CHAPTER 5: LUNG CANCER TREATMENT OVERVIEW

INTRODUCTION

Lung cancer is currently treated with three forms of therapy: chemotherapy, radiation therapy, and surgery. They are used alone or in combination depending on the type of lung cancer and the stage of the disease. This chapter discusses basic concepts about each of these forms of therapy and their uses in the treatment of lung cancer. *Chapters 6* and *7* review specific treatments for small cell and non-small cell lung cancer.

Health care providers use specific language when discussing cancer treatment options. The beginning of this chapter explains many of the terms used. Familiarity with these medical terms will help you better understand your treatment options and make discussions with your health care providers easier. Many of the definitions presented in this section are derived from the National Cancer Institute's online dictionary at www.nci.nih.gov/dictionary. This is a good resource for understandable definitions of medical terms. If one of your providers uses a term you are not familiar with, ask him or her to explain it. Remember, there is no such thing as a silly question, especially when you are discussing something as important as your health.

TALKING ABOUT TREATMENT OPTIONS: LEARNING THE LANGUAGE

Response to Therapy

Doctors define your response to therapy in different ways. A *complete response* is the disappearance of all signs of cancer. This does not always mean the cancer has been cured because there can be residual cancer that is undetectable. For this reason, your doctors may use the phrase 'apparently cancer-free' if you have a complete response to treatment. A complete response is also called a complete remission.

A *partial response* or partial remission is a decrease in the size of a tumor or the extent of cancer in the body, or halting disease progression. In clinical trials, researchers usually specify what qualifies as a partial response by setting a threshold percentage of tumor shrinkage that must occur. When your doctor says you are responding to therapy, it is important to understand that a response to therapy is not necessarily the same thing as a cure. Your cancer may respond to treatment but not be eliminated from your body. Only when cancer is completely eliminated from the body is it considered cured.

Progressive disease means the cancer is growing and/or spreading. If you are on treatment and have disease progression, that particular treatment should be stopped because it is not working for you.

Treatment Descriptors

First line treatment is the first therapy used to treat your cancer.

People who have not had any previous treatment for their cancer are *treatment naïve*.

People who have not had previous chemotherapy for their cancer are *chemonaïve*.

Curative intent refers to cancer therapy used to try to cure the disease.

Multimodality therapy or combined modality therapy includes two or more forms of cancer treatment used together or in succession.

Adjuvant therapy is treatment given after the primary treatment to increase the chance of a cure. Lung cancer adjuvant therapy may include chemotherapy, radiation therapy, or both.

Neoadjuvant therapy is treatment given before the primary treatment to increase the chance of a cure. Examples of neoadjuvant therapy used to treat lung cancer include chemotherapy, radiation therapy, or both. Another term for neoadjuvant therapy is *induction therapy*.

Second line treatment is any form of therapy used after first line cancer therapy. Second line treatment may be used if the cancer did not respond to first line therapy or if there is disease

progression after first line therapy has been completed. *Salvage therapy* is another term for second line treatment.

Palliative therapy is treatment given to relieve symptoms caused by advanced cancer. Palliative therapy is not curative and does not alter the course of the disease, but can significantly improve *quality of life*. The effectiveness of palliative therapy is usually described in terms of percent response and *time to progression*. Time to progression is the length of time the treatment is able to keep the cancer from growing and/or spreading.

Treatment Effectiveness: Making Sense of the Numbers

Treatment effectiveness is expressed using data from clinical trials. For information about clinical trials, see *Chapter 8*. Treatment effectiveness is described in many different ways. Before discussing some common terms used to describe treatment effectiveness, a word of caution about numbers. Clinical trials are conducted to evaluate the safety and effectiveness of new treatments. The numbers generated in clinical trials are very important because they allow researchers to compare one treatment to another. However, when it comes to an individual person trying to make treatment decisions, effectiveness numbers should not be over interpreted. Effectiveness numbers can help you compare the probability that one treatment versus another will lead to the response you seek. They should not be taken to indicate your <u>personal</u> chance of responding to a given therapy. For example, you may hear treatment with a certain chemotherapy drug is associated with a 40% response rate. This means 40% of all people treated with the drug in a clinical trial setting responded to it. It does <u>not</u> mean you personally have a 40% chance of responding to the drug.

Currently, no one can tell you your personal chance of responding to a given therapy because each person's situation is unique. Researchers are working hard to find reliable tests to predict how an individual person's cancer will respond to a specific treatment. However, such tests are not yet available. Many factors contribute to whether an individual person responds to a specific treatment. The genetic makeup of the cancer, the immune system of the patient, the presence of other illnesses, age, and gender are examples of the many factors that may contribute to whether a specific cancer responds to a given therapy.

People are not statistics. In the end, what matters is your response to a specific treatment not the response rates seen in clinical trials. Use response rates to help you make treatment decisions, but do not allow them to influence your overall state of mind or to destroy your sense of optimism. Your experience with lung cancer will be unique and may vary greatly from the statistics you read and hear.

> **It was very discouraging when I saw the raw numbers. I thought this is almost a death sentence. I was at the library, and went to the gentleman at the reference desk and said, "I think this book may be out dated." The gentleman said, "Look, you really only have two statistics to chose from – 0% or 100%". You have to handle statistics like water off a duck's back … I chose to take control and think positively about my recovery.**
> **– Larry, diagnosed with Stage IIIA NSCLC at age 61**

Cancer survival statistics are given in specific timeframes. One-, two-, and five-year survival statistics are commonly discussed. One-year survival is the percentage of people on a specific treatment who are alive one year after beginning treatment. Two-year survival is the percentage of people alive two years after beginning a specific treatment. Five-year survival is the standard marker for cure. People alive and cancer-free five years after beginning treatment are generally considered cured of their disease. When you read or hear about cancer survival statistics, these refer to five-year survival unless another time interval is specifically stated. Five-year survival is sometimes called long-term survival.

It is important not to overestimate the applicability of treatment trial numbers to your personal situation. While these numbers are very important, they cannot predict your personal response to any given treatment. No one can predict this. Similarly, no one can predict the outcome of your disease. Survival statistics for lung cancer can be discouraging. Keep in mind, there are survivors. You may well be one of them!

Statistical Terms

You may come across some unfamiliar statistical terms in your search for information about lung cancer. You will certainly come across some of these terms if you look at medical journals. The term *mean* is another word for the average value in a set of measurements. It is calculated by adding all the measurements together and dividing by the number of

measurements taken. For example, consider the following results from a study measuring time to disease progression for people receiving a new treatment for lung cancer.

Person 1	10 months
Person 2	6 months
Person 3	10 months
Person 4	7 months
Person 5	2 months
Person 6	10 months
Person 7	10 months
Person 8	1 month

$$\text{Mean time to disease progression} = \frac{10+6+10+7+2+10+10+1}{8} = \frac{56}{8} = \textbf{7 months}$$

Median is the middle value in a set of measurements. Using the same information from the previous example, the middle number is half-way between 7 and 10. In this example, the median time to disease progression is 8 ½ months, the midway point between 7 and 10.

1 2 6 (**7** **10**) 10 10 10

Both measures of effectiveness are based on the same set of results. However, this example clearly demonstrates how the statistical term chosen to describe the effectiveness of a treatment affects the value of the number reported.

Studies of treatment effectiveness usually report a *p-value* along with significant findings. A p-value is a numeric representation of how certain researchers are that their findings are true. The lower the p-value, the more likely it is the finding is true and not due to coincidence. The p-value is usually represented in parentheses after an important finding, for example ($p=0.01$) or ($p<0.001$).

You may encounter the term *confidence interval* or CI. A confidence interval is a range of values that is reasonably certain to contain the true value. For example, researchers may report a median time to disease progression of 8 months with a 95% CI of 6.5-9.0. This

means researchers are 95% certain the true median time to disease progression is between 6.5 and 9 months.

CHEMOTHERAPY

What Is Chemotherapy?

Chemotherapy is broadly defined as the use of medicines to treat disease. In the field of cancer, chemotherapy is the use of drugs (medicines) to kill cancer *cells*. Cancer chemotherapy drugs are also called *cytotoxic drugs*.

Cancer cells divide rapidly. They divide at a higher rate than most normal cells of the body. Chemotherapy drugs use this characteristic of cancer cells to preferentially cause their death while leaving most normal cells unharmed. Some cytotoxic drugs interfere with the cell division cycle. This prevents cancer cells from reproducing. Other chemotherapy drugs cause genetic damage the cancer cell is unable to repair ultimately leading to cell death. Although chemotherapy drugs work in different ways, they all target mechanisms active in cells that are rapidly growing and dividing. Chemotherapy drugs with different mechanisms of action are frequently used together to increase the overall response to treatment.

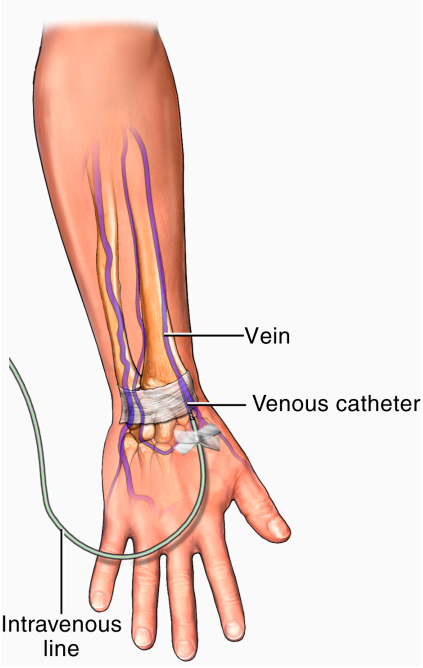

*Figure 1: Intravenous Infusion Setup**

Why Is Chemotherapy Used?

Cancer chemotherapy is *systemic therapy*, meaning the entire body is exposed to the treatment. Chemotherapy is used when there is clear evidence the cancer has spread beyond the original tumor or if there is reason to suspect there may be undetectable cancer cells (*micrometastasis*) in the body. Chemotherapy may be used in lung cancer treatment for one or more reasons:

- to achieve a complete response and potential cure
- to slow cancer growth and prolong life
- to prevent cancer spread
- to shrink tumors and relieve disease related symptoms

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Even when chemotherapy does not lead to cure, studies have consistently shown it can help people with lung cancer live longer, more comfortable lives.

How Are Chemotherapy Drugs Given?

Many chemotherapy drugs must be given directly into the blood stream by an intravenous (IV) line (see Figure 1). This *route of administration* (how a drug is given) is necessary for chemotherapy drugs that would be broken down and inactivated by the digestive processes of the stomach and intestines. However, some chemotherapy drugs can be taken by mouth without any loss of anti-cancer activity.

Chemotherapy drugs are administered on different schedules. Some drugs are given over a few hours; others are given in continuous drip over a few days. Whatever the specific administration schedule, most chemotherapy drugs are given in cycles. Drugs given in cycles are administered periodically with breaks between doses. Each complete administration of the chemotherapy drugs you are taking (including breaks) is called a *treatment cycle*. Chemotherapy drugs are given in cycles because it takes time for the drugs to have the desired effect on the cancer cells. Cyclic treatment also allows normal cells time to recover between chemotherapy treatments. Chemotherapy treatments may be weekly, biweekly, monthly, or on another schedule. The time between treatment cycles depends on the drug(s) used. The number of cycles used in a treatment protocol also depends on the drug(s) used.

Chemotherapy Side Effects

Chemotherapy can cause a wide range of side effects. Many of the side effects are related to the fact that these drugs do not selectively kill cancer cells but interfere with the processes of any rapidly dividing cell. Therefore, tissues in the body that normally grow and divide rapidly can be damaged as a side effect of chemotherapy. For example, bone marrow cells that produce *red blood cells*, white blood cells, and platelets can be damaged by chemotherapy drugs causing the levels of these blood elements to drop. This condition is called *myelosuppression*. The cells lining the inside of the mouth and throat also divide rapidly and are susceptible to chemotherapy drugs. As a result, many people on chemotherapy experience mouth sores, dryness, and taste changes. Hair follicles can also be damaged by

chemotherapy drugs leading to partial or complete hair loss (*alopecia*). These are just a few examples of possible chemotherapy side effects.

Dose-limiting side effects of chemotherapy are severe physical side effects that can be potentially life threatening. Myelosuppression is a common example of a dose-limiting side effect. These side effects may make it necessary to lower the dose of the offending drug and/or prolong the time between treatments. In extreme cases, treatment with the offending drug may need to be discontinued.

Each chemotherapy drug has the potential to cause different side effects. The list of possible side effects associated with a particular chemotherapy drug is called its *side effect profile*. The number and severity of side effects experienced from any given drug varies greatly from person to person. The drug, its dosage, and your body's reaction to the drug influence the occurrence of chemotherapy side effects and their severity.

Possible side effects associated with various chemotherapeutic drugs used to treat lung cancer include:

- constipation
- diarrhea
- *fatigue*
- hair loss (alopecia)
- loss of appetite (*anorexia*)
- mental fatigue, slow thinking, faulty memory
- mouth sores, dry mouth, taste changes
- myelosuppression including *anemia* (low red blood cell count), *neutropenia* (low white blood cell count), and *thrombocytopenia* (low platelet count)
- nausea and vomiting
- numbness, tingling, pain in the hands and feet (*peripheral neuropathy*)

The appendix *Chemotherapy Side Effect Profiles* contains information about the potential side effects of specific chemotherapy drugs commonly used to treat lung cancer. *Chapter 10:*

Supportive Care contains detailed information about the prevention and treatment of chemotherapy side effects.

RADIATION THERAPY

What Is Radiation Therapy?

Many people with lung cancer are treated with radiation therapy or *radiotherapy*. Radiotherapy uses high-energy radiation called *ionizing radiation* to stop cancer cell division. This prevents the formation of new cancer cells. Ionizing radiation reacts with the water inside cells causing damage to the genetic material. Normal cells can usually repair this type of damage, but most cancer cells cannot. The damaged cancer cells eventually die as a result. The dose or amount of energy deposited in a treatment area is expressed in rads or gray (Gy).

1 Gy = 100 rad

1 rad = 0.01 Gy

The dose of radiation given for cancer therapy is several thousand times greater than the amount of radiation you are exposed to during an imaging x-ray. A machine called a linear accelerator is usually used to deliver radiotherapy.

Why Is Radiation Therapy Used?

Radiotherapy is a local form of cancer therapy. This means it affects only cells in the treatment area as opposed to a systemic therapy (like chemotherapy) that affects cells throughout the body.

Radiotherapy is frequently used in lung cancer as adjuvant therapy, which means it is used in combination with surgery and/or chemotherapy. The goal of radiotherapy used in this way is to cure the cancer. Adjuvant radiotherapy can be used to:

- shrink a tumor before surgery
- increase the response of cancer cells to treatment by administering it along with or following chemotherapy
- destroy any remaining cancer cells that may be left behind after cancer surgery

Radiotherapy is also used as palliative therapy to relieve disease-related symptoms and prolong life when cure is not possible. Palliative radiotherapy is often lower dose and given over a shorter period of time than adjuvant radiotherapy. Radiation therapy is also used to treat or prevent brain *metastasis*.

How Are Radiation Treatments Given?

Radiation treatments can be given externally or internally. *External beam radiation* is radiotherapy delivered from outside the body. *Brachytherapy* is radiation delivered from within the body. Currently, standard radiation treatments for lung cancer are delivered externally. Brachytherapy is an area of active lung cancer research.

Radiation oncologists are doctors who specialize in the use of radiotherapy to treat cancer. Planning is an important aspect of radiotherapy. A radiation oncologist decides the total dose of radiation you will receive and the treatment schedule. The total radiation dose is divided into smaller doses or *fractions* that are administered over a period of weeks. Fractionating the total radiation dose limits damage to healthy tissues without compromising treatment effectiveness. The total radiation dose and treatment schedule depend on:

- the size and location of the tumor(s)
- other treatments you are receiving
- the presence of distant metastasis
- your overall health

Fractionated radiation treatments are usually given five days per week with weekends off. The time off gives normal cells time to recover from radiation damage. Treatments continue for 2-7 weeks depending on the intent of the therapy. It is very important not to miss any scheduled treatments. Missed treatments decrease the total radiation dose delivered and can reduce overall treatment effectiveness.

Before your external radiation treatments begin, you will go through a process called *simulation*. Simulation allows doctors to precisely map the radiotherapy target area and limit

the exposure of healthy tissue to the radiation. The radiation target area is called the *treatment field* or *port*.

Radiotherapy for Brain Metastasis

Metastatic brain tumors are often treated with *whole brain radiation therapy* (WBRT). This external beam radiotherapy is used for people who have one or more metastatic brain tumors. WBRT is usually effective at relieving symptoms associated with these tumors.

Stereotactic radiosurgery (SRS) is another form of radiation treatment for metastatic brain tumors. SRS is generally used on people who have one small brain tumor (less than 3 cm or 1¼ inches). It can also be used on multiple tumors if they are small. SRS treatment requires immobilization of the head to prevent any movement during treatment. In some cases, this involves placing a metal halo called a skeletal fixation device on the head. The halo is fixed to the bones of the head. It is removed after treatment is completed. Some newer SRS systems use tiny metal markers placed in the bones of the head instead of a halo. The halo or markers allow doctors to precisely map the area of the brain to be treated.

SRS treatment directs high-energy radiation toward the tumor in a very accurate way that limits radiation damage to healthy brain tissue. Unlike WBRT that takes place over several weeks, SRS is performed in a single treatment. There are three forms of SRS: cobalt 60 or photon systems, linear accelerator systems, and particle beam or proton systems. Photon systems are widely available in specialized radiologic treatment centers. The most common SRS photon system is known by the brand name Gamma Knife®. Linear accelerator systems are also widely available and are often referred to by the abbreviation 'linac.' Brand names of linac systems include X-Knife®, CyberKnife®, and Clinac®. Proton systems are in limited use in the United States. The type of SRS equipment used does not appear to be related to treatment outcome.

Side Effects of Radiation Therapy

Side effects of radiation therapy are largely due to radiation damage of healthy tissues. Small fractional doses are usually associated with fewer and less severe late-occurring side effects

than larger doses are. Most side effects from radiotherapy are local, that is, they occur only in the treatment field. Common side effects of radiotherapy include:

- cough
- shortness of breath
- chest discomfort
- fatigue – usually begins the second or third week of treatment and often increases over time during treatment
- hair loss in the treatment field
- loss of appetite
- mouth problems – mouth sores, dry mouth, cavities in the teeth
- skin problems in the treatment field – redness, irritation, dryness, itching, skin darkening
- sore throat, hoarseness and/or difficulty swallowing (*esophagitis*)
- impaired mental functions (with whole brain radiation)

Skin is a rapidly dividing tissue, which makes it susceptible to radiotherapy. Skin in the treatment field often gradually becomes red or darkened, much like a sunburn or tan. The area may be sore, dry, and/or itchy. Washing with warm water, mild soap, and avoiding tight or itchy clothes will help keep the irritation under control. Talk with your radiation oncologist before using any lotions or creams as some can interfere with the delivery of radiation to the target area. Protect the treatment field with a hat or other clothing if you are going to be in the sun.

Radiation to the lungs is associated with short-term side effects and late complications that can develop after treatment is completed. Esophagitis is inflammation of the esophagus (the tube that takes food from the mouth to the stomach). Radiotherapy directed toward the center of the chest can damage the cells lining the esophagus. This causes sore throat, pain, and difficulty swallowing. A diet of liquids and soft foods can make eating easier during treatment. Pain medication may be needed. The lining of the esophagus usually heals within one month after treatment has been completed.

Radiation pneumonitis occurs in 2-9% of people who receive radiation therapy for lung cancer. It is the result of damage to the lining of the airways and air sacs. Women are slightly more prone to develop this complication than men are. Smoking increases the risk for both men and women. Radiation pneumonitis can occur anytime in the six months after completion of therapy but most commonly occurs 4-6 weeks after treatment completion. The symptoms of radiation pneumonitis are cough, low fever, shortness of breath, and/or pain with breathing. Contact your radiation oncologist immediately if you develop any of these symptoms. The steroid prednisone (Cortan®, Deltasone®) is commonly used to treat radiation pneumonitis. Azathioprine (Imuran®) and cyclosporine (Neoral®, Sandimmune®) are also used to treat this condition.

Radiation fibrosis may develop after radiation pneumonitis as the body tries to repair previously healthy lung tissue. Radiation fibrosis is lung tissue scarring that is the result of ongoing inflammation. Fibrosis develops gradually, usually over a period of 1-2 years after radiotherapy. Physical therapy and pulmonary rehabilitation can help prevent or alleviate the symptoms of radiation fibrosis.

Amifostine (Ethyol®) is being actively studied as a potential *radioprotectant*, a drug that protects healthy tissues from the damaging effects of radiotherapy without interfering with treatment effectiveness. Studies to date are encouraging especially with respect to esophagitis and radiation pneumonitis.[1,2] However, results are still preliminary and additional research is needed to define the potential role of amifostine.

Whole brain radiation therapy can cause impairments in thinking processes in long-term cancer survivors. The severity of these impairments vary and can include such things as slowed thinking, impaired short-term memory, difficulty retrieving words, decreased ability to perform math functions, and others.

Chapter 10: Supportive Care has additional information about other possible radio-therapy side effects and their management.

SURGERY FOR LUNG CANCER

When Is Surgery Used?

Surgery is a local treatment for lung cancer. It is used to attempt a cure or to alleviate symptoms. Lung cancer that has not spread can potentially be cured with surgery, which is often combined with chemotherapy and/or radiotherapy. An overview of chest surgeries used to treat lung cancer is presented in this section. Specific situations in which surgery is used are discussed in *Chapters 6* and *7*.

Studies have shown that greater experience with lung cancer treatment is associated with more successful surgical outcomes.[3-6] Surgical candidates are encouraged to find a thoracic surgeon who is experienced in lung cancer surgery. It is best to have your surgery at a hospital that also has experience caring for lung cancer surgery patients.

Surgical Chest Procedures

Lobectomy is the removal (*resection*) of the lobe of the lung affected by cancer. This is the most common surgery performed for lung cancer. *Pneumonectomy* is the surgical removal of the entire lung affected by cancer. This procedure is usually performed only if the cancer cannot be completely removed with a lobectomy. These two procedures are generally preferred over less extensive surgeries, if they can be tolerated by the patient. Preexisting lung problems such as *chronic obstructive pulmonary disease* (COPD) or *chronic bronchitis* may prevent use of these extensive lung surgeries.

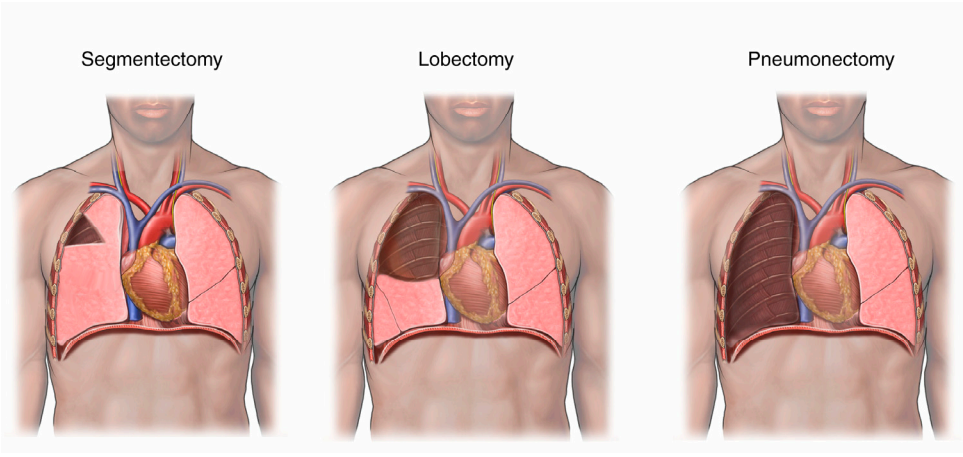

*Figure 2: Surgical Procedures Used to Treat Lung Cancer**

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A *wedge resection* is the removal of a wedge-shaped section of tissue surrounding the cancerous tumor. A wedge resection is performed on growths near the surface of the lung when a more extensive procedure cannot be tolerated. A *segmentecomy* or *bronchopulmonary segment resection* is another lung sparing operation that involves removal of only the section or segment of the lung lobe that contains the tumor. A *sleeve resection* is a procedure used to remove tumors in the main airways (the right and left main bronchus). The area with the tumor is removed and the ends on either side are sewn together to re-establish airflow.

All lung cancer operations include examination and removal of lymph nodes in the *mediastinum*. Removal of multiple lymph nodes in the area is called *mediastinal lymph node sampling*. Removal of nearly <u>all</u> the lymph nodes is called a *mediastinal lymph node dissection*.[7, 8] Neither of these procedures insures the removal of all cancer cells that may be present.

Surgical resection of lung cancer is usually performed using an open chest procedure called a *thoracotomy*. The chest cavity is opened, the ribs are separated, and the lungs are exposed. A thoracotomy is major surgery and usually requires a hospital stay of at least one week. *Video-assisted thoracoscopy* (VATS) is a less invasive procedure that can be used for some lung cancer resections. The procedure is performed through a rigid tube called a *thoracoscope*, which is inserted into the chest through one or more small incisions. A tiny video camera is also inserted into the chest through another small incision. Pictures of the chest cavity are projected onto a screen in the operating room to give the surgeon a better view of the area. VATS is performed under general anesthesia, but the chest cavity is not opened and the ribs are not separated. Early studies indicate VATS may cause less postoperative pain than thoracotomy.[9-12] Additional studies are needed to determine if VATS and thoracotomy are equally effective with respect to long-term outcomes.

A *thoracic surgeon* is a doctor who specializes in surgery of the chest. Lung surgery is complex. You are encouraged to seek a well-qualified thoracic surgeon if you are going to have surgical treatment for your lung cancer.

Surgical Side Effects and Possible Complications

All surgical procedures cause postoperative pain. The severity of the pain depends on the extent of the procedure, the surgical technique used to perform the operation, and your personal sensitivity to pain. Immediately after surgery, strong pain medicines are often needed. Morphine (MSIR, MS-Contin®, Roxanol®, Oramorph-SR®), oxycodone (Oxycontin®, Roxicodone®), hydromorphone (Dilaudid®, Hydrostat®), and fentanyl (Duragesic®, Fentanyl Oralet®, Sublimaze®, Innovar®) are examples of medicines that may be used. As the pain becomes less intense, less potent pain relievers are used such as codeine, hydrocodone (Vicodin®, Lortab®), dihydrocodeine (DHC), oxycodone (Percodan®, Percocet®, Tylox®, Roxiprin®), meperidine (Demerol®), and propoxyphene (Darvon®, Darvocet®). Eventually, you will be switched to a mild pain reliever such as acetaminophen (Tylenol®), ibuprofen (Advil®, Motrin®, Nuprin®), or naproxen (Naprosyn®) until your pain is gone. *Chapter 10: Supportive Care* has additional information on pain management.

Possible complications of chest surgery include:

- bleeding
- infection
- air leakage from the lung
- fluid accumulation in the lung (*pulmonary edema*)
- poor inflation of an area of the lung (*atelectasis*)

Your surgeon will manage these complications with appropriate therapy if they arise.

FUTURE DIRECTIONS IN LUNG CANCER THERAPY

Many dedicated researchers are exploring new ways to treat lung cancer. This section presents a brief overview of some promising new fields of discovery. All the treatments discussed in this section are currently experimental. Whether these techniques come into routine use depends on if they are found to be safe and effective in ongoing clinical trials. You may have access to some of these treatments in a clinical trial setting.

Talk with your cancer care provider if you are interested in participating in a clinical trial. See *Chapter 8* for information about participating in a clinical trial.

Radiation Therapy Research

Researchers are working on several new techniques to enhance the effectiveness of radiation therapy. Areas of active research are reviewed in the following pages.

Radiosensitizers

Radiosensitizers are substances that make cancer cells more susceptible to the effects of radiation. Some radiosensitizers being studied increase the oxygen level in cancer cells. A low level of oxygen in cancer tumors reduces the effectiveness of radiation therapy. Other radiosensitizers promote cell death by disabling DNA repair mechanisms. Additional mechanisms for enhancing the radiosensitivity of cancer cells are also being investigated.

Radioprotectants

The total dose of radiation used to treat cancer is often limited by damage to healthy tissues in the radiation treatment field. Radioprotectants are substances that protect healthy tissues from radiation damage without reducing its effectiveness on cancer cells. An effective radioprotectant would potentially permit an increase in the total radiation dose, which could enhance cancer control and/or elimination.

Treatment Schedule Variations

Radiation oncologists have known for quite some time that small doses of radiation given over a protracted time interval are more effective than larger doses given over a shorter period. Splitting a total radiation dose into smaller doses is called fractionation. Researchers are currently exploring the use of various *hyperfractionation* schedules in which people receive two or three separate radiation doses per day. If the individual doses are adjusted so that the total radiation dose is delivered in a shorter timeframe than would normally be

required, the treatment is referred to as *accelerated hyperfractionation*. Various hyperfractionated and accelerated hyperfractionated treatment schedules are currently under investigation for the treatment of lung cancer.

Brachytherapy

Brachytherapy is radiotherapy delivered from within the body. Brachytherapy is a well-established treatment for prostate cancer in men and cervical cancer in women. It can also be used to shrink lung tumors causing airway blockage. The process involves placing a small tube in the airway near the tumor and then inserting tiny radioactive pellets into the tube. The pellets are left in place for several hours before being removed. One or two treatments are usually sufficient to relieve the blockage. Researchers are studying the possibility of using brachytherapy along with external beam radiotherapy to enhance response to treatment. Investigators are also studying the effectiveness of *intraoperative brachytherapy*, which involves placing small radioactive pellets at specific sites in the chest during lung cancer surgery.

Chemotherapy Research

Several new chemotherapy drugs have been developed in recent years. These agents are being studied in clinical trials to determine the safest and most effective dosage, timing, and drug combinations.

Predicting Response to Therapy

Scientists can currently use a tissue sample from your cancer and test to determine if it is likely to respond to specific chemotherapy drugs. At present, this testing is experimental because the overall accuracy of testing and its effect on treatment outcomes have not been clearly established. However, easily accessible and reliable testing to predict the response of a specific cancer to specific drugs is being actively researched.

Inhaled Chemotherapy

Lung cancer arises from cells lining the airways of the lungs. This allows the opportunity for a unique form of delivering anticancer therapy by breathing the

agent into the airways. Resmycin® is an inhaled form of the chemotherapy drug doxorubicin that is currently in clinical trials. Researchers are also examining the inhaled administration of other anticancer agents.

Targeted Therapy

Most chemotherapy drugs act on any rapidly dividing cells, not just cancer cells. Targeted therapy is designed to act on unique characteristics, damage, or activities of cancer cells. These therapies are designed to act specifically on cancer cells while leaving normal cells unaffected. The development of targeted therapies requires defining the abnormalities of cancer cells, and then designing drugs that affect the targeted abnormalities. See Table 1 for examples of targeted therapy drugs for lung cancer in clinical trials at the time of this writing.

Table 1: Experimental Targeted Therapies for Lung Cancer

Generic Name	Trade Name	Target Activity
OSI-774, erlotinib	Tarceva®	anti-epidermal growth factor receptor (EGFR)
lonafarnib	Sarasar®	farnesyl transferase inhibitor
tipifarnib, R115777	n/a	farnesyl transferase inhibitor
imatinib	Gleevec®	tyrosine kinase inhibitor
ZD6474	n/a	VEGF receptor tyrosine kinase inhibitor
7-hydroxystaurosporine, UCN-01	n/a	G kinase inhibitor
suberoylanilide hydroxamic acid	n/a	histone deacetylase (HDAC) inhibitor
bortezomib	Velcade®	proteasome inhibitor

Antiangiogenic Compounds

As cancer cells multiply and grow, tumors must establish a blood supply to survive. The process of growing new blood vessels is called *angiogenesis*. Researchers have identified several substances that slow or inhibit the process of angiogenesis. These substances are called *antiangiogenic compounds*. Endostatin and angiostatin are two such compounds that have received extensive media attention. Many ongoing clinical trials are investigating the effectiveness of these and other antiangiogenic compounds in combination with standard forms of lung cancer treatment.

The drug thalidomide (Thalomid®) became famous in the 1950s when it was found to cause serious birth defects in the children of women who took the drug to control nausea and vomiting. In recent years, thalidomide has become a drug of interest to cancer researchers because of its antiangiogenic properties. Clinical trials with thalidomide and thalidomide-like compounds are currently underway.

Other antiangiogenesis compounds currently under investigation for lung cancer treatment include:

- 2-methoxyestradiol (2-ME)
- AE-941 (Neovastat®)
- carboxyamidotriazole (CAI)
- celecoxib (Celebrex®)
- combretastatin A4 phosphate
- squalamine

Matrix Metalloprotease Inhibitors

Matrix metalloproteases (MMPs) are a group of naturally occurring enzymes that help break down the structures between cells to make room for healthy new tissue. These enzymes are important in many normal body processes including new blood vessel development, tissue growth, and wound healing. MMPs are used by cancer cells to invade surrounding healthy tissue and spread to other parts of the body. MMPs may also contribute to the development of new blood vessels that allow tumors to grow.

Drugs that block the actions of MMPs are called *matrix metalloprotease inhibitors* (MMPIs). In recent years, several clinical trials involving MMPIs have been stopped before their completion because of toxic side effects. At the time of this writing, the only MMPI in clinical trials was BMS-275291. However, scientists continue to search for safe MMPIs that may help slow or arrest lung cancer growth.

Antineoplastons

Antineoplastons are small protein molecules (called peptides) that were first described by Dr. Stanislaw R. Burzynski in 1976. Dr. Burzynski reports that these peptides act to 'normalize' cancer cells. However, there have been no scientific studies to date to verify his claims. Recently, the National Cancer Institute funded clinical studies to determine if antineoplastons have a role in cancer therapy. Antineoplastons A10 and AS2-1 are currently being tested in lung cancer trials.

Immunotherapy and Biological Response Modifiers

The immune system plays a major role in the body's response to cancer. *Immunotherapy* is a broad term that refers to a variety of ways the immune system might be used to treat cancer. Some immunotherapy methods use substances called *biological response modifiers* (BRMs). BRMs can affect immune responses and other body functions. Cancer researchers are exploring the possibility that BRMs may be able to alter the body's response to cancer and prevent cancer metastasis.

Cytokines

Cytokines are naturally occurring proteins that act as messengers and regulators of the immune system. Interferon, interleukin, and tumor necrosis factor are cytokines that have anticancer activity. However, this effect is highly variable from one person to another and has only been seen with certain cancers. There are significant side effects associated with use of cytokine therapy. Use of these agents is currently experimental, but cytokine research continues.

Monoclonal Antibodies

Antibodies are proteins manufactured by immune cells. They attach to specific sites on cells thereby marking them for destruction by the immune system. Antibodies are very specific. Each antibody type will only interact with a specific attachment site much like a lock and key (see Figure 3).

The specific binding of antibodies makes them attractive for cancer therapy. If antibodies can be developed that bind to cancer cells but not normal cells, they would be ideal cancer therapy delivery vehicles. This concept led to the term 'magic bullets' to describe monoclonal antibody therapy.

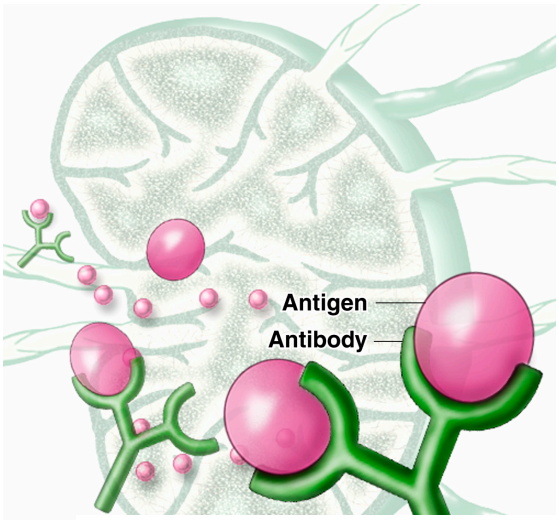

*Figure 3: Antigen-Antibody Binding**

A monoclonal antibody solution contains a huge number of identical copies of a single, specific antibody. The antibody is mass-produced using cloning technology. Trastuzumab (Herceptin®) is a monoclonal antibody approved by the Food and Drug Administration (FDA) for use in women with breast cancer. The binding site of trastuzumab (the HER2 receptor) is also found on cancer cells from other sites in the body including the lung, prostate, and colon. Clinical studies are currently underway to determine if Herceptin® can be used effectively with these other cancer types. Other monoclonal antibodies currently being investigated for the treatment of lung cancer include:

- bevacizumab, rhuMab-VEGF (Avastin®)
- cetuximab (Erbitux®)
- LCG-Mab (lung cancer gene monoclonal antibodies)
- BEC2 (Mitumomab®)
- TriGem®
- anti-anb3 integrin (Medi-522®)
- ABX-EGF

Immunotoxins

Immunotoxins are monoclonal antibodies that have a toxin (a cell destroying substance) attached to them. Two immunotoxins currently in lung cancer clinical trials are LMB-9 and SSI (dsFv)-PE38.

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Immunoconjugates

Immunoconjugates are monoclonal antibodies that have chemotherapy drugs attached to them. These substances are intended to deliver chemotherapy only to cancer cells while leaving healthy cells untouched. An example of an immunoconjugate currently in clinical trials is SGN-15, which delivers the chemotherapy drug doxorubicin.

Cancer Vaccines

A *vaccine* is a substance given to stimulate the immune system to act against a specific target. Scientists are studying several different vaccines that could eventually be used to treat lung cancer. Examples include:

- SRL172 (*Mycobacterium vaccae*)
- GVAX® and other autologous tumor cell vaccines (vaccines made from a sample of a person's tumor)
- p53 peptide vaccines

Chemoprevention

Chemoprevention is the use of specific substances to reverse, suppress, or prevent cancer. Lung cancer chemoprevention is being studied to find substances that will:

- prevent lung cancer in people at risk for the disease such as current and former smokers
- reverse pre-cancerous changes in the airways of people who have not yet developed lung cancer
- prevent recurrence in people who have been treated for lung cancer
- prevent second lung cancers in people who have been cured of lung cancer

Many potential chemopreventive substances are currently in various stages of testing (see Table 2). You should not begin taking any substance for chemoprevention without first discussing it with your doctor. Some substances have actually been found to increase lung cancer risk. Taking any substance without first consulting with your doctor could end up doing more harm than good.

Table 2: Substances With Lung Cancer Chemopreventive Potential

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
aspirin
ibuprofen
sulindac (Clinoril®)
celecoxib (Celebrex®)
rofecoxib (Vioxx®)
Retinoids and Carotenoids
9-cis-retinoic acid
13-cis-retinoic acid
N-4-hydroxyphenyl retinamide (4-HPR)
all-trans retinoic acid (ATRA)
bexarotene
TAC-101
6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437)
inhaled retinyl palmitate
Targeted Agents
farnesyl transferase inhibitors
ZD1839 (Iressa®), tyrosine kinase inhibitor
Nutritional Supplements
selenium
vitamins C, D, and E
N-acetylcysteine (NAC)
polyphenols
(from green and black teas)
curcumin
(from the spice turmeric)
allyl sulfur compounds
(as in garlic)
isothiocyanates
myoinositol
anethole dithiolethione (ADT, Sialor®)
4-methyl-5-pyrazinyl-3H-1, 2-dithiolw-3-thione (oltipraz)
terpenes (found in cherries and lavender)
limonene (found in citrus fruits, black pepper, and mangoes)

Cryoablation

Cryoablation is the use of very cold temperatures to kill cancerous tissue with little damage to surrounding healthy tissues. A small metal guide about the size of pencil lead is used to deliver argon gas to the target tissue. The gas kills the tissue by causing immediate freezing. This technique is FDA-approved for prostate cancer therapy and certain gynecological procedures. Investigators are studying the potential use of this technique to treat pre-cancerous and early lung cancer lesions. Cryoablation currently has no role in established lung cancer.

Gene Therapy

Lung cancer occurs when the genetic material of cells lining the airways is damaged. *Gene therapy* aims to interrupt the cancerous process by replacing lost or damaged genes, or blocking the expression of damaged genes. Replacement genes are inserted into cancer cells by genetically altered viruses that do not cause disease. The expression of damaged genes is blocked by substances that interfere with the processes that lead to production of proteins by cancer cells. Clinical trials are ongoing with the following:

- G3139, oblimersen (Genasense®)
- Angiozyme®
- RPR/INGN 201, Ad p53 (adenovirus p53)

Radiofrequency Ablation

Radiofrequency ablation is a technique involving placement of a small wire or electrode into a target tissue and transmitting radio waves to destroy the cells in the area around the electrode. This technique is commonly used to treat some types of abnormal heart rhythms. Researchers are exploring the use of this process to control lung cancer.

MAKING TREATMENT DECISIONS

Treatment decisions for people with lung cancer are complex. There is no such thing as a standard treatment that is suitable or advisable for every person with a specific type and stage of lung cancer. It is often said that the practice of medicine is both a science and an art. The best of the science of lung cancer treatment as we know it today is presented in *Chapter 6: Treatment of Small Cell Lung Cancer* and *Chapter 7: Treatment of Non-Small Cell Lung Cancer*. These chapters present treatment guidelines and recommendations based on clinical trial data. However, a guideline recommendation should not be interpreted to mean that the recommended treatment is the best possible option for everyone. Each person with lung cancer is different. The disease manifests itself differently in each person. Each person's underlying circumstances are also unique. Therefore, lung cancer treatment must be individualized to meet the specific needs and circumstances of each person on a case-by-case

basis. This is where the art of medicine comes into play along with trust in your care providers.

The treatment guidelines presented in *Chapters 6* and *7* should be used as a framework to help you know what questions to ask when you are discussing treatment options with your cancer care providers. The guidelines should not be considered treatment recommendations. Only your cancer care providers, who have access to your medical history and are aware of all the specifics of your case, can make treatment recommendations. Ultimately, the decision about what treatment options you want to pursue is up to you. The information presented in this book is here to provide you with background information to assist you with the decision making process, not to tell you what to choose.

SUMMARY

Lung cancer is treated with various forms of surgery, chemotherapy, and radiation therapy. Surgery and radiation therapy are local treatments used to treat cancer in specific areas of the body. Chemotherapy is a systemic treatment, a therapy used to treat cancer cells throughout the body. Lung cancer treatment usually involves a combination of different therapies. The treatment options for your cancer will depend on the type of cancer you have, the spread of the disease, other illnesses you have, your overall health, and your personal preferences.

Members of your cancer care team will advise you about the possible advantages and risks associated with each of your treatment options. Teamwork among your health care providers is a cornerstone of quality care for lung cancer. You are encouraged to seek the advice of qualified lung cancer specialists with whom you feel comfortable and who are willing to work with the other members of your cancer care team. Evaluate your treatment options in terms of what therapies best match your treatment goals. While others can provide you with expert advice, all treatment choices are ultimately up to you.