FNA) biopsy*. In this procedure, a needle is inserted through the chest wall into the lung tumor. Small tissue samples are collected through the needle. This procedure is performed using either computerized tomography (CT) or *fluoroscopy* (another x-ray technique) to help the doctor direct the needle into the precise location of the tumor. Local anesthesia is used to numb the skin where the needle is inserted, and a mild sedative is used to relax the patient. The procedure is usually performed on an outpatient basis.

Thoracoscopy

Thoracoscopy is another surgical procedure in which an endoscope is inserted into the chest space. Thoracoscopy has limited use in lung cancer diagnosis, but is sometimes used to biopsy a suspicious tumor and regional lymph nodes.

Thoracoscopy has the advantages of allowing the surface of the lung to be examined and permitting sampling of any pleural effusion that may be present.

Video-assisted thoracoscopy (VATS) is a technique in which a tiny video camera is inserted into the chest by a small incision separate from the incision used for the thoracoscope. Pictures of the chest cavity are projected onto a screen during the procedure to give the surgeon a better view of the area. VATS and routine thoracoscopy procedures are performed under general anesthesia and usually require an overnight stay in the hospital.

Thoracotomy

In rare instances, doctors are unable to biopsy a suspicious lung tumor using the already mentioned techniques. In these situations, a *thoracotomy* may be performed. A thoracotomy is major surgery performed under general anesthesia. The chest is opened and the rib cage is separated to expose the lungs. A biopsy of the tumor is performed and the tissue is examined under the microscope while the patient is still in the operating room. If cancer is found, the surgeon will sample regional lymph nodes to determine if a surgical cure is possible. Again, the lymph nodes are examined while the patient is still in the operating room. If surgical cure is possible, a potentially curative operation will be performed. Diagnosis and treatment are performed at the same time in this unusual situation. The hospital stay after a thoracotomy is usually a week or longer.

THE LUNG CANCER STAGING PROCESS

Lung cancer staging is the process of classifying the extent of spread of the cancer from the original tumor to other parts of the body according to standard criteria. Staging is important for two reasons. It helps your doctors determine which treatments are likely to be most effective for you. It also helps determine what the course of your illness (*prognosis*) is likely to be. Lung cancer stage is the primary factor influencing the prognosis of the disease.

Lung cancer stages range from I through IV. Stages are typically expressed using Roman numerals where I = one, II = two, III = three, and IV = four. In general, the lower the stage, the less the cancer has spread. The higher the stage, the more extensive is the spread of the disease. The general trend in terms of prognosis is the lower the stage, the better the prognosis.

Three factors are used to determine lung cancer stage. These factors are expressed using the *TNM classification system*. The three factors of the TNM system are as follows.

T: tumor characteristics including size, location, and local invasion

N: regional lymph node involvement

M: metastasis status

Lung cancer staging can include numerous tests and surgical procedures. Generally, health care providers try to establish the M factor (a person's metastasis status) as early as possible in the staging process. The reason for this is that any distant metastasis automatically moves a person to stage IV. The presence of distant metastasis is usually established with imaging tests, which are much less invasive than procedures such as bronchoscopy and mediastinoscopy that are used to establish lymph node involvement and tumor characteristics. If distant metastasis is present and a person's stage has been established as IV, no further staging procedures are needed. Therefore, determining a person's M-status is undertaken early in the staging process to spare people who are stage IV unnecessary procedures.

Determining Metastatic Status

The state of metastasis (**M**) is defined as follows.

- M0:** No distant metastasis found.
- M1:** Distant metastasis is present.

Physical findings and presenting symptoms may raise suspicion of metastatic disease in a specific organ or area of the body. Under such circumstances, scans will be focused on that specific area. However, metastatic disease is often asymptomatic at the time of diagnosis, which necessitates a thorough search for distant, asymptomatic metastatic tumors. Imaging tests commonly used to screen for metastatic disease are listed below.

- CT scans - *abdomen, pelvis*, and brain
- MRI scans - brain
- PET scans - whole body
- *ultrasonography* –abdomen and liver
- *bone scans* – whole body

CT, MRI, and PET scans were discussed in the previous section under *Imaging Tests*.

Ultrasonography uses special frequency sound waves to visualize internal organs. Bone scans are similar to PET scans. A radioactively labeled substance that is taken up by actively growing and dividing cells is injected into the body. A scan is later taken of the entire body

to look for 'hot spots' in the skeleton. Hot spots are areas in the skeleton with high uptake of the radiolabeled chemical that may indicate metastatic disease.

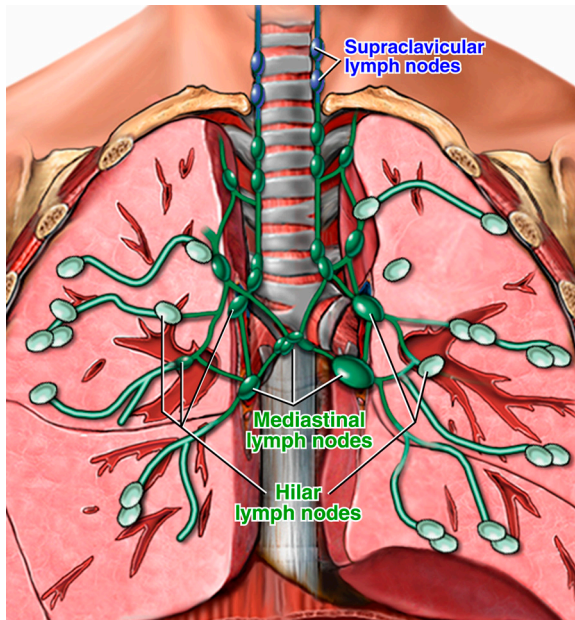


Figure 4: Regional Lymph Nodes of the Lungs*

Determining Regional Lymph Node Status

The regional lymph nodes of the chest are divided into three major areas, the *hilar lymph nodes*, the *mediastinal lymph nodes*, and the *supraclavicular lymph nodes* (see Figure 4). The trachea splits into the right and left main bronchus in the mediastinum. The main bronchus enters the lung at the *hilum*. The lymph nodes in this area are called the hilar lymph nodes; these lymph nodes are located within the lung. The mediastinal lymph nodes are located in the middle of the chest, in and around the trachea and the

esophagus. The mediastinal lymph nodes are located outside of the lungs. The supraclavicular lymph nodes are those just above the collarbones. Cancer in lymph nodes beyond the hilar, mediastinal, and supraclavicular lymph nodes is considered evidence of distant metastasis.

Two additional terms are important to understand the staging of regional lymph node involvement. *Ipsilateral* refers to lymph nodes on the same side of the chest as the primary tumor. *Contralateral* refers to lymph nodes on the opposite side of the chest as the primary tumor.

Regional lymph node status is divided into the following categories.

- N0:** No evidence of cancer in the regional lymph nodes
- N1:** Cancer in the ipsilateral hilar lymph nodes
- N2:** Cancer in the ipsilateral mediastinal lymph nodes
- N3:** Cancer in the contralateral lymph nodes or in the supraclavicular area

Regional lymph nodes can be sampled and staged with the following procedures.

- bronchoscopy
- mediastinoscopy
- thoracoscopy and VATS
- thoracotomy

As imaging technologies advance, researchers continue to study the correlation between regional lymph node staging as determined by imaging studies compared to tissue sampling. Although tissue sampling remains the standard for staging, especially among people who are potential candidates for surgery, imaging techniques may have a more significant role in lung cancer staging in the future.^{14, 15} One particularly promising technology is the combined use of CT and PET scanning known as in-line CT-PET scanning. Preliminary results indicate that combining the strengths of these two imaging techniques yields better results than either technique used alone.¹⁶⁻¹⁸

Determining Tumor Characteristics

The categories for lung cancer tumor classification take into account the size, location, and local invasiveness of the primary tumor. Tumor characteristics are determined using the same methods used for diagnosis and evaluation of the regional lymph nodes. The specific tests used vary from one person to another depending on his or her unique history, symptoms, and physical findings. The tumor categories and their descriptors are:

T0: No evidence of primary tumor

Tis: Carcinoma *in situ*

T1: Tumor that is less than 3 cm (1½ inches) in size and is completely surrounded by lung tissue

T2: Tumor that is larger than 3 cm (1½ inches) but is still surrounded by lung tissue and is not invading the chest wall or any of the structures in the mediastinum

T3: Tumor of any size that invades the chest wall, diaphragm, or the pleura of the mediastinum or heart; a T3 cancer is potentially respectable (surgically removable)

T4: A tumor of any size that invades the structures of the mediastinum or a vertebral body (a backbone)

The area where the trachea divides into the right and left main bronchus is called the *carina*. If a tumor is close to the carina, it may not be operable if the remaining airways cannot be sewn together. Therefore, tumors involving the carina are T4 tumors. Tumors associated with a malignant pleural (around the lung) or a pericardial (around the heart) effusion are also T4 tumors, as are separate tumor nodules in the same lung lobe. T4 tumors are generally inoperable.

NON-SMALL CELL LUNG CANCER STAGES

Using the TNM classification system, non-small cell lung cancer is divided into four stages. Your doctor must know the stage of your disease in order to recommend treatment options. A general summary of the stages is reviewed in this section.

Stage I

Stage I NSCLC is characterized by a cancerous tumor that has not spread. There is no evidence of cancer in any lymph nodes. The difference between stage IA and stage IB disease is the size of the primary tumor. With stage IA disease, the tumor is 3 cm (1½ inches) or less in size. With stage IB disease, the tumor is larger than 3 cm (1½ inches) in size. Stage I NSCLC is local disease and is potentially curable with surgery.

The stage I TNM designations are:

Stage IA: T1N0M0

Stage IB: T2N0M0

Stage II

Stage II NSCLC is characterized by a primary tumor that has spread to the hilar lymph nodes (the N1 area) on the same side as the tumor. With stage IIA, the tumor is a T1 (3 cm or less). With stage IIB, the tumor is a T2 (greater than 3 cm).

A tumor involving the chest wall without hilar lymph node involvement (T3, N0) is also considered stage IIB disease. Stage II NSCLC is potentially curable with surgery, although the chance of recurrence is higher than for people with Stage I disease.

The stage II TNM designations are:

- Stage IIA: T1N1M0
- Stage IIB: T2N1M0 or T3N0M0

Stage III

Stage III is the most complex of the stages, and there are significant differences in the treatment of stage IIIA versus stage IIIB disease. Stage IIIA disease includes a tumor that has invaded the chest wall, diaphragm, or the pleura of the mediastinum or heart, and has ipsilateral hilar or mediastinal lymph node involvement (T3N1M0 or T3N2M0). Smaller tumors that involve the ipsilateral mediastinal lymph nodes are also stage IIIA (T1N2M0 or T2N2M0). Stage IIIA is potentially operable. Preoperative treatment is used for some people and is currently under evaluation in many clinical trials.

Stage IIIB disease includes any size tumor that has invaded any of the vital structures of the mediastinum, the carina, or a vertebral body (T4 tumors), with or without regional lymph node involvement (T4N0M0, T4N1M0, T4N3M0). Lesser tumors (T1-3) that are associated with contralateral lymph node involvement or any supraclavicular lymph node involvement are also stage IIIB. People with stage IIIB disease are generally not considered candidates for surgical cure because it is often physically impossible to remove all the cancerous tissue with this degree of spread.

The stage III TNM designations are:

- Stage IIIA: T3N1M0, T3N2M0
T1N2M0 or T2N2M0
- Stage IIIB: T4N0M0, T4N1M0, T4N2M0
T1N3M0, T2N3M0, T3N3M0, T4N3M0

Stage IV

Stage IV NSCLC is assigned whenever there is distant metastasis, that is, spread of the disease beyond the regional lymph nodes. The TNM designation for stage IV NSCLC is any T, any N, and M1.

Special Cases

Stage 0 (zero) represents carcinoma *in situ*. This unique situation refers to the presence of an identifiable area of cancer cells that are confined to a local area and have not grown through the top lining of the lung. Carcinoma *in situ* is curable and incapable of spreading. The TNM designation for carcinoma in situ is Tis. Since there is currently no organized screening program for lung cancer, the percentage of people newly diagnosed with lung cancer who have stage 0 disease is very low.

Occult lung cancer is another uncommon situation in which tumor cells are found in the sputum or *bronchial washings* (rinse solution obtained during bronchoscopy), but no primary tumor can be seen on imaging studies or on direct examination with a bronchoscope. The TNM designation for occult lung cancer is Tx.

Table 1 gives the lung cancer TNM descriptors according to the International System for Staging Lung Cancer.

Table 1: TNM Descriptors*

PRIMARY TUMOR (T)	
Tx	Primary tumor cannot be assessed OR Tumor proven by the presence of malignant cell in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i>
T1	Tumor less than or equal to 3 cm in its greatest dimension, surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (that is, not in the main bronchus) The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1
T2	Tumor with any of the following features of size or extent: <ul style="list-style-type: none">• greater than 3 cm in its greatest dimension• may extend into the main bronchus if it remains more than 2 cm from the carina• may invade the visceral pleura• may be associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

TNM Descriptors, Continued	
T3	Tumor of any size that directly invades any of the following: <ul style="list-style-type: none"> • chest wall (including superior sulcus tumors) • diaphragm • mediastinal pleura • parietal pericardium <p style="text-align: center;">OR</p> Tumor in the main bronchus less than 2 cm from the carina but without involving the carina <ul style="list-style-type: none"> • may be associated with atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades any of the following: <ul style="list-style-type: none"> • mediastinum • heart or great vessels • trachea • esophagus • vertebral body • carina <p style="text-align: center;">OR</p> Tumor with a malignant pleural or pericardial effusion <p style="text-align: center;">OR</p> Tumor with a satellite tumor nodule(s) within the same lobe as the primary tumor
REGIONAL LYMPH NODES (N)	
N_x	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to the ipsilateral peribronchial and/or ipsilateral hilar lymph nodes <p style="text-align: center;">OR</p> Direct extension of the primary tumor into intrapulmonary nodes
N2	Metastasis to the ipsilateral mediastinal and/or subcarinal nodes
N3	Metastasis to any of the following nodes: <ul style="list-style-type: none"> • contralateral mediastinal • contralateral hilar • ipsilateral or contralateral scalene • supraclavicular

*Adapted from: Mountain CF. Revisions in the international system for staging lung cancer. *Chest*. 1997;111:1710-1717. Used with permission.

SMALL CELL LUNG CANCER STAGES

The TNM classification and staging system is applicable to both SCLC and NSCLC. While the TNM system is used for SCLC in some research settings, most health care providers more commonly categorize SCLC as either limited or extensive stage disease. This classification system was created by the Veterans Administration Lung Cancer Study Group after it became clear that relatively small differences in the extent of tumor and/or lymph node involvement had little impact on response to therapy or prognosis among people with

SCLC. Most doctors believe the reason for this finding is that most SCLCs undergo early and widespread metastasis.

People with SCLC are staged with limited or extensive disease based on the extent of the disease in the chest. People whose disease is confined to one lung, the mediastinum, and regional lymph nodes are categorized with limited stage SCLC. Limited stage disease can be enclosed in a single radiation therapy field. Approximately 30% of people with SCLC have limited stage disease at diagnosis. Limited stage corresponds to stages I through IIIB of the TNM staging system.

Extensive stage SCLC has spread to the contralateral lung, is associated with a malignant pleural effusion, or is accompanied by distant metastasis. Approximately 70% of people with SCLC have extensive stage disease at the time of diagnosis. Extensive stage corresponds to stage IIIB with pleural effusion and stage IV of the TNM staging system.

SUMMARY

Medicine is both an art and a science. The science of lung cancer diagnosis and staging involves many different procedures and technologies. The art of lung cancer diagnosis and staging involves matching the unique history, physical findings, and symptoms of each person suspected of having lung cancer with the appropriate tests.

The processes of diagnosis and staging often overlap. The ultimate goal of both processes is to determine the type and extent of the lung cancer. Accurate diagnosis and staging are important so your health care providers can direct you toward the most effective treatments for your unique circumstances.