Lung Cancer CHOICES

2nd Edition

Diverse Viewpoints and Choices for Your Lung Cancer Journey

Caring Ambassadors Program, Inc.
LungCancerCAP.org

Lung Cancer Choices, 2nd Edition

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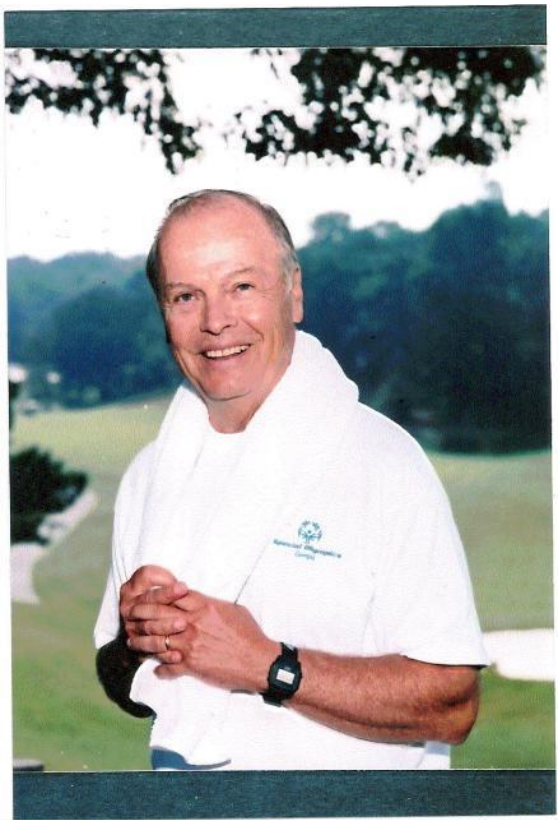
Dedication



Ken Giddes

The Caring Ambassadors Program dedicates ***Lung Cancer Choices*** to program founder, Ken Giddes.

Ken Giddes of Dunwoody, Georgia, survived nearly eight years after the diagnosis of non-small cell lung cancer. He died January 27, 2001, surrounded by his family.

Ken had a successful career with Republic Financial Corporation, which supported his development of the "Caring Ambassador" program, in which he traveled the country to meet other survivors and talk about living with lung cancer. Ken also was a "phone buddy" to hundreds of lung cancer patients and their loved ones.

Ken was our mentor and the epitome of a Caring Ambassador, reaching out to others who were struggling to survive a life-changing, life-threatening illness. Ken was and still is our inspiration. He inspires us today to continue the Caring Ambassadors Lung Cancer Program.

To Ken and all the patient advocates who have and are working tirelessly around the world for their respective causes, we thank you.

Acknowledgments

The Caring Ambassadors Lung Cancer Program is profoundly grateful to the authors of the book for their dedication, generosity, time, and expertise. Without their commitment to this project, we would be unable to offer this important resource to the lung cancer community.

Like a family, the Caring Ambassadors Lung Cancer Program has a core of support upon which it stands and draws on for strength. ***Lung Cancer Choices, 2nd Edition*** would not be possible without the love and generosity of the Hewit Family Foundation, Republic Financial Corporation, the Gleser Family, the Andrews Family, Jessica Steinberg, and the Dietrich Family. Thank you for all you do for the Caring Ambassadors Program and for the community.

Last but not least, the Caring Ambassadors Lung Cancer Program acknowledges the lung cancer community —the people who bravely face the challenges of living with lung cancer, the loved ones who offer them steadfast support and comfort, the healthcare providers who work to provide the best possible treatment options, and the advocates who work tirelessly to provide hope, support, and improve the future for those at risk for developing lung cancer and those living with the disease. We are proud to work side-by-side with you to meet the community's needs.

Thank you to our sponsor for their generous support.

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Using *Lung Cancer Choices*

Introduction

The Caring Ambassadors Program is pleased offer the 2nd *Edition of Lung Cancer Choices*. We hope that the information in the book will help you in your journey and provide the information you need to receive the best treatment and supportive care for your disease. We are excited to announce that we have added an additional chapter on smoking cessation. See Chapter 11: *How to Quit Smoking Confidently and Successfully*.

Being diagnosed with a lung cancer is a life-altering event.

You will be bombarded with information and advice from your healthcare providers, your friends and family, from strangers on the internet, and from countless other sources. It is essential that you take ownership of your own healthcare decisions, and, in order to do so, you must be informed and you must be a proactive ambassador for your own health.

The key to navigating the road ahead is to remember…

This is Your Journey and these are Your Choices.

How you go about maintaining your health, and whomever you decide to consult for your healthcare is up to you. However, we urge you to gather information about the different treatment options you are considering. This will help you make informed decisions about the options that are best suited to your treatment goals.

Each person with lung cancer is unique, and each reader of *Lung Cancer Choices* also is unique. Recognizing that your informational needs are personal and may change with time, *Lung Cancer Choices* has been written so that each chapter can be read and understood on its own.

You may find medical words in the book that are new to you. The definitions of these words can be found within the chapter or are in the *Glossary* at the back of the book. Becoming familiar with these words will help you better understand lung cancer. It might also help you communicate more easily with your healthcare providers.

Purpose of *Lung Cancer Choices*

Lung Cancer Choices was written with several purposes in mind:

- to provide information about lung cancer to help you make decisions about lung cancer treatment options.
- to provide a balanced view of the currently available treatment options from Western medicine, complementary and alternative medicine (CAM), and Chinese medicine.

- to help you communicate more effectively with healthcare providers.
- to help you become empowered to be the best advocate for your own healthcare.

Making Informed Decisions

Potentially life-changing decisions are one aspect of having a serious illness such as lung cancer. Each of us is unique in how we make decisions. Some people want to know everything they possibly can about their disease. They want to make all their own treatment decisions. Other people prefer to have their healthcare providers make treatment decisions based on their knowledge and expertise. Some prefer having a friend or family member seek out and sort through information. Many use a combination of approaches.

We hope *Lung Cancer Choices* will help you understand your disease and some of the healthcare options available to you. Knowledge empowers you to ask the necessary questions to become your own best advocate. When your questions have been asked and answered, you and your healthcare providers will be in the best possible situation to determine the best treatment approach for you.

An Important Note to the Reader

This book was created to provide information about a variety of approaches to the treatment and management of lung cancer. The information presented in *Lung Cancer Choices* has been made available by The Caring Ambassadors Program for educational purposes only. The Caring Ambassadors Program and the authors of *Lung Cancer Choices* believe that access to good information leads to better decisions. However, this book is ***not*** a substitute for medical advice. It is critically important that you consult your healthcare provider about any matter concerning your health. The information is not intended to present the only, or necessarily best, methods or procedures, but is intended to represent the approach, view, or opinion of the authors that may be helpful to other people in similar situations.

Each chapter and section of the book has been authored independently. Therefore, each chapter reflects the unique approach of the author to the treatment of lung cancer, based on his or her medical discipline and experience. For this reason, an author is responsible only for the accuracy of the information presented in his or her chapter section. Any statement about commercial products are solely the opinion of the author and do not represent an endorsement or evaluation of these products by The Caring Ambassadors Program. These statements may not be used for any commercial purpose or advertising.

The choice of treatment for lung cancer is a personal one. We encourage you to carefully assess the information provided here and elsewhere, and to work with your healthcare providers to choose treatment approaches that meet your individual needs.

Lung Cancer Choices, 2nd Edition

Table of Contents

Chapter

1

The Diagnosis and Staging of Lung Cancer

Tze-Ming Chen, MD, FCCP

Lung cancer is the leading cause of cancer-related mortality in the United States. Swift diagnosis, simultaneous staging, and the performing mutation analyses, when indicated, permits rapid initiation of appropriate treatment which is the objective of the evaluation of every patient with a suspected or known lung cancer. A multi-disciplinary diagnostic thoracic tumor board evaluation guiding the use of combined positron emission tomography-computed tomography, endobronchial ultrasound guided fine needle aspiration, endoscopic ultrasound guided fine needle aspiration, electromagnetic navigational bronchoscopy, mediastinoscopy, thoracentesis, video-assisted thoracoscopic surgery, and or computed tomography or ultrasound guided fine needle aspiration is critical in our opinion to achieve this goal.

Introduction

Lung cancer remains the leading cause of cancer-related mortality in the United States despite advances in chemotherapeutic options and surgical technique. The evaluation of patients with suspected or known lung cancer requires accurate and preferably rapid diagnosis and staging to facilitate the optimal treatment regimen: surgical resection, surgical resection with adjuvant chemotherapy, chemotherapy alone, or chemotherapy in conjunction with radiation therapy. Currently, staging may include combined positron emission tomography - computed tomography (PET-CT) imaging, endobronchial ultrasound guided-fine needle aspiration (EBUS-FNA), endoscopic ultrasound guided-FNA (EUS-FNA), electromagnetic navigational bronchoscopy, mediastinoscopy, thoracentesis, video-assisted thoracoscopic surgery (VATS), and or computed tomography (CT) or ultrasound guided FNA.

In this chapter, I will review the current system for staging non-small cell lung cancer (NSCLC), the different diagnostic and staging options, and a brief discussion about the importance of mutation analyses in guiding treatment for patients with advanced stage disease. I will then provide a summary of our center's approach towards lung cancer diagnosis and staging with supporting literature where available.

Staging Background

The current staging system[1] published in 2010 continues with the pre-existing method of assessing tumor size and its affect on the surrounding lung tissue or its interaction with non-lung tissue (T), the extent of spread of lung cancer to lymph nodes (N) (Figure 1), and the presence or absence of metastatic spread of lung cancer outside of lung tissue (M). The TNM classification system is then used to derive a stage of NSCLC which ranges from localized disease (IA) to wide-spread disease (IV) providing information on expected prognosis and survival.

Diagnostic and Staging Modalities

Combined PET-CT

PET is an imaging technique that captures the level of metabolic activity of different tissues. Patients are given an intravenous injection of 2-(18F)fluoro-2-deoxy-D-glucose (FDG) followed by imaging 60 minutes later. The degree of metabolic activity correlates with the level of FDG uptake which is reported as a standardized uptake value (SUV). A number of studies have demonstrated the accuracy of PET for the diagnosis of lung cancer in pulmonary nodules and masses[2-6] as well as for staging evaluation.[7, 8] A study by Gould (2001) reports that PET fails to detect lung cancer in 3.2% of cases but 22.2% of the time it falsely suggests the presence of cancer.[5] More recently, Fischer (2009) demonstrated that combined PET-CT improves the selection of patients with known or suspected lung cancer for surgery by decreasing the number of patients with advanced stage lung cancer undergoing surgery.[9] An earlier trial found similar benefits with PET imaging alone.[10]

Delayed PET imaging is also of interest. Cancer continues to increase FDG uptake over 1.5 to 5 hours.[11] Thus, an increase in the SUV of nodules, masses, or lymph nodes over time may suggest a cancerous etiology.[12-14]

It is important to realize that FDG uptake also occurs in inflammatory and infectious processes thereby limiting its ability to discriminate between these and cancers. Hara (2003) reported a mean SUV of 6.45 + 2.30 for 14 patients with tuberculosis while 97 untreated patients with lung cancer had a mean SUV of 5.29 + 2.72.[15] This emphasizes the importance of obtaining tissue confirmation of cancer for FDG-avid lesions.

False negatives can result from the limited spatial resolution of PET scanners affecting the accuracy of this test in subcentimeter lung nodules as well as small lymph nodes.[8] In addition, some lung cancers such as bronchioloalveolar carcinomas and carcinoid tumors have been reported to have negative PET imaging results.[16-20] Patients with poorly controlled diabetes mellitus or high blood glucose levels are also more likely to have false negative studies as a result of the elevated levels of endogenous glucose competing for uptake with FDG.

Cancers with low or negative PET signal appear to be associated with better prognoses.[21] In addition, the change in activity with chemotherapy correlates with histopathologic response.[22, 23]

Endobronchial Ultrasound-Guided Fine Needle Aspiration (EBUS-FNA)

Prior to the development of EBUS-FNA, patients who were candidates for surgical resection of suspected or diagnosed lung cancer often required a staging mediastinoscopy to evaluate for potential spread of cancer to lymph nodes in the mediastinum, the area within the chest located between the two lungs that contains the trachea, esophagus, heart, and the great vessels. However, mediastinoscopy is associated with a complication rate of as high as 2-3%, and more importantly is unable to sample certain lymph nodes such as hilar (station 10, 11, 12), para-aortic (station 6), or aortopulmonary window (station 5) lymph nodes. Consequently, subsequent thoracotomy has been reported to result in no tumor resection in up to 10% of patients because of detection of advanced stage lung cancer at the time of surgery.[24] EBUS-FNA is an alternative minimally invasive technique that complements mediastinoscopy by its ability to access lymph node stations 2, 3, 4, 7, 10, and 11 (Table 1).

EBUS is a bronchoscopic technique that utilizes ultrasound to identify and permit real-time ultrasound-guided needle biopsy of paratracheal, hilar, and interlobar lymph nodes. Krasnik (2003) reported their initial experience with EBUS-FNA of mediastinal and hilar lesions under general anesthesia.[24] These investigators reported accurate sampling of lymph nodes from stations 1, 2, 4, 7, and 10, with 9 diagnoses of malignancy and 2 diagnoses of benign disease. Yasufuku (2004) reported their experience with 70 patients who underwent EBUS-FNA of mediastinal (stations 2, 3, 4, and 7) and hilar (stations 10 and 11) adenopathy under local anesthesia, reporting a sensitivity and specificity for malignancy of 95.7% and 100%, respectively.[25] Five of the sampled lymph nodes were described as 1 cm or less in diameter with the 2 false-negative biopsies occurring in lesions between 1.1 and 2.0 cm. Yasufuku (2005) published additional EBUS-FNA experience with 105 patients reporting a sensitivity and specificity for malignancy of 94.6% and 100%, respectively.[26] Additional studies report sensitivities and specificities for malignancy of 88.9% - 94% and 96.4% - 100%, respectively.[27-29] These studies have demonstrated that EBUS-FNA is a minimally invasive alternative as well as a complementary procedure to mediastinoscopy for mediastinal and hilar staging, respectively, for known or suspected NSCLC.

Table 1.

Biopsy Method	Accessible Lymph Node Stations
EBUS-FNA	2, 3, 4, 7, 10, 11
EUS-FNA	4, 5, 7, 8, 9
Cervical Mediastinoscopy	1, 2, 3, 4, anterior 7
Anterior Mediastinoscopy	5
Extended Cervical Mediastinoscopy	6
VATS	Ipsilateral mediastinal lymph nodes

Endoscopic Ultrasound-guided Fine Needle Aspiration (EUS-FNA)

EUS is an additional minimally invasive ultrasound-based technique which uses esophagogastro-endoscopy to sample para-esophageal lymph nodes. These include paratracheal (station 4), aortopulmonary window (station 5), posterior subcarinal (station 7), paraesophageal (station 8), and pulmonary ligament (station 9) lymph nodes (Table 1). Consequently, this technique complements both mediastinoscopy and EBUS-FNA with the additional advantage of being able to access stations 8 and 9 as well as subdiaphragmatic structures including the celiac nodes and the adrenal glands.

Studies evaluating EUS-FNA for lung cancer, excluding one, have demonstrated sensitivities and specificities for malignancy of 87% - 96% and 100%, respectively which is comparable to EBUS-FNA.[30-35] However, one study reported a lower sensitivity and specificity of 86% and 83%, respectively.[36] Overall, these studies demonstrate that EUS is a valuable diagnostic and staging tool for patients with suspected or known NSCLC.

Guidance-assisted Bronchoscopy

One of the most significant limitations to using bronchoscopy for the diagnosis of early stage lung cancer is the inaccuracy of bronchoscopy directed biopsy of lung nodules. A recent advance in bronchoscopy called electromagnetic navigation is now able to overcome this limitation for select lesions that are more than 1 to 1.5cm in diameter. This system marries CT imaging with bronchoscopy allowing the physician to determine the position of the bronchoscope and a special guidance catheter within the lung of a patient. By performing pre-procedural planning, the physician is now able to maneuver a guidance catheter through a patient's airways to biopsy lung nodules that are concerning for cancer. In addition, the system allows the placement of fiducial markers around the lung nodule to facilitate treatment with stereotactic radiation.

The major limitations to the success of the procedure include the patient's ability to tolerate bronchoscopy and its associated sedation, the size of the lesion of interest as well as its location, the experience of the physician performing the procedure, and that the actual biopsy is not performed under real-time visualization of the target. In addition, this procedure is not recommended for patients who have an implanted cardioverter defibrillator or pacemaker due to potential interference between these devices and the electromagnetic field created by the bronchoscopy system.

Risks of the procedure include pain, bleeding, or collapsed lung. However, these risks occur less frequently when compared to CT-guided biopsy or CT-guided placement of fiducial markers.

An alternative approach is to utilize a radial endoscopic ultrasound. This device can be inserted through a standard bronchoscope and maneuvered into the lung tissue to help localize a lung nodule for biopsy. As with the electromagnetic navigational bronchoscopy system, the limitation of this technique is that the ultrasound probe is then removed so that a biopsy catheter can be inserted so that the biopsy is not under real-time visualization of the target.

Cervical and Anterior Mediastinoscopy

Mediastinoscopy involves an incision at the base of the neck just above the suprasternal notch, followed by the insertion of a mediastinoscope along the length of the trachea to permit sampling of the paratracheal lymph nodes (stations 1, 2, 3, and 4) as well as anterior subcarinal lymph nodes (Table 1). An extended cervical mediastinoscopy allows access to the para-aortic lymph nodes (station 6). The video mediastinoscope, introduced in 1994,[37] permits easier handling and visualization during the procedure as well as potential access to posterior subcarinal lymph nodes.[38, 39]

A number of studies have evaluated the performance of mediastinoscopy. The largest was a retrospective review of all mediastinoscopies performed by the Cardiothoracic Surgery Division at Washington University School of Medicine between January 1988 and September 1998.[40] 1,745 patients underwent cervical mediastinoscopy with known or suspected lung cancer. 422 (24%) of these patients were found to have N2 or N3 disease. 107 patients were deemed non-surgical candidates due to comorbid conditions and 947 of the remaining 1,216 patients were found to have lung cancer after thoracotomy. N2 nodal involvement was detected at the time of thoracotomy in 76 of the 947 patients representing an 8% false negative rate. 4 deaths (0.05%) and 12 complications (0.6%) occurred. Additional large studies report false negative rates of 3%[41] and 9%.[42] About half of the false negative results (42-57%) were due to lymph nodes that are not accessible by mediastinoscopy.[43]

The major limitations to performing mediastinoscopy are bleeding disorders, severe hyphosis, contraindications to general anesthesia, tracheostomy, or previous chest radiation. The scarring and fibrosis associated with radiation or prior procedures significantly increase the risk of damage to mediastinal organs and vasculature during attempted blunt dissection with the mediastinoscope.

Anterior mediastinoscopy (Chamberlain procedure) permits the evaluation of the aortopulmonary window lymph nodes (Table 1). This involves an incision at the level of the 2nd or 3rd intercostal space to the left of the sternum and the placement of a mediastinoscope to visualize and biopsy visible lymph nodes. The procedure has not been extensively studied but 2 studies have reported false negative rates of 0% [44] and 11%.[45] It is generally well tolerated and most patients can avoid an overnight hospital stay.[43]

Thoracentesis

Patients with pleural effusions that layer at least 1 cm on lateral decubitus chest radiographs are easily assessed for malignancy by thoracentesis. This procedure requires only local anesthesia with 1% lidocaine and the placement of a temporary drainage catheter to remove the available pleural fluid. The procedure can be performed in an outpatient setting and is generally well tolerated by the patient. One often discussed complication is lung collapse also referred to as pneumothorax. A prospective study of 506 thoracenteses in 370 patients reported 18 (4%) pneumothoraces.[46] Additional complications include catheter insertion site pain, coughing, hemothorax, localized infection, intraabdominal organ injury, and post-expansion pulmonary edema. Contraindications to performing thoracentesis include bleeding disorders unless reversible, infection or abscess of the overlying skin, and the inability to localize a pocket of fluid for sampling.

Pleural fluid analysis will obtain a diagnosis of metastatic adenocarcinoma in 70% of cases but only 20% of squamous cell carcinomas will be detected this way.[47] The rate of detection is dependent upon the type of carcinoma, the number of pleural fluid specimens obtained, and the extent of pleural involvement.[48]

Video-assisted Thoracoscopic Surgery

VATS or thoracoscopy is a surgical method that permits the surgeon to evaluate the pleural space and ipsilateral lymph nodes. The procedure requires general anesthesia, single lung ventilation, and usually a short hospital stay but is usually well tolerated with an average complication rate of 2%.[49-53] The most common complication was prolonged air leaks.

An important application of VATS is to directly visualize tumors that are radiographically staged T4. Eggeling (2002) found that thoracoscopy upstaged 4 patients after discovering cancerous fluid collections while down staging 6 patients thought to have mediastinal invasion on computed tomography (CT).[51] The authors report a sensitivity and specificity for the accurate prediction of pathologic T4 lesions using CT to be 64.7% and 69%, respectively. This and additional publications[53, 54] support the use of VATS to confirm T4 lesions designated by CT prior to categorizing the cancer as unresectable. Thoracoscopy can also evaluate the pleural space for malignancy in patients with pleural effusions that are cytologically negative on repeated thoracentesis or in patients with pleural abnormalities detected on CT. In addition, VATS provides an alternative approach to anterior and extended cervical mediastinoscopy for the evaluation of lymph node stations 5 and 6, respectively (Table 1).

Computed Tomography or Ultrasonography Guided Fine Needle Aspiration

Patients with suspected or known NSCLC who are found to have extra-thoracic disease on PET-CT imaging should undergo tissue biopsy to confirm a metastatic focus. This can be achieved using CT-guided or ultrasound guided fine needle aspiration. The procedure is generally very well tolerated and can be performed in an outpatient setting.

Targetable Mutations in Lung Cancer

The diagnostic evaluation of a patient with suspected lung cancer in the early 21st century includes 3 specific goals:

1. Does the patient have lung cancer and if so, what type of lung cancer is present?
2. What is the pathologic stage of lung cancer?
3. If appropriate, are specific mutations present in the lung cancer that could be targeted by a specific therapy?

Using the techniques described above, the ideal for an individual patient would be to achieve these 3 goals in a single procedural setting. Currently, this is possible but as the number of targeted

mutations increases, we may reach a point where a separate diagnostic procedure is needed to obtain enough tissue for all of the testing needed to determine the most appropriate first line treatment.

Epidermal Growth Factor Receptor

The most prevalent targetable mutation is epidermal growth factor receptor (EGFR). This particular mutation is most frequently found in lung adenocarcinomas and is more frequent in women, never smokers, and patients of East-Asian origin. Activating mutations of exons 19 and 21 are sensitive to EGFR tyrosine kinase inhibitors (TKIs). Clinical trials have now demonstrated that patients with advanced stage lung adenocarcinomas with activating mutations of EGFR in either exon 19 or 21 have demonstrated significant prolongation of progression free survival when compared to standard doublet chemotherapy. Interestingly, the presence of an activating EGFR mutation virtually excludes the presence of other activating mutations. Treatment with EGFR TKIs are currently available in the United States.

Anaplastic Lymphoma Kinase (ALK) - Rearrangements

ALK rearrangements are primary found as fusions to echinoderm microtubule-like protein 4 (EML4) and have been detected in 4%[55] to 7% of NSCLCs[56]. Patients with an EML4-Alk mutation are more likely to have lung adenocarcinoma, more likely to be light to never smokers, more likely to be men, and tend to be younger.[57] Treatment with the ALK-inhibitor, crizotinib, is currently available in the United States. Second-generation ALK-TKIs are currently in clinical development.

Kirsten Rat Sarcoma virus (KRAS)

KRAS is one of a number of enzymes that regulates cell growth and division and mutations of this gene occur in 25 to 30% of lung adenocarcinomas and more likely to be found in patients with lung cancer who have a smoking history. Unfortunately, there are no currently available KRAS targeted therapies and the identification of a KRAS mutation portends a poor response to both targeted and standard chemotherapy. While inhibitors have been reported in the literature, these potential therapies are years from clinical trials.

C-ros Oncogene 1 (ROS1)

While rare (1 to 2% of NSCLCs), mutations of ROS1 are more likely to be found in patients with lung adenocarcinomas who were never smokers and are younger in age. Targeted treatment with crizotinib is an option though clinical trials are ongoing.

Additional Mutations

Currently, a number of clinical trials evaluating the utility of targeting additional mutations are either ongoing or are in development. These potential targets include AKT, BRAF, DDR2, FGFR, HER2, MET, PD-1, PIK3CA, PTEN, and RET. A detailed review of these potential future treatments is beyond the scope of this chapter.

Who Should Undergo Mutation Analyses?

Currently, all patients with pathologically confirmed advanced-stage lung adenocarcinoma should have biopsy specimens sent for EGFR and ALK mutation analyses to aid the medical oncologist in their treatment decision as recommended by a number of

medical societies including the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology regardless of gender, ethnicity, or smoking history. Interestingly, a recently published meta-analysis has revealed a discordance rate of 12% between the primary tumor and metastatic lymph node tissue for the presence of an EGFR activating mutation where the primary tumor is more likely to harbor the mutation.[58] The clinical significance of this finding is not yet clear.

Patients with adenosquamous carcinoma have also been shown to have a high prevalence of activating EGFR mutations (3 of 5 patients)[59] and consequently should also have their biopsies sent for mutation analyses. However, controversy currently exists regarding testing for EGFR and EML4-ALK in patients with non-adenocarcinoma lung cancers. While EGFR mutations have been reported in patients with squamous cell carcinoma (3 of 116 patients[59] and 0 of 454 patients)[60], most medical societies today are recommending EGFR mutation analyses in patients with lung adenocarcinoma, adenosquamous carcinoma, suspected lung adenocarcinomas, or poorly differentiated suspected lung cancers.

The key point to emphasize is that the goal of the proceduralist performing the biopsy is to keep the 3 above-mentioned goals in mind - diagnosis, stage, and if appropriate tissue for mutation analyses.

Thoracic Tumor Board Diagnostic and Staging Algorithm

Our center has established a Diagnostic Thoracic Tumor Board that brings together the knowledge and expertise of physicians from pulmonology, oncology, radiology, nuclear medicine, and thoracic surgery. The group has developed an evidence-based algorithm for the diagnosis and staging of patients with suspected or known lung cancer (Figure 2). It is our opinion that patients with suspected or known lung cancer should receive rapid, cost-effective, accurate diagnosis and staging so that the appropriate treatment may be initiated in a timely manner. Our goal for all patients is to have a diagnosis and cancer stage within 7 days of referral and to have the appropriate treatment initiated within 14 days.

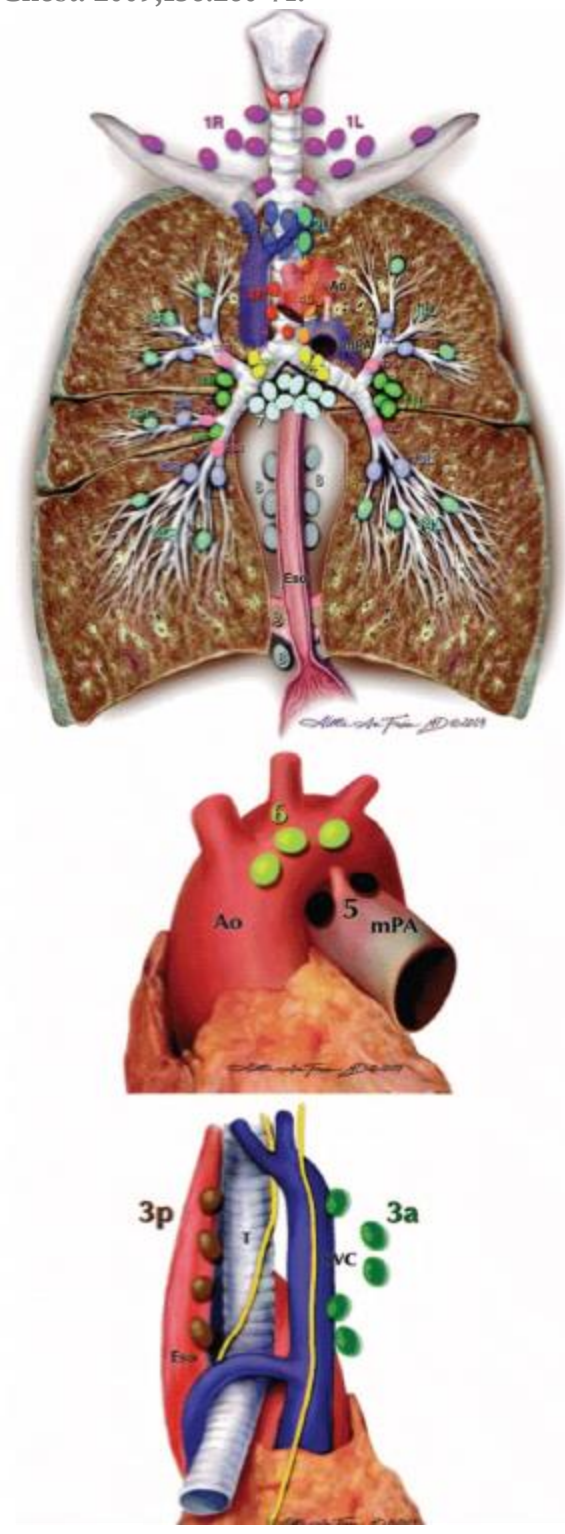
All patients we evaluate with suspected or known NSCLC and who are potential candidates for surgical resection undergo PET-CT to evaluate for mediastinal disease and possible distant metastases. This practice is supported by 2 studies. Fischer (2009) published a prospective randomized trial evaluating the effect of combined PET-CT on the number of futile thoracotomies performed in patients with highly-suspected or newly diagnosed NSCLC.[9] Futile thoracotomy was defined as a final diagnosis of a benign process, pathologically proven NSCLC stage IIIA-N2, IIIB, or IV disease, inoperable T3 or T4 disease, or recurrent malignancy or death from any cause within 1 year of randomization. A significant decrease in futile thoracotomies was achieved using PET-CT pre-operatively compared to conventional staging (21 of 60 vs. 38 of 73, p=0.05). A similar result was reported in an earlier publication using PET.[10]

Diagnosis if not previously made and staging is achieved by biopsy of the PET-avid lesion that would achieve the most advanced TMN stage. Biopsy methods for lymph nodes within the chest are described in Table 1. The preferred route of biopsy of mediastinal lymph nodes is to start with either EBUS or EUS depending upon the lymph node of interest. If the biopsy result is negative by EBUS or EUS, a confirmatory mediastinoscopy is necessary prior to proceeding to surgical resection.

Conclusion

Lung cancer survival is strongly associated with the stage of disease and the resulting application of appropriate treatment. With the introduction of combined PET-CT, EBUS, and EUS to mediastinoscopy, patients can now be accurately staged avoiding unnecessary thoracotomies. To improve the timely application of appropriate staging and diagnostic studies, a multidisciplinary panel of physicians is important and in our opinion essential.

Figure 1: Schematic of the lymph node stations within the chest – derived from Figure 4. of Chest. 2009;136:260-71.



Supraclavicular zone
1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone
2R Upper Paratracheal (right)
2L Upper Paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower Paratracheal (right)
4L Lower Paratracheal (left)

AORTIC NODES

AP zone
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone
7 Subcarinal

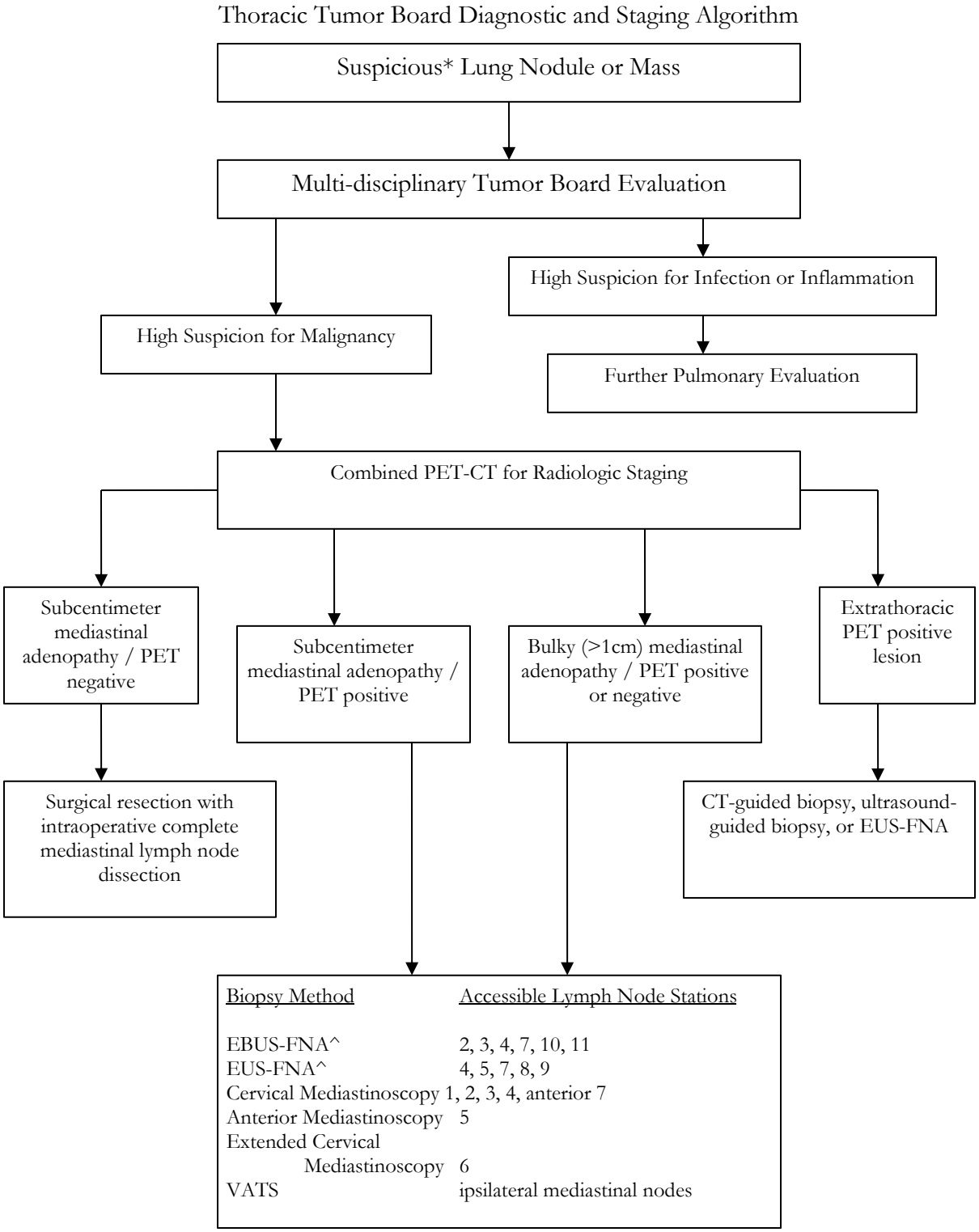
Lower zone
8 Paraesophageal (below carina)
9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone
10 Hilar
11 Interlobar

Peripheral zone
12 Lobar
13 Segmental
14 Subsegmental

Figure 2.



* Spiculated lesion on imaging, increasing size on serial computed tomography imaging, PET-avid lesion, significant smoking history, and or age greater than 50
^ preferred procedure but biopsies negative for malignancy require lymph node sampling for confirmation

References:

1. Edge, S.B. and C.C. Compton, The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*, 2010. 17(6): p. 1471-4.
2. Sazon, D.A., et al., Fluorodeoxyglucose-positron emission tomography in the detection and staging of lung cancer. *Am J Respir Crit Care Med*, 1996. 153(1): p. 417-21.
3. Saunders, C.A., et al., Evaluation of fluorine-18-fluorodeoxyglucose whole body positron emission tomography imaging in the staging of lung cancer. *Ann Thorac Surg,* 1999. 67(3): p. 790-7.
4. Weber, W., et al., Assessment of pulmonary lesions with 18F-fluorodeoxyglucose positron imaging using coincidence mode gamma cameras. *J Nucl Med*, 1999. 40(4): p. 574-8.
5. Gould, M.K., et al., Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA*, 2001. 285(7): p. 914-24.
6. Fletcher, J.W., et al., A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules. *J Nucl Med*, 2008. 49(2): p. 179-85.
7. Pieterman, R.M., et al., Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med*, 2000. 343(4): p. 254-61.
8. Gould, M.K., et al., Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Ann Intern Med*, 2003. 139(11): p. 879-92.
9. Fischer, B., et al., Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med,* 2009. 361(1): p. 32-9.
10. van Tinteren, H., et al., Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet*, 2002. 359(9315): p. 1388-93.
11. Hamberg, L.M., et al., The dose uptake ratio as an index of glucose metabolism: useful parameter or oversimplification? *J Nucl Med*, 1994. 35(8): p. 1308-12.
12. Kubota, K., et al., Advantage of delayed whole-body FDG-PET imaging for tumour detection. *Eur J Nucl Med,* 2001. 28(6): p. 696-703.
13. Matthies, A., et al., Dual time point 18F-FDG PET for the evaluation of pulmonary nodules. *J Nucl Med*, 2002. 43(7): p. 871-5.
14. Uesaka, D., et al., Evaluation of dual-time-point 18F-FDG PET for staging in patients with lung cancer. *J Nucl Med*, 2008. 49(10): p. 1606-12.
15. Hara, T., et al., Uptake rates of 18F-fluorodeoxyglucose and 11C-choline in lung cancer and pulmonary tuberculosis: a positron emission tomography study. *Chest*, 2003. 124(3): p. 893-901.
16. Erasmus, J.J., et al., Evaluation of primary pulmonary carcinoid tumors using FDG PET. *AJR Am J Roentgenol*, 1998. 170(5): p. 1369-73.
17. Higashi, K., et al., Fluorine-18-FDG PET imaging is negative in bronchioloalveolar lung carcinoma. *J Nucl Med*, 1998. 39(6): p. 1016-20.
18. Kim, B.T., et al., Localized form of bronchioloalveolar carcinoma: FDG PET findings. *AJR Am J Roentgenol,* 1998. 170(4): p. 935-9.
19. Heyneman, L.E. and E.F. Patz, PET imaging in patients with bronchioloalveolar cell carcinoma. *Lung Cancer*, 2002. 38(3): p. 261-6.
20. Marom, E.M., et al., T1 lung cancers: sensitivity of diagnosis with fluorodeoxyglucose PET. *Radiology*, 2002. 223(2): p. 453-9.
21. Cheran, S.K., N.D. Nielsen, and E.F. Patz, Jr., False-negative findings for primary lung tumors on FDG positron emission tomography: staging and prognostic implications. *AJR Am J Roentgenol,* 2004. 182(5): p. 1129-32.
22. Hoekstra, C.J., et al., Prognostic relevance of response evaluation using [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with locally advanced non-small-cell lung cancer. *J Clin Oncol*, 2005. 23(33): p. 8362-70.

23. Pottgen, C., et al., Value of 18F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in non-small-cell lung cancer for prediction of pathologic response and times to relapse after neoadjuvant chemoradiotherapy. *Clin Cancer Res*, 2006. 12(1): p. 97-106.
24. Krasnik, M., et al., Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions. *Thorax*, 2003. 58(12): p. 1083-6.
25. Yasufuku, K., et al., Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. *Chest*, 2004. 126(1): p. 122-8.
26. Yasufuku, K., et al., Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer*, 2005. 50(3): p. 347-54.
27. Herth, F.J., et al., Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *Eur Respir J*, 2006. 28(5): p. 910-4.
28. Herth, F.J., et al., Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax*, 2006. 61(9): p. 795-8.
29. Sun, W., et al., The diagnostic value of endobronchial ultrasound-guided needle biopsy in lung cancer and mediastinal adenopathy. *Diagn Cytopathol*, 2010. 38(5): p. 337-42.
30. Silvestri, G.A., et al., Endoscopic ultrasound with fine-needle aspiration in the diagnosis and staging of lung cancer. *Ann Thorac Surg*, 1996. 61(5): p. 1441-5; discussion 1445-6.
31. Fritscher-Ravens, A., et al., Diagnostic value of endoscopic ultrasonography-guided fine-needle aspiration cytology of mediastinal masses in patients with intrapulmonary lesions and nondiagnostic bronchoscopy. *Respiration*, 1999. 66(2): p. 150-5.
32. Fritscher-Ravens, A., et al., Mediastinal lymphadenopathy in patients with or without previous malignancy: EUS-FNA-based differential cytodiagnosis in 153 patients. *Am J Gastroenterol*, 2000. 95(9): p. 2278-84.
33. Wallace, M.B., et al., Endoscopic ultrasound-guided fine needle aspiration for staging patients with carcinoma of the lung. *Ann Thorac Surg*, 2001. 72(6): p. 1861-7.
34. Wiersema, M.J., E. Vazquez-Sequeiros, and L.M. Wiersema, Evaluation of mediastinal lymphadenopathy with endoscopic US-guided fine-needle aspiration biopsy. *Radiology*, 2001. 219(1): p. 252-7.
35. Eloubeidi, M.A., et al., Endoscopic ultrasound-guided fine-needle aspiration in patients with non-small cell lung cancer and prior negative mediastinoscopy. *Ann Thorac Surg*, 2005. 80(4): p. 1231-9.
36. Gress, F.G., et al., Endoscopic ultrasonography, fine-needle aspiration biopsy guided by endoscopic ultrasonography, and computed tomography in the preoperative staging of non-small-cell lung cancer: a comparison study. *Ann Intern Med*, 1997. 127(8 Pt 1): p. 604-12.
37. Sortini, A., et al., [Video-assisted mediastinoscopy. A new application of television technology in surgery]. *Minerva Chir*, 1994. 49(9): p. 803-5.
38. Leschber, G., G. Holinka, and A. Linder, Video-assisted mediastinoscopic lymphadenectomy (VAMLA)--a method for systematic mediastinal lymphnode dissection. *Eur J Cardiothorac Surg*, 2003. 24(2): p. 192-5.
39. Venissac, N., M. Alifano, and J. Mouroux, Video-assisted mediastinoscopy: experience from 240 consecutive cases. *Ann Thorac Surg*, 2003. 76(1): p. 208-12.
40. Hammoud, Z.T., et al., The current role of mediastinoscopy in the evaluation of thoracic disease. *J Thorac Cardiovasc Surg*, 1999. 118(5): p. 894-9.
41. Coughlin, M., et al., Role of mediastinoscopy in pretreatment staging of patients with primary lung cancer. *Ann Thorac Surg*, 1985. 40(6): p. 556-60.
42. Luke, W.P., et al., Prospective evaluation of mediastinoscopy for assessment of carcinoma of the lung. *J Thorac Cardiovasc Surg*, 1986. 91(1): p. 53-6.
43. Detterbeck, F.C., et al., Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*, 2007. 132(3 Suppl): p. 202S-220S.
44. Best, L.A., et al., The contribution of anterior mediastinotomy in the diagnosis and evaluation of diseases of the mediastinum and lung. *Ann Thorac Surg*, 1987. 43(1): p. 78-81.
45. Page, A., et al., Surgical treatment of bronchogenic carcinoma: the importance of staging in evaluating late survival. *Can J Surg*, 1987. 30(2): p. 96-9.
46. Aleman, C., et al., The value of chest roentgenography in the diagnosis of pneumothorax after thoracentesis. *Am J Med*, 1999. 107(4): p. 340-3.

47. Light, R.W., Clinical practice. Pleural effusion. *N Engl J Med*, 2002. 346(25): p. 1971-7.
48. Light, R.W., Pleural diseases. *Curr Opin Pulm Med*, 2003. 9(4): p. 251-3.
49. Landreneau, R.J., et al., Thoracoscopic mediastinal lymph node sampling: useful for mediastinal lymph node stations inaccessible by cervical mediastinoscopy. *J Thorac Cardiovasc Surg*, 1993. 106(3): p. 554-8.
50. Loscertales, J., et al., The use of videoassisted thoracic surgery in lung cancer: evaluation of resectability in 296 patients and 71 pulmonary exeresis with radical lymphadenectomy. *Eur J Cardiothorac Surg*, 1997. 12(6): p. 892-7.
51. Eggeling, S., et al., Invasive staging of non-small cell lung cancer--a prospective study. *Eur J Cardiothorac Surg*, 2002. 22(5): p. 679-84.
52. Massone, P.P., et al., The real impact and usefulness of video-assisted thoracoscopic surgery in the diagnosis and therapy of clinical lymphadenopathies of the mediastinum. *Ann Surg Oncol*, 2003. 10(10): p. 1197-202.
53. Sebastian-Quetglas, F., et al., Clinical value of video-assisted thoracoscopy for preoperative staging of non-small cell lung cancer. A prospective study of 105 patients. *Lung Cancer*, 2003. 42(3): p. 297-301.
54. De Giacomo, T., et al., Thoracoscopic staging of IIIB non-small cell lung cancer before neoadjuvant therapy. *Ann Thorac Surg*, 1997. 64(5): p. 1409-11.
55. Rikova, K., et al., Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell,* 2007. 131(6): p. 1190-203.
56. Koivunen, J.P., et al., EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. *Clin Cancer Res*, 2008. 14(13): p. 4275-83.
57. Shaw, A.T., et al., Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol*, 2009. 27(26): p. 4247-53.
58. Wang, F., et al., Comparison of Epidermal Growth Factor Receptor Mutations between Primary Tumors and Lymph Nodes in Non-small Cell Lung Cancer: a Review and Meta-analysis of Published Data. *Asian Pac J Cancer Prev*, 2014. 15(11): p. 4493-7.
59. Yashima, H., et al., Assessment of DDR2, BRAF, EGFR and KRAS mutations as therapeutic targets in non-adenocarcinoma lung cancer patients. *Mol Clin Oncol,* 2014. 2(5): p. 714-718.
60. Marchetti, A., et al., EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. *J Clin Oncol*, 2005. 23(4): p. 857-65.

Chapter

2

Surgery for Lung Cancer Patients

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Introduction

Surgery is one of the main options for treating patients who are diagnosed with lung cancer. Sometimes surgery is the only treatment necessary, and sometimes surgery is combined with chemotherapy and/or radiation therapy. It is not always easy to determine which treatment or combination of treatments may be necessary. Therefore, meeting with a surgeon who is specially trained in lung surgery is an important step in the management of lung cancer.

Many patients are nervous about surgery. We hope that this chapter will prepare the patient and his or her support team for meeting with a surgeon and for surgery. This chapter has been divided into 7 sections to address the following questions:

1. When is surgery used to treat lung cancer?
2. What types of surgery are used to treat lung cancer?
3. How do I prepare for surgery?
4. What can I expect the day of surgery?
5. What can I expect during the hospital stay?
6. What is the recovery from lung surgery like?
7. Am I cured?

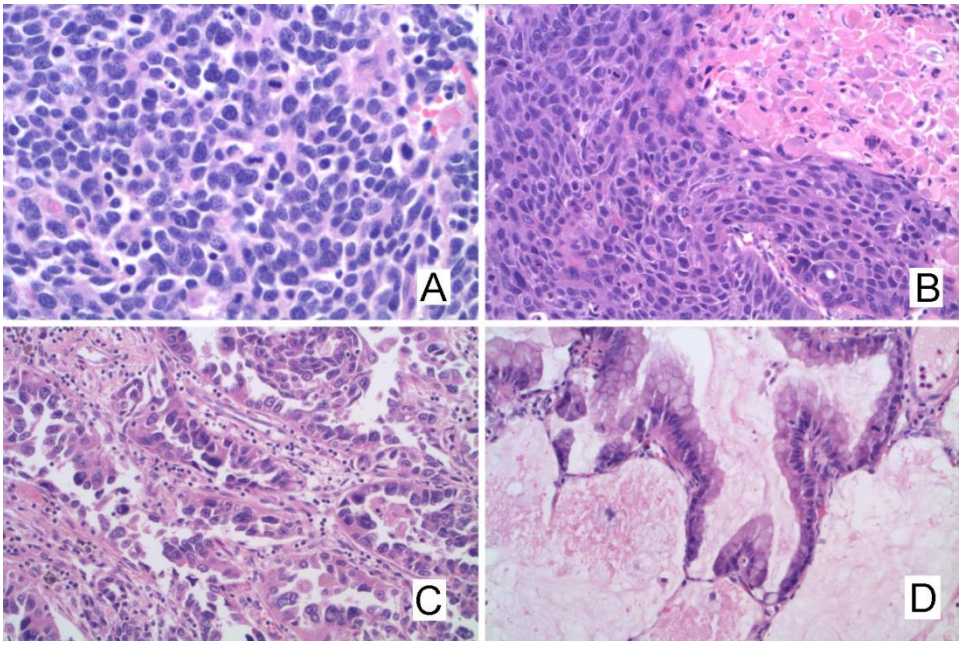
1. When Surgery is used to Treat Lung Cancer

The first important decision about surgery is choosing when to operate and when not to operate, because not everyone with lung cancer will benefit from surgery. There are two categories of lung cancer: small cell lung cancer and non-small cell lung cancer (Figure 1). Surgery is not usually used to treat people with small cell lung cancer, and most of this chapter will discuss non-small cell lung cancer.

Surgery for Non-small Cell Lung Cancer

Non-small cell lung cancer includes several different subtypes (Figure 1), but the treatment for all these subtypes is similar. After a person is diagnosed with non-small cell lung cancer, the decision to proceed with surgery is based on two factors: (1) the stage of the cancer and (2) the ability of the patient to function without the cancerous portion of lung. We will discuss these two factors in the next two sections of this chapter.

Figure 1: Lung Cancer, as seen through the microscope



Images courtesy of Jey-Hsin Chen, MD, PhD

Figure 1: A: Small cell carcinoma. B: Squamous cell carcinoma. C: Adenocarcinoma. D: Bronchoalveolar carcinoma. B, C, and D are all different types of non-small cell lung cancer.

Lung Cancer Staging from the Surgeon's Perspective

After a diagnosis of cancer has been made, the most important question is, "How far has it spread?" The medical term for the answer to this question is the "stage" of the cancer. With imaging tests, usually the combination of a positron emission tomography (PET) scan and a computed tomography (CT) scan, the surgeon can determine the location of the cancer and whether the cancer is confined to the lung or has spread to other areas in the body such as lymph nodes, the other lung, the brain, or other organs. These findings allow the surgeon to classify lung cancer into one of the four stages. Surgery has a potentially curative role in non-small cell lung cancers that are stages I to III (Table 1).

Table 1. Treatment of Lung Cancer by Stage[1]

Stage	Defining characteristics	Common treatment options
I	Small tumor with no lymph node involvement	Usually surgery, sometimes followed by chemotherapy, sometimes radiation therapy
II	Larger tumor or lymph node involvement, but only nodes within the affected lung	Usually surgery, usually followed by chemotherapy, sometimes radiation
III	Tumor very large or invasive, or lymph node involvement in the central chest (mediastinum)	Usually chemotherapy and radiation, sometimes followed by surgery
IV	Distant spread	Usually chemotherapy, sometimes radiation therapy. Rarely surgery to relieve specific symptoms

Surgery usually is the first step in the treatment of Stage I and II non-small cell lung cancers. In Stage III cancers, chemotherapy with or without radiation therapy is given first and surgery follows if it will potentially be beneficial. The distinguishing feature between stages I, II, and III is the involvement of lymph nodes with cancer. In stage I, cancer has not spread to the lymph nodes. In stage II, the lymph nodes that are involved are located within the section of lung being removed. In stage III, the lymph nodes involved are outside of the lung and organized around the main airway in the center of the chest, in the area of the body called the mediastinum (Figure 2). When the cancer has spread to the lymph nodes in the mediastinum, surgery alone is not enough treatment. Studies have shown that chemotherapy with or without radiation therapy, sometimes combined with surgery, has a better outcome than surgery alone for treatment of Stage III cancers.

Figure 2: Mediastinum

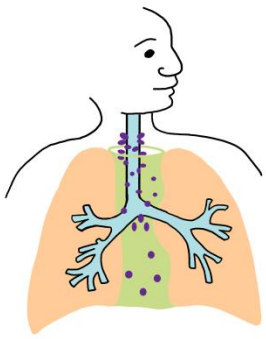


Illustration by Alexandra Hunt, MD

Figure 2: The green-shaded area is the mediastinum. Purple dots around the airways are the mediastinal lymph nodes.

Therefore, it is important to determine whether the lymph nodes in the center of the chest (the mediastinum) are involved with cancer, because these nodes determine whether or not surgery is the first treatment. Imaging studies such as PET and CT scans are the first tests to evaluate the mediastinal lymph nodes, but in 8% to 10% of cases there is cancer in these nodes that is missed by PET and CT scans.

Imaging tests also may be falsely positive when there is actually no cancer in the mediastinal nodes. It is important to know more definitely whether the cancer involves the mediastinal nodes, to decide whether to start with surgery or chemotherapy, so a biopsy (a small tissue sample) of the mediastinal lymph nodes usually is recommended before lung cancer surgery.

Mediastinal lymph nodes may be biopsied in several different ways. The two most common ways are (1) with a bronchoscope (a flexible camera that is inserted through the windpipe) and ultrasound imaging guiding a small needle or (2) an operation (mediastinoscopy). During mediastinoscopy, a surgeon makes a small incision in the neck just above the breastbone and puts a camera behind the breastbone to take tissue samples of the mediastinal lymph nodes around the windpipe. (Figure 3)

Figure 3: Mediastinoscopy

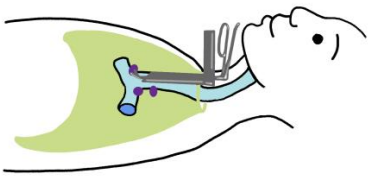


Illustration by Alexandra Hunt, MD

Figure 3: Mediastinoscopy: a scope and instruments are used to sample the mediastinal lymph nodes.

If the biopsy of the mediastinal lymph nodes shows no cancer, then we presume the patient to be in stage I or II and recommend surgical removal of the lung cancer. However, if there are cancer cells in these lymph nodes, chemotherapy with or without radiation therapy usually is the first treatment, sometimes followed by surgery.

Surgery in Stage IV Cancer

If cancer has spread to distant sites, it may not be possible or beneficial to remove all the cancer with surgery. Additionally, if the cancer invades structures that cannot be removed (for example, the heart), then surgery may not be appropriate as primary treatment. However, there can be a role for surgery in widespread cancer if surgery will help relieve some of the symptoms caused by the cancer. If the cancer is blocking an airway, a limited procedure might be done to unplug the airway. When advanced cancer blocks the lymph channels draining the space around the lung, fluid can build up in this space. Surgery may be required to drain this space and re-expand the lung to relieve the symptoms associated with the fluid. However, most surgery for lung cancer is done for limited disease (lower stages), usually with the goal of curing the cancer. Occasionally, stage IV cancer that has spread to only a single location outside of the lung such as the brain or adrenal gland may be a candidate for surgical treatment of both the metastasis and the primary lung cancer. This special situation should be discussed with the cancer team.

Preoperative Testing

Even if a cancer can be removed based on the results of the staging tests, not every person can have part of their lung removed and return safely to their normal life outside the hospital. Every operation has risks, and one of the difficult aspects of surgery is choosing which people will do well after surgery and which people will have difficulty recovering from surgery. Surgeons use many different tests to help predict which patients should or should not have surgery.

The most important test we use to decide when to operate is the simplest: a thorough history and physical examination. The surgeon asks questions about the patient's current state of health and past medical history, and performs a physical examination to make sure the patient is prepared for the operation.

Problem areas that come up during the history and physical examination may be evaluated with more testing. There are two major areas to evaluate with all of these tests: we want to make sure that the patient is healthy enough to safely have surgery, and we want to find any other health problems that can be improved before the operation. For example, diabetes should be well controlled before surgery, and it is very important to stop smoking before lung surgery. (See Chapter 11: *How to Quit Smoking Confidently and Successfully*) After dealing with each person's individual health problems, the preoperative workup for lung surgery focuses on the lungs and the heart.

Lung and Heart Function

Surgery for lung cancer usually involves removing part of a person's lung. Therefore, it is important to be sure that the person will be left with enough functioning lung after surgery to provide oxygen to, and eliminate carbon dioxide from, the body. A simple test such as climbing stairs or walking as far as possible in six minutes may be used to give an overall idea of heart and lung fitness, but more detailed testing usually is required before lung surgery.

The tests most commonly used to evaluate the lungs before surgery are called pulmonary function tests. These tests check the lung volumes, air flows, and gas exchange capabilities. They give a baseline measure of lung function and help predict whether the lungs will be able to do their job adequately after part of the lung is removed during surgery. The tests are designed to measure how much air can be moved in and out of the lungs, and how quickly gases diffuse from the lungs into the blood. The tests involve breathing through a machine which measures air flow, and inhaling a marker gas (a very small amount of carbon monoxide) to test how quickly that gas is removed from the air in the lungs. It is important to stop smoking before the pulmonary function test, because blood levels of carbon monoxide are elevated after smoking and this can interfere with the test. Medication may be given during the test to determine whether lung function can be improved with medication.

If a person's pulmonary function tests show limited lung function, then a quantitative ventilation/perfusion scan (QV/Q scan) is used to determine how much air and blood flow go to each section of the lung. This allows the surgeon to calculate how much lung function will remain after the section of lung containing the cancer is removed, thus predicting how the person will respond to surgery. If concerns remain after the QV/Q test, the patient may be asked to have other testing, including exercise tests and blood tests. The purpose of all the lung function tests is

to predict whether there will be enough lung function remaining to allow the patient to return to normal life after surgical removal of the part of the lung with the cancer.

Often it is also necessary to evaluate the patient's heart before lung surgery because the risk factors for heart disease are often present in patients who develop lung cancer. Furthermore, surgery places the body under stress. The body mobilizes every resource available to heal after surgery, and this effort can place major stress on the heart, especially when an entire lung has been removed (pneumonectomy). Therefore, it is important to check that the heart is functioning adequately before performing an operation. In some cases, a history and physical examination can provide enough information to reassure the treatment team that the heart will be able to safely power the body through the stress of surgery. If further testing is required, it may be simply an electrocardiogram (ECG). Another test that might help predict how the heart will respond to the stress of surgery is a stress test, in which stress is placed on the heart by walking on a treadmill or by injecting a medication that stresses the heart. Imaging of the heart may include an ultrasound test or a scan. If any problems with the heart are found during testing, additional procedures or medicines may be required to make sure the heart is as ready as possible before surgery.

Alternatives to Surgery

If surgery is not recommended after the staging workup and heart and lung testing, there are several alternative treatments available. These treatments also may be used before or after surgery, to give the best chance that cancer will not spread to other parts of the body or recur in the lungs. Radiation therapy can be used to kill cancer cells in a particular part of the body. The radiation is focused at the known or suspected location of the cancer. New highly-focused radiation techniques allow maximum doses of radiation to be delivered precisely to the cancer, killing the cancer while sparing as much normal tissue as possible. In some people with stage I or II cancers with poor lung function, focused radiation may be recommended instead of surgery. Chemotherapy medicines, given either intravenously or as pills, kill cancer cells throughout the body. Chemotherapy medicines spread through the entire body, and they can kill cancer cells that haven't been discovered or are too small to show up on imaging.

Surgery for Small Cell Lung Cancer

Small cell lung cancer is very different from non-small cell lung cancer. Small cell lung cancer tends to spread more quickly than non-small cell cancer, and surgery alone has a very small chance of curing small cell lung cancer, even in the early stages. Chemotherapy and radiation are the primary treatments for most small cell lung cancers. However, surgery may benefit a small group of patients with early small cell lung cancer, used in combination with chemotherapy, with or without radiation therapy. Surgical sampling of the lymph nodes from the middle of the chest is also part of the staging workup of small cell lung cancer if surgery is contemplated. (See Chapter 5: *Treatment for Small Cell Lung Cancer*)

2. Types of Surgery to Treat Lung Cancer

Various approaches may be used to remove lung cancer. The most common approach is an incision between the ribs to access the lung and surrounding lymph nodes (Figure 4a). This incision (a

thoracotomy) wraps around the side of the chest, parallel with the ribs, and allows the surgeon direct access to the lungs and the other contents of the chest.

Figure 4a: Thoracotomy

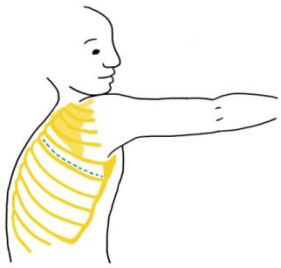


Illustration by Alexandra Hunt, MD

To limit the pain and shorten the recovery after surgery, sometimes it is possible to do surgery without performing a full thoracotomy. One way to do this is to use a video camera that goes into the chest through a small incision, combined with instruments that enter the chest through other small incisions. This type of surgery is called video-assisted thoracic surgery (VATS) (Figure 4b). A further refinement of VATS is to mount the instruments to a robot (Figure 4c), which allows very precise control when manipulating the lung and delicate surrounding tissues.

Figure 4b: Video-Assisted Thoracic Surgery (VATS) and robotic thoracic surgery incisions

Illustration by Alexandra Hunt, MD

Figure 4c: Robotic thoracic surgery

Illustration by Alexandra Hunt, MD

Besides deciding on which approach will be used to remove the portion of lung containing the cancer, a surgeon must decide exactly what to remove. The first priority is to remove the cancer. It is important to remove some normal surrounding lung along with the cancer, because there are microscopic extensions of the cancer that can grow and cause cancer recurrence if they are not removed. The most common surgery for lung cancer removes the entire lobe containing the cancer, together with the lymph nodes inside the lobe (Figure 5a). Removing the entire lobe allows the best possibility for long term survival.[2] If there will not be enough healthy lung left after an entire lobe is removed, the surgeon may decide to remove a wedge of lung or the segment that contains the cancer (Figure 5b). If the tumor is too close to the center of the chest, or if the main airways of the lung are involved, sometimes it may be necessary to remove the entire lung that is affected by cancer (a pneumonectomy, Figure 5c). Airways may be divided and sewn back together (a "sleeve resection"), if this allows complete removal of the cancer without removing as much healthy lung tissue (Figure 5d). In addition to removing the part of the lung that is affected by the cancer, lung cancer surgeons remove lymph nodes in the chest at the time of lung surgery, to make sure that the cancer has not spread to these lymph nodes.

Figures 5a-d: Types of Resection

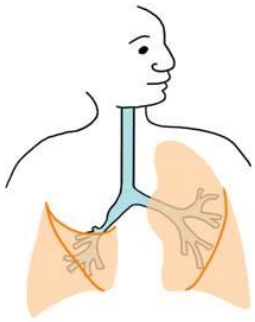


Figure 5a: Lobectomy

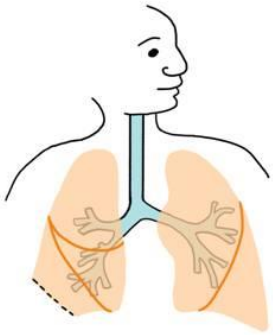


Figure 5b: Wedge Resection

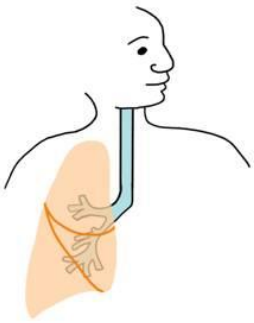


Figure 5c:
Pneumonectomy

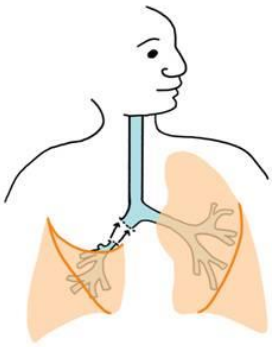


Figure 5d:
Sleeve resection

Illustrations by Alexandra Hunt, MD

3. How do I Prepare for Surgery?

Deciding to proceed with surgery can be intimidating because many aspects of surgery are beyond the patient's control, and this loss of control can be frightening. However, there are many factors about surgery that the patient *can* control, and in this section we will discuss a few things that the patient can do to make their surgery go more smoothly.

Preoperatively, the most important thing that a person can do is to stop smoking if they have not done so already. Smoking before surgery puts people at risk for serious complications (Table 2).

Table 2. Risks of Smoking at the Time of Surgery[3,4]

Complication	Smokers	Non-smokers
Pneumonia	23%	3%
Incisional complications	16%	3%
Cardiovascular complications	10%	0%

Smoking paralyzes the tiny hairs called cilia that clear secretions out of the airways. Keeping the lungs clean after surgery is an important way to prevent complications after surgery, such as infections and inadequate lung function. Quitting smoking is a simple step that can dramatically improve the chances that surgery will go well, but quitting can be very difficult to do. There are many resources available to help people quit smoking, and the chance of being able to quit successfully is much better if these resources are used.[5] Even if a smoker cannot quit long term, they can improve their outcome after surgery if they are able to stop smoking before surgery[6] (ideally at least 8 weeks before surgery[7]) and stay off cigarettes until they have successfully healed from surgery.[8] (See Chapter 11: *How to Quit Smoking Confidently and Successfully*).

Besides quitting smoking, there are several other things that a person who is anticipating surgery can do to proactively take some control over their surgical course. The patient's body will be stressed by the surgery, so it is important to prepare as much as possible beforehand. Exercise, proper nutrition, and vitamins (including antioxidants) can help prevent complications from surgery. Even if there are only one or two weeks between the diagnosis and the scheduled date of surgery, every day helps. Making the body as healthy as possible before surgery is a good way to be an active participant in the fight against the cancer.

A daily exercise routine can improve the fitness of the heart and lungs and prepare the body for the stress of surgery. It is important to get approval from your doctor before starting an exercise regimen. Proper nutrition, including a high protein diet, can build up the body's store of building blocks to use during recovery after the operation.[9] Vitamins and antioxidants can be important to help fight off infections and rebuild tissues after surgery.[10]

4. What Can I Expect the Day of Surgery?

The day of surgery can be frightening because most people do not know what surgery will be like. This section will describe what to expect on the day of surgery, so there are fewer unknowns and fewer surprises.

It is important to arrive at the hospital in plenty of time before the scheduled surgery, to make sure that there is enough time to get ready. After the patient arrives at the hospital, he or she is registered into the hospital system and receives an identifying band to remind all the hospital staff of his or her correct identity, which will be checked repeatedly to make sure that the correct procedures are performed on the correct patient. An intravenous line usually is started for medications. Various tests may be performed, such as blood tests, to make sure that there are no surprises during the course of the operation. Many of the same questions will be asked to recheck the correct information about the patient, such as allergies to medications.

The patient may be asked to stop certain medications before surgery. This is especially important with some blood pressure medications and medications that interfere with blood clotting such as aspirin, warfarin, and clopidogrel. Supplements and naturopathic formulations should be noted on the medication list. Fish oil, omega-3 supplements, *Ginkgo biloba*, and vitamin E can slow blood clotting and should be discussed with the surgeon. To decrease the possibility of vomiting during anesthesia or sedation, it is important to not eat or drink anything before the procedure. Your doctor will give specific guidelines, but the usual rule is that there should be no food or drink consumed after midnight before surgery. Morning medications usually may be taken with a sip of water.

The patient will meet many new people the day of surgery. There will be an operating room nurse who is in charge of making sure that the operating room works properly. In the operating room, the scrub technologist is in charge of making sure that the surgeon has the equipment he or she needs and keeping the surgical field sterile. The surgeon usually will have an assistant. There will be a doctor or a specialized nurse who will give anesthesia. The anesthetist may talk to the patient about placing an epidural catheter, which is a way of delivering pain medication directly to the fibers in the spinal cord that conduct pain signals to the brain.

The patient will be given an anti-anxiety medication before going to the operating room. In the operating room, the patient will be asked to move onto the operating room bed. This bed is quite narrow, so that the surgeon can easily reach the patient. The patient will be covered in warm blankets because it is important to maintain the body's usual temperature during the operation to help prevent the patient from getting complications. General anesthesia, in which the patient is completely asleep, is required for most lung operations. After the patient is asleep, the anesthetist places a breathing tube through the mouth into the windpipe. This tube sometimes causes a sore throat after surgery. The patient is positioned on the operating room bed, the skin is scrubbed with an antibacterial scrub, and the patient is covered in sterile drapes. A safety pause is performed to confirm that the correct surgery is being performed on the correct patient and the correct side.

The surgeon makes a skin incision, either a small one for the video camera or a larger incision for open surgery. The tissues of the chest wall are moved out of the way, and an opening is made between the ribs large enough to perform the procedure. After the surgeon can see inside the chest, the first step of the procedure is a careful inspection to make sure that the cancer has not spread further than the preoperative

workup indicated and to look for any surprises. If the inspection does not reveal any reason to stop the operation, the surgeon then mobilizes the lung so that it can be moved around more easily into the field of view. Mobilization involves dividing bands of scar tissue and ligaments that hold the lung in place in the chest cavity. After the lung can move freely, the surgeon carefully dissects the lung containing the cancer away from the rest of the body. Specially designed staplers that seal tissue while it is being cut are used to assist with the dissection. The surgeon is always quite careful to not spill cancer into the chest cavity to minimize possibility that the cancer will spread after surgery.

The specimen is removed from the body and given to the pathologist, who carefully cuts the specimen into thin slices, stains the slices, and examines them using a microscope. The pathologist confirms the type of the cancer and assesses how large it is, where it is in relation to the cut edges of the lung and the underlying tissues, and whether lymph nodes are involved. Just like the cancer was staged with imaging and an examination before surgery, the pathologist stages the cancer based on the resected specimen. The staging by the pathologist helps decide whether more therapy (chemotherapy, radiation, or further surgery) is required. The pathologist also tells the surgeon whether the cut edges are free of cancer. If not, more tissue may be taken to get a clean margin. After the cancer has been removed, the surgeon examines the remaining healthy tissues to make sure that all bleeding has stopped, that the remaining lung inflates well, and that no air is leaking out of the remaining healthy lung. After the surgeon is satisfied, he or she usually places a drain to evacuate air and fluid out of the space between the chest wall and the lung (the pleural space). The lung naturally falls away from the chest wall and collapses on itself, but the drain can help hold the lung up against the chest wall. Finally, the surgeon closes the incision and applies sterile dressings. After the procedure is complete, the patient wakes up in the recovery room. Most people are not aware that any time has passed between when anesthesia was started and when they wake up in the recovery room.

Most people stay in the recovery room for a few hours while the anesthesia wears off. There are nurses in the recovery room who carefully monitor patients to make sure that everything is going well after surgery. A chest radiograph usually is done in the recovery room to recheck that the lung has completely re-expanded after surgery and that the tubes and drains are in the correct locations. After the patient is awake enough to leave the recovery room, he or she is brought to a bed in the hospital to continue recovery.

5. What Can I Expect During the Hospital Stay?

Hospital care after major lung surgery is very important for a full recovery. This is one of the most important times for a lung cancer patient to play an active role in his or her care. The more a person is able to clean out and re-expand their lungs after surgery, the smaller is the possibility of getting an infection in the collapsed lung or the space around the lung. For this reason, the surgical team, the nurses, and the physical and respiratory therapists will be repeatedly reminding the patient to cough, take deep breaths, and get out of bed to move around. Staying active after surgery helps the lungs re-expand completely, and helps prevent many different types of complications.[11]

However, it can difficult to be active after surgery because chest surgery can be quite painful. There are many different ways to control pain after surgery, and the hospital team may select a variety of approaches to deal with the pain from surgery. An epidural catheter is a small tube placed alongside the spinal column just outside the membranes that surround the spinal cord. It allows for a continuous dose of medication

to be delivered to the nerves in the spinal cord that transmit pain signals to the brain. A well placed epidural catheter is one of the most effective ways to control pain after chest surgery.[12]

Local anesthetics are medications that block the transmission of pain signals along nerve fibers. They may be used in an epidural catheter, or they may be used to directly block the nerves that supply the chest wall, either during or after surgery. Narcotics (also known as opiates) are another class of medications that help control pain after major surgery. They block pain receptors in the brain, spinal cord, and other tissues. Narcotics may be given through an epidural catheter, intravenously (either by a nurse, or with a machine that gives a dose every time a button is pressed), or by mouth. Narcotics can have several unpleasant side effects, such as constipation, confusion, decrease in the drive to breathe, and itching. To limit the amount of narcotics needed to control pain after surgery, many other types of medicines may be used to help control pain. Pain control is important to keep the patient comfortable and allow the patient to move around, cough, and do breathing exercises to prevent complications after surgery.

The entire team in the hospital is focused on preventing the common problems that may occur after surgery. This is the reason that they gather so much data about each patient. Nurses and nurse's aides check vital signs (including the pain level) several times each day to identify any potential problem early in the course of its development. Radiographs may be taken at several different times during the hospital stay, to make sure that the lung stays fully expanded and that no space develops between the lung and the chest wall. If a chest drain is in place, it is carefully inspected and the amount of fluid coming out of the drain is recorded. Every medication that has been given is documented. All this documentation is focused on making sure that the patient continues to get better all the time, and that any complications that develop are found early.

Despite careful monitoring, complications may occur after surgery. Percentages cited in parentheses are from a large series of lung surgery patients studied at several different hospitals.[13] Air leaks are common after lung surgery (8% persist for > 7 days). They happen when the air in the lung leaks into the pleural space (which is the space between the lung and the chest wall). The body is usually able to seal the leak on its own, but large leaks may require repeat surgery.

Heart problems are common after lung surgery because many people with lung cancer have heart disease, and chest surgery can disturb the heart's normal rhythm. Irregular heart rhythms such as atrial fibrillation occur (14%) after surgery, and heart attacks can occur in the postoperative period (< 1%). The body swells and retains fluid in response to injury, and this fluid may take some time to clear after surgery. Infections are a potential complication of any type of surgery. Pneumonia (3%) and infection of the pleural space (1%) are the most common infections after lung surgery. There is a risk of bleeding after any surgery, but the risk of serious bleeding during or after lung surgery is low (2% need blood transfusion, 1% to 2% need reoperation).

Finally, there is a risk that the person with lung cancer cannot function effectively on the amount of lung remaining after the cancer is removed. This is called respiratory failure (5%), and may result in the need for a mechanical ventilator for a short time after surgery, which is a machine that breathes for patients in the Intensive Care Unit (ICU). Some patients with respiratory failure may need portable supplemental oxygen to breathe at home.

6. What is the Recovery from Lung Cancer Surgery Like?

Recovery does not stop after discharge from the hospital, and problems may occur after the patient returns home. It is important to continue to exercise on a regular basis after coming home after surgery and to keep the lungs clean with lung exercises such as coughing and deep breathing. Pain does not stop after leaving the hospital, and a combination of pain medications may be needed to keep pain at a tolerable level. Narcotic pain medications cause constipation, so it is important to make sure that people who are taking narcotics continue to have regular bowel movements. Stool softeners, fiber, and choosing a healthy diet can help keep the bowels moving.

After lung surgery, lung function usually slowly improves with time, as the remaining lung heals and starts to compensate for the lung that was taken out during surgery. Many people need oxygen for a short time after surgery, and some people are discharged from the hospital with portable oxygen for home use. Oxygen requirements usually decrease with time, and most people that were not on home oxygen before surgery do not require long term oxygen treatment after surgery. The scars also slowly remodel with time and become less noticeable.

The surgeon will want to continue to see the patient in clinic to make sure that the recovery from surgery continues to progress, to answer any questions that may arise, and to put a plan in place for dealing with the cancer in the future. This plan usually involves periodic imaging and checkups to make sure the cancer does not recur. Chemotherapy, radiation, and other treatments may be recommended in addition to surgery either before or after the operation.

7. Am I Cured?

The goal of most cancer surgery is to cure the cancer permanently. After the patient has recovered from surgery, the surgeon and other members of the cancer team will discuss the results of surgery and the final analysis by the pathologist with the patient. Patients who are eligible for surgical treatment usually have early stage cancers, so they are more likely to have long-term survival and cure. However, the long term prognosis after lung cancer surgery is highly variable and depends on the available treatments and the final stage of the cancer.

With modern surgery, possibly accompanied by chemotherapy and radiation, it is common for people with early stage lung cancer to be completely cured (Table 3).

Table 3. Five-Year Survival

Stage I	Stage IIA	Stage IIB	Stage IIIA	Stage IIIB	Stage IV
50-75%	36-46%	26-36%	19-24%	7-9%	2-13%

Table 3. The Percentage of Patients with Non-small Cell Lung Cancer who are Alive Five Years After Diagnosis[14, 15]

For physicians, cure or survival is measured at the five-year mark. Although many people may return to their normal lives after surgery, people often wonder if the cancer will return. The longer people live after

completing their treatment, the smaller risk they have of having the cancer recur. Five years after treatment is completed, we consider a patient to be cured, and we celebrate this landmark with all of our patients who reach it.

Conclusion

Lung cancer is a frightening diagnosis, but treatments have markedly improved in recent years. Surgery to remove the lung that contains the cancer is the mainstay of treatment in early stage non-small cell lung cancer. Successful surgery is a partnership between the surgeon and the patient. The surgeon will thoroughly evaluate the patient with lung cancer to determine if surgery is the best option. The patient should actively participate in his or her care by stopping smoking, remaining active or becoming more active, and eating a healthy diet. The patient and the surgeon need to work together to make sure that the surgical and non-surgical care of lung cancer give the best potential for long term cure of the cancer and a quick return to normal life.

References

1. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2(8):706-14.
2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. *Ann Thorac Surg*. 1995;60(3):615-623.
3. Barrera R, Shi W, Amar D, et al. Smoking and timing of cessation: impact on pulmonary complications after thoracotomy. *Chest*. 2005;127:1977-83.
4. Møller AM, Villebro N, Pedersen T, et al. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet*. 2002;359(9301):114-7.
5. Browning KK, Ahijevych KL, Ross P, et al. Implementing the Agency for Health Care Policy and Research's Smoking Cessation Guideline in a lung cancer surgery clinic. *Oncol Nurs Forum*. 2000;27(8):1248-54.
6. Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. *Anesthesiology*. 2010;112(1):102-7.
7. Warner MA, Offord KP, Warner ME, et al. Role of preoperative cessation of smoking and other factors in postoperative pulmonary complications: a blinded prospective study of coronary artery bypass patients. *Mayo Clin Proc*. 1989;64(6):609–16.
8. Lindström D, Sadr Azodi O, Wladis A, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: a randomized trial. *Ann Surg*. 2008;248(5):739-45.
9. Koretz RL, Avenell A, Lipman TO, et al. Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. *Am J Gastroenterol*. 2007;102(2):412-29.
10. Nathens AB, Neff MJ, Jurkovich GJ, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Ann Surg*. 2002;236(6):814-22.
11. Das-Neves-Pereira JC, Bagan P, Coimbra-Israel AP, et al. Fast-track rehabilitation for lung cancer lobectomy: a five-year experience. *Eur J Cardiothorac Surg*. 2009;36(2):383-91.
12. Svircevic V, van Dijk D, Nierich AP, et al. Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. *Anesthesiology*. 2011;114(2):271-82.
13. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Annals Thorac Surg*. 2006;81(3):1013-9.
14. Rami-Porta R, Crowley JJ, Goldstraw P. The revised TNM staging system for lung cancer. *Ann Thorac Cardiovasc Surg*. 2009;15(1):4-9.

15. Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J (editors). SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program, NIH Pub. No. 07-6215, Bethesda, MD, 2007..

Chapter

3

Chemotherapy for Non-small Cell Lung Cancer

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Introduction

There are several treatment strategies available for non-small cell lung cancer (NSCLC). These include surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, and palliative care. Patients may be treated with one type of treatment or a combination of treatments. This chapter reviews the use of chemotherapy and targeted therapies in the treatment of NSCLC.

Chemotherapy is a form of treatment that is distributed throughout the body to kill cancer cells. Chemotherapy kills not only the rapidly dividing cancer cells but also some rapidly dividing normal cells in the body. It is usually given intravenously. Some of the normal cells that can be affected by chemotherapy include cells in the gastrointestinal tract, bone marrow, and hair follicles. This effect on normal tissue results in side effects.

Chemotherapy agents that are selected to treat NSCLC have been approved for use after extensive clinical research. Some of these chemotherapy agents have been approved in combination with each other. Chemotherapy agents are identified by the generic name and brand names, and either name is used when treatment is explained to patients (Appendix 1).

Targeted therapies are agents that target unique abnormalities found in specific tumors. These therapies function by inhibiting the blood supply to tumors and inhibiting growth factors needed for tumor growth. Cancerous tumors require blood supply for nutrition and to survive. This process is referred to as angiogenesis. Some targeted therapies, such as monoclonal antibodies, prevent tumor cells from developing blood vessels therefore blocking nutrition, leading to tumor death. These agents are referred to as anti-angiogenic agents. The most common anti-angiogenic agents block the vascular endothelial growth factor (VEGF). Other targeted therapies, called small molecules, block growth factors or "driver-mutations" that are needed for tumors to grow and spread. It is necessary to identify if tumor cell growth relies on a "driver-mutation" to survive. The most common driver mutation targets in lung cancer are epidermal growth factor receptor (EGFR), EML4-ALK, and HER2.1, 2 Targeted therapies may be administered intravenously or taken orally. Targeted therapies may be referred to by their generic or brand names (Appendix 2).

Treatment Team

Treatment of lung cancer requires a multidisciplinary approach. Several healthcare professionals are involved in patient care, and each has expertise in the treatment of lung cancer. It is valuable to seek treatment at a facility that has a lung cancer specialty program and a treatment team with which the patient is comfortable.

Medical Oncologist

Following a diagnosis of NSCLC, the patient is referred to a medical oncologist, a physician who specializes in the medical management of cancer. In cancer centers, hospitals, or large clinics, the physicians may specialize in one type of cancer. In smaller community practices, the oncologist may treat patients with a variety of cancers. It is important for the patient to see an oncologist who has a special interest in treating lung cancer.

The medical oncologist reviews the medical history, pathology, and diagnostic tests, and performs a physical examination. Treatment recommendations are based on the stage of the disease, physical condition, functional status and history of previous treatment for cancer. Functional or Performance status is assessed by the ability of the patient to carry out their normal daily activities (Table 1).

The medical oncologist prescribes and monitors response to treatment and performs follow-up evaluations. The decision to administer chemotherapy does not depend on a patient's age, and many studies have shown that elderly patients can successfully receive chemotherapy.[3] However, treatment of lung cancer varies from one person to another, and the type of chemotherapy prescribed may depend on the specifics of the patient's disease.

Table 1. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry out all daily activities
1	Decreased activity, but able to walk and carry out light activities
	(light house work or office work)
2	Able to walk and care for self, but unable to carry out any work activities.
	Up and active > 50% waking hours
3	Able to do only minimal self-care; confined to bed or chair > 50% waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to
	bed or chair

Advanced Practice Provider (Nurse Practitioner or Physician Assistant)
The oncology advanced practice provider is an integral member of the treatment team. An advanced practice nurse has received additional master's level education and certification beyond nursing school. Physician Assistants complete a master's level education beyond undergraduate education. The advanced practice provider is involved in the overall coordination of the cancer care, performs physical examinations, and may diagnose and treat health problems related to cancer and cancer treatment. The advanced practice provider may order diagnostic tests, perform certain procedures, and prescribe medications and other treatments.

Oncology Nurse
The oncology nurse works closely with the physician and advanced practice provider to provide optimal care to the patient and family. This nurse has special training and certification in administering chemotherapy and managing side effects. The oncology nurse may start the intravenous line, administer the chemotherapy, and monitor for symptoms during and after the infusion. This nurse also reinforces education about managing side effects and coordinates additional nursing services needed in the home.

Social Worker
A licensed clinical oncology social worker specializes in assessing psychological, social, and emotional concerns, counseling support for cancer patients and families, and assisting with referrals to hospital and community resources. The oncology social worker may collaborate with the interdisciplinary team about care plans at different stages of illness. Many oncology social workers facilitate support groups for patients and families and may offer groups that address the needs of specific cancer patients such as those with lung cancer. The patient may find out about available social work services by asking their care providers, local hospital, or cancer organizations such as the American Cancer Society.

Pharmacist
A licensed pharmacist who specializes in oncology may be part of your treatment team if the patient is being treated at a large oncology practice, designated cancer center or hospital. The pharmacist will review your treatment regimen, medications and prepare your chemotherapy infusion. They are available to help council you about how to take your medications/chemotherapy, what the expected side effects are, and how to self-manage common side effects as well as educate you when to seek medical care.

Nutritionist
A licensed nutritionist specializes in assessing nutritional needs during treatment. This healthcare specialist may assist the patient and family monitor dietary intake and may provide suggestions to improve nutrition during and after treatment.

Chemotherapy for Lung Cancer

Goals of Treatment

The purpose of chemotherapy treatment may vary, depending on the patient's situation. Treatment goals may include curing the cancer, keeping the cancer under control and preventing it from spreading (metastasizing) to other areas of the body, decreasing tumor size to minimize pain and other negative symptoms (palliative), and treating recurrent disease.

Chemotherapy may be administered at different times and in different sequences during the disease course. Neoadjuvant chemotherapy, given before surgery, may decrease tumor size, so surgery is more effective. Adjuvant chemotherapy is given after surgery to kill tumor cells that might be remaining in the body. Concurrent chemotherapy is chemotherapy given with radiation therapy. This may be done before or after surgical resection (tri-modality treatment). Chemotherapy can also be given along without regards to surgery or radiation therapy.

Administration of Chemotherapy

Chemotherapy and some targeted therapies may be given in an infusion center clinic, a physician's office, or a hospital. The safest location for receiving treatment may depend on the type of chemotherapy and duration of infusion. Chemotherapy agents may be used alone or in combination with other agents, and treatment is given on a schedule, in blocks of time known as cycles. The specific cycles vary depending on the treatment combination. Each chemotherapy cycle usually is followed by a recovery period to allow the normal cells to repair. However, the chemotherapy schedule may be changed when the patient experiences severe side effects from treatment.

Chemotherapy is given intravenously via the bloodstream throughout the entire body. Techniques for intravenous chemotherapy include:

- Peripheral intravenous: A catheter or needle is inserted into an arm vein on the day of the chemotherapy infusion, and is removed at the end of treatment.

- Infusion port: This is a more permanent device that is placed under the skin, includes a catheter that tunnels into a larger vein, and remains in place throughout the treatment course. A specially trained chemotherapy nurse places a needle into the port through the skin to administer chemotherapy, give hydration, and draw blood samples. Only specially trained nurses or providers can access the port. When the needle is not in place, the patient may participate in normal activities, including showering.

- Peripherally inserted central catheter (PICC): This is a catheter placed through a large vein in the arm, neck, or chest for chemotherapy, hydration, or drawing blood. The catheter extends outside the body, and only specially trained chemotherapy nurses access this catheter. This catheter requires a bandage dressing over the exit site to prevent infections. The catheter must be protected from getting wet. The chemotherapy nurse educates patients in how to care for the catheter and dressing at home.

- Pump: Some chemotherapy treatments require a continuous infusion for several hours or days. An infusion pump ensures that the accurate about of chemotherapy is infused into the body at a specific rate.

Some chemotherapy drugs are given as an injection into the skin or muscle, and some are taken by mouth. Targeted therapies are usually taken by mouth in pill form on a daily basis.

Targeted therapies that are taken orally usually have to be ordered through a specialty pharmacy. The processing of the prescription may take several days. In many cases, the prescription will be delivered to the patient via US postal mail. It is important for the patient to notify their healthcare team if there is delay in obtaining the prescription. Once the patient receives the prescription for the targeted oral therapy, health care provider may want to review with the patient specific instructions for taking the therapy. Often targeted therapies need to be taken hours after or before meals and other medications.

Evaluation before the start of chemotherapy includes a physical examination to assess performance status (Table 1) and pulmonary, cardiac, and neurologic function. Blood tests, diagnostic tests, and other procedures are necessary. Blood tests are obtained on a regular schedule to evaluate for side effects of treatment. The complete blood count assesses white blood cells, red blood cells (hemoglobin or hematocrit), and platelets. Complete metabolic chemistry panel includes assessment of electrolytes (potassium, calcium, sodium, chloride, and magnesium), kidney function, and liver function.

Prior to starting treatment, prescriptions are provided for supportive care medications that may be required during chemotherapy. Supportive care medications are those that treat the side effects of your cancer treatment. It is important to have the prescriptions filled before treatment and tell the healthcare team about any difficulties obtaining or starting the medications as prescribed. Smoking should be stopped before chemotherapy, and many centers offer smoking cessation counseling. Exercise is important to maintain energy, and it is important to have a balance between maintaining physical activity and getting adequate rest. A normal, balanced diet is recommended during treatment. It is important that the patient informs the healthcare team about all medications, including non-prescription ("over the counter") medication, because some medications may interfere with the chemotherapy, making treatment less effective or side effects more severe.

Treatment Procedure

On the day of treatment, the patient is evaluated by the physician or advanced practice provider to evaluate and address any changes in how the patient is feeling. The height and weight are measured because these measurements are used to calculate the dose of chemotherapy. The oncology nurse will insert the intravenous line or access the infusion port. Intravenous fluids (hydration) may be given before the chemotherapy. Other medications are given to help prevent side effects of treatment such as nausea or allergic reaction. The nurse administers the chemotherapy through the intravenous line, either by syringe or pump infusion. During and after treatment, the patient is monitored closely and notifies the nurse about any unusual symptoms or side effects. Information is

given to the patient about the chemotherapy and possible side effects, and a schedule for future appointments is provided.

During and after chemotherapy, the patient is routinely evaluated, for potential side effects, with a physical examination and blood tests. The healthcare team asks the patient about any possible side effects, symptoms of disease, and strategies they have used for symptom management. The patient is encouraged to contact the healthcare team for any unusual side effects or new symptoms that occur post chemotherapy infusion.

The oncologist performs tests intermittently throughout the treatment course to assess the effectiveness of treatment. This evaluation may include a computerized tomography (CT) scan, magnetic resonance imaging (MRI) scan, or positron emission tomography (PET) scan. The MRI and CT scans provide a 3-dimensional view of the organs examined, and the PET scan may distinguish normal cells from tumor cells that are rapidly dividing. The diagnostic tests may be compared with tests from the time of diagnosis. The radiologist and oncologist review the imaging tests to measure the tumor response to treatment.

If the cancer has been surgically removed, the patient might receive a prescribed number of cycles of chemotherapy with or without radiation therapy. After completing this regimen, repeat (restaging) scans are performed. However, if chemotherapy is the primary treatment modality, restaging scans are usually done after every two to three cycles of chemotherapy.

Chemotherapy for Different Cancer Stages

Early Stage Lung Cancer (Stage I and II)

Stage I NSCLC is a small tumor with no lymph node involvement. Stage II NSCLC is a small or larger tumor with lymph node involvement confined to one lung. The initial treatment of choice for stage I and II NSCLC is surgery, but chemotherapy may be incorporated into the treatment plan as well.[4-12] Radiation therapy, including stereotactic radiosurgery may be necessary if the primary tumor is not able to be surgically removed.[4] Stage I NSCLC may recur at local (regional) or distant (metastatic) sites. If the disease recurs at the same site, the area may be treated with local radiation therapy. Patients may be asked to participate in clinical trials to investigate adjuvant (postoperative) chemotherapy.

For stage II NSCLC, chemotherapy and surgery are effective treatments and improve patient survival. Chemotherapy may be used before surgery (neoadjuvant) or after surgery (adjuvant). Neoadjuvant chemotherapy may decrease the tumor size so surgery may be less extensive. Chemotherapy also may treat cancer cells that may have traveled to other parts of the body (micrometastasis) but cannot be identified with current diagnostic scans.

Stage IIIA Lung Cancer

Stage III A NSCLC is a large tumor with invasion or lymph node involvement in the central chest region (mediastinum). Most cases of stage IIIA NSCLC are not surgically resectable because of the large extent of disease. Stage IIIA NSCLC often receives combination treatment, with four to six cycles of chemotherapy, in one of the following schedules:[4, 9-16] (Table 2,3,4)

- Neoadjuvant chemotherapy: This is chemotherapy before surgery.
- Induction chemotherapy before concurrent chemotherapy: This is chemotherapy alone before a course of chemotherapy and radiation therapy.
- Neoadjuvant chemotherapy with concurrent radiation: Chemotherapy and radiation therapy may be given together before surgery.
- Neoadjuvant therapy with sequential radiation: If the combination of both chemotherapy and radiation may not be tolerated, the patient may be given the combination of treatments in a sequence, one treatment after completion of the other.

Table 2. Adjuvant Chemotherapy for Stage IIIA Non-small Cell Lung Cancer

Chemotherapy Regimen	Schedule
Cisplatin, day 1 and 8 Vinorelbine days 1, 8, 15, 22	Every 28 days x 4 cycles
Cisplatin, day 1 Vinorelbine, days 1, 8, 15, 22	Every 28 days x 4 cycles
Cisplatin, day 1 Vinorelbine, days 1 and 8	Every 21 days x 4 cycles
Cisplatin, day 1 Etoposide, days 1 to 3	Every 28 days x 4 cycles
Cisplatin, day 1 Gemcitabine, days 1 and 8	Every 21 days x 4 cycles
Cisplatin, day 1 Docetaxel, day 1	Every 21 days (x 2-4 cycles)
Cisplatin, day 1 Pemetrexed, day 1	Every 21 days (x 2-4 cycles)
Carboplatin, day 1 Paclitaxel, day 1	Every 21 days (x 2-4 cycles)

Table 3. Concurrent Chemotherapy with Radiation Therapy for Stage IIIA Non-small Cell Lung Cancer

Chemotherapy	Radiation Therapy (Concurrent with Chemotherapy)
Cisplatin, days 1,8, 29, and 36 Etoposide, days 1 through 5 and days 29 through 33	Total dose, 61 cGy Typically 6 weeks, daily (Monday through Friday)
Carboplatin, day 1 Pemetrexed, day 1 Every 21 days, x 4 cycles (non-squamous)	Typically 7 weeks
Cisplatin, day 1 Pemetrexed, day 1 Every 21 days, x 3 cycles (non-squamous)	Typically 7 weeks
Cisplatin, days 1 and 29 Vinblastine, weekly x 6	Typically 6 weeks, daily (Monday through Friday)

Table 4. Sequential Chemotherapy with Radiation Therapy for Stage IIIA Non-small Cell Lung Cancer

Chemotherapy	Radiation Therapy (After Chemotherapy)
Carboplatin, every 3 weeks x 2 cycles Paclitaxel, every 3 weeks x 2 cycles	30 doses
Cisplatin, days 1 and 29 Vinblastine, weekly on days 1, 8, 15, 22, 29	30 dose

Advanced Stage Lung Cancer (Stages IIIB and IV)

Stage IIIB NSCLC is unresectable disease with local involvement. Stage IV NSCLC includes extensive local spread or metastasis of the cancer to other regions in the body such as the brain, liver, or adrenal glands or the development a malignant pleural or pericardial effusion. The treatment goals for advanced stage disease include prolonging survival and controlling symptoms.[17-19] Supportive care includes treatment that controls symptoms, but may not necessarily treat the cancer directly.

Treatment for advanced stage lung cancer, with no known driver mutation, usually consists of combination treatment that includes a platinum chemotherapy agent. If the patient has a poor performance status, a single agent may be used.

Patients with non-small cell lung cancer, who are being considered to receive systemic chemotherapy, should be assessed with a genetic test on their tumor biopsy for a mutation of the epidermal growth factor receptor (EGFR) and EML4-ALK. Patients who have the EGFR mutation may receive oral treatment with erlotinib or afatinib.[40] Either erlotinib or afatinib may be selected as first line treatment. If patients develop a resistance to the first therapy, the second EGFR agent may be started. Patients with an EML4-ALK mutation may receive oral treatment with crizotinib.[39] If there is progression of disease or resistance to therapy ceritinib may be utilized.[41] There is much research on additional tumor driver mutations including KRAS, ROS and BRAF. In the future, there are likely to be additional targets and targeted therapies for patients with lung cancer.

Patients who do not have the EGFR or EML-4/ALK, mutation may be treated with combination chemotherapy if they are in healthy condition or a single agent if they have poor performance status. Selection of chemotherapy also is based on the specific type of NSCLC. Treatment usually is given for four to six cycles if there is tumor response or stable disease. It is standard for two chemotherapy drugs to be used together (doublet). Treatment options for different types of NSCLC include [4]:

Non-squamous cell NSCLC:

1. Cisplatin/Carboplatin-based doublet with or without bevacizumab
2. Cisplatin/Carboplatin-based doublet and cetuximab
3. Cisplatin/Carboplatin and pemetrexed
4. Vinerelbine and cetuximab

Squamous cell NSCLC

1. Cisplatin/Carboplatin and gemcitabine
2. Carboplatin and Abraxane
3. Vinerelbine and cetuximab

Maintenance Therapy for Advanced NSCLC

Maintenance therapy consists of ongoing administration (beyond four to six cycles) of at least one chemotherapy or targeted agent given during primary treatment. The goal is to extend long-term benefit from primary treatment. Examples of maintenance therapy include:

- Bevacizumab, continued after four to six cycles of cisplatin/carboplatin-doublet and bevacizumab.
- Cetuximab, continued after four to six cycles of cisplatin/carboplatin-doublet and cetuximab

- Pemetrexed: continued after four to six cycles of cisplatin/carboplatin and pemetrexed for patients with non-squamous cell NSCLC.
- Bevacizumab & Pemetrexed after four to six cycles of cisplatin/carboplatin, pemetrexed & bevacizumab.

Switch maintenance is the initiation of a new chemotherapy agent after primary treatment is completed. Examples of switch maintenance therapy include:

- Pemetrexed after four to six cycles of cisplatin/carboplatin-doublet for patients with non-squamous cell NSCLC.
- Docetaxel after four to six cycles of cisplatin/carboplatin-doublet in patients with squamous cell carcinoma.

Clinical trials are supervised research studies that investigate the effectiveness and safety of new cancer treatments or the combination of new treatments with established treatments. The trials are designed to compare new treatment strategies with the current standard of care and to improve survival outcomes. (See Chapter 6: *Clinical Trials and Emerging Therapies for Lung Cancer*)

Recurrent Non-small Cell Lung Cancer

Second line treatment is treatment for disease progression or recurrence. The physician does a complete review of the disease, treatment history, and reviews new and previous diagnostic scans. It is important for the physician to understand how well the patient tolerated the first line of treatment and if there are any residual side effects. Frequently, a different combination of chemotherapy drugs is used if the disease recurs soon after completing the first line of treatment. Radiation therapy and surgery may be considered depending on the site of recurrence.

Continuation After Disease Progression

Targeted agents such as erlotinib, afatinib, crizotinib and ceritinib may be continued in the setting of disease progression in patients with EGFR and ALK mutations. The chemotherapy portion of the regimen is discontinued.

Chemotherapy Side Effects

Chemotherapy for NSCLC can cause many unwanted side effects. These side effects occur because chemotherapy drugs kill both cancer cells and rapidly dividing normal cells. Healthy cells that may be affected include bone marrow, blood, intestinal, oral, and hair cells. Not every side effect of chemotherapy may be experienced. Frequency and severity of side effects may depend on factors such as the dosage, route (intravenous or oral), frequency (how often chemotherapy is given), and response of the individual body to the chemotherapy. The patient should speak with the oncology team about specific side effects that may be expected and about how to prevent and treat them.

Side effects of chemotherapy include and are not limited to anemia, leukopenia, thrombocytopenia, nausea, vomiting, diarrhea, constipation, mucositis, peripheral neuropathy, alopecia, infection, pain, and fatigue. The patient may also experience changes in appetite, skin, nails, vision, hearing, or cognition. The patient may have flu-like symptoms, including body and muscle aches, fever, chills, headache, and nasal congestion.

Bone Marrow Suppression

Bone marrow is a thick, pasty liquid inside bones where new red blood cells, white blood cells, and platelets are formed. When bone marrow suppression occurs from chemotherapy, production of these cells is decreased. Bone marrow suppression is diagnosed with a complete blood count, a blood test that measures the number of red blood cells, white blood cells, and platelets. Bone marrow suppression may include anemia (a decrease in red blood cells), leukopenia (a decrease in white blood cells), and thrombocytopenia (a decrease in platelets), and is more likely to occur with more cycles of chemotherapy.

Chemotherapy induced anemia is caused by the impairment of the cellular products needed to make red blood cells in the bone marrow as well as a decrease in the production of erythropoietin, a substance produced by the kidney. [20] The platinum chemotherapy agents such as Cisplatin and Carboplatin are well known to cause anemia. Signs and symptoms of anemia include weakness, fatigue, dizziness, lightheadedness, shortness of breath, and pallor of the fingernails, palms of the hands, eyelids, and inside of the mouth. Anemia may be prevented by eating a diet rich in iron and folate, including red meats and green leafy vegetables, drinking plenty of fluids, and doing mild exercise daily such as walking for 15 to 30 minutes. Medical evaluation is advised for symptoms of increased fatigue, inability to do normal activities, shortness of breath, chest pain, bleeding, or inability to think clearly. Treatment for anemia may include a blood transfusion or drugs such as epoetin alfa or darbepoetin alfa, however these drugs are not indicated for all cancer patients and have risk for developing blood clots, high blood pressure, and seizures. [20]

When leukopenia (decrease in the white blood cell count) occurs the body is prone to infections. There are many different types of white blood cells. The neutrophils make up most of the white blood cell count. Usually, the white blood cell count is lowest 10 to 14 days after chemotherapy. A decrease in the number of neutrophils (neutropenia) occurs during this time.

It is extremely important to take measures to prevent infection during chemotherapy by washing the hands frequently, avoiding large crowds, limiting time spent with small children as they carry a lot of germs and avoiding sick individuals. Most infections arise from bacteria from the patient's own mouth, airway, skin, urinary tract, or rectum. It is important for the patient to bathe daily and perform oral care 3-4 times a day as well as good perineal care. The patient should contact their healthcare provider immediately if they develop a high fever (temperature equal to or greater than 100.4°F), chills, new onset of cough or shortness of breath, burning with urination, vaginal discharge, or pain, swelling, redness, or warmth at an intravenous site or any site of injury. Severe untreated neutropenia is very dangerous. Patients should be treated with antibiotics immediately.[21] If the white blood cell count is expected to decrease, treatment with growth factors such as filgrastim or pegfilgrastim within 24 to 48 hours after chemotherapy may decrease the length of leukopenia and thus decreasing the risk of developing infections.

Platelets help the blood form clots in response to injury. With thrombocytopenia (low platelet count), blood clot formation is impaired. Signs include easy bleeding or bruising, purple or red spots (petechiae) on the skin, blood in the urine, bloody or black stools, and extreme weakness. Treatment may include a platelet transfusion or administration of growth factors. Patients should use a soft bristle toothbrush, only use electric razors, and protect themselves from injury.

Nausea and Vomiting

The most common side effect of chemotherapy is nausea and vomiting. Nausea and vomiting are caused by different impulses received from the digestive track and the brain. Anti-nausea medications block different pathways and neurotransmitter receptors. [22-24] Several antiemetic drugs are available and work differently to prevent and treat different types of nausea, including acute, delayed, anticipatory, breakthrough, or refractory nausea (Table 5). Different antiemetic drugs commonly are used in combination and may be given before, during, or after chemotherapy. When the optimal antiemetic regimen is used, nausea or vomiting may be prevented.

Nausea and vomiting also may be managed by decreasing unnecessary motion, eating slowly, eating small frequent meals and avoiding large meals, and sipping on water, ginger ale, or electrolyte-rich fluids. Behavioral therapies useful for nausea induced by chemotherapy include acupuncture, acupressure, guided imagery, and relaxation methods. The patient should contact their provider if they experience uncontrollable or ongoing nausea, projectile vomiting, severe stomach pain or bloating, weight loss, or vomit that is bloody or appears like coffee grounds.

Risk factors for developing nausea and vomiting including the female gender, history of prior chemotherapy induced nausea and vomiting, younger than 50 years of age, dehydration, electrolyte imbalances, past history of motion sickness, brain metastases, anxiety, bowel obstruction or slow bowl transit, and use of opioids to control pain. [25]

Table 5. Common Antiemetic Drugs for Nausea and Vomiting Induced by Chemotherapy [22-24]

Dexamethasone (Decadron®)
Ondansetron (Zofran®)
Dolasetron (Anzemet®)
Granisetron (Granisol®, Kytril®, Sancuso®)
Palonosetron (Aloxi®)
Aprepitant or Fosaprepitant (Emend®)
Prochlorperazine (Compazine®)
Promethazine (Phenergan®)
Metoclopramide (Reglan®)
Haloperidol (Haldol®)
Lorazepam (Ativan®)
Alprazaolam (Xanax®)
Scopolamine Transdermal Patch

Diarrhea

Diarrhea is defined as two to three loose or watery bowel movements daily. When the intestines are not working properly, the fluid remains in the stool and causes loose or watery bowel movements. If untreated, diarrhea can cause dehydration and loss of important electrolytes that are needed for normal function. Diarrhea can cause dizziness, weakness, fatigue, weight loss, nausea, abdominal pain, abdominal cramping, or bloating.

The primary treatment for diarrhea is fluid replacement and stool bulking. This can be done by drinking electrolyte-rich fluids such as water, juice, soup broth, or commercially available electrolyte drinks and consuming bulking foods such as bananas, rice, apple sauce, oat cereal, toast, crackers, or potatoes. Patients with diarrhea should avoid consuming caffeinated beverages, alcohol, milk products, and high fiber, high fatty, spicy, and gas producing foods such as beans, nuts, raw vegetables, corn, dried fruits, or hot peppers. Many nonprescription products can help stop diarrhea, including loperamide (Imodium®) or bismuth subsalicylate (Pepto-Bismol®). However, sometimes diarrhea can be so severe that prescription medications are prescribed such as diphenoxylate and atropine (Lomotil®).

The patient should keep a record of the number of loose stools per day and clean the area around the rectum thoroughly. The patient's provider should be notified immediately for diarrhea that does not resolve and is associated with fever, inability to eat or drink, decreased urination, or bloody or black stools.

Constipation

Constipation occurs when bowel movements are infrequent (no bowel movement in 3 days) or stool is difficult to pass. Cancer-related constipation is mainly caused by chemotherapy and medications to treat cancer pain. Prevention of constipation includes eating a diet high in fiber (grains, beans, and vegetables), drinking 8 glasses of fluids daily, walking or exercising regularly, and establishing a bathroom routine. Medications to treat and prevent constipation include stool softeners and laxatives. The provider should be contacted if a patient develops constipation that is associated with abdominal pain, vomiting, or inability to eat, hard impacted stool that will not come out, or absence of a bowel movement in 4 to 5 days. These symptoms occur with stool impaction and bowel obstruction, which are serious complications of constipation.

Fatigue

Eighty percent of patients receiving chemotherapy experience fatigue. [26] Fatigue is the feeling of tiredness. [27] Fatigue can be caused by cancer its self, treatments for cancer such as chemotherapy or radiation therapy, and the side effects of therapy including anemia, electrolyte abnormalities, dehydration, malnutrition, lack of physical activity, lack of sleep, pain, or emotional distress. [26] Fatigue can affect how patients feel physical, emotionally, and spiritually, as well as interfere with the ability to function or socialize. [26] Patients usually report having fatigue within 1 to 2 days after the first chemotherapy treatment, throughout therapy, and weeks to months and sometimes even a year after treatment.

Since fatigue can be caused by many different factors, a combination of treatment approaches is necessary. Fatigue can be managed by maintaining a healthy diet, avoiding long naps during the day (keep under 1 hour), postponing activities that are not essential, doing moderate physical activity such as walking, and participating in relaxation activities such as yoga, massage, or acupuncture.[26-27] Treating problems such as pain, sleep disturbance, infection, or anemia also decrease fatigue. Symptomatic anemia related fatigue is sometimes treated with blood transfusions or red blood cell stimulating products. Steroids or medications that increase patient's appetite can also be helpful. It is helpful to keep a record or weekly diary of the onset of fatigue, factors that aggravate or improve fatigue, and the effect of fatigue on activities of daily living. [27] Patients should contact their provider if they experience an increase in their fatigue, the inability to get out of bed or think clearly, fever, or chills.

Alopecia

Alopecia is temporary or permanent hair loss. This occurs because chemotherapy damages the hair follicle, causing the hair to break. Some chemotherapy drugs cause thinning of the hair without complete hair loss. Chemotherapy may affect the hair on the head, eyelashes, eyebrows, face, underarm, leg, and pubic area. Most people report a tingling sensation before the hair falls out, usually two to three weeks after the first chemotherapy treatment.

Hair loss cannot be prevented, so being prepared is important. Before starting chemotherapy, the patient may purchase hats, scarves, or wigs. After hair loss, it is important to protect the skin from extreme warm (sun burn) or cold temperatures and to keep the skin lubricated with ointments and creams to avoid dryness. After chemotherapy is completed, the hair may grow back however this usually begins within three months after the last treatment.[28]

Cutaneous (Skin and Nail) Changes

Changes to the skin and nail may occur due to chemotherapy especially if a patient is being treated with a targeted chemotherapy such as Afatinib, Cetuximab, Erlotinib, or Gefitinib. Rash is the most common skin related side effect from targeted therapies. [29] The rash is usually acneform (looks like acne with pustules or white heads) and is located on the face, chest, abdomen, or thighs.[30] It is important for the patient to not pop the pustules as this could lead to infection requiring antibiotics. Patient's skin can also become itchy, scaly, rough, and dry. Bathing with nonirritating soaps and water as well as applying fragrance free emollients, creams, and lotions to moisturize the skin can provide symptom relief. Patients should avoid bath salts or lotions that contain alcohol as they can dry out the skin. Epidermal growth factor receptor inhibitors can cause paronychia or nail fold swelling and cracking in the fingers and toes. Skin and nail changes can wax and wane and/or spontaneously resolve. [29] For the most part, reducing the dose or interrupting therapy for a brief period of time is the most effect way to manage moderate to severe cutaneous reactions related to targeted therapies. [29-30] At times topical or oral antibiotics may be given to help reduce symptoms related to targeted therapy induced acneiform rashes. Both, targeted and non-targeted based chemotherapies can cause the skin may become sensitive to sunlight therefore staying out of direct sunlight and wearing sunscreen is important.

Mucositis

Mucositis is inflammation and ulceration of the lining of the mouth, throat, and digestive tract. This occurs due to direct cellular kill by chemotherapy as well as the release of oxidative, inflammatory and metabolic by-products. [31] Mucositis can be very painful and irritating requiring pain medications and alteration in nutritional intake. Symptoms may include an abnormal sensation in the mouth, redness, swelling, sores, difficulty swallowing, bleeding, and mouth pain. Mucositis can also cause nausea and vomiting. Medications can be used to prevent mucositis from developing or becoming worse. It is important to maintain good nutrition and oral hygiene to prevent abnormal bacteria or fungi from growing inside the mouth. It also is important to keep the mouth and lips moist to prevent cracking which can lead to infection. The patient should avoid using a hard bristle toothbrush and alcohol-based mouthwash, which can irritate the lining of the mouth and gums. [32] The patient should notify the practitioner for any changes in the mouth, inability to swallow, pain or discomfort when swallowing, sores or white patches in the mouth or on the tongue, bleeding from the gums, fever, or other signs of infection. Medications and oral rinses (saline solutions, baking soda solutions) may alleviate symptoms.

Ototoxicity

The platinum-based chemotherapy drugs that are used to treat NSCLC, such as cisplatin and carboplatin, may cause inner ear damage, high pitch hearing loss, and ringing in the ears (tinnitus). Other medications such as antibiotics and diuretics can produce the same effects. Hearing loss is painless and may not be noticed until it becomes severe and irreversible. Signs and symptoms of hearing loss include turning the head while having a conversation, increasing the volume of the television or radio, or unclear, muffled, or quiet sounds. The patient should report changes in hearing to the practitioner, who may examine the ears and determine if hearing loss has occurred. A hearing test (audiogram) may be done before, during, or after chemotherapy to assess hearing.

Ocular Toxicities

Changes in vision and eye toxicities are side effects of systemic chemotherapies as well as targeted therapies. Some of the most common eye problems experienced by patients include: blepharitis (inflammation of the eyelids, redness, crusting and flaking of the skin on the lids); conjunctivitis (inflammation and redness of the conjunctiva); epiphora (excessive tear production); photophobia (sensitivity to light); photopsia (ocular pain); trichomeglay (long eyelashes that get misdirected or go inward instead of outward); diplopia (double vision), visual floaters and blurry vision. Treatment for vision changes includes artificial tears or lubricants, topical steroids, anti-inflammatory medications, good eye hygiene, warm compresses, avoiding light exposure, and occasionally discontinuation of chemotherapy. Prompt referral to an ophthalmologist is important when a patient experiences severe pain, swelling, redness, or sudden onset of any type of visual impairment. [33-34]

Cognitive Dysfunction

Cognitive change also known as "chemo brain" is a decrease in mental sharpness. Chemotherapy is one of many causes of cognitive dysfunction. Patients can develop memory impairment, difficulty

completing tasks, the inability to learn new skills, trouble with word finding or completing sentences, misplacing objects, confusing dates, and overall feeling mentally slow. Cognitive changes can be short or long term. Patient should notify their providers when "chemo brain" interferes with their normal daily activities and their ability to work. [35]

Peripheral Neuropathy

Some chemotherapy drugs can cause damage to nerve fibers and lead to peripheral neuropathy, causing numbness, tingling, burning, and loss of vibratory sensation in the hands and feet.[36] Peripheral neuropathy may interfere with normal activities and may cause difficulties performing fine motor movements such as buttoning a shirt, writing, or picking up utensils. Sensing pain or changes in temperature, driving, walking, cooking, or brushing the teeth may also become difficult. Extremely hot or cold temperatures may aggravate numbness and tingling and may cause severe burns or frostbite injury. Therefore, extreme caution is necessary. It is recommended patients wear gloves near the refrigerator/freezer and potholders when cooking. Falls should be avoided by removing objects from the floor, securing area rugs, cleaning spills, and illuminating a room before entering.

Some medications may be given for peripheral neuropathy. Although several medications are not approved by the United States Food and Drug Administration for the treatment of peripheral neuropathy, they may decrease the unpleasant symptoms of numbness and tingling. These medications include antidepressants, anti-seizure medication such as gabapentin, topical creams that contain capsaicin, and anesthetic creams or patches that contain lidocaine. Other helpful therapies may include acupuncture, physical therapy, massage, occupational therapy, and transcutaneous electrical nerve stimulation.

The patient should contact the provider if the peripheral neuropathy becomes worse, interferes with self-care or activities of daily living, or causes stumbling, falling, loss of balance, injury, or muscle spasms in the mouth, jaw, fingers, or toes.

Conclusion

The patient should speak with the oncology provider or nurse about specific side effects that may be expected from the chemotherapy, and how these side effects will be prevented and treated. It is important to keep a list of the presence and severity of all side effects experienced. This list may give the oncology provider valuable information about how to treat the symptoms. In additional, the patient should keep the telephone numbers of their providers and clinic available in case of severe illness, high fever, or symptoms that require immediate medical attention.

Appendix 1. Chemotherapy Drugs for Non-small Cell Lung Cancer and Common Side Effects*

Chemotherapy Drug	Common Side Effects
Cisplatin (Cis-diamminedichloroplatinum, CDDP, Platinol®)	Kidney damage (nephrotoxicity), nausea and vomiting, decrease in the red cell, white cell, and platelet counts (bone marrow suppression), nerve damage (neurotoxicity), high pitch hearing loss and ringing in the ears (ototoxicity), eye damage (ocular toxicity), metallic taste of foods, loss of appetite, hair loss (alopecia), infertility, liver function changes, possible vascular events (heart attack, stroke, clot formation), SIADH (syndrome of inappropriate antidiuretic hormone secretion)
Etopiside (VP-16, VePesid®)	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), nausea and vomiting, anorexia, hair loss (alopecia), inflammation and ulceration in the mouth, throat, and intestines (muscositis), infusion reaction (fever, chills, shortness of breath, increased heart rate, facial and tongue swelling, low blood pressure), metallic taste in the mouth during infusion, redness at the injection site, skin changes (radiation recall reaction – skin reaction that occurs on an areas that has been previously radiated)
Carboplatin (Paraplatin®)	Kidney damage (nephrotoxicity), nausea and vomiting, decrease in red cell, white cell, and platelet counts (bone marrow suppression), nerve damage (neurotoxicity), hair loss (alopecia), infertility, liver function changes, allergic reaction (skin rash, itchiness, hives, shortness of breath, low blood pressure)
Paclitaxel (Taxol®)	Decrease in red cell, white cell, and platelet counts (bone marrow suppression), infusion reaction (skin rash, flushing, redness, shortness of breath, low blood pressure), nerve damage (neurotoxicity), heart rate changes, hair loss (alopecia), inflammation and ulceration in the mouth, throat, and intestines (muscositis), diarrhea, liver and kidney function changes, nail bed changes (onycholysis)

Chemotherapy Drug	Common Side Effects
Vinorelbine (Navelbine®)	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), nausea and vomiting, constipation, diarrhea, inflammation and ulceration in the mouth, throat, and the intestines (muscositis), liver function changes, injury and inflammation the vein, nerve changes (neurotoxicity), hair loss (alopecia), general fatigue, infusion reaction (shortness of breath, low blood pressure, facial flushing, rash), SIADH (syndrome of inappropriate antidiuretic hormone secretion)
Gemcitabine (Gemzar®)	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), nausea and vomiting, flu like symptoms (fever, muscle and body aches, chills, headaches), liver function changes, pulmonary toxicities(shortness of breath or drug induced pneumonitis), infusion reaction (facial flushing and swelling, headache, shortness of breath, low blood pressure), protein or blood in the urine, skin rash on the chest and extremities, swelling of the lower extremities, radiation recall skin reactions.
Docetaxel (Taxotere®)	Decrease in the white blood cell count (neutropenia), allergic reaction (skin rash, skin redness, low blood pressure, shortness of breath), fluid retention, dry itchy skin rash (maculopapular rash), hair loss (alopecia), inflammation and ulceration in the mouth, throat, and intestines (muscositis), diarrhea, nausea and vomiting, generalized fatigue, liver and kidney function changes, phlebitis or swelling at the injection site.
Pemetrexed (Alimta®)	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), skin rash, diarrhea, nausea and vomiting, inflammation and ulceration in the mouth, throat and intestines (mucositis), fatigue, changes in the liver and kidney function

Chemotherapy Drug	Common Side Effects
Albumin-Bound Paclitaxel (Abraxane)	Myelosupression (decrease in white blood cells, red blood cells, and platelets), ocular or visual disturbances, fatigue, weakens, alopecia, nausea, vomiting, mucositis, liver toxicities, neurotoxicity's (peripheral neuropathy and paresthesias), injection site reactions, cardiac toxicities (chest pain, high blood pressure, elevated heart rate, blood clot in the lungs), peripheral edema (swelling of the extremities)
Topotecan (Hycantin®)	Myelosuppression, nausea, vomiting, diarrhea, abdominal pain, headache, fever, fatigue, alopecia (hair loss), liver toxicities, blood in the urine.

*Adapted from Chu E and Devita VT. Physicians' Cancer Chemotherapy Drug Manual (2014).[37]

Appendix 2. Targeted Therapy Drugs for Non-small Cell Lung Cancer and Common Side Effects*

Targeted Therapy	Mutation Target	Dose	Side Effects
Afatinib (Gilotrif®)	EGFR	40 mg orally, once daily Take 1 hour before or 2 hours after a meal	Diarrhea, rash, nail fold swelling in the fingers and toes (paronychia), dry skin, bullous and exfoliative skin disorders, decrease appetite, stomatitis, lung toxicity (interstitial lung disease), liver toxicities, inflammation of cornea (keratitis), visual changes, increase risk for heart dysfunction
Bevacizumab (Avastin®)	Vascular endothelial group factor (VEGF)	Given intravenously once every 3 weeks	Nose bleeds (epistaxis), high blood pressure, decreased wound healing, gastrointestinal perforation, protein in the urine (proteinuria), infusion reaction (fever, chills, hives, facial flushing, fatigue, headache, shortness of breath, lip swelling, low blood pressure), possible lung bleeding (pulmonary hemorrhage) or vascular events (heart attack, stroke), dizziness, depression
Ceritinib (Zykadia®)	EML4-ALK	750 mg orally, once daily on an empty stomach, do not take within 2 hours of a meal	Diarrhea, nausea, vomiting, abdominal pain, liver toxicities, lung toxicity (interstitial lung disease/pneumonitis), heart dysfunction, decreased heart rate, high blood sugar (hyperglycemia), fatigue, decrease appetite, constipation
Cetuximab (Erbitux®)	EGFR	Given intravenously usually weekly	Itchy and dry skin, acne skin rash on face and chest, nail fold swelling in the fingers and toes (paronychial inflammation), lung toxicity (cough, shortness of breath, interstitial lung disease), infusion reaction (fever, chills, rash, flushing, fatigue, headache, shortness of breath, lip swelling, low blood pressure), low magnesium, generalized malaise

Targeted Therapy	Mutation Target	Dose	Side Effects
Crizotinib (Xalkori®)	ELA4-ALK	250 mg orally, twice daily with or without food	Liver and kidney toxicities, decrease heart rate and contractility, lung toxicity (decrease in pulmonary function, pneumonia, interstitial lung disease/pneumonitis, shortness of breath, cough) visual disturbances (double and blurry vision, floaters/flashes, visual brightness, reduced visual acuity), diarrhea, nausea, vomiting, decrease appetite, fatigue, peripheral neuropathy
Erlotinib (Tarceva®)	EGFR	150 mg orally, once daily	Dry and itchy skin, acneiform rash on face and chest, diarrhea, nausea and vomiting, mucositis, increased cough, shortness of breath, fever, liver function changes, anorexia, pink eye (conjunctivitis), inflammation of cornea (keratitis), nail changes (paronychia), hair growth abnormalities (alopecia, thinning of hair with increased fragility, darkening and increased thickness of eyelashes and eyebrows), possible GI hemorrhage
Gefitinib (Iressa®)	EGFR	250mg orally, daily	High blood pressure, dry itchy skin, acneiform rash, liver function changes, anorexia, nausea and vomiting, mucositis, conjunctivitis, inflammation of cornea (keratitis), abnormal eyelash growth, inflammation of the eyelash follicle (blepharitis), possible coughing up blood or GI hemorrhage
Sunitinib (Sutent®)	Vascular endothelial group factor (VEGF)	50mg orally daily for 4 weeks every 6 weeks	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), high blood pressure, yellowish discoloration in the skin, skin rash, dryness or cracking of the skin, nose bleeds (epistaxis), fatigue, diarrhea, altered taste, abdominal pain, inflammation and ulceration in the mouth, throat, and intestines (muscositis), increase risk for heart dysfunction, adrenal insufficiency, low thyroid function (hypothyroidism)

*Adapted from Chu E and Devita VT. Physicians' Cancer Chemotherapy Drug Manual (2014).[37]

References

1. Planchard, D. (2013). Identification of driver mutations in lung cancer: first step in personalized cancer. *Targeted Oncology*. 8: 3-14.
2. Reck, M., Heigener, D.F., Mok, T., Soria, J.C. & Rabe, K.F. (2013). Management of non-small cell lung cancer: recent developments. *The Lancet*. 382: 709-719.
3. Gridelli C, Perrone F, Gallo C, et al. (2003). Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst*. 95(5): 362-72.
4. National Comprehensive Cancer Network. (2014). *NCCN Clinical Practice Guidelines in Oncology: Non-smallCell Lung Cancer* [v.4.2014]. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
5. Strauss GM, Herndon JE, Maddaus MA, et al. (2008). Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 26(31): 5043-51.
6. Pepe C, Hasan B, Winton TL, et al. (2007). Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. *J Clin Oncol*. 25(12): 1553-61.
7. Scott WJ, Howington J, Feigenberg S, et al. (2007). Treatment of non-small cell lung cancer, stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 132(3 Suppl.): 234S-242S.
8. Douillard JY, Rosell R, De Lena M, et al. (2006). Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol*. 7(9): 719-27.
9. Burdett SS, Stewart LA, Rydzewska L. (2007). Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *Cochrane Database Syst Rev*. 3: CD006157.
10. O'Rourke N, Roqué I, Figuls M, et al. (2010). Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev*. 6:CD002140.
11. Pignon JP, Tribodet H, Scagliotti GV, et al. (2008). Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 26 (21): 3552-9.
12. Felip E, Rossell R, Maestre JA, et al. (2010). Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol*. 28(19): 3138-45.
13. Arriagada R, Bergman B, Dunant A, et al. (2004). Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 350(4): 351-60.
14. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ*. 1995; 311(7010): 899-909.
15. Rowell NP, O'Rourke NP. (2004). Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev*. 4:CD002140.
16. Anderson CS, Curran WJ (2010). Combined modality therapy for stage III non-small-cell lung cancer. *Semin Radiat Oncol*. 20(3):186-91.
17. Jett JR, Schild SE, Keith RL, et al. (2007). Treatment of non-small cell lung cancer, stage IIIB: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 132(3 Suppl): 266S-276S.
18. Fidias P, Novello S. (2010). Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 28(34): 5116-23.
19. Delbaldo C, Michiels S, Rolland E, et al. (2007). Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease. *Cochrane Database Syst Rev*. 4: CD004569.
20. National Comprehensive Cancer Center Network (2014). *NCCN Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy induced Anemia.* [V.1.2015]. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/anemia.pdf.
21. National Comprehensive Cancer Network (2014). *NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections.* [V.1. 2014]. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
22. Basch E, Prestrud AA, Hesketh PJ, et al. (2011). Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 29(31): 4189-98.
23. National Comprehensive Cancer Network (2014). *NCCN Clinical Practice Guidelines in Oncology: Antiemesis.* [V.2.2014]. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf

24. Roila F, Herrstedt M, Aapro R, et al. (2010). Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol.* 21 (suppl5): v232-v243.
25. Wickham, R. (2013). Chemotherapy-induced nausea and vomting- where we stand now. *Oncology Hematology Review (US).* 9(2): 154-160.
26. Koornstra RHT, Peters M, Donofrio S, et al. (2014). Management of fatigue in pateints with cancer – a practical overview. *Cancer Treatment Reviews.* 40: 791-799.
27. National Comprehensive Cancer Network (2014). *NCCN Clinical Practice Guidelines in Oncology: Cancer Related Fatigue.* [V.1.2014]. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf
28. Reeves DM. (2004). Alopecia. In: Yarbo CH, Frogge MH, Goodman M. eds 3. Cancer Symptom Management. Sudbury, MA: Jones and Bartlett. Pp. 561-570.
29. Williams L, Fuhrman A, Robison J et al. (2014). Skin Reactions. *ONS PEP.* Retrieved from https://www.ons.org/practice-resources/pep/skin-reactions
30. Kiyohara Y, Yamazaki N, Kishi A. (2013). Erlotinib-related skin toxicities: treatment strategies in pateints with metastatic non-small cell lung cancer. *J Am Acad Dematol.* 69(30): 463-472.
31. Lalla RV, Bowen J, Barasch A et al. (2014). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer.* 120:1453-1461.
32. Beck SL. Mucositis. (2004). In: Yarbo CH, Frogge MH, Goodman M. eds 3. Cancer Symptom Management. Sudbury, MA: Jones and Bartlett. Pp. 276-292.
33. Olivier H, Bakalian S, Levy C, et al. (2014). Ocular adverse events of molecularly targeted agents approved in solid tumours: a systemic review. *European J of Cancer.* 50,638-648.
34. Augustoni F, Platania M, Vitali M, et al. (2014). Emerging toxicities in the treatment of non-small cell lung cancer: ocular disorders. *Cancer Treatment Reviews.* 40,197-203.
35. Evens K, Eschiti VS. (2006). Cognitive effects of cancer treatments: "chemo brain: explained. *Clin J of Onc Nursing.* 13(6): 661-666.
36. Van Horn A, Harrison C. (2013). Neurologic complications of cancer and cancer therapy. *Clin J of Onc Nursing.* 17(4): 418-424.
37. Chu E, Devita VT. (2014). Physicians' Cancer Chemotherapy Drug Manual. Sudbury,MA: Jones and Bartlett.
38. Socinski M.A, Bondarenko I, Karaseva NA, et al. (2012). Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. *J Clin Oncol.* 30:2055-2062.
39. Shaw A.T, Yeap BY, Solomon BJ, et al. (2011). Effect of crizotinib on overall survival in patients with advanced non-small cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncology.* 12:1004-1012.
40. Sequist, L.V., Yang, JC-H, Yamamotoa, N., et. Al. (2013). Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J. Clin Oncol.* 3327-3334
41. Shaw, A.T, Kim D-W, Mehra R, et al. (2014) Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med.* 370:1189-1197.
42. Gilotrif® (afatinib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; November 2013. Retrieved from https://www.gilotrif.com/content/dam/internet/pm/gilotrif1/com_EN/documents/Gilotrif.pdf
43. Zykadia(TM) (ceritinib) Prescribing Information. East Hanover, New Jersey, USA: Novartis Pharmaceuticals Corporation; April 2014. Retrieved from http://www.pharma.us.novartis.com/product/pi/pdf/zykadia.pdf

Chapter

4

Radiation Therapy for Non-Small Cell Lung Cancer

Join Y. Luh, MD, FACP and Charles R. Thomas, Jr., MD

Introduction

Radiation is a form of energy that has both beneficial and harmful effects on humans. When used properly in controlled settings, radiation can effectively treat lung cancer, and this effect can be intensified with chemotherapy given at the same time. Radiation therapy is the medical use of radiation to treat cancer and some non-cancerous benign tumors. Radiation for cancer works by damaging the DNA of cancer cells. Cancer cells are much more sensitive to the lethal effects of radiation than normal cells because cancer cells have difficulty repairing DNA damage. In addition, cancer cells are more sensitive to the effects of radiation and DNA damage because they divide much more rapidly than normal cells.

Lung cancers are categorized into two groups: small cell lung cancer and non-small cell lung cancer. Radiation may be used for small cell lung cancers, as discussed in the section about small cell lung cancer. This chapter will focus on the use of radiation therapy for non-small cell lung cancer.

Principles of Radiation Therapy for Non-small Cell Lung Cancer

Overview

The treatment of non-small cell lung cancer depends on the cancer stage and the patient's overall condition. Treatment options may include surgery, radiation therapy, chemotherapy, and any combination of these options. Radiation therapy may be used before surgery, frequently in combination with chemotherapy, to make a tumor smaller and easier to remove. Radiation can be given after surgery, with or without chemotherapy, to kill any cancer cells that may still be present after surgery. Radiation, frequently with concurrent chemotherapy, may be used to treat lung cancers that are too extensive to remove surgically. In some circumstances, radiation therapy can be used alone, without surgery or chemotherapy.

The most common form of radiation therapy is external beam radiation therapy. With external beam radiation therapy, the patient lies on a table and a beam or multiple beams are emitted from a machine known as a linear accelerator. The beams are directed to the tumor and surrounding tissues that may also contain cancer cells. The beams penetrate the skin, other tissues, and organs before reaching the tumor target. External beam radiation therapy is given daily during the week, Monday through Friday, typically for 6 to 7 weeks. Scheduling the radiation treatment this way allows for an effective dose of radiation during the week to kill the cancer cells, and allows the patient and normal cells to recover during the weekend from the effects of radiation. The treatment takes 5 to 10 minutes, depending on the type of linear accelerator used.

The typical dose of radiation given for most lung cancers ranges from 6000 to 7000 cGy (centigray), depending on the stage and whether or not chemotherapy is included. Such a high dose of radiation cannot be given all at once to a patient without lethal side effects. Therefore, the dose given per treatment is 180 to 200 cGy, which usually is well tolerated by patients. The unit centigray replaces the older term "rad" as a measure of radiation dose; 100 centigray is equal to 1 gray (Gy), which is equal to 1 Joule per kilogram of tissue (1 Joule = 1 Newton-meter).

Radiation Treatment Team

The delivery of radiation therapy requires several individual team members that play a crucial role in the successful treatment of patients. Radiation oncologists are medical doctors, frequently certified by the American Board of Radiology, who design and direct the radiation treatment plan. These are the physician specialists during radiation therapy who provide evaluation, simulation (discussed next), weekly treatment visits, and follow-up visits after completing treatment.

Radiation oncology nurses provide detailed education to patients on the clinical aspects of radiation treatment. They provide counseling on managing any side effects of treatment and tips on how to decrease the intensity of side effects. They often are the team members who address patient concerns and communicate more serious issues to the radiation oncologist.

Dosimetrists help calculate and optimize the treatment plan designed by the radiation oncologist. They work to ensure that the intended dose of radiation prescribed by the radiation oncologist is delivered to the patient. They work closely with the radiation oncologist to determine the optimal angles, fields, and energy of radiation needed for a treatment plan.[1]

Medical physicists perform scheduled quality assurance tests to ensure that linear accelerators are working properly. They work closely with radiation oncologists and dosimetrists to help design the radiation treatment plan. They often supervise the dosimetrist in making sure the treatment plan is feasible and tailored to the individual patient.

Radiation therapists operate the linear accelerators, place patients in the correct position, give the daily radiation treatments, and keep an accurate record of treatments given.[1] Other staff members are important to patients receiving lung radiation, including social workers, physical therapists, occupational therapists, dieticians, and respiratory therapists.

Simulation

After the consultation with the radiation oncologist and a decision has been made for a lung cancer patient to receive radiation therapy, the patient first must undergo simulation. Simulation is a procedure where a radiation oncologist and a simulation technician (usually a radiation therapist) place the patient in the exact position for treatment to ensure that the radiation hits the correct target consistently. The patient lies down on the back, usually with the arms placed above the head. There may be immobilization devices such as handlebars for the patient to hold onto above the head. Custom cradles may be molded to conform to the patient for lying in the same position for each treatment. Skin marks (which may be washed off) and permanent tattoos (pinpoint dots, no larger than a mole) are placed and lined up with laser pointers in the room to make sure the patient can lie in the same position each day. Radiographs are taken after the patient's treatment position has been determined (Figure 1).

Figure 1. Radiation Therapists Simulating a Patient

Some radiation therapy facilities will place a belt around the patient's abdomen to encourage the patient to take more shallow breaths during simulation and treatment. This is done to decrease the distance that the lung tumor may move up or down during breathing. Other techniques that help regulate the effect of

breathing on tumor location include timed breath holding and the use of respiratory tracking (gating) systems that electronically follow the movement of the tumor (discussed in more detail below).[2]

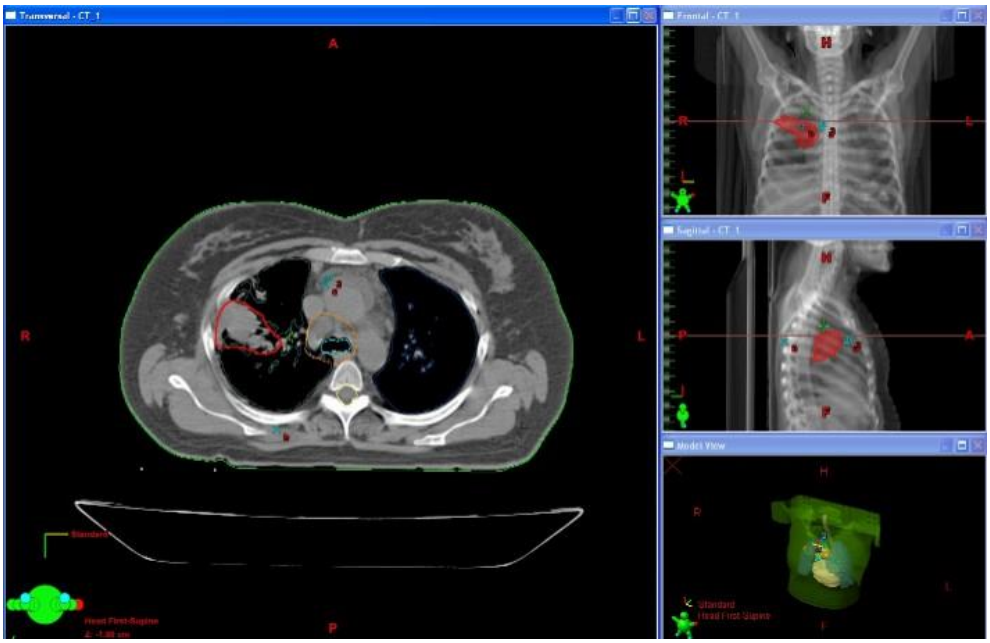
Subsequently, a CT (computed tomography) scan of the neck and chest is done in the treatment position with all the immobilization devices in place. This CT scan will provide a computerized 3-dimensional digital virtual model of the patient's chest and internal organs. The radiation oncologist and dosimetrist use this model to design a patient's radiation treatment fields on a planning computer equipped with radiation treatment planning software. This planning or simulation CT scan is different from the diagnostic CT scan used to help diagnose and stage the lung cancer. Intravenous contrast is sometimes used at the discretion of the radiation oncologist designing the treatment fields, and this contrast can provide better detail about the extent of the lung cancer. Planning CT scans for simulation typically take less time to obtain than diagnostic scans. Furthermore, planning CT scans are not read or interpreted by a diagnostic radiologist, but are processed with treatment planning software to help design the treatment fields.

Some institutions use 4-dimensional CT, which is a planning CT scan that tracks how a patient's breathing cycle affects the location of the lung tumor (a technique known as respiratory gating).[2] The distance a tumor moves up, down, or sideways can be useful to the dosimetrist to determine the margin size around the tumor required for planning treatment.

Treatment Planning

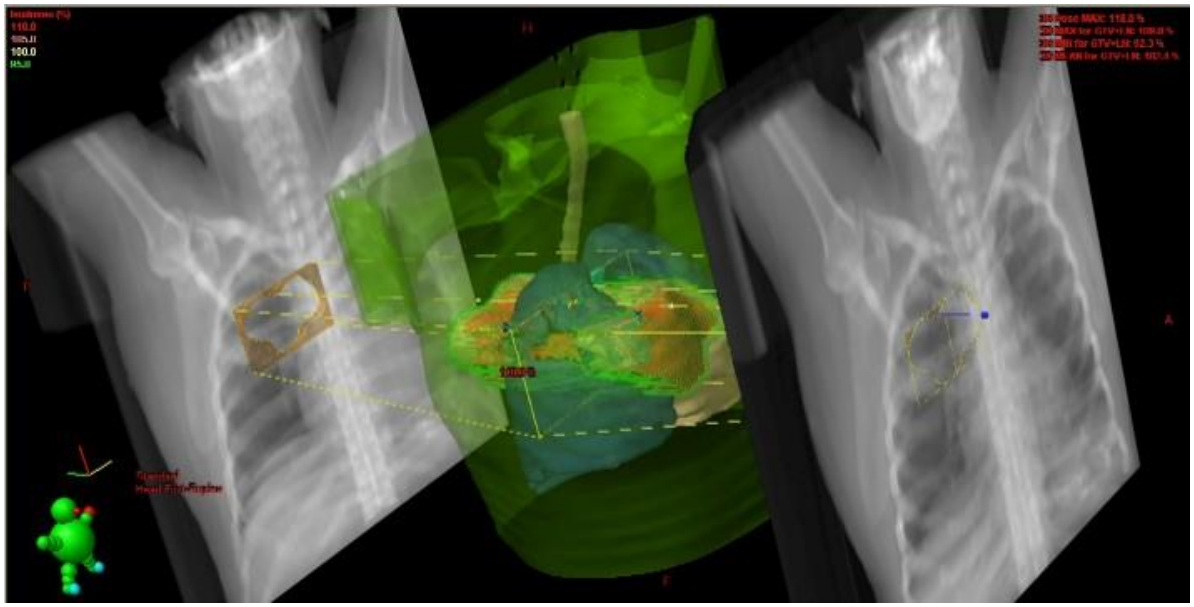
After simulation is completed, the radiation oncologist, dosimetrist, and medical physicist develop a treatment plan. The simulation CT scan images are electronically sent to a computer with treatment planning software. The slices of the CT scan are reviewed and the anatomic structures, such as the lungs, heart, and spinal cord, are outlined or contoured in different colors. The sum of the slices of these contours define the volume of the anatomic structures (Figure 2). The radiation oncologist, using information from positron emission tomography (PET) scans, diagnostic CT scans, and other reports, will contour the actual tumor and lymph nodes involved with cancer. The volume of the actual tumor is called the gross tumor volume, and the gross tumor volume frequently is contoured in red.[3] At some centers, the dosimetrist can take a PET scan (previously obtained to stage the tumor) and fuse this with the simulation CT scan. Because the lung tumor and regional lymph nodes light up brightly on the PET scan, fusion with the simulation CT scan can greatly help the radiation oncologist define the volume of the cancer with more accuracy.

Figure 2. Contours of Normal Organs and the Gross Tumor Volume



After the normal tissue volumes and gross tumor volume have been defined, the tumor is more clearly seen in relation to other organs. The dosimetrist or radiation oncologist set up portals or fields that encompass the gross tumor volume and the involved mediastinal lymph nodes. The mediastinum is a space in the middle of the chest that includes the esophagus, trachea, and large blood vessels above the heart; this space is rich in lymph nodes and lymph vessels, making it a common place for lung cancer to spread.[3]

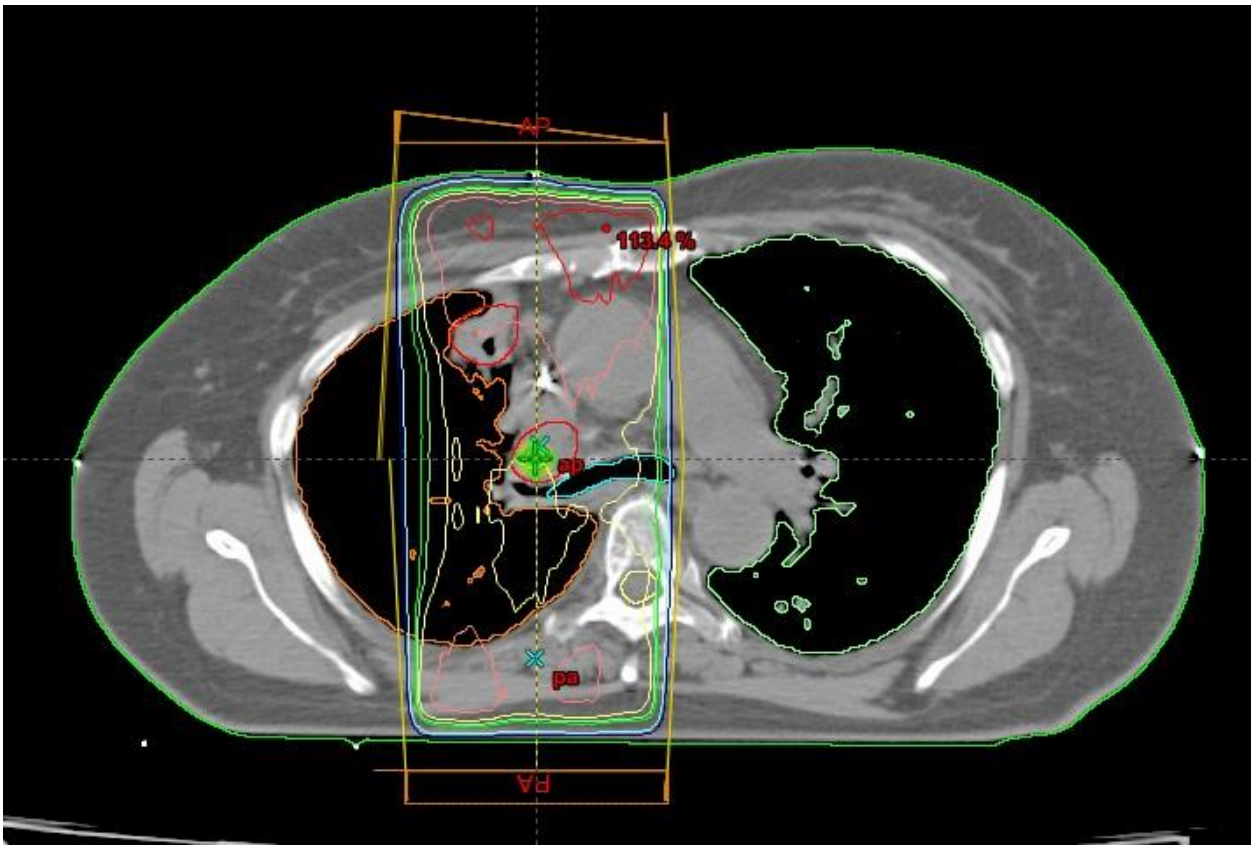
Figure 3. Computer Generated Image of Chest Fields



A typical method used to treat lung cancer involves two fields: one field is oriented facing the patient's front chest (anteroposterior [AP]) and one field is oriented facing the patient's back (posteroanterior [PA]). The term AP/PA is used to describe this setup (Figure 3).

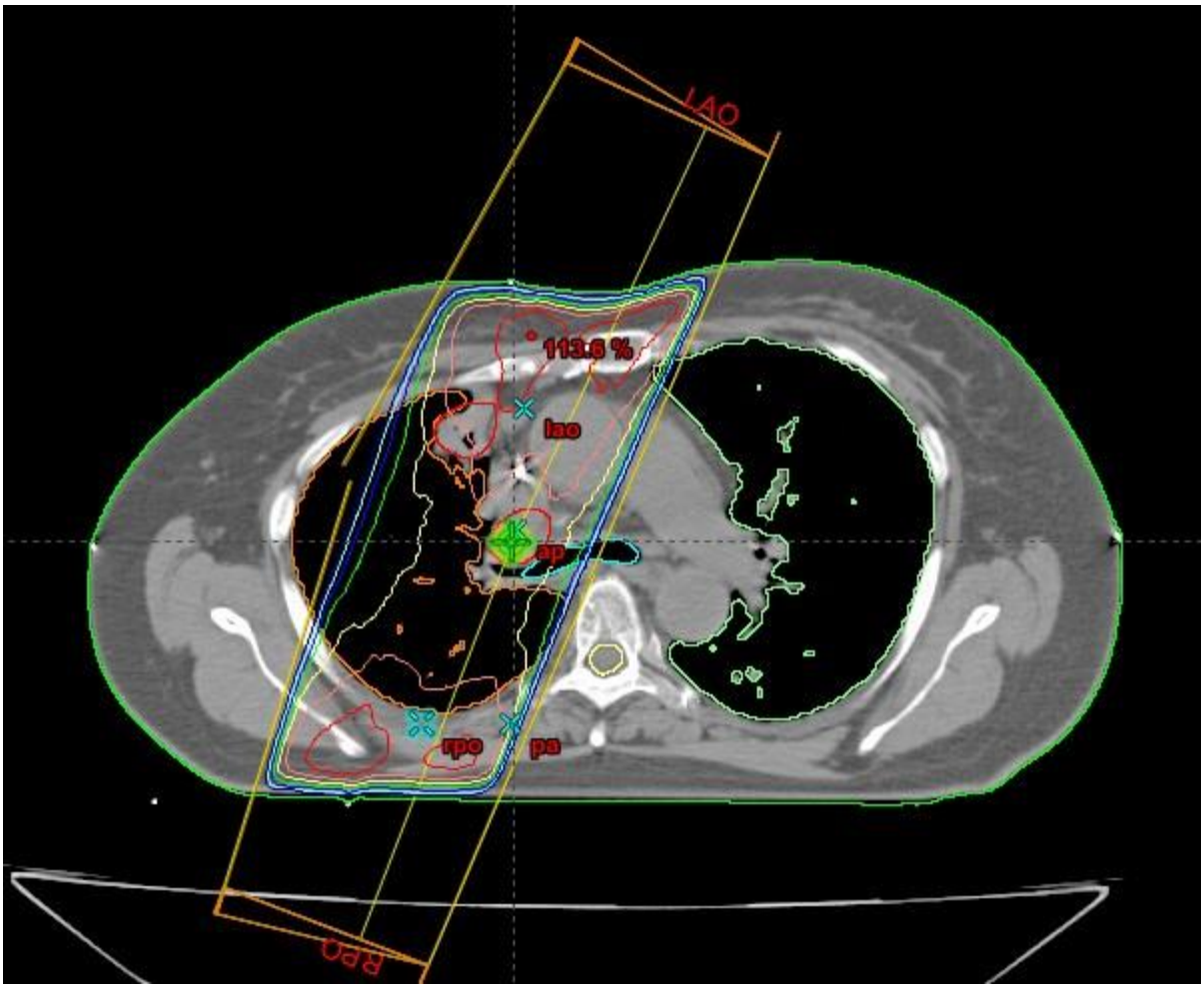
The initial AP/PA fields frequently include the spinal cord (Figure 4a). The spinal cord can usually tolerate 5000 cGy before the risk of spinal cord damage occurs. Radiation oncologists usually aim to keep the spinal dose below 4500 to 5000 cGy, but may use a lower dose when chemotherapy is used concurrently with radiation. Most lung cancer treatments involve doses of 6000 to 6600 cGy, so the patient cannot be treated using AP/PA fields for the entire treatment. Therefore, the patient is treated using AP/PA fields to a dose between 4000 to 5000 cGy, and then the fields must be modified. As you can see from Figure 4a, the radiation dose is shaped more like a rectangle and results in some normal lung getting the similar doses as the tumor volume.

Figure 4a. Orientation of AP/PA Fields Including the Spinal Cord



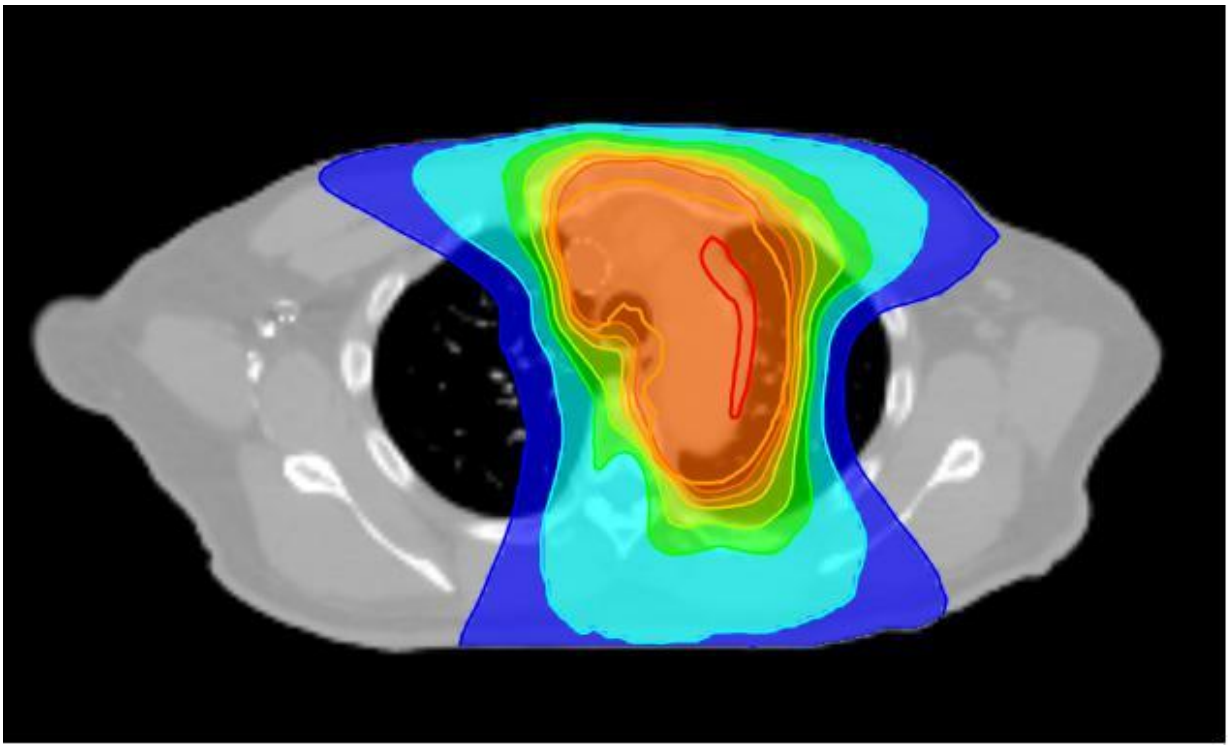
The modified fields are called the off cord boost. The typical method of designing an off cord boost is to change the angle of the fields to oblique fields that are diagonal and avoid the spinal cord (Figure 4b). Attempts are made to include the involved lymph nodes with the gross tumor volume and safely avoid the spinal cord. However, if this is not possible, the off cord boost may treat only the gross tumor volume. The inclusion of the involved lymph nodes in the off cord boost can sometimes be done with the use of intensity modulated radiation therapy.

Figure 4b. Oblique Fields Angled to Avoid the Spinal Cord



A technique known as intensity modulated radiation therapy (IMRT) uses multiple beams or fields directed at the gross tumor volume and involved lymph nodes. A 1.5 to 2.0 cm margin frequently is placed around the gross tumor volume to account for tumor motion (from breathing), setup variation, and patient motion. IMRT has been a popular method of treating lung cancers because the intensity of each beam directed at the tumor can be varied to where the sum of all the beams adds up to a dose cloud that better conforms to the shape of the tumor (Figure 5). Although IMRT allows a radiation oncologist to spare more normal lung and other normal tissues from the high dose meant for the tumor, it spreads low dose radiation to a larger area. Despite this, IMRT is instrumental in tracking dose to any organ and limiting the radiation dose to these areas. The technical aspects of IMRT are beyond the scope of this chapter, but a helpful website with information on IMRT can be found at http://www.radiologyinfo.org/en/info.cfm?pg=imrt.

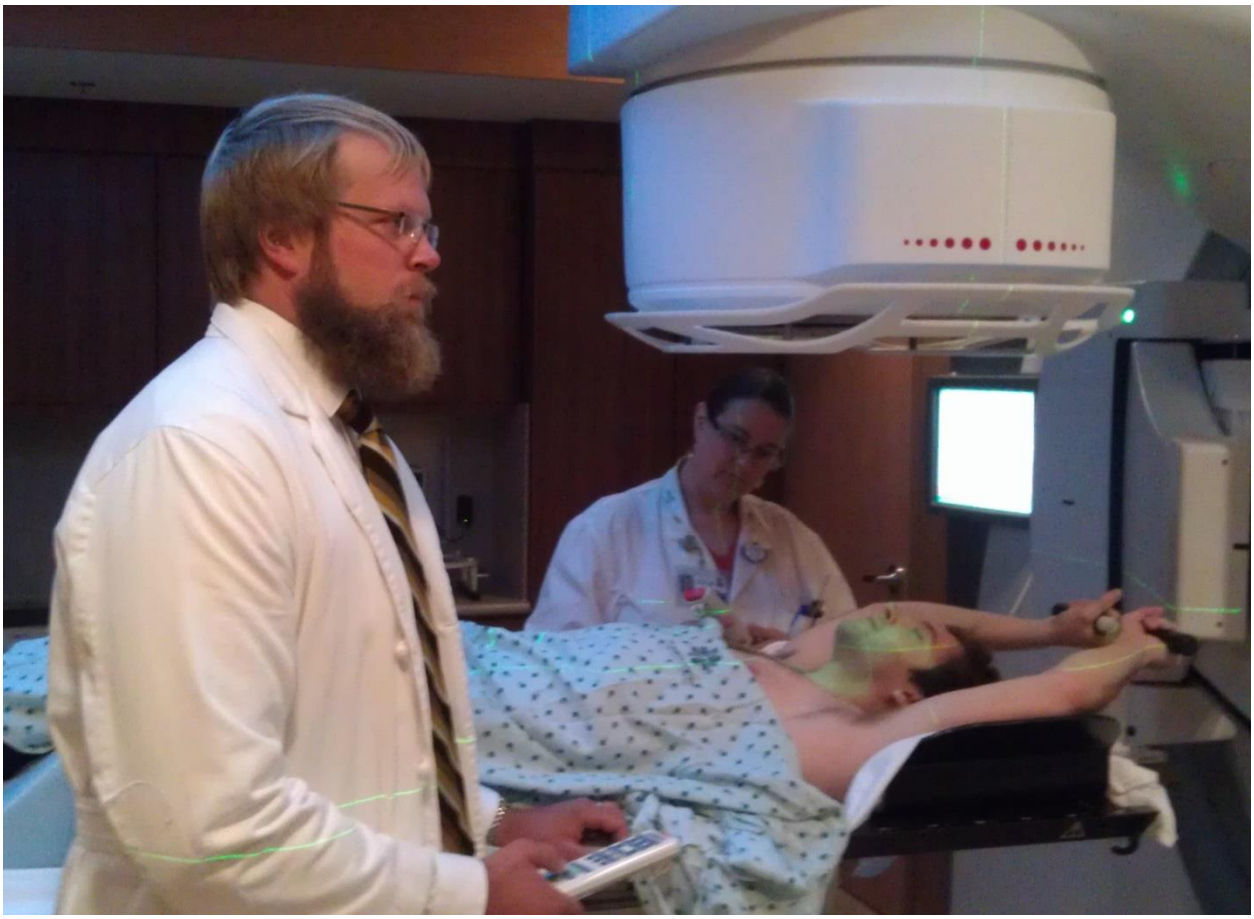
Figure 5. A rendering of dose in an IMRT plan



When the field designs have been completed, the dosimetrist will calculate how effective the fields may provide the radiation dose to the gross tumor volume. The dosimetrist will also calculate how much radiation the surrounding tissues are receiving, such as the spinal cord, heart, and lungs. If any of these tissues receive radiation beyond a maximum threshold, then the fields must be adjusted. The V20 is the volume of both lungs that receive ≥ 20 Gy (2000 cGy); dosimetrists attempt to keep the V20 below 30% because the risk of a serious side effect known as radiation pneumonitis increases dramatically if V20 > 35%.[4]

After the treatment plan is completed, the patient returns to the radiation therapy department for a block check or verification procedure (Figure 6). The patient is placed on the actual treatment machine (linear accelerator) in the same position as in the simulation CT scanner. Radiographs are made and reviewed to make sure that the images match the images on the planning CT scan and are consistent with the CT based treatment plan. Many treatment centers make a cone beam CT scan on the treatment table and overlay this CT with the planning CT scan to give a more precise confirmation of the accuracy of the field being treated and to enable any needed adjustments because of setup variations.

Figure 6. A Block Check or Verification Before Starting Treatment



Treatment

Radiation treatment usually is started the day after the block check or verification. For most lung cancer patients, radiation is given every day from Monday to Friday, with weekends off, for approximately 7 weeks. The patient is on the treatment table receiving radiation for 5 to 10 minutes (Figure 7) and usually is in the department for < 1 hour. The time of the entire session includes arrival at the waiting room, changing into a gown, getting in the treatment position on the treatment table, and having the radiation therapist make any needed adjustments.

Figure 7. A Patient on the Table of a Linear Accelerator Receiving Radiation Treatment

The patient will meet with the radiation oncologist once a week on a specified day to review how the patient is feeling. During these weekly visits, the patient can ask any questions that may not have been addressed during the consultation. The radiation oncologist will check to see if there are any side effects from the radiation treatment and may prescribe medication to help with these side effects. In many centers, a radiograph or CT scan is made every 5 treatments for quality assurance to confirm that the correct field is being treated. Shifts in the field are sometimes made if the fields diverge slightly from the planning CT fields.

Radiation Therapy for Different Stages

Stage I and II Non-Small Cell Lung Cancer

Surgery, usually a lobectomy, is the typical treatment for Stage I and II non-small cell lung cancer. However, not all patients have surgery, either because of a personal preference to avoid surgery or because of medical conditions, such as severe emphysema or heart disease, that increase the potential risk of surgery and anesthesia. If surgery cannot be done for a stage I or II non-small cell lung cancer, radiation therapy is a good alternative.

Radiation therapy for stage I and II non-small cell lung cancer includes a total dose of 6600 to 7000 cGy to the gross tumor volume, in doses of 180 to 200 cGy per day over 7 weeks. Stage I and II non-small cell lung cancers do not have mediastinal lymph node involvement, and only the gross tumor volume and any involved adjacent lymph nodes are treated.[5]

Many patients cannot commit to a 7-week course of daily radiation therapy, especially if they must travel long distances to reach a radiation treatment facility. In these cases, effective doses of radiation can be given over a shorter period of time if larger doses are given per treatment, a technique called hypofractionation. However, larger doses per treatment may result in more long term tissue scarring, especially in long term survivors. Therefore, to minimize the effect of lung scarring caused by hypofractionation, radiation must be limited to a much smaller volume of tissue. For very weak patients who are too sick to come for treatment for 7 weeks, hypofractionation with 4800 cGy in fractions of 400 cGy over 12 treatments (2 weeks and 2 days) has been used successfully.[6]

Stereotactic radiosurgery (SRS) is a technique in which a very high dose of radiation is given to a small area over a short period of time, either as a single treatment or 5 treatments over one week. The term SRS has always applied to patients being treated for brain tumors. Radiosurgery, contrary to what the term implies, is not surgery and does not involve any incision or cutting by the radiation oncologist, but the high dose of radiation results in the killing of the tumor as if it was surgically removed. The high precision of the multiple beams used in stereotactic radiosurgery results in the margins around the gross tumor volume being much smaller (0.5 cm to 1.0 cm) than with typical radiation therapy techniques.

Stereotactic radiosurgery for tumors other than the brain is known as stereotactic body radiation therapy (SBRT), stereotactic ablative radiotherapy (SABR), or extracranial radioablation (ECRA). This method is widely used for medically inoperable patients with stage I or II non-small cell lung cancer, with comparable or better outcomes when compared with typical radiation therapy techniques.[5,7] Dose fractionation in stereotactic body radiation therapy includes either a total dose of 6000 cGy given in 3 treatments of 2000 cGy over a period of 2 weeks, or a total dose of 5000 cGy given in 5 treatments of 1000 cGy daily over 1 week. A patient may be treated with SBRT for non-small cell lung cancer if the tumor is ≤ 5 cm in greatest diameter and peripheral to the mediastinum.[8]

Stage III Non-Small Cell Lung Cancer

Most cases of stage IIIA and IIIB non-small cell lung cancer are inoperable (except for some cases of stage IIIA cancer) because of the extent of disease. For patients with inoperable stage IIIA and stage IIIB non-small cell lung cancer, recommendations for treatment in the National Comprehensive Cancer Network include concurrent chemotherapy and chest radiation therapy. The first doses of chemotherapy and radiation therapy are given on the same day. Depending on the drug selected, the chemotherapy is given at varied intervals, but radiation therapy is given daily. The typical dose of radiation therapy, when given with chemotherapy, is 6000 to 6300 cGy given in 180 to 200 cGy fractions over 7 weeks.[9] The typical intravenous chemotherapy regimens given in combination with radiation therapy are: (1) cisplatin (days 1, 8, 29, and 36) and etoposide (days 1 to 5 and 29 to 33); (2) cisplatin (weeks 1 and 4) and vinblastine (weekly); or (3) weekly carboplatin and paclitaxel.[9]

For stage III non-small cell lung cancer that is marginally or borderline operable, measures can be taken to increase the potential for success with surgery. This can include giving chemotherapy or chemotherapy with radiation therapy before surgery to decrease the size of the lung mass and mediastinal lymph nodes. If radiation is given with chemotherapy with the intention of doing surgery later, the radiation dose is only

4500 cGy, and the patient has another CT scan with or without a positron emission tomography (PET) scan to evaluate response. If the tumor appears operable, then surgery is done. However, if the lung cancer remains inoperable, then the patient would be given further radiation for a total dose of 6300 cGy with chemotherapy, similar to other patients with inoperable non-small cell lung cancer.[9]

In some cases in which surgery is done for a stage I or II non-small cell lung cancer, postoperative evaluation of the mediastinal lymph nodes that had been sampled during surgery may show these nodes to be positive for cancer. In this situation, the stage of non-small cell lung cancer is revised to stage III. For this patient, surgery alone is not sufficient treatment, and the patient will require chemotherapy and radiation.[10]

If there is suspicion that there is cancer remaining in the patient after surgery, demonstrated by a positive margin of resection (meaning there are cancer cells at the edge where the surgeon had excised the tumor), then radiation therapy (usually to a dose of 5000 cGy) is given with concurrent chemotherapy. If the surgery was complete with clear margins of resection (a rind of normal tissue surrounds the tumor), then the chemotherapy and radiation are given separately; typically, chemotherapy is given initially, followed by radiation therapy to a dose of 5000 cGy.[9]

Stage IV Non-Small Cell Lung Cancer

In stage IV non-small cell lung cancer, the cancer has spread to the opposite lung, metastasized to a different organ (such as the liver, brain, or bones), or produced fluid containing cancer cells within the space surrounding the lung (a condition known as a malignant pleural effusion). The primary treatment for patients with stage IV non-small cell lung cancer is chemotherapy. Radiation therapy to the lung does not improve the lifespan of a patient with stage IV non-small cell lung cancer and is not routinely used in these cases. However, if a patient with stage IV cancer has a large lung mass that is causing chest pain, difficulty swallowing, or shortness of breath, radiation therapy to the lung mass may be given, typically in doses from 3000 cGy (10 treatments of 300 cGy fractions over 2 weeks) to 5000 cGy (20 treatments of 250 cGy fractions over 4 weeks).[11,12]

Stage IV lung cancers may frequently spread or metastasize to the brain. When metastases occur in multiple sites of the brain, radiation therapy frequently is given to the entire brain to shrink the existing tumors and prevent new brain metastases from forming. The most common dose given for whole brain radiation therapy is 3000 cGy (10 treatments of 300 cGy fractions over 2 weeks). If a patient has ≤ 3 brain metastases and all the lesions are ≤ 3 cm in diameter, the patient may have surgery to remove the metastases, followed by whole brain radiation to prevent new tumors from forming,[13] or the patient could be treated with stereotactic radiosurgery (SRS). Stereotactic radiosurgery for brain metastases has the advantage of allowing for less brain radiation but the disadvantage that new brain metastases could form in areas that were not radiated.

When lung cancer spreads to the vertebrae, patients may experience severe back pain. The growing cancer could compress the spinal cord and cause paralysis. These metastases can be removed surgically, especially if there only one metastatic lesion. In this case, radiation therapy is given 2 weeks after surgery to prevent the cancer from recurring in the spine.[14] If metastases are too extensive to remove surgically, radiation

therapy alone is used, most commonly at a dose of 3000 cGy (10 treatments of 300 cGy fractions over 2 weeks).

Alternate Forms of Radiation Therapy for Non-Small Cell Lung Cancer

Proton beam therapy is a form of external beam radiation therapy that uses protons (usually from a hydrogen atom) instead of x-rays. Proton beams do not have any exit dose beyond the target tumor. Therefore, the radiation from proton beams is deposited only along the path of the beam to the tumor, and no radiation is given behind the tumor, so the patient receives less radiation to nearby normal tissue. Proton beam therapy is available only in a few centers in the United States and is used in unique situations. such as in children with brain or spinal tumors where it is critical to protect as much normal tissue from radiation.[1] Proton beam therapy is especially useful in patients who have been treated with conventional radiation therapy multiple times and need repeat treatment to the same area.

With brachytherapy, the radioactive sources are placed in or just next to the tumor. High dose rate brachytherapy involves the accurate placement of a powerful radiation source, usually iridium-192, into the tumor for several minutes through a tube called a catheter.[1] Endobronchial brachytherapy involves the placement of a catheter into a lung bronchus or bronchiole where there is a tumor. The iridium-192 source is placed into the catheter where it remains for a few minutes, exposing a small area of the lung to a high dose of radiation. Endobronchial high dose rate brachytherapy is useful for treating pain, shortness of breath, cough, and hemoptysis (coughing up of blood).[15]

Side Effects of Lung Radiation Therapy

Acute side effects occur when a patient is receiving lung radiation therapy with or without chemotherapy. These include redness and irritation of the skin overlying the radiation treatment portals; inflammation of the esophagus (esophagitis) causing heartburn or a feeling that something is stuck in the throat; irritation of the lung causing a dry cough; inflammation of the sac surrounding the heart causing chest pain (pericarditis); electric shock sensations in the low back or legs when bending the neck (Lhermitte sign); and generalized fatigue. These acute side effects typically resolve 2 weeks after completing chest radiation therapy.

Subacute side effects occur 1 to 6 months after completing radiation therapy. These side effects are less frequent and may include radiation pneumonitis, which is inflammation of the lung that causes chest pain, fever, and cough.[16] As mentioned above in the section on treatment planning, radiation pneumonitis occurs infrequently, especially when the V20 (volume of both lungs receiving ≥ 20 Gy or 2000 cGy) is no more than 35%. Your radiation oncologist, dosimetrist, and physicist work hard to ensure that the least amount of radiation possible goes to normal lung without sacrificing coverage of the lung tumor. Treatment of radiation pneumonitis includes corticosteroids such as prednisone or dexamethasone.

Another rare subacute side effect is pericardial effusion or tamponade, in which fluid accumulates in the pericardium (the sac surrounding the heart), causing pressure on the heart, neck vein distention, shortness of breath, and a rapid heart rate. Pericardial effusions may resolve spontaneously, but in some cases, treatment may include needle aspiration to drain the excess fluid, or diuretics.

Long term side effects of lung radiation therapy include pulmonary fibrosis (permanent scarring of the radiated lung tissue), esophageal fibrosis and stricture (scarring and narrowing of the esophagus that causes difficulty swallowing and treated with esophageal dilation), constrictive pericarditis (shrinkage of the sac surrounding the heart, that may require surgical removal), and damage to the heart muscle and blood vessels that may increase the risk of heart failure and heart attack. These long term side effects are uncommon because modern radiation therapy techniques have resulted in better sparing of normal tissues and organs.

The authors wish to thank Debra Monaco CMD, RT (R) (T), Charlie McCracken RT (R)(T) CMD, BS, and Steve Rhodes, BS RT(T) CMD for submitting some of the treatment planning images used in this chapter.

References

1. American Society for Radiation Oncology. Radiation Therapy for Cancer. Fairfax, VA: American Society for Radiation *Oncology*, 2009.
2. Zhang J, Xu GX, Shi C, et al. Development of a geometry-based respiratory motion-simulating patient model for radiation treatment dosimetry. *J Appl Clin Med Phys*. 2008:9(1):2700.
3. Kong FM, Ritter T, Quint DJ, et al. Consideration of Dose Limits for Organs at Risk of Thoracic Radiotherapy: Atlas for Lung, Proximal Bronchial Tree, Esophagus, Spinal Cord, Ribs, and Brachial Plexus. *Int J Radiat Oncol Biol Phys*. 2010 Oct 7. [Epub ahead of print].
4. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys*. 1999;45(2):323-9.
5. Chang JY, Bradley JD, Govindan R, et al. Inoperable Non-Small Cell Lung Cancer -Definitive Radiotherapy for Stage I/II. In: Halperin EC, Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:1086-7.
6. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer. *Radiother Oncol*. 1996;41:41-4.
7. Timmerman RD, Paulus R, Galvin J, et al. Stereotactic Body Radiation Therapy for Medically Inoperable Early-stage Lung Cancer Patients: Analysis of RTOG 0236. *Int J Radiat Oncol Biol Phys*. 2009; 75(3S):S3.
8. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol*. 2006;24(30):4833-9.
9. Jabbari S, Hansen EK, Haas-Kogan DA. Non-small Cell Lung Cancer. In: *Handbook of Evidence-Based Radiation Oncology*. New York, NY: Springer; 1994:221-247.
10. Douillard JY, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys*. 2008;72(3):695-701.
11. Hayman JA, Abrahamse PH, Lakhani I, et al. Use of palliative radiotherapy among patients with metastatic non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2007;69(4):1001-7.

12. Tsuji SY, Wara WM. Palliation and Benign Conditions. In: *Handbook of Evidence-Based Radiation Oncology*. New York, NY: Springer; 1994:675-690.
13. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280(17):1485-9.
14. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet*. 2005;366(9486):643-8.
15. Nag S, Scruggs GR. Clinical Aspects and Applications of High-Dose-Rate Brachytherapy. In: Halperin EC, Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:560-582.
16. Chang JY, Bradley JD, Govindan R, Komaki R. Toxicity of Normal Tissue. In: Halperin EC, Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:1102-4.

Chapter

5

Treatment of Small Cell Lung Cancer

Ariel Lopez-Chavez MD, MS

Introduction

There are two main types of lung cancer, non-small cell lung cancer and small cell lung cancer.[1] It is important that all patients with lung cancer know what type of cancer they have because the treatments for each type of cancer are different, and effective treatment for one type may not be effective for a different type of cancer.

In this chapter, treatment of small cell lung cancer will be discussed. See Chapters 2, 3, and 4 for the treatment for non-small cell lung cancer.

Before Treatment

Biopsy

Small cell lung cancer is usually found when a patient presents to the doctor complaining of symptoms such as shortness of breath, persistent cough, bone pain, or other symptoms. Although rare, this cancer sometimes is found during a routine medical examination.

Before considering treatment options, it is important to confirm the diagnosis of lung cancer with a biopsy, in which a piece of the cancer is taken and examined under the microscope.[1,2,3]

The most common ways of taking a biopsy in patients with small cell lung cancer include:

Bronchoscopy. In this procedure, a camera in the form of a very thin tube is inserted through the mouth and pushed down the throat and into the lungs, to take a small piece of the lung cancer. This procedure is done with anesthesia so the patient does not feel discomfort or pain.

Computed tomography (CT) guided biopsy. Sometimes a needle, guided by a CT scan, can be passed through the skin to get a piece of the cancer. This can be done in any part of the

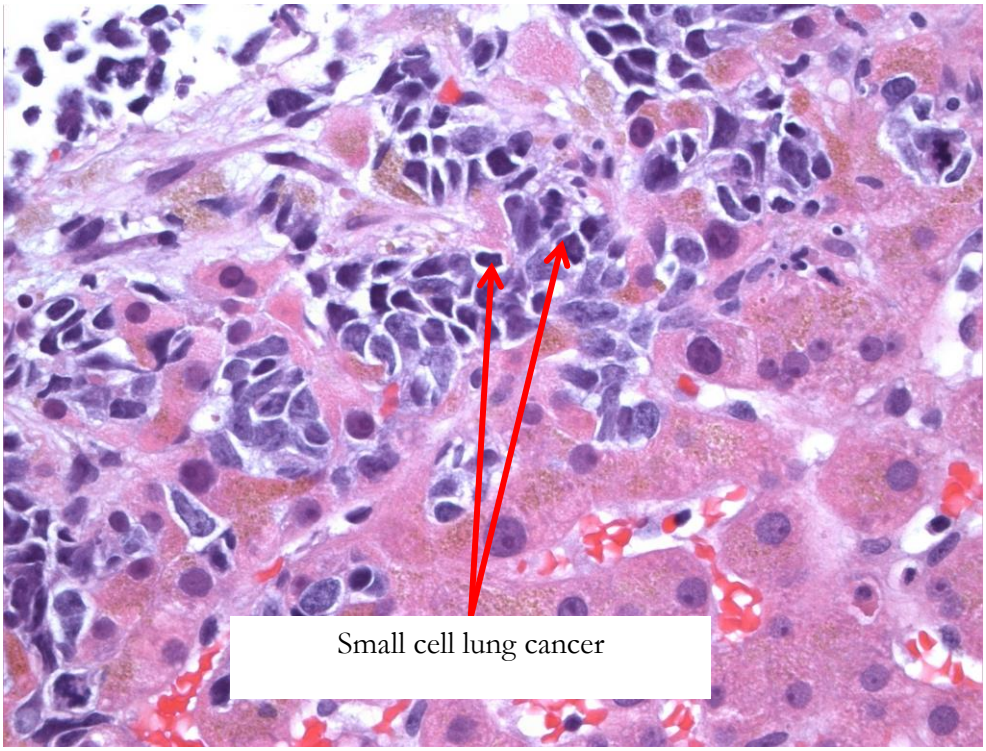
body that can be safely accessed with a needle. For this procedure, we also use anesthesia to help minimize any pain.

Surgery. Sometimes it is necessary to perform a regular operation to get the piece of cancer needed to make the diagnosis of lung cancer.

The type of procedure used to get the biopsy will depend on the location of the cancer and the safest place to take the biopsy. This is a very important procedure, without which it is not possible to treat the cancer. Unfortunately, these procedures are not always successful in obtaining a sample of the cancer, and in some occasions the procedure must be repeated. Although this is not common, it is important that patients keep this in mind so that they are prepared in case the procedure must be repeated.

After a piece of the cancer is obtained, it is sent to a pathologist, a physician that specializes in looking at cancers under the microscope. This physician will make the diagnosis and will determine what kind of cancer it is.

Figure 1. Microscopic image of a small cell lung cancer taken with a microscope (The cancer cells are the small purple cells in the top half of the picture)



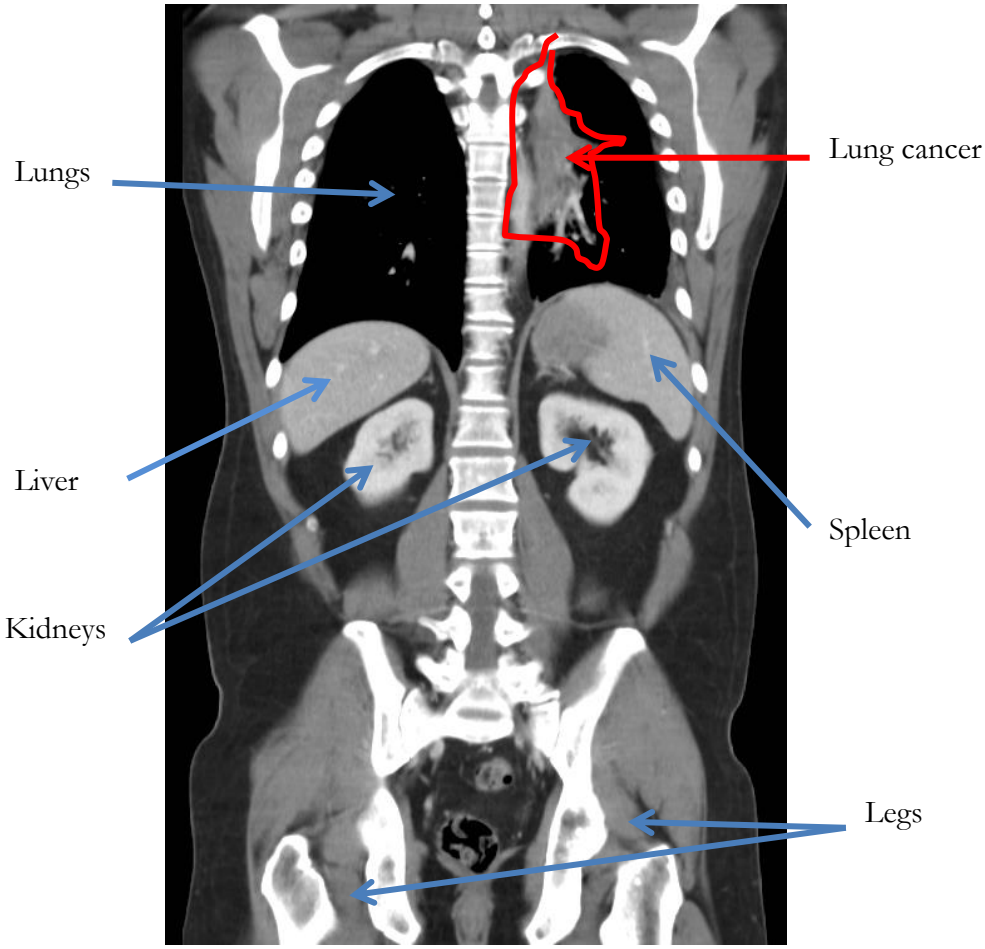
Radiographs and Other Imaging Tests

After getting the biopsy and confirming the diagnosis of small cell lung cancer, the next step is getting radiographs and other types of imaging studies that give pictures of the inside of the body.[1,2,3] By the time a biopsy has been done, many of these studies may already have been obtained, but additional studies might be needed before treatment.

The purpose of these studies is to evaluate size and location of the cancer, so it can be best treated. Among the most common type of imaging studies that are done for patients with small cell lung cancer include:

CT scan of the chest and abdomen: this specialized radiographic test has the purpose of taking internal pictures of the chest, abdomen, and pelvis for a close look at the lungs, heart, liver, kidneys, and other organs. (Figure 2)

Figure 2. CT scan of the chest and abdomen with a cancer in the left lung.

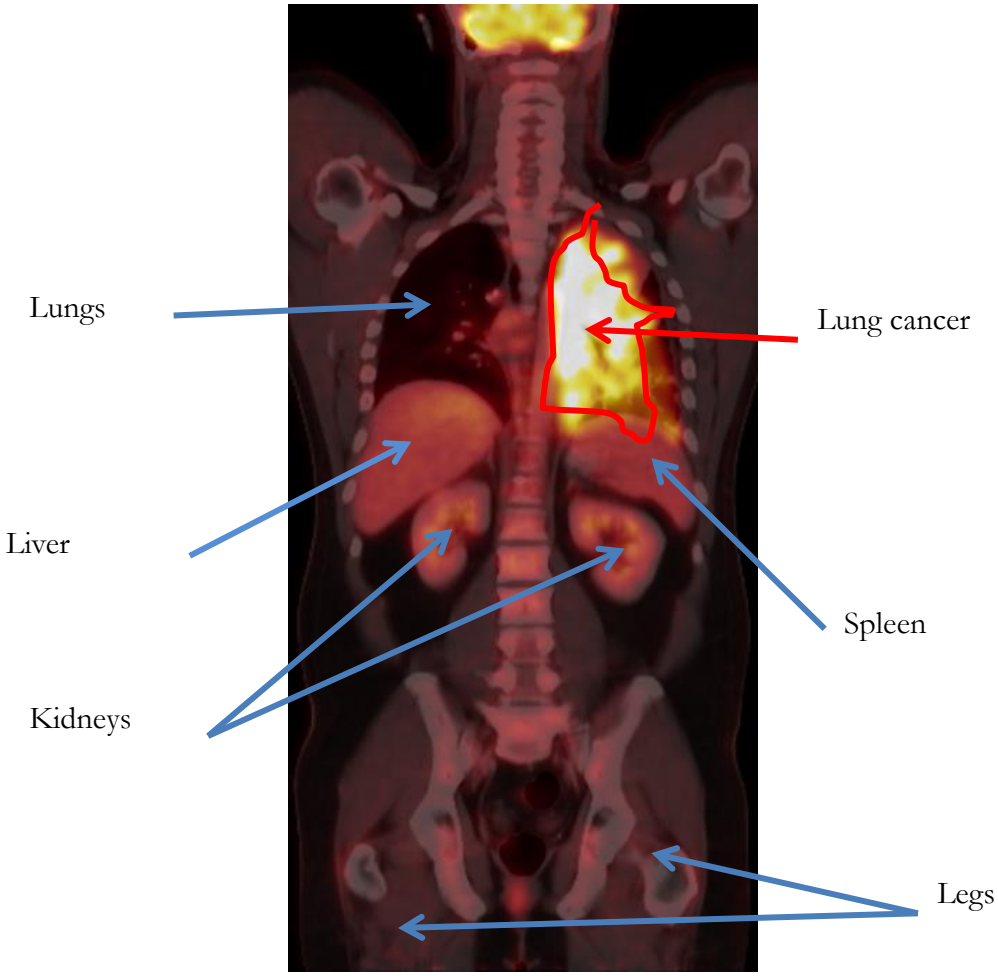


Magnetic Resonance Imaging (MRI) of the brain: this test is done because small cell lung cancer often spreads to this part of the body.

Bone scan: this study gives a view of the bones, to see if there is any spread of the lung cancer there. Small cell lung cancer frequently may spread to the bones.

Positron Emission Tomography (PET) scan: this special type of study looks at the entire body for areas where the cancer may have spread. (Figure 3)

Figure 3. Positron Emission Tomography (PET) scan which shows involvement of cancer in the left lung.



Blood Tests

Before starting treatment for lung cancer, laboratory tests are important to evaluate how the different organs in the body are working.[1,2,3] Although radiographs provide pictures of important organs such as the liver, lungs, and kidneys, laboratory analyses of the patient's blood help determine the

function of some of these organs. Some of the most important laboratory analyses that are performed in patients with small cell lung cancer include:

- Kidney tests: creatinine and blood urea nitrogen (BUN)
- Liver tests: Alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin
- Bone marrow tests: complete blood count
- Electrolytes: sodium, potassium, chloride, magnesium, and phosphate

These are routine tests that are commonly performed in many patients with cancer and other diseases. These tests are performed many times before, during, and after treatment to carefully monitor the function of these organs.

Staging

After the blood tests, radiographs, and biopsies are completed, the physicians determine the stage of the cancer.[1, -3-6] The stage is an indication of the size and location of the cancer. This is very important because the treatment and prognosis depend on the stage of the cancer. Small cell lung cancer typically is divided into two stages:

- Limited stage: the cancer is limited to the lungs only and has not spread outside the lungs. In addition, to be considered limited stage, we need to be able to safely treat the cancer using radiation therapy.

- Extensive stage: this term applies to cancers that have spread outside the lungs to other parts of the body. However, even if the cancer is confined to the lungs, it is considered extensive stage if it is too big to be safely treated with radiation.

It is important that patients know this information because the treatments and expectations are different according to the stage of the cancer.

Small cell cancer also may be staged based on the Tumor-Nodes-Metastasis (TNM) staging classification system. If this system is used, then small cell lung cancer may be one of four stages. Stages I, II, III are limited stage disease, except that some patients with stage III may have extensive stage disease. In the TNM classification system, stage IV is equivalent to extensive stage disease.[4]

Treatment for Limited Stage Small Cell Lung Cancer

There are two main options for the treatment of limited stage small cell lung cancer: surgery or a combination of chemotherapy and radiation therapy.

Surgery

It is important to note that surgery is only rarely an option of treatment for patients with small cell lung cancer. However, sometimes it can be an option with excellent results in very carefully selected patients.[5]

Surgery is an option only for those patients who have very small cancers that are localized in the lungs and that have not spread to any lymph nodes or other organs. In addition, the patient must be fit and healthy enough to undergo surgery, because there are risks of surgery including intraoperative death.

Unfortunately, small cell lung cancer usually grows very quickly, and by the time it is diagnosed, it frequently will have spread to the lymph nodes or outside the lungs. Only < 5% of patients with small cell lung cancer can have their tumors removed by surgery.[5]

If the cancer is small enough to be taken out by surgery, the next step would be to make sure that the cancer has not spread to the lymph nodes or to organs outside the chest. For this purpose, a biopsy of the lymph nodes is taken from the middle of the chest, typically by one of two methods:

- Endobronchial ultrasonographic biopsy is a procedure in which a tube is inserted through the mouth and down the throat, and an ultrasound device helps to identify and biopsy the lymph nodes in the chest with a very small needle.

- Mediastinoscopy is a minor operation in which a small incision is made in the bottom of the neck and a small camera is inserted to identify and biopsy the lymph nodes.

After a biopsy of the lymph nodes is taken, the pathologist checks to make sure that the cancer has not reached the lymph nodes. If the lymph nodes are clear of cancer, then the next step would be to remove the cancer with surgery.

After the cancer is removed, it is necessary to treat any microscopic cells that may have remained despite the surgical procedure. These microscopic cells are treated with chemotherapy, typically cisplatin and etoposide. In addition, if the cancer is later found to have invaded the lymph nodes, it may be necessary to add radiation therapy to the treatment.

In summary, surgery is an option for only < 5% patients with small cell lung cancer. For surgery to be an option, the cancer usually must be smaller than 1 or 2 inches and limited to the lungs without spreading into the lymph nodes. Chemotherapy is still needed even after surgery is done.[1,5]

Combination of Chemotherapy and Radiation Therapy

The treatment of choice for most patients with limited stage small cell lung cancer is a combination of radiation therapy and chemotherapy because surgery usually is not a good option.[1,3,6]

The two physicians in charge of this treatment include a medical oncologist and a radiation oncologist. The medical oncologist is in charge of the chemotherapy and the radiation oncologist is in charge of the radiation therapy. These two treatments are received in separate places with different staff and offices. It is helpful to identify a person in each department that is responsible for coordinating care and being available for questions.

It is very important to stop smoking before starting therapy. Several research studies suggest that patients who stop smoking during treatment have better chances of being cured from their disease and living longer compared with patients who continue to smoke.[8] The patient can ask the doctors to get help with the process. Additional information about stopping smoking is available by calling 1-800-QUIT-NOW or reviewing www.smokefree.gov. *(*See Chapter 11: *How to Quit Smoking Confidently and Successfully)*

Chemotherapy

Most patients with small cell lung cancer are treated with chemotherapy.[1,6] Even patients who have a cancer that is completely removed by surgery will require chemotherapy after surgery, and other patients with limited stage small cell lung cancer will need chemotherapy in combination with radiation therapy.

The most common type of chemotherapy for patients with small cell lung cancer is a combination of two drugs: cisplatin or carboplatin and etoposide. These drugs are both given through the veins as an infusion. This infusion can be given through a small catheter that is inserted in one of the veins in the arm or through a more permanent type of catheter called a Peripherally Inserted Central Catheter (PICC), also placed in the arm. This type of chemotherapy is given over three consecutive days.

During the first day, both cisplatin and etoposide are given. Before the infusion begins, the doctors and nurses draw some blood for laboratory tests to make sure that everything is safe for the chemotherapy to be given. This ensures that the kidneys, liver, and bone marrow are healthy enough to tolerate the chemotherapy. The next step is to give intravenous fluids and other medications to prevent nausea or vomiting during or after the chemotherapy. These preparatory procedures usually take approximately 2 to 3 hours.

Then, the chemotherapy is given as an infusion for another 2 to 3 hours. After the chemotherapy, more fluids are received to make sure that the patient stays well hydrated and the kidneys do not suffer any damage from the chemotherapy. The entire process usually takes 5 to 6 hours from start to finish. After this is done, the patient goes home and comes back the next day.

The second and third days of the chemotherapy are shorter (approximately 2 to 3 hours) because only the etoposide is given. In addition, there usually is no need for laboratory tests or additional hydration. Medications are given to help avoid nausea.

This chemotherapy usually is given once every 21 days, and this period of time is called a "cycle." In between the administration of chemotherapy, the body recovers from side effects and gets ready for the next cycle. This chemotherapy usually is given for a total of 4 cycles. Each cycle lasts approximately 3 weeks, so the entire chemotherapy regimen occurs for approximately 12 weeks.

Most people do not feel anything unusual while receiving the chemotherapy. If the appropriate medications are received to prevent nausea, there should be no problems while receiving the chemotherapy. The side effects usually occur after the chemotherapy is given.

Chemotherapy Side Effects

Although chemotherapy can be associated with many potential side effects, not all of them will affect each patient. Some patients do not have any side effects and other patients have many side effects. We review the most common and important side effects.

High Risk of Infection

Infection is one of the most serious side effects of chemotherapy. Any infection in patients who are receiving chemotherapy is considered a serious problem. These infections are varied and may present with flu symptoms, cough, shortness of breath, sore throat, diarrhea, ear pain, urinary symptoms, and other symptoms. The most common presenting symptom is fever. Although some patients have a fever and feel fine, it is important to understand that any fever while receiving chemotherapy should be treated as an emergency.

The risk of getting an infection is high because chemotherapy kills white blood cells, which defend the body against infections. When chemotherapy kills the white blood cells, the body is more susceptible to infection. However, the white blood cells grow back within a few days and then the body can fight infections.

As a matter of precaution, it is important to avoid sick people, to eat only in places with good hygienic standards, and to make sure that food at home is washed well. However, there is no need to go to extreme measures such as wearing a surgical mask. It is enough precaution to keep a distance from sick people and maintain good hygiene at home.

Fatigue

Both chemotherapy and radiation treatments may cause fatigue. This usually is worst on the first few days after the chemotherapy treatment and usually improves during the second and third week. As more chemotherapy and radiation therapy treatments are received, the fatigue may become more pronounced. However, fatigue typically improves after the chemotherapy and radiation therapy treatments are completed.

The fatigue can be caused by anemia (a decrease in the amount of red blood cells in the body) that is caused by the chemotherapy. These red blood cells transport oxygen from the lungs to the rest of the body. When the amount of red blood cells in the system is decreased, the patient feels more fatigued. If the red blood cells decrease too low, a transfusion of red blood cells may be required.

Nausea and Vomiting

Although nausea is a very common symptom associated with chemotherapy, very potent anti-nausea medications may be helpful. The medications for the prevention of nausea include aprepitant, fosaprepitant, ondansetron, granisetron, dexamethasone, lorazepam, prochlorperazine, and metochlopramide.

Hair Loss

Hair loss typically happens after two weeks of receiving the first chemotherapy treatment, and the hair is completely lost after the second cycle of therapy.

Other Side Effects

Other potential side effects include poor appetite, mouth sores, diarrhea, and increased risk of bleeding. Although it can be overwhelming to read about all the potential side effects of these treatments, most patients tolerate therapy relatively well and without major complications.

Radiation Therapy

An effective way to treat limited stage small cell lung cancer is to give radiation therapy at the same time as chemotherapy.[1,6] The type of radiation used for small cell lung cancer is external beam radiation, in which nothing is placed inside the body to give the radiation.

Before receiving the radiation, the patient meets with the radiation oncologist for simulation, a process in which images of the tumor are made to help formulate a specific plan of treatment. Subsequently, radiation treatment usually is started on the same day as the beginning of chemotherapy.

Radiation therapy is given with a machine that appears similar to a CT scan machine. The patient lies down flat on the machine table and it is given the radiation. For patients with small cell lung cancer, radiation is given either once or twice daily, and the radiation treatment just takes a few minutes. Radiation therapy is given every day from Monday through Friday for three to six or seven weeks, depending on whether the treatments are given once or twice daily or whether interruptions in the treatment have occurred.

Radiation Side Effects

When radiation therapy and chemotherapy are combined, more side effects usually occur than with either treatment alone. In addition to the side effects described for chemotherapy, the following side effects may be specific to radiation therapy.

Heartburn or Painful Swallowing

Heartburn or painful swallowing may be a very common side effect of radiation therapy and is caused by irritation of the esophagus by the radiation. This usually starts as a sensation of acid reflux or heartburn in the middle of the chest. It can become more painful, and patients can complain of difficulty swallowing or pain when swallowing. These symptoms can be treated with pain medication and drugs to decrease stomach acid.

Skin Irritation or Burning

Skin irritation and changes in skin color may be noticed during the radiation treatment. Sometimes this can appear and feel like a burning in the chest. This side effect resolves a few days after the radiation is stopped.

Lung Irritation or Inflammation

Although the radiation is aimed at killing the cancer, it also may damage and cause irritation or inflammation of the healthy lungs. This usually is not a problem during the radiation treatment but the lungs may become inflamed several months later. This usually presents as cough or shortness of breath. These symptoms should be discussed with the doctors.

Other Radiation Side Effects

Other potential side effects noted in the section about chemotherapy may occur as side effects of combined chemotherapy and radiation treatment for small cell lung cancer.

Additional Treatments

After the radiation therapy is completed, patients usually need to complete two more cycles of chemotherapy. There are a total of four cycles of chemotherapy: two during radiation therapy and two more after radiation therapy is completed.

After the full chemotherapy regimen has been administered, another CT scan is done to evaluate the efficacy of the treatment by comparing the size of the cancer before and after chemotherapy.

Prophylactic Cranial Irradiation

If the cancer has responded to therapy, additional radiation therapy to the brain (prophylactic cranial irradiation) is recommended.[8]

Although chemotherapy and radiation therapy are considered the definitive treatment for limited stage small cell lung cancer, the cancer usually recurs in a large percentage of patients, mainly in the brain. Therefore, to prevent the cancer from recurring in the brain, radiation therapy to the brain is recommended. This usually is given with a similar type of machine used for radiation therapy to the lungs, by the same doctors, and scheduled once daily for approximately two weeks. In several studies, this causes significant improvement in the life expectancy of patients with this disease.

Brain irradiation usually is very well tolerated. The most frequent side effects include fatigue, scalp irritation, and memory or cognitive problems. Most side effects usually resolve after treatment is completed, but the memory and cognitive problems can be long lasting.[9]

Follow-up

After all therapy is completed, the patient is followed very closely until recovery from all side effects associated with chemotherapy and radiation.[1] Side effects usually start to improve after two weeks of the final chemotherapy, with more energy, increased appetite, and resolution of nausea. Most side effects are resolved in one or two months after the treatments have been completed. In addition, the hair usually will start growing back in a couple of months.

Late side effects may occur such as inflammation of the lungs or other side effects from radiation. For this reason, it is important to tell the doctors about any new symptoms that occur after treatment has ended.

Regular visits are recommended with the medical oncologist every one to two months initially, and then less frequently if the patient is feeling well. At every visit the doctor reviews symptoms and performs a physical examination and blood tests. Additionally, the chest CT scan is repeated to make sure that the cancer is still under control; this is done every two to four months initially, later every four to six months, and only once annually after three years. After five years, there is no need to repeat the CT scans.

It is important that patients make every effort to quit smoking, because this will decrease their risk of getting another cancer or having a recurrence of their treated cancer.

Prognosis

The intention of treatment for limited stage small cell lung cancer is to cure the cancer.[1,6,10] It is expected that 70% to 90% of patients that receive treatment will have a response to therapy, with the cancer shrinking

significantly in the majority of patients.

However, in the long term the cancer recurs in most patients. Only 41% to 47% patients are alive after two years and 16% to 26% are alive at five years.[6] These estimates are for patients that receive treatment. For patients who are too sick to receive any kind of treatment or who do not wish to receive treatment, the life expectancy usually is < 1 year, sometimes just a few months.

Although the prognosis is poor, 26% of patients are well and alive five years after they had started treatment for limited stage small cell lung cancer with a combination of chemotherapy and radiation. For patients that do not receive treatment, most are not alive one year after diagnosis. If the cancer recurs, the treatment is similar to the cancer for patients with extensive stage small cell lung cancer.

Extensive Stage or Recurrent Small Cell Lung Cancer

Extensive stage small cell lung cancer is a type of cancer that has spread beyond one lung to invade other organs such as the liver, brain, and bones. Treatment options for this stage of small cell lung cancer include chemotherapy and radiation therapy. Surgery is not an available option for patients with extensive stage small cell lung cancer because the cancer that has spread to other organs cannot be safely removed surgically and may recur quickly.[1,2,5] Spread of this type of cancer includes invasion of blood, lymph nodes, and other organs, with microscopic cells that cannot be detected on radiographs or removed.

Chemotherapy

Chemotherapy is the only treatment that can reach all the areas of the body to which the cancer has spread.[1,11-16] The chemotherapy regimens for patients with extensive stage small cell lung cancer usually include a combination of two drugs. The most common combinations of drugs include cisplatin or carboplatin in combination with etoposide or irinotecan. These combinations all are equally effective in treating small cell lung cancer. The combination choice is based on factors such as age and other medical problems.

These drugs are all given as an infusion through the veins using a small catheter or PICC. The combinations that contain etoposide are given over three consecutive days.

During the first day, both the cisplatin or carboplatin and the etoposide are given. Before the infusion begins, blood tests are done to make sure that the kidneys, liver, and bone marrow are all healthy enough to tolerate the chemotherapy. Fluids are then given through the veins, and medications are given to prevent nausea or vomiting during or after the chemotherapy. This preparation usually takes 2 to 3 hours.

The chemotherapy is given as an infusion that requires 2 to 3 hours. After the chemotherapy, more fluids are given to ensure good hydration and kidney function. The entire process requires 5 to 6 hours, and the patient then goes home and returns the next day.

The second and third days of chemotherapy are shorter because etoposide is the only drug given, and blood tests and hydration are not required. Medications are given to prevent nausea, and the entire visit in the infusion center is 2 to 3 hours.

This chemotherapy usually is given once every 21 or 28 day cycle. In between treatments, the body recovers from side effects and prepares for the next cycle. The chemotherapy is given for a total of 4 cycles, so the treatment period typically spans 12 to 16 weeks. Symptoms and side effects of chemotherapy for extensive stage or recurrent small cell lung cancer are similar to that for limited stage small cell lung cancer.

Radiation Therapy

The combination of chemotherapy and radiation therapy also is typically not an option for patients with extensive stage small cell lung cancer.[1,2,5,6] However, radiation therapy sometimes can be added to the treatment of extensive small cell lung cancer to help with specific parts of the body that may be affected by symptoms such as pain. In these cases, the purpose of radiation therapy is to help relieve specific symptoms such as pain. Nevertheless, recent evidence suggests that giving radiation therapy to the cancer localized in the chest area may be beneficial. This approach may delay the advancement of the cancer and in some cases it may actually increase the chances of surviving the cancer for a few patients.

Prophylactic Cranial Irradiation

If the cancer has responded to therapy, additional radiation therapy to the brain (prophylactic cranial irradiation) may be recommended[1,17,18]. Follow-up schedules are similar to those for limited stage small cell cancer. However, this modality of treatment is controversial in patients with extensive stage SCLC. Thus, it is recommended that patients discuss the pros, cons and latest research evidence with their doctors.

Additional Treatments and Follow-up

Although the majority of patients who receive chemotherapy have shrinkage of the cancer and an improvement in quality of life, the cancer usually grows back either during or after the chemotherapy regimen.[17,18,21] After the cancer grows back, options for further treatment with chemotherapy include topotecan, paclitaxel, docetaxel, irinotecan, ifosfamide, gemcitabine, vinorelbine, and etoposide. The main purpose of treating the cancer with these drugs is to improve some of the symptoms associated with the cancer, but < 25% patients respond to this chemotherapy.

Prognosis

Extensive stage small cell lung cancer cannot be cured.[1,8,10,13,17,20] The purpose of treatment for extensive stage small cell lung cancer is to improve the symptoms associated with the cancer and prolong life span. In 60%

to 70% patients that receive treatment, a response to the first therapy is achieved and the cancer shrinks significantly.

Approximately 50% patients that receive treatment remain alive after 10 to 11 months, but > 50% patients die in < 1 year and < 5% are alive after 3 years. For those patients who are too sick to receive treatment or do not wish to receive treatment, life expectancy usually is < 2 or 3 months or just a few weeks. Nevertheless, chemotherapy is recommended because it may be effective in shrinking the cancer and helping with symptoms such as pain.

Clinical Trials

The efficacy of the available treatments for small cell lung cancer is limited. Although most patients have improvement of symptoms and the tumor may shrink initially, the cancer usually recurs or becomes resistant to therapy.

The treatments for small cell lung cancer do not usually cure people of their disease and much work is needed to make treatments better. This is done with research and clinical trials. A clinical trial is a research project designed to evaluate whether or not a drug is effective in the treatment of a particular disease.

Some people are afraid of participating in clinical trials because they may fear that they will not receive adequate treatment for their disease. However, this is not the case in clinical trials involving cancer patients. Most or all of the clinical trials conducted in lung cancer patients are designed to make certain that all patients receive standard or adequate treatment for their disease.

Patients may speak with doctors about clinical trials, ask questions, and try to participate if possible. They receive excellent medical care while participating in clinical trials, and there is the possibility of benefit from receiving a new type of treatment. In addition, participation in clinical trials may contribute to better treatments for other patients.

References

1. NCCN Guidelines Version 2.2012 Small Cell Lung Cancer. *National Comprehensive Cancer Network Guidelines*, 2012.
2. Simon GR, Turrisi A. Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):324S-339S.
3. DeVita V, Hellman S, Rosenberg S. *Cancer Principles and Practice of Oncology*. 2001.
4. Lababede O, Meziane M, Rice T. Seventh edition of the cancer staging manual and stage grouping of lung cancer: quick reference chart and diagrams. *Chest*. 2011;139(1):183-9.
5. Yu JB, Decker RH, Detterbeck FC, et al. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. *J Thorac Oncol*. 2010;5(2):215-9.
6. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340(4):265-71.

7. Videtic GM, Stitt LW, Dar AR, et al. Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. *J Clin Oncol.* 2003;21(8):1544-9.
8. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med.* 1999;341(7):476-84.
9. Le Péchoux C, Laplanche A, Faivre-Finn C, et al. Clinical neurological outcome and quality of life among patients with limited small-cell cancer treated with two different doses of prophylactic cranial irradiation in the intergroup phase III trial (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01). *Ann Oncol.* 2011;22(5):1154-63.
10. Chute JP, Venzon DJ, Hankins L, et al. Outcome of patients with small-cell lung cancer during 20 years of clinical research at the US National Cancer Institute. *Mayo Clin Proc.* 1997;72(10):901-12.
11. Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol.* 1985;3(11):1471-7.
12. Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *J Natl Cancer Inst.* 1991;83(12):855-61.
13. Horn L, Dahlberg SE, Sandler AB, et al. Phase II study of cisplatin plus etoposide and bevacizumab for previously untreated, extensive-stage small-cell lung cancer: Eastern Cooperative Oncology Group Study E3501. *J Clin Oncol.* 2009;27(35):6006-6011.
14. Horn L, Zhao Z, Sandler A, et al. A phase II study of carboplatin and irinotecan in extensive stage small-cell lung cancer. *Clin Lung Cancer.* 2011;12(3):161-5.
15. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol.* 1992;10(2):282-91.
16. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol.* 2002;20(24):4665-72.
17. Kim YH, Mishima M. Second-line chemotherapy for small-cell lung cancer (SCLC). *Cancer Treat Rev.* 2011;37(2):143-50.
18. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol.* 2006;24(34):5441-7.
19. Greenspoon JN, Evans WK, Cai W, et al. Selecting patients with extensive-stage small cell lung cancer for prophylactic cranial irradiation by predicting brain metastases. *J Thorac Oncol.* 2011;6(4):808-12.
20. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med.* 2007;357(7):664-72.
21. Ettinger DS, Jotte R, Lorigan P, et al. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. *J Clin Oncol.* 2010;28(15):2598-603.

Chapter

6

Clinical Trials and Emerging Therapies for Lung Cancer

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Introduction

Clinical research is being done to develop new lung cancer treatments. Some newer treatments are commercially available, and others are available only to patients who participate in clinical trials. Targeted therapies may pinpoint specific molecular changes to prevent tumor cells from dividing out of control. Traditional chemotherapy attacks any rapidly dividing cells, but targeted therapy concentrates on specific abnormalities unique to cancer cells, resulting in fewer side effects and potential for improved cancer control. Targeted therapies may be used alone or in combination with other treatments to improve overall care. However, targeted therapies often apply to a select group of patients who have tumors with unique mutations, and these therapies are not appropriate for all patients. Current research is being done to evaluate the best use of these newer targeted agents to improve quality of life and longevity of patients.

Additional new treatments for lung cancer include vaccines and immunotherapy. Researchers and clinicians are hopeful that these therapies will improve outcomes for patients diagnosed with lung cancer. Despite these new treatments, chemotherapy remains an important treatment option, and researchers continue to evaluate newer chemotherapy agents to treat lung cancers. Other areas of research include targeted agents and chemotherapy for lung cancer maintenance (prevention of relapse) and medications to prevent lung cancer (chemoprevention) in patients at high risk for developing this disease.

Clinical Trials

In research laboratories, scientists have been identifying new substances that show promise in fighting different types of cancer cells. Following extensive testing, clinical trials are done to establish whether or not these substances are effective in people. The purpose of clinical trials is to identify new agents that will improve survival or quality of life more than other currently available treatment options.

Clinical trials of new drugs are done in a series of phases, each with a specific purpose. If the drug is safe and provides benefit in an early phase trial, it is further tested in subsequent phases:

- Phase 1: the drug is tested for the first time in people to establish safety, tolerability, dosage, and treatment schedule for subsequent studies.
- Phase 2: the drug is tested in more people to determine efficacy, safety, and side effects.
- Phase 3: the drug is tested in a larger group of people to determine whether or not the new drug is more effective than existing treatments. Side effects and safety also are monitored.
- Phase 4: after approval by the United States Food and Drug Administration (FDA), the drug is available for treatment in the general population and further monitored for safety, efficacy, and long-term side effects.

During phases 1 to 3, the drugs are available only to patients who participate in the clinical trial. In phase 4, the drugs are commercially available through drug stores and special pharmacies. Clinical trials are available at major medical centers, but are increasingly becoming available at smaller community medical centers due to the expansion of hospital networks. A list of all clinical trials available for lung cancer patients is provided on the Internet site of the National Cancer Institute (http://www.cancer.gov/clinicaltrials/search), and the treating oncologist also may recommend trials that are available locally.

Some new drugs that have a major increase in efficacy, compared with older therapies, are granted FDA Fast Track Status, and the FDA expedites the availability of these new treatments to patients who have limited options. Drugs with Fast Track Status are available only in clinical trials but may move through the clinical trial process and become widely available more quickly.

Targeted Therapy

Chemotherapy drugs may be effective because they kill cancer cells that multiply rapidly. However, many normal cells also multiply rapidly, such as cells of the digestive tract, hair follicles, and blood; when these normal cells are affected by chemotherapy drugs, undesirable side effects occur. Targeted therapy includes newer drugs that interfere with specific aspects of cancer cells, avoiding damage to normal cells. Targeted therapy consists of either monoclonal antibodies (names ending in "-ab") that target the outside surface of the cancer cell or small molecules (names ending in "-ib") that target the inside of the cancer cell.

As genetic research advances, great strides are being taken to better understand the molecular make-up of tumors, and to determine the mechanisms which drive tumor growth, development, and spread to other organs. The wider availability of full genome sequencing of tumor DNA is opening up the opportunity for true personalized medicine, in which therapies are targeted to the specific genetic make-up of an individuals' tumor. Genome sequencing offers the opportunity to identify rare mutations and then design a treatment plan to block the exact mechanism that is making the cancer grow. Examples of well-studied mutations that are common in lung cancer are EGFR mutation and EML4-Alk rearrangement. Several drugs used to target these mutations have been approved by the FDA, while many of the novel agents listed below are available only through clinical trials.

Monoclonal Antibodies

Monoclonal antibodies are proteins that attach to receptors on the cell surface. The cell surface receptors may be stimulated by proteins, and this may start a controlled series of reactions inside the cell that may increase cellular growth and development. In cancer cells, the normal controls may be absent, and cellular replication proceeds uncontrolled. Antibodies are normally produced by the immune system to fight infections caused by bacteria or viruses, and the body produces specific antibodies for each type of infectious agent (antigen) to which the body is exposed. Monoclonal antibodies are designed and produced in a laboratory to bind with a very specific target, such as a cell surface receptor or other defect unique to cancer cells.

Monoclonal antibodies can fight cancer cells by:

(1) turning off the series of reactions in the cells by blocking the receptors,
(2) targeting specific defects in the cancer cells or labeling the cancer cells, making them more vulnerable to destruction by the body's immune system, or
(3) delivering other drugs or substances directly to the cancer cells.

Onartuzumab (MetMAb®) is a monoclonal antibody that is currently being tested in clinical trials. Overexpression of Met, a receptor protein, may occur in 75% patients with NSCLC, and high Met protein is associated with poor prognosis. Combining onartuzumab with the small molecule drug erlotinib (Tarceva®) has been demonstrated to improve survival compared to survival with erlotinib alone.[1] Onartuzumab is given at a medical office by intravenous injection. Common side effects include fatigue, nausea, and vomiting.

Trastuzumab is a monoclonal antibody that targets HER2 overexpression. It has been used in HER2 positive breast cancer (received FDA approval for this application in 1998), and is now being evaluated in lung cancers with the same mutation. Common side effects include nausea, vomiting, loss of appetite, fatigue and muscle/joint aches. Cardiac toxicity can be a serious complication, and warrants close monitoring. Allergic reaction may occur during the infusion of this drug. If used in combination with chemotherapy it may contribute to decreased white blood cell count and increased risk of infection.

Small Molecules

Small molecule drugs enter the cell and block the sequence of reactions that cause cellular proliferation. By blocking this sequence of reactions in cancer cells, the small molecule drugs kill the cancer cells and slow or stop tumor growth. In normal cells, tyrosine kinase enzymes activate a phosphorylation cascade that regulates signals sent to the cell nucleus and governs the timing of cellular proliferation, differentiation, and programmed cell death (apoptosis). In malignant cells, this communication cascade may be switched on permanently, resulting in unregulated cellular proliferation and tumor growth. Tyrosine kinase inhibitors are small molecule drugs that interfere with this sequence of reactions, stopping cell proliferation and causing cell death. New tyrosine kinase inhibitors continue

to be studied for use in lung cancer, and several are now commercially available for patients with specific, targetable mutations in tumor DNA. During treatment with small molecules the cancer cells may develop a second mutation that confers resistance to first line therapy. Identifying second line therapies that continue to exploit the underlying driver mutation but also block the resistance mutation is becoming increasingly important.

EGFR pathway inhibitors:

AZD9291 is an oral agent being evaluated for use in patients with an Epidermal Growth Factor Receptor (EGFR) mutation that have progressed on first line therapy such as Tarceva or Gilotrif. It has been demonstrated to be highly effective in patients with EGFR mutations that develop resistance to first line therapy as a result of secondary T790 mutation. In this subset of patients over 60% of those treated had response.[2] Side effects were mild, and included diarrhea, rash and nausea. Currently this drug is only available through clinical trial participation.

CO-1686 is an oral irreversible EGFR inhibitor that has less impact on healthy cells than other EGFR inhibitors. Although still in early phase trials, it has shown activity in up to 60% of patients, both in a first line setting as well as those who have developed a T790 mutation.[3] Side effects tend to be mild, with less diarrhea and rash than traditional EGFR inhibitors. Mild nausea, hyperglycemia, myalgia and decreased appetite were also observed. Currently this drug is only available through clinical trial participation.

ALK inhibitors:

Xalkori® (Crizotinib) received FDA approval for treatment of NSCLC in patient with an ALK rearrangement in 2011. It is a small molecule drug that targets the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) mutation. ALK rearrangement is present in 4% to 5% people with NSCLC, primarily those with adenocarcinoma, and is more common in women and people who had never smoked. However, use of this medication is being expanded, and it is currently being evaluated for use in trials for patients with other rare mutations in their tumor DNA, such as ROS-1 rearrangements and mesenchymal-epithelial transition (MET) amplification.[4] Xalkori has marked results in patients with these mutations[5], with > 50% patients responding for an average > 6 months but over time patients develop resistance to the drug. Common side effects include visual disturbance, nausea, diarrhea, vomiting, edema (particularly in the legs), and constipation.

AP-26113 is an ALK-inhibitor that is being evaluated for use both in the first line as well as second line settings for patients whose tumors harbor an EML4-ALK rearrangement. This compound is tolerated quite well, and although clinical trial data are not yet available, it appears to have a high level of activity.[6] Common side effects are mild and include diarrhea, nausea, vomiting, and decreased liver function.

MEK inhibitor:
Selumetinib (AZD6244; ARRY-142886) is a small molecule drug being studied in early phase clinical trials. It inhibits the mitogen-activated protein kinases MEK-1 and MEK-2. It has activity against tumors with a specific mutation (KRAS), often resistant to standard chemotherapy[7]. It stops cellular proliferation and induces apoptosis in some cell lines. Common side effects include rash, diarrhea, nausea, vomiting, hypertension, visual disturbance, and decreased liver function.

Vaccines

A newer approach to treating NSCLC uses vaccines to treat lung cancer or decrease the risk of recurrence. Analogous to vaccines that may prevent the spread of viruses, cancer vaccines stimulate the immune system to identify and attack cancer cells without damaging normal cells. Vaccines are made with genetic material from cancer cells, and many trials are ongoing.

Belagenpumatucel-L (Lucanix®) currently is being studied for people with stage III and IV NSCLC. It is given as a series of monthly injections for 12 months. A positive effect was seen in early studies, with higher doses having a higher response rate.[8] Common side effects include injection site reaction and flu-like symptoms.

L-BLP25 (Stimuvax®) currently is being studied for people with inoperable stage III and IV NSCLC. It targets the Mucin 1 (MUC1) protein on the surface of cancer cells. The MUC1 protein is a good target because overexpression of this protein in cancer cells may cause decreased apoptosis, decreased immune function, and increased resistance to chemotherapeutic agents. Currently in phase 3 clinical trials, L-BLP25 has shown a survival benefit in treated patients.[8] Common side effects include injection site reaction, nausea, vomiting, diarrhea, and flu-like symptoms.

TG4010 is targeted immunotherapy based on a pox virus (the Modified Vaccinia Ankara virus) that codes for the MUC1 tumor-associated antigen and interleukin-2. TG4010 has been assessed in combination with first-line chemotherapy in advanced NSCLC and has shown an improvement in progression-free survival. Common side effects include injection site reaction and flu-like symptoms.[9]

Melanoma-associated antigen 3 (MAGE-A3) is an Antigen-Specific Cancer Immunotherapeutic (ASCI) protein that is being studied for people diagnosed with early stage NSCLC that has been completely removed by surgery. People are eligible to receive this treatment if their tumor tissue tests positive for MAGE-A3, present in 30% to 40% people with NSCLC. Initial studies have shown decreased cancer recurrence, and this treatment is being tested in a phase 3 clinical trial.[10] Side effects are very minimal.

Immunotherapy

Cancers develop and spread in part because they evade detection by the immune system. The goal of immunotherapy is to make cancer cells recognized as abnormal by the immune system, enabling the natural immune defense mechanisms to eliminate the cancer. With immunotherapy, side effects are mild because the drugs affect only certain types of cells, and they use the body's own defenses (not cytotoxic drugs) to kill cancer cells.

Several antibodies are currently being evaluated that target certain immune checkpoints that have been shown to play a role in cell signaling and driving cancer growth. Some of the most promising developments in treating lung cancer have been seen in trials evaluating the Programmed Death 1 (PD-1) receptor pathway, including Novolumab (BMS-936558), Pembrolizumab (formerly Lambrolizumab or MK-3475), MPDL3280A (made by Roche) and Medi4736 (made by Medimmune). The receptor PD-1 is found on immune cells (T cells), and when activated, it can suppress the ability of the immune system to recognize and attack cancer cells. Similarly, PD-L1 is the ligand to which PD-1 binds on the surface of the tumor cell. By blocking these receptor sites with targeted antibodies, it is possible to increases the body's own defenses against cancer. This change to cell signaling enhances the immune system so that it can recognize and attack cancer cells.[11]

Data on efficacy of these drugs continues to emerge, but they appear to be effective in 20% or more of patients, in some cases offering complete response and eradicating evidence of the cancer. At this time it appears that expression of PD1 marker on the cell surface is correlated with higher response rates.[12-13] These drugs have a very different side effect profile than traditional chemotherapy drugs, and are typically well tolerated. However, because these medications increase the activity of the immune system, it is possible for the immune system to attack healthy cells along with cancer cells. Side effects are remarkably mild, but rare severe drug toxicities have occurred. Adverse effects commonly manifest as a result of an inflammatory response, and can occur nearly anywhere in the body – skin (rash), eyes (iritis/uveitis), colon (colitis/diarrhea), lungs (pneumonitis), liver (hepatitis), and kidneys (nephritis). Due to the inflammatory nature of the side effects, steroids are used to control and reverse these inflammatory-mediated reactions. At this time administration of these drugs to people with auto-immune conditions is prohibited, as the reaction of the compromised immune system is unclear and such exposure poses undue risk to patients.

Ipilimumab and Tremelimumab are monoclonal antibodies that inhibit the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathway. Although these have been used extensively in the treatment of melanoma, they are now being evaluated in NSCLC, typically in combination with the Anti-PD1 class of drugs. They have a similar side effect profile to the Anti-PD1 antibodies, including rash, diarrhea/colitis, hepatitis, iritis/uveitis, hormonal changes and pneumonitis. However, side effects tend to be more common with Anti-CTLA-4 drugs compared to Anti PD-1 and Anti-PD-L1 compounds.[14]

Chemotherapy

Although much research is focusing on new approaches to lung cancer treatment, research also is being done to develop new drugs for chemotherapy or improve existing chemotherapy regimens. Combination therapy has long been the hallmark of cancer treatment. As promising new agents are

identified, they are evaluated in clinical trials in an effort to identify novel treatment modalities that will improve quality of life and prolong survival. Multiple trials evaluating the addition of small molecules, monoclonal antibodies, as well as immunotherapy are currently underway.

Amrubicin is approved by the FDA for use in treating breast cancer, and it is being investigated for use in treating small cell lung cancer. It is an anthracycline, a highly effective class of chemotherapy drugs that has a high risk of cardiac toxicity (damage to the heart). However, amrubicin does not cause the same amount of cardiac toxicity observed with other anthracyclines, even at high doses.[15] Common side effects include decreased bone marrow function (anemia, neutropenia, and low platelet counts).

Maintenance Therapy

Maintenance therapy is given to patients in remission, to prevent relapse of cancer. Erlotinib (Tarceva®) was approved by the FDA in 2010 as a maintenance therapy for NSCLC patients who completed at least four cycles of platinum-based therapy, and who have disease that has not progressed.[16] Pemetrexed (Alimta®) was approved by the FDA in 2008 as a maintenance therapy for patients with non-squamous NSCLC who completed at least four cycles of platinum-based therapy, and who have disease that has not progressed.[17] Bevacizumab (Avastin®) has not been approved by the FDA for maintenance treatment in NSCLC, but it frequently is continued as a single agent after being used in combination with other chemotherapy drugs in the initial or induction treatment.

Chemoprevention

Multiple studies have been conducted in an effort to identify compounds that might prevent the development of lung cancer. Unfortunately, to date none have been identified that have demonstrated a dramatic decrease in cancer rates.[18] Antioxidants and anti-inflammatory drugs like COX-2 inhibitors did not show a decreased cancer incidence, but aspirin seemed to slightly decrease risk in several studies, particularly in those at highest risk for developing lung cancer.[19]

Pioglitazone hydrochloride (Actos®), a drug used in treating type 2 diabetes mellitus, is being evaluated as a drug that may slow or prevent the growth of tumors in patients with NSCLC. Currently it is being evaluated in patients with a smoking history who are at risk for developing lung cancer. A trial considering it in patients with stage IA through IIIA NSCLC was terminated early due to low enrollment. However, pre-clinical data are promising.

Lung cancer screening programs:

Avoiding exposure to tobacco smoke and smoking cessation remain the best defense against lung cancer. (See Chapter 11, *How to Quit Smoking Confidently and Successfully*) However, novel screening algorithms are being developed for use of low-dose screening CT scans in order to identify both those individuals at highest risk for lung cancer, as well as to identify cancers in an early, asymptomatic, surgically resectable and thus more treatable stage. The best lung cancer screening programs are comprehensive, and include the services of pulmonary experts, as well as oncologists

and counselors who can educate patients regarding their risk of developing cancer as well as interpret and appropriately act on any screening test results.

Conclusion

Lung cancer is a devastating diagnosis, but research is improving the options for treatment of this disease. Chemotherapy is the mainstay of treatment for most advanced lung cancers. New therapies are available that may improve outcomes for patients with lung cancers associated with certain mutations. Other agents are being studied in clinical trials, and more therapies should become available in the future. With advances in lung cancer treatment, patients should benefit with improved tolerance and response to treatment, and lung cancer may evolve to a chronic disease that can be managed for longer periods.

References

1. Spigel DR et al. Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer. JCO October 7, 2013 JCO.2012.47.4189
2. Ranson, M. et al. Preliminary results from a Phase I study with AZD9291: an irreversible inhibitor of epidermal growth factor receptor (EGFR) activating and resistance mutations in non-small cell lung cancer (NSCLC). European Cancer Conference (Amsterdam, 2013)
3. http://www.clovisoncology.com/files/CO1686_Oral_ASCO2014_FINAL.pdf
4. Rossi A1, Maione P1, Sacco PC et al. ALK inhibitors and advanced non-small cell lung cancer (Review). Int J Oncol. 2014 Aug;45(2):499-508. doi: 10.3892/ijo.2014.2475. Epub 2014 May 29.
5. Ou SH, Kwak EL, Siwak-Tapp C et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification.J Thorac Oncol. 2011 May;6(5):942-6. doi: 10.1097/JTO.0b013e31821528d3.
6. Katayama R et al. Therapeutic strategies to overcome Crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. PNAS May 3, 2011 vol. 108 no. 18 7535-7540
7. Garon EB, Finn RS, Hosmer W, et al. Identification of common predictive markers of in vitro response to the Mek inhibitor selumetinib (AZD6244; ARRY-142886) in human breast cancer and non-small cell lung cancer cell lines. Mol Cancer Ther. 2010;9(7):1985-94.
8. Morgensztern D, Goodgame B, Govindan R. Vaccines and immunotherapy for non-small cell lung cancer. J Thorac Oncol. 2010;5(12 Suppl. 6):S463-S465.
9. Quoix E, Ramlau R, Westeel V, et al. Therapeutic vaccination with TG4010 and first-line chemotherapy in advanced non-small-cell lung cancer: a controlled phase 2B trial. *Lancet Oncol.* 2011;12(12):1125-33.
10. Meng J, Fang B, Liao Y, et al. Apoptosis induction by MEK inhibition in human lung cancer cells is mediated by Bim. *PLoS One*. 2010;5(9):e13026.
11. Brahmer JR, Tykodi SS, Chow LQM, et al. Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366:2455-2465
12. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012; 366:2443-2454)
13. Brahmer, J Harnessing the Immune System for the Treatment of Non–Small-Cell Lung Cancer JCO March 10, 2013 vol. 31 no. 8 1021-1028
14. Khobta N. et al. Ipilimumab: its potential in non-small cell lung cancer. Therapeutic Advances in Medical Oncology March 2012 vol. 4 no. 2 43-50).

15. Ettinger DS, Jotte R, Lorigan P, et al. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. *J Clin Oncol*. 2010;28(15):2598-603.
16. Cappuzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicenter, randomised, placebo-controlled phase 3 study. *Lancet Oncol*. 2010;11(6):521-9.
17 Belani CP, Brodowicz T, Ciuleanu T, et al. Maintenance pemetrexed (Pem) plus best supportive care (BSC) versus placebo (Plac) plus BSC: A randomized phase III study in advanced non-small cell lung cancer (NSCLC). J Clin Oncol. 2009;27(18 Suppl.):CRA8000.
18. Kathuria H et al. Updates and Controversies in the Rapidly Evolving Field of Lung Cancer Screening, Early Detection, and Chemoprevention Cancers 2014, 6, 1157-1179; doi:10.3390/cancers6021157
19. Xu, J.; Yin, Z.; Gao, W.; Liu, L.; Wang, R.; Huang, P.; Yin, Y.; Liu, P.; Yu, R.; Shu, Y. Meta-analysis on the association between nonsteroidal anti-inflammatory drug use and lung cancer risk. Clin. Lung Cancer 2012, 13, 44–51, doi:10.1016/j.cllc.2011.06.009).

Chapter

7

Supportive Care

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Introduction

Advances in early detection and the development of new treatment options have increased survival rates for lung cancer patients over the last decade. However, many of these improvements are associated with long-term side effects during the course of the disease. It is important to address the longitudinal effects of treatment and recognize the need for supportive care interventions for patients. Many treatment options available in standard care or clinical trials are accompanied by known side effects. Advances in supportive care have changed the cancer experience for many patients. Supportive care is a valuable part of the success of treatment and helps to provide positive outcomes. As a result, practitioners are better prepared to address and prevent cancer-related symptoms.

Supportive care is a term that refers to treatment that aims to decrease or eliminate symptoms associated with cancer. The goal is to maximize comfort, minimize suffering, and ensure the highest quality of life. Supportive care focuses on treating cancer-related symptoms, preventing and managing treatment-related side effects, recognizing and supporting psychosocial distress, and helping to develop strategies for improving quality of life.[1] Comprehensive supportive care may address symptoms that occur at diagnosis and during or after treatment.

Being diagnosed with lung cancer is a life changing event that can have a profound effect on the physical, emotional, and psychosocial aspects of one's well-being. There are many symptoms and side effects associated with lung cancer diagnosis and treatment. These symptoms can interfere with the ability to function and perform daily activities, decreasing the patient's quality of life, especially if symptoms are ignored and go untreated. Lung cancer patients have more unmet supportive care needs than patients with other cancers. Lung cancer is often associated with a heavy disease burden and patients can derive benefit from supportive care interventions, thus limiting impact. Supportive care interventions can improve well-being and survival for cancer patients.[2] Intervening early may decrease unnecessary suffering and enable patients to feel strong enough to be active participants in their own cancer care. The goal of supportive care is to provide patients with the best quality of life throughout the cancer experience, enabling them to perform daily activities and engage in activities that bring them joy and happiness.

Supportive care is important throughout the continuum of cancer care. Supportive care needs may change during the course of the disease and assessment, including diagnosis, treatment, survivorship, and end of life.[3] People living with cancer may experience varied symptoms during the course of the disease, such as more psychological concerns and symptoms at the time of diagnosis than at later stages of treatment.[4] However, physical symptoms may become an immediate concern during treatment.[5] As the disease and physical symptoms progress, patients may experience difficulties in coping with the situation.[2] Patients with advanced cancer or disease progression must address a change or deterioration of physical health, resulting in psychological and social concerns.[4] The management of these symptoms and psychological distress is important to optimize quality of life.

Symptom Management

Multidisciplinary healthcare teams provide comprehensive assessment and consultation for lung cancer patients. The teams are integral to ensure a holistic treatment approach, treating the whole person and not just the cancer itself. The primary treatment team includes a physician (medical oncologist, radiation oncologist, or thoracic surgeon, depending on the course of treatment) and a primary nurse. As supportive care needs emerge, a patient may be referred to other members of the team, such as social workers, psychiatrists, palliative care/supportive care clinicians, or dietitians, to make further assessments and supportive care recommendations. The most important member of the treatment team is the patient. Many of the symptoms and side effects associated with lung cancer diagnosis are subjective and require self-reporting and monitoring. Open communication with clinicians about any symptoms or side effects makes the patient a partner in the care and helps the healthcare team understand and recognize the onset of side effects. A comprehensive supportive care plan with the healthcare team enables the highest possible mental, emotional, and physical well-being. The goal includes controlling symptoms related to the lung cancer and treatment, and concurrently providing psychosocial care to improve quality of life. Most symptoms can be effectively controlled and managed, and new supportive care treatments are being developed.

The most important member of the treatment team is the patient.

There are many side effects associated with lung cancer and treatment. Symptoms and side effects vary between patients and treatments during the course of the disease. Effectively communicating any changes experienced can prevent unnecessary suffering or interruption of treatment. With the growing research and knowledge of these side effects, medications and self-help strategies can be recommended to help prevent symptoms before they occur. However, if new symptoms arise, effective treatments can be prescribed to help control them. It is important to know that symptoms can be managed successfully if they are addressed and treated early.

Patients, family members, and members of the health care team should openly and honestly discuss expectations before the start of each new therapy. Having an open dialogue about treatment goals and an understanding about the potential side effects can ease distress and anxiety. Patients should ask questions and gather as much information as possible to help them assess whether the benefits of treatment outweigh the potential effect on their quality of life.

Some sample questions include:

- What are the reported side effects associated with this treatment?
- How often do patients experience these side effects?
- How are side effects managed?
- Will I still be able to do the activities that I value (i.e. golfing, running, traveling, swimming, and knitting)?
- Do the benefits of the treatment or specific drug outweigh the risk of side effects?

Asking these questions can help in the decision about treatment and better prepare the patient recognize and handle when the side effect occurs. While the side effect profiles for standard of care treatment regimens are well documented, the side effect profiles for clinical research trials may be less known and depending on the phase of the trial side effects may be unknown. When participating in a clinical trial, it is of great importance to learn about the side effects that previous patients have experienced while on the experimental regimen. It is also important to also accurately document and report any side effects you may experience while on a trial. Preparing for making a treatment decision is an important time for patients to relay their value system to the healthcare team. Some patients value their physical appearance, and the loss of hair during treatment would have a major negative effect on their self-image and social activity level. Knowing this, the clinician may be able to discuss some treatment options with minimal or no hair loss.

Communicating Symptoms

Communication is a vital part of symptom management. Symptom documentation in a journal is an excellent way for patients to participate in their care and should be an integral part of the cancer experience. Documenting the onset of new symptoms and being able to effectively communicate this information can have a major effect the success of treatment (Figure 1). Daily symptom tracking, especially while receiving treatment, helps patients identify any changes in their physical, psychological, and emotional health. Maintaining this crucial information can help assess and manage the supportive care needs of the patient. The ability to reference and chart the progress of specific issues enables the patient to have an open dialogue with the team. Furthermore, keeping a journal is important in self-help strategies. When managing fatigue, a patient can refer to the journal and identify periods during the day of both high and low energy, and then try to accomplish essential tasks during periods of high energy.

In this chapter, we focus on the physical and psychosocial symptoms associated with lung cancer and identify supportive care strategies to improve quality of life. Information provided can help patients be aware of potential symptoms and recognize the early onset of symptoms. Patients can better tolerate treatment by working quickly to address any symptoms. The goal is to openly communicate about any symptoms or changes in function to ensure the best quality of life and active participation in all decisions during and after treatment.

Figure 1. Sample Symptom Management Journal

Record the symptoms that your are experiencing. Provide enough details to be able to accurately describe the occurrence to your health care team. Record any steps taken to help relive the symptom(s) (medications, self-help strategies, etc…). You can download this worksheet.

	My Symptom Management Journal
	Date: Time:
	Symptom:
	DURATION: When did the symptom(s) begin? How long did it last?
	INTENSITY: On a scale of 0 – 10 (10 being the worst you have experienced), how would you describe your symptom(s)?
	LOCATION: Where are you experiencing the symptom(s)? (Be specific)
	POSSIBLE TRIGGERS: What makes it worse?
	POSSIBLE RELIEF/TREATMENT: What provides relief?
	Because of this symptom, I have been unable to engage in the following activities:
	Questions or instructions from my health care team Spoke to: Time: AM/PM
	Suggested Strategies for Symptom Management: ✸ ✸ ✸

The Changing Role of Palliative and Supportive Care Services

The word *palliative* means to relieve from suffering. The field of palliative care had previously focused on care related to end of life. There has been an increased understanding of the importance of palliative care services being integrated into all aspects of cancer care. There has been a new focus on the value of services being provided through diagnosis, treatment, survivorship, and later increased levels of needs at the end of life. Palliative care services should be integrated into every aspect of comprehensive care.

Palliative care focuses on the management of pain and other distressing symptoms. The goal is to prevent and relieve symptoms to support quality of life. Services can be delivered concurrently with life-prolonging treatments, not just end of life care. For advanced stage lung cancer patients, early palliative care can cause major improvements in quality of life, decreased psychological symptoms, and survival benefits.[6,7] There is important value to providing palliative care throughout the continuum of care.

Physical Symptoms Associated with Lung Cancer

Fatigue

Fatigue is among the most common problems experienced by patients, occurring in approximately 90% patients receiving treatment.[8,9] Fatigue is disruptive and debilitating because it affects all aspects of life. Some patients report that fatigue is worse than nausea or pain that can be controlled with medications.[8] Persistent fatigue can negatively affect quality of life because patients may have less energy to perform typical daily activities and activities they value.

Causes and Assessment

Fatigue is the overall feeling of being tired physically, mentally, and emotionally.[8] Patients may describe fatigue as general weakness, persistent lack of energy, exhaustion, lack of motivation, and inability to concentrate. Contributing factors to fatigue include pain, anemia, psychological distress, sleep disturbance, nutritional deficiency, prescription medications, and cancer treatment. Chemotherapy agents may cause changes in blood count levels. Platinum-based chemotherapy agents, taxanes, and pemetrexed may cause anemia and fatigue symptoms in lung cancer patients.[4] Fatigue can linger for 1 to 7 years after cancer treatment has been completed.[10] A change in breathing capacity may cause fatigue. For those who have undergone surgery, breathing capacity could be impaired and can lead to fatigue and lack of energy.

Fatigue could be caused by an underlying psychosocial issue. Depression and fatigue may be concurrent symptoms,[8] and an assessment may be conducted to determine the current level of psychological distress. Sleep disturbance occurs in 30% to 75% of cancer patients, ranging from insomnia (lack of sleep) to hypersomnia (too much sleep).[8] Some patients frequently wake up during the night or have difficulty falling asleep, and both can lead to fatigue.

New medications or the interactions between several medications may cause fatigue. The health-care team can evaluate current medications and may need to adjust the dosage, switch to an alternative medication, or recommend the discontinuation of a certain medication. Some of the

common prescriptions that are associated with fatigue include antidepressants, sleep medication, and pain medication (analgesics).

Poor nutrition or changes in eating habits can contribute to fatigue and lack of energy. The body requires balanced nutrition including good carbohydrates, proteins, fats, vitamins, minerals, and fluids. When there is an imbalance, the body may have difficulty producing the necessary energy to function properly. Cancer patients often experience changes in their nutrition and levels of nutrients. These deficiencies could be caused by changes in metabolism, poor appetite, nausea, vomiting, or diarrhea.

Fatigue level can vary from patient to patient and can fluctuate throughout the course of the cancer. Fatigue is subjective, and it is important that patients recognize any changes in energy level and discuss these changes with the healthcare team. Clinicians may assess the level of fatigue, the underlying causes, and contributing factors. Blood tests may determine that anemia is the primary cause of the fatigue. After careful evaluation, the healthcare team can help determine the level to which fatigue is interfering with function and make appropriate recommendations.

Pharmaceutical interventions may be recommended after the underlying causes are identified. If insomnia is the cause, a sleep aid or anti-anxiety medication might be prescribed. Fatigue can persist after active cancer treatment is completed, and continued assessment is important.

Strategies for Management of Cancer-related Fatigue

By understanding and monitoring fatigue, patients can reduce distress and better cope with the disease. While on active treatment, daily self-monitoring of fatigue is important, and having a symptom journal may enable patients to chart levels of fatigue, activity patterns, and potential causes. The journal may provide important detailed information for discussion with the healthcare team. Questions for patients may include:

- On a scale of 0 (no fatigue) to 10 (worst fatigue ever experienced), what is the level of fatigue today?
- When did the fatigue begin?
- How has fatigue progressed since onset?
- What makes the fatigue worse?
- What makes the fatigue better?

Self-help techniques that may help with fatigue include energy conservation, a technique that focuses on the deliberate management of energy to avoid depletion. Patients can prioritize important activities and pace themselves throughout the day. Energy conservation also includes eliminating or delegating any nonessential tasks. Patients can seek the assistance of their support system, including family, friends, and neighbors, to help with these nonessential activities.

Referencing the symptom journal can help patients identify patterns of peaks in energy levels. These peaks provide an opportunity to accomplish tasks of value. For example, if taking a walk is important, this may be done at times of increased energy during the day. Increasing physical

activity may boost energy levels. Sleep disturbance may be alleviated with increased physical activity and limiting caffeine and naps late in the day. Patients participating in moderate activity may have better outcomes of cancer care and may experience fewer side effects. In some cases, psychosocial interventions, nutritional consultation, and cognitive therapy are useful tools to decrease the effects of fatigue. Nutritional assessment and consultation with a dietitian can help ensure that patients are getting the proper balance of nutrients, hydration, and electrolytes. Fatigue symptoms usually decrease, and energy levels improve, after treatment has been completed, but some patients experience prolonged fatigue. It is important that intervention begins early so that fatigue does not affect function, increase distress, and impair the ability to cope with the disease and treatment.

Gastrointestinal (GI) Symptoms Associated with Lung Cancer

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting are often associated with the onset of treatment, but are not caused by all chemotherapy agents. Nausea and vomiting can have a major effect on quality of life. Uncontrolled nausea and vomiting will decrease quality of life and may cause nutritional deficiencies, metabolic imbalances, decline in functional ability, and withdrawal from therapy.[11]There have been major advances that effectively control and prevent nausea and vomiting. Antiemetic drugs prevent nausea and vomiting and are frequently given to patients receiving chemotherapy.

The healthcare team can estimate the type of symptoms experienced from the class of chemotherapy drug, dosage of radiation, or surgery. Nausea and vomiting are classified as acute, delayed, anticipatory, breakthrough, and refractory. Acute nausea and vomiting occur within 24 hours after treatment. Delayed nausea and vomiting occur after 24 hours following treatment, typically within 48 to 72 hours after treatment, lasting up to a week, and are likely to occur with chemotherapy agents such as cisplatin and carboplatin. Anticipatory nausea and vomiting, triggered by thoughts of starting a new cycle of treatment, may occur in 20% patients. Breakthrough nausea and vomiting occur when anti-nausea medications fail, and the healthcare team may increase the dosage or prescribe an alternative antiemetic medication. It is easier to prevent nausea and vomiting from occurring than to control it, so clinicians often prescribe antiemetic medications prior to the start of the treatment cycle. Common antiemetics include ondansetron, palonosetron, dolasetron, prochlorperazine, and promethazine, and drug selection is based on the treatment regimen and side effect profile. These medications come in liquid, tablet, and suppository forms. In some cases, the antiemetic is given concurrently with chemotherapy infusion. Depending on the treatment, the treatment team may recommend that the patient continue taking the medication for several days.

Strategies to Manage Nausea and Vomiting

The risk of developing chemotherapy-induced nausea and vomiting can often be predicted based on the drug regimen, so it is important to communicate the symptoms, if any, prior to the start of each new therapy. It is important to relay any change or breakthrough nausea experienced. If this occurs, there are several different medications that can be prescribed. Antiemetic medication can be prescribed to alleviate anticipatory nausea. In addition, behavioral therapy or systematic desensitization can be successful to decrease anticipatory nausea. It is important that the patient stay hydrated and have increased fluid intake (small amounts frequently) because dehydration can

make symptoms worse. In addition, breathing exercises and relaxation are important ways to alleviate symptoms.

Constipation

Constipation can be uncomfortable and accompanied by abdominal discomfort and cramping. It can be caused by physical weakness, changes in appetite, decreased activity, and medications such as pain medications. Constipation may be relieved by relaxation, increased physical activity, and altered diet including an increase in fluids, vegetables, fruits, and fiber. If symptoms persist, discussion with the healthcare team may be helpful. Maintaining a journal of symptoms can provide useful information, including duration of the constipation and alleviating factors, to help develop a treatment plan. Before taking herbal supplements, laxatives, or stool softeners, the patient should check with the healthcare team to ensure these nonprescription medications will not interact with any treatment medications.

Changes in Weight

Weight loss may progress during the disease and may be distressing because it can be easily seen. The causes of continued weight loss can include a metabolic reaction to the cancer; difficulty swallowing because of persistent cough, dyspnea, or radiation-induced esophagitis; depression; and side effects of treatment including poor appetite, mouth sores, nausea, vomiting, difficulty swallowing, sore throat, dry mouth, or a change in taste sensation.

The most serious and distressing form of cancer-related weight loss and weakness is cancer cachexia. The patient loses body fat and lean muscle mass. Although weight loss can be a symptom associated with all stages of lung cancer, cancer cachexia is associated with advanced or metastatic lung cancer.

The healthcare team checks a patient's weight at each follow-up visit, and the patient should also monitor changes in weight. If weight loss is substantial and intervention is needed, an appetite stimulant might be prescribed, such as megestrol, dexamethasone, or prednisone. When the loss of muscle mass has occurred, an anabolic steroid might be prescribed.

It is important to maintain a healthy, balanced diet. With weight loss during treatment, eating foods to "bulk up" may not address muscle loss because high caloric foods may cause weight gained from fat. It is essential that a balanced diet is consumed, rich in vitamins, minerals, proteins, and carbohydrates.

Consulting with a nutritionist or registered dietitian can be helpful to develop a diet that meets the patient's individualized needs. Earlier determination of the cause of weight loss may provide a better result. If the weight loss is caused by difficulty in swallowing, nausea, vomiting, or mouth sores, it is imperative that the underlying causes are addressed. Although patients might not feel like eating, it is important to keep up their energy and strength. Maintaining healthy nutrition while undergoing treatment can help boost the immune system and help the patient tolerate treatment.

Weight gain - Patients may experience weight gain during treatment because of prescribed medications, such as steroids, including prednisone that may cause increased appetite and weight gain. In addition, some medications may cause fluid retention. Weight gain should be discussed with the healthcare team, and a nutritional consultation may be necessary. (See Chapter 8*: Nutrition in the Patient with Lung Cancer*)

Respiratory Symptoms of Lung Cancer

Cough

Cough is a very common symptom of lung cancer. Persistent cough may be an early symptom that may lead to a lung cancer diagnosis and may be a troubling symptom throughout the disease course, interfering with speech, eating, and sleeping. Coughing is a natural response to irritation of the airways, and it is the body's way of clearing out the airways to eliminate any foreign substance. Cough may be dry or productive. Dry cough can be caused by allergies, inhalation of irritants, sore throat, asthma, or sinusitis. Productive cough, which is the coughing up of phlegm (mucus), is a result of chest congestion or excess fluid in the lungs, and may be caused by the common cold, pneumonia, flu, or bronchitis. It is important to note if the phlegm (mucus) is blood streaked (hemoptysis). While hemoptysis is common in lung cancer, the frequency and quantity of blood should be communicated to the treatment team to determine its acute or chronic nature.

The development of a cough that interferes with normal activities should be reported. Recognizing and intervening early can help to decrease unnecessary suffering. Tumors can also partially block or completely block airways and could be the primary cause of a cough and infection. If infection occurs, antibiotics may be prescribed or a procedure may be done to unblock the airways.[12]The healthcare team may evaluate symptoms and recommend a cough suppressant to help alleviate symptoms. Although mild nonprescription cough suppressants are available, persistent symptoms that interfere with daily life may be treated with bronchodilators or opiate drugs.

Difficulty Breathing (Dyspnea)

Dyspnea is labored, difficult breathing, often leading to discomfort. It may be felt as fast, shallow breathing, chest tightness or pressure, suffocation, and shortness of breath. Patients may say, "I feel like I cannot catch my breath." Dyspnea may be associated with other respiratory conditions such as asthma, chronic obstructive pulmonary disorder, or emphysema. Dyspnea may be present at rest and increased during physical exertion. Dyspnea may evoke anxiety that may worsen other symptoms. The monitoring of respiratory symptoms is important for maintaining quality of life.

Causes of dyspnea include infection, accumulation of fluid in or around the lungs (pleural effusion), or recent surgery. It is important to discuss the onset of these symptoms with a member of the healthcare team. The treatments may vary and could include supplemental oxygen or prescribed medications such as steroids or bronchodilators. If dyspnea is related to a pleural effusion, surgery (pleurodesis) may be an option to remove the excess fluid. Approximately 50% to 70% patients with a pleural effusion experience dyspnea. Recent studies show that pharmacological interventions such as opioids may provide relief for patients. Self-help strategies can be helpful, including; controlled breathing, coping skill training, focused abdominal breathing, meditation, and relaxation techniques.

Other Symptoms of Lung Cancer

Skin Conditions

A rash is a noticeable change in skin color, texture, and appearance. It may be localized to a part of the body or may affect the entire body. Rashes can cause discomfort and affect appearance and self-esteem. Skin inflammation and rash may be a side effect of some chemotherapy agents, and these rashes can be mild to severe, affecting the face, scalp, neck, and back. The irritation is characterized by redness and may resemble acne, which can be uncomfortable. The healthcare team should be informed of a rash.

Treatment may include antibiotics and topical creams. If symptoms become severe, the chemotherapy drug may be changed or discontinued until symptoms resolve. Self-help strategies to control and manage treatment-related skin irritation include avoiding the sun and ultraviolet light, avoiding hot showers, staying hydrated, and using fragrance-free and sensitive skin products.

Changes in Blood Cell Counts (Anemia and Neutropenia)

Chemotherapy and radiation can cause myelosuppression, which is suppression of the bone marrow, resulting in low blood cell count levels. Red blood cells carry oxygen throughout the body.

Anemia (low red blood cell count) may occur as a result of cancer or chemotherapy, resulting in fatigue and weakness. After evaluation to determine the cause of the anemia, patients may be prescribed medications, such as epoetin or darbepoetin, or a transfusion of packed red blood cells.

White blood cells help to fight infection,[13] and neutropenia (low white blood cell count) is a risk factor for the development of infection in cancer patients. Fever is an early sign of infection, and it is important to report any elevated body temperature. Elevated temperature (> 100ºF) could indicate infection and should be monitored closely. Additional signs of infection include chills, pain, swelling, redness at an incision site, mouth sores, and diarrhea. If patients experience any of these symptoms, they should immediately contact their treatment team. In many cases, antibiotics may be prescribed. It is especially important to report any fever or other symptoms when patients are participating in clinical research trials.

Effective strategies to prevent and manage infections in neutropenic cancer patients have led to better outcomes. Medications that may prevent blood counts from dropping include filgrastim and pegfilgrastim.

Cancer-Related Pain

Pain is a frequent and distressing symptom associated with lung cancer. Pain is the most common cause of disability and associated with sleep disturbances, anxiety and dyspnea, all impacting quality of life when not controlled.[14] The patient may experience pain as a result of cancer pressure on a nerve, spread to the bone, or treatment. Pain is subjective and pain tolerance varies.

The National Comprehensive Cancer Network NCCN defines cancer pain as a sensory and emotional response associated with actual or potential tissue damage.[15] Reporting pain early and referral to

supportive cancer services are crucial for the management of any pain. Pain is experienced in 25% newly diagnosed patients, 33% patients undergoing treatment, and 75% patients with advanced stage disease.[15]

In most patients, cancer pain can be controlled with prescribed medication and behavioral strategies. However, unrelieved pain may have a major negative effect on the quality of life, and pain can inhibit normal activities. Chronic pain robs patients of comfort and affects motivation, social interactions, and activities.

Early treatment of pain is preferred. A comprehensive assessment may provide a detailed description to ensure effective management. Pain levels are self-reported, and analog scales are used by clinicians.

Patients can assess the level of pain by asking the following questions:

- On a scale of 0 to 10 (0, no pain; 10, the worst pain ever experienced), what is the current level of pain?
- Where is the pain located?
- How does it feel or how can the pain be described (i.e. aching, stabbing, dull)?
- When does relief occur and how long does it last?
- What activities make the pain worse?
- What activities are being avoided because of the pain?

The pain scale is an effective way to describe the magnitude of pain experienced (mild, 1 to 3; moderate, 4 to 6; severe, 7 to 10). There also are non-verbal cues, such as body language and facial expressions that family members can use to be aware of the pain level experienced by a patient. Treatment can be tailored and individualized. Medications can cause new side effects or can make existing side effects worse, so the goal is to minimize the pain experienced and limit the potential side effects of pain medications. It is important to openly discuss expectations and goals associated with symptom management.

Neuropathic pain is a chronic, often debilitating, condition affecting many cancer patients. Signs and symptoms can vary from patient to patient. Cancer patients experience neuropathic pain as a result of nerve compression by the tumor or neurotoxicity of chemotherapy agents.[16] Chemotherapy-induced peripheral neuropathy is a subset of cancer neuropathic syndromes. When chemotherapy-induced peripheral neuropathy is present, treatment is stopped and time is allowed for nerves to recover. Stopping anti-tumor treatment is a difficult decision. Patients and providers must weigh the potential benefits of treatment against the devastating short- and long-term impairment. Neuropathy can be a major cause of symptom distress. It can produce high levels of pain, numbness, burning sensations, discomfort, sensorimotor dysfunction, and interference with daily activities.

Strategies for Pain Management

After a thorough evaluation, interventions can help decrease pain. Pain relieving medications (analgesics) include non-opioids such as naproxen, ibuprofen, aspirin, nonsteroidal anti-inflammatory drugs (NSAID), and acetaminophen. Acetaminophen is an analgesic and antipyretic but not an anti-inflammatory drug, and may be cautioned for those with compromised liver and kidney function. These medications are suggested for mild pain. Opioids frequently are prescribed for moderate pain, and these include hydrocodone, codeine, oxycodone, propoxyphene, or tramadol. If pain is severe, stronger opioids are prescribed, such as morphine, oxycodone, or

fentanyl. Pain medications come in varied forms and delivery systems (tablets, liquid, patches, suppositories, and injections). For patients with difficulty swallowing, a liquid may be prescribed.

Opioids can cause new side effects or can make existing side effects worse. Opioids cause constipation, nausea, and skin itchiness (pruritis). Pruritis occurs in 10% to 50% patients taking opioids.[17] Some symptoms can be anticipated and measures can be taken for prevention. Opioid-induced constipation can be treated with stool softeners or dietary changes and increased fluid intake. Severe pain may be relieved with interventional therapies, including nerve blocks or an injection between vertebrae.[15] It is important to report side effects promptly to the healthcare team. Maintaining information in the symptom journal about pain provides important information that the treatment team can use to help relieve pain.

Self-Help Strategies and Behavioral Interventions

Complementary and alternative medicine strategies or integrative techniques can be used to help alleviate cancer-related pain, including meditation, yoga, acupuncture, and massage. Many patients do not report all levels of pain experienced because they feel that pain is a normal effect of cancer, they fear becoming addicted to pain medication, or they fear side effects. For those who have concerns about medication, these techniques can be powerful because they focus on the mind-body relationship and help the body relax, which has benefits far beyond pain control.

Pain can be controlled by cognitive techniques such as guided imagery (for example, in a state of relaxation, think about a positive image that evokes a sense of calm, such as a walk on the beach), hypnosis, distraction, or behavioral techniques such as activity pacing, behavioral goal setting, and relaxation. Biofeedback may cause voluntary relaxation of muscles. The benefits of massage include reduction in pain, anxiety, fatigue, and nausea.[18]

Psychological Symptoms Associated with Lung Cancer

The diagnosis of lung cancer is a stressful and life changing event for the patient and entire family, with psychological, social, and emotional challenges. Patients describe having to find a new sense of "normal" because the disease has such far reaching effects on all aspects of daily life. This life threatening illness can have severe effects on psychological health.

The stress associated with cancer can manifest physically and psychologically. Although the psychological changes may be more difficult to recognize, they are just as important and should be addressed. It is very common to have emotional and psychological distress in cancer patients. It may occur immediately after diagnosis and throughout treatment, and may worsen as the condition deteriorates.[2] Many of the drugs used in cancer treatment can affect the balance of chemicals in the brain and contribute to changes in behavior, mood, sleep patterns, and anxiety levels.

Psychological distress may cause a lack of motivation to engage in meaningful activities, a reduction in cognitive and social functioning, and an overall increased level of fatigue. It is important that an open discussion occurs with the healthcare team about all aspects of the treatment, and activities that are meaningful to the patient are identified. If treatment and side effects prevent the patient from engaging in these activities, psychological distress levels and coping ability can be drastically affected. Depression is

especially common in lung cancer patients, and those receiving a lung cancer diagnosis may experience higher levels of distress compared with other cancer diagnoses, in part because of the advanced stage of the cancer at diagnosis and the heavy burden of symptoms frequently associated with lung cancer.[17]

Functional impairment, which is the inability to carry out functional activities, is the most important risk factor for the development of depression. For every increment of physical impairment, the risk of depression is increased by 41% because the patient can no longer perform the same level of activities as before diagnosis or treatment.[19] Patients must rely on others, and this loss of independence can lead to distress and depression.

A cancer diagnosis generates feelings of sadness, anger, anxiety, and fear. Patients and families struggle with quickly having to define, put into context, comprehend, and make important decisions. The initial adaptation to a diagnosis can be influenced by pre-exiting psychological factors.[20] Patients who have a past history of depressive disorders (diagnosed or undiagnosed) should be carefully monitored throughout the cancer course, because the events associated with the diagnosis serve as triggers for depression. A history of depressive disorders can be worsened or aggravated by the cancer course. People deal with their diagnosis in the context of their social environment, and the social support system can positively or negatively influence how a patient copes with the illness.

A cancer diagnosis and treatment may cause cognitive changes. "Chemo-brain" is a term often used to describe a group of symptoms related to effects of cancer treatment. Symptoms include levels of forgetfulness, difficulty concentrating, and difficulty with multitasking. This can become a very distressing and lingering symptom.

There may be unmet psychological burdens experienced in tobacco-related disease, including elements of blame or guilt that patients place on themselves. This can severely affect coping ability and the seeking of supportive services. Early assessment and treatment of these symptoms are crucial for maintaining quality of life. There are treatments and strategies that can help patients better cope throughout the cancer course.

Distress

The overall psychological burden of the cancer experience is referred to as distress. Distress is a multi-factorial emotional, psychological, social, and spiritual experience that can interfere with the ability to cope with a cancer diagnosis and treatment.[21] The prevalence of distress varies by cancer type and ranges from 35% to 43% in lung cancer.[21] There are many symptoms of cancer-related distress. Patients can feel general denial, sadness, anger, fear, or vulnerability. These feelings are normal responses to coping with the disease. This generalized distress can progress to more severe depression and anxiety, and cause an inability to cope with daily life.

Distress can affect quality of life during the entire course of the illness. Many (25% to 40%) cancer survivors continue to suffer from sadness, often severe enough to require intervention.[22] The end of treatment can also be a time of heightened distress because there is uncertainty about cancer recurrence. Furthermore, responsibilities that are often placed on hold during treatment must now be addressed. In addition, the patient may face the loss of a strong support system because of decreased contact with members of treatment team, family, or friends.

Psychological issues often are unreported for many reasons, including the general stigma about psychological issues or feeling that symptoms are expected. Although there are varied levels of distress, mild symptoms may affect normal daily activities, and this should be discussed with the healthcare team. Mild distress includes fear, uncertainty, worry, sadness, poor sleep, poor concentration, or thinking much about the illness. Mild distress can become severe, so it is important to evaluate distress levels frequently, identify distress early, and intervene. Early evaluation and screening can lead to timely management of distress and minimize interference with daily activities. Distress may be unrecognized and only 10% patients receive support for distress.[22]

Assessment and Strategies for Self-Help

The National Comprehensive Cancer Network (NCCN) recommends screening all cancer patients for psychological distress at each follow-up visit.[23-25] The Distress Thermometer is a standardized survey frequently used to measure and evaluate distress. The Distress Thermometer quantifies stress on a scale from 0 to 10 (0, no distress; 10, extreme distress), based on the answer to the question, "How is your level of distress today?" or "How is your level of distress been during the past week?" The Distress Thermometer may be accompanied by a 38-item problem list, which may identify problems in five different categories: practical, family, emotional, physical, and spiritual or religious. Greater distress is associated with negative outcomes, including non-adherence to treatment recommendations, poor satisfaction with overall care, and decreased quality of life.

The healthcare team may include professionals who are experts in psycho-oncology, including social workers, chaplains, palliative care specialists, psychologists, and psychiatrists. Experts in this field can assess and provide critical support for patients and their families. A patient's coping style and perceived social support are two important factors positively associated with adaption to distress. Social supports, community resources, and support groups may be helpful, including teleconference calls, personal counseling, and group meetings. The choice of resource is based on comfort level of the patient and availability of community resources, including individuals who have experience, and expressing emotions may help the patient and family cope with the disease.

Each individual may cope differently with each situation, frequently within the context of the individual's social structure. A good support system may help patients openly discuss new symptoms and may help in the recognition of new or abnormal symptoms.

Anxiety

Anxiety is a normal response to a diagnosis of cancer, but it often is inadequately treated, can impede daily functioning and can have a substantial negative effect on quality of life. Anxiety can manifest as physical symptoms such as gastrointestinal disturbances, restlessness, sweats, palpitations, dyspnea, and panic attacks. It also can manifest as behavioral symptoms such as feelings of uneasiness, restlessness, loss of concentration, excessive intrusive thoughts, and seeking continual reassurance or comfort from outside.[26] Some anxiety is normal, but persistent anxiety that disrupts daily functioning is termed maladaptive anxiety and requires intervention.

Anxiety can occur at any time in a patient's cancer course, including the time of diagnosis, treatment, and survivorship, when anxiety may develop about the possibility of recurrent cancer. The healthcare team can

assess symptoms and determine the primary causes of the anxiety. Anti-anxiety medication and antidepressants may be prescribed.

Depression

Depression may include sadness, lack of interest in normal activities, fatigue, and low energy. Reactive depressive symptoms, including denial and anger, may be a normal reaction to a stressful and unexpected event. These symptoms become problematic when they interfere with normal life and daily living. Depression is often under reported and undertreated. This may be attributable to the perceived stigma associated with the disease. The National Comprehensive Cancer Network (NCCN) reports the following symptoms associated with depression: low mood, difficulty concentrating and remembering, irritability, loss of sexual interest, changes in emotions, loss of interest in social activities, changes in sleep, loss of energy and motivation, fatigue, anxiety, feelings of hopelessness, frequent or excessive worry, panic attacks, physical symptoms such as upset stomach, and increased interest in alcohol.[21]

There are antidepressant drugs, anti-anxiety medications, and self-help techniques that can help a patient cope. Cognitive behavioral therapies, relaxation, and improving problem solving skills may be useful. Cognitive behavioral therapy may improve coping and decrease psychological symptoms.[21] Patients should be reassured that acknowledging psychological symptoms and talking with members of the healthcare team are not signs of weakness. Addressing symptoms and developing coping skills can have a positive effect on the cancer course and improve outcomes.

Conclusion

There are many side effects associated with a lung cancer diagnosis and treatment. These symptoms can negatively affect a patient's well-being and quality of life. It is important to prepare for, identify, and recognize symptoms early and communicate about symptoms to decrease any unnecessary suffering or interruption in the course of treatment.

Supportive care is valuable to patients and families who must cope with lung cancer. Patients play an important role in understanding and profiling the symptoms associated with newer classes of therapies. Communication with the treatment team can help prevent and manage symptoms and help future patients by creating a side effect profile for each specific treatment. Clinicians continue to gain a better understanding of the prevalence of specific symptoms and are developing effective strategies to better manage lung cancer symptoms.

References

1. Malin JL, O'Neill SM, Asch SM, et al. Quality of supportive care for patients with advanced cancer in a VA medical center. *J Palliat Med.* 2011;14(5):573-7.
2. Fitch MI, Steele R. Supportive care needs of individuals with lung cancer. *Can Oncol Nurs J.* 2010;20(1):15-22.
3. Witta SE. Supportive care. *J Thorac Oncol.* 2010;5(12 Suppl 6):S472-3.

4. Boehmer L, Waqar S, Butler S, et al. Summary of presentations from the 46th annual meeting of the American Society of Clinical Oncology (2010): focus on supportive care issues related to lung cancer. *J Thorac Oncol.* 2011;6(3):645-9.
5. Sanders SL, Bantum EO, Owen JE, et al. Supportive care needs in patients with lung cancer. *Psychooncology* 2010;19(5):480-9.
6. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363(8):733-42.
7. Dahlin CM, Kelley JM, Jackson VA, et al. Early palliative care for lung cancer: improving quality of life and increasing survival. *Int J Palliat Nurs.* 2010;16(9):420-3.
8. Berger AM, Abernethy AP, Atkinson A, et al. Cancer-related fatigue. *J Natl Compr Canc Netw.* 2010;8(8):904-31.
9. Shun SC, Lai YH, Hsiao FH. Patient-related barriers to fatigue communication in cancer patients receiving active treatment. *Oncologist.* 2009;14(9):936-43.
10. Recovery issues in cancer survivorship: a new challenge for supportive care. Alfano CM, Rowland JH. Cancer J. 2006 Sep-Oct;12(5):432-43. Review.Ettinger DS, Armstrong DK, Barbour S, et al. Antiemesis. Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2009;7(5):572-95.
11. St. John Tina (2009). With Every Breath: A lung cancer guidebook (Rev. ed.) [Available at www.lungcancerguidebook.org/book]
12. Segal BH, Freifeld AG, Baden LR, et al. Prevention and treatment of cancer-related infections. *J Natl Compr Canc Netw.* 2008;6(2)122-74.
13. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain: examining quality of life in diverse cancer survivors. *Cancer.* 2011 May 1;117(9):1994-2003. doi: 10.1002/cncr.25761. Epub 2010 Nov 18.Swarm R, Abernethy AP, Anghelescu DL, et al. Adult cancer pain. *J Natl Compr Canc Netw.* 2010;8(9):1046-86.
14. Cleeland CS, Farrar JT, Hausheer FH. Assessment of cancer-related neuropathy and neuropathic pain. *Oncologist* 2010;15 (Suppl 2):13-8.
15. Levy MH, Back A, Benedetti C, et al. NCCN clinical practice guidelines in oncology: palliative care. *J Natl Compr Canc Netw.* 2009;7(4):436-73.
16. Cassileth BR, Keefe FJ. Integrative and behavioral approaches to the treatment of cancer-related neuropathic pain. *Oncologist* 2010;15 (Suppl 2):19-23.
17. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. *J Clin Oncol.* 2000;18(4):893-903.
18. Zabora J, Brintzenhofe Szoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. *Psychooncology* 2001;10(1):19-28.
19. Holland JC, Andersen B, Breitbart WS, et al. Distress management. *J Natl Compr Canc Netw.* 2010;8(4):448-85.
20. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE. Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. *Cancer* 2008;113(4):870-8.
21. Bogaarts MP, Den Oudsten BL, Roukema JA, et al. Development of the Psychological Distress Questionnaire- Breast Cancer (PDG-BC): a breast cancer-specific screening instrument for psychosocial problems. *Support Care Cancer.* 2011;19(10):1485-93.
22. Jacobsen PB, Donovan KA, Trask PC, et al. Screening for psychologic distress in ambulatory cancer patients. *Cancer. 2*005;103(7):1494-502.
23. Voogt E, van der Heide A, van Leeuwen AF, et al. Positive and negative affect after diagnosis of advanced cancer. *Psychooncology* 2005;14(4):262-73.
24. Buchanan D, Milroy R, Baker L, Thompson M, Levack P. Perceptions of anxiety in lung cancer patients and their support network. *Supportive Care in Cancer* 2009;18(1):29-36.
25. Sarna L, Padilla G, Holmes C, Tashkin D, Brecht ML, Evangelista L. Quality of life of long-term survivors of non-small-cell lung cancer. *J Clin Oncol.* 2002 Jul 1;20(13):2920-9. PMID:12089220
26. Gonzalez BD1, Jacobsen PB, Depression in lung cancer patients" the role of perceived stigma. *Psychooncology*. 2012 Mar;21(3):239-46. doi: 10.1002/pon.1882.

Chapter

8

Nutrition in the Patient with Lung Cancer

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Introduction

Nutrition is important in cancer prevention, treatment, and survivorship. Food provides the building blocks needed by cells for protection, repair, and healing. The benefits of good nutrition during cancer treatment include improved quality of life and decreased frequency of side effects, complications, and treatment breaks.

Lung cancer treatment can create a burden of healing that can overwhelm even a healthy patient's nutritional reserve. The cancer can affect appetite, digestion, and use of nutrients. Treatment regimens such as surgery, chemotherapy, and radiation can cause side effects that interfere with adequate nutritional intake. A patient's nutritional status can deteriorate during the course of treatment. Decisions about treatment modality or chemotherapy medication may be determined based on general health performance status scores.[1] Weight loss and decreased ability to eat adequately influence those performance scores and treatment options.[2]

Many people begin lung cancer treatment already experiencing some decreased appetite (anorexia) and meal portion size. Anorexia may be noted as disinterest in usual favorite foods, a decrease in the enjoyable taste experienced with foods or beverages, and an early sense of fullness when eating (early satiety).

Among patients with advanced non-small cell lung cancer, 61% have been found to be malnourished. The effect of anorexia and early satiety is evidenced by decreased oral intake and increased weight loss. Malnutrition is associated with worse outcomes in patients treated for cancer, because nutritional deficiencies can decrease response to therapy, quality of life, and even survival.[3] Taking action to improve nutritional status may improve strength, energy level, and protect quality of life.

The goal of nutrition in treatment is to keep the healing process moving as efficiently as possible. In this chapter, we review the factors in effect during lung cancer and treatment; the goals of nutrition and healing; the common barriers to eating and effective strategies to manage these barriers; and resources to use during treatment and into survivorship.

Protecting Lean Body Mass

During recovery from cancer treatment, it is important to maintain muscle or "lean body mass" and preserve nutrition status. This will help maintain optimal health, quality of life, and allow you to participate in your usual activities. Muscle wasting can result in debilitation, decreased functional status, and decreased quality of life.[4] Maintenance of good nutrition status during treatment may even improve response to cancer treatment.[5]

For some people, the first sign of illness may be an unexpected or involuntary weight loss. Some people may have reacted to this weight loss and decreased interest in food with a happy exclamation, "Oh good - I've been trying to lose weight!" or "My doctor told me I should lose 20 pounds," and patients may allow the weight loss to continue, believing that the process must eventually stop. However, weight loss with a diagnosis of lung cancer is different than intentional weight loss from dieting.

Involuntary weight loss may occur in 50% people with lung cancer, and even a weight loss of 5% may have an effect on health outcomes. Some involuntary muscle loss occurs when people feel ill, and cannot eat enough to maintain their weight. As skeletal muscle is lost, patients experience fatigue, lack of energy for daily activities, decreased ability to move with balance and safety, and decreased ability to cough and clear pulmonary secretions. As smooth muscle is lost, a person may have delayed stomach emptying and feel satiated or feel full; there may be decreased digestion associated with increased nausea as well as a loss of cardiovascular function associated with lightheadedness or dizziness.[6]

Cancer cachexia is a syndrome that results in a progressive loss of muscle mass and leads to progressive functional impairment. It is associated with a lack of appetite and negative energy and protein balance. The best way to modify the effect of cachexia is to treat the cancer, and adequate nutrition is, once again, imperative to tolerate and continue the treatment. It is important to identify these symptoms early, called "pre-cachexia", and act to treat the factors that are barriers to eating. [7] Medications, such as appetite stimulants, may be helpful in managing cancer cachexia, and this option may be discussed with the physician.[8]

Nutritional counseling which focuses on food choice and behaviors related to meals and snacks has been found to be effective in addressing lung cancer malnutrition and cachexia. Medical Nutrition Therapy, a technique used by Registered Dietitians, may help patients to increase protein and calorie intake, improve weight status, and protect quality of life in lung cancer patients undergoing treatment. [9,10] Many cancer centers have specially trained Registered Dietitians who are dedicated to the nutritional care of cancer patients. If the cancer center does not have an oncology dietitian, a referral may be obtained from the doctor or the Commission on Dietetic Registration to find a board certified specialist in oncology nutrition – who has the credential "C.S.O.".

Nutrition and Healing

Each time a patient receives a treatment for cancer - surgery, chemotherapy, or radiation therapy – the body responds to the treatment with a process of healing. Healing requires nutrients, extra calories, and additional protein. People receiving treatment for lung cancer may use more calories than when they were not sick, this state of increased demand for calories and protein is termed "hyper-metabolic."

The primary nutritional goal is to prevent or stabilize weight loss, and a secondary goal to regain lost weight. The importance of increasing calories is slightly greater than increasing grams of protein; if weight loss continues despite high protein intake, the protein will be utilized for calories and will not be available for structural repair. Therefore, caloric content should be considered in addition to protein intake. It is useful to have a general expectation of the amount of calories and protein per day needed, and this may be estimated by the oncology dietitian (Table 1).

Table 1. Caloric and Protein Requirements during Healing in Patients Treated for Lung Cancer*

Body Weight	Calories needed	Protein needed
(pounds)	(cal/day)	(gm/day)
110	1500 – 1750	60 to 75
130	1750 – 2060	70 to 90
150	2050 – 2375	80 to 100
170	2300 – 2670	90 to 115
190	2575 – 3010	100 to 130
210	2850 – 3325	115 to 140

*Values estimated with the following equations[11]

Calorie range per day during healing = [30 x body weight (kg) to 35 x body weight (kg)]

Protein grams range per day during healing = [(1.2 to 1.5) x body weight (kg)]

One pound = approximately 2.21 kg

For overweight patients, the normal or ideal weight for the patient's height is used in the calculations. Refer to a BMI chart to estimate a normal weight for height.

Higher protein intake may be contraindicated in patients with kidney or liver disease.

Weight variation of several pounds in a short period of time is likely due to hydration or fluid shifts.

Add an average of 250 extra calories per day to gain a pound in 2 weeks or 500 extra calories per day to gain a pound in 1 week.

Hydration and Fluid Balance

Hydration or adequate fluid intake is important to feel well during treatment. Hydration is cumulative, and it can take several days to become dehydrated or to achieve adequate hydration. Fluid needs may be increased due to chemotherapy, fever, perspiration, diarrhea, use of oxygen, or the presence of chronic obstructive pulmonary disease (COPD). An early symptom of dehydration is fatigue or lack of energy. Mild chronic dehydration may also increase fatigue and contribute to constipation. A fluid deficit of 1% body weight may decrease metabolic function by 5%.[12] Symptoms of dehydration include: Thirst, dry mouth, decreased urine output, concentrated or darker colored urine, decreased skin turgor, headache and dizziness.

Patients may consider tracking daily fluid intake to ensure adequate hydration. It helps to measure favorite cups and mugs to make it easier to estimate the volume of fluid consumed. It is best to drink fluids throughout the day, drinking half of their fluid requirements during the first half of the day. Some patients prefer to plan their fluid intake by the hour, and drink 1 cup per hour, during the day. Most liquids may be included as part of daily hydration, including milk, juice, smoothies, milkshakes, and soda. Caffeinated beverages may be included as part of daily fluid intake if caffeine consumption is less than 300 mg per day (the equivalent of 2 cups of coffee); caffeine may cause the stomach to empty faster and therefore may be dehydrating.

Many foods such as fruits, soups, gelatin, ice cream, and frozen desserts include absorbable fluid. Fluids intended for rehydration, called "sport drinks," have a small amount of carbohydrates and electrolytes to help them absorb more effectively. Choices of fluids may be based on taste preference and variety to ensure adequacy. Daily fluid requirements may be estimated using the chart below (Table 2).

Table 2. Fluid Requirements During Healing in Patients Treated for Lung Cancer*

Body weight	**Fluid needed**	
(pounds)	**(fluids ounces/day)**	**(cups/day)**
110	50	6 ¼
130	65	8 ¼
150	75	9 1/2
170	85	10 ½
190	95	11 ½
210	105	13

*Fluid per day = [body weight (pounds) / 2.21] = average ounces.

You may need additional fluid if you are experiencing diarrhea, fever, or other increased fluid loss.

Strategies to Help Lung Cancer Patients Eat Enough Food

Information found on the television, in magazines and on the internet regarding "good nutrition" is most commonly focused on helping people reduce their risk for various diseases. However, the nutrition focus during lung cancer treatment is different, with the goal of getting enough calories and protein. Oncology specialists recommend that "all calories are good calories," and the aim is to make eating as tolerable and interesting as possible, and remove any unnecessary diet restrictions.

Be Flexible

Cultural traditions and expectations regarding "what makes a meal" may need to be modified, such as changing expectations of eating three large meals a day, to planning six small meals instead. If simple foods are tolerated better, the patient may consider using non-traditional meal choices; such as pancakes for lunch and scrambled eggs at the evening meal. Although some worry about not eating enough at meals if they are snacking more often, snacking has been found to increase total intake without affecting meal intake, especially if snacks are timed approximately two hours before the next meal.[13]

A good quality snack may be created by combining any two of the following food groups: Breads /starches; Meats/nuts/beans/eggs; Milk/ dairy products; Fruits/vegetables (Table 3).

This technique provides a combination of carbohydrates, proteins, and fats. The goal for a good quality snack (or small meal) is about 250 calories and about 6 grams of protein. Some patients prefer to drink their calories when solid foods are difficult to eat. Beverages that contain calories and protein can be used as a snack by itself, or as a meal replacement.

Table 3. Examples of Good Quality Snacks

Trail mix with nuts and dried fruit
Egg custard made with milk and eggs
Cheese and crackers
Chicken salad on a piece of toast
Yogurt (full fat) with fruit topping
Apple slices dipped in peanut butter
Cookies and milk
Smoothie made with orange sherbet and milk

Making Every Bite Count

Many foods and beverages are available in a full fat or high calorie option (for example choosing whole milk instead of skim milk). Some can be enhanced to maximize nutrient density by adding protein powders or calorie enhancers (for example adding Cream to a milkshake instead of milk). Using more fat in dishes may be helpful for those who experience dyspnea (shortness of breath) because fat requires less oxygen in the digestion process, thus higher fat meals may minimize oxygen requirements.

As appetite may decrease with cancer treatment, using more fat is an effective way to maximize caloric intake. Some people who have followed a low cholesterol diet must rediscover fat-containing foods. Monounsaturated fats or "heart healthy" fats may be emphasized, such as olive, nut, or fish oils, to achieve a higher caloric density. Some physicians will allow all fat containing foods during cancer treatment to aid in the taste and palatability of dishes.

Each teaspoon of oil, butter, or margarine contains 45 to 50 calories. By adding one teaspoon of fat to each meal and snack, caloric intake is increased by approximately 250 calories daily without having to eat a larger volume of food. Another strategy is to add one tablespoon of heavy cream to any milk-containing food or beverage, thus increasing the calorie content of that food by approximately 50 calories. These additions are almost invisible to the person who is trying to maximize caloric intake.

Diabetic Concerns

Many people who follow a diabetic diet which limits carbohydrate intake. Diabetic diets are often liberalized during cancer treatment to allow more carbohydrate content when appetite is decreased and meal size is reduced. Carbohydrate counting or substitution may help increase caloric intake. This may be a difficult idea for patients who may have followed their doctor's advice for many years to avoid simple sugars and carbohydrate-rich foods. Many doctors also liberalize the blood glucose goals of patients during cancer treatment, and may consider using medication to manage blood glucose—not food restriction.

A common strategy for people with diabetes to maximize their oral intake is to have both low carbohydrate and regular carbohydrate foods available. If eating is minimal, the regular carbohydrate containing food item may be used. If consumption is close to usual portion sizes and frequency, the lower carbohydrate versions are used. An example with yogurt: choose a full carbohydrate version when it is the only food eaten for lunch, but choose a low sugar yogurt if it follows a sandwich and bowl of soup.

Be aware of the symptoms of low blood glucose in patients who take diabetic medications, as decreased oral intake while continuing to take diabetic medications may cause low blood sugar or hypoglycemic episodes. These symptoms may include lack of concentration, clammy sweats, shaking or tremors, changes in vision, lightheadedness, or dizziness. If any of these symptoms occur, the blood glucose level should be checked and if low, carbohydrates should be provided. Strategies to prevent hypoglycemic episodes include eating and drinking small amounts more frequently during the day; planning an evening snack before going to sleep; and discussing modifications of medication with the diabetes physician. Diabetic patients may also consider carrying glucose tablets or hard candy, and keeping some juice at home to drink if blood sugar drops.

Steroids may cause hyperglycemia. If blood sugars are elevated after steroids are provided, the preferred treatment is diabetic medication, and not food restriction.

Vitamins and Mineral Supplements

Vitamin, mineral, and other antioxidant supplements have been studied for many years. Several studies have examined the use of supplemental antioxidants in patients with advanced non-small cell lung cancer receiving chemotherapy. Most studies have not shown protective benefit of antioxidants during treatment, nor reduction in cytotoxic side effects.[14] The VITAL Study (Vitamins and Lifestyle Study) determined that people at risk for developing lung cancer, particularly smokers, should not use beta carotene supplements, retinol or lutein supplements for disease prevention. The study found the longer people took the supplements, the more they increased their risk for lung cancer.[15] Another study, focusing on the mineral selenium, found that people deficient in selenium benefited by supplementation, however; increased rate of lung cancer occurred in people taking selenium who were not deficient.[16] Use of antioxidant nutrient supplementation (i.e. Vitamin C, Vitamin E, Selenium and others) are not recommended during radiation therapy or during alkylating chemotherapies. The Academy of Nutrition and Dietetics (formerly American Dietetic Association) Evidence Analysis library has graded and compared the nutrition research and is not currently recommending the use of any high-dose oral antioxidants at this time for cancer prevention nor during cancer treatment.[17]

Studies are currently underway to evaluate the impact of omega-3 fatty acids (fish oils) and physical activity as an intervention useful for interrupting the pre-cachexia syndrome, through their anti-inflammatory effects. Omega-3 oils can be found in fish such as salmon, halibut, fresh tuna, as well as flax seed and walnuts.[18,19]

The best approach for nutrient supplementation should be individualized to each person's background, genetic profile, lab tests, and cancer risk. Blood tests can be done to assess current levels of nutrients and potential advisability of supplementation. Recommendations about supplements may be discussed with the physician or oncology dietitian.[16]

Managing Side Effects and Complications

Early identification and active intervention for side effects is important to protect quality of life. A large component of cancer treatment is geared to managing symptoms and side effects. Effective use of medication may facilitate symptom control and side effect management. The patient may speak with the health care team members about medications that may help control symptoms. Nutritional intervention may focus on lifestyle changes and behavior modification to address symptoms or side effects.

Anorexia and Early Satiety

Some patients with lung cancer may have anorexia (loss of appetite), but maintaining adequate food and fluid intake are important for health maintenance and healing. How does a patient eat if there is no appetite or hunger? Anorexia may be very difficult to address because the patient may not feel hungry, even though the body shows signs of hunger including weakness, fatigue, exhaustion, excessive sleeping, and inability to concentrate.

Anorexia may be described as a "searching for foods that interest the taste buds" or "not being able to find something that sounds good." Other people describe the feeling as "just not ever hungry". Early satiety is often described as "feeling full after only a few bites". The disinterest in meals can result in a stressful cycle of forced eating, and in severe cases, people may state that they "would rather spit food out than swallow it" or "the food balls up in the mouth, and they just can't swallow it."

This starvation mode can be interrupted in a purposeful way. One well tolerated approach is to transition from several large meals each day to smaller, more frequent meals and snacks. By eating and drinking frequently, creating scheduled snacking times (even small amounts), can provide fuel adequate to improve weakness and fatigue. The anorectic patient should consciously think about eating to provide vital nourishment to the muscles and immune system, and should not expect appetite or hunger to drive eating. In other words "don't wait to feel hungry—eat because it is time to eat". If the anorexia is severe, appetite stimulant medications may be considered.

If the patient plans to eat and drink every 2 to 3 hours during the day, portion size may be much smaller. For those who cannot eat much, it is adequate to snack on very small portions every 30 to 60 minutes, for example: 2 ounces of a milkshake taken each hour provides at least 1500 calories over a day. These small amounts are not overwhelming and they may add up during the day to provide sufficient calories, protein, and fluid. Some patients use a kitchen timer, cell phone alarm, or watch to remind them to eat. Avoid asking the patient "Are you hungry?" or "What do you want to eat?" Instead, try asking "What could you eat (or drink) right now?"

A frustrating feature of anorexia is the inability to think of foods that are enjoyable. When the anorexic patient thinks of something that may be enjoyable, interest in the food disappears before the food is available. Appetite is quickly "switched off like a light," and smelling the item during cooking can make it impossible to take a single bite of the dish. This frustration may be managed by reminding patients and families that food preparation is a team effort. The goal of the family is to help provide food options, and the patient tries to approach eating and drinking. The patient makes the ultimate decision about eating or drinking.

Anorectic patients may be unable to eat a food repeatedly or tolerate leftovers. Therefore, it is advisable to rotate through items and make small batches. Food may be served to the patient frequently, almost as a "surprise". Consider keeping a record of foods and beverages that taste good or sometimes are tolerable, which may depend on the day of the treatment cycle, fatigue, or other factors. If the food does not taste good, the patient should just try another type of food. Creating a list of tolerable foods reassures the patient that some foods are acceptable and appealing, and may help stimulate ideas for other food choices. Many people experiencing anorexia for solid food still feel thirst, and can use nutritious beverages to provide calories, protein as well as fluid.

Taste Changes

Taste alterations may be the side effect of the cancer itself, the chemotherapy regimen, infection, or certain medications. Most taste changes develop and dissipate depending on the timing of the treatments. Taste changes may limit appetite but may be managed as follows: (1) "cardboard" taste may be improved by adding more flavor; (2) metallic taste is managed by using bland flavors; (3) salty taste is

controlled by choosing low salt foods; and (4) sickly sweet taste is improved by choosing low sugar foods. Specific suggestions may be helpful in managing taste changes (Table 4).

Table 4. Specific Suggestions for Managing Taste Changes in Patients with Lung Cancer

1. Identify flavors that come through as "true" or accurate; consider similar foods to develop a greater number of tolerated food items.
2. If tart or sour flavors are appealing, use a small glass of fruit juice or lemonade to drink when eating, to refresh the taste buds. Add a small dish of fruit at each meal.
3. Limit excessively sweet taste by using homemade foods and beverages that are made with less sugar, or add milk or plain yogurt to high calorie beverages to decrease sweetness. Water down juices or pour over ice to reduce the sweetness of juices.
4. Limit excessively salty taste by choosing low salt foods or cook homemade meals without salt.
5. Marinate foods with tangy or vinegar flavors. Use strong flavored sauces or toppings such as barbeque sauce or salad dressings.
6. If red meat is unappealing, use alternative protein source such as chicken, fish, meat salads, eggs, beans, nuts, or cheese.
7. Try a pickle or pickled vegetable at meals to excite the taste buds. Add flavor with brown sugar, maple syrup, honey, cinnamon, jams, berries, and dried fruits.
8. Season tasteless foods with ketchup, hot sauce, Tabasco, vinegars, mustards, hot peppers spices and herbs. Use gravies and sauces to enhance flavors.
9. Drink beverages and soups with a straw, perhaps from cup with a lid, so the patient does not see, smell, or taste much of the liquid.
10. Use cold plates and cold foods to reduce exposure to food odor.
11. Add a slice of lemon, orange or cucumber to flavor water.
12. Examine the mouth for red or white patches that may indicate an infection, and report any signs of thrush to the doctor.
13. Clean the mouth and tongue after each meal.
14. Use sugar-free mints, candies, and gums to refresh the mouth.
15. Metallic taste may be reduced with plastic cutlery.

Nausea and Vomiting

Nausea and vomiting are common side effects of many chemotherapy regimens. Most cancer centers use medication routinely to minimize nausea or vomiting. It may be helpful to maintain a record each day of a treatment cycle that nausea occurs, including the time of day and factors that influence the nausea. Distinguish and note whether what triggers or effects the nausea or queasiness. This may help the health care team identify whether nausea is anticipatory, acute, delayed, or breakthrough. Each of these types of nausea may be treated differently with medication and behavioral strategies. (Table 5)

Table 5. Specific Suggestions for Managing Nausea and Vomiting in Patients with Lung Cancer

1. Eat and drink small volumes at frequent intervals throughout the day. Imagine "trickling" the food and beverages through the digestive tract. For some people, nausea is worse when the stomach is empty or when they become hungry.
2. Identify good times of day to eat, and eat more calories and protein foods at those times.
3. Choose foods that are easy to digest and move quickly out of the stomach.
4. Bland, starchy foods digest quickly: potatoes, toast, noodles, rice, dry cereal, pretzels, or crackers.
5. Clear liquids digest rapidly: broth based soups, juice, soda, gelatin, Popsicles.
6. Sour and tart flavors help decrease nausea. Use lemon with food, or put an orange or lemon slice in a cup of ice water. Some people like pickles or pickled foods with their meal.
7. Use cold plates to decrease exposure to odors. Avoid being around cooking odors.
8. Foods and beverages made with ginger are a natural way to soothe the stomach: ginger tea, ginger snaps, ginger ale, ginger candies.
9. Avoid foods that are greasy, fried, pungent, or strongly spiced.
10. Review medication use with your medical provider: Optimize use of anti-nausea medications, and address reflux, and constipation.

Other

Mucositis is a painful inflammation and ulceration of the mucous membranes of the mouth and digestive tract that may be a complication of chemotherapy or radiation therapy. Oral mucositis ("mouth sores") may cause difficulties with eating, including chewing solid food and drinking hot or acidic beverages. Radiation esophagitis is an inflammation of the esophagus after radiation therapy that may cause painful swallowing. Nutritional modifications may be helpful in minimizing symptoms and nutritional deficiencies resulting from these conditions (Table 6). Fatigue and food safety are additional issues that warrant special considerations.(Table 7 and 8)

Table 6. Specific Suggestions for Managing Mucositis and Radiation Esophagitis in Patients with Lung Cancer

1. Eat small, frequent meals throughout the day. Schedule eating and drinking at least every 2 to 3 hours.
2. Keep a record of the amount of fluid intake to avoid dehydration, especially if there is pain with swallowing.
3. Choose soft, moist, foods that are easy to eat. Cut food into small portions and chew carefully.
4. Chop, puree, or blend food into a soft or drinkable texture.
5. Use high calorie beverages to maximize calorie intake between or after meals.
6. Before eating, moisten food with gravy, bland sauces, or soups.
7. Room temperature foods and liquids may cause less pain than those that are hot or cold.
8. Avoid dry, scratchy, greasy, spicy, or acidic foods.
9. Drink liquids with a large lumen straw to avoid contact with mouth ulcers.
10. If swallowing causes pain, take pills with a spoonful of yogurt, apple sauce, or pudding.
11. Talk with the doctor about medications that may numb or coat the mouth or esophagus. If food is caught in the esophagus, or a lump-like sensation is present after swallowing, reflux medication may be helpful.

Table 7. Specific Suggestions for Managing Fatigue in Patients with Lung Cancer

1. Convenience foods or frozen meals are adequate if fatigue hinders meal preparation. Pick up a prepared meal at the grocery store, for example: a baked chicken, rolls, and potato salad.
2. Schedule meals and snacks at frequent intervals to maximize the energy provided from food. Plan your larger meals for the time of day you have the most energy.
3. Choose foods that are easy to chew and swallow. Soft and moist foods require less effort to eat.
4. Use single serving containers, plastic cutlery, and paper plates to decrease cleanup. Organize your kitchen to keep common or tempting foods in easy reach.
5. Select meals that are easy to prepare. All food is helpful, and there are no rules about what to eat during different parts of the day. A patient may have three meals a day made from breakfast foods (breakfast, oatmeal and juice; lunch, scrambled eggs and toast; dinner, pancakes with a glass of milk)
6. Alternate beverages that have calories with water for fluids. A small glass of juice or milk with a meal will add to the nutritional value of the meal.
7. If you are not able to eat much because you are fatigued: Use oral nutritional drinks as snacks or even as meal replacements. Many people find drinking is easier than eating.
8. Keep a list of groceries and allow others to shop or prepare food for you. Give family and friends specific information of how to assist you: include preferences for brands and flavors.
9. Balance rest with activity, talk with your doctor about a gentle exercise plan to prevent muscle loss.

Example menu:

Breakfast: Instant oatmeal made with whole milk, juice, coffee with cream

Snack: ¼ cup of Trail Mix, 6 oz. Yogurt

Lunch: 8 oz. can of Cream Soup, Peanut butter and Jelly sandwich, potato chips, Instant Ice Tea

Snack: Ice Cream Bar

Dinner: Baked chicken (already prepared at grocery store), Salad mix (bagged), Instant mashed potato, gravy (out of jar), green beans (canned), glass of chocolate milk

Snack: Graham crackers, Vanilla pudding (single serve container)

Table 8. Food Safety Suggestions for Patients with Lung Cancer *

1. Safety practices are especially important when the immune system is weakened, such as during chemotherapy or periods of neutropenia.
2. Wash hands before food preparation and before eating.
3. Food preparation surfaces should be cleaned thoroughly with dish soap and water and allowed to air dry.
4. Promptly refrigerate leftovers. Do not let food sit on the counter to cool down before refrigeration.
5. Break up large batches of food into smaller containers so they cool quicker in the refrigerator.
6. Discard leftovers stored at room temperature more than 2 hours, and discard leftovers that are more than 2 days old. When in doubt, throw it out.
7. Keep cold food at 40ºF (4.5ºC) or cooler.
8. Thaw frozen foods in the refrigerator; do not thaw foods on the counter at room temperature.
9. If you thaw food in the microwave, cook it immediately to 185 ºF (85ºC).
10. Avoid eating pink or undercooked meat. Cook raw meat to an internal temperature of 185 ºF (85ºC).
11. Avoid cross contaminating foods and food contact surfaces with raw meats.
12. Use separate cutting boards for meat and produce. Use clean utensils and food platters.
13. Wash raw fruits and vegetables. Ask the doctor if you should use only cooked or canned fruits and vegetables.
14. Wash can lids before opening.

* Based on general guidelines from the United States Food and Drug Administration[20]

Resources for Treatment and Survivorship

The National Cancer Institute (NCI) offers a comprehensive, free resource to patients undergoing cancer treatment regarding nutrition: Eating Hints: Before, During and After Cancer Treatment.[21] A free copy can be ordered at 1-800-4-CANCER (1-800-422-6237). It can be accessed online for free at: http://www.cancer.gov/cancertopics/coping/eatinghints/page1
It is also available in Spanish. Other resources are available on the Internet site of the National Cancer Institute www.cancer.gov.

The American Cancer Society (ACS) offers a booklet: Nutrition for the Person with Cancer During Treatment: A Guide for Patients and Families.[22] A free copy can be ordered at 1-800-227-2345. It is also available online at: http://www.cancer.org/acs/groups/cid/documents/webcontent/002903-pdf.pdf. It is also available in Spanish as well as other languages. Other resources are available on the Internet site of the American Cancer Society www.cancer.org.

The American Institute for Cancer Research (AICR) offers a comprehensive guide for nutrition and cancer prevention information. The 2nd Expert Report (Food, Nutrition, Physical Activity, and the Prevention of Cancer) includes reviews of thousands of nutrition and cancer studies, to help develop public policy and personal prevention recommendations.[23] In addition, the AICR routinely updates recommendations for each cancer type, reviewing the most recent research and then combining it with previously reviewed data. The website http://www.aicr.org also offers updates on new research as it occurs, recipes and links to reputable resources.

The American Cancer Society offers a report and Internet link that provides recommendations for cancer survivorship, American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity.[24] and an overview of common nutritional concerns, Nutrition and Physical Activity During and After Cancer Treatment: Answers to Common Questions.[25]

Another good resource can be found at www.cookforyourlife.org.[26] An educational website that offers ideas and recipes for patients in cancer treatment as well as healthy recipes to assist survivors implement cancer prevention diet recommendations. It includes videos offering food preparation tips and cooking technique demonstrations.

References

1. National Comprehensive Cancer Network Guidelines for Patients, Version 2010. www.nccn.com. http://www.nccn.org/patients/guidelines/nscl/#94 Accessed 8/20/14.
2. Ross PJ, Ashley S, Norton A, et al. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? *Br J Cancer.* 2004; 90(10): 1905-1911.
3. Andreyev HJ, Norman AR, Oates J, et al. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer.* 1998;34:503-9.
4. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med.* 1980;69:491-7.
5. Ovesen L, Allingstrup L, Hannibal J, et al. Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. *J Clin Oncol.* 1993;11:2043-9.
6. Preventing the loss of muscle mass in patients with involuntary weight loss. *J Support Oncol.* 2006;4(2):90-2.
7. Fearon K. Cancer cachexia and fat-muscle physiology. *N Engl J Med,* 2011:365(6):565-567.
8. Adams LA, Shepard N, Caruso RA, et al. Putting evidence into practice: evidence-based interventions to prevent and manage anorexia. *Clin J Oncol Nurs.* 2009;13(1):95-102.
9. Bauer JD, Capra S. Nutrition intervention improves outcomes in patients with cancer cachexia receiving chemotherapy - a pilot study. *Support Care Cancer.* 2005;13:270-4.

10. Glimelius B, Birgegård G, Hoffman K, et al. Improved care of patients with small cell lung cancer. Nutritional and quality of life aspects. *Acta Oncol.* 1992;31(8):823-32.
11. Leser, M. Oncology Nutrition Dietetic Practice Group. Clinical Nutrition for Oncology Practice: Chapter 22, Nutrition and Lung Cancer.
12. Rhoda KM, Porter MJ, Quintini C. Fluid and electrolyte management: putting a plan in motion. *JPEN J Parenter Enteral Nutr.* 2011;35(6):675-85.
13. McCarthy D, Weihofen D. The effect of nutritional supplements on food intake in patients undergoing radiotherapy. *Oncol Nurs Forum.* 1999;26(5):897-900.
14. Pathak AK, Bhutani M, Guleria R, et al. Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. *J Am Coll Nutr.* 2005;24(1):16-21.
15. Satia JA, Littman A, Slatore CG, et al. Long-term use of beta-carotene, retinol, lycopene, and lutein supplements and lung cancer risk: results from the VITamins And Lifestyle (VITAL) study. *Am J Epidemiol.* 2009;169:815-28.
16. Harvie, M. Nutritional supplements and cancer: Potential benefits and proven harms. 2014 ASCO Educational Book. e478-e486.
17. Recommendations summary: Oncology (Onc) lung cancer: chemotherapy and use of antioxidant vitamins C, E and beta-carotene oral supplements. *ADA Evidence Analysis Library.* http://www.adaevidencelibrary.com/template.cfm?template=guide_summary&key=1836&highlight=Lung%20cancer&home=1 Accessed 8/20/14.
18. Payne C, Larkin PJ, McIlfatrick S, et al. Exercise and nutrition interventions in advanced lung cancer: A systematic review. *Curr Oncol.* 2013; 20(4): e321-e337.
19. Girolamo F, Situlin R, Mazzucco S, et al. Omega-3 fatty acids and protein metabolism: Enhancement of anabolic interventions for sarcopenia. *Co-clinical Nutrition.* 2014;17(2):145-150.
20. United States Department of Agriculture. Kitchen Companion: Your safe food handbook. http://www.fsis.usda.gov/wps/wcm/connect/6c55c954-20a8-46fd-b617-ecffb4449062/Kitchen_Companion_Single.pdf?MOD=AJPERES Accessed: 8/20/14.
21. National Cancer Institute. Eating Hints: Before, During, and After Cancer Treatment. http://www.cancer.gov/cancertopics/coping/eatinghints.pdf. US Department of Health and Human Services, National Institutes of Health. NIH Publication No. 11-2079. 2011. Accessed 8/20/14.
22. American Cancer Society. Nutrition for the Person with Cancer During Treatment: A Guide for Patients and Families. http://www.cancer.org/acs/groups/cid/documents/webcontent/002903-pdf.pdf Accessed 8/20/14.
23. American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer. 2007. http://www.dietandcancerreport.org/expert_report/report_overview.php Accessed: 8/20/14.
24. Kushi, L., Doyle, C., Mccullough, M., Rock, C., Demark-Wahnefried, W., Bandera, E., Gapstur, S., Patel, A., Andrews, K., Gansler, T., American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA: A Cancer Journal for Clinicians.* 2012;62(1):30-67.
25. American Cancer Society. Nutrition and Physical Activity During and After Cancer Treatment: Answers to Common Questions. http://www.cancer.org/Treatment/SurvivorshipDuringandAfterTreatment/NutritionforPeoplewithCancer/nutrition-and-physical-activity-during-and-after-cancer-treatment-answers-to-common-questions. Accessed 8/20/14.
26. Cook For Your Life. www.cookforyourlife.org. Accessed 8/20/14.

Chapter

9

Complementary and Alternative Medicine and Chinese Medicine in Lung Cancer

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Introduction

Complementary and alternative medicine (CAM) in lung cancer may include Chinese medicine, Western herbal therapy, relaxation and visualization techniques, prayer, exercise, nutritional supplementation, and dietary therapy. In this chapter, the primary focus will be on Chinese medicine and related therapies that may be used in conjunction with other complementary and alternative therapies and Western medicine.

Chinese Medicine

In China and many parts of the United States today, people with various types of cancer seek out Chinese medicine in addition, or as an alternative, to Western medical treatment. In lung cancer, Chinese medicine is used primarily for supportive adjunctive care in conjunction with Western treatments of surgery, chemotherapy, and radiation therapy. When intensive Western treatments are being used, Chinese medicine can relieve negative side effects and improve the treatment outcome.

In 2007 and 2013, a multidisciplinary panel of experts in oncology and integrative medicine updated the guidelines and made recommendations on complementary therapies for use in lung cancer patients. These include acupuncture, massage therapy, mind-body modalities, nutrition, botanicals, and exercise.[1,2] In the evidence-based clinical practice guidelines the American College of Chest Physicians (ACCP) panel recommended that all patients with lung cancer be asked specifically about the use of CAM and given counseling as it is important to minimize potential harm or delay in treatment. In addition, the panel concluded that mind-body modalities and massage therapy can decrease anxiety, mood disturbance, and chronic pain; acupuncture may help control pain and other side effects; and herbal products and other dietary supplements should be evaluated for side effects and potential interactions with chemotherapy and other medications.[1,2]

In China, where Chinese medicine is used in conjunction with Western medicine in hospitals and clinics, men and women undergoing various treatments for cancer are offered the choice to use Chinese herbal medicine, acupuncture, *Qi Gong*, and exercise as adjunctive therapies to reduce side effects and increase the efficacy of the Western treatment. Extensive research about CAM is being done in Chinese hospitals and oncology settings in conjunction with Western research approaches and treatments.

Chinese medicine is a system of medicine that has been used for thousands of years in the treatment of health imbalances and disease. Therefore, there is a particular interest in exploring research about Chinese traditional medicine in cancer and treatment options.

The Foundations of Chinese Medicine

Traditionally, Chinese medicine has relied on the following forms of treatment to prevent or remedy disease and disorders: herbal therapy, acupuncture, acupressure/massage, dietary therapy, and exercise and meditation (often in the form of *Qi Gong*). These therapies are used to help the body restore balance and harmony in the mind, body, and spirit, especially when the body is attacked by a disease causing "pernicious influence" or disrupted by internal imbalances.

There are three main areas of contrast between Western and Chinese medicine: general approach to symptoms and disease, approach to cancer, and synergy between Western and Chinese medicine.

General Approach to Symptoms and Disease

The Western medicine approach includes the design of drugs and other therapies to treat a specific disease or disorder. In Western medicine, different people who have the same diagnosis might be prescribed the same drug to treat the problem.

In contrast, a symptom such as pain may be viewed as a symptom of several possible disorders and disharmonies affecting an individual's mind, body, and spirit. Chinese medicine treatment focuses on identifying the underlying disharmony (diagnosis) and creating an individualized treatment suited to that diagnosis. This makes double-blind controlled studies difficult to create because each individual person in a study may be treated differently. However, it is sometimes possible for various types of rigorous research to be conducted.

Chinese medicine traditionally did not discuss viruses, bacteria, or cancer and did not view the immune system and disease resistance in the same way as Western medicine. Therefore, it has been difficult for Western physicians and researchers to understand that Chinese medicine treatments may attack these causes of disease.

The goals of treatment are often different in Chinese and Western medicine. Western medicine is usually designed as an "all or nothing" proposition — either the therapy cures the disease or does not. In contrast, Chinese medicine may produce healing in the mind, body, and spirit, even in the presence of persistent disease.

In the 21st century, Western scientific insights and Chinese treatment of the mind, body, and spirit have begun to overlap. There is no contradiction between the two systems. When clearly understood, they can strengthen and complement each other.

Approach to Cancer

Traditional Chinese medicine treatments and Western therapies approach cancer treatment from different points of view. Although most Western cancer therapies focus on killing the cancer or eliminating the tumor, the primary goal of Chinese traditional medicine is to create wholeness and harmony within a person, allowing the body to heal itself. Chinese medicine strives to make the internal constitution stronger and focuses on immune functions that allow the body to fight cancer. Western medicine is just beginning to look at some of these concepts and treatments. Instead of primarily focusing on the effect of Chinese medicine treatments on tumor-eradicating abilities, it may be more beneficial to study the effect of Chinese traditional medicine on immune responses.

Chinese medicine should be evaluated on its own terms and in light of its own treatment goals and objectives, not in terms of treatment goals and objectives defined by Western medicine. In Western medicine, the focus is on eradicating illness after it appears in the body. In contrast, Chinese traditional medicine has a focus on disease prevention, accomplished by creating balance and harmony in the body's various systems.

Studies that evaluate the efficacy of a treatment to prevent disease are difficult and take many years to complete. These studies are needed to fully understand the efficacy of Chinese medicine.

Chinese medicine and other therapies that might be used as alternative therapies are most commonly used in Asia as primary therapy in treating early stages of certain types of cancer, although not as primary treatment in lung cancer. However, most Western studies are designed to evaluate the effectiveness of Chinese medicine in treating very late stage cancers. Yet, this is frequently a stage when any treatment may be much less successful, harder to tolerate, or more difficult for patient compliance. The rationale for this research is that if it works in very late stages, then is it likely to work in earlier stages. However, in the traditional Chinese medicine literature, there is little indication that the recommended Chinese medicine therapies will stop cancer in a very late stage. Nevertheless, studies that focus on supportive treatment and palliative care in late stage disease may be helpful. Dismissing a treatment because it is not effective in very late stage cancer may deny scientists and practitioners the opportunity to study an effective treatment for early stage cancer.

Synergy between Western and Chinese Medicine

Western medicine may be improved by the simultaneous use of traditional Chinese medicine therapies. In China, and in some centers in the West, people undergoing chemotherapy, surgery, and radiation therapy treatment have the choice to use Chinese medicine therapies as adjuncts to decrease side effects and increase the efficacy of Western medical treatment.

A recent meta-analysis that evaluated Chinese herbs in conjunction with platinum-based chemotherapy in non-small cell lung cancer concluded that Chinese herbal medicine based on

Astragalus (a Chinese herb) may increase effectiveness of platinum-based chemotherapy when used in combination with the chemotherapy. [2]

Herbal formulas based on the Chinese herb *Ji Xue Teng (Spatholobus)* may decrease bone marrow suppression and may enable continuation of chemotherapy treatments at a normal schedule. In mice, an extract of *Spatholobus* may stimulate the proliferation of bone marrow cells and relieve the bone marrow depression caused by chemotherapy.[3]

Acupuncture

Acupuncture is the art of inserting fine sterile metal needles into certain body or ear points to control the body's energy flow. Acupuncture is painless and often accompanied with a sensation of heaviness, warmth, or movement of energy at the insertion point or along the energy channels. Acupuncture may relieve pain, rebalance energy, and heal symptoms. Electrostimulation also may be used with acupuncture for pain.

Western science has documented several mechanisms to explain how acupuncture works.[4] Acupuncture may stimulate serotonin levels within the brain, resulting in a sense of well-being and pain relief.[5] In addition, acupuncture has anti-inflammatory effects, which may help relieve symptoms and decrease inflammation. Acupuncture also may be effective in improving liver function, evidenced by improved liver function tests (transaminases).[6]

Acupuncture and acupressure as adjunctive cancer treatment have been studied for postoperative nausea and vomiting, chemotherapy-related nausea and vomiting, and pain relief.[7] Acupressure is a type of massage or touching therapy that uses the principles and theory of acupuncture and Chinese medicine. In acupressure, the same points as acupuncture are used on the body, but these are stimulated with finger or other pressure instead of inserting needles.

Several studies have evaluated acupuncture point Pericardium 6 (P6) for both acupuncture and acupressure in nausea and vomiting resulting from chemotherapy and surgery. When electroacupuncture was used for the prevention of postoperative nausea and vomiting, electrostimulation of acupuncture points or ondansetron was more effective than a placebo, with greater degree of patient satisfaction. However, electrostimulation of acupuncture points was more effective than ondansetron in controlling nausea. Stimulation of the acupuncture point P6 also may relieve pain, and electroacupuncture had better pain relief in the recovery room than either ondansetron or placebo.[7] The 2013 ACCP guidelines recommend acupuncture and related techniques (with the caveat that the evidence is somewhat weak) in patients having nausea and vomiting from either chemotherapy or radiation therapy, as well as an adjunct treatment option as in patients with cancer related pain and peripheral neuropathy with inadequate control of symptoms.[2]

Acupuncture Contraindications

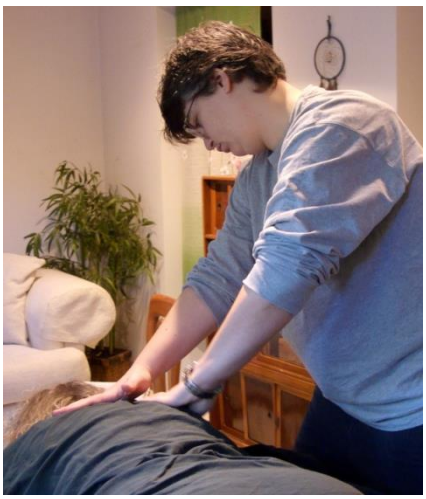
Acupuncture may be contraindicated in patients with bleeding disorders. Careful evaluation of laboratory studies and patient response may be necessary for safe treatment.

People with allergies to metal should not use acupuncture. Some people with cancer have increased autoimmune reactions.

Rarely, some people develop "needle sickness" which is a temporary sense of faintness or lightheadedness and cannot tolerate acupuncture.

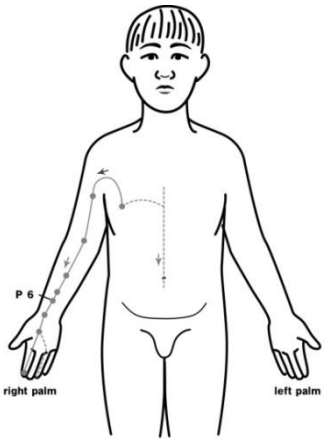
Acupressure and Massage

There are many forms of massage and bodywork that can be used by people diagnosed with lung cancer including acupressure, Tui Na (*Qi Gong*), shiatsu, Thai massage, deep tissue massage, and long stroke massage (including Esalen and Swedish). Several studies show improvement of symptoms in people with cancer who receive massage. In a study of 1290 people with cancer who received massage, symptom scores were decreased by 50%.[8]



Several studies in the use of the acupuncture point Pericardium 6 (P6) in women with breast cancer showed that nausea and vomiting from chemotherapy may be decreased when used in conjunction with conventional drug treatments. Furthermore, a large clinical trial performed in several cancer centers concluded that acupressure was helpful at decreasing the amount and intensity of chemotherapy induced nausea and vomiting in women with breast cancer.[9]

People with cancer are best treated by specially trained practitioners trained in oncology massage, who know which areas to avoid and which kind of bodywork is appropriate. Swollen areas, fractures, skin infections, or severe hematomas should not be massaged. Lumps and areas of swelling should be checked by a Western healthcare practitioner before massaging. It is best to seek medical advice before having therapeutic bodywork if the patient has phlebitis, thrombosis, varicose veins, severe acute back pain, or fever. This is especially important in immunocompromised individuals, including people having chemotherapy, patients with HIV infection, and others with low immunity. The Society for Oncology Massage states:



The Pericardium Channel

> "Oncology massage does not try to "fix" anything and, unlike many massage modalities, is not a series of techniques or applied protocols. Rather, it is the ability of the therapist to recognize and safely work within clinically established guidelines, considering the patient's unique circumstance… Oncology massage education for massage therapists is important for clinical safety and therapeutic benefit. Adaptations to massage therapy techniques may be indicated both during treatment and for the rest of a person's life after treatment."[13]

Chinese Herbal Medicine

There are many Chinese and Western herbs used by people with cancer. Herbs should be prescribed by a qualified certified practitioner of herbal medicine. In some states, where practitioners are licensed to practice acupuncture or naturopathic medicine and are also qualified to practice herbal medicine, that is a big plus. Licensure in many states does not include herbal medicine. Therefore, national certifying bodies, such as the National Commission on the Certification of Acupuncture and Oriental Medicine, which gives diplomas based on professional qualifications (ex. graduation from a nationally accredited college) in conjunction with passing a rigorous examination. My opinion is that licensed practitioners are required to adhere to professional standards for safety and more likely to be safe (their licenses depend on it), and they often use formulas that are practitioner based which generally have a higher safety and authenticity profile of herbal formulations. This may also be true for diplomates in states without licensure that includes herbal medicine. The patient may inquire about the professional training of the practitioner and the types of herbs used.

Chinese Herbs Used in Adjunctive Cancer Treatment

The list of herbs used in adjunctive support for cancer treatment is growing. There are individual herbs such as *Astragalus (Huang Qi), American Ginseng (Xi Yang Shen), Ganoderma Mushroom (Ling Zhi or Rei Shi), Maitake Mushroom*, and *Cordyceps (Dong Chong Xia Cao)* that are used in cancer supportive treatment. The type of herbs used may vary with the severity of the disease, type of disease, and treatment (chemotherapy, radiation, surgery, or immunotherapy).

Some herbs may be contraindicated with some types of chemotherapy and others may improve the effect of chemotherapy. Herbal formulas based on *Astragalus* may increase effectiveness of platinum-based chemotherapy.[2] Furthermore, a large treatment effect was found when adding *Astragalus*-based herbal treatment to standard chemotherapy regimens for non-small cell lung cancer. Specifically, the *Astragalus*-based herbal treatment improves survival, increases tumor response, improves performance status, or reduces chemotherapy toxicity. [2]

Formulas based on *Ji Xue Teng (Spatholobus)* are used to help support people with cancer during and after chemotherapy and radiation treatments. Anecdotal experience in our clinic suggests that a *Spatholobus*-based Chinese herbal formula designed by the author may help support patients undergoing cancer treatment (Marrow Plus®, Health Concerns**,** 8001 Capwell Drive, Oakland, CA 94621). Support includes improving levels of fatigue, improving blood counts and decreasing anemia and neutropenia, allowing for less side effects of medications, and importantly, increasing the ability of a person undergoing chemotherapy and radiation treatment to fulfill the treatment plan developed by the oncology team.

Drug-Herb Interactions

The use of Chinese medicine as part of lung cancer treatment may be optimized with practitioners who use traditional methods together with modern research practices. Western practitioners such as licensed naturopathic or integrative medical doctors may use CAM treatments that are evidence-based. Traditional herbal and dietary methods have been used for centuries, but newer technologies

of nutritional supplementation and concentrated herb extracts should be studied for safety and efficacy. For more information go to:
http://www.integrativeonc.org/index.php/docguide

There are conflicting opinions and evidence about the use of herbs and supplements together with chemotherapy and radiation therapy, particularly among oncologists and cancer researchers who may be more focused on ensuring proper chemotherapy and radiation therapy than on the herb or supplement program. Therefore, it is important to be aware of potential adverse interactions between drugs, herbs, and some supplements, and the practitioner should consider the most up-to-date information to ensure maximum safety and efficacy.

Practitioners of Chinese and herbal medicine may provide the patient's Western physician, oncologist, pharmacist, or other healthcare provider with information about the individualized treatment. It is important to disclose all herbs and supplements proposed for a patient's treatment to the oncology team for review before implementing the treatment plan. This is a prudent course of action for all practitioners who work with cancer patients, especially those undergoing intensive chemotherapeutic treatments.

Chinese medicine studies that emphasize the alleviation of side effects and improving Western treatment may be the most beneficial to pursue presently, in addition to studies about cancer prevention.

Herb and Supplement Certification

Herbal formulas and nutritional supplements may be manufactured to different standards of purity and quality, such as Good Manufacturing Practices (GMP) for food or pharmaceutical products. Pharmaceutical GMP standards are stricter than food standards, and this may be important for potency of a product. Furthermore, pharmaceutical GMP includes higher standards of testing for pesticides, toxins, bacteria, and molds, and proper identification of label ingredients. The GMP standards provide guidelines for the manufacturing site, methods of production, and quality control. Manufacturing guidelines vary from country to country. For example, Australian standards are among the strictest in the world, because Australian dietary and herbal supplements are subject to the same guidelines as pharmaceuticals, which is not the case in the United States. The guidelines require attention to manufacturing processes including cleanliness of building and grounds, equipment maintenance, personnel and training, sanitation and hygiene, air and water purification, production, and documentation. It is advised that patients ask practitioners about the company that manufactures the herbs, including company location, formulas, and manufacturing standards, and defer taking herbal formulas or supplements until this information is available.

Companies can provide certificates of analysis for their products. A certificate of analysis is an authenticated document, issued by an appropriate authority that certifies the quality and purity of pharmaceuticals, animals, and plants being produced or exported. This certificate documents the formula for the ingredients, the amount of each raw material and ingredient, and the results of all the tests performed on a particular lot of the product. In some cases, albeit rare, herbs may be misidentified and added to formulas without proper authentication. Most cases of herbal toxicity are not caused by proper herbs given in the correct doses, but are caused by inclusion of the wrong herb

or supplement in a formula. Therefore, herb identification and authenticity is an important aspect of herb manufacturing.

Food Therapy

Dietary therapy is an important part of Chinese medicine and complementary and alternative medicine. In Chinese medicine, food therapy and diet are the first treatments given to people who are trying to stay well and remain in balance or who are experiencing illness. In Chinese thought, the digestion must be kept healthy or a person can easily become ill. Food intake is very important to healthy digestion and assimilation of food. Therefore, anything that disrupts the function of the organs of digestion is injurious to the body's energy.

Some of the concepts of Chinese medicine most important for digestion include eating at regular times and eating cooked foods. Chinese medicine theory considers that energy is required to warm the stomach to digest foods, and cold and raw foods may be injurious to the digestive energy and should be eaten sparingly; this is especially important for people who have been sick and have had stomach pain and nausea often due to cancer treatment. (The issue of raw or cooked food is controversial, and raw food advocates argue that cooking may destroy enzymes in food important to digestion.) Furthermore, Chinese medicine advocates eating foods that are in season and grown as close to home as possible, because these foods are fresher and have more food energy and more *Qi*. Herbs can be added to foods to increase food vitality, especially for specific health conditions.

Rice is the basic food used for healing in Chinese medicine, but other grains may be used including quinoa, barley, rye, and buckwheat. Congee is a special grain porridge that is considered a very therapeutic food and used traditionally during chronic weakness diseases and convalescence from illnesses. When people diagnosed with lung cancer are being treated with chemotherapy, recovering from surgery, or having other debilitating treatments, congee is a good and easy option for nutrition and recovery. There are many varieties of congee suitable for different conditions and symptoms, and a Chinese medicine practitioner can provide recipes specific to the patient's situation.

The basic method of making congee is to cook one cup of rice (or other grains) in seven to nine cups of filtered water for six to eight hours. This can be done overnight and it is ideal to use a slow cooker such as a crock pot or any cooking pot. Herbs and/or meat or vegetables are added as directed by the Chinese medicine practitioner for the patient's specific condition.

Traditional Chinese families serve congee to the whole family weekly with herbs such as *Ginseng, Dong Quai, Codonopsis, Red Dates, Ginger*, and *Astragalus*. *Astragalus* is good in immune tonic congee. Soups are highly recommended in Chinese food therapy. Chicken soup is considered very healing by the Chinese, and many soups that are tonics are based on chicken broth. Congees may also use chicken broth as a base with specific herbs for the patient's condition.

Tips for Eating – For You and Your Family Members

- Eat in a peaceful setting. Stop for half a minute to take a deep breath, switch gears if you need to, and slow down to really enjoy your food.
- Eat slowly enough to chew adequately.
- Eat with others whose company you enjoy.
- Eat plenty of lightly cooked (steamed or parboiled) fresh vegetables (not an excess of raw food), whole grains, beans, protein, and seaweeds. Eat one serving of steamed or cooked dark leafy greens daily, such as kale, collard greens, or broccoli. These are very rich in nutrients.
- Eat a cooked meal in the morning, the cool part of the day. This is also an important time to include good quality protein for energy throughout the day.
- In the afternoon, the warm part of the day, you may include cooling foods, such as salad or fruit if desired, and protein to regulate blood sugar.
- In the evening, eat a lighter cooked meal no later than 3 hours before bed for sounder sleep.
- Some people feel better "grazing" or eating smaller meals throughout the day. This can be helpful to people who have small appetites and have trouble gaining weight. Eating frequent small meals is also less stressful on the heart. During chemotherapy treatment this is often very helpful to decrease nausea and stomach pain.
- Drink plenty of water, but not too much water with meals.
- Avoid eating junk food, processed food, sugar, and food with preservatives on a regular basis.
- Include organic foods and home cooked foods as much as possible.
- Soups are quick and simple, nutritious, delicious, and easy to freeze and reheat.

Qi Gong: Exercise and Meditation

The Benefits of Exercise in Lung Cancer

Chronic or life-threatening illness can make a person feel as if the body is beyond his or her control. Exercise and meditation can take control over quality of life and the vitality of the mind, body, and spirit. Exercise can help decrease stress and depression, strengthen the cardiovascular system, improve appetite, maintain muscle mass, improve and maintain digestion, and avoid constipation and/or diarrhea associated with medication.

Moderate exercise is recommended, starting with 20-minute periods, three times weekly. The benefits of exercising are extensive, and regular exercise is advised. However, stamina and tolerance

for stress may ebb and flow during the course of disease and treatment. Therefore, break periods may be required, and exercise programs may be resumed when the patient has more energy and endurance.

In the general population, regular exercise that oxygenates the blood and tones the muscles helps people live longer, look younger, and think more clearly. Exercise also has emotional and spiritual benefits. In general, people with a normal stress response should get as much exercise as possible. However, patients who have lung cancer must evaluate the risks of exacerbating symptoms because of overexertion, and *Qi Gong* may be helpful in this situation.

Benefits of Qi Gong Exercise

Qi Gong is the traditional Chinese discipline that focuses on breathing and movement of *Qi* ("life force")[10] to increase physical harmony and strength and establish spiritual and emotional peace. There are numerous different schools of practice, some very vigorous (including martial arts) and others extremely gentle. Careful, relaxed breathing is the foundation of most *Qi Gong* movements.

The energy-conserving, *Qi*-channeling practice of *Qi Gong* is designed to keep a person healthy and fit without causing stress and exhaustion. Furthermore, patients who have excessive fatigue, shortness of breath, fluid retention, or neuropathy may be required to avoid strenuous exercise; in these situations, *Qi Gong* meditation and breathing exercises can become the primary way to obtain exercise.

The Chinese practice of *Qi Gong* may improve outcomes for people with cancer, including improved immune responses and decreased symptoms associated with cancer treatment. However, most studies are small and the evidence is varied. *Qi Gong* therapy may have an inhibitory effect on cancer growth, both *in vitro* and *in vivo,* but repeat studies are unavailable for confirmation.[10] Furthermore, *Qi Gong* in cancer patients may improve quality of life and mood status and decrease inflammatory markers and side effects of cancer treatment.[11]

Exercise: The Circle of Qi

This exercise was designed by *Qi Gong* master Larry Wong of San Francisco to circulate *Qi* throughout the body, replenish depleted *Qi*, and calm the *Shen* (spirit).

Sit on the floor cross-legged style or in a lotus position. If that is uncomfortable, you may stand up or lie down during these breathing routines.

Inhale to a count of four to eight, depending on comfort. There are two breathing techniques you can use, Buddha's Breath and Taoist's Breath.

> For Buddha's Breath, inhale, extending your belly as you fill it up with air from the bottom of your lungs upward; exhale by pushing the air out from the bottom of your lungs first, contracting the lower rib cage and abdominal muscles, and then the upper torso.

For Taoist's Breath, inhale, contracting your abdomen; exhale, letting your abdomen relax outward. You may practice these breathing techniques on alternate days.

As you inhale, imagine the air and your *Qi* flowing evenly along the pathways of the channels.

Become aware of the air as it enters through your nostrils and moves down the center of your chest to a spot on your abdomen about 1 to 2 inches below the navel. This is the area the body called the *dan*.

Now breathe out slowly and evenly, releasing the breath from the abdomen, up through the lungs, and out your slightly open mouth.

As you exhale, imagine that the *Qi* that was at the *dan* is moving down through your pelvis, through your crotch, and up your tailbone to your lower back.

Keep exhaling in a slow, steady, smooth stream that passes gently over your lips.

As you inhale again, follow the *Qi* as it moves up along your back to your shoulders.

Exhale and move the *Qi* up to the back of the head, over the top of your head, down your forehead, and returning to the nose.

At first it may be difficult to follow the flow of *Qi* through its cycle. Be patient and keep your breathing calm and your mind relaxed while focusing on your inhaling and exhaling.[12]

References

1. Cassileth BR, Deng GE, Gomez JE et al. Complementary therapies and integrative oncology in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):340S-354S.
2. Deng GE, Rausch SM, Jones LW et al. Complementary therapies and integrative medicine in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines (3rd edition). Chest. 2013 May;143(5 Suppl):e420S-36S. doi: 10.1378/chest.12-2364.
3. McCulloch M, See C, Shu XJ et al. Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. *J Clin Oncol*. 2006;24(3):419-30.
4. Fu Q , Luo X-q, Tang Y, et al. Study on Antitumor Activity in Vivo and Effect on Hematopoiesis of Extract of Spatholobus suberctus Dunn. *Chinese Journal of Information on Traditional Chinese Medicine* 2008.
    a. http://en.cnki.com.cn/Article_en/CJFDTOTAL-XXYY200812016.htm
5. Shen J. Research on the neurophysiological mechanisms of acupuncture: review of selected studies and methodological issues. *J Altern Complement Med*. 2001;7 (Suppl 1):S121-7.
6. Sugai GC, Freire Ade O, Tabosa A, et al. Serotonin involvement in the electroacupuncture- and moxibustion-induced gastric emptying in rats. *Physiol Behav.* 2004;82(5):855-61.
7. Zijlstra FJ, van den Berg-de Lange I, Huygen FJ, et al. Anti-inflammatory actions of acupuncture. *Mediators Inflamm*. 2003;12(2):59-69.
8. Gan TJ, Jiao KR, Zenn M, et al. A randomized controlled comparison of electro-acupoint stimulation or ondansetron versus placebo for the prevention of postoperative nausea and vomiting. *Anesth Analg*. 2004;*99*(4):1070-5.
9. Cassileth BR, Vickers AJ. Massage therapy for symptom control: outcome study at a major cancer center. *J Pain*

Symptom Manage. 2004;28(3):244-9.
10. Dibble SL, Luce J, Cooper BA, et al. Acupressure for chemotherapy-induced nausea and vomiting: a randomized clinical trial. *Oncol Nurs Forum*. 2007;34(4):813-20.
11. Chen K, Yeung R. Exploratory studies of Qigong therapy for cancer in China. *Integr Cancer Ther*. 2002;1(4):345-70.
12. Oh B, Butow P, Mullan B, et al. Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized controlled trial. *Ann Oncol*. 2010;21(3):608-14.
13. Cohen MR, Doner K. The Chinese Way to Healing: Many Paths to Wholeness. Lincoln NE: Authors Choice Press; 2006.
14. Society for Oncology Massage. http://www.s4om.moonfruit.org/#/health-care-professionals/4558534846

Chapter

10

Lung Cancer in People who have Never Smoked

Heather Wakelee, MD

Introduction

Lung cancer is the leading cause of cancer death for both men and women in the United States, and globally it is the leading cause of cancer death in men and the second leading cause in women.[1] Smoking is the most common cause of lung cancer, but there are many people who have never smoked who develop lung cancer. Lung cancer in people who have never smoked is more common in Asia, especially women.[1] The causes of lung cancer in people who have never smoked are not well understood. Lung cancer treatments can work differently in people who have never smoked.

Frequency

People who have never smoked ("never-smokers") are defined as people who have smoked < 100 cigarettes in their lifetime. The information about how many people develop cancer each year comes from cancer registries that have information about the type of cancer and age of the person, but no information may be available about smoking history. Therefore, it is unknown exactly how many people with lung cancer do or do not smoke. We can make estimates though about how many people with lung cancer have developed the disease without a smoking history.

Worldwide, approximately 15% to 20% of men with lung cancer, and 50% of women with lung cancer, are people who have never smoked.[1] In the United States, approximately 1 in 10 men, and 1 in 5 women, with lung cancer are people who have never smoked.[2] The number of men who have never smoked and who develop lung cancer each year is similar to the number of men who develop multiple myeloma, a cancer of the immune system. The number of women who have never smoked and who develop lung cancer each year is similar to the number of women who develop cervical cancer.

It is unknown whether the frequency of developing lung cancer is increasing in people who have never smoked. A study in Swedish construction workers who had never smoked showed an increased frequency of lung cancer in the 1990s compared with the 1970s.[3] In the United States, more women who had never smoked died of lung cancer in the 1980s and 1990s than in the 1960s.[4] However, there is no other evidence of an increased incidence of lung cancer in people who have never smoked, and some

studies show no increase.[5,6] These types of studies are difficult to do because we do not have smoking information available in the same databases that capture information about the number of patients who develop lung cancer. There is a sense among doctors who treat lung cancer that the number of people with lung cancer who have never smoked is increasing. Studies are being done to try to get a better answer to that question, but at this time it remains unknown.

Characteristics

There are several known differences between lung cancer in smokers and people who have never smoked, including the specific type of cancer. Lung cancer in smokers frequently is often a type called "small cell lung cancer" or a form of "non-small cell lung cancer (NSCLC)" known as "squamous cell carcinoma". Adenocarcinoma, a different type of NSCLC, is more common in people who have never smoked.[1,7] However, people with a smoking history can also develop adenocarcinoma of the lung and those who have never smoked are rarely diagnosed with squamous cell lung cancer or small cell lung cancer. The only way to know what kind of lung cancer it is for sure is to have a biopsy that is examined by a pathology doctor.

It is also known that lung cancer in people from certain racial/ethnic groups is more often seen in never-smokers than in other racial groups. This is true for people of Asian ancestry and Hispanics.[8-10] Most of the risk is seen in women. We know that the percentage of women with lung cancer who have never smoked is higher than the percentage of men with lung cancer who have never smoked.[2] The reason for these differences is not known. People are looking at air pollution as a cause of lung cancer in never-smokers.

Tumors from patients who have never smoked frequently have different changes in the DNA than the tumors from smokers, including changes in a protein known as the epidermal growth factor receptor (EGFR).[11-16] Tumors with specific changes in the EGFR protein are more likely to shrink when treated with drugs that attack the EGFR protein, (such as erlotinib, gefitinib and afatinib). Another change that is more common in people with no smoking history who develop lung cancer is with the Anaplastic Lymphoma Kinase (ALK) gene.[17,18] The drugs crizotinib and ceritinib are used to treat lung cancer patients who have the ALK gene rearrangement.[19] Other changes in DNA are frequently different between lung cancer tumors from smokers and people who have never smoked, and the major DNA change that is important for the cancer can be identified in approximately half of patients in research studies. Most commonly, patients have only a single major change in the DNA, and a patient with a change in the EGFR gene usually does not also have an ALK gene rearrangement. Testing for these DNA changes is now considered standard for patients who have been diagnosed with non-small cell lung cancer, especially adenocarcinoma, to help guide treatment and better understand the disease in each individual. There are lung cancer patients who have never smoked who do not have any of these gene mutations. However, it is important that testing is done to look for EGFR and ALK at a minimum in lung cancer patients who have never-smoked. These gene changes can also been seen in patients with a smoking history who develop lung cancer, but they seem to be more common in patients without a smoking history.

The Causes

The causes of lung cancer in people who have never smoked are unknown, but several factors may increase the risk .[20] (Table 1) Second hand smoke may cause 20% of the lung cancers in people who have never smoked[21,22] Air pollution may cause 5% of cases of the disease.[23] Indoor air pollution, such as fumes from cooking oil and smoke from burning coal, may increase lung cancer risk, especially in Asia.[24]

Radon is a colorless, odorless, radioactive gas that occurs naturally in some parts of the United States and other countries. Some homes have high levels of radon, and this can be tested with home kits. People who live in homes with high levels of radon are at a higher risk of developing lung cancer, whether or not they smoke.[25,26]

Jobs that expose people to toxic substances, such as uranium, asbestos, chromium, and arsenic, may increase the risk of developing lung cancer.[27-29] Arsenic may be present in drinking water in some areas such as Taiwan and Chile.[30,31] Nutritional deficiencies may contribute to the development of cancer, and people who eat more fruits and vegetables may be at lower risk for developing lung cancer.[32-35]

Lung damage from radiation therapy may increase the risk of developing lung cancer. Furthermore, lung cancer risk may be increased in people who have the human papilloma virus, but not everyone agrees with that risk.[36] At this time there is no proof that human papilloma virus causes lung cancer. People with family members who have lung cancer have a slightly higher risk of developing lung cancer, but the magnitude and cause of this risk are unknown.[20, 37-40] Research is being done to try to find what changes in the DNA (genes) may make certain families at higher risk for lung cancer. So far we don't know any DNA changes that are definitely linked to a higher risk of lung cancer in families and we don't have a test to help people know if they are at risk. This research is ongoing.

Table 1. Possible Causes of Lung Cancer in People Who have Never Smoked

	Second hand smoke
	Radon exposure
	Other toxins (asbestos, chromium, or arsenic)
	Dietary factors (diet deficient in fruits and vegetables)
	Air pollution (including cooking fumes)
	Radiation therapy to the chest
	Other lung diseases such as idiopathic pulmonary fibrosis
	Human papilloma virus (controversial)
	Other family members with lung cancer
	Differences in ability to fix DNA damage

Treatment of Lung Cancer in People who have Never Smoked

People with lung cancer who have never smoked may live longer, but may or may not respond better to chemotherapy, than smokers with lung cancer. Basic treatment usually is similar for people with lung cancer whether or not they have a smoking history.

People who have never smoked and who have lung cancer are more likely to have changes in specific genes. Though we do not know what causes the changes, we do know that specific gene changes can be the driving force in a cancer. These gene changes are not seen in the normal cells from a person with lung cancer, only in the cancer cells.

The gene changes we know the most about that are more common in the lung cancer of people who are never smoked are in the genes Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK). In recent years more gene changes that can be the driving force behind lung cancer in never smokers have been discovered. There are specific treatments available for people with lung cancer with changes in some of these genes such as erlotinib, gefitinib or afatinib for EGFR gene mutations and crizotinib or ceritinib for ALK gene changes.[13,41]

For most people diagnosed with stage IV (also called metastatic or advanced stage) non-small cell lung cancer the first treatment is chemotherapy. Chemotherapy can also work very well for patients with tumors with specific gene mutations; however, if we find the gene mutation before chemotherapy is started we usually start with a drug "targeted" to treat the gene mutation. It is very important for all patients with advanced stage lung cancer, especially patients who are never-smokers where it is more common, to have their tumor tested for the gene changes.

Patients with metastatic lung cancer who have specific EGFR gene changes should receive erlotinib, gefitinib, or afatinib as the initial treatment, even before the typical chemotherapy regimen, based on studies that have shown that they have a higher chance of shrinking the tumor than chemotherapy for these patients.[13,41] People who start therapy with a "targeted" drug also have a longer time before the cancer starts to regrow and new treatment is needed.

Erlotinib is not usually added to chemotherapy because the results of combining chemotherapy and erlotinib or gefitinib are not better than giving the chemotherapy alone as the first course of treatment. Recent studies are looking at whether or not to continue the "targeted" drug after it stops working as well and chemotherapy will be started. Current research is also evaluating whether erlotinib may help prevent the return of cancer in people with early stage lung cancer that had been removed with surgery. So far the studies have not proven that erlotinib after surgery leads to improved chance of cure. There are studies being done in Asia and the United States though to explore that question.

For patients who have the ALK gene rearrangement (most common in lung cancer patients who have never smoked), the drug crizotinib is now available to be given either after completion of chemotherapy in patients with metastatic non-small cell lung cancer, or before the chemotherapy is started.[19] Most recently a study proved that crizotinib works better than chemotherapy as the first treatment in patients with the ALK gene rearrangement in their tumor.[42] In 2014 the drug ceritinib (LDK378) was approved in the United States for patients with tumors with ALK gene rearrangements whose tumor was growing after the use of crizotinib.[43] There are now many other drugs being developed for use in ALK+ lung cancer.

Other mutations that can be the driving force behind lung cancer and offer other treatment options if they are found are also being investigated.

Many other gene changes that can lead to lung cancer have been discovered in the past few years.[44] Some of these are also known to be cancer causing in other cancers like melanoma (BRAF mutations) and many have other targeted therapy available (HER2 mutations). Regardless of smoking status, the gene mutation profile of a lung cancer is now important for deciding on the best treatment. The gene mutations that have specific therapies are more common in cancer in never smokers.

Conclusions

Lung cancer can happen to anybody, whether or not that person has ever smoked. Though, overall, lung cancer is very similar in patients whether or not they have a history of smoking, there are some differences. These include the types of people with the disease (never-smokers with lung cancer are more likely to be women, Asian, or Hispanic and potentially younger), and the type of lung cancer (adenocarcinoma is more common in never-smokers).

Some causes of lung cancer other than smoking have been identified, including second-hand smoke, radon exposure, cooking fumes, family history, and others. We know that patients with the disease who are never-smokers are more likely to have mutations in the EGFR gene, ALK gene rearrangements or other gene changes in the tumor that can change treatment plans. Patients who have specific EGFR gene changes have a better response to EGFR blocking drugs like erlotinib and afatinib, and patients with the ALK gene rearrangement usually respond well to crizotinib or ceritinib. Further research will provide more information about the cause of this type of lung cancer and how to best treat patients with this illness. People who want to know more about this topic can look at recent reviews that have been written for doctors.[7,45]

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69-90.
2. Wakelee HA, Chang ET, Gomez SL, et al. Lung cancer incidence in never smokers. *J Clin Oncol.* 2007;25:472-8.
3. Boffetta P, Järvholm B, Brennan P, et al. Incidence of lung cancer in a large cohort of non-smoking men from Sweden. *Int J Cancer.* 2001;94:591-3.
4. Thun MJ, Henley SJ, Burns D, et al. Lung cancer death rates in lifelong nonsmokers. *J Natl Cancer Inst.* 2006;98:691-9.
5. Peto R, Darby S, Deo H, et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ.* 2000;321:323-9.
6. Kawaguchi T, Matsumura A, Fukai S, et al. Japanese ethnicity compared with Caucasian ethnicity and never-smoking status are independent favorable prognostic factors for overall survival in non-small cell lung cancer: a collaborative epidemiologic study of the National Hospital Organization Study Group for Lung Cancer (NHSGLC) in Japan and Southern California Regional Cancer Registry databases. *J Thorac Oncol.* 2010;5:1001-10.
7. Subramanian J, Govindan R. Lung cancer in 'Never-smokers': a unique entity. *Oncology* (Williston Park). 2010;24:29-35.

8. Ou SI, Ziogas A, Zell JA. Epidemiology study of people who have never smoked with non-small cell lung cancer (NSCLC): High percentages of Asian and Hispanic female people who have never smoked and the significance of Asian ethnicity. *J Clin Oncol.* 2008;26:425s (Abstr #8004).
9. Epplein M, Schwartz SM, Potter JD, et al. Smoking-adjusted lung cancer incidence among Asian-Americans (United States). *Cancer Causes Control.* 2005;16:1085-90.
10. Gomez SL, Chang ET, Shema SJ, et al. Survival following non-small cell lung cancer among Asian/Pacific Islander, Latina, and Non-Hispanic white women who have never smoked. *Cancer Epidemiol Biomarkers Prev.* 2011;20:545-54.
11. Sonobe M, Manabe T, Wada H, et al. Mutations in the epidermal growth factor receptor gene are linked to smoking-independent, lung adenocarcinoma. *Br J Cancer.* 2005;93:355-63.
12. Kosaka T, Yatabe Y, Endoh H, et al. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res.* 2004;64:8919-23.
13. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. *N Engl J Med.* 2005;353:133-44.
14. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A.* 2004;101:13306-11.
15. Pham D, Kris MG, Riely GJ, et al. Use of cigarette-smoking history to estimate the likelihood of mutations in epidermal growth factor receptor gene exons 19 and 21 in lung adenocarcinomas. *J Clin Oncol.* 2006;24:1700-4.
16. Tam IY, Chung LP, Suen WS, et al. Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. *Clin Cancer Res.* 2006;12:1647-53.
17. Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. *Clin Cancer Res.* 2009;15:5216-23.
18. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol.* 2009;27:4247-53.
19. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* 2010;363:1693-703.
20. Brenner DR, Hung RJ, Tsao MS, et al. Lung cancer risk in never-smokers: a population-based case-control study of epidemiologic risk factors. *BMC Cancer.* 2010;10:285.
21. Wu A. Carcinogenic effects, in Shopland DR, Zeise L, Dunn A (eds): Health Effects of Exposure to Enrironmental Tobacco Smoke. Bethesda, MD, National Cancer Institute, 1999.
22. Vineis P, Alavanja M, Buffler P, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst.* 2004;96:99-106.
23. Vineis P, Hoek G, Krzyzanowski M, et al. Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health.* 2007;6:7.
24. Kleinerman RA, Wang Z, Wang L, et al. Lung cancer and indoor exposure to coal and biomass in rural China. *J Occup Environ Med.* 2002;44:338-44.
25. Krewski D, Lubin JH, Zielinski JM, et al. A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health A.* 2006;69:533-97.
26. Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ.* 2005;330:223.
27. Alberg AJ, Brock MV, Samet JM. Epidemiology of lung cancer: looking to the future. *J Clin Oncol.* 2005;23:3175-85.
28. Gottschall EB. Occupational and environmental thoracic malignancies. *J Thorac Imaging.* 2002;17:189-97.
29. Neuberger JS, Field RW. Occupation and lung cancer in nonsmokers. Rev *Environ Health.* 2003;18:251-67.
30. Chen CL, Hsu LI, Chiou HY, et al. Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan. *JAMA.* 2004;292:2984-90.
31. Ferreccio C, González C, Milosavjlevic V, et al. Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology.* 2000;11:673-9.
32. Wakai K, Ando M, Ozasa K, et al. Updated information on risk factors for lung cancer: findings from the JACC Study. *J Epidemiol.* 2005;15 Suppl 2:S134-9.

33. Feskanich D, Ziegler RG, Michaud DS, et al. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *J Natl Cancer Inst.* 2000;92:1812-23.
34. Galeone C, Negri E, Pelucchi C, et al. Dietary intake of fruit and vegetable and lung cancer risk: a case-control study in Harbin, northeast China. *Ann Oncol.* 2007;18:388-92.
35. Gorlova OY, Weng SF, Hernandez L, et al. Dietary patterns affect lung cancer risk in never smokers. *Nutr Cancer.* 2011;63:842-9.
36. Cheng YW, Chiou HL, Sheu GT, et al. The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. *Cancer Res.* 2001;61:2799-803.
37. Wu AH, Fontham ET, Reynolds P, et al. Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. *Am J Epidemiol.* 1996;143:535-42.
38. Brownson RC, Alavanja MC, Caporaso N, et al. Family history of cancer and risk of lung cancer in lifetime non-smokers and long-term ex-smokers. *Int J Epidemiol.* 1997;26:256-63.
39. Gorlova OY, Zhang Y, Schabath MB, et al. Never smokers and lung cancer risk: a case-control study of epidemiological factors. *Int J Cancer.* 2006;118:1798-804.
40. Bailey-Wilson JE, Amos CI, Pinney SM, et al. A major lung cancer susceptibility locus maps to chromosome 6q23-25. *Am J Hum Genet.* 2004;75:460-74.
41. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361:947-57.
42. Mok T, Kim DW, Wu YL, Solomon BJ, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, et al. First-line crizotinib versus pemetrexed-cisplatin or pemetrexed-carboplatin in patients with advanced ALK-positive non-squamous non-small cell lung cancer: Results of a phase III study (Profile 1004) Proceeding of ASCO 2014, abstr 8002
43. Shaw AT et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014 Mar 27;370(13):1189-97
44. (Zhang Y, Sun Y, Pan Y, et al. Frequency of Driver Mutations in Lung Adenocarcinoma from Female Never-Smokers Varies with Histologic Subtypes and Age at Diagnosis. Clinical Cancer Research 2012;18:1947-1953)
45. Rudin CM, Avila-Tang E, Harris CC, et al. Lung cancer in never smokers: molecular profiles and therapeutic implications. *Clin Cancer Res.* 2009;15:5646-61.

Chapter

11

How to Quit Smoking Confidently and Successfully

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Introduction

Smoking cessation (quitting smoking) is one of the best things we can do to help our bodies protect us from disease, fight illness, undergo treatment, and help our bodies heal. Research shows that 70% of people who smoke want to quit and that 41% of smokers have tried to quit for at least one day in the past year. [1] There are many reasons why people want to quit smoking and better health is often at the top of the list.[2] Unfortunately, many people who actively smoke have had many quit attempts that were unsuccessful; this can be discouraging and it can prevent people from trying to quit again.

It can be difficult to know how to approach quitting smoking, find the support you need, and be successful in quitting for good. The content in this chapter will give you the key information you need to understand how nicotine dependence occurs, what happens when you stop nicotine, how to avoid the unpleasant symptoms of nicotine withdrawal, and most importantly, how to quit smoking safely and effectively.

Chemicals in Cigarettes

Cigarettes contain tobacco and up to 7,000 other ingredients, including many that are harmful to our health.[3] When smoking a cigarette, toxic gases including carbon monoxide (which is poisonous) and chemicals, such as tar, are inhaled and build up in the blood.[4] These gases and chemicals are circulated throughout the body and cause damage to the body's cells. Additionally, cigarettes contain nicotine. Nicotine is the notable ingredient that causes physical and mental dependence and makes it so hard to quit smoking.[5]

How Nicotine Affects the Brain

When a cigarette is smoked, the gas and chemicals are inhaled into the lungs. These substances quickly travel from the lungs into the arterial blood and the left side of the heart. The left side of the heart moves the oxygenated blood out to the body and straight to the brain. The transfer of nicotine, from the time a puff is inhaled from a cigarette to the time it is delivered to the brain, occurs quickly, within three to ten seconds.

Nicotine is clever in how it works in the brain. It easily attaches to a receptor in the brain called the nicotinic acetylcholine receptor. Everyone has these receptors in the brain but for smokers, these receptors are stimulated by nicotine in a way that the non-smoker does not experience. When the nicotine attaches to the receptor, neurotransmitters (chemicals that your body makes) are released from that receptor. Dopamine is the most dominant neurotransmitter released when nicotine is consumed. This chemical stimulates the reward center in the brain and makes it happy, creating a pleasurable experience. Dopamine also enhances levels of energy and concentration, stabilizes mood, and suppresses appetite. The instant gratification and other positive side effects are all reasons why people continue to smoke.[5]

Why Nicotine Withdrawal Happens

The more cigarettes smoked, the more circulating nicotine is present and attaches to the nicotinic acetylcholine receptors. This results in higher dopamine levels in the brain. Nicotine begins losing its stimulating effects soon after it is inhaled and is gone within two hours. When the nicotine is metabolized and disappears in the body/brain, the receptors are empty, the dopamine levels drop, and the receptors start begging for more nicotine; this is when withdrawal symptoms kick in and there is an urge to smoke.

Identifying Nicotine Withdrawal Symptoms

The physical and mental changes that people experience when their nicotine levels drop can be difficult to cope with for many reasons. Most of the withdrawal experience is due to the drop in dopamine levels in the brain. Withdrawal symptoms can occur with any changes in the use of nicotine including missing a cigarette, cutting back on typical intake of nicotine, or stopping the use of nicotine all together. These symptoms, their intensity, and their frequency vary from person to person and directly relate to the amount of nicotine previously used.[4]

Common symptoms of withdrawal include anxiety, irritability, agitation, and a drop in mood or even depression. People also experience disturbance in their sleep, difficulty with concentration, changes in bowel function, increased appetite, and urges to smoke.[4] These symptoms are unpleasant and, if not prevented or treated, will cause a very strong urge to smoke again. Replenishing nicotine by having just one cigarette will ease or eliminate these

symptoms and this is why people often revert to smoking, because it makes the symptoms of withdrawal go away, almost instantly.

When quitting smoking, staying away from cigarettes is the most important part of both short-term and long-term success in staying quit. There are methods of quitting smoking that are proven to minimize and even prevent the unpleasant and detrimental symptoms of withdrawal from nicotine.

What it Takes to Quit Successfully

There are many ways to quit smoking and stay quit. People are able to quit on their own but it can be a challenge to do this alone. You will have much more success if you get support and counsel from a health care professional or a specialist trained in how to quit smoking. Using nicotine replacement therapy and/or a prescription medication to quit at least doubles the chances of long-term success and in some cases even quadruples the chances of quitting for good.[5-7]

Options for Quitting Smoking: Nicotine and Non-Nicotine Therapy

Understanding the way nicotine affects the brain and how withdrawal occurs is important when quitting smoking. Moreover, knowing how to minimize and even prevent withdrawal symptoms is vital in successfully quitting. The following are descriptions of what is available to help people quit smoking and practical approaches to using these methods in quitting.[8]

Nicotine Replacement Therapy
Nicotine replacement can be a very effective approach to quitting smoking because the body absorbs the nicotine in the blood stream and finds its way to the brain but toxic chemicals are not being inhaled in your lungs. When nicotine reaches the brain, it attaches to the nicotinic acetylcholine receptors and releases dopamine. Nicotine replacement therapy mimics having a cigarette and delivers nicotine to the brain, preventing and treating withdrawal symptoms.[5]

The most important thing to remember when using nicotine replacement therapy is to be sure to get enough nicotine replacement; if not used properly, it will not work for you. Often people feel that the patch, gum, or lozenge did not work for them and this is usually because they were not getting enough replacement of nicotine to prevent symptoms of withdrawal. Getting enough nicotine with a combination of the long-acting patch and a short-acting method will make quitting smoking much easier and provide a smoother transition off cigarettes.

Transdermal patch, a long-acting nicotine replacement:
Nicotine replacement is available in a patch that delivers nicotine continuously over 24 hours.[7] The patch is considered a long-acting delivery method because it sends a

steady amount of nicotine through your skin to the blood then the brain. It is important to dose the patch according to how many cigarettes are smoked in a day so that you get enough nicotine. A cigarette is equal to about 1mg of nicotine and the patch should be dosed 1mg for every cigarette smoked in a typical day. Choosing the right dosed patch will give an optimal delivery of nicotine to the brain and minimize or prevent withdrawal symptoms.[6,8,9]

Patch Dosing Recommendation[9]

< 10 cigarettes/day (< 1/2 pack per day)	**7mg patch**
10 or more cigarettes/day (> 1/2 pack per day)	**14mg patch**
20 cigarettes/day (1 pack per day)	**21mg patch**
➢ **20 cigarettes/day**	**Dose patch to the number of cigarettes smoked per day with the guidance of your health care provider**

The patch should be changed every 24 hours. It is recommended to use the initial patch dose for one full month and then step down the patch doses every 2-4 weeks until off the lowest dose.

Example: If you start the regimen at 21 mg, use this dose every day for 4 weeks, then step down to a 14mg patch for 2-4 weeks, then step down to a 7mg patch for 2-4 weeks, and then stop.[9] In this example, you would use a patch for a total of 8-12 weeks (2-3 months) after you quit smoking; this ensures a smooth landing in getting off nicotine safely and effectively. <u>You should know that this is longer than many people think they need to use patches.</u>

S**hort-acting nicotine replacement:**
Nicotine replacement is available in several forms of short-acting delivery methods. These short-acting doses of nicotine are very important in the success of using nicotine replacement therapy in quitting smoking. Even if you use the transdermal patch for continuous nicotine replacement, you may have urges to smoke and withdrawal symptoms. Treating these cravings with one of the following four options of nicotine replacement is one of the most effective ways to avoid lapsing or relapsing with a cigarette.

Nicotine Gum – the gum is available in 2mg and 4 mg doses. It is important to know that the gum only works if it is absorbed through the mucosal gum lining of your mouth. The best way to use the gum is to start with the lower dose first, chew it until there is a peppery/spicy, tingly sensation, then park it between the gum and cheek for 5 minutes. Then chew it again until there is another sensation and park it. Continue this cycle for 30 minutes in order to get all the dose of nicotine the gum has to offer. It is safe to chew up to 20 pieces of gum a day for breakthrough cravings and withdrawal symptoms. [6,8,9] This product is available over the counter.

How to Make the Gum Work Best for You - If the nicotine gum is chewed like a regular stick of chewing gum and you swallow the nicotine, you may experience nausea or indigestion and the nicotine will not be absorbed in your stomach. You will not absorb the nicotine because of the acid in the stomach. Also, avoid carbonated drinks and acidic foods and beverages before and during use of the nicotine gum because these too will destroy the nicotine in the gum.[9]

Nicotine Lozenge – The lozenge is similar to the nicotine gum. It is available in 2mg and 4mg doses and, like the nicotine gum, the lozenge needs to be between tucked between the gum lining of the mouth and cheek to be absorbed. The standard starting dose is the 2mg lozenge, which delivers the equivalent of nicotine in one cigarette. Like the nicotine gum, avoid acidic foods or beverages right before use and when a lozenge is in the mouth. This product is also available over the counter.[6,8,9]

Nicotine Nasal Spray – The nasal spray contains nicotine that is delivered through the mucosal wall of the nose. When using it, it is important to spray it against the nasal wall and NOT inhale it into the upper region of the nasal passages. One spray in each nostril delivers a similar dose of one cigarette. This product is available by prescription only.[6,8,9]

Nicotine Inhaler – The nicotine inhaler is a popular method of short-acting nicotine delivery for people who have a strong attachment to the ritual of holding and handling a cigarette. Although this is called an "inhaler", the nicotine delivery is taken in by puffing on the inhaler, not taking a deep inhalation, or "drag", as would be done with a cigarette. The nicotine is absorbed through the mucosa of the mouth so it is important to only inhale or puff the medication into the mouth (not the lungs) for optimal absorption. This product is available by prescription only [6,8,9] and is different from an e-Cigarette, which is discussed later in this chapter. ***Your pharmacist can teach you how to use an inhaler.***

Non-Nicotine/Prescription Medication Therapy Options

Bupropion SR

Bupropion SR is a long acting prescription medication that is commonly used to help people quit smoking. It has shown to double the success rates in quitting smoking and works well with the nicotine replacement therapies. It is also known as "Zyban" and "Wellbutrin".

Some people are hesitant to take this medication because they have heard that it is used for depression and do not want to take an "antidepressant". It is true, bupropion is used for depression because it allows more of the neurotransmitters, dopamine and norepinephrine, to circulate in the brain.

Remember that nicotine drives the dopamine levels up and this is why the brain experiences a mood elevation when smoking. When the dopamine levels drop with

the withdrawal of nicotine, the brain can experience agitation, anxiety, and depressive mood changes. Bupropion helps in the transition off cigarettes/nicotine because it allows more dopamine to circulate and the brain does not experience an abrupt withdrawal off the dopamine. It reduces the craving for cigarettes, helps with the anxiety of quitting smoking, and often suppresses appetite and controls weight gain associated with quitting smoking.[4-6,9] Talk to your healthcare provider to determine if bupropion is the right medication for you.

Varenicline

Varenicline is a prescription medication that is commonly used to help people quit smoking. Varenicline has shown an increased success rate in quitting smoking of up to four fold.[9] It is also known as "Chantix".

This medication works by attaching to the nicotinic acetylcholine receptors in the brain and causes the same release of dopamine that nicotine does. This medication mimics the presence and action of nicotine and tricks the brain into thinking it has nicotine on board.[4-6,9] Because of the way this medication mimics the presence of nicotine and attaches to the nicotinic acetylcholine receptors in the brain, you would not benefit from using nicotine replacement therapies; Varenicline should be used alone.

This medication reduces the craving for nicotine and reduces withdrawal symptoms. Some people are hesitant to take this medication because they have heard of potential side effects including vivid dreams. Talk to your healthcare provider to determine if Varenicline is the right medication for you.

In-Person Counseling and Quitting Smoking

Nicotine replacement therapy and non-nicotine medication therapies clearly show effectiveness in helping people quit smoking, long-term. There is also strong scientific evidence that shows formal counseling sessions added to either nicotine replacement therapy or non-nicotine medication therapy greatly enhances the sustained success rates of quitting smoking. The more counseling sessions that a person is involved with, the higher the success rate.[6] The counseling could simply be talking to someone in your health care provider's office.

Alternative Approaches to Quitting

There are many alternative approaches and treatments to helping quit smoking. People use these therapies for added control of withdrawal symptoms. Some of the more common methods are acupuncture, hypnosis, and herbal preparations. These approaches have not been widely studied. Currently, research does not show these methods are effective in long-term success in quitting smoking. However, many people have success using them, especially when combined with other evidence-based therapies, as discussed in this chapter.

Web-based On-line support

There are web-based smoking cessation resources on the internet. These online resources provide support and counseling options. There is not a lot of existing evidence that these resources are highly effective when used as the only approach to quitting smoking. However, using them in combination with nicotine replacement and/or non-nicotine therapy likely has a much greater chance of success in quitting.

American Lung Association/Freedom From Smoking
www.ffsonline.org

U.S. Department of Health and Human Services
www.smokefree.gov

Become An Ex
www.becomeanex.org

Healthways
www.quitnet.com

Quit Lines

There are telephone-quit lines available in most states. The services they offer vary depending on the funding for that program, but they typically provide telephone counseling by trained quit coaches plus follow-up telephone calls. The counselors are trained in helping people quit smoking and can assist in making a personalized quit plan. They will provide educational resources and many will mail nicotine replacement therapy, including the long-acting nicotine patch and either the gum or lozenge, free of charge. With a prescription, some are also able to offer medications like Zyban (Bupropion) and Chantix (Varenicline) at reduced cost.

The quit line specific to any state in the U.S. or any of the Canadian provinces can be located by calling the North American Quitline Consortium (NAQC) at 1-800-QUIT-NOW or by visiting their website at http://www.naquitline.org. You can also find out about local resources through your local public health department or by searching online using your specific state or city and "quit smoking" as keywords.

Many employers, especially large employers, have contracts with a professional quit line service that employees, and even family members of employees, can benefit from. The services and resources they provide are similar to the public quit lines. Call your Human Resources department at your job to see if they provide this benefit.

Support Groups

Support groups are often available through local community centers, medical centers, hospitals, public health departments, and local chapters of the American Lung Association and American Heart Association. Someone trained in tobacco cessation counseling usually runs these groups. The support groups can be a good way to connect with other people who are working on quitting, gather tips and ideas about how to quit successfully, and find much needed support when trying to quit and staying quit for good.

Electronic Cigarettes (e-Cigarettes)

Many people are asking about the use of electronic cigarettes, also known as e-Cigarettes, as a replacement for conventional cigarettes or as aids in quitting smoking. Electronic cigarettes are battery-operated devices that deliver nicotine and other chemicals to the body through an inhaled vapor rather than a combustible gas. Some people feel that electronic cigarettes may be safer for your health because you do not "light up" or create combustible gases while using them. There is no data to suggest that electronic cigarettes are effective in quitting smoking, in fact they may contribute to sustained dependence on nicotine and smoking cigarettes, making it difficult to quit smoking. These products and their ingredients are not currently regulated and monitored by the Federal Food and Drug Administration. Therefore, the safety of electronic cigarettes is not known and using them is not recommended at this time.[10-13]

How to Deal with Lapses and Relapses

When quitting smoking it is common to experience a lapse in the quit attempt. A lapse is when a single or a few cigarettes are smoked. A relapse is when regular smoking is resumed and lasts longer than seven days. It often occurs when people encounter strong triggers for smoking including stressful situations or events.[4] This can also occur if treatment is stopped too soon.

Lapses and relapses are sometimes part of the road to success in quitting long-term.[6] When a lapse or relapse occurs, people often feel bad about this disruption in the success of their quit attempt. In either case, it is possible to successfully resume the quit attempt. This can be done by returning to the approaches and methods that helped quit in the first place. Avoid negative talk to yourself or others who have had a lapse or relapse and remember to avoid triggers and focus on previous success and the goal of quitting for good.

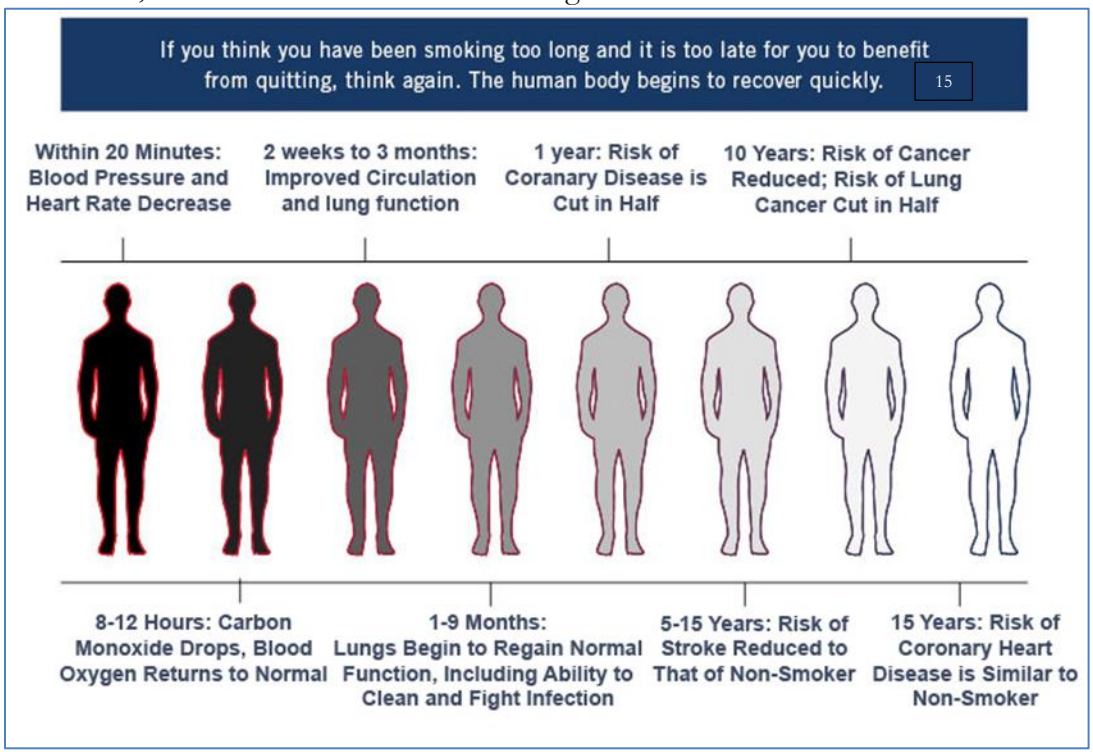
Identifying Triggers to Use Tobacco

When quitting smoking, it is important to address your lifestyle, rituals, and behaviors that are associated with smoking. Make a list of activities, people, or things that trigger the urge to have a

cigarette. Be aware of these triggers and, if possible, make a plan to avoid them by restructuring your daily routines. Tell people close to you or those you encounter frequently that you are quitting smoking; this will help them, help you, in your efforts.

Conclusion

Quitting smoking is one of the best actions you can take to protect your health. Quitting helps your body prepare for medical treatment, improves your chances for optimal response to treatment, and enhances your ability to heal following surgery.[14] Regardless of how long you have smoked, quitting smoking has immediate and long-term health benefits; it is never too late to quit.[4] It can be difficult to quit, but with the right tools and knowledge about the best and most effective approaches to quitting smoking, quitting successfully with confidence, is a more realistic and obtainable goal.



References

1. Orleans CT. Increasing the demand for and use of effective smoking-cessation treatments reaping the full health benefits of tobacco-control science and policy gains--in our lifetime. *Am J Prev Med.* 2007;33(6 Suppl):S340-8.
2. Lee CW, Kahende J. Factors associated with successful smoking cessation in the United States, 2000. *Am J Public Health.* 2007;97(8):1503-9.
3. Centers for Disease Control and Prevention. Chemicals in tobacco smoke. 2014 [August 12, 2014]; Available from: http://www.cdc.gov/tobacco/data_statistics/sgr/2010/consumer_booklet/chemicals_smoke/.
4. McEwen A. Manual of smoking cessation : a guide for counsellors and practitioners. Oxford ; Malden, MA: Blackwell Pub.; 2006.
5. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane database ofsystematic reviews.* 2013;5:CD009329.
6. U.S. Department of Health & Human Services. Treating Tobacco Use and Dependence: 2008 Update: Public Health Service; 2008.
7. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. *Cochrane database of systematic reviews.* 2012;11:CD000146.
8. Pharmacotherapy for smoking cessation in adults [database on the Internet]. Up To Date. 2014 [cited August 4, 2014].
9. Burke MV, Ebbert JO, Hays JT. Treatment of tobacco dependence. Mayo *Clin Proc.* 2008;83(4):479-83.
10. American Cancer Society. Electronic cigarettes (e-cigarettes). *CA Cancer J Clin.* 2014;64(3):169-70.
11. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet.* 2013;382(9905):1629-37.
12. Schraufnagel DE, Blasi F, Drummond MB, Lam DC, Latif E, Rosen MJ, et al. Electronic cigarettes. A position statement of the forum of international respiratory societies. *Am J Respir Crit Care Med.* 2014;190(6):611-8. Epub 2014/07/10.
13. United States Food and Drug Administration. Electronic Cigarettes (e-Cigarettes). 2014 [09/15/2014]; Available from: http://www.fda.gov/newsevents/publichealthfocus/ucm172906.htm.
14. de Hoyos A, Southard C, DeCamp MM. Perioperative smoking cessation. *Thoracic surgery clinics.* 2012;22(1):1-12.
15. Nevada Tobacco Users Help-line. The good news about quitting. 2014 [August 4, 2014]; Available from: http://www.livingtobaccofree.com/Default.aspx?id=TheGoodNewsAboutQuitting.

Lung Cancer Choices Resource Directory

American Cancer Society
The American Cancer Society (ACS) offers programs that help cancer patients, family members, and friends cope with the treatment decisions and emotional challenges they face.
Telephone: 1-800-492-0329
Internet site: http://www.cancer.org

Brain Tumor Society
The Brain Tumor Society is a national non-profit agency that provides information about brain tumors and related conditions for patients and their families. Financial assistance is given through the agency's BTS CARES Financial Assistance Program. This program provides supplementary financial assistance to individuals experiencing financial need. This program covers specific nonmedical costs related to a primary brain tumor diagnosis. Direct medical expenses are not covered.
Telephone: 1-800-770-8287
Internet site: http://www.tbts.org

CancerCare
CancerCare is a national non-profit agency that offers free support, information, financial assistance, and practical help to people with cancer and their loved ones. Financial assistance is given in the form of limited grants for certain treatment expenses.
Telephone: 800-813-4673
Internet site: http://www.cancercare.org/get_help/assistance/cc_financial.php

Chronic Disease Fund (CDF)
The Chronic Disease Fund is an independent 501(c)(3) non-profit charitable organization that helps underinsured patients with chronic disease, cancers or life-altering conditions obtain the expensive medications they need.
Telephone: (972) 712-0201
Internet site: http://cdfund.org/

The Healthwell Foundation
The HealthWell Foundation® is a non-profit, charitable organization that helps individuals afford prescription medications they are taking for specific illnesses. The Foundation provides financial assistance to eligible patients to cover certain out-of-pocket health care costs.
Telephone: 800-675-8416
Internet site: http://www.healthwellfoundation.org

Partnership for Prescription Assistance
The Partnership for Prescription Assistance brings together America's pharmaceutical companies, doctors, other health care providers, patient advocacy organizations and community groups to help qualifying patients who lack prescription coverage get the medicines they need through the public or private program that's right for them. Many will get them free or nearly free.
Telephone: 1-888-477-2669
Internet site: https://www.pparx.org/about.php

Patient Access Network Foundation (PANF)
Patient Access Network (PAN) Foundation is an independent, not-for-profit foundation established in 2004, dedicated to assisting patients who cannot afford the out-of-pocket costs associated with their treatment needs. With 20 disease-specific funds, PAN assists the underinsured in accessing health care treatments.
Telephone: 866-316-PANF (7263)
Internet site: http://www.patientaccessnetwork.org

Patient Advocate Foundation
Patient Advocate Foundation is a national non-profit organization that seeks to safeguard patients through effective mediation assuring access to care, maintenance of employment, and preservation of their financial stability relative to their diagnosis of life threatening or debilitating diseases.
Telephone: 1-800-532-5274
Internet site: http://www.patientadvocate.org/

Pharmaceutical Company Patient Assistance Programs

Some pharmaceutical companies offer prescription drug programs to make specific drugs available to people who could not otherwise afford them. Generally, your doctor must apply to these programs on your behalf. However, you can call and obtain the applications and information to help speed the process. Eligibility requirements and program operations vary greatly from one program to another.

Following are listings of pharmaceutical company patient assistance programs for some of the drugs commonly used by people with lung cancer.

Amgen, Inc.
Amgen's patient assistance programs are a continuum of services designed to provide access through free goods and other support services to qualifying uninsured and underinsured patients. In addition, Amgen makes donations to third-party co-pay assistance foundations. To enroll, please call the appropriate hotline number listed below.
Telephone: 1-800-272-9376
Internet site: http://www.amgen.com/patients/assistance.html

Sanofi-aventis
The Sanofi-aventis patient assistance program offers free medication to people who otherwise cannot afford their medications. Patients must meet financial and other program-specific criteria to be eligible for assistance. To find out how to apply for medication assistance from the Sanofi-aventis patient assistance program, register for free at http://www.RxAssist.org.

Bayer Corporation
The Bayer Healthcare Pharmaceuticals patient assistance program offers free medication to people who otherwise cannot afford their medications. Patients must meet financial and other program specific criteria to be eligible for assistance. To find out how to apply for medication assistance register for free at http://www.RxAssist.org.

Bristol-Myers Squibb Company
The Bristol-Myers Squibb Patient Assistance Foundation, Inc. is a non-profit organization. The Foundation was established in 1998 to provide temporary assistance to qualifying patients with a financial hardship who generally have no private prescription drug insurance and are not enrolled in a prescription drug coverage plan through Medicaid or any other federal, state, or local health program.
Telephone: 1-800-736-0003
Interent site: http://www.bmspaf.org/

Eli Lilly and Company
Lilly Oncology
For Gemzar® and Alimta®, Lilly provides assistance with obtaining reimbursement. If patients do not have insurance and are unable to obtain other financial assistance, they may be eligible to obtain Lilly oncology products through the patient assistance program. For information about obtaining reimbursement assistance and patient assistance, visit the Gemzar or Alimta websites.
Gemzar: http://gemzar.com/hcp/reimbursement.jsp?reqNavid=7.3
Alimta: http://www.alimta.com/professionals/reimbursement.jsp?reqNavId=5.3

Food and Drug Administration (FDA), Single Patient Investigational New Drug Program
Patients who are not eligible for a clinical trial and who are in an immediate medical crisis may be able to receive drugs that are not yet FDA-approved. Your doctor would have to apply to the FDA for permission to use the drug, an approval known as a Single Patient IND for Compassionate or Emergency Use. Contact information appears below. The FDA usually responds to an application within 24 to 48 hours.
Telephone: CDER Oncology Drug Products (most cancer drugs): 301-594-2473
CBER Oncology Branch (for biologicals): 301-827-5093
Internet site: www.fda.gov/cder/cancer/singleIND.htm

Genentech, Inc.
Genentech Access Solutions helps patients access their medicines and explore possible solutions to coverage or reimbursement issues. For patients and their healthcare providers, Genentech Access Solutions provides: coverage and reimbursement, patient assistance, and informational resources. Call (866) 4 ACCESS / (866) 422-2377 between the hours of 6 a.m. and 5 p.m. PST Monday through Friday or 24/7 through our website
https://www.genentechaccesssolutions.com/index_pc.jsp

GlaxoSmithKline (GSK)
"GSK For You" features information on patient assistance programs from other resources, too. Please browse the Internet site to see if you may be eligible to save on your prescription drugs.
Telephone: 1-888-825-5249
Internet site: http://www.gskforyou.com/index.htm

Merck & Company, Inc.
Merck Patient Assistance Program
This private and confidential program provides medicine free of charge to eligible individuals, primarily the uninsured.
Telephone: 1-800-727-5400
Internet site: http://www.merck.com/merckhelps/patientassistance/home.html

Novartis Pharmaceuticals
Novartis Oncology Reimbursement Program
PAP Enrollment
The Novartis Pharmaceuticals Corporation's Patient Assistance Program (PAP) provides assistance to patients experiencing financial hardship who have no third party insurance coverage for their medicines.
Telephone: 1-800-277-2254
Internet site: http://www.pharma.us.novartis.com/about-us/our-patient-caregiver-resources/index.jsp

Ortho Biotech Products
The OrthoBiotech Products patient assistance program offers free medication to people who otherwise cannot afford their medications. Patients must meet financial and other program specific criteria to be eligible for assistance. To find out how to apply for medication assistance from the OrthoBiotech Products register at http://www.RxAssist.org.

Pharmacia Corporation
TreatFirst is a reimbursement counseling and patient assistance program for Pharmacia Corporation's single-source oncology and supportive care therapy products. The program is designed to provide reimbursement support and assist patients who are financially needy, receiving outpatient care in the US by a US physician.
Telephone: 1-877-744-5675
Internet site: http://www.patientsinneed.com/general_info.asp

Purdue Pharma
The Purdue Pharma patient assistance program offers free medication to people who otherwise cannot afford their medications. Patients must meet financial and other program specific criteria to be eligible for assistance. To find out how to apply for medication assistance from the Purdue Pharma patient assistance program, at http://www.RxAssist.org.

Lung Cancer Choices Glossary

A

abnormality (ab-nohr-MAL-uh-tee): A growth or area of tissue that is not normal. An abnormality may or may not be cancer or likely to become cancer.

adenocarcinoma (ADD-in-oh-kar-sin-OH-muh): A type of non-small cell lung cancer. Types of lung cancer are determined by the type of cells in the cancer.

adjuvant therapy (ADD-joo-vent THAIR-uh-pee): Treatment given after the main treatment to help cure a disease.

alcohol (AL-kuh-hall): Wine, beer, or liquor (such as gin or whiskey).

antiangiogenesis therapy (AN-tee-an-jee-oh-JEN-uh-sis THAIR-uh-pee): Using drugs or other treatments to stop new blood vessels from forming in tumors to try to limit tumor growth.

antibodies (AN-tee-BAH-deez): Proteins in the body made by the immune system that fight infection and disease.

arsenic (AHR-sin-ik): A mineral that can occur naturally in rocks and soil, sometimes used as a poison used to kill weeds and pests. Arsenic is also used in some cancer treatments to kill cancer cells.

asbestos (ess-BEST-iss): A natural material that is made of tiny threads or fibers. The fibers can enter the lungs as a person breathes. Asbestos can cause many diseases, including cancer. Asbestos was used to insulate houses from heat and cold. It has also been used in car brakes, in shipyards, and for other purposes. Some old houses still have asbestos in their walls or ceilings.

B

beta-carotene (BAY-tuh KAYR-uh-teen): A vitamin found in orange, bright yellow, and dark green fruits and vegetables.

biological therapy (bye-uh-LAH-juh-kul THAIR-uh-pee): Treatment to boost the immune system's power to fight infections and other diseases. It can also be used to lessen side effects of some treatments. Also called immunotherapy, biotherapy, or biological response modifier (BRM) therapy.

biopsy (BY-ah-psee): To remove cells or tissues from the body for testing and examination under a microscope.

bladder (BLAD-ur): A small sac that holds urine before it passes from the body. The bladder is in the lower part of the belly.

bronchi (BRAHNK-eye): The large airways connecting the windpipe to the lungs. The single form is bronchus. See also bronchial carcinoma.

bronchial carcinoma (BRAHN-kee-yul kar-sin-OH-muh): Cancer that grows in the bronchi, which are the large airways connecting the windpipe to the lungs.

bronchoalveolar carcinoma (BRAHN-koh-al-vee-OH-lur kar-sin-OH-muh): Bronchoalveolar carcinoma (BAC) is a subtype of lung cancer. BAC tumors can be more diffuse (spread out) than other lung cancers.

bronchoscopy (brahn-KAH-skuh-pee): A way to look at the inside of the windpipe, the bronchi, and/or the lungs using a lighted tube. The tube is inserted through the patient's nose or mouth. Bronchoscopy may be used to find cancer or as part of some treatments.

C

cancer registry: A database of cancer cases including information about when they occurred, the type of cancer, and other information.

carcinogen (kar-SIN-uh-jin): Something that causes cancer.

carotenoids (kuh-RAH-tuh-noydz): Pigments made by plants that are commonly found in orange fruits and vegetables and some dark green vegetables. Some carotenoids are used to make vitamin A.

CAT scan: A set of detailed pictures of areas inside the body, taken from different angles. The pictures are made by a computer linked to an X-ray machine. Other names for a CAT scan are computerized axial tomography, computed tomography (CT scan), and computerized spiral (helical) CT scan.

cervical mediastinoscopy (SUR-vuh-kul MEE-dee-eh-stye-NAH-skuh-pee): A surgical procedure to examine the central area of the chest, called the mediastinum. (The heart, windpipe, bronchi, blood vessels, lymph nodes, and esophagus are found here.) The doctor makes a small incision (cut) in the neck to get to the mediastinum. Cervical mediastinoscopy can be used to help learn the stage of disease. It also helps doctors see if cancer has spread to the lymph nodes.

chemoprevention (KEE-moh-preh-VEN-shin): Using things such as drugs or vitamins to try to prevent or slow down cancer. Chemoprevention may be used to help keep someone from ever getting cancer. It is also used to help keep some cancers from coming back.

chemotherapy (KEE-moh-THAIR-up-ee): primarily refers to the treatment of cancer with an antineoplastic drug or with a combination of such drugs into a standardized treatment regimen.

chest radiograph: a picture of the inside of the chest, made with x-rays.

cholesterol (kuh-LES-tur-all): Cholesterol comes from many foods, especially animal products like meat, milk, and cheese. It is used to make hormones and for several other purposes. It also is made by the cells of the body.

chromium (KROH-mee-yum): A kind of metal that comes in different forms and is found in rocks and soil. Some forms are also produced during industrial processes. Chromium is also one of the chemicals found in cigarette smoke.

clinical trial: Process used to evaluate the effectiveness and safety of new medications, procedures, or medical devices by monitoring their effects on large groups of people; the testing usually required by the Food and Drug Administration before approving a new drug, procedure or medical device

> **phase 1 trial** – This is the first clinical trial for studying an experimental drug or treatment in humans. Phase 1 trials are usually small (10-100 people) and are used to determine safety and the best dose for a drug. These trials provide information about side effects, and how the body absorbs and handles the drug. People in these trials usually have advanced disease and have already received the best available treatment.
>
> **phase 2 trial** – Phase 2 trials examine whether a drug or therapy is active against the disease it is intended to treat. Side effects are studied. A phase 2 trial is a noncomparative study, meaning the therapeutic effects and side effects of the experimental treatment are not compared to another drug or a placebo.
>
> **phase 3 trial** – Phase 3 trials are conducted to find out how well a drug or therapy works compared to standard treatment or no treatment. Phase 3 trials are large studies and usually involve several hundred to thousands of patients.
>
> **controlled clinical trial** – A controlled clinical trial divides participants into study groups to determine the effectiveness and safety of a new treatment. One group receives the experimental treatment. The other group receives placebo (an inactive substance) or the standard therapy; this group is called the control group. Comparison of the experimental group with the control group is the basis of determining the safety and effectiveness of the new treatment.
>
> **randomized clinical trial** – A randomized clinical trial involves patients who are randomly (by chance) assigned to receive either the experimental treatment or the control treatment (placebo or standard therapy).

colon cancer (KOH-lin KAN-sur): Cancer that begins in the colon, or large intestine.

D

dosimetrists: carefully calculate the dose of radiation to make sure the tumor gets enough radiation. They develop a number of treatment plans that can best destroy the tumor while sparing the normal tissues. Many of these treatment plans are very complex. Dosimetrists work with the doctor and the medical physicist to choose the treatment plan that is just right for each patient. Many dosimetrists start as radiation therapists, and then, with very intensive training, become dosimetrists. Others are graduates of one-to-two-year dosimetry programs. The Medical Dosimetrist Certification Board certifies dosimetrists. (radiologyinfo.org)

dysphagia (dis-FAY-jee-yuh): Trouble swallowing.

dyspnea (DISP-nee-yuh): Shortness of breath.

E

EGFR inhibitors: Stands for epidermal growth factor receptor inhibitors. Epidermal growth factor is a protein in the body that stimulates some cells, including some cancer cells, to grow and multiply. EGFR inhibitors are a class of anti-cancer drugs. They work by blocking epidermal growth factor from stimulating cells to grow.

emphysema (em-fuh-ZEE-muh): A disease that affects the tiny air sacs in the lungs. Emphysema makes it harder to breathe. People who smoke have a greater chance of getting emphysema.

esophagitis (ee-SAH-fuh-JY-tis): Inflammation of the esophagus (the tube that carries food from the mouth to the stomach).

esophagus (eh-SAH-fuh-gus): The tube that carries food from the throat to the stomach.

evidence (EV-uh-dins): Information that is collected in an orderly way about a disease or its treatment. This information often comes from research. Evidence helps doctors and scientists understand what treatments work best on different diseases.

extensive stage SCLC: SCLC stands for small cell lung cancer. SCLC is usually staged as either "limited" or "extensive." Extensive SCLC is cancer that has spread beyond the lung to other parts of the body. See also oat cell and small cell lung cancer.

F

fibrosis (fy-BROH-sis): The growth of fibrous (resembling fibers) tissue.

first line therapy: The first course of treatment used against a disease.

G

gene (jeen): The basic unit of heredity. Genes decide eye color and other traits. Genes also play a role in how high a person's risk is for certain diseases. See also inherited.
gene therapy: Treatment that changes a gene. Gene therapy is used to help the body fight cancer. It also can be used to make cancer cells more sensitive to treatment.

Gray (Gy): The amount of radiation used in radiation therapy is measured in gray (Gy), and varies depending on the type and stage of cancer being treated.

H

hilar (HIGH-lar): Referring to the central portion of each lung where the bronchi, arteries, veins, and nerves enter and exit the lungs.

hypofractionation (HY-poh-FRAK-shuh-NAY-shun): Radiation treatment in which the total dose of radiation is divided into large doses and treatments are given less than once a day. Also called hypofractionated radiation therapy.

I

immune system (ih-MYOON SIS-tim): The complex group of organs and cells that defends the body against infections and other diseases.

infusion: the therapeutic introduction of fluid other than blood into a vein.

inherited (in-HAIR-uh-tid): Something that is passed on from parents to their children. When traits are passed on from one generation to the next, it is called heredity.

K

kidney (KID-nee): A bean-shaped organ that filters waste products from the body and forms urine that is passed into the bladder. Human beings are born with two kidneys, one on each side of the lower back.

L

large cell cancer: A type of non-small cell lung cancer where the cancer cells are large and abnormal.

larynx (LAIR-inks): Voice box. The larynx is part of the breathing system and is found in the throat.

limited stage small cell lung cancer (SCLC): SCLC stands for small cell lung cancer. SCLC is usually staged as either "limited" or "extensive." Limited stage generally means the cancer is found only in one lung and its nearby tissue. See also oat cell and small cell lung cancer.

linear accelerator (LIH-nee-er ak-SEH-leh-RAY-ter): A machine that uses electricity to form a stream of fast-moving subatomic particles. This creates high-energy radiation that may be used to treat cancer. Also called linac, mega-voltage linear accelerator, and MeV linear accelerator.

lobe: A part of an organ, such as the lung.

lobectomy (loh-BEK-tuh-mee): Surgery to remove a lobe of an organ.

low-dose CAT scan: A CAT scan that uses smaller amounts of X-rays than a regular CAT scan.

lymph nodes (LIMF nohdz): Small glands that help the body fight infection and disease. They filter a fluid called lymph and contain white blood cells.

M

mediastinum (mee-dee-uh-STYE-nim): The part of the body between the lungs. The heart, windpipe, esophagus, bronchi, and lymph nodes are found in this area.

medical physics: generally speaking the application of physics concepts, theories and methods to medicine. A medical physics department may be based in either a hospital or a university. Clinical medical physicists are often found in Diagnostic and Interventional Radiology, Nuclear Medicine, and Radiation Oncology.

mesothelioma (mez-uh-thee-lee-YOH-muh): A tumor in the lining of the chest or abdomen (stomach area).

metastasis (muh-TASS-tuh-sis): When cancer spreads to other parts of the body.

MRI (**M**agnetic **R**esonance **I**maging): A type of body scan that uses a magnet linked to a computer to make detailed pictures of areas inside the body. An MRI can be used to find cancer.

N

neoadjuvant therapy (NEE-oh-ADD-joo-vent THAIR-uh-pee): Treatment given before the main treatment to help cure a disease.

neutropenia (noo-truh-PEE-nee-yuh): An abnormal decrease in a type of white blood cells. The body needs white blood cells to fight disease and infection.

nickel (NIK-ul): A kind of metal found in soil and often used in alloys and in industry.

O

oat cell: Another name for small cell lung cancer. The name "oat cell" comes from the fact that the cells look like oats. See also extensive SCLC and limited SCLC.

oncologist (ahn-KAH-luh-jist): A doctor who specializes in studying and treating cancer.

ototoxicity (oh-tuh-tok-sis-i-tee): having a harmful effect on the organs or nerves concerned with hearing and balance.

P

pancreas (PAN-kree-yus): A large gland that helps digest food and also makes some important hormones.

pericarditis: Inflammation of the pericardium (the fibrous sac surrounding the heart).

peripheral neuropathy (puh-RIF-uh-rul noo-RAH-puh-thee): Numbness, tingling, burning, or weakness that usually begins in the hands or feet. Some anticancer drugs can cause this problem.

PET scan (**P**ositron **E**mission **T**omography **S**can): A PET scan is a way to find cancer in the body. In a PET scan, the patient is given radioactive glucose (sugar) through a vein. A scanner then tracks the glucose in the body. The scanner's pictures can be used to find cancer, since cancer cells tend to use more sugar than other cells.

phlegm (flem): Thick mucus from the airways of the body.

pleura (PLOO-rah): The thin lining that covers the lungs and the inside of the chest wall that cushions the lungs. The pleura normally releases a small amount of fluid. The fluid helps the lungs move freely during breathing.

pleural effusion (PLOO-rul eh-FYOO-zhin): When too much fluid collects between the lining of the lung and the lining of the inside wall of the chest.

pneumonectomy (noo-muh-NEK-tuh-mee): Surgery to remove a lung.

pneumonitis (NOO-moh-NY-tis): Inflammation of the lungs. This may be caused by disease, infection, radiation therapy, allergy, or irritation of lung tissue by inhaled substances.

primary cancer: The first or original cancer diagnosis.

prognosis (prahg-NOH-sis): The course a disease is likely to follow, including how long it will last, what the result will be, and the chances for recovery.

prostate cancer (PRAH-stayt KAN-sur): Cancer that begins in the prostate, which is a gland in men. The prostate is about the size of a walnut and sits just below the bladder.

pulmonologist (pull-min-AH-luh-jist): A doctor who specializes in studying and treating diseases of the lungs.

Q

quartile (KWOR-tyl): A term used in medical statistics to mean a group containing one-quarter or 25 percent of the total.

R

radiation (ray-dee-AY-shin): The emission of energy in waves or particles. Often used to treat cancer cells.

radiation oncologist (RAY-dee-YAY-shun ahn-KAH-luh-jist): A doctor who has special training to treat cancer patients with radiation.

radiation therapist (RAY-dee-AY-shun THAYR-uh-pist): A health professional who gives radiation treatment.

radon (RAY-dahn): An odorless, colorless gas known to increase risk of cancer. Radon comes from rocks and dirt and can get trapped in houses and buildings.

recurrence: When cancer comes back after a period when no cancer could be found.

resection: Surgery to remove tissue, an organ, or part of an organ.

S

selenium (seh-LEE-nee-um): A mineral found in rocks and soil, often used in electronics and other industries. It is also a mineral the body needs in small amounts.

silica (SILL-uh-kuh): A substance found in rocks, sand, and quartz as well as some workplaces.

small cell lung cancer: A type of lung cancer made up of small, round cells. Small cell lung cancer is less common than non-small cell lung cancer and often grows more quickly. The name is often shortened to SCLC. Another name for SCLC is oat cell cancer. See also extensive SCLC and limited SCLC.

spiral (helical) CT scan: Pictures created by a computer linked to an X-ray machine that scans the body in a spiral path. Also called helical computed tomography.

sputum (SPEW-tim): Mucus and other things brought up from the lungs in coughing.

sputum cytology (SPEW-tim sie-TAH-luh-jee): A screening test for lung cancer. In this test, doctors look at phlegm under the microscope to check for cancer cells.

squamous cell carcinoma (SQUAY-mus SEL kar-sin-OH-muh): A type of non-small cell lung cancer that begins in the squamous cells of the lungs. Squamous cells are found in the skin, the lining of the hollow organs (such as the stomach), and in the breathing and digestive tracts.

stage: How much cancer is in the body and how far it has spread.

stereotactic radiosurgery (STAYR-ee-oh-TAK-tik RAY-dee-oh-SER-juh-ree): A type of external radiation therapy that uses special equipment to position the patient and precisely give a single large dose of radiation to a tumor. It is used to treat brain tumors and other brain disorders that cannot be treated by regular surgery. It is also being studied in the treatment of other types of cancer. Also called radiation surgery, radiosurgery, and stereotaxic radiosurgery.

stereotactic body radiation therapy (STAYR-ee-oh-TAK-tik): A type of external radiation therapy that uses special equipment to position a patient and precisely deliver radiation to tumors in the body (except the brain). The total dose of radiation is divided into smaller doses given over several days. This type of radiation therapy helps spare normal tissue.

T

thoracic surgeon (thuh-RASS-ik): A doctor who specializes in chest, heart, and lung surgery.

TNM — A system for describing stages of cancer. T describes the size of the tumor and whether it has grown into nearby tissues. N describes any lymph nodes involved. M describes metastasis.

toxicity (tahx-SIS-uh-tee): How toxic or poisonous something is.

trachea (TRAY-kee-yuh): The airway connecting the larynx to the lungs; windpipe.

V

vaccine (vax-EEN): A substance meant to help the immune system respond to and resist disease.

VATS (**V**ideo-**A**ssisted **T**horacoscopic **S**urgery): A surgical procedure performed inside the chest with the help of a camera on a tube. In VATS, several small incisions (cuts) are made in the chest. Doctors insert the tube with the camera through one incision, and tools to work with through the others. The camera helps the doctors see inside the chest to operate.

W

wedge resection: Surgery to remove a wedge-shaped piece of tissue.

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About the Editors

Lorren Sandt is a co-founder and the Executive Director of the Caring Ambassadors Program. She managed the Hepatitis C Program of the Caring Ambassadors Program since its inception in 1999 until 2013. Lorren is a co-editor and a contributing author, to Hepatitis C Choices, 5th Edition, a one-of-a-kind, patient-centered book authored by a team of more than 25 multi-disciplined experts in hepatitis C. She has worked on policy changes at both the state and federal level since 2001. Ms. Sandt is a nationally recognized leader in hepatitis advocacy. In 2013, The National Viral Hepatitis Roundtable honored Ms. Sandt with the Michael Carden Award for more than a decade of policy work on behalf of those living with viral hepatitis. In 2001, The Hepatitis C Global Foundation honored Ms. Sandt with the Ronald Eugene Duffy Memorial Award for Patient Activism: for leadership and mentoring of patients, making them advocates for their own health.

Cindy Langhorne joined the Caring Ambassadors Program, Inc. in August of 2007 as the Lung Cancer Program Director. Ms. Langhorne brings over fourteen years of programmatic and managerial experience in the field of lung cancer advocacy and has worked with public and private community stakeholders. Ms. Langhorne's compassion for lung cancer patients and their families and her dedication to improving the burdens of lung cancer one life at a time are extraordinary. Ms. Langhorne is a well-respected local, regional, and national advocate for lung cancer and issues that affect those living with or at risk for the disease. Ms. Langhorne is also the acting Co-Chair for the Lung Cancer Action Network (LungCAN®). The Lung Cancer Action Network (LungCAN®) is a collaborative group of lung cancer advocacy organizations who have come together to raise public awareness of the realities of lung cancer with the intention of increasing funding for detecting, treating and curing the disease.