CHAPTER 7: TREATMENT FOR NON-SMALL CELL LUNG CANCER

INTRODUCTION

This chapter provides an overview of treatment for non-small cell lung cancer (NSCLC). Treatment options are discussed according to the spread of the disease. As you read this chapter, keep in mind that each person’s treatment plan is unique to his or her situation. Information is provided to help you discuss treatment options with your cancer care team. However, treatment recommendations are not given. Many factors unique to your situation must be taken into account to make these crucial decisions. Only your cancer care team can make treatment recommendations.

Ongoing clinical trials are evaluating how best to treat NSCLC. This chapter presents current treatment standards at the time of its writing. However, state of the art lung cancer care is constantly evolving. Ask your cancer care team about new treatment options and clinical trials you may want to consider. You may want to seek the advice of more than one expert before deciding on a treatment plan.

Surgery, chemotherapy, and radiation treatments are used to treat NSCLC. A medical oncologist is an expert in the chemotherapeutic treatment of cancer. A radiation oncologist is the professional to consult about radiotherapy. Surgical candidates should consult a thoracic surgeon, a surgeon who specializes in chest surgery.

Your cancer care team will provide you with information about your treatment options, but all treatment decisions are ultimately up to you. No one is more qualified than you are to make decisions about what options best suit your goals and preferences. Seek information and expert advice, and then decide what is best for you.
OVERVIEW OF NON-SMALL CELL LUNG CANCER

Lung cancer arises from abnormal *epithelial cells* in the airways of the lungs. Epithelial cells cover all free surfaces in the body including the airways. Lung cancer is divided into two main types based on how it looks under the microscope: small cell lung cancer (SCLC) and non-small cell lung cancer. In the United States, approximately 80% of lung cancers are NSCLC and 20% are SCLC. SCLC and NSCLC have different patterns of growth and spread. They are also treated differently. In 1999, the World Health Organization (WHO) and the International Association for the Study of Lung Cancer (IASLC) updated their classification system for lung tumors. The information presented in this chapter uses the terminology of the 1999 WHO/IASLC classification system.¹

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

**Adenocarcinoma**

Adenocarcinoma cells have a glandular appearance (see Figure 1). The majority of these tumors produce a thick fluid called *mucin.*

*Figure 1: Microscopic View of Adenocarcinoma*

The incidence of adenocarcinoma has increased over the past three decades. Scientists are not certain why this has occurred but influences may include changes in smoking habits, dietary patterns, and environmental and occupational factors.

Characteristics of adenocarcinoma include:

- Adenocarcinoma accounts for approximately 40% of all lung cancers in the United States and approximately 55% of NSCLCs.

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Variants of adenocarcinoma include acinar adenocarcinoma, papillary adenocarcinoma, bronchioloalveolar adenocarcinoma, and other mixed subtypes.

- Adenocarcinoma is the most common form of lung cancer in women and people who have never smoked. This form of lung cancer is also the most common type seen in people less than age 50.
- Adenocarcinomas are the most common form of lung cancer associated with scarring of the lung tissue.
- Adenocarcinomas most often occur in the outer regions of the lungs.
- A subtype of adenocarcinoma called bronchioloalveolar adenocarcinoma (BAC) arises in the alveoli (the air sacs of the lung). BAC tends to be slow growing and appears less likely to metastasize than other forms of NSCLC. For this reason, BAC has a more favorable prognosis than other forms of NSCLC.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is also known as epidermoid carcinoma. This form of NSCLC has decreased in frequency over the past three decades but is still the most common form of lung cancer among men who are current or former smokers. Squamous cells are large, flat cells (see Figure 2).

These tumors often produce a substance called keratin, which is seen under the micro-scope. Characteristics of SCC include:

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

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SCC tumors often invade neighboring structures.

- SCC rarely occurs in people who have never smoked.

**Large Cell Carcinoma**

The cells of large cell carcinoma (LCC) are the largest of the various types of NSCLC. The cells are generally highly undifferentiated or immature in appearance (see Figure 3).

Some experts believe these tumors represent adenocarcinomas or squamous cell carcinomas that are so undifferentiated as to be unrecognizable. Characteristics of large cell carcinoma include:

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

See *Chapter 3: Lung Cancer Overview* for additional information about lung cancer development, growth, and spread.

**OVERVIEW OF NON-SMALL CELL LUNG CANCER STAGING**

Accurate staging of NSCLC is critical because treatment options depend on the spread of the disease. 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 and what the course of your illness (your prognosis) is likely to be. Lung cancer stage is the primary factor that influences prognosis.

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Lung cancer stages are based on three factors. These factors are expressed using the TNM classification system. The three factors of the TNM system are:

- **T**: tumor characteristics including size, location, and local invasion
- **N**: regional lymph node involvement
- **M**: metastasis status

Non-small cell lung cancer is divided into four stages using the TNM classification system. 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. The distribution of stage at diagnosis for people with NSCLC is:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>13-24%</td>
</tr>
<tr>
<td>Stage II</td>
<td>5-10%</td>
</tr>
<tr>
<td>Stage III</td>
<td>31-44%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>32-39%</td>
</tr>
</tbody>
</table>

**Non-Small Cell Lung Cancer Stages**

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

**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 (see Figure 4). In stage IIA, the tumor is a T1 (3 cm or less). In 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. However, the chance of recurrence is higher than for people with stage I disease.

![Figure 4: Regional Lymph Nodes of the Lungs Used to Determine Stage*](image)

**Stage III**

Stage III is the most complex of the NSCLC stages. There are significant differences in the treatment of stage IIIA versus 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). The term ipsilateral refers to structures on the same side of the chest as the primary tumor (see Figure 4). Smaller tumors that involve the ipsilateral mediastinal lymph nodes are also stage IIIA (T1N2M0 or T2N2M0). Stage IIIA is potentially operable disease. Preoperative treatment is used for some people and is currently under evaluation in clinical trials.

Stage IIIB disease includes any size tumor that has invaded any of the vital structures of the mediastinum, the carina, or a bone of the spine (T4 tumors), with or without regional lymph node involvement (T4N0M0, T4N1M0, T4N3M0). Smaller tumors (T1-3) associated with contralateral lymph node involvement or supraclavicular lymph node involvement are also stage IIIB. The term contralateral refers to structures on the opposite side of the chest as the primary tumor. A separate tumor nodule in the same lobe of the lung as the primary tumor

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is called a satellite lesion. This is stage IIIB disease regardless of the size of the primary tumor. If there is a second tumor in a different lobe from the primary tumor, this is stage IV disease.

A unique form of stage IIIB disease involves a lung tumor and the presence of cancer cells in pleural fluid (malignant pleural effusion), but no evidence of metastatic disease. This situation is often referred to as ‘wet IIIB’ disease. It is treated the same way as stage IV disease. Most clinical trials involving people with stage IV disease also include patients with wet IIIB disease.

People with stage IIIB disease are generally not candidates for surgical cure because it is usually not possible to remove all the cancerous tissue with this degree of spread. People with T4N0 tumors are sometimes an exception to this general rule. A thoracic surgeon should thoroughly evaluate anyone with T4N0 disease to determine if surgical removal of the cancer is possible.

Stage IV
Stage IV NSCLC is assigned whenever there is distant metastasis, that is, spread of the disease beyond the regional lymph nodes.

Special Cases
Stage 0 (zero) represents carcinoma in situ. This unique situation refers to the presence of a local area of cancer cells that 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 recommended screening for lung cancer, the percentage of people 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 tests or with direct examination using a bronchoscope. The TNM designation for occult lung cancer is Tx.
Most people with lung cancer wonder about their prognosis. The spread of disease at diagnosis is clearly linked to prognosis. 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 alive one year after diagnosis. Two-year survival is the percentage of people alive two years after diagnosis or beginning a specific treatment. Five-year survival is the standard marker for cure. People alive and cancer-free five years after diagnosis 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. Table 1 shows one and five-year survival rates for NSCLC by stage at diagnosis.

<table>
<thead>
<tr>
<th>NSCLC Stage</th>
<th>One-Year Survival</th>
<th>Five-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>up to 90%</td>
<td>61-67%</td>
</tr>
<tr>
<td>IB</td>
<td>72-94%</td>
<td>38-57%</td>
</tr>
<tr>
<td>IIA</td>
<td>84-88%</td>
<td>37-55%</td>
</tr>
<tr>
<td>IIB</td>
<td>60-77%</td>
<td>24-39%</td>
</tr>
<tr>
<td>IIIA</td>
<td>52-64%</td>
<td>13-23%</td>
</tr>
<tr>
<td>IIIB</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>IV</td>
<td>17%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Survival statistics for lung cancer can be discouraging. Remember, no one can predict the outcome of your disease. Keep in mind, there are survivors! You may well be one of them.

**BEFORE TREATMENT**

**Pretreatment Evaluation**

A diagnosis of NSCLC is based on the results of a tissue sample (biopsy) of your tumor. After diagnosis, you will undergo a series of tests called the *initial work-up* or evaluation. The
National Comprehensive Cancer Network treatment guidelines for NSCLC\(^5\) recommend the following tests and procedures for the initial NSCLC work-up:

- medical history and complete physical examination
- chest x-ray
- CT scan of the chest, *abdomen* (belly), and adrenal glands
- blood tests including *red blood cell* count, white blood cell count, platelet count, liver tests, and kidney function tests

Your health care providers will determine a *presumptive stage* of your disease based on the initial work-up. At this point, the stage of your disease is presumptive because additional tests may show the actual stage is different from what it appears to be based on the initial work-up.

Depending on the presumptive stage of your disease after initial work-up, you may need additional pretreatment tests.

**Additional Work-Up for Presumptive Stage I and IIA**

People with presumptive stage I or IIA NSCLC are often advised to undergo a bronchoscopy and/or *mediastinoscopy*. Alternatively, if the CT scan is normal or shows suspicious lymph nodes that can clearly be removed at surgery, the doctor may recommend surgical removal of the cancer and a complete evaluation of the mediastinal lymph nodes at the time of surgery.

Bronchoscopy involves putting a small, flexible tube called a bronchoscope into the large airways of the lungs. The bronchoscope allows the doctor to see inside the airways and take tissue samples. A bronchoscopy is recommended for people with presumptive stage I and IIA disease to check for cancer in the regional lymph nodes, central airways, and other areas of the lungs.

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 just above the breastbone into the central area of the chest (the mediastinum). This procedure is
performed in presumptive stage I or IIA NSCLC to sample the mediastinal lymph nodes. In some cases, mediastinal nodes can be sampled using a needle inserted through the esophagus instead of performing a mediastinoscopy. Ultrasound is used to guide this sampling process. Disease that has spread to the mediastinal nodes will be re-categorized as stage III.

Positron emission tomography (PET) scanning is another staging tool sometimes used in people with NSCLC. Results from early studies indicate PET scans may be useful for non-invasive staging of the mediastinal lymph nodes. The National Comprehensive Cancer Network NSCLC practice guidelines state PET scans are optional as part of the pretreatment evaluation of people with stage I and IIA disease. The guidelines further state positive PET scan findings should usually be confirmed by tissue sampling or another radiologic test. The American College of Chest Physicians guidelines recommend PET scans to evaluate the mediastinal lymph nodes of all people who are surgical candidates.

Additional Work-Up for Presumptive Stage IIB and IIIA
People with presumptive stage IIB or IIIA NSCLC are advised to undergo a bronchoscopy and mediastinoscopy to check for additional tumors and/or mediastinal lymph node spread. The risk of distant spread is higher with these stages than it is with lower stages. Therefore, a magnetic resonance imaging (MRI) scan of the brain and a bone scan are recommended to check for unsuspected metastasis. The American College of Chest Physicians and the National Comprehensive Cancer Network guidelines both recommend PET scans as part of the pretreatment evaluation for people with stage IIB and IIIA NSCLC.

Treatment Preparations
Researchers have found a person’s performance status affects his or her NSCLC prognosis. Performance status is a measure of how well a person is able to perform ordinary tasks and carry out daily activities. Oncologists use very specific criteria to gauge your overall health and performance status. The ECOG and Karnofsky scales are commonly used to gauge performance status (see Tables 2 and 3). As you prepare for treatment, you may want to assess your lifestyle and health habits. Does your lifestyle enhance your overall health?
Table 2: ECOG Performance Status Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG Performance Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
</tbody>
</table>

Table 3: Karnofsky Performance Status Scale*  

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal health</td>
<td>100%</td>
</tr>
<tr>
<td>Minor symptoms</td>
<td>90%</td>
</tr>
<tr>
<td>Normal activity with some effort</td>
<td>80%</td>
</tr>
<tr>
<td>Unable to carry on normal activity but able to care for oneself</td>
<td>70%</td>
</tr>
<tr>
<td>Requires occasional help with personal needs</td>
<td>60%</td>
</tr>
<tr>
<td>Disabled</td>
<td>50%</td>
</tr>
<tr>
<td>Requires considerable assistance and medical care</td>
<td>40%</td>
</tr>
<tr>
<td>Severely disabled, in hospital</td>
<td>30%</td>
</tr>
<tr>
<td>Very sick, active support needed</td>
<td>20%</td>
</tr>
<tr>
<td>Moribund</td>
<td>10%</td>
</tr>
</tbody>
</table>

*originally developed by Drs. David Karnofsky and Joseph Burchenal

If you are a smoker, it is best to stop smoking. Some people believe that once they have been diagnosed with lung cancer, it does not matter if they continue to smoke. This is not true. A recent study showed current smoking was associated with a less favorable prognosis among people who underwent surgery for NSCLC.13 Most thoracic surgeons strongly encourage people to stop smoking before surgery because smoking increases the risk of complications. Smoking can worsen many symptoms of lung cancer and its treatment including mouth sores, shortness of breath, and peripheral neuropathy.

Smoking damages your health. Stopping smoking will greatly enhance your overall health. Smoking cessation is difficult because nicotine addiction is very powerful. Talk with your
cancer care providers about smoking cessation programs, nicotine replacement therapy, and use of the drug bupropion (Zyban®) to help you successfully stop smoking.

Lung cancer treatment is hard on the body. You need to take in enough calories to meet the energy demands treatment places on your body. Talk with your doctor if you are losing weight or are having problems with your appetite. He or she may suggest a consultation with a nutritionist or dietician before beginning treatment. He or she can advise you about the number of calories you need and give you tips to ensure you are getting adequate nutrition.

Exercise is another important factor in your overall health. Continue your current program if you already exercise regularly. You may need to modify your routine if the energy demands of treatment cause fatigue. If you are not currently exercising, talk with your health care providers about beginning a gentle exercise program. All forms of exercise are helpful and there are many choices. Anything that gets you up and moving is exercise including walking, biking, gardening, golfing, dancing, yoga, swimming, and many other activities. Be sure to discuss your exercise program with your health care providers to ensure it is safe for you.

Urgent dental work should be performed before beginning treatment. Mouth sores and problems with the teeth are common side effects of chemotherapy and some forms of radiation therapy. Healthy gums and teeth help prevent or reduce the severity of these problems.

When To Begin Treatment
Lung cancer grows for many years before it is large enough to be detected. Once you have been diagnosed, you may be anxious to begin treatment right away. However, unless your doctor tells you otherwise, you may benefit from taking a few days to organize your thoughts and make plans before starting treatment. You may want to use the time to arrange time off from your job, plan for household help, or collect information about your disease. Planning can help reduce your stress, which can make it easier to cope with the challenges of
treatment. You may want some quiet time with loved ones and friends to gather your physical and emotional strength before treatment begins.

While taking a few days to gather your thoughts and make plans can be beneficial before beginning treatment, lengthy delays should be avoided. Long delays could lead to tumor growth and/or spread of disease, lessening your chance for a cure.

I had six days to think about my surgery. I met and talked with a lot of professional people in that time period. So, by the date of the surgery, I felt that [it] was my best option.
– Sandra, diagnosed with stage II NSCLC in 1998 at age 53

Talk with your cancer care providers about any symptoms you are experiencing. Initiating treatment of disease-related symptoms before therapy begins can make cancer treatments easier to tolerate. Supportive care treatments can begin while you and your cancer care team are developing your treatment strategy.

It is your choice what treatments you want to receive. Discuss the purpose, potential side effects, and expected results of each treatment option with your cancer care team. Use your cancer care providers as consultants to aid you in making decisions. Alternatively, you may decide to give your primary cancer doctor permission to choose the treatment he or she believes is the best option for you. This is as valid a decision as any other you might make. You are the most qualified person to decide how to manage your cancer care.

**TREATMENT FOR NON-SMALL CELL LUNG CANCER**

Deciding on the appropriate treatment for NSCLC is a complex, multi-step process. Treatment options depend on the stage of disease and other factors. There are eight categories of NSCLC stages, and 18 different TNM classifications of these stages. Table 4 shows the TNM classes included in each of the lung cancer stages.
Table 4: TNM Classifications in the Four Stages of NSCLC

<table>
<thead>
<tr>
<th>NSCLC Stage</th>
<th>TNM Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>TisN0M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1M0 T3N0M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3N1M0 T1N2M0 T2N2M0 T3N2M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4N0M0 T4N1M0 T4N2M0 T1N3M0 T2N3M0 T3N3M0 T4N3M0</td>
</tr>
<tr>
<td>IV</td>
<td>anyT any N M1</td>
</tr>
</tbody>
</table>

Factors other than the T, N, and M characteristics of the disease that are taken into consideration when deciding on treatment options include:

- the number of lymph nodes with cancer cells present in them
- the presence or absence of tumor cells in the edges of surgical specimens
- performance status
- coexisting illnesses, especially pre-existing lung diseases

Clearly, decision making in NSCLC can get quite complex. It is not possible to present all the potential combinations of factors that lead to specific treatment recommendations. Each person’s situation is unique. Only qualified cancer care professionals, who have access to your medical records and test results, are able to make treatment recommendations. The overview of NSCLC treatment presented in this section provides you with general treatment concepts. Use these concepts as points of discussion when talking with your cancer care providers about treatment options. As you read the treatment overviews, keep in mind there are exceptions and other considerations that may lead your doctor to make recommendations that differ from what you read here.
The American Cancer Society and The National Comprehensive Cancer Network (NCCN) have collaborated to produce Lung Cancer Treatment Guidelines for Patients. This document presents the NCCN lung cancer treatment guidelines that were originally written for cancer care providers in easy-to-understand language for patients. Consult these guidelines if you have questions about your treatment options. The guidelines can be downloaded free of charge from the American Cancer Society (ACS) Internet site at www.cancer.org/docroot/ETO/ETO_10.asp. You can also obtain the guidelines by calling the American Cancer Society toll-free at 800-ACS-2345. The NCCN Internet site has an interactive version of these guidelines. The interactive format will take you through a treatment decision-tree based on your stage of disease and other specific circumstances. The NCCN/ACS interactive lung cancer guidelines are available at www.nccn.org/patient_gls/_english/_lung/index.htm.

Stage 0 (Carcinoma in Situ)
Carcinoma in situ is cancer confined to a small area of the lung that has not grown through the lining of the airway. This is stage 0 disease (TisN0M0). Stage 0 disease is uncommon.

The standard treatment for stage 0 NSCLC is surgical removal of the cancer. A limited procedure such as a wedge resection or segmentectomy is usually performed. If the lesion occurs in a lobar bronchus (the main airway of a lung lobe), a lobectomy is considered the standard of care. Photodynamic therapy is being studied as an alternative to surgery for stage 0 disease.\textsuperscript{15,16} At this time, it is an option for people who do not want surgery or cannot tolerate surgery for medical reasons. The long-term effectiveness of photodynamic therapy compared to surgery has yet to be determined. Electrocautery, cryoablation, and brachytherapy are being investigated as other non-surgical treatment options for stage 0 disease.\textsuperscript{17-20}

Stage IA (T1N0M0), IB (T2N0M0), and IIA (T1N1M0) NSCLC
Surgical removal of the cancer is usually recommended for people who have had a bronchoscopy and a mediastinoscopy without evidence of spread to the mediastinal lymph nodes. A lobectomy (removal of the affected lobe of the lung) or pneumonectomy (removal of the entire affected lung) are the preferred procedures.\textsuperscript{21-23} You may not be able to tolerate these extensive procedures if you have pre-existing lung disease such as chronic obstructive pulmonary
disease (COPD) or chronic bronchitis. In such circumstances, a less extensive procedure may be chosen such as a wedge resection, segmentectomy, or sleeve resection. The surgeon will thoroughly examine the primary tumor and lymph nodes in the chest during surgery. Lymph nodes can be sampled more thoroughly during surgery than during a mediastinoscopy. The American College of Chest Physicians guidelines state all patients undergoing surgical resection for stage I or II NSCLC should have an intraoperative mediastinal lymph node evaluation. Some surgeons prefer to do a complete mediastinal lymph node dissection while others prefer systematic sampling of the lymph nodes.

If unexpected, suspicious lymph nodes are found during surgery, they can be sampled and sent to the laboratory to check for cancer cells while you are still in the operating room. The results from the samples will be reported back to the surgeon. In cases where the surgeon finds cancer in the mediastinal nodes that can be surgically removed, he or she will proceed with removal of the cancer along with a mediastinal lymph node dissection. If unsuspected cancer is found that cannot be completely removed, the surgical resection may be abandoned.

<table>
<thead>
<tr>
<th>exploratory surgery and resection (if possible)</th>
</tr>
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<tbody>
<tr>
<td>↓</td>
</tr>
<tr>
<td>no cancer in surgical margins</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>no additional treatment          or</td>
</tr>
<tr>
<td>radiotherapy ± chemotherapy*            or</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>cancer cells in surgical margins</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>additional surgery</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>radiotherapy ± chemotherapy*</td>
</tr>
</tbody>
</table>

* Chemotherapy is not routinely recommended by the American College of Chest Physicians.

The piece of lung removed during surgery will be sent to the laboratory. The edges of the removed tissue (the surgical margins) will be examined under a microscope to be sure there are no cancer cells present. Additional therapy is generally not needed if there is no evidence of cancer in the surgical margins. If cancer cells are found in the surgical margins, the National Comprehensive Cancer Network guidelines recommend either another surgery to remove more lung tissue or radiotherapy with or without chemotherapy to treat the remaining cancer cells.
Radiation therapy is usually the recommended for people are unable to tolerate surgery or choose not to have surgery.\textsuperscript{24}

\textbf{Stage IIB (T3N0M0) and IIIA (T3N1M0) NSCLC}

Stage IIB and IIIA tumors are more extensive than stage I and IIA tumors. They may have spread to lymph nodes near the tumor within the lung, and/or invaded the chest wall or other structures near the lungs such as the ribs, diaphragm, or the covering of the mediastinum. The greater extent of disease increases the likelihood that the cancer may have spread beyond the chest. The National Comprehensive Cancer Network and American College of Chest Physicians guidelines both recommend pretreatment PET scans for stage IIB and IIIA disease.\textsuperscript{5,9} The National Comprehensive Cancer Network guidelines also recommend an MRI of the brain and a bone scan for people who have these presumptive stages of disease.\textsuperscript{5}

If the MRI and bone scan show no evidence of distant spread and your surgeon decides he or she can probably remove the tumor, exploratory surgery is usually recommended (see Treatment Pathway 1). Lymph nodes will be thoroughly examined and sampled during surgery. If there are no unexpected findings during surgery, the cancer will be removed.

Complete resection may be the full extent of your treatment. In specific circumstances, radiation therapy with or without chemotherapy may be recommended after surgery if there is any suspicion residual cancer cells may have been left behind during surgery.

\begin{center}
\textbf{Treatment Pathway 1}
\end{center}

\textbf{surgery} \downarrow \downarrow
\textbf{no cancer in surgical margins} \downarrow \downarrow
\textbf{cancer cells in surgical margins}
\textbf{no additional treatment} \downarrow \downarrow
\textbf{additional surgery}
\textbf{or radiotherapy} \pm \textbf{chemotherapy} \textbf{or radiotherapy} \pm \textbf{chemotherapy}

If the location or spread of your tumor make it unresectable, your cancer care providers may recommend initial treatment using radiotherapy with or without chemotherapy (see
Treatment Pathway 2). After initial treatment, the tumor may become resectable. Your oncologist and surgeon will determine if this is possible. If surgical removal is not possible, additional chemotherapy and/or radiotherapy may be recommended depending on your initial treatment.

**Treatment Pathway 2**

radiotherapy + chemotherapy

↓

surgery

no surgery; cancer cannot be resected

↓

no additional treatment or additional radiotherapy + chemotherapy

The treatment of stage IIB and IIIA NSCLC is being studied by many investigators. Many unanswered questions remain about what therapeutic protocols constitute the most effective treatment for these stages of disease. A clinical trial may represent an opportunity to take advantage of the latest research and treatments if participating in a clinical trial is of interest to you. Talk your options over carefully with the members of your cancer care team.

**Stage IIIA NSCLC (T1N2M0, T2N2M0, T3N2M0)**

The three TNM classifications in this treatment group have in common N2 lymph node involvement. This means the mediastinal lymph nodes on the same side of the chest as the original tumor have cancer cells in them. People with this presumptive stage of disease are advised to have a bronchoscopy, mediastinoscopy, or another procedure to permit sampling of the mediastinal lymph nodes. Cancer cells found in contralateral lymph nodes or in nodes above the collarbone (supraclavicular nodes) lead to reclassification as stage IIIB. An MRI scan of the brain, a bone scan, and a PET scan are recommended to check for distant metastasis. If distant metastasis is found, the disease is reclassified as stage IV.

Exploratory surgery may be indicated for some people to check more thoroughly for lymph node involvement. If lymph node involvement is limited and the surgeon is able to remove all visible cancer, a resection will be performed. Radiotherapy with or without chemotherapy is recommended in the National Comprehensive Cancer Network guidelines for people with stage IIIA disease after recovery from primary surgery (see Treatment Pathway 1).
However, your doctor will evaluate your specific circumstances before making a recommendation.

In some cases, chemotherapy with or without radiotherapy is the initial treatment for stage IIIA disease (see Treatment Pathway 2). If the cancer responds to these treatments, surgical resection may then be performed. Surgery may be followed with additional chemotherapy and/or radiation therapy.

**Treatment Pathway 1**

- surgery
- radiotherapy ± chemotherapy†

**Treatment Pathway 2**

- chemotherapy ± radiotherapy
- cancer responds
- cancer does not respond
- surgery and completion of radiotherapy
- completion of radiotherapy + chemotherapy
- ± chemotherapy†

†Chemotherapy is not routinely recommended according to the American College of Chest Physicians Lung Cancer Diagnosis and Management Guidelines.25

The American College of Chest Physicians guidelines state platinum-based chemotherapy should be used in addition to radiotherapy for people with stage IIIA NSCLC who have good performance status but are not surgical candidates.25

**Stage IIIB NSCLC (T4N0M0, T4N1M0, T4N2M0)**

These are unique TNM classifications of stage IIIB NSCLC. The tumor is large and has invaded nearby structures but has no or limited spread to the regional lymph nodes. Bronchoscopy, mediastinoscopy, MRI of the brain, a bone scan, and a PET scan are recommended to check for more extensive regional lymph node spread and distant metastasis.
tumor is resectable (some T4N0 or N1)  ⇒  Treatment Pathway 1 or 2

tumor is not resectable (T4N2)  ⇒  radiotherapy ± chemotherapy‡

‡Combined radiotherapy and chemotherapy is considered the standard of care by the American College of Chest Physicians for people with unresectable stage IIIB NSCLC who have good performance status and minimal weight loss.21

After testing, people with apparent T4N0 or T4N1 disease are likely to be referred to a thoracic surgeon to evaluate whether the cancer can be completely resected. However, the surgical treatment of people with T4N1 disease is controversial and must be decided on a case-by-case basis. Those with T4N1 disease who do undergo surgery are often given induction therapy to shrink the tumor before surgery.

In cases where the cancer is judged resectable, surgery may be performed as initial treatment. Surgery is usually followed by radiotherapy with or without chemotherapy (see Treatment Pathway 1). However, in most cases, chemotherapy with or without radiation therapy is recommended before surgery. Surgery is usually followed with radiotherapy if it has not already been given (see Treatment Pathway 2).

Unresectable tumors (T4N2) are usually treated using radiotherapy with or without chemotherapy. In some cases, unresectable disease may become resectable following chemotherapy and/or radiotherapy. A percentage of people who undergo surgical resection in these circumstances achieve long-term survival. It is not currently known whether surgical resection in this situation offers improved survival.

### Treatment Pathway 1

- surgery
  - radiotherapy ± chemotherapy

### Treatment Pathway 2

- chemotherapy ± radiotherapy
  - surgery
    - radiotherapy (if not already given)
**Stage IIIB NSCLC (T1N3M0, T2N3M0, T3N3M0, T4N3M0)**
These TNM classifications of stage IIIB disease all have N3 lymph node involvement. This means the disease has spread to the contralateral lymph nodes (those on the opposite side of the chest from the original tumor). This degree of spread is not treatable with surgery because the cancer cannot be completely removed. Bronchoscopy, mediastinoscopy, MRI of the brain, a bone scan, and a PET scan are recommended to check for correct staging and distant metastasis. Recommended treatment for these classifications of IIIB disease is chemotherapy and radiotherapy. Recent studies suggest giving chemotherapy and radiotherapy at the same time (*concurrently*) may be slightly more effective than giving one treatment followed by the other. However, the differences appear to be small, and there is greater toxicity when chemotherapy and radiation are given concurrently rather than in succession. Discuss the relative risks and benefits of concurrent treatment with your oncologist.

**Stage IV NSCLC**
NSCLC is categorized as stage IV if there is evidence of distant metastasis. With rare exceptions, stage IV disease is generally incurable. Treatment for stage IV disease is primarily palliative and supportive. Treatments are used to prolong life, improve *quality of life*, and relieve symptoms. Studies have shown that people with good performance status at the time of diagnosis have a more favorable prognosis than those with poor performance status. It is up to you how aggressive you want your treatment to be.

Chemotherapy is the primary treatment for advanced NSCLC. Chemotherapy options are reviewed in the following section. Radiation therapy is commonly used for symptom relief. *Chapter 10: Supportive Care* has information about treatments for many of the symptoms associated with advanced NSCLC.

A small percentage of people with stage IV NSCLC have a single brain tumor as the only site of metastasis. In this situation, the American College of Chest Physicians recommends aggressive treatment of both the primary lung tumor and the brain tumor because this is potentially curable disease. A thorough search for other sites of metastasis should be undertaken. This often includes bronchoscopy or mediastinoscopy, a bone scan, and a PET scan.
scan. However, the work-up for each person is individualized. If there is no evidence of other sites of disease, a complete resection of the lung tumor may be recommended. Surgery may be combined with radiotherapy and/or chemotherapy. The brain tumor may be treated surgically or with stereotactic radiosurgery. See Chapter 5: Lung Cancer Treatment Overview for additional information about the treatment of brain metastasis. The five-year survival for people in this unique group of stage IV NSCLC who are aggressively treated is 16-30\%.32

Similarly, a single adrenal gland tumor with a primary lung tumor and no other metastatic disease may be treated aggressively with curative intent. Complete surgical resection of both the adrenal and lung tumors is associated with a five-year survival of 10-23\%, although this treatment has been attempted in only a small number of patients.32-34 The National Comprehensive Cancer Network guidelines state that even if cure is not achieved, prolonged life and improved quality of life are possible.5

CHEMOTHERAPY OPTIONS FOR NON-SMALL CELL LUNG CANCER

Chemotherapy is an important tool in the treatment of NSCLC. It is used as neoadjuvant, primary, and adjuvant therapy. Neoadjuvant therapy is treatment given before the primary treatment to increase the chance of a cure. Adjuvant therapy is treatment given after the primary treatment to increase the chance of a cure.

Many chemotherapy agents are active against NSCLC. The choice of chemotherapy agents, timing of treatment, and dosing schedule are individualized to meet each person’s unique situation, needs, and preferences.

Neoadjuvant and Adjuvant Chemotherapy
As of this writing, there is no clear consensus regarding what the optimal neoadjuvant and adjuvant chemotherapy regimens are for the different stages of NSCLC. Numerous clinical trials are currently underway to answer these important questions. Table 5 shows some of the drugs included in previous and ongoing trials.
### Table 5: Chemotherapy Drugs Being Studied for NSCLC Neoadjuvant and Adjuvant Treatment

<table>
<thead>
<tr>
<th>Generic Names</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>— New Agents Being Studied —</strong></td>
<td></td>
</tr>
<tr>
<td>docetaxel</td>
<td>Taxotere®</td>
</tr>
<tr>
<td>gefitinib</td>
<td>ZD1839, Iressa®</td>
</tr>
<tr>
<td>gemcitabine</td>
<td>Gemzar®</td>
</tr>
<tr>
<td>irinotecan (CPT-11)</td>
<td>Camptosar®</td>
</tr>
<tr>
<td>paclitaxel</td>
<td>Taxol®</td>
</tr>
<tr>
<td>topotecan</td>
<td>Hycamin®</td>
</tr>
<tr>
<td>vinorelbine</td>
<td>Navelbine®</td>
</tr>
<tr>
<td><strong>— Other Agents Being Studied in Combination Protocols —</strong></td>
<td></td>
</tr>
<tr>
<td>5-fluorouracil (5-FU)</td>
<td>Adrucil®</td>
</tr>
<tr>
<td>carboplatin</td>
<td>Paraplatin®</td>
</tr>
<tr>
<td>cisplatin</td>
<td>Platinol®</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>Cytoxan®, Neosar®</td>
</tr>
<tr>
<td>doxorubicin</td>
<td>Adriamycin®</td>
</tr>
<tr>
<td>etoposide</td>
<td>VePesid®, Etopophos®, Toposar®</td>
</tr>
<tr>
<td>ifosfamide</td>
<td>Ifex®</td>
</tr>
<tr>
<td><strong>— Other Agents Being Studied in Combination Protocols (cont.) —</strong></td>
<td></td>
</tr>
<tr>
<td>mitomycin</td>
<td>Mitomycin C®, Mutamycin®</td>
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<td>teniposide</td>
<td>Vumon®</td>
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<td>uracil + ftorafur</td>
<td>Uracil + Tegafur®</td>
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<tr>
<td>vincristine</td>
<td>Oncovin®, Vincasar PES®, Vincrex®</td>
</tr>
<tr>
<td>vindesine</td>
<td>Eldisine®</td>
</tr>
</tbody>
</table>

**Chemotherapy for Advanced NSCLC**

The National Comprehensive Cancer Network and American College of Chest Physicians lung cancer guidelines both state the standard of care for first line therapy for stage IV NSCLC is platinum-based chemotherapy with one of the newer chemotherapy agents.\[^4,31\] Platinum-based therapy is combined treatment with cisplatin (Platinol®) or carboplatin (Paraplatin®) plus one or more other chemotherapy drugs. Table 6 shows chemotherapy combinations currently considered standard of care. To date, these choices are considered comparable, that is, none of them is clearly superior to the others.
There is no single chemotherapy combination or protocol recommended for all people with advanced NSCLC. Several active chemotherapy combinations are in use. The choice of chemotherapy drugs is individualized on a case-by-case basis. The choice of drugs is influenced by your overall health, other illnesses or conditions you may have, and your personal preferences.

Several drugs are in clinical trials for first and second line treatment of advanced NSCLC, most in combination with drugs that have known activity against NSCLC. Examples include bevacizumab (Avastin®), bexarotene (Targretin®), celecoxib (Celebrex®), DEAE-rebeccamycin, exisulind (Aptosyn®), infliximab (Remicade®), irinotecan (Camptosar®), lonafarnib (Sarasar®), oblimersen (Genasense®), pemetrexed (Alimta®), polyglutamate paclitaxel (Xyotax®), suramin, tipifarnib, thalidomide (Thalomid®), and tretinoin (Retin-A®). Talk with your cancer care team if you are interested in participating in a clinical trial.

There is no clear consensus about the number of chemotherapy cycles needed for maximum benefit. However, research has shown that with current chemotherapy regimens, treatment beyond six cycles for first line therapy is probably not useful and adds to treatment-related toxicity. The National Comprehensive Cancer Center Network guidelines recommend 4-6 cycles of chemotherapy. The American College of Chest Physicians guidelines recommend 3-4 cycles of chemotherapy. Clinical trials are underway to address this issue.
RESPONSE TO THERAPY

Evaluation During Treatment: Is It Working?
There are many ways to determine if treatment is working. Your symptoms are a possible indicator of response to treatment. Symptom improvement may be an indication that treatment is helping. Your doctor will perform a physical examination at each office visit. He or she will check for any changes that may give information about how your body is responding to treatment. The examination also helps your doctor decide if any tests need to be done. Imaging tests such as chest x-rays or CT scans are often used to check the size of the tumor(s) in response to therapy. The timing of these tests varies. Your doctor may check tumor size after your first cycle of chemotherapy or may wait until after several cycles have been administered. How your cancer care team monitors you for treatment response depends on what treatments are being used, how you are tolerating treatment, and other factors. Discuss your specific monitoring protocol with your providers.

Follow-Up After Completion of Curative-Intent Treatment
People who have no apparent signs of cancer after completing treatment must be carefully monitored for recurrent disease and the development of a second primary lung cancer. The National Comprehensive Cancer Network guidelines recommend a physical examination and chest x-ray every three to four months for two years, then every six months for three years, then yearly thereafter. These guidelines also recommend an annual spiral CT scan of the chest because it is more sensitive than a chest x-ray. However, there was not complete agreement among NCCN members on this recommendation.5

The American College of Chest Physicians recommendations for follow-up after curative intent treatment are slightly different. These guidelines recommend physical examination and chest x-ray or CT scan every six months for two years, then annually thereafter.66 Discuss your specific follow-up plan with your cancer care team. Be sure to attend every follow-up visit. Also, be aware of signs and symptoms that may indicate a recurrence of disease. Talk this over with your cancer care doctor. Call your doctor immediately if you experience any new symptoms that may indicate a recurrence of disease. Do not wait until your next scheduled appointment.
**Monitoring for Disease Progression in Advanced NSCLC**

People with advanced NSCLC are usually treated with 3-6 cycles of chemotherapy. Many people will experience stabilization of their disease, or a partial or complete response to treatment. Your ongoing care will depend on your symptoms, supportive care treatments, and other needs. Physical examinations, symptoms of disease, chest x-rays, blood tests, and other tools are used to monitor for disease progression.

**TREATMENT FOR DISEASE PROGRESSION IN ADVANCED NSCLC**

The majority of people treated for advanced NSCLC will eventually experience progression of their disease. Disease progression means the cancer begins to grow again and may possibly spread. People who experience disease progression but are still feeling relatively well may decide to try second line chemotherapy. The use of second line chemotherapy in people with good performance status is supported by both the National Comprehensive Cancer Network and American College of Chest Physician NSCLC treatment guidelines.\(^5\)\(^,\)\(^31\)

The choice of second line chemotherapy is dependent on the first line treatment used, your overall health, and other factors. Recently, gefitinib (ZD 1839, Iressa\(^@\)) was approved by the Food and Drug Administration as second line, single agent therapy after treatment failure with platinum-based combination therapy and docetaxel. Clinical trials are also available to people who have had disease progression after first line therapy. Regardless of whether you have second line chemotherapy, your cancer care team will continue to provide supportive care.

**TREATMENT FOR RECURRENT DISEASE**

NSCLC can recur locally or as distant metastasis. *Local recurrence* is return of the cancer at the original site. Table 7 shows the National Comprehensive Cancer Network treatment recommendations for problems caused by local recurrences.
Local recurrence will trigger a work-up much like the initial work-up to evaluate the spread of disease. If there is no evidence of distant metastasis and the recurrence can be removed, surgery is usually recommended. This is usually followed with radiotherapy and/or chemotherapy.

The presence of distant metastasis leads to treatment for advanced NSCLC. Platinum-based chemotherapy is recommended for systemic (whole body) control of disease. Local symptoms are treated as they are for anyone who has advanced NSCLC. It is up to you how aggressive you want to be with treatment for recurrent disease. No matter what you choose, your cancer care team will continue to provide the supportive care you need.

**SUMMARY**

Treatment for NSCLC is based on the extent of your disease. Local disease with limited spread may be cured with surgery. More advanced spread often requires combination treatment with surgery, chemotherapy, and/or radiotherapy. Advanced NSCLC is treated primarily with chemotherapy. Radiotherapy is commonly used to treat local symptoms of advanced disease. Many supportive and palliative care techniques are available to help alleviate disease symptoms. You may want to consider one of the many NSCLC clinical trials available when evaluating your treatment options.
The choice of treatment depends on the stage of your disease, overall health, personal preferences, and other factors. No single approach can be used effectively for all cases of NSCLC. Your treatment plan must be individualized to meet your specific situation, needs, and preferences.

Questioning your cancer care team can help you better understand your treatment options and feel more comfortable with your decisions. Additional sources of information can be found in the Resource Directory.