Lung Cancer CHOICES 5th Edition

Diverse Viewpoints and Choices for Your Lung Cancer Journey

CaringAmbassadors.org

Lung Cancer
CHOICES
5th Edition

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Dedication

The Caring Ambassadors Program dedicates *Lung Cancer Choices, 5th Edition* to program founder, Ken Giddes and former Board of Director member, Jessica Steinberg.

Ken

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

Ken had a successful career with Republic Financial Corporation, which supported the development of the Caring Ambassadors Lung Cancer Program. He traveled the country to meet other survivors and talk about living with lung cancer. Ken also was a "phone buddy" (one of the first in the country) to over 300 lung cancer patients and their loved ones in eight years and presented at meetings with patients, their loved ones, and the oncology community.

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

Jessica

Jessica Steinberg passed away on her 50th birthday, October 7, 2021. She is survived by two wonderful sons who mean the world to her. Jessica was only 39 years old when she was diagnosed with lung cancer. She was determined to see her boys graduate high school, which she did.

Jessica was a vivacious and determined person who loved to help others. Jessica wrote and shared, "Empowered, My Journey-My Choices" to encourage and inspire others living with lung cancer to take charge of their journey! Jessica was not only survivor, but a sur-THRIVE-r. Jessica treated her disease holistically and was involved in multiple clinical trials. She believed that hope is contagious, and that music is powerful. She would say, ***"it's time to put your brave boots on!"***

Jessica served on the board of directors for Caring Ambassadors Program and offered a unique patient-experience point of view.

Jessica, you will be missed, your light will continue to shine in our hearts!

"A hero is an ordinary individual who finds the strength to persevere and endure in spite of overwhelming obstacles.

- Christopher Reeve

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Acknowledgments

The Caring Ambassadors Lung Cancer Program is profoundly grateful to the book's authors for their dedication, generosity, time, and expertise. Without their commitment to this project, we would be unable to offer this valuable resource to the lung cancer community (see About the Authors).

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*, 5th Edition would not be possible without all our donors' love and generosity, especially our board members, Randy Dietrich, Rob Gleser, MD, Chuck Singleton, and Jessica Steinberg. Thank you for all you do for the Caring Ambassadors Program and the community.

Finally, 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 support and comfort. The healthcare providers who work to provide the best treatment options and supportive care. And the advocates who work tirelessly to give hope and comfort. Together we can 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.

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Introduction

A Message from Cindy Langhorne-Hatfield

The Caring Ambassadors Program is pleased to provide you *Lung Cancer Choices*, 5th Edition. Through *Lung Cancer Choices*, we offer you a message of HOPE!

There are always "choices and hope" for all people facing lung cancer, whether you live with the disease yourself or are the loved one of someone who is. For many people, hope grows when you have the information and support you need to make health care decisions that suit your personal goals and circumstances. At Caring Ambassadors, we are committed to helping improve the overall wellness of people living with lung cancer through information, education, and personal choice.

The good news is that lung cancer treatment and management options have changed dramatically over the past decade by adding new targeted therapies and immunotherapy drug options. Testing to detect specific biomarkers has become more common as precision medicine continues to evolve. With more treatment options approved for various types and stages of lung cancer, it is essential to understand all your treatment options. Therefore, we are pleased to add two additional chapters for the 5th Edition. Chapter 2: *Comprehensive Biomarker Testing* and Chapter 14: *Sexuality and the Lung Cancer*.

Caring Ambassadors is honored to be serving the lung cancer community. We hope that the information provided will help you make treatment and supportive care decisions during your journey. Our heartfelt thanks to all who contributed to *Lung Cancer Choices*.

"The greatest joys are found not only in what we do and feel, but also in what we hope for.
- Bryant H. McGill

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Using Lung Cancer Choices

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 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 so they can make all their own treatment decisions. Other people prefer to have their healthcare providers make treatment decisions based on their knowledge and expertise. Some like having a friend or family member seek out and sort through information. Many use a combination of approaches.

You may find medical words in the book that are new to you. You can find the definitions within the chapter or 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 efficiently with your healthcare providers.

We hope *Lung Cancer Choices* will help you understand your disease and some of the health care 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.

Each chapter and section of the book has been authored independently and reflects the unique approach of the author to the treatment of lung cancer, based on their medical discipline and experience. For this reason, an author is responsible only for the accuracy of the information presented in their 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 health care providers to choose treatment approaches that meet your individual needs.

Visual Glossary

Questions to Ask your Doctor

Scientific evidence or medical terminology

Private Reflections or questions to ponder on your journey

Questions to Ask When Choosing Your Providers

Once you've learned more about your diagnosis it is time to make your provider choices, it can be helpful to set up one-on-one consultations. A consult will help you get a better sense of whether you and a provider are a good match. Prepare for your consult by making out a list of questions and the qualities that are important to you in a health care provider. Check all the questions you want to ask. You may want to create a separate list for each member of your team.

Are you board certified or licensed in your field?

How much experience do you have treating my type and stage of cancer? Can you provide me with any results or outcomes?

Do you like to tackle lung cancer head-on, or do you typically take a more conservative 'wait and see' approach?

Will you support integrative treatment approaches, such as complementary therapies and lifestyle modifications, for the management of side effects? (for your Western medicine providers)

Will you support my Oncology treatment choices and help me manage side effects? (for your Complementary and Alternative providers)

How can I communicate with you outside of appointment times? What is your availability?

Who can I contact with any questions or problems I may experience?

Should a family member or friend come with me to my appointments?

You might want to ask yourself: Did the provider use language you could understand and take time to listen to your concerns and answer your questions? What was their communication style?

Do you have a Dietitian/Nutritionist on staff? If not, will you refer me to one?

Will you help me find a social worker/patient navigator to help guide me through treatment?

Will you help me find a doctor to give me another opinion on the best treatment plan for me?

Choosing Providers and Insurance

A consult may or may not be covered by your insurance or healthcare plan, so make sure you are clear on the costs upfront. There are several factors to consider when choosing which health care providers you will include on your health care team.

Is the provider covered by your insurance or healthcare plan? Will the provider accept your healthcare plan?

Which hospital (if any) does the healthcare provider work with? Is the hospital covered by your insurance?

Will I have a case manager to help with insurance questions?

Will my insurance plan cover your Dietitian/Nutritionist or other nutrition services provided by your office?

What should I expect for out-of-pocket costs?

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Chapter 1

The Diagnosis and Staging of Lung Cancer

Tze-Ming Chen, MD, FCCP

Introduction

Lung cancer remains the leading cause of cancer-related mortality in the United States despite advances in chemotherapeutic options and surgical techniques. The evaluation of patients with suspected or known lung cancer requires accurate and preferably rapid diagnosis and staging to guide the optimal treatment regimen: surgical resection, surgical resection with adjuvant chemotherapy, chemotherapy alone, chemotherapy in conjunction with radiation therapy, or use of targeted therapies. 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), guidance assisted bronchoscopy, mediastinoscopy, thoracentesis, pleuroscopy, video-assisted thoracoscopic surgery (VATS), and or computed tomography (CT) or ultrasound guided FNA.

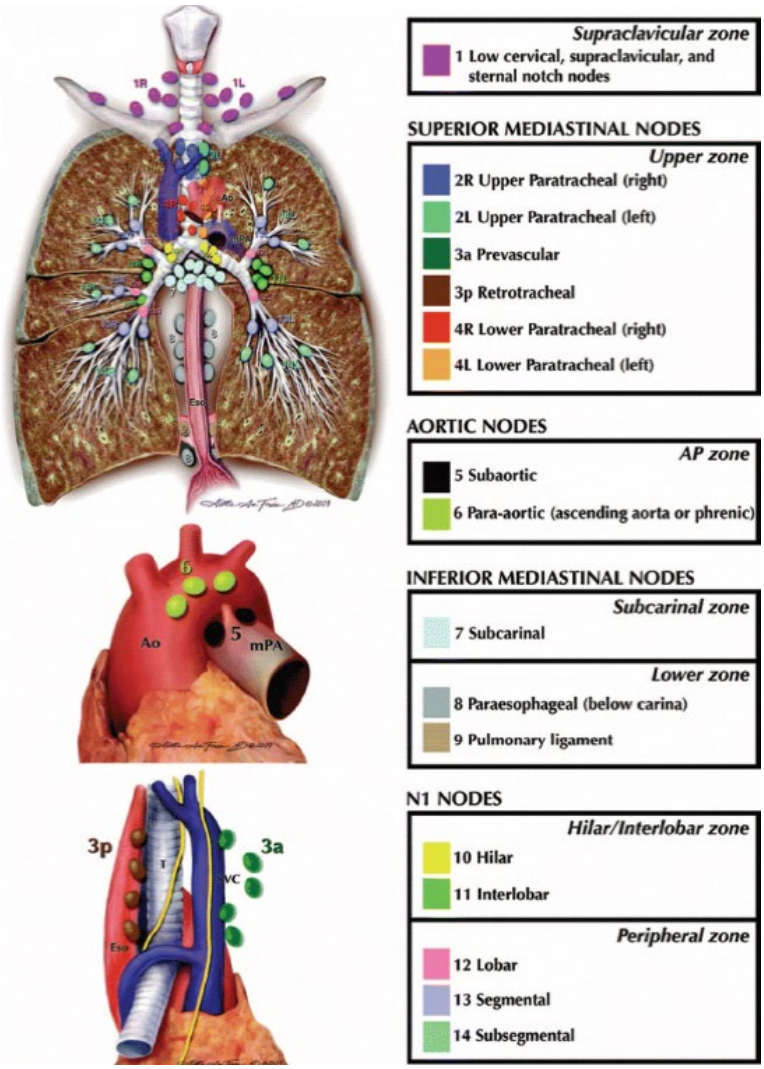
Lung cancer survival is strongly associated with the stage of disease and the resulting application of appropriate treatment.

This chapter 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 8th Edition of the American Joint Commission on Cancer TMN staging system for non-small cell lung cancer which became the worldwide standard in 2017 continues with the existing method of assessing tumor size and its effect on the surrounding lung tissue or its interaction with non-lung tissue (T), the extent of spread of lung cancer to lymph nodes (N) and the presence or absence of metastatic spread of lung cancer outside of lung tissue or to the contralateral lung(M).[1] (Figure 1)[2] 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. Each edition builds on an international database of patients with lung cancer to provide a common basis for communicating the extent of cancer and prognosis. The 9th edition is under development at the time of the writing of this chapter.

Figure 1: Schematic of the lymph node stations within the chest[2]



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 as well as for staging evaluation.[3-4] In 2009, a study 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.[5] A subsequent retrospective study evaluating patients with clinical stage IA non-small cell lung cancer found PET-CT to have a sensitivity of 44%, specificity of 83%, positive predictive value of 78%, and negative predictive value of 91% compared to surgery for detection of mediastinal lymph node metastases.[6]

More recently, a team reviewed 64,103 veterans diagnosed with non-small cell lung cancer between September 2000 and December 2013 and found that PET-CT use increased over time and its use improved stage appropriate therapy for all stages of NSCLC while improving mortality in a risk-adjusted model.[7] With lung cancer screening detected lung nodules, PET-CT has a role in selected patients to aid in the risk stratification of indeterminate lung nodules measuring greater than 10 mm in diameter or with evidence of growth if the lesion is less than 10 mm.[8]

We now have more clarity when deciding which patients should undergo invasive mediastinal staging in the setting of negative PET-CT results. Research in 2017 evaluated 284 consecutive patients with PET- CT staged T1 to 2, N0 non-small cell lung cancer who then underwent either endobronchial ultrasound or mediastinoscopy sampling of mediastinal lymph nodes. 7% of these patients were found to have occult (hidden) N2 disease with PET-CT and EBUS / mediastinoscopy having a negative predictive value of 92.9% and 96.3%, respectively. In addition, occult N2 disease was more likely to be present in patients with T2 disease compared with those with T1 disease (11.8% compared with 3.6%, $p=0.009$). Pure solid lesions were also more likely to have N2 disease compared to tumors with any ground glass (12.6% compared to 3.1%, $P < 0.001$) and patients with central tumors were more likely to have occult N2 disease compared to patients with peripheral lesions (17.5% compared with 4.4%, $p < 0.001$). Consequently, the authors recommend invasive mediastinal staging for patients with central and solid tumors while those with peripheral ground glass lesions may not warrant such an approach.[9]

Ground glass opacifications (GGO) are a subset of pulmonary nodules or masses with non-uniformity and less density than solid nodules. GGO are usually described as either pure ground glass or part solid (subsolid) nodules.

Detecting brain metastases is challenging with PET-CT as FDG is avidly taken up by brain tissue. One retrospective study suggests this imaging modality may assist in selecting patients for brain MRI with a sensitivity of 72% and specificity of 100%.[10]

It is important to realize that FDG uptake also occurs in inflammatory and infectious processes thereby limiting its ability to discriminate between these processes and cancers.[11] Therefore, it is important to obtain 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.[12] In addition, some lung cancers such as bronchioloalveolar carcinomas and carcinoid tumors have been reported to have negative PET imaging results.[13] 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.[14] In addition, the change in activity with chemotherapy correlates with histopathologic response.[15]

Re-evaluation by PET/CT after neoadjuvant chemotherapy in a 2016 retrospective study of 17 patients with non-small cell lung cancer with N2 lymph node involvement demonstrated a sensitivity of 100% and specificity of 94%.[16]

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

EBUS-FNA is a minimally invasive technique that complements mediastinoscopy by its ability to access lymph node stations 2, 3, 4, 7, 10, and 11. (Table 1)

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

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. In 2003, a group reported their initial experience with EBUS-FNA of mediastinal and hilar lesions under general anesthesia.[17] 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. Subsequent studies have demonstrated that EBUS-FNA is a minimally invasive, highly accurate alternative as well as a complementary procedure to mediastinoscopy for mediastinal and hilar staging for patients with known or suspected NSCLC.[18-24]

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. Overall, these studies demonstrate that EUS is a valuable diagnostic and staging tool for patients with suspected or known NSCLC.[25-26]

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. Electromagnetic navigation is able to overcome this limitation for select lesions that are more than 1 to 1.5 cm 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.

> *When it is obvious that the goals cannot be reached, don't adjust the goals, adjust the action steps.*
>
> *- Confucius*

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.

In early 2018, a new guidance bronchoscopy system was approved by the FDA, robotic bronchoscopy. This new technology provides greater maneuverability within patient airways improving our ability to reach peripheral lung nodules as well as improved stabilization of bronchoscope and biopsy tools within these airways once the target has been reached with improvement in the feasibility and accuracy of lung nodule biopsies. A study in 2020, described a comparison of successful sampling of artificially produced peripheral lung nodules in cadavers between radial endobronchial ultrasound bronchoscopy, electromagnetic navigational bronchoscopy, and robotic bronchoscopy. These investigators found that robotic bronchoscopy had the highest rate of successful biopsy with the lowest rate of missed biopsy. With the robotic system, 10% of attempts sampled the center of the lesion, 65% within the periphery of the lesion, 10% passed through the nodule with the tip of the needle on the other side, 10% had the biopsy needle just outside of the lesion, and 10% of the biopsies missed the nodule. There were no situations where the robotic system was unable to localize the lesion, whereas 35% of the radial endobronchial ultrasound bronchoscopy and 15% of the electromagnetic navigational bronchoscopy biopsy attempts failed to localize the lesion.[27]

A more recent study in 2021 evaluated the feasibility and safety of robotic bronchoscopy in localizing peripheral lung nodules in patients in a prospective multicenter trial. 54 patients consented and underwent robotic bronchoscopic localization and biopsy of peripheral lesions with a median diameter of 23 mm. 32 of these nodules were in contact with a visible airway on CT imaging. A diagnosis was made in 40 patients (74.1%) with malignancy being the etiology in 33 patients. If the lesion surrounded the airway, the diagnostic yield was 80.6%. If the lesion was adjacent to but not surrounding the airway, the diagnostic yield dropped to 70%. Importantly, pneumothorax complicated robotic bronchoscopy in 2 (3.7%) of the 54 cases, one of which required a chest tube (1.9%).[28]

As this is a new technology, additional trials are being conducted evaluating the clinical utility of robotic bronchoscopy in the evaluation of peripheral lung lesions including the PRECIsE and

TARGET trials.[29-30] Currently, multiple centers across the United States have adopted this technology and are actively utilizing it to assist in the work-up of possible lung cancer lesions.

Radial Endobronchial Ultrasound Bronchoscopy (rEBUS)

An adjunctive diagnostic device is the radial endoscopic ultrasound. This device can be inserted through a standard bronchoscope and maneuvered into the lung tissue to help localize a nodule for biopsy. The major limitation with this modality is that the bronchoscopist must maneuver the probe to the nodule with studies suggesting that in 6 to 31% of cases, the lung nodule could not be visualized.[31-34] In addition, 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. Consequently, the biopsy is not under real-time visualization of the target.

In current practice, a guidance system is used to maneuver a working channel to the lesion of interest followed by confirmation that the catheter is in the correct position using the radial ultrasound. Because the ultrasound probe is removed to allow insertion of the biopsy catheter, the operator is still left without real-time imaging during the actual biopsy.[35]

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 permits easier handling and visualization during the procedure as well as potential access to posterior subcarinal lymph nodes.[36-37]

The major limitations to performing mediastinoscopy are bleeding disorders, severe kyphosis, contraindications to general anesthesia, tracheostomy, or previous chest or neck 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% and 11%.[38-39] It is generally well tolerated, and most patients can avoid an overnight hospital stay.[40]

Thoracentesis

Patients with pleural effusions that layer at least 1 cm on lateral decubitus chest radiographs are easily assessed for malignancy by thoracentesis. If the fluid is trapped in pockets in the pleural space or loculated, then ultrasound guidance can permit safe sampling of the fluid. 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.[41] 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.[42] The rate of detection is dependent upon the type of carcinoma, the number of pleural fluid specimens obtained, and the extent of pleural involvement.[43]

Medical Thoracoscopy (Pleuroscopy)

Pleuroscopy is a procedure that allows access to the pleural space (the potential space between the inner surface of the chest wall and the outer surface of the lung) using an endoscope. In the setting of a diagnosis of or suspicion for lung cancer with a large pleural effusion, pleuroscopy can allow removal of pleural fluid for diagnosis and staging while also potentially relieving shortness of breath or chest discomfort related to the presence of the fluid. In addition, if there are suspicious lesions seen on CT imaging or during the procedure along the inner chest wall lining, biopsies of these lesions can be done. Studies have demonstrated a high diagnostic yield for pleural effusions.[44-46]

If the pleural effusion is refractory and causing symptoms as described above, medical thoracoscopy can also assist with pleurodesis. These interventions can also be performed during a video-assisted thoracoscopic surgery as described in the next section of this chapter but a medical thoracoscopy is usually more limited in its scope and more easily tolerated. It is usually performed by a pulmonologist under conscious sedation with local anesthesia or the patient can undergo general anesthesia. Successful pleurodesis reported in recent publications ranges between 78% and 88% for malignant effusions with a lower success rate for malignant effusions related to lung cancer (72.3%).[47-48]

Complications of medical pleuroscopy include pain usually from the chest tube placed at the end of the procedure, infection, bleeding, a persistent air leak resulting from a tear of the visceral pleural surface, or subcutaneous emphysema which is the result of air entering the subcutaneous tissue.

More serious but rare complications include death, development of fluid in the lung when it re-expands after the fluid has been removed, or air entering the bloodstream. If cancer is present in the pleural space, there is also a risk of seeding the surgical site with tumor resulting in tumor growth through the site. This final complication is more common with mesothelioma.

In summary, medical thoracoscopy is a diagnostic option for pleural effusions that remain undiagnosed despite thoracentesis as well as a therapeutic approach for pleurodesis in refractory pleural effusions.

Video-Assisted Thoracoscopic Surgery

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

An important application of VATS is to directly visualize tumors that are radiographically staged T4. Several studies support the use of VATS to confirm T4 lesions designated by CT prior to categorizing the cancer as unresectable.[50-51] 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 provide 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 targetable mutations increases, we may reach a point where a separate diagnostic procedure is needed to obtain enough tissue for all the testing performed to determine the most appropriate first-line treatment.

Currently, the National Comprehensive Cancer Network (NCCN) recommends testing patients with advanced stage non-small cell lung cancer for gene alterations to identify potentially effective therapy targets.[52] The potential targets include but are not limited to epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), B-Raf proto-oncogene (BRAF), KRAS proto-oncogene (KRAS), programmed death ligand 1 (PD-L1), MET proto- oncogene (MET), RET proto-oncogene (RET), erythroblastic oncogene B (ERBB2) also frequently called human epidermal growth factor receptor 2 (HER2), and tumor mutational burden (TMB). Consequently, we attempt to obtain as much tumor tissue as possible to send for a broad panel- based molecular profiling test to identify whether an actionable mutation is present.

If the patient is too ill or at too high risk for serious complications to undergo tissue sampling to test for these mutations, a peripheral blood sample also referred to as a liquid biopsy could be used to try to assess for these gene alterations though the NCCN recommends tissue sampling if and when possible. See Chapter 2: *Comprehensive Biomarker Testing*

Thoracic Tumor Board Diagnostic and Staging Algorithm

Today, most cancer centers have Tumor Boards which have been shown to improve the staging of cancer. Our center has an established Diagnostic Thoracic Tumor Board that brings together the knowledge and expertise of physicians from pulmonology, interventional pulmonology, medical oncology, radiation oncology, radiology, and thoracic surgery. To help us risk stratify lung lesions, we employ Lung RADS 1.1 for lung cancer screening detected lesions and Fleischner Society Guidelines 2017 for incidentally detected lung nodules.[53-54] 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 recommendation for management including a diagnosis and stage if lung cancer is suspected 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. 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.[4-5] 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.[55]

Diagnosis if not previously made and staging is achieved by biopsy of the PET-avid lesion that would achieve the most advanced TNM 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 recommended prior to proceeding to surgical resection.

Conclusion

Lung cancer survival is strongly associated with the stage of disease at the time of diagnosis and the resulting application of appropriate treatment. With the appropriate application of combined PET-CT, EBUS, EUS , and or mediastinoscopy, patients can now be accurately staged avoiding unnecessary surgery.

The reasons above are the reason our team believes so strongly in the importance of having a multidisciplinary panel of physicians to improve the timely application of appropriate staging and diagnostic studies.

Questions to Ask about Your Initial Diagnosis and Diagnostics

When you meet with your doctor, you will hear a lot of information. These questions may help you learn more about your cancer and what you can expect next.

What type of cancer do I have?

What is the stage of my cancer?

Has it spread to other areas of my body?

How serious is my cancer?

Will I need more tests before treatment begins? Which ones?

Can I receive a 2nd opinion before treatment begins?

Should I consider a clinical trial before treatment begins?

Lab Tests

A laboratory (lab) test is a procedure in which a health care provider takes a sample of your blood, urine, other bodily fluids, or body tissue to get information about your health. Some lab tests are used to help diagnose, screen, or monitor a specific disease or condition.

What tests will you be conducting on my blood?

What is considered normal range for these tests?

Why run those particular tests?

How long will it take to get the results?

What does this test result mean for me?

What does it mean if the results are negative or not clear?

How will the results affect my treatment?

Will I need these blood tests again? If so, why and when?

Will these tests be covered by my insurance?

Imaging

The easiest way for a physician to determine the cause of many cancers is through imaging. There are many types of machines today and each one has its own risks and benefits. You may be offered an X-ray, a magnetic resonance imaging (MRI), a computerized axial tomography (CAT scan), or an ultrasound.

Why do I need to have this imaging?

What are the benefits?

Are there any complications or side effects from the recommended imaging?

How long will it take to get the imaging results?

What does it mean if the image results are negative or not clear?

What does this mean for me? How will the results affect my treatment?

Will I need these images again? If so, why and when?

Will these imaging diagnostics be covered by my insurance?

Biopsy

What are you trying to find with the biopsy?

Are there any complications or side effects from having a biopsy?

Are there any alternatives to having a biopsy?

Is this done in your office or a hospital?

How long is the procedure?

How long is my recovery time?

Do I need to bring someone with me to the appointment?

How long will it take to get the test results?

What does this mean for me? How will the results affect my treatment?

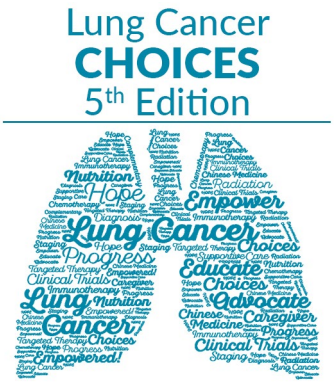
How often will I have to have a biopsy?

Will the biopsy be covered by my insurance?

"Though you feel like you're not where you're supposed to be, you shouldn't worry because the next turn you take, it will lead you to where you wanna go.

- Ellen

Notes



Chapter 2

Comprehensive Biomarker Testing

Kelly E. Goodwin, MSN, ANP-BC

Introduction

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer related deaths worldwide. Lung cancer rates vary significantly by sex, age, race/ethnicity, socioeconomic status and geography and lung cancer is found across all smoking histories.[1] While patient characteristics are diverse, so is the disease itself. Lung cancer is broadly classified as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). NSCLC represents approximately 85% of total lung cancer diagnoses with adenocarcinoma (40%) and squamous cell carcinoma (25%) being the most commonly occurring histologies, or subtypes.[2] Curative and palliative therapies for lung cancer include intravenous or orally administered systemic therapies, radiation therapy or surgery and are dependent on staging, pathology and patient considerations.

Lung cancer rates vary significantly by sex, age, race/ethnicity, socioeconomic status and geography and lung cancer is found across all smoking histories.

Systemic therapy for lung cancer historically consisted of chemotherapy. Chemotherapy works by non-specifically killing cells that are growing or dividing and while it can help improve quality of life and survival in some patients it is also associated with significant toxicities due to the unintended effects on normal cells. Precision medicine, also known as personalized medicine, is a medical model that aims to customize treatments based on individual variability in genes, environment, and lifestyle. Through sequencing the genetic material of normal tissues and cancers scientists have been able to identify genetic alterations, often called mutations,

that interfere with the normal functioning of cells. Some mutations change genes that control cell growth so that they are always active and promote unchecked cell growth. Some other cancer-promoting mutations inactivate genes whose normal function is to slow or stop cell growth. A better understanding of the molecular pathways that contribute to NSCLC and other malignancies since the early 2000s has led to the development of specific targeted therapies and immunotherapies that have helped to improve survival rates and decrease treatment-related toxicities for certain subsets of patients with NSCLC. More than a dozen new drugs for the treatment of NCSLC have been approved since 2013, marking an exciting and hopeful time in lung cancer research and care.[3]

Biomarkers

Biomarkers are molecules in the blood or tissue that can result from mutations in genes. Biomarkers help to link subsets of patients to certain therapies – they can serve as prognostic markers and can help predict response, resistance or toxicity to certain drugs. Lung cancer biomarkers arise from somatic mutations, alterations in genes that occur in tissues. Somatic alterations are different from germline (noncancer) alterations in that they are not inherited from one's parents and are not passed on to one's offspring. Germline mutations occur in the sperm or egg and at a very early age in fetal development such that they are presumed to be present in all of a person's cells. Somatic mutations are classified as driver mutations when they encode for proteins critical to cell growth, differentiation and survival. Passenger mutations are those genetic variants that are less essential to transforming or maintaining the change of a noncancerous cell into a malignant cell.[4]

Oncogenesis is the complex, multi-step process by which normal cells transform into cancer cells. Genetic changes in a group of cells can cause normally functioning cells which are usually controlled by inhibition loops or other physiologic signals – analogous to "on" or "off" switches – to grow and behave abnormally. Cells which have undergone oncogenic transformation as the result of a driver mutation are stuck in the "on" position and their survival is dependent on a signal from that driver in order to survive. Reliance on, or addiction to, the oncogenic driver mutation makes certain lung cancers more susceptible to targeted therapies.

Oncogenesis is the complex, multi-step process by which normal cells transform into cancer cells.

The American Society of Clinical Oncology (ASCO), the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), the Association for Molecular Pathology (AMP) and the National Comprehensive Cancer Network (NCCN) have issued guidelines for biomarker testing for patients with lung cancer since the early 2010s.[5] Cancer promoting mutations in NSCLC were historically thought to occur in patients with a never or light smoking history and an adenocarcinoma histology and earlier versions of these guidelines reflected this

understanding by recommending biomarker testing for specific target populations.[6] However, research has shown that cancer promoting mutations can be found across all lung cancer histologies and smoking histories.[7] With improved biomarker testing techniques, an expanding list of molecular targets and more approved and emerging therapies, comprehensive biomarker testing is an essential part of the evaluation and management of all patients diagnosed with NSCLC.[8]

Biomarker Testing Methods

Somatic driver mutations in NSCLC can be the result of many different types of genetic changes – gene deletions, insertions and rearrangements are among the most common – and can be identified through a number of different testing modalities. Despite the importance of biomarker testing in the management of patients with NSCLC, there is wide variability in uptake in testing in clinical practice,[9] testing methodologies, resulting timelines, time to initiation of therapy and payor coverage. Surgeons, interventional radiologists, interventional pulmonologists and pathologists are crucial members of the multidisciplinary team caring for patients being evaluated for NSCLC.

While there is no single standard platform for molecular testing, tissue-based testing remains the gold standard. Because driver mutations develop early in the process of transformation from normal cell to malignant cell, tumor samples from either the primary tumor or a metastatic lesion are appropriate for molecular testing.[10] Once tissue has been procured through a diagnostic biopsy, confirmation of adequate tumor cellularity occurs and histology has been determined (squamous versus non-squamous), the tissue sample may undergo biomarker testing.

Clinically useful biomarker tests are those which can be performed on available samples, are at least semi-automated, do not rely on a single operator or interpreter, are cost effective and have a fast turnaround time (two weeks or less).[11] The type of testing employed depends on the type of mutation under investigation – DNA mutations, chromosome abnormalities or gene expression.

The most common testing techniques include, but are not limited to, polymerase chain reaction testing (PCR) of DNA or RNA (the genetic material that converts DNA into proteins), Fluorescence in-situ testing (FISH), Immunohistochemistry (IHC) and Next Generation Sequencing (NGS). These tests are collectively referred to as companion diagnostics because they help to match a patient to a specific drug or therapy. Testing can be performed through a hospital based, accredited laboratory or a number of commercial services.

DNA sequencing and DNA allele-specific testing are forms of single gene tests which use PCR to examine either the entire length of a gene or a specific region of a chromosome for the presence of a pre-specified mutation. While a relatively quick turnaround time of less than one week is an advantage to these testing techniques there are several disadvantages including lower sensitivity (a higher probability of a false negative), the potential to exhaust the tissue sample through multiple single gene tests, low cost effectiveness and the inability to identify new abnormalities.[12]

Fluorescence in-situ testing (FISH) is a testing technique which allows for the detection of gene rearrangements, translocations, amplifications or deletions through visualizing and mapping the genetic materials in cells. FISH is useful for examining specific genes, portions of genes or for understanding larger chromosomal abnormalities. Short sequences of single stranded DNA called "probes" are created to match a portion of the gene under evaluation; each probe is "labelled" with a fluorescent dye. As DNA is double stranded, identifying rearrangements uses hybridizing DNA probes of different colors that separate when two parts of a gene have broken apart.[13] FISH testing can only detect a pre-specified mutation, requires significant technical expertise to perform and interpret and requires a minimum of 50-100 well preserved tumor cells within the tissue sample. FISH results are typically available in about 6 days.[14]

Immunohistochemistry (IHC) testing is used to detect the presence of certain proteins in cells or tissues that may be overexpressed, whether or not there is an alteration in the genes. This technique preserves the spatial context or architecture of the tissue sample. The role of IHC testing in NSCLC continues to evolve but it is a rapid (one day) and reliable test for several of the most common driver mutations found in NSCLC.[15]

Next generation sequencing (NGS) is a broad-based testing technique which allows for the analysis of multiple genetic alterations at the same time. DNA fragments from the biopsied sample are purified, amplified, isolated, and then compared to a known mutation "library" and a normal reference sample. Several hospital-based and commercial targeted lung cancer NGS tests are available which can test for 10s-100 alterations.[16] Single gene testing requires "purer" cancer samples for adequate sensitivity and can exhaust tissue when run sequentially. NGS can be financially expensive though more cost effective than a la carte testing and the median turnaround time for results is close to 2-3 weeks. Rapid and ultra-rapid testing of some of the most common mutation types can be added as an adjunct to NGS testing for patients with significant symptoms and certain pathologic or clinical features. These rapid or ultra-rapid testing pathways can return results in 9 days or less than 2 days respectively and can significantly shorten the time between diagnosis and initiation of a life sustaining therapy.[17] NGS reports can contain a large amount of information and require careful interpretation before finalizing a treatment plan. Acknowledging the importance of comprehensive biomarker testing for patients with recurrent, metastatic, refractory or stages III or IV cancer, the Centers for Medicare and Medicaid finalized a National Coverage Determination in 2018 that covers diagnostic laboratory tests using NSG in order to assist oncologists and patients in making more appropriate and timely treatment decisions and determining candidacy for clinical trials.[18] Private payor reimbursement is variable but many oncologists, pathology departments and commercial labs have processes to advocate for reduced out of pocket costs to the patient.

While tissue based biomarker testing remains the gold standard for genetic analysis of NSCLC, "liquid biopsies" can be considered when a tumor is inaccessible, or a tissue biopsy is considered too high risk. Liquid biopsies detect fragments of circulating tumor DNA (ctDNA) that is shed into the bloodstream when the cancer is most active (at the time of diagnosis or when cancer is progressing on a therapy). ctDNA testing has significant benefits – it is less invasive than a traditional tissue

biopsy, it is quick (7-10 days) and easily repeatable. The sensitivity of detecting target mutations with ctDNA is 60-80% and depends on tumor location, size, blood supply and detection method used (PCR vs NGS).[19] Because of the increased risk of false negative ctDNA tests, liquid biopsies should not serve as stand-alone testing – tissue based testing should be considered if clinical suspicion for an activating mutation is high. The US FDA has approved ctDNA tests to identify EGFR mutation positive patients and one of the tests uses NGS to also identify genetic abnormalities in 55 genes.[20] It is likely that as more data emerge the use of liquid biopsies to assess other molecular abnormalities will become more widespread.[21]

Lung Cancer Biomarkers

Lung cancer is one of the most genetically complex cancer types according to data from The Cancer Genome Atlas (TCGA) with genetic alterations identified in up to two-thirds of newly diagnosed advanced lung cancers. Historically driver mutations have been thought to occur primarily in non-squamous tumors and to be mutually exclusive.[22] However, recent studies have shown clinically significant, actionable mutations in approximately 10% of squamous cell tumors[23] and overlapping driver mutations in up to 12% of non-squamous NSCLC.[24] Coexistence of driver mutations is clinically relevant because it may provide targets for additional or combination therapy and may help to identify potential sensitivity or resistance to a particular type of targeted therapy.

Lung cancer is one of the most genetically complex cancer types according to data from The Cancer Genome Atlas (TCGA) with genetic alterations identified in up to two-thirds of newly diagnosed advanced lung cancers.

In 2020 and 2021 the NCCN updated their guidelines for routine molecular testing in newly diagnosed NSCLC recommending testing be performed via a broad, panel-based approach, most typically performed by NGS, so that testing is done for all of the actionable biomarkers at the same time, including the established and emerging biomarkers. The expert panel recommended that smoking status, small biopsy specimens, and mixed histology should no longer be used when considering whether to perform biomarker testing. Furthermore, while acknowledging the lower incidence of driver mutations in advanced squamous cell NSCLC, the panel cited the cumulative incidence of actional alternations in squamous cell tumors and the effectiveness of targeted therapies as justification for recommending comprehensive biomarker testing for tumors of squamous histology. The goal of these expanded guidelines is to identify rarer mutations for which effective drugs may be available and to identify patients for appropriate clinical trials to advance the care of all patients with NSCLC.[25]

Common biomarkers in NSCLC

EGFR (Epidermal Growth Factor Receptor) mutations are the most common targetable mutations found in lung adenocarcinomas accounting for nearly 20% of NSCLC and are often found in younger patients, Asian patients and patients with a never or light smoking history. EGFR mutations can be detected with PCR or NGS testing. EGFR exon19 deletions, L858R point mutations and some exon19 insertions are associated with responsiveness to multiple oral EGFR targeted therapies. Targeted therapies for these EGFR mutations have been less effective for EGFR exon20 insertion mutant NSCLC, which represents about 10% of EGFR mutations and only 2% of overall lung adenocarcinomas, but two new therapeutic options to be used after initial treatment with chemotherapy (one oral and one administered by infusion) are expected to be available for this variant in 2021.[26]

ALK (Anaplastic Lymphoma Kinase) gene rearrangements have been found in 3-5% of patients with NSCLC and can be found using FISH, IHC and numerous NGS methods. ALK rearrangements are more frequently found in younger, male, never smokers with adenocarcinoma histology and ALK positive disease is associated with responsiveness to multiple oral ALK inhibitors.[27]

ROS1 (ROS proto-oncogene 1) rearrangements, typically genetic translocations, have been identified by FISH or NGS though some variants may be under reported. ROS1 mutations act as the driver mutation in 1-2% of NSCLCs and are more frequently identified in younger, Asian, never smokers with adenocarcinoma histology. The presence of ROS1 rearrangement predicts responsiveness to oral ROS1 targeted therapies.[28]

BRAF (B-raf proto-oncogene) mutations, detected through PCR and NGS methods, are found in up to 4% of NSCLC though only the V600E variant has been associated with responses to BRAF inhibition given in combination with another class of drugs targeted the MEK pathway. BRAF + MEK inhibition is an oral therapy. BRAF mutations are most commonly found in patients with a smoking history.[29]

MET (mesenchymal-epithelial transition) exon14 skipping mutations or MET gene amplifications are found in approximately 2-4% of NSCLC through RNA based NGS testing. Variants in MET are associated with response to oral therapies which inhibit MET. MET exon 14 skipping mutations are more frequently identified in patients with nonsquamous tumor histology, older, female and are less likely to be non-smokers.[30]

RET (rearranged during transfection) rearrangements are detected by FISH, RNA based NGS or PCR testing in 1-2% of lung adenocarcinomas and are associated with responses to oral RET inhibitors. RET rearrangement occur more frequently in younger patients and in never smokers.[31]

KRAS (Kirsten rat sarcoma) mutations are found in approximately 25% of patients with lung adenocarcinoma and is generally associated with smoking. KRAS G12C is the most common KRAS mutation found in lung cancers and is responsible for approximately 1 in every 8 lung

adenocarcinomas. The first KRAS G12C inhibitor was approved in June 2021 for the treatment of disease following progression on or intolerance of first line treatment for advanced disease.[32]

NTRK 1/2/3 (neurotrophic tyrosine receptor kinase) gene fusions have been found in approximately 1% of NSCLC via FISH, IHC, PCR and NGS testing and is associated with sensitivity to oral NTRK inhibitors. NTRK fusions occur in NSCLCs across sexes, ages, smoking histories, and histologies.[33]

PD-L1 (programmed death-ligand 1) is a protein found on cancer cells, including NSCLC, which helps the cancer to hide from the immune system. PD-L1 expression can be detected using IHC and is reported as the proportion of tumor cells exhibiting staining. The proportion of PD-L1 informs the decision to pursue immunotherapy alone (PD-L1>50%) or chemotherapy plus immunotherapy combinations (PD-L1>1%) in patients with newly diagnosed NSCLC.[34]

TMB (tumor mutational burden) is not currently recommended for NSCLC but is emerging as an independent predictor of response to immunotherapy.[35]

HER2 (human epidermal growth factor receptor 2) mutations have been reported in 1-3% of NSCLC tumors, are most frequently detected using PCR or NSG testing and predominantly affect never smokers. The majority of HER2 mutations occur in women with adenocarcinomas. Anti-HER2 therapies are currently in development and may be accessed through clinical trial participation.[36]

Additional emerging biomarkers include **PTEN, FGFR1, PDGFRA and DDR2**. These alterations are most commonly found in squamous cell lung cancers. Multiple therapies directed at these variations are currently in development.[37]

Conclusion

As our understanding of genetic drivers in NSCLC evolves and more therapeutic options become available, patients are living longer and challenging the traditional concept of cancer survivorship. A collaborative, multidisciplinary approach to the evaluation and management of NSCLC that utilizes comprehensive biomarker testing for all patients with newly diagnosed NSCLC regardless of age, gender, smoking history or histology and for patients with identified actionable mutations whose cancer is acquiring resistance to targeted therapies is critical to ensuring that patients receive the therapy that is most likely to improve their survival and quality of life.[38]

> *Life is 10% what happens to you and 90% how you react to it.*
>
> *- Charles R. Swindoll*

Questions to Ask about Comprehensive Biomarker Testing

What are you trying to find with the biomarker tests?

Are there any complications or side effects from these tests?

Are there any limitations of biomarker testing?

How are the tests performed?

Can I have a liquid biopsy at the same time as biomarker testing?

How long will it take to get the test results?

Have I already had any biomarker tests? Which ones? If so, what are my results?

What does it mean if the test results are negative or not clear?

What does this mean for me? How will the results affect my treatment?

Will I need these tests again? If so, why and when?

Will these tests be covered by my insurance?

Notes

Lung Cancer
CHOICES
5th Edition

Chapter 3

Surgery for Lung Cancer Patients

Adam J. Bograd, MD, Maria Cattoni, MD, Lisa M. Brown, MD, MAS, Ben M. Hunt, MD, MSc, and Brian E. Louie, MD, MHA, MPH, FRCSC, FACS

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 or radiation therapy or both. 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 the surgery, which is a normal, common reaction. We hope 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 seven sections to address the following questions:

- When is surgery used to treat lung cancer?
- What types of surgery are used to treat lung cancer?
- How do I prepare for surgery?
- What can I expect the day of surgery?
- What can I expect during the hospital stay?
- What is the recovery like from lung surgery?
- Am I cured?

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.

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. Furthermore, some people diagnosed with lung cancer may not be good candidates for surgery based on functional testing. There are two categories of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). (Figure 1) Surgery is not usually used to treat people with small cell lung cancer, although some exceptions exist. 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 the surgery is based on two factors: (1) the stage of cancer and (2) the ability of the patient to function without the cancerous portion of the lung. We will discuss these two factors in the next two sections of this chapter.

Figure 1. Lung Cancer, as seen through the microscope. A: Small cell carcinoma. B: Squamous cell carcinoma. C: Adenocarcinoma. D: Adenocarcinoma with lepidic features. B, C, and D are all different types of non-small cell lung cancer.

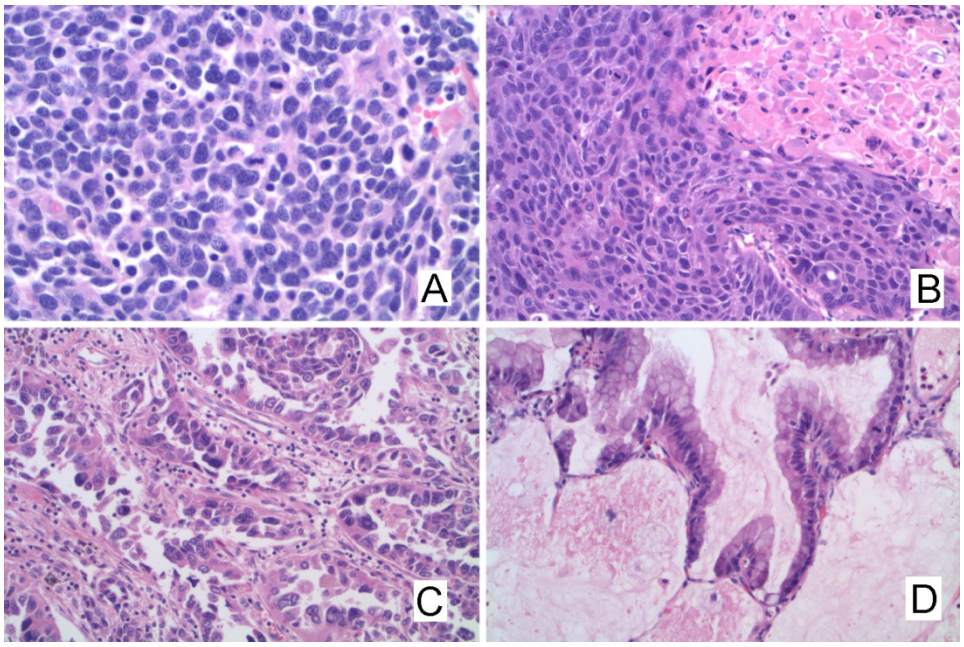


Image courtesy of Jey-Hsin Chen, MD, PhD

Lung Cancer Staging from the Surgeon's Perspective

After a diagnosis of lung cancer has been made, the most important question is, "How far has it spread?" This process is called staging, more specifically, *clinical staging*. Staging is first determined by using imaging tests such as a positron emission tomography (PET) scan, a computed tomography (CT) scan, and often a brain MRI. From these tests, the surgeon can determine the location of cancer and assess whether 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 the cancer into one of four groups called "stage" (stage I, stage II, stage III, stage IV).

Usually, the combination of chest computed tomography scan (CT) and positron emission tomography (PET) are enough to determine the location and dimension of the lung cancer and whether it has already spread to other areas of the body such as the lymph nodes, the liver, the bones, and the adrenal glands. Generally, for stage IB and above, a Brain MRI (magnetic resonance imaging) will be obtained to make sure there has been no spread to the brain.

Determining the clinical stage of lung cancer helps the treating physicians determine the optimal treatment, as provided by organizations, the most common being the National Comprehensive Cancer Network (NCCN). In summary, lung cancer treatment is stage directed and specific.

Even though the PET, CT, and brain MRI are very good at detecting the spread of lung cancer to the liver, the bones, the adrenal glands, and the brain, there is an 8-10% chance of missing cancer in the lymph nodes in the center of the chest. (Figure 2) Since determining the presence of cancer in the mediastinal lymph nodes is necessary to define the cancer stage, it is important to know more definitely whether cancer involves the mediastinal lymph nodes. Therefore, a biopsy (a small tissue sample) of the mediastinal lymph nodes is sometimes recommended before lung cancer surgery in certain instances. This is referred to as "mediastinal staging."

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

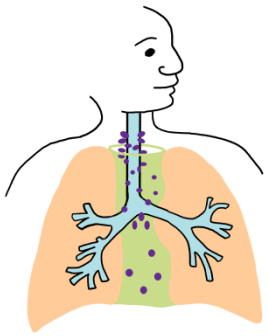


Illustration by Alexandra Hunt, MD

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 into the lymph node or (2) an operation (mediastinoscopy). During a 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: a scope and instruments are used to sample the mediastinal lymph nodes

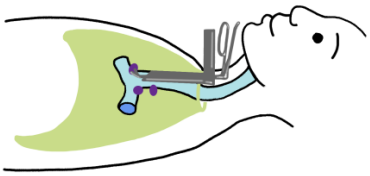


Illustration by Alexandra Hunt, MD

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 as the initial treatment. However, if there are cancer cells in these lymph nodes, chemotherapy with or without radiation therapy is usually the first treatment, sometimes followed by surgery. This is referred to as induction or neo-adjuvant therapy.

The importance of defining the cancer stage is due to the fact that lung cancer at different stages requires different treatments. Surgery has a potentially curative role in non-small cell lung cancers that are stages I to III and in very select cases of stage IV lung cancer. (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, but radiation is an alternative, sometimes followed by chemotherapy
II	Larger tumor or lymph node involvement, but only lymph nodes within the same 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 to other organs (brain, liver, bone, adrenal, contralateral lung)	Usually chemotherapy, sometimes radiation therapy, and immunotherapy, rarely surgery

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. One distinguishing feature (other than size of the tumor) 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 same 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) Stage IIIA lung cancer involves mediastinal lymph nodes on the same side of the chest as the primary lung cancer; surgery may be utilized in Stage IIIA disease. Recently, immunotherapy has been utilized on a clinical trial basis, both pre- and post-op, in patients with more advanced stage lung cancer. Stage IIIB lung cancer denotes the spread of cancer to lymph nodes either on the opposite side of the chest or above the clavicles; surgery is typically not an option for Stage IIIB lung cancer, with a few, limited exceptions. When cancer has spread to the lymph nodes in the mediastinum, surgery alone is not appropriate. In this case, studies have shown that chemotherapy with or without radiation therapy, sometimes combined with surgery, has a better outcome than surgery alone.

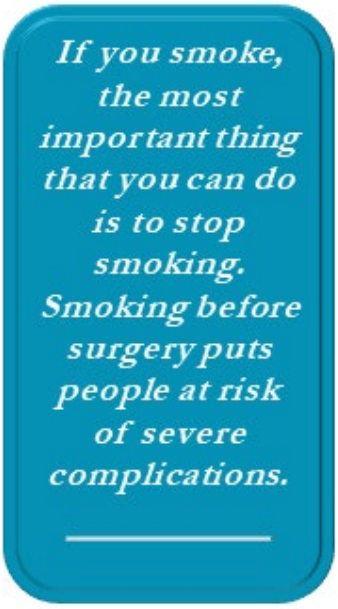
Surgery in Stage IV Cancer

If cancer has spread to distant sites, it may not be possible or beneficial to remove all cancer with surgery. Additionally, if 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 cancer. If the

tumor 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 cancer. Occasionally, stage IV cancer has spread to only a single location outside of the lung, such as the brain or adrenal gland, and may be a candidate for surgical treatment of both the metastasis (the single cancer location outside of the lung) and the primary lung cancer. This is referred to as "oligometastatic disease." This special situation should be discussed with the cancer team (the surgeon, the oncologist and the radiation oncologist). Certain targeted therapies and immunotherapies are also being increasingly utilized in advanced-stage lung cancer However, specific testing of the tumor for certain "markers" is required to see if the tumor qualifies for treatment with these modalities.

Preoperative Testing

Even if lung 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 patient can undergo surgery safely and be able to live with less of the lung after 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 exam 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 issues to consider preoperatively: to make sure that the patient is healthy enough to safely have surgery, and to find any other health problems that can be improved before the operation. For example, diabetes should be well controlled before surgery since it impacts wound healing. If you smoke, it is very important to stop smoking before lung surgery in order to reduce the risk of respiratory complications after surgery. See Chapter 13: *How to Quit Smoking Confidently and Successfully*. After dealing with each person's health problems, the preoperative workup for lung surgery focuses on the lungs and the heart in order to evaluate the performance of these two organs.

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 that measures the airflow 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 the 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 tests, 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 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 (echocardiogram) or a scan (myocardial perfusion study). If any problems with the heart are found during testing, additional procedures (such as cardiac catheterization) 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 after treatment. 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 cancer, killing 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 minimal 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. Surgery for small cell lung cancer is reserved for patients with small lung tumors and no evidence of spread to the lymph nodes. Therefore, a 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 1: *Diagnosis and Staging of Lung Cancer* and Chapter 6: *Treatment for Small Cell Lung Cancer*.

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: the blue line corresponds to the chest incision

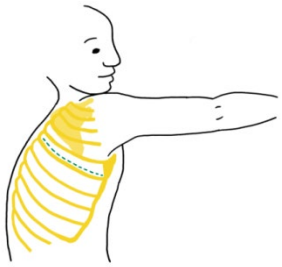


Illustration by Alexandra Hunt, MD

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. However, it is important to be aware that even if the surgeon plans to do the operation using the VATS approach or the robot, sometimes it is necessary to convert during the operation to a bigger incision (thoracotomy). Most patients with early-stage lung cancers should have their resection with a minimally invasive technique, either VATS or robotic.

Figure 4b. Video-Assisted Thoracic Surgery (VATS) and robotic thoracic surgery incisions: the blue lines correspond to the chest incisions.

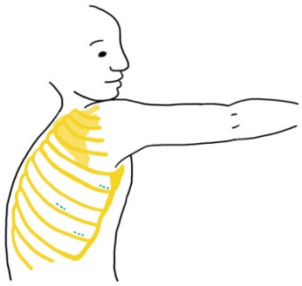


Illustration by Alexandra Hunt, MD

Figure 4c. Robotic thoracic surgery

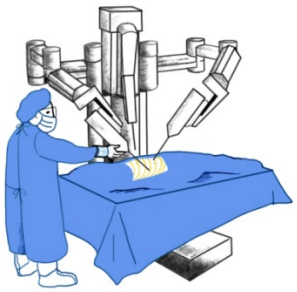


Illustration by Alexandra Hunt, MD

Besides deciding which approach will be used to remove the portion of the lung containing cancer, a surgeon must decide exactly what to remove. The priority is to remove cancer. It is important to remove some normal surrounding lung along with the cancer, because there are microscopic extensions of 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 cancer, together with the lymph nodes inside the lobe (lobectomy) (Figure 5a) Removing the entire lobe allows the best possibility for long term survival and remains the gold-standard.[2] However, recent studies have been evaluating whether the resection of the cancer within a smaller part of the lung (segmentectomy) has the same results, in term of survival and probability of cancer recurrence that occurs when removing the entire lobe (lobectomy). The results of these studies will be available in the next years. In patients with adequate pulmonary function, a sublobar resection (either a wedge or segmentectomy) should be reserved for early-stage (<2cm) or slow-growing subtypes (i.e., carcinoid) or lung cancer.

In patients where there will not be enough healthy lung left after an entire lobe is removed, the surgeon may decide to remove just the tumor with a small amount of surround lung, termed a "sub-lobar resection." This may consist of either a wedge resection or a segmentectomy that contains 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 (pneumonectomy) (Figure 5c) Airways may be divided and sewn back together ("sleeve resection"), if this allows complete removal of cancer without removing as much healthy lung tissue. (Figure 5d) In addition to removing the part of the lung that is affected by cancer, lung cancer surgeons remove lymph nodes in the chest at the time of lung surgery, to evaluate whether cancer has spread to these lymph nodes.

"Do what you can with all you have, wherever you are.

- Theodore Roosevelt

Figures 5a-d. Types of Resection

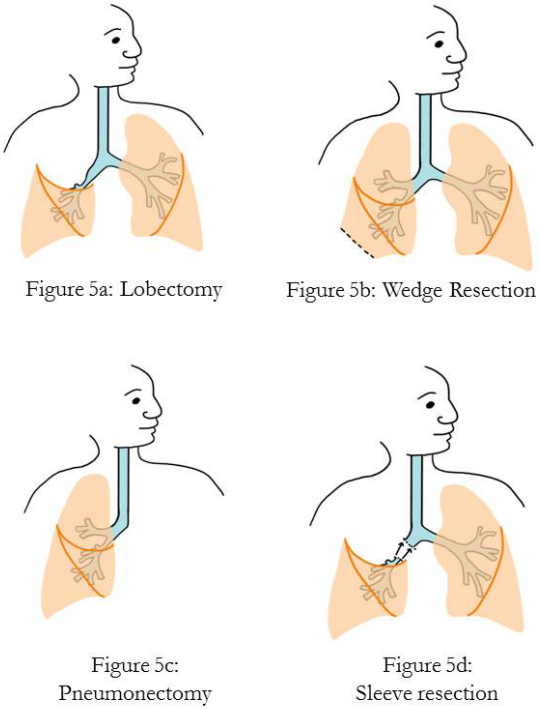


Figure 5a: Lobectomy

Figure 5b: Wedge Resection

Figure 5c: Pneumonectomy

Figure 5d: Sleeve resection

Illustrations by Alexandra Hunt, MD

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 the surgery that the patient *can* control. In this section, we will discuss a few things that the patient can do to make their operation go more smoothly.

If you are a current smoker, 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 of severe 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 secretion 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. Stopping smoking at least 4-6 weeks before surgery and remaining smoke-free after surgery may reduce your risk of post-operative complications by 50% in some studies. 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 (ideally at least 6-8 weeks before surgery[7]) and stay off cigarettes until they have successfully healed from surgery.[6-8] See Chapter 13: *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 take some control over their surgical course proactively. The surgery will stress the patient's body, 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 cancer.

Exercise, proper nutrition, and vitamins (including antioxidants) can help prevent complications from surgery.

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. Certain institutions have intensive exercise "pre-habilitation" programs that may be used pre-operatively for some patients; patients should ask their physicians if they would benefit from such programs. 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]

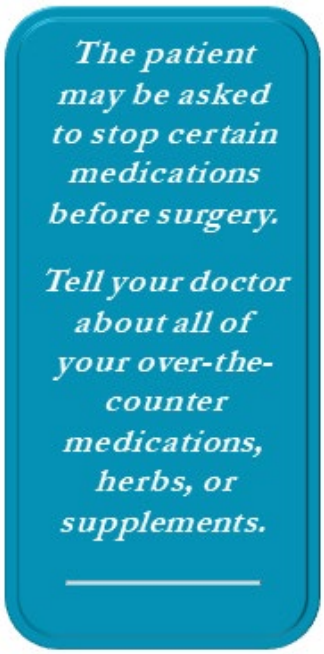
What Can I Expect the Day of Surgery?

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.

Your surgeon should give you specific instructions regarding how to prepare for your day of surgery. 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. Generally, one should aim to arrive at least 2 hours before surgery unless otherwise instructed. Be sure to bring your identification, insurance card, and other items you may need to make your hospital stay more comfortable (loose-fitting clothing, slippers,

personal hygiene items). Try to refrain from bringing valuables to the hospital. All jewelry should be removed, as it has the potential to impact some instruments used in surgery.

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 operation. A repeat electrocardiogram may be performed in some cases. 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. Blood thinners have different rates in which they clear the body, so it is important to find out exactly how many days prior to surgery they need to be stopped. Surgery may be canceled if these blood thinners are not stopped in time. 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, but one should check with their surgeon regarding which medications to take and if it is allowable to take them with a sip of water the morning of surgery. Often there is input regarding this from the anesthesia team, so asking these questions well ahead of time may alleviate issues.

The night before surgery and again the morning of surgery, you will be asked to use antibacterial soap. This soap is most commonly chlorhexidine based.

The patient will meet many new people the day of surgery, however each one of these people are here to ensure that your surgery is performed safely and efficiently. 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.

Occasionally, 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 cancer has not spread further than the preoperative workup indicated and to look for anything unexpected. 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 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 not to spill cancer into the chest cavity to minimize the possibility that 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 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 cancer based on the resected specimen. This is known as the pathologic stage and will guide the surgeon as to if more therapy (chemotherapy, radiation, or further surgery) post-operatively is required. A formal pathology report usually takes 5-7 days to complete. The pathologist is sometimes asked to tell the surgeon whether the cut edges are free of cancer; this is done immediately in the operating room with a "frozen section." If not, more tissue may be taken to get a clean margin. After 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. This drain (called chest drain or chest tube) stays in place until the lung is sealed, and there is no drainage; which is usually 1-3 days after surgery. 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 had passed between when anesthesia was started and when they wake up in the recovery room.

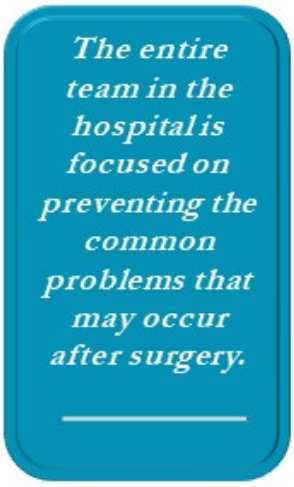
Most people stay in the recovery room for a few hours while the anesthesia wears off. There are nurses in the recovery room who carefully monitor patients to make sure that everything is going well after surgery. A chest radiograph usually is done in the recovery room to recheck that the lung has completely 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.

What Can I Expect During the Hospital Stay?

Hospital care after major lung surgery is very important for a full recovery. After surgery 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 can clean out and re-expand their lungs after surgery, the smaller the possibility of getting an infection in the collapsed lung or space around the lung. For this reason, the surgical team, the nurses, and the physical and respiratory therapists will repeatedly be 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] Your care team will assist you in the use of an "incentive spirometer." This is a small device that will improve your ability to take a deep breath and strengthen your respiratory muscles. You will be asked to use this multiple times per hour, every hour you are awake.

Being active after surgery can be difficult because chest surgery can be quite painful. However, 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 the surgery. One of those is placing a small tube, called epidural catheter, alongside the spinal column just outside the membranes that surround the spinal cord. This tube allows a continuous dose of medication to be delivered to the nerves in the spinal cord that transmit pain signals to the brain in order to control the pain. A well placed epidural catheter is one of the most effective ways to manage 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. Many other types of medicines may be used to help control pain to limit the number of narcotics needed. 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. Chest drains are typically left in place until drainage is under a certain threshold, and leakage of air has stopped. Most surgeons err on the side of caution with removing chest drains as they are sometimes difficult to reinsert if removed too early. 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. In certain instances of small persistent leaks, patients may be asked to go home with a chest drain in place temporarily.

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 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 a 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 tumor 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.

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 from

surgery. 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, choosing a healthy diet, and an active life 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 the 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 cancer in the future. This plan usually involves periodic imaging and checkups to make sure cancer does not recur. Chemotherapy, radiation, and other treatments may be recommended in addition to surgery according to the final results obtained by the pathologist after analyzing the cancer, the lung and the lymph nodes resected during the surgery. This determines the final stage of cancer more accurately than the preoperative tests and is more determinant of 5-year overall survival than the clinical stage.

Am I Cured?

The goal of most cancer surgery is to cure 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 earlier 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 pathologic stage of cancer. The details of the pathology report, namely the size and characteristics of the primary tumor (T-stage), as well as if there is cancer in the lymph nodes (N-stage), will be used to decide if post-operative chemotherapy and/or radiation is needed. Furthermore, molecular testing of tumor cells is becoming increasingly more common as data emerges regarding the use of targeted and immune therapies in the post-operative setting. See Chapter 2: *Comprehensive Biomarker Testing in Lung 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. The Percentage of Patients with Non-small Cell Lung Cancer who are Alive Five Years After Diagnosis[14-15]

Stage IA	Stage IB	Stage IIA	Stage IIB	Stage IIIA	Stage IIIB	Stage IV
81-92%	67-74%	60-65%	51-61%	34-50%	7-26%	2-13%

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 cancer will return. The longer people live after completing their treatment, the smaller the risk they have of having 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. However, during these five years, it's important to follow a surveillance program to detect early cancer recurrence or new lung cancer. This program that is generally proposed by the surgeon and consists of both periodical physical examination and imaging tests should be completed by the patient.

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 gives the best potential for the long-term cure of cancer and a quick return to normal life.

"Act as if what you do makes a difference. It does.
- William James

Questions to Ask Your Thoracic Surgeon

Is surgery an option for me? If so, what kind of surgery do you suggest?

What are the risks, benefits and alternatives to surgery?

How much of the lung will be removed?

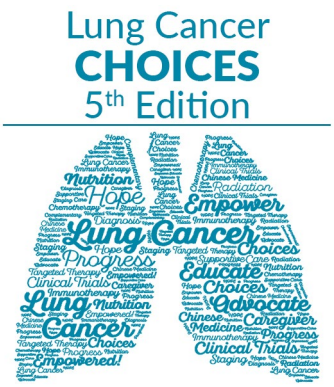
How will removal of the lung affect my breathing?

What is my recovery time in the hospital and at home?

If I have pain, how will it be controlled?

Do I need to arrange to have someone to help me with daily activities after surgery?

Notes



Chapter 4

Systemic Therapy for Non-Small Cell Lung Cancer (Chemotherapy, Targeted Therapy, and Immunotherapy)

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Introduction

The treatment of lung cancer depends upon the cell type, stage, and mutational characteristics identified. The first distinction is the tumor histology: small cell (SC) or non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 85% of all lung cancer. The major sub-types are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. NSCLC can be further characterized by specific mutations that "drive the growth" of the tumor. The stage describes the extent of disease present at diagnosis.

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. Historically, chemotherapy has been the foundation of systemic treatment. However, over the past decade, clinical trials have led to the advancement of several new approaches to systemic therapy. The goals of therapy for patients with advanced disease are to control disease, prolong survival and maintain quality of life. Treatment decisions are based on the extent of disease (organs involved), burden of disease (symptoms), histology (adenocarcinoma versus squamous cell carcinoma), the presence of driver mutations (EGFR, ALK, ROS1, BRAF, KRAS, MET ex14 skipping, RET, NTRK 1/2/3), and level of PD-l expression. This chapter reviews the use of systemic therapies used in the treatment of NSCLC, including chemotherapy, targeted therapies, and immunotherapy.

Systemic Therapy: Treatment using substances that travel through the blood stream, reaching and affecting cells all over the body.

Chemotherapy

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 other therapies. Chemotherapy agents are identified by the generic name and brand names, and either name is used when treatment is explained to patients.[1] (Appendix 1)

Targeted Therapies

Targeted therapies are agents that interfere with cancer cell proliferation by blocking specific signals (or processes) that drive tumor growth. Targeted therapies include small molecules that disrupt cell division from inside cancer cells and monoclonal antibodies that target receptors on the tumor cell surface. Monoclonal antibody therapies function by inhibiting the blood supply to tumors and inhibiting growth factors needed for tumor growth. Cancerous tumors require blood supply for nutrition 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) and are administered intravenously.

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, ROS-1, BRAF, MET ex 14 skipping, RET, HER2, NTRK 1/2/3, and KRAS.[2] Each of these "driver mutations" occur independently. Therefore, patients do not harbor more than one mutation initially. However, tumors may mutate further after therapy and develop an additional mutation of resistance. It is important to identify if there is a "driver-mutation" as if present, informs treatment selection.

Targeted therapies are agents that interfere with cancer cell proliferation by blocking specific signals (or processes) that drive tumor growth.

Several targeted therapies have been approved that target specific mutations. These are taken orally. Targeted therapies may be referred to by their generic or brand names. Patients must follow directions carefully for how to take the oral targeted therapies. Taking with food and other medications may impact absorption and metabolism of the treatment, which may increase the risk of toxicity. (Appendix 2)

Immunotherapy

Ideally, the immune system in your body should recognize tumor cells as foreign, then seek and destroy or eliminate the cancer cells. However, cancer cells have developed mechanisms to "hide" or evade immune recognition by blocking specific immune checkpoints on the immune cells. In effect, the tumor cells put the "breaks" on the immune system. Therapies that target these pathways are referred to as immune checkpoint inhibitors. Several immune "checkpoint inhibitors" have been investigated over the past several years that demonstrate an effect in restoring the immune system's ability to recognize tumor cells.[1, 3-4] Programmed Death 1 (PD-1) receptor is found on immune cells (T-cells), when activated, the immune cell function is suppressed. Programmed Death Ligand (PD-L1) is found on cancer cells in varying degrees. The interaction of the PD1 & PD-L1 pathway "halts" the immune response. Immune checkpoint inhibitors that attach to the PD1 receptor on immune T-cells or the PD-L1 ligand on tumor cells block the interaction of this pathway. This restores the pathway and eliminates the tumor's ability to escape. The level of PD-L1 expression can be tested on tumors. There is some evidence that higher expression of PD-L1 correlates with higher responses to therapy. However, even if the tumor has a low expression of PD-L1, responses to therapy have still been noted. Immune checkpoint inhibitors that have been approved may be referred to by the generic or brand names. (Appendix 3)

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. It is also important for patients to be actively involved in treatment decision making. This patient-centered approach to care is called "shared decision making."

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, tumor mutational status, diagnostic tests, and performs a physical examination. Treatment recommendations are based on this

information as well as 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.[5] (Table 1)

The medical oncologist prescribes and monitors response to treatment and performs follow-up evaluations. The decision to administer systemic therapy does not depend on a patient's age, and many studies have shown that elderly patients can successfully receive chemotherapy.[1] However, the treatment of lung cancer varies from one person to another, and the type of systemic therapy prescribed will depend on the specifics of the patient's disease.

Table 1. Eastern Cooperative Oncology Group (ECOG) Performance Status[5]

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 housework or office work).
2	Able to walk and care for self, but unable to carry out any work activities, up and active more than 50% of waking hours.
	Able to do only minimal self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.

Advanced Practice Provider (Nurse Practitioner or Physician's Assistant)
The oncology advanced practice provider is an integral member of the treatment team. An advanced practice nurse (APRN) has received additional master's and/or doctoral level education and certification beyond nursing school. Physician Assistants (PA) 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 specific procedures, 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, targeted therapy, and immunotherapy; and managing side effects. The oncology nurse may start the intravenous line, administer the therapy, and monitor for symptoms during and after the infusion. This nurse also reinforces education about managing side effects and coordinates additional nursing or supportive services needed in the home.

Social Worker
A licensed clinical oncology social worker (LCSW) 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 Caring Ambassadors and the American Cancer Society.

Pharmacist
A licensed pharmacist who specializes in oncology may be part of the treatment team if the patient is being treated at a large oncology practice, designated cancer center, or hospital. The pharmacist will review the treatment regimen, medications, and prepare the therapy for infusion or prepare and dispense oral therapy. In some cases, oral therapies must be ordered through specialty pharmacies as there is a restriction on their distribution. Specialty pharmacists can assist in assuring the timely delivery of these therapies. Pharmacists are available to help counsel the patient about how to take the medications/therapy, what the expected side effects are, and how to self-manage common side effects. As well as educate about 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 in monitoring dietary intake and may provide suggestions to improve nutrition during and after treatment. See Chapter 9: *Nutrition in the Patient with Lung Cancer*

Other
Throughout therapy, other specialists may be consulted to help manage symptoms of the lung cancer or side effects of the treatment. Specialists include pulmonologist, interventional pulmonologist, cardiologist, endocrinologist, dermatologist, nephrologist, and others. Some larger institutions offer additional services that provide an extra layer of support in meeting patient care needs. These may include palliative care, integrative or complimentary therapy. The entire team collaborates to assure alignment of the patients' treatment goals.

There are **71** NCI-Designated Cancer Centers, located in **36** states and the District of Columbia, that are funded by NCI to deliver cutting-edge cancer treatments to patients. Of these **71** institutions:

- **13** are Cancer Centers, recognized for their scientific leadership, resources, and the depth and breadth of their research in basic, clinical, and/or prevention, cancer control, and population science.
- **51** are Comprehensive Cancer Centers, also recognized for their leadership and resources, in addition to demonstrating an added depth and breadth of research, as well as substantial transdisciplinary research that bridges these scientific areas.
- **7** are Basic Laboratory Cancer Centers that are primarily focused on laboratory research and often conduct preclinical translation while working collaboratively with other institutions to apply these laboratory findings to new and better treatments.

Most of the NCI-Designated Cancer Centers are affiliated with university medical centers, although several are freestanding institutions that engage only in cancer research.

NCI also offers the National Clinical Trials Network, once known as cooperative groups. These large networks of researchers, doctors, and other health care professionals do clinical trials across the country. Review and search a complete list of NCI-designated cancer centers here: https://www.cancer.gov/research/nci-role/cancer-centers

"It's always hard to deal with injuries mentally, but I like to think about it as a new beginning. I can't change what happened, so the focus needs to go toward healing and coming back stronger than before.

- Carli Lloyd

Systemic Therapy for Lung Cancer

Goals of Treatment

The purpose of systemic therapy treatment may vary, depending on the patient's current status. 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.

The schedule of chemotherapy, targeted therapy, and immune therapy administration varies in time and sequence by the regimen selected and goals of therapy. Neoadjuvant therapy is given before surgery in an attempt to decrease tumor size, so surgery is more effective. Adjuvant therapy is given after surgery to kill tumor cells that might be remaining in the body. Concurrent is the administration of two modalities of therapy at the same time, such as chemotherapy given with radiation therapy, done before or after surgical resection (tri-modality treatment). Chemotherapy, targeted therapies, and immunotherapy may be given in combination or can be administered alone.

Administration of Therapy

Chemotherapy, immune therapy, 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 therapy and duration of infusion. Specific therapy agents may be used alone or in combination with other agents. Treatment is given on a schedule, in blocks of time known as cycles. The specific cycles vary depending on the treatment combination. Each therapy cycle may be followed by a recovery period to allow the normal cells to repair. However, the treatment schedule may be changed when the patient experiences severe side effects from treatment.

Chemotherapy, immune therapy, and some targeted therapies are usually given intravenously via the bloodstream so that it is circulated throughout the entire body. Some treatment 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 daily.

Techniques for intravenous chemotherapy include:

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

Infusion port
This is a more permanent device that is placed under the skin which is attached to a catheter that tunnels into a larger vein and remains in place throughout the treatment course. A specially trained oncology nurse places a needle into the port through the skin to administer treatment, give hydration, and draw blood samples. Topical creams may be applied prior to the insertion of the needle to

minimize discomfort. The physican or advanced practice provider can prescribe this cream. When the needle is in place, an occlusive dressing is placed over it to secure it in place. 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 therapy, hydration, or drawing blood. The catheter extends outside the body, and only specially trained oncology 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 oncology nurse educates patients on how to care for the catheter and dressing at home.

Pump
Some treatments require a continuous infusion for several hours or days. An infusion pump ensures that the correct amount of therapy is infused into the body at a specific rate.

Treatment Procedure

On the day of treatment, the patient is evaluated by the physician or advanced practice provider to assess and address any changes in the patient's status. The height and weight are measured because these measurements are used to calculate the dose of therapy. The oncology nurse will insert the intravenous line or access the infusion port. Intravenous fluids (hydration) may be given before the therapy. Other medications may be administereed to help prevent side effects of treatment such as nausea or allergic reaction. The nurse administers the therapy through the intravenous line, either by syringe or pump infusion. During, and after treatment, the nurse monitors the patient closely for any possible adverse reactions. The patient must notify the nurse about any unusual symptoms. Information is given to the patient about the therapy and possible side effects, and a schedule for future appointments is provided.

Following treatment, 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 the disease, and strategies they have used for symptom management. The patient is encouraged to contact the healthcare team between visits for any unusual side effects or symptoms that develop post-treatment infusion. It may be necessary for the patient to come back to the clinic or office for further examination and evaluation.

Oral

Targeted therapies that are taken orally usually have to be ordered through a specialty pharmacy as they are closely regulated with restricted distribution. The processing of the prescription may take several days. In many cases, the medicine will be delivered to the patient via mail delivery. The patient needs to notify their healthcare team if there is a delay in obtaining the prescription. Once the patient receives the prescription for the targeted oral therapy, the health care provider may want to meet with the patient to review specific instructions for taking the therapy. Some targeted therapies need to be taken hours after or before meals and other medications, as taking with food may impair the absorption of the therapy. Other oral therapies may be taken with food. In addition, there is a potential for interactions between targeted therapies and other drugs, including over the counter medications. Patients should review all medications with their care team to minimize toxicities.

Evaluation before the start of therapy includes a physical examination to assess performance status and major organ functions such as pulmonary, cardiac, gastrointestinal and nervous system. (Table 1) Blood tests, diagnostic tests, and other procedures are necessary. Blood tests are obtained on a regular schedule to evaluate organ tolerance and potential 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 the assessment of electrolytes (potassium, calcium, sodium, chloride, and magnesium), kidney function, and liver function. Additional tests may also be necessary based on the specific therapy (i.e., further blood tests, urine tests, or electrocardiogram [ECG] or pulmonary function tests [PFTs]).

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. The prescriptions should be filled before treatment. Patients should tell the healthcare team about any difficulties obtaining or starting the medications as prescribed. If you smoke, smoking should be stopped before therapy, and many centers offer smoking cessation counseling. Exercise is vital 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. Patients should inform the healthcare team about all medications, including non-prescription ("over the counter") medication. Some medications may interfere with the chemotherapy, making treatment less effective or side effects more severe. See Chapter 8: *Supportive Care*, and Chapter 9: *Nutrition in the Patient with Lung Cancer*, and Chapter 13: *How to Quit Smoking Confidently and Successfully.*

The oncologist performs tests intermittently throughout the treatment course to assess the effectiveness of treatment. This evaluation may include 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 cancer has been surgically removed, the patient might receive a prescribed number of cycles of therapy 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.

Precautions:

Chemotherapy, targeted therapy, and immune therapy agents can harm developing unborn babies. It is essential that patients (male and female) receiving chemotherapy, targeted therapy, or immune therapy, use effective birth control measures to prevent pregnancy while on therapy and for up to six months following completion of therapy. These treatment measures can cause congenital disabilities and or lead to the death of a fetus. In addition, women receiving therapy should not breastfeed as these therapies may be passed onto an infant in breast milk. The length of time for precautions will vary by the type of treatment and should be discussed in detail with your provider.

Oral targeted therapies and supportive therapies must only be handled by the patient. **They must be kept out of reach of children in a secure childproof container.** Oral therapies may be toxic to children and persons for whom it was not prescribed. **In some cases, they can cause life-threatening events or death.**

Treatment by Cancer Stages

Patients diagnosed with NSCLC will have their disease assessed for the size of the tumor (T), the extent of lymph node involvement (N) and the extent of metastasis to other regions (M). These three factors contribute to the TNM staging of the NSCLC. One of the initial treatment decisions is based on the TNM stage.

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 with lobectomy, segmentectomy, or pneumonectomy. Adjuvant (post-surgery) chemotherapy or targeted therapy may be incorporated into the treatment plan for patients at high risk of recurrence.[1, 6-7] Radiation therapy, including stereotactic radiosurgery may be necessary if the primary tumor is not able to be surgically removed or if the patient is not able to undergo surgery.[8] Stage I NSCLC may recur at local (regional) or distant (metastatic) sites. If the disease recurs at the same location, 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 or targeted therapies may be used before surgery (neoadjuvant) or after surgery (adjuvant). Neoadjuvant chemotherapy may decrease the tumor size so that 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. Radiation therapy may be recommended following surgery and chemotherapy to minimize local recurrence.[9]

Stage IIIA Lung Cancer

Stage IIIA NSCLC is a large tumor with or without invasion or lymph node involvement in the central chest region (mediastinum). Most cases of stage IIIA NSCLC are not surgically resectable because of the vast extent of disease. Therefore, combination chemotherapy and radiation therapy will be employed to decrease the extent of disease and provide opportunity for surgical resection. Stage IIIA NSCLC often receives combination treatment, with four to six cycles of chemotherapy. The most common regimens used are cisplatin with etoposide and carboplatin with paclitaxel weekly. Treatment is administered in one of the following schedules: [1, 6-7, 10]

Neoadjuvant chemotherapy: Chemotherapy before surgery
Induction chemotherapy before concurrent chemotherapy: Chemotherapy alone before a course of chemotherapy and radiation therapy.

Neoadjuvant chemotherapy with concurrent radiation
Chemotherapy and radiation therapy is given together before surgery. Neoadjuvant therapy may be given sequentially if the combination of both might not be tolerated. Chemotherapy is administered first, followed by radiation therapy.

Adjuvant chemotherapy or postoperative radiation therapy
May be used to minimize local recurrence.

For patients with unresectable stage III NSCLC, concurrent chemotherapy and radiation therapy is the first-line of therapy. Following the completion of this, adjuvant treatment with durvalumab (immunotherapy) may be recommended in select patients.[11] Durvalumab is an immune checkpoint inhibitor. It is administered every two weeks for up to one year.[12]

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 cancer to other regions in the body such as the brain, liver, or adrenal glands or the development of a malignant pleural or pericardial effusion. The treatment goals for advanced-stage disease include prolonging survival and controlling symptoms.[1, 13-15] Supportive care includes treatment that controls symptoms but may not necessarily treat cancer directly.

Patients with non-small cell lung cancer, of adenocarcinoma histology, who are being considered to receive systemic therapy, should have their tumor tissue assessed for genetic markers or mutations of the epidermal growth factor receptor (EGFR), EML4-ALK, ROS 1, BRAF, RET, ERB2 (HER2), KRAS, MET ex 14 skipping and NTRK 1/2/3.[1-2] Also, tumor tissue should be assessed for the level of PD-L1 expression on the tumor surface.

EGFR mutations occur in approximately 15% of NSCLC adenocarcinomas. Patients whose tumors harbor an EGFR exon 19 deletions/L858R-mutation should receive oral therapy with an EGFR inhibitor. EGFR inhibitors include osimertinib, erlotinib, gefitinib, and afatinib.[1, 13-14, 16] Osimertinib is the preferred first-line treatment as this targets EGFR as well as a known mechanism of resistance known as T790M.[1, 17-18] EGFR inhibitor erlotinib may be administered in combination with anti-VEGF inhibitors (bevacizumab or ramucirumab) in certain cases. If cancer progresses on first-line treatment, patients may be asked to undergo a repeat biopsy of the tumor to test for specific markers of resistance.[17-19] Patients with EGFR exon 20 insertion mutations may be treated with amivantamab-vmjw, which is a bispecific EGFR directed and MET receptor directed antibody.[20] Tumors with EGFR exon 20 insertion mutations typically do not respond to previously approved EGFR inhibitors. This EGFR inhibitor is administered intravenously. (Appendix 2)

Patients with an EML4-*ALK* mutation (approximately 4% of NSCLC adenocarcinoma) should receive oral therapy with an EML4-*ALK* inhibitor. Currently approved EML4-ALK inhibitors include alectinib (preferred first-line), brigatinib, lorlatinib, ceritinib and crizotinib. [1, 21-26] Dabrafenib & Trametinib in combination or vemurafenib are approved for BRAF mutation.[27-28] Entrectinib, crizotinib, ceritinib and cabozantinib for ROS1 rearrangements (1-2% of NSCLC).[21, 28-29] Larotrectinib and Entrectinib are approved for NTRK fusion mutations.[30-31] Capmatinib, tepotinib and in certain circumstances, crizotinib are approved for MET ex 14 skipping mutations (3% of NSCLC).[32-33] KRAS is the most common driver mutation in lung cancer. Selpercatinib or pralsetinib are approved as first line treatment for RET rearrangement mutations. KRAS G12C occurs in a subset of KRAS positive cases. [34] Sotorasib is the only approved KRAS G12C inhibitor.[35] (Appendix 2).

There is much research on therapies that target other tumor driver mutations. Currently, there is very little data on mutational drivers in NSCLC squamous histology. In the future, there are likely to be additional targets and targeted therapies for patients with lung cancer. If cancer progresses on first-line treatment with targeted therapy, patients may be asked to undergo a repeat biopsy of the tumor to test for specific markers of resistance.[19] In some cases, this information can be obtained through a "liquid biopsy", a blood test.

For patients who do not have a mutation for which there is an approved targeted therapy, treatment will be dependent upon the level of PD-L1 expression in the tumor and specific patient considerations that influence the use of immunotherapy.[1, 3, 13-15] Single agent immune checkpoint inhibitor may be recommended for those whose tumor PD-L1 expression is high. A combination of immune checkpoint inhibitor with chemotherapy (+/- an angiogenic targeted therapy) or duel

checkpoint inhibitors, may be recommended for patients with lower PD-L1 expression, for those in which the results are not available, those with a high tumor burden or rapidly progressing disease. Potential contraindications to immune checkpoint therapy may include previous underlying auto-immune diagnosis, prior organ transplant, and requirement of high dose steroids.[1, 3, 13-15] (Appendix 3)

Combination chemotherapy is recommended in patients who are in relatively healthy condition, unable to receive immune checkpoint therapy and without a driver mutation. Systemic chemotherapy is the standard of care for the majority of patients diagnosed with NSCLC.

The selection of chemotherapy is based on the specific type of NSCLC (eg, adenocarcinoma vs. squamous cell carcinoma), organ function (ie kidney, liver, bone marrow) and patient related factors including age, performance status and comorbidities.[1, 36] Treatment is usually 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). The combination usually consists of a combination of a platinum chemotherapy agent (cisplatin or carboplatin) and a second chemotherapy agent. In some cases, a third agent, such as a monoclonal antibody that targets vascular endothelial growth factor (VEGF) is added if patients are eligible to receive. A single agent or lower-dose weekly regimens may be used if a patient has poor performance status. Approved treatment options for NSCLC are listed in Appendices 1-3.

Maintenance Therapy for Advanced NSCLC

In most cases, combination therapies with chemotherapy, immune therapy and targeted therapies are administered for four to eight cycles. If patients' tumors have responded to therapy and toxicity profile is favorable, maintenance therapy will be recommended. Maintenance therapy consists of ongoing administration (beyond four to eight cycles) of at least one immune checkpoint inhibitor, chemotherapy, or targeted agent given during the primary treatment. The goal is to extend long-term benefit from primary treatment. Examples of maintenance therapy include immune checkpoint inhibitors (pembrolizumab, atezolizumab), pemetrexed, bevacizumab, and cetuximab.[1, 36-38]

Switch maintenance is the initiation of a new chemotherapy agent after primary treatment is completed. Examples of switch maintenance therapy include pemetrexed or docetaxel.[1, 36-38]

Second-Line Treatment for Non-Small Cell Lung Cancer

Second-line treatment is a treatment for disease that has progressed or recurred. 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. Several immune checkpoint inhibitors and chemotherapy agents are approved in the second-line setting.

For patients that are not eligible for treatment on immune therapy, a different combination of chemotherapy drugs is used. Radiation therapy and surgery may be considered depending on the site of recurrence.

Second-line treatment is a treatment for disease that has progressed or recurred.

Continuation After Disease Progression

If a patient has been on combination treatment with chemotherapy and targeted therapy, the chemotherapy portion of the regimen is discontinued. However, the targeted agent may be continued in the setting of disease progression in patients with driver mutations while awaiting the next line of therapy.[36]

Clinical Trials

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. Patients may be invited to participate in clinical trials at any stage of disease. See Chapter 7: *Clinical Trials and Emerging Therapies for Lung Cancer*.

Chemotherapy and Targeted Therapy Side Effects

Chemotherapy and targeted therapies for NSCLC can cause many unwanted side effects. These side effects occur because of the mechanism of action of the therapy. 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. Targeted therapy side effects are related to the specific pathway of cellular blockade. Not every side effect of chemotherapy or targeted therapy may be experienced. Frequency and severity of side effects may depend on factors such as the dosage, route

(intravenous or oral), frequency (how often therapy is given), and response of the individual body to the therapy. 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 and targeted therapy include and are not limited to fatigue, bone marrow suppression (anemia, leukopenia, thrombocytopenia, infection), gastrointestinal (anorexia [loss of appetite], nausea, vomiting, diarrhea, constipation, mucositis), or dermatologic (alopecia, pruritis, rash, nail changes). The patient may also experience flu-like symptoms, including body and muscle aches, fever, chills, headache, and nasal congestion, peripheral neuropathy or changes in vision, hearing, or cognition. (See Appendix 1 and 2)

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, the 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. 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. Drink plenty of fluids and try 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.[39]

When leukopenia or neutropenia (a 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. Patients will be at risk of developing infections during this time.[40-41]

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 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 100.4F), 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.[40-41] 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. There is an "on-body" infusion device for pegfilgrastim that may be applied at the end of your infusion. This device will automatically infuse pegfilgrastim at 24 hours post chemotherapy completion and eliminates the need for you to have to return to the clinic for administration.

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.

Anorexia, 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 tract and the brain. Anti-nausea medications block different pathways and neurotransmitter receptors.[42-44] Several antiemetic drugs are available and work on different pathways to prevent and treat different types of nausea, including acute, delayed, anticipatory, breakthrough, or refractory nausea. They may be available as oral or intravenous. (Table 2) Different antiemetic drugs commonly are used in combination and may be given before, during, or after chemotherapy. Your health care team will estimate the likelihood that your chemotherapy regimen will trigger nausea and vomiting when prescribing a prevention strategy.[42] When the optimal antiemetic regimen is used, nausea or vomiting may be prevented or minimized.

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. See Chapter 11: *Integrative Medicine, Complementary Therapies, and Chinese Medicine in Lung Cancer*. 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 include the female gender, history of prior chemotherapy induced nausea and vomiting, younger than 50 years of age, dehydration, electrolyte imbalances, history of motion sickness, brain metastases, anxiety, bowel obstruction or slow bowel transit, and use of opioids to control pain.[42]

Table 2. Common Antiemetic Drugs for Nausea and Vomiting Induced by Chemotherapy [42-44]

Serotonin (5-HT3) antagonists	Neurokinin-1 (NK1) antagonist
Granisetron (Granisol®, Kytril®, Sancuso®) Ondansetron (Zofran®) Palonosetron (Aloxi®) Dolasetron (Anzemet®)	Aprepitant or Fosaprepitant (Emend®) Rolapitant (Varubi®)
Combination 5-HT3 and NK1 antagonist	
Netupitant/palonsetron (Akynzeo®) Fosmetopetent/palonesetron	
Other	
Dexamethasone (Decadron®) Dronabinol (Marinol®) Prochlorperazine (Compazine®) Promethazine (Phenergan®) Alprazaolam (Xanax®) Haloperidol (Haldol®) Lorazepam (Ativan®) Olanzapine (Zyprexa®) Metoclopramide (Reglan®) 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 essential 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. Drink electrolyte-rich fluids such as water, juice, soup broth, or commercially available electrolyte drinks and consume 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 more severe that prescription medications are prescribed such as diphenoxylate/atropine (Lomotil®) or octreotide.[45-46]

The patient should keep a record of the number of loose stools per day or change in ostomy output 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.[47-48] Prevention of constipation includes eating a diet high in fiber (grains, beans, and vegetables), drinking eight 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. Fatigue is the feeling of overwhelming tiredness. Fatigue can be caused by cancer, 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.[49] Fatigue can affect how patients feel physically, emotionally, and spiritually, as well as interfere with the ability to function or socialize. 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 many varied factors can cause fatigue, 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 a moderate physical activity such as walking, and participating in relaxation activities such as yoga, massage, or acupuncture. 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 the patient's appetite can also be helpful. It is useful 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. Patients should contact their provider if they experience an increase in their fatigue, the inability to get out of bed or think clearly, or fever, or chills.

Alopecia

Alopecia is temporary or permanent hair loss. Alopecia 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 usually 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 (sunburn) or cold temperatures and to keep the skin lubricated with ointments and creams to avoid dryness. After chemotherapy completion, the hair may grow back; however, this usually begins within three months after the last treatment.[31] Scalp hypothermia is a cooling systems used before, during and after chemotherapy infusions to help reduce hair loss in patients with certain cancer diagnoses. These cooling methods work by narrowing blood vessels beneath the skin of the scalp, reducing the amount of chemotherapy that reaches hair follicles. There are no controlled clinical trials to support the use in patients with lung cancer.

Cutaneous (Skin and Nail) Changes

Changes to the skin and nail may occur due to chemotherapy, especially if a patient is being treated with targeted therapies (EGFR inhibitors, ALK inhibitors, monoclonal antibodies, and immune therapies).[50-51] Rash is the most common skin-related side effect from targeted therapies.[36] The rash is usually acneiform (looks like acne with pustules or whiteheads) and is located on the face, chest, abdomen, or thighs.[50-51] It is important for the patient not to pop the pustules as this could lead to infection requiring antibiotics. The 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 or spontaneously resolve. For the most part, reducing the dose or interrupting therapy for a

brief period is the most effective way to manage moderate to severe cutaneous reactions related to targeted therapies. 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 to become sensitive to sunlight, therefore, staying out of direct sunlight and wearing sunscreen is essential.

Mucositis

Mucositis is inflammation and ulceration of the lining of the mouth, throat, and digestive tract. Mucositis occurs due to direct cellular kill by chemotherapy, as well as the release of oxidative, inflammatory, and metabolic by-products.[52-54] 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. 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).[36, 55-56] 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); trichomegaly (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 visual impairment.[57-58]

Cognitive Dysfunction

The cognitive change, also known as "chemo brain," is a decrease in mental sharpness. Chemotherapy is one of the 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. The patient should notify their providers when "chemo brain" interferes with their normal daily activities and their ability to work.[59-60]

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, 61] Peripheral neuropathies may interfere with normal activities and may cause difficulties performing fine motor movements such as buttoning a shirt, writing, or picking up utensils. When experiencing 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 (TENS) a therapy that uses low-voltage electrical current for pain relief. See Chapter 11: *Integrative Medicine, Complementary Therapies, and Chinese Medicine in Lung Cancer.*

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.

Immunotherapy Side Effects

Side effects of immune therapy will be discussed separately, as the mechanism of how they develop, and the necessary management is usually different than the side effects of other systemic treatments. Immune therapy treatments are typically well-tolerated. The most common side effects are fatigue and myalgias. These are usually low grade. Immune-related adverse events (IrAE's) are unique class-specific effects of the inflammatory response on healthy cells. These are caused by inflammation and attack on healthy cells and organs. In general, these are low grade or mild. However, if left unmanaged, they can proceed to severe and even life-threatening. IrAE's can affect any body organ system. The pattern of occurrence can be immediately after a dose, after several doses, or even after discontinuation of therapy. They can affect more than one organ system at a time. The severity may increase with combination therapy. Systems affected include (but not limited to) those in Table 3.[36, 62-69]

Management of IrAE's includes delaying or stopping the immune checkpoint inhibitor therapy. In many cases, the IrAE will resolve on its own. However, it may be necessary to undergo further evaluation, testing, and treatment to prevent more serious progression of the IrAE. As these are inflammatory in nature, steroids are used to control and reverse the inflammation of most of the IrAE's. Steroid dosing is dependent on the seriousness of the IrAE and typically continue over several weeks.[62-69] It is important to adhere to the steroid schedule, as missing or discontinuing doses, can lead to a flare of the toxicity that can be life-threatening. Additional supportive medications may be prescribed to minimize the side effects of the steroids.

In some cases, additional immunosuppressant therapy may be required to treat the IrAE. Endocrine IrAE's are usually treated with replacement of the endocrine hormone that is deficient. In most cases, the patient will require hormone replacement for the rest of their life. The healthcare team may consult with other sub-specialists to assist in the management of the IrAE. It is imperative that patients notify the healthcare team immediately of the onset of any symptoms so that these can be properly evaluated and treated.

Table 3. Immune Related Adverse Events

Organ system	**IrAE**	**Symptoms**	**Self-Strategies**
Gastrointestinal	Diarrhea, colitis, nausea, mucositis, perforation	Abdominal pain or cramping, loose stools	Maintain adequate hydration; Avoid spicy foods
Dermatologic	Rash, Mucositis	Rash, itching, blistering, skin peeling, mouth tenderness	Sunscreen & protection, sunglasses; emollient lotions
Pulmonary	Pneumonitis	Shortness of breath, difficulty breathing, cough, chest pressure	Smoking cessation; avoid inhaled irritants
Endocrine	Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, hyperglycemia, diabetes	Fatigue, palpitations, sluggishness, headache, decreased focus, anxiety	Maintain adequate rest
Liver	Hepatitis (inflammation of the liver)	Decreased function of liver, increase in liver enzymes	Avoid taking over the counter medications that are metabolized by liver (i.e. acetaminophen); Avoid alcohol consumption
Kidneys	Nephritis	Decreased function of kidneys, increase in fluid retention	Avoid taking over the counter medications that are metabolized by kidney (i.e. NASAIDS); Maintain adequate hydration
Pancreas	Pancreatitis	Nausea, abdominal discomfort, emesis	Avoid alcohol and high fat food content

Organ system	IrAE	Symptoms	Self-Strategies
Cardiac	Pericarditis, Myocarditis	Increased shortness of breath, arrythmias, chest pressure or pain	Minimize drug-drug reactions by reviewing all new medications with health care team
Musculoskeletal	Myalgias, Arthralgias	Muscle or joint aches or inflammation, decreased range of motion of joint	Maintain health exercise and range of motion
Nervous System	Peripheral Neuropathy, myasthenia gravis, Guillain Barre	Decreased sensation, impaired ambulation	Use caution when handling hot/cold materials; May need walking aide
Eyes	Uveitis, iritis, conjunctivitis	Impaired vision, dryness, itching, pain, swelling	Lubricating eye drops

Conclusion

Shared decision making is an essential component of treatment for NSCLC. Patients should discuss goals of care with the oncology provider at the time of diagnosis and throughout the course of therapy, particularly when ever new treatment decisions need to be made. The patient should speak with the oncology provider or nurse about specific side effects that may be expected from the chemotherapy, targeted therapy, and immune therapy. Discuss how these side effects might be prevented and how they will be monitored 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 addition, 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.

Questions to Ask Your Medical Oncologist

You may want to ask your doctor some of the following questions before you decide on your lung cancer treatment.

What are the ways to treat my type and stage of cancer?

What are the benefits and risks of each of these treatments?

What treatment do you recommend? Why do you think it is best for me?

When will I need to start treatment?

Will I need to be in the hospital for treatment? If so, for how long?

What is my chance of recovery with this treatment?

How will we know if the treatment is working?

Would a clinical trial (research study) be right for me?

Questions About Chemotherapy

What type of chemotherapy will I receive and how long will the treatment last?

What are the benefits and risks of chemotherapy?

What are the side effects of chemotherapy?

How often do patients experience these side effects?

How are the side effects managed?

Questions About Immunotherapy

Cancer immunotherapy is one of today's newest approaches to treating cancer. Lung cancer has been a major area of focus in immunotherapy research, and several immunotherapy medicines are now available for the treatment of specific types of advanced lung cancer.

What is immunotherapy?

Is immunotherapy right for me? Do I need to be tested in order to be put on an immunotherapy treatment?

What are the potential benefits?

What are the potential side effects?

How is immunotherapy given, and how often do I undergo treatment? Where do I undergo treatment?

How long will I have to receive immunotherapy treatment?

Questions About Targeted Therapy

Targeted therapy is the foundation of precision medicine that is technically considered chemotherapy, however, target therapy goes after the cancer cell's inner workings, it is a type of cancer treatment that targets the changes in cancer cells that help them grow, divide, and spread.

What is targeted therapy?

Are there any medications that target my type of lung cancer?

What type of targeted therapy will I receive and how long will the treatment last?

What are the benefits and risks of targeted therapy?

What are the side effects of targeted therapy?

How often do patients experience these side effects?

How are the side effects managed?

Will this therapy be covered by my insurance?

Notes

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 (mucositis), 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 (mucositis), diarrhea, liver and kidney function changes, nail bed changes (onycholysis)
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 (mucositis), 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)

Chemotherapy Drug	Common Side Effects
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 (mucositis), 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
Albumin-Bound Paclitaxel (Abraxane®)	Myelosuppression (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 paresthesia's), 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 (2021).[36]

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

Targeted Therapy	**Dose**	**Side Effects**
EGFR Inhibitors		
Osimertinib (Tagrisso™)	80mg orally, daily, with or without food	Diarrhea, rash, dry skin, nail changes (redness, swelling, pain, nail breakage). Severe lung and cardiac effects
Erlotinib (Tarceva®)	150mg orally, once daily. Take 1 hour before or 2 hours after a meal	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 gastrointestinal (GI) hemorrhage
Afatinib (Gilotrif®)	40mg 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
Gefitinib (Iressa®)	250mg orally, daily, with or without food	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 gastrointestinal (GI) hemorrhage

Targeted Therapy	Dose	Side Effects
EGFR Inhibitors, continued		
Dacomitinib (Vizimpro®)	45mg orally once daily without food	Diarrhea, rash, nail/cuticle changes, mouth sores, decreased appetite, dry skin, weight loss, hair loss, cough, interstitial lung disease
Amivantamab-vmjw	Intravenously. Rate based on week of infusion. Week 1, days 1 & 8; then weekly for 4 weeks, followed by administration every 2 weeks starting with week 5	Rash, dry skin, itching, 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), nausea, vomiting, low phosphorus, increased blood glucose, decreased sodium
Cetuximab (Erbitux®)	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
Necitumumab (Portrazza™)	Intravenously over 60 minutes on days 1 & 8 of each 3-week cycle	Skin rash, inflammation of the eyes & fingers (conjunctivitis & paronychia). magnesium deficiency, muscle weakness, blood clots, infusion reaction

Targeted Therapy	Dose	Side Effects
EML4-ALK Inhibitors		
Alectinib (Alecensa®)	Take 600mg every 12 hours (2 times daily). Take four- 150mg capsules at each dose for total of 8 capsules daily. Take with food	Fatigue, constipation, swelling in hands, feet, ankles, and eyelids; Muscle weakness or tenderness, lung (pneumonitis), liver, or cardiac toxicities
Crizotinib (Xalkori®)	250mg 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
Ceritinib (Zykadia™)	750mg 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 (hyper-glycemia), fatigue, decrease appetite, constipation
Brigatinib (Alunbrig®)	90mg orally, once daily for 7 days, if tolerated increase to 180mg orally once daily.	Nausea, diarrhea, fatigue, cough, headache, lung toxicity (interstitial lung disease/pneumonitis), hypertension, decreased heart rate, visual disturbances, increase in blood sugar levels (hyperglycemia), increase in pancreatic enzymes
Lorlatinib (Lorbrena®)	100mg orally once daily	Fluid retention, peripheral neuropathy, cognitive effects, shortness of breath, fatigue, weight gain, joint aches, mood changes, diarrhea, increased lipid, heart arrythmias

Targeted Therapy	Dose	Side Effects
BRAF V600E Inhibitors		
Dabrafanib (Tafinlar®) & Trametinib (Mekinist®)	Dabrafanib: 150mg orally twice daily, at least 1 hour before or 2 hours after a meal Trametinib:2mg orally once daily, at least 1 hour before or 2 hours after a meal.	Headache, fever, joint aches, hair loss, hand-foot redness, swelling & pain; secondary cancers; bleeding, enlargement of heart (cardiomyopathy), visual disturbances, rash, hyperglycemia, anemia, colitis, deep vein thrombosis & pulmonary embolism (blood clotting), interstitial lung disease
Vemurafenib (Zelboraf®)	960 mg twice daily with or without a meal.	Joint aches, rash, hair loss, fatigue, sensitivity to sun, nausea, skin itching, vision changes
ROS 1 Inhibitors		
Cabozantinib (Cabometyx®)	60 mg orally daily	Diarrhea, fatigue, decreased appetite, nausea, hypertension, vomiting, constipation, hand-foot rash
Crizotinib (Xalkori®)	250mg 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
Ceritinib (Zykadia™)	750mg 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 (hyper-glycemia), fatigue, decrease appetite, constipation

Targeted Therapy	Dose	Side Effects
ROS 1 Inhibitors, continued		
Entrectinib (Rozlytrek®)	600 mg once daily	Fatigue, constipation, taste changes, swelling, dizziness, diarrhea, nausea, shortness of breath, muscle aches, vision changes. Increased risk for skeletal fractures, elevation of liver enzymes, low uric acid, ECG changes, congestive heart failure.
Lorlatinib (Lorbrena®)	100mg orally once daily	Fluid retention, peripheral neuropathy, cognitive effects, shortness of breath, fatigue, weight gain, joint aches, mood changes, diarrhea, increased lipid, heart arrythmias
NTRK Inhibitor		
Entrectinib (Rozlytrek®)	600 mg daily	Fatigue, constipation, taste changes, swelling, dizziness, diarrhea, nausea, shortness of breath, muscle aches, vision changes. Increased risk for skeletal fractures, elevation of liver enzymes, low uric acid, ECG changes, congestive heart failure
Larotrectonib (Vitrakvi®)	100mg orally twice daily	Fatigue, nausea, dizziness, vomiting, cough, impaired liver function, constipation, diarrhea, neurotoxicity, peripheral neuropathy

Targeted Therapy	Dose	Side Effects
MET ex 14 skipping Inhibitors		
Capmatinib (Tabrecta®)	400 mg orally twice daily with or without food	Swelling in extremities, nausea, fatigue, vomiting, shortness of breath and decreased appetite; Interstitial lung disease, elevation of liver function tests, photosensitivity to sun
Tepotinib (Tepmetko®)	450 mg orally once daily with food	Swelling, fatigue, nausea, diarrhea, musculoskeletal pain, shortness of breath, interstitial lung disease; Laboratory abnormalities: liver enzymes, lymphocytes, amylase, sodium, albumin, hemoglobin
RET Inhibitor		
Selpercatinib (Retevmo®)	80 mg orally twice daily with or without food	Hypertension, ECG changes, bleeding, alterations in liver enzymes, hypersensitivity, altered wound healing, fatigue, diarrhea, nausea, vomiting, swelling.
Pralsetinib (Gavreto®)	400 mg orally once daily on empty stomach. No food for at least 2 hours before and one hour after	Hypertension, interstitial lung disease, pneumonitis, constipation, fatigue, musculoskeletal pain, diarrhea; Laboratory abnormalities: decreased white blood cells, hemoglobin, platelets, phosphate, calcium sodium; Increase in liver enzymes.
KRAS B12C Inhibitor		
Sotorasib (Lumakras®)	960 mg orally once daily; with or without food	Diarrhea, muscle aches, nausea, fatigue, cough, shortness of breath, Interstitial lung disease; increase in liver function tests, increased urine protein, decreased sodium

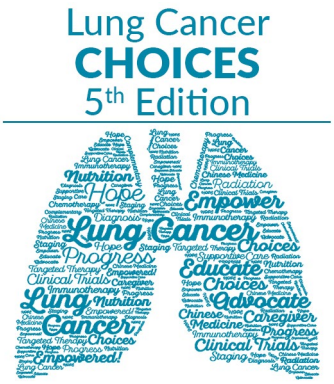
Targeted Therapy	Dose	Side Effects
VEGF Inhibitors		
Bevacizumab (Avastin®)	Given intravenously over 90 minutes for the first dose and 30mg for subsequent doses, every 3 weeks.	Nose bleeds (epistaxis), high blood pressure, decreased wound healing, gastrointestinal perforation, protein in the urine (proteinuria), 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
Ramucirumab (Cyramza®)	Intravenously over 60 minutes every 2 weeks	High blood pressure; diarrhea; bleeding, blood clots, fistula formation and delayed wound healing
Sunitinib (Sutent®)	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 (mucositis), increase risk for heart dysfunction, adrenal insufficiency, low thyroid function (hypothyroidism)

*Adapted from Chu E and Devita VT. Physicians' Cancer Chemotherapy Drug Manual (2021).[36]

Appendix 3. Immune Therapy Drugs Approved for Non-Small Cell Lung Cancer

Drug	Target	Dosing
Cemiplimab-rwlc (Libtayo®)	PD-1	Intravenous over 30 minutes every 3 weeks. First line: PD-L1 Tumor Proportion Score (TPS) score >50%)
Pembrolizumab (Keytruda®)	PD-1	Intravenous over 30 minutes every 3 weeks First-line: Combination with chemotherapy or monotherapy every 3 or 6 weeks Second-line: monotherapy every 3 weeks
Nivolumab (Opdivo®)	PD-1	Intravenous over 60 minutes every 2-or 4-weeks monotherapy second-line or in combination with ipilimumab
Atezolizumab (Tecentriq®)	PD-L1	Intravenous over 30 minutes First-Line: Combination with chemotherapy & Bevacizumab every 3 weeks; or monotherapy every 2, 3 or 4 weeks Second-line: single agent
Durvalumab (Imfinzi®)	PD-L1	Intravenous over 30 minutes every 2 or 4 weeks, monotherapy following chemotherapy & radiation therapy
Ipilimumab	CTLA-4	Intravenous every six weeks with nivolumab every 2 weeks or Intravenous every six weeks with nivolumab and chemotherapy every three weeks. First line: with PD-L1 >1%

*Adapted from Chu E and Devita VT. Physicians' Cancer Chemotherapy Drug Manual (2021).[36]



Chapter 5

Radiation Therapy for Non-Small Cell Lung Cancer

Join Y. Luh, MD, FACP, FACR 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 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. See Chapter 6: *Treatment for 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 with concurrent chemotherapy (chemoradiation), may be used to treat lung cancers that are too extensive to remove surgically. Radiation therapy can also 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 often 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 cancer cells and allows the patient and normal cells to recover during the weekend from the effects of radiation. The treatment takes 2 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 better 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 who have completed medical school and at least five years of residency training before joining the workforce. They are frequently certified by the American Board of Radiology (although they are not diagnostic radiologists). Radiation oncologists talk to, examine, and counsel patients for consultation, and design and direct the radiation treatment plan. Radiation oncologists are the physician specialists during a patient's radiation therapy who provide evaluation, simulation (discussed next), weekly treatment visits, and follow-up visits after completing treatment. (Figure 1)

> *Whenever you find yourself doubting how far you can go, just remember how far you have come. Remember everything you have faced, all the battles you have won, and all the fears you have overcome.*
>
> *- Anonymous*

Figure 1. A radiation oncologist confers with a medical physicist to develop a radiation treatment plan for a lung cancer patient

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.

The delivery of radiation therapy requires several individual team members that play a crucial role in the successful treatment of patients.

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. In some institutions, X-rays are taken after the patient's treatment position has been determined.

Figure 2. A CT scan of the neck and chest is done in the treatment position with all immobilization devices in place

Some radiation therapy facilities will gently 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. (Figure 2) 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 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 lung cancer especially when lymph nodes in the chest are to be included into the treatment fields. Planning CT scans for simulation typically take less time to obtain than diagnostic scans. Furthermore, planning CT scans are not routinely 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. For tumor located in the middle or lower parts of the lung, there is likely to be movement of the tumor that coincides with respiration. In such cases, patients can be instructed to hold their breaths for up to 30 seconds at a time. During the breath holding intervals, the tumor is less likely to move.

Treatment Planning

After the simulation is completed, the radiation oncologist, dosimetrist, and medical physicist develop a customized treatment plan that is designed for the individual patient. 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, esophagus, chest wall, ribs, 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 3) The radiation oncologist, using information from positron emission tomography (PET) scans (Figure 4), 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 a bright color such as 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 cancer with more accuracy. In fact, using a PET scan with treatment planning results in more accurate targeting of the tumor, resulting in less radiation to normal tissues, less chance of the tumor growing back, and slightly longer survival than patients getting treatment planning with CT alone.[4]

Figure 3. Contours of Normal Organs and the Gross Tumor Volume

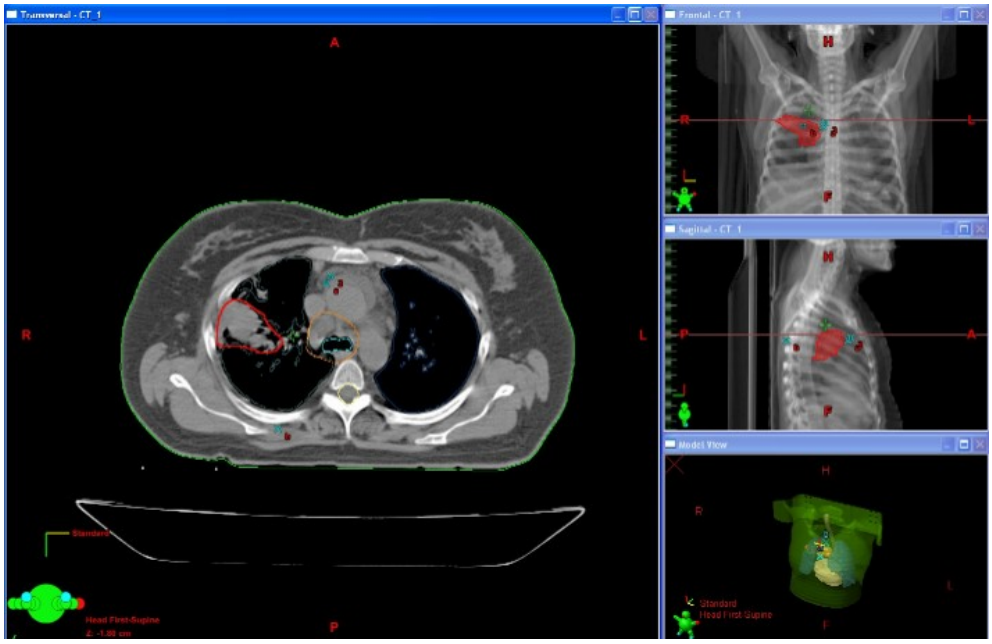
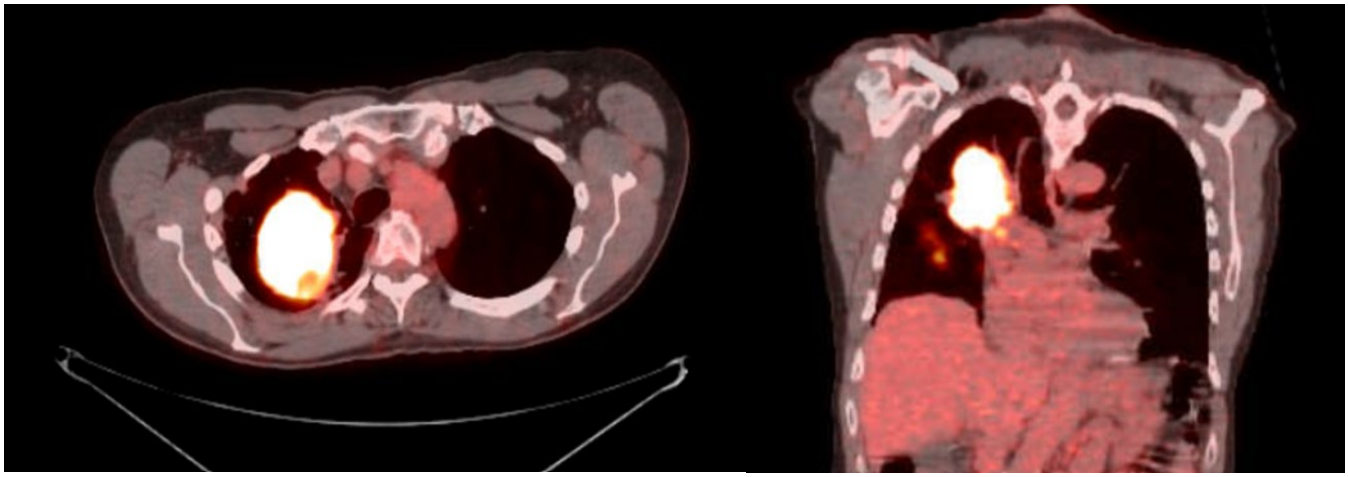


Figure 4. PET/CT scan showing location and shape of active lung cancer

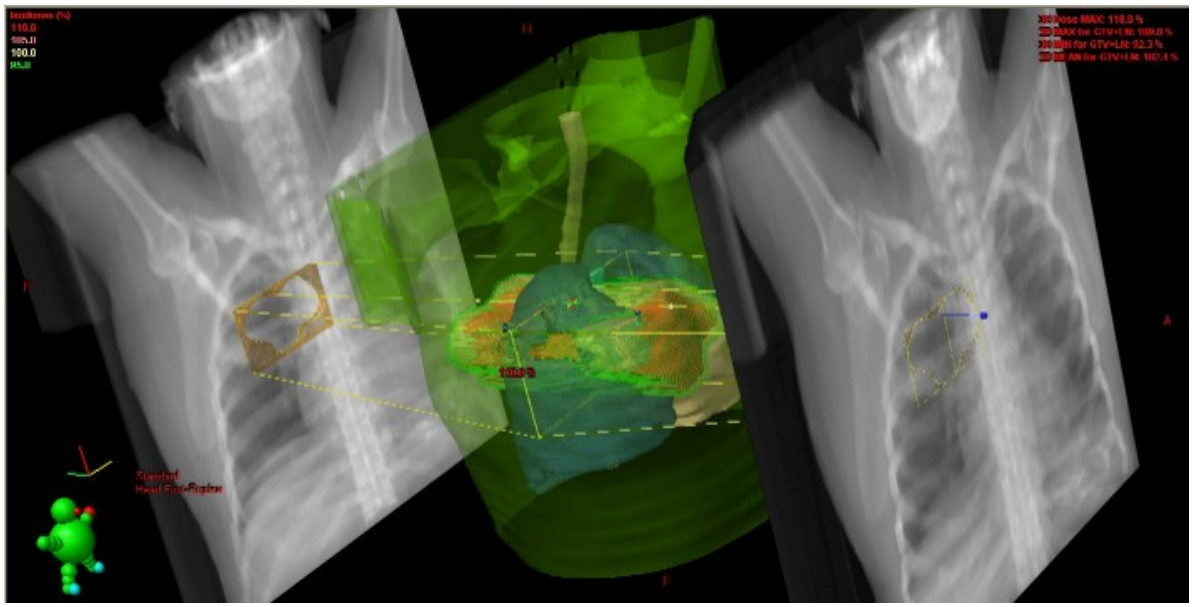


After the normal tissue volumes and gross tumor volume have been defined, the tumor is more clearly seen in relation to other organs. The dosimetrist or radiation oncologist set up portals or fields that encompass the gross tumor volume and the involved mediastinal lymph nodes. The mediastinum is a space 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]

Three-Dimensional Conformal Radiation Therapy

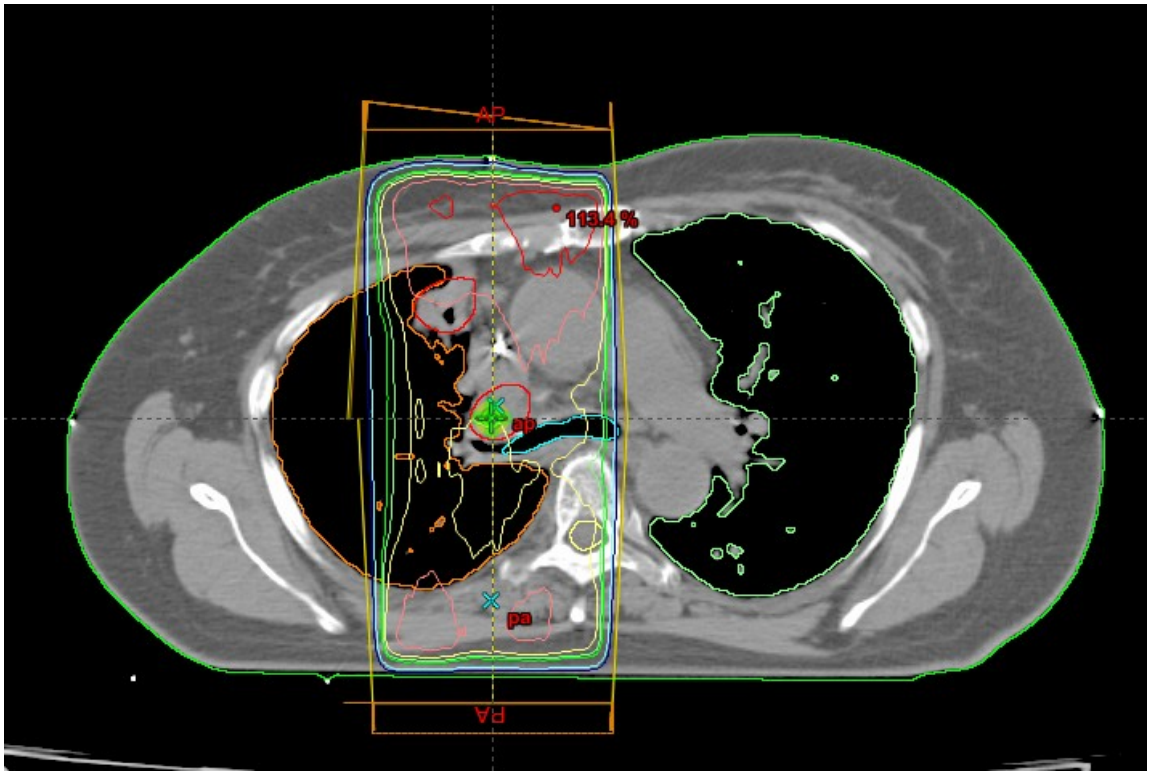
The classic method used to treat lung cancer involves two fields: one field is oriented facing the patient's front chest (anteroposterior [AP]) and one field is oriented facing the patient's back (posteroanterior [PA]). The term AP/PA is used to describe this setup. (Figure 5) This method is used much less in the United States in favor of intensity modulated radiation therapy (IMRT) discussed in the next section.

Figure 5. Computer Generated Image of Chest Fields



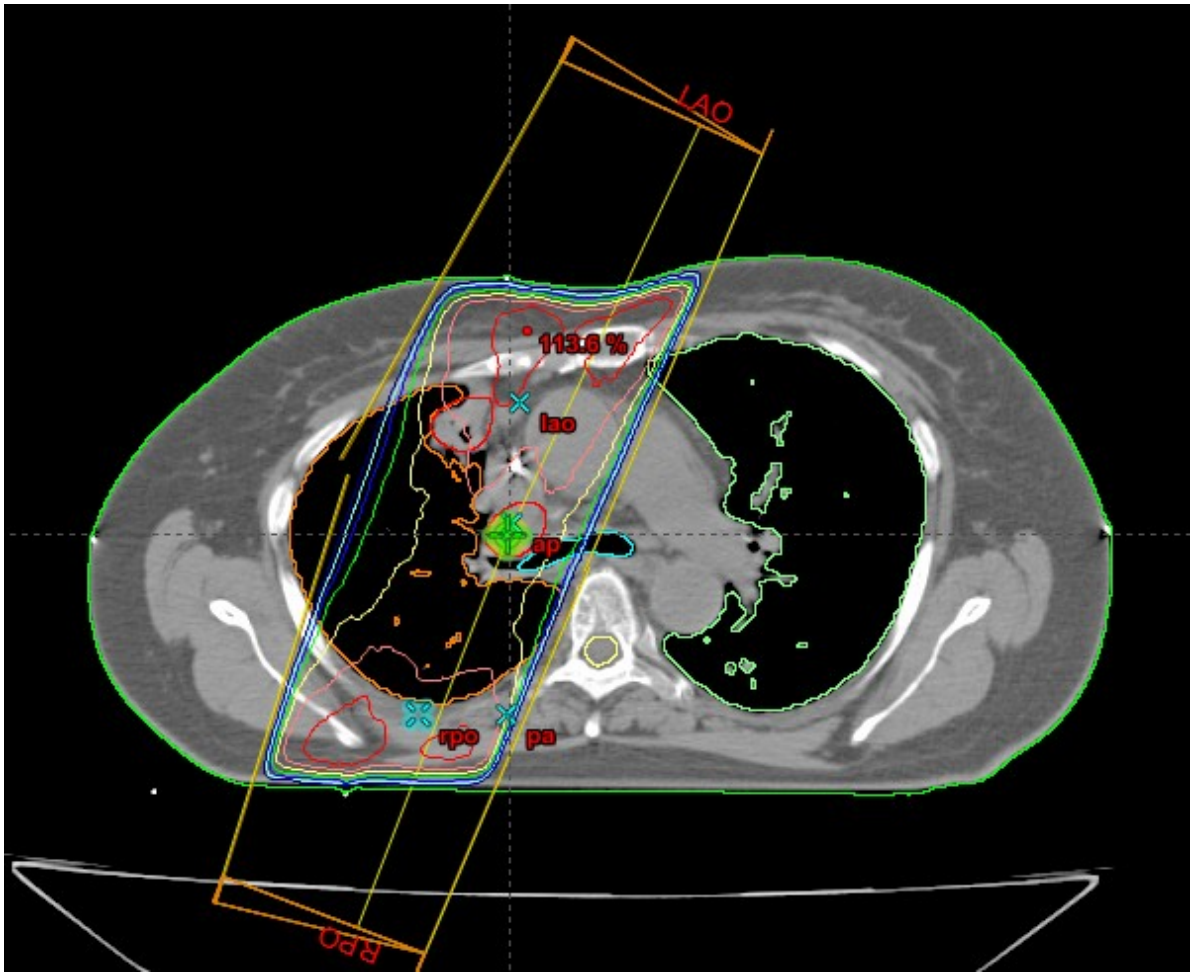
The initial AP/PA fields frequently include the spinal cord. (Figure 5a) The spinal cord can usually tolerate 5000 cGy before the risk of spinal cord damage occurs. Radiation oncologists usually aim to keep the spinal dose below 4500 to 5000 cGy but may use a lower dose when chemotherapy is used concurrently 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 5a, the radiation dose is shaped more like a rectangle and results in some normal lung getting the similar doses as the tumor volume.

Figure 5a. 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 where they are oblique where they are diagonal and avoid the spinal cord. (Figure 5b) 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.

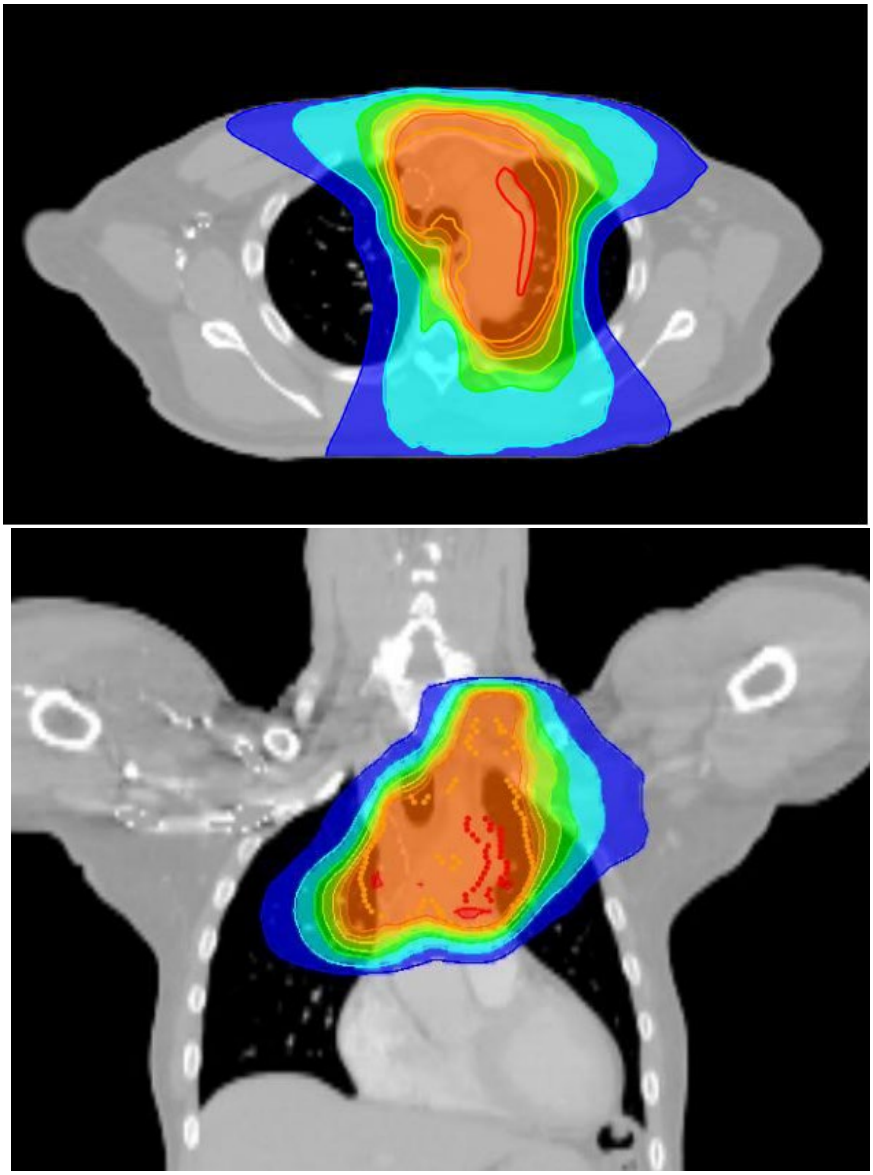
Figure 5b. Oblique Fields Angled to Avoid the Spinal Cord



Intensity Modulated Radiation Therapy

A technique known as intensity-modulated radiation therapy (IMRT), uses multiple beams or fields directed at the gross tumor volume and involved lymph nodes, and is becoming a recognized standard technique used to treat lung cancer. A 1.0 to 2.0 cm margin frequently is placed around the visible tumor to account for tumor movement (from breathing, setup variation, and patient motion). IMRT has been the preferred 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 6) 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 can dose to any organ and can limit the radiation dose to normal organs that do not need to be radiated. 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.

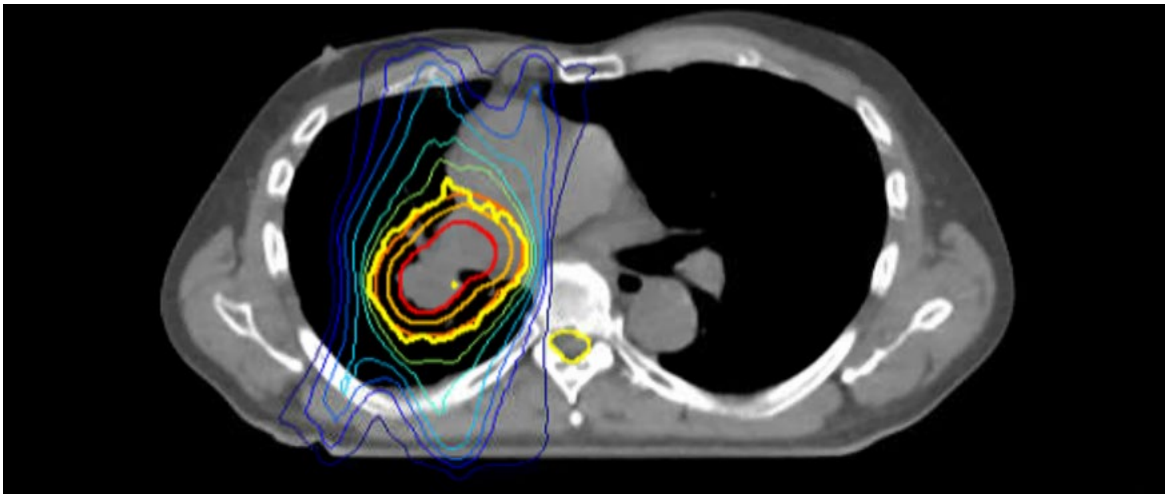
Figure 6. Rendering of Doses in an IMRT Plan



Images courtesy of Steve Rhodes, M.S., R.T.(T), CMD

Traditional IMRT uses a "fixed-field" or "step and shoot" approach which uses a limited number of beam angles to treat the lung cancer. A newer version of IMRT is volumetric modulated arc therapy (VMAT) which uses continuous arcs of radiation beams providing many more angles for IMRT planning, resulting in a smoother shape of radiation. VMAT can deliver the treatment much faster (one to two minutes) than a typical fixed-field technique (five to fifteen minutes). Newer linear accelerators tend to deliver treatments faster. (Figure 6a)

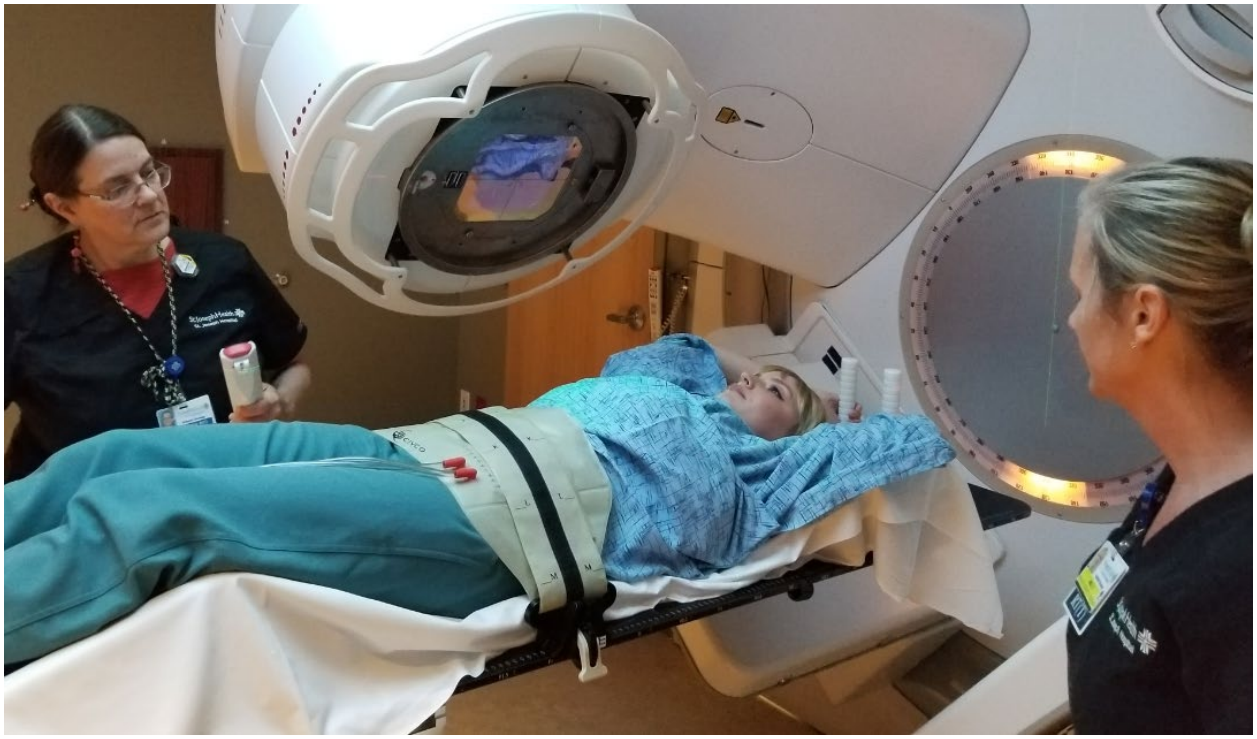
Figure 6a. A 7-field "step and shoot" IMRT plan



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%.[5]

After the treatment plan is completed, the patient returns to the radiation therapy department for a block check or verification procedure. (Figure 7) 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 perform a low energy CT scan called a cone beam CT (CBCT) 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 (see section on Quality Assurance). Whether you receive 3D conformal, multi-field IMRT, or VMAT, your radiation oncologist will determine which technique is best for your specific case.

Figure 7. 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 seven weeks. The patient is on the treatment table receiving radiation for 5 to 10 minutes sometimes fewer with a newer machine. (Figure 8) Patients are usually in the department for 20 to 30 minutes or less, to include 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.

"Courage doesn't always roar, sometimes it's the quiet voice at the end of the day whispering, I will try again tomorrow.

- Mary Anne Radmacher

Figure 8. 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. See *Questions to Ask*

Quality Assurance

Traditionally, an X-ray is taken every five treatments with a beam's eye view of the treatment fields. The radiation oncologist would compare this X-ray to images (digitally reconstructed radiographs, DRR's) generated from the planning CT scan with the treatment fields in place to ensure that the tumor is being targeted accurately. It is difficult to see actual organs in these films, with mainly bones serving as landmarks for the treatment fields. If the fields are off by more than 5 to 10 mm, the radiation oncologist will instruct the radiation therapist to make a shift in the direction(s) to offset the difference. This technique has largely been replaced by image-guided radiation therapy (IGRT) with onboard cone-beam computed tomography (CBCT) in which a low energy CT scan is done prior to every treatment and aligned to the treatment planning CT scan. This form of IGRT has become very popular and allows the radiation therapist to more realistically align the patient's daily anatomy to the treatment planning CT structures, instead of just bones.[6] (Figure 9 and 10)

Figure 9. (Left) A digital reconstructed radiograph (DRR), reconstructed from the patient's planning simulation CT and (Right) a port film taken from the linear accelerator with the patient on the table. Note the port film is similar to a plain X-ray and lacks detail in soft tissues, so the physician relies on bones to determine the accuracy of the field.

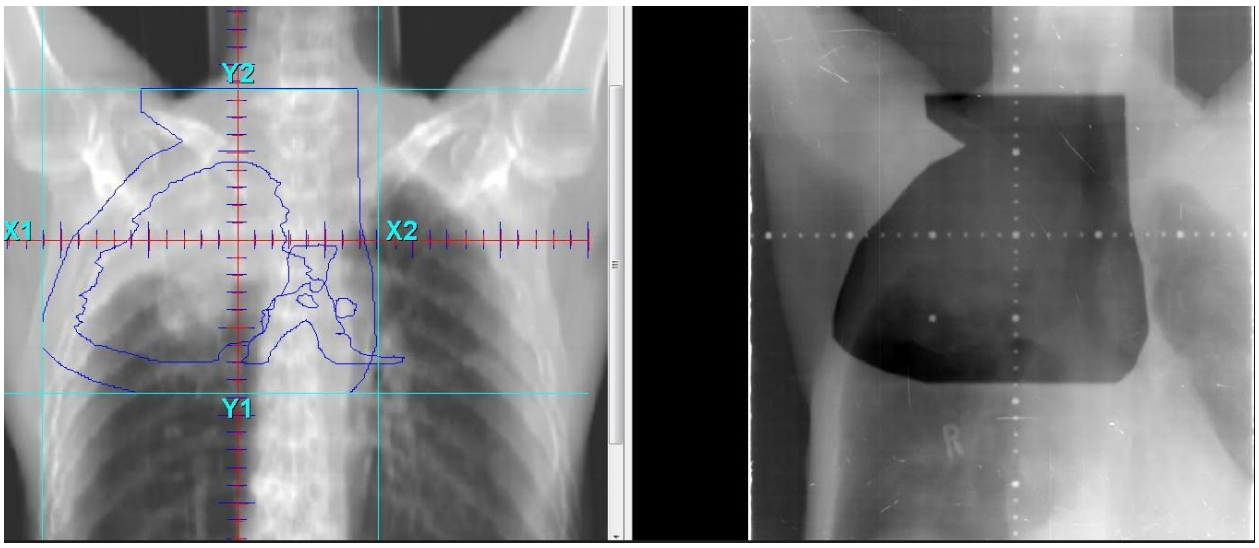
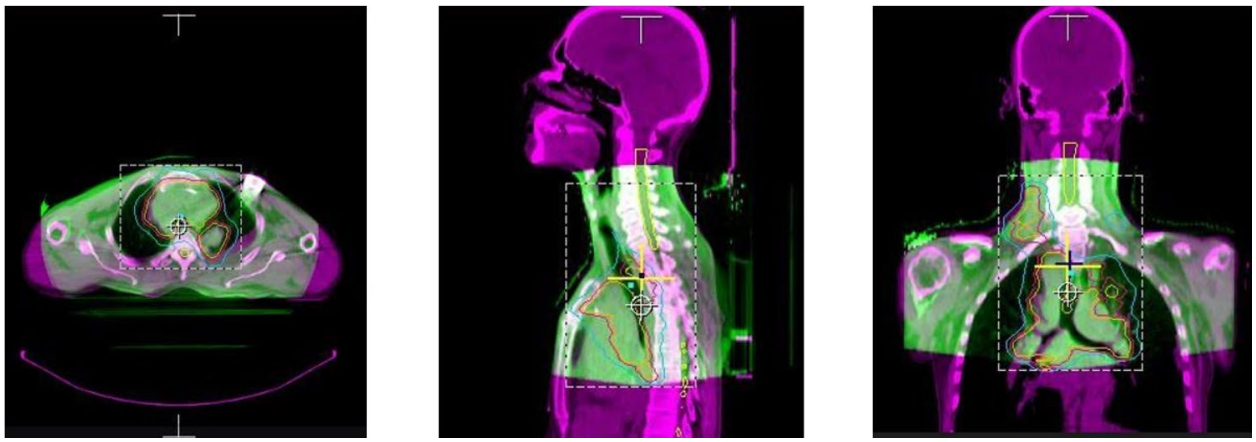


Figure 10. Modern image guided radiation therapy (IGRT) with the use of cone beam CT. The purple images are taken from the patient's planning simulation CT and the green images are the cone beam CT taken from the linear accelerator with the patient on the table. Note the increased detail and ability to see the organs and tumor in 3 different planes.



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 risk of

surgery and anesthesia. If surgery cannot be done for stage I or II non-small cell lung cancer, radiation therapy is a good alternative.

Conventional Radiation

In centers that do not have access to stereotactic radiation techniques (discussed below), conventional radiation therapy for stage I and II non-small cell lung cancer is still an accepted treatment. Conventional radiation for lung cancer gives a total dose of 6600 to 7000 cGy to the lung tumor volume, in doses of 180 to 200 cGy per day over seven weeks. Stage I and II non-small cell lung cancers have not spread to the lymph nodes in the middle of the chest between the lungs (mediastinum), so only the lung tumor is treated, making the amount of tissue radiated much smaller.[7]

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 if larger doses are given per treatment, a technique called hypofractionation. However, larger doses per treatment may result in more tissue scarring, especially in long term survivors. Therefore, to minimize the effect of lung scarring caused by hypofractionation, radiation must be limited to a smaller volume of tissue. For fragile patients who are too sick to come for treatment for seven weeks, hypofractionation with 4800 cGy in fractions of 400 cGy over 12 treatments (2 weeks and 2 days) has been used successfully.[8]

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

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 five treatments over one week. The term SRS has always been used to describe this technique 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. (Figure 11) Gamma Knife, CyberKnife, and linear accelerator-based SRS (TomoTherapy®, Elekta VMAT, and RapidArc®) are examples of proprietary methods of delivering SRS using a linear accelerator. Gamma Knife® is only used for SRS to brain lesions.

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 five treatments over one week.

Stereotactic radiosurgery for tumors *outside of the brain* is known as stereotactic body radiation therapy (SBRT), stereotactic ablative radiotherapy (SABR), or extracranial radioablation (ECRA). SBRT is the most common term to describe any type of stereotactic radiosurgical technique to treat tumors in the spine, lung, liver, pancreas, adrenal glands, or lymph nodes—anything outside the brain. This method is widely used for patients with stage I or II non-small cell lung cancer who are either too frail for surgery or do not want surgery, with comparable or better outcomes when compared with the conventional radiation therapy techniques described above.[7, 9] Dose schedules in stereotactic body radiation therapy includes either a total dose of 2500 to 3400 cGy in one single treatment, 4500 to 6000 cGy given in 3 treatments of 1500 to 2000 cGy over a period of one to two weeks, a total dose of 4800 cGy given in 4 treatments of 1200 cGy, 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 lung tumor is ≤ 5 cm in greatest diameter and peripheral to the mediastinum (more to the side of the chest rather than the middle).[10] Larger tumors or tumors closer to the middle of the chest (mediastinum) that are right next to important organs (heart, esophagus, main bronchi, aorta, superior vena cava) are more safely treated with doses of 6000 to 7000 cGy over eight to ten treatments. CyberKnife and linear accelerator based SBRT (TomoTherapy®, Elekta VMAT, and RapidArc®), are examples of proprietary methods of delivering SBRT. Again, Gamma Knife® is not used in SBRT because it is only used for brain tumors.

Figure 11. A Rendering of Dose and Beams in a SBRT Plan

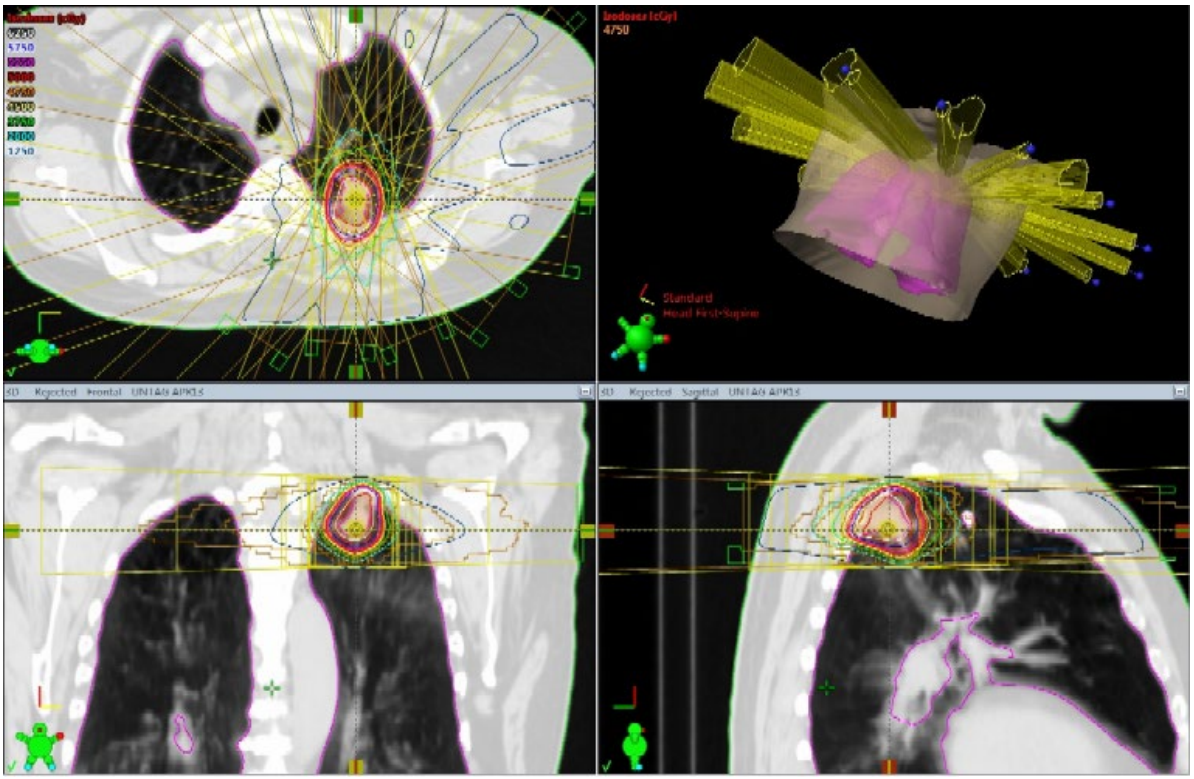


Image courtesy of Steve Rhodes, M.S., R.T.(T), CMD

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 (NCCN) 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 varying intervals, but radiation therapy is given daily. The typical dose of radiation therapy, when given with chemotherapy, is 6000 to 7000 cGy given in 180 to 200 cGy fractions over seven weeks. 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.[11]

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 at least 6000 cGy with chemotherapy, similar to other patients with inoperable non-small cell lung cancer.[11]

Radiation Therapy After Surgery

In some cases, in which surgery is done for a stage I or II non-small cell lung cancer, post-operative evaluation of the mediastinal lymph nodes that had been sampled during surgery may show these nodes to be positive for cancer (N2 stage in the TNM staging system). 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.[12]

If there is a 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.[11]

Stage IV Non-Small Cell Lung Cancer

In stage IV non-small cell lung cancer, 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. The various drugs used in stage IV non-small cell lung cancer are discussed in more detail in the chapter on chemotherapy for non-small cell lung cancer. See Chapter 4: *Systemic Therapy for Non-Small Cell Lung Cancer*.

Radiation therapy to the lung typically does not improve the lifespan of a patient with stage IV non-small cell lung cancer and is not routinely used in these cases.[13] However, if a patient with stage IV cancer has a large lung mass that is causing chest pain, facial/neck/arm swelling, difficulty swallowing, shortness of breath (collectively known as superior vena cava syndrome), or bleeding from the windpipes, radiation therapy to the lung mass may be given, typically in doses from 3000 cGy (10 treatments of 300 cGy fractions over two weeks) to 5000 cGy (20 treatments of 250 cGy fractions over four weeks).[14-15]

Palliative Radiation Therapy for Sites of Metastases in Stage IV Non-Small Cell Lung Cancer

Stage IV lung cancers may spread or metastasize to the brain. When metastases occur in multiple sites of the brain (usually more than ten tumors), 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), although patients with a good performance status with estimated survival of more than 6 months can receive 3750 cGy (15 treatments of 250 cGy over 3 weeks), as a more "gentle" treatment that may result in less cognitive side effects, although there is no clinical trial data to support this. Side effects of whole-brain radiation therapy (WBRT) include fatigue, drowsiness, alteration in taste/smell, hair loss, and scalp itchiness. The primary long-term effect of WBRT is short term memory loss. WBRT in adults does not cause personality changes, Alzheimer's disease, or mental retardation. Typically, an engineer or accountant will have more difficulty doing math in their heads and will have to write things down. Memantine, a drug FDA approved to treat Alzheimer's dementia, has been shown to reduce the rate of decline in memory, executive function, and processing speed in patients receiving WBRT.[16] Another technique to preserve brain function is to avoid treating the part deep in the brain that has a major role in learning and memory called the hippocampus. This technique is call hippocampal-avoiding (HA) WBRT. As long as no brain metastases are seen in the hippocampus, HA WBRT is safe and effective.[17]

If a patient has five or less brain metastases and all the lesions are 3 cm or less in diameter, the patient may have surgery to remove the metastases, followed by whole-brain radiation to prevent new

tumors from forming,[18] or followed by stereotactic radiosurgery (SRS) to the resection cavities (the "hole" left after tumor removal). The patient could also be treated with just stereotactic radiosurgery (SRS). SRS 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. Nevertheless, with follow up MRI brain imaging done every 3 to 4 months, patients can be monitored for any new brain metastases. SRS is becoming the preferred form of radiation therapy over WBRT for those with "limited" brain metastases (typically 5 or less, although this standard is changing).[19] (Figure 12) As mentioned previously SRS can be given using a variety of proprietary methods such as Gamma Knife® (see gammaknife.com) or linear accelerator SRS (TomoTherapy®, Elekta VMAT, and RapidArc®).

Figure 12. A Rendering of Dose and Beams in a SRS Plan

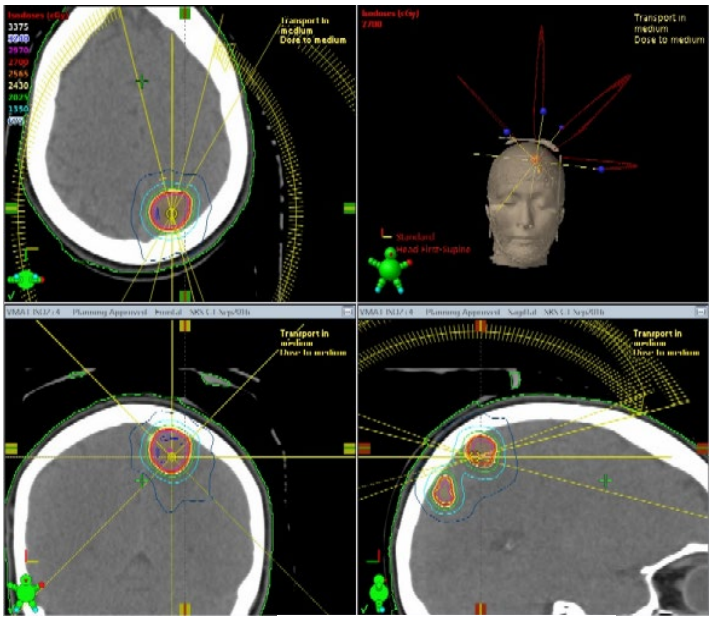


Image courtesy of Steve Rhodes, M.S., R.T.(T), CMD

When lung cancer spreads to the vertebrae, patients may experience severe back pain. Growing cancer could compress the spinal cord and cause paralysis. These metastases can be removed surgically, especially if there is only one metastatic lesion. In this case, radiation therapy is given 1 to 2 weeks after surgery to prevent cancer from recurring in the spine.[20] 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 two weeks). In cases where a previously treated vertebral body metastasis comes back, stereotactic body radiation therapy (SBRT) can be used to better avoid previously treated tissue and concentrate radiation to the areas involved by cancer, using techniques similar to SRS of the brain.

Lung cancer can also spread to the liver, adrenal glands, and bones. When this occurs while the patient is receiving systemic therapy (chemotherapy, biologic therapy, with or without

immunotherapy), this is a sign that the cancer has become resistant to the drug(s). Radiation therapy (either conventional radiation or SBRT) can be used to treat these areas if surgery is not an option. Palliative radiation is effective in reducing or eliminating pain in patients where cancer has spread to any bone (ribs, hips, vertebra, etc.).

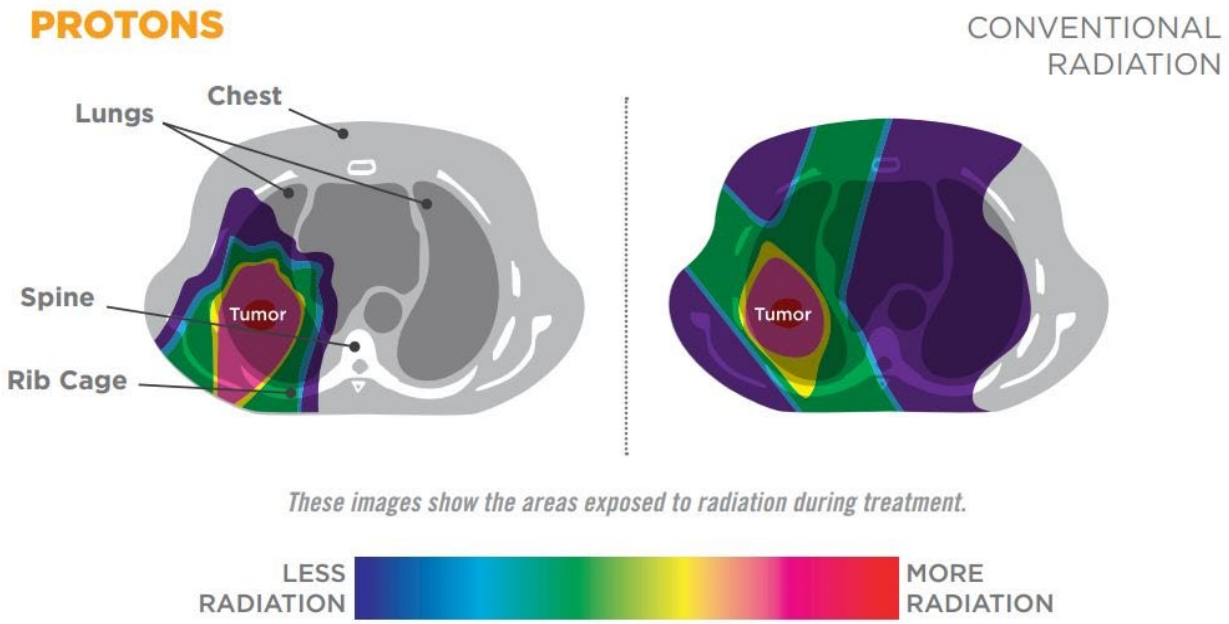
The term "oligometastatic disease" describes a Stage IV patient with limited metastases, to 1 to 2 organs. In the past, these patients were still treated with just systemic therapy, but research has shown that for patients with fewer than three metastatic tumors, and stable (not progressing) disease, radiation therapy to these affected areas improves survival (17 months) compared to getting systemic therapy alone (10 to 12 months).[21]

The term "oligometastatic disease" describes a Stage IV patient with limited metastases, to 1 to 2 organs.

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 slightly over 20 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] In lung cancer, proton beam therapy is especially useful in patients who have previously been treated with conventional radiation therapy and need repeat treatment to the same area. (Figure 13)

Figure 13. A Rendering of Dose in a Proton Plan Versus a 3-D Conformal Plan



Graphic courtesy of Provision Center for Proton Therapy in Knoxville, TN | ProvisionProton.com

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).[22]

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 two weeks after completing chest radiation therapy.

With regards to the skin reaction over the skin of the chest corresponding to the treatment portals, the intensity of the reaction is typically increased when chemotherapy is given during the radiation treatment. The skin over the back (posterior chest) tends to be more affected than the front (anterior chest). Patients can get a sunburn-like reaction with a painful burning sensation that can progress to skin peeling (often called desquamation). Although the skin effects are well tolerated by most

patients, a small number of patients can develop severe redness and skin peeling and require daily wound care. Fortunately, such severe skin reactions are not frequent. The skin heals fairly quickly after completing radiation, and most redness and peeling resolve in 4 to 6 weeks. By the 3-month mark, there may be a tan corresponding to the radiation treatment fields. Permanent skin scarring occasionally occurs in those with more severe skin reactions during treatment.

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.[23] As mentioned above in the section on treatment planning, radiation pneumonitis infrequently occurs, 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 in which fluid accumulates in the pericardium (the sac surrounding the heart), causing tamponade (pressure on the heart) with symptoms such as 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 have become less common because modern radiation therapy techniques have resulted in better sparing of normal tissues and organs.

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Everything can be taken from a man but one thing: the last of human freedoms – to choose one's attitude in any given set of circumstances, to choose one's own way.

- Viktor E. Frankel

Questions to Ask Your Radiation Oncologist

The treatment of lung cancer depends on the type and stage and the patient's overall condition. Radiation therapy is one of the main options for treating patients who are diagnosed with lung cancer.

Why do I need radiation therapy?

What is my treatment regimen and how long will it last?

Can I miss a few treatments?

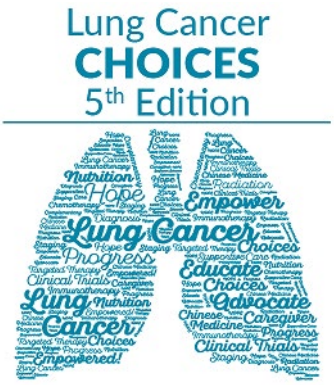
What are the side effects from radiation therapy?

How often do patients experience these side effects?

How are the side effects managed?

Can I continue my usual work and exercise schedule?

Notes



Chapter 6

Treatment of Small Cell Lung Cancer

Ticiana Leal, MD, Selina K. Wong, MD, FRCPC, Join Y. Luh MD, FACP, FACR, and Charles R. Thomas, Jr. MD

Introduction

An estimated 235,760 new cases of lung cancer will be diagnosed in the United States in 2021. There are two main types of lung cancer, non-small cell lung cancer and small cell lung cancer. Small cell lung cancer (SCLC) accounts for 12 to 15% of all new lung cancer diagnosis and approximately 30, 000 deaths.[1] It is important that all patients with lung cancer know what type they have because the treatments for each are different and treatment for one type may not be effective for another.

There are two main types of lung cancer, non-small cell lung cancer and small cell lung cancer.

This chapter will review the approach to small cell lung cancer. See Chapter 4: *Systemic Therapy for Non-Small Cell Lung Cancer* and Chapter 5: *Radiation Therapy for Non-Small Cell Lung Cancer* for the treatment of non-small cell lung cancer (NSCLC).

Signs and Symptoms

The typical patient with small cell lung cancer has a history of smoking, but may be a current or former smoker of either gender and is usually in their sixth to seventh decade of life. Patients may have symptoms, signs, and/or laboratory test abnormalities caused directly by the primary tumor, those related to spread of tumor within the chest cavity or to distant sites like other organs, and those

related to paraneoplastic syndromes.[2-3] Paraneoplastic syndromes are group of rare disorders that are triggered by an abnormal immune system response to a cancerous tumor.[4] Patients may present with symptoms of shortness of breath, cough, or chest pain due to disease in the chest. For patients with disease outside the chest, symptoms depend on the location of spread such as bone pain with bone metastases or headaches and dizziness in patients with central nervous system (CNS) disease involving the brain. Constitutional symptoms may include weakness, loss of appetite, weight loss or fever.[3, 5] These parameters alone do not help to clearly distinguish small cell lung cancer from non-small cell lung cancer.

Before starting on treatment, it is important to have a biopsy to confirm the diagnosis of small cell lung cancer.

Before Treatment

Biopsy

Before starting on treatment, it is important to have a biopsy to confirm the diagnosis of small cell lung cancer. A biopsy is when a piece of tissue is taken and examined under a microscope. The type of biopsy performed depends on the location of the tumor.

Many different methods may be used to obtain a biopsy, including:

A bronchoscopy: a patient is put to sleep with anesthesia and a very thin tube is inserted through the mouth or nose and pushed into the lungs. This procedure may be used to sample the lung tissue and/or a lymph node within the chest. An ultrasound may be used in an endobronchial ultrasound (EBUS) to assist in the procedure.

CT or ultrasound-guided biopsy: a needle guided by a CT scan or ultrasound is passed through the skin to obtain a piece of tissue.

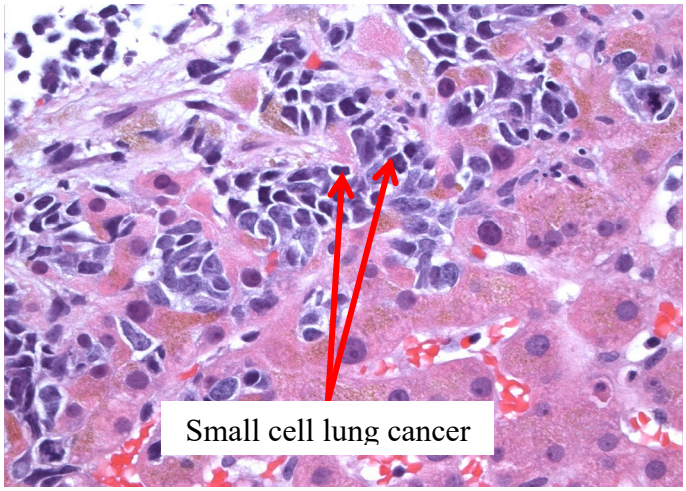
A thoracentesis: in some patients presenting with fluid in the chest, a needle may be placed into the chest, and fluid is removed. The fluid is sent for evaluation of cancer cells.

Surgery: rarely, it is necessary to operate to obtain tissue to make a cancer diagnosis.

Although it is not common, if there is not enough tissue in the original biopsy, a second biopsy may be required.

The biopsy specimen will be sent to a pathologist, a physician who specializes in looking at tissue samples. The pathologist will make the diagnosis and will determine what kind of cancer it is. Small cell lung cancer may occur alone or combined with other tumors. (Figure 1)

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)

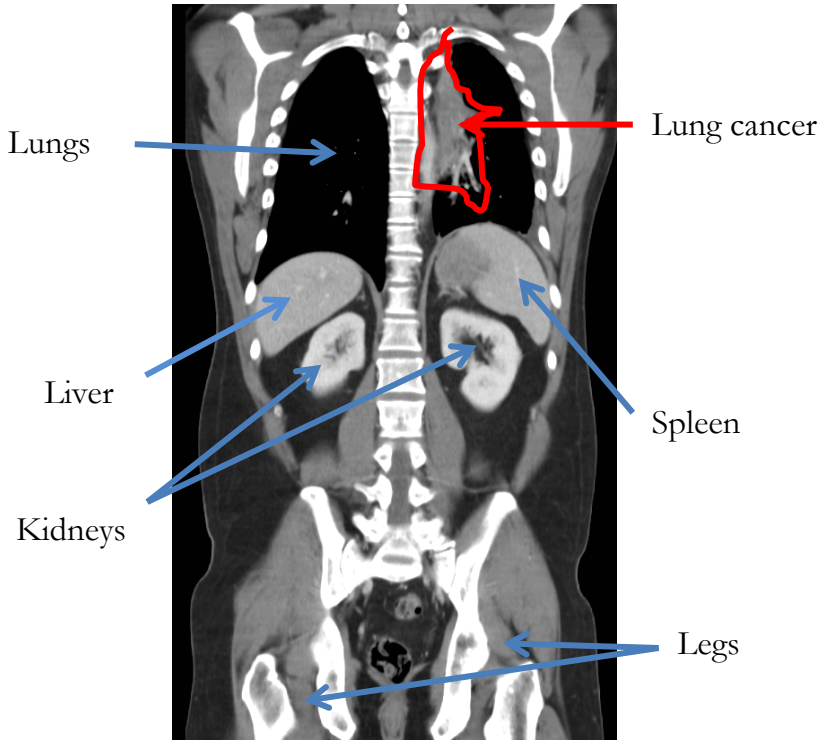


Radiology Tests

Once a diagnosis is established, radiograph imaging studies will be performed to determine the location of cancer within the body. The purpose of the testing is to stage the cancer, determine if treatment will be curative or if a cure is not possible. Some of these tests may have been done prior to the biopsy and may not need to be repeated.

CT (CAT) scan of the chest, abdomen, and pelvis: this test has the purpose of looking for cancer that may be in the lungs, lymph nodes, liver, adrenal glands, bones, and other organs. (Figure 2)

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

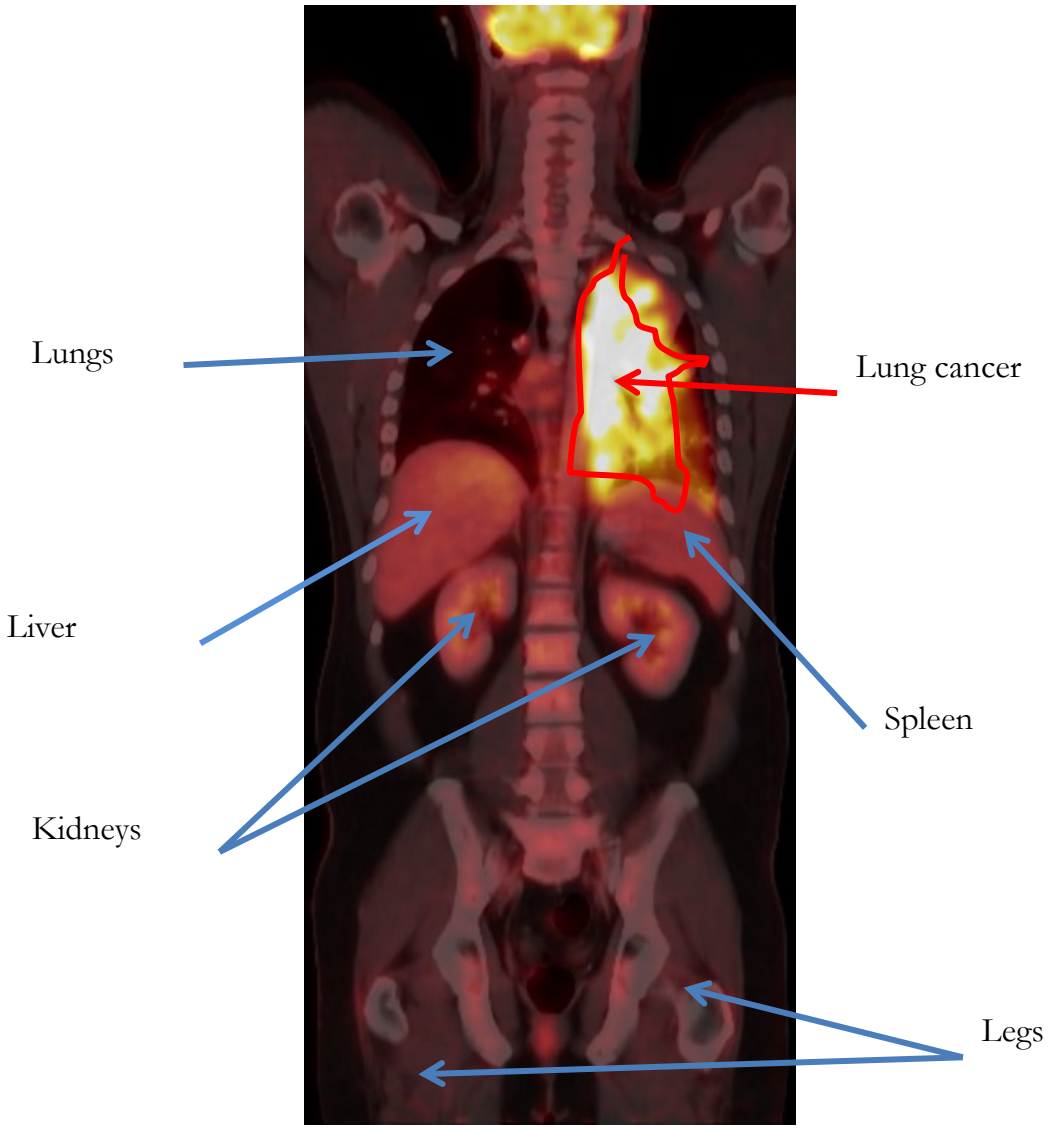


Magnetic resonance imaging (MRI) of the brain: this test is done because small cell lung cancer may spread to the brain. Some patients cannot have an MRI scan and a CT scan with intravenous (IV) contrast of the brain may be done instead.

Bone scan: this test is done because small cell lung cancer may spread to the bones. If a patient is having a PET scan a bone scan is generally not necessary.

Positron Emission Tomography (PET) scan: because small cell lung cancer may spread anywhere in the body, this test is done to look at the entire body, except for the brain. PET scans measure increased levels of sugar (or glucose) that is being metabolized by the tumor as well some normal organs that may not have any active cancerexten (including the brain, heart, liver, and kidneys). (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, blood tests are needed to evaluate how different organs in the body are working. The results may impact what treatment is prescribed. These tests are described below and are commonly performed in most patients with a cancer diagnosis and may be repeated regularly during or after treatment.

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, phosphate and magnesium.

Staging

Stage is an indication of the size and location of the cancer. Approximately 60-70% of patients are diagnosed with small cell lung cancer will have extensive stage (or Stage IV) disease at presentation. This means that the tumor has spread outside of the chest. Although there is a shift in recommendations for the staging of small cell lung cancer most patients are still diagnosed using the traditional staging system of limited-stage disease and extensive-stage disease.[6] Patients with limited-stage disease have cancer confined to the lung that can be treated with a combination of chemotherapy and radiation therapy and the goal of therapy is generally cure. Patients with extensive-stage disease have cancer that has spread within or beyond the lung and the cancer may not be cured with either systemic therapy or radiation therapy. Regardless of stage, patients with small cell lung cancer often experience an initial response to treatment.

The Tumor-Node-Metastasis (TNM) staging system is a newer system also used to stage small lung cancer. Using this system, small cell lung cancer may be staged as one of four stages, Stage I, II, III which are similar to limited-stage disease and Stage IV which is the same as extensive-stage disease. Staging is imperative to know prior to embarking on treatment.

Treatment for Limited Stage Small Cell Lung Cancer

Surgery

Surgery is reserved for patients with small tumors confined to the lung and that have not spread to lymph nodes. Prior to surgery, lymph node sampling is performed via one of two methods:

Endobronchial ultrasound biopsy (EBUS) as mentioned above is a procedure where a tube is inserted through the mouth or nose into the airway and an ultrasound device is used to help identify lymph nodes that will be biopsied. This has become the preferred method to sample lymph nodes in patients with suspected cancers.

Mediastinoscopy is used in cases where lymph nodes cannot be accessed via EBUS. This is a minor surgery where a small incision is made at the bottom of the neck and a camera is placed into the chest to identify lymph nodes to biopsy.

If surgery is performed to remove the tumor from the lung, chemotherapy is recommended once the patient has recovered from surgery to treat microscopic disease, which are residual cancer cells that may be present but are not able to be seen with any imaging or the naked eye. If lymph nodes are

found to be involved at the time of surgery, it will be necessary to have both chemotherapy and radiation after surgery.

Due to the extensive and infiltrative nature of small cell lung cancer, surgery has not traditionally been a part of small cell lung cancer management. In less than 5% of cases, small cell lung cancer is diagnosed in very early stages (stage I-IIA; T1-2, N0, M0) and surgery may be considered for those who have undergone sampling of the mediastinal (mid-chest) lymph nodes to prove that these are not involved.[7] More commonly, limited-stage small-cell lung cancers are stage IIB or beyond (T1-2, N1, M0). After completing investigations demonstrating no distant metastases (i.e., spread to the other lung or to other organs), these cases are typically treated with both chemotherapy and chest radiation given concurrently.

Combination of Chemotherapy and Radiation Therapy

Combined chemotherapy and radiation therapy is recommended for most patients with limited-stage small cell lung cancer. While a medical oncologist will oversee the chemotherapy, a radiation oncologist will oversee the radiation therapy during treatment.

Combined chemotherapy and radiation therapy is recommended for most patients with limited-stage small cell lung cancer.

If the patient is a current smoker, smoking cessation is very important prior to starting on therapy. Several studies have suggested that patients who stop smoking prior to initiation of therapy have higher chances of cure and living longer compared to patients who continue to smoke.[8] Patients can ask their doctors for resources to help them quit smoking. Additional information is available by calling 1-800-QUIT-NOW, reviewing www.smokefree.gov or Chapter 13: *How to Quit Smoking Confidently and Successfully.*

"Having a superpower has nothing to do with the ability to fly or jump, or superhuman strength. The truest superpowers are the ones we all possess: willpower, integrity, and most importantly, courage.

- Jason Reynolds

Chemotherapy

Chemotherapy is an important component of treatment for patients with small cell lung cancer, whether given after surgery (i.e., adjuvant therapy), concurrently with radiation, or in extensive-stage disease (discussed below).[7]

The most common chemotherapy regimen for the treatment of small cell lung cancer in the United States is a combination of a platinum agent , either cisplatin or carboplatin, plus etoposide.[9] Your medical oncologist will choose between cisplatin or carboplatin by considering your other medical conditions and the different side effect profiles of each drug. Chemotherapy is given daily for 3 days in a row and repeated 3 weeks later. In between each cycle, the body recovers from the side effects of chemotherapy and gets ready for the next treatment. Each 3-week period is called a "cycle" and most commonly, a total of 4 cycles are given. Altogether, this means that chemotherapy treatment is given over a total of 12 weeks (3 weeks per cycle x 4 cycles). Concurrent chemotherapy and radiation for limited stage small cell lung cancer does not always require both to be started on exactly the same day. Often to prevent delays to treatment start, patients may receive 1-2 cycles of chemotherapy alone before radiation is added.

Chemotherapy is given intravenously through a needle that is inserted into the veins. Some patients may have an IV inserted into the vein that can be removed each day at the end of treatment while other patients may require a peripherally inserted catheter (PICC) or an implanted port that are placed in the vein and remains in the vein throughout the entire treatment.

The platinum and etoposide are both given on the first day and may take anywhere from 4-6 hours because additional fluids and medications are given prior to chemotherapy. Additional fluids are given prior to platinum-based chemotherapy due to the tendency of these agents to damage the kidneys without proper pre-hydration with fluids. These drugs can also cause nausea and vomiting, but pre-medications given before each treatment help to prevent these symptoms. Etoposide is given on its own on the second and third days, and takes about two hours to administer.

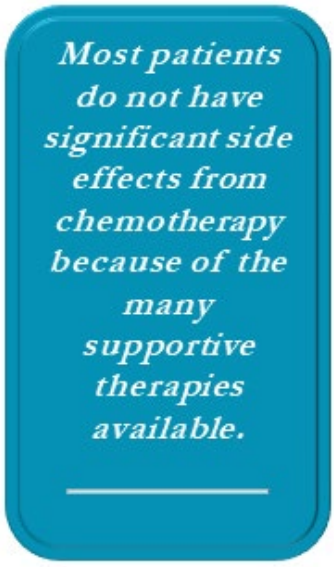
Most people do not feel anything unusual while receiving chemotherapy. However, patients may start to notice side effects 2-4 days after chemotherapy is administered.

Chemotherapy Side Effects

Most patients do not have significant side effects from chemotherapy because of the many supportive therapies available. However, important side effects to remember include:

Increased risk of infection: this is one of the most serious side effects of chemotherapy. Any patient with a fever (temperature higher than 100.4ºF), during chemotherapy needs to seek immediate medical attention.

Some patients may not have a fever and instead develop flu-like symptoms, cough, shortness of breath, pain with urination, diarrhea, or ear pain among other symptoms. You should seek medical attention if you have these symptoms as you may have an infection.



The increased risk of infection is because chemotherapy kills white blood cells, which normally are responsible for defending the body against infections. However, white blood cells grow back between each cycle. As a matter of precaution, it is important for patients to wash their hands regularly, avoid large crowds and sick people, and eat foods that come from trusted sources.

Fatigue: Both chemotherapy and radiation therapy may cause fatigue. This is normally the worst the first few days after chemotherapy and usually improves during the second and third week of each cycle. Fatigue can accumulate with each cycle of chemotherapy and radiation therapy. Fatigue will typically improve once all therapy is completed.

Nausea and Vomiting: As described above, nausea and vomiting have become less common with the modern day use of potent anti-nausea medications. Medications are typically given in a preventative fashion and as needed. Pre-medications are given routinely before chemotherapy is administered regardless of whether or not patients have nausea/vomiting in order to prevent the development of any nausea/vomiting. In addition, patients are given medications to take home and use as needed should they require. These may include aprepitant or fosaprepitant which are given with chemotherapy as well as ondansetron, granisetron, dexamethasone, promethazine, prochlorperazine, metoclopramide and/or lorazepam which may be given with therapy or to take at home.

Hair Loss: Hair loss typically occurs within 3-4 weeks of starting chemotherapy. Hair often starts to grow back about one month after completing chemotherapy, but may be delayed in patients who are treated with radiation to the brain.

Other Side Effects: Other side effects of therapy include mouth sores, loss of appetite, diarrhea, easy bruising and bleeding (due to decreased hemoglobin and/or platelets), dehydration and damage to the kidneys, ringing in the ears (i.e., tinnitus) or numbness and tingling in the fingers and toes (i.e., peripheral neuropathy). All chemotherapy side effects should be discussed with a medical oncologist. See Chapter 8: *Supportive Care.*

Radiation Therapy

The techniques of radiation therapy for the treatment of limited stage small cell lung cancer are similar to what is done for Stage IIIA to IIIB non-small cell lung cancer—radiation therapy given concurrently with 4 to 6 cycles of chemotherapy. The same team approach is used in consultation, simulation, treatment planning, patient education, treatment delivery, and quality assurance. See Chapter 5: *Radiation Therapy for Non-Small Cell Lung Cancer* for additional technical details.

Unlike non-small cell lung cancers, limited-stage small cell lung cancers are best treated with radiation twice a day using a lower dose per treatment, at least 6 hours apart, based on a famous clinical trial that showed patients with limited stage small cell lung cancer did better with twice a day treatments (4500 cGy in 150 cGy fractions given twice a day over 30 treatments in 3 weeks). The trial compared this twice daily method to the same dose of once a day radiation that nobody uses (4500 cGy in 180 cGy fractions given once a day over 25 treatments).[10] Treating a patient twice a day is harder on the patient due to increasing the daily treatment time and increases the acute side effects. Therefore in practice, many radiation oncologists will treat patients to total doses of 6000 to 7000 cGy in 180 to 200 cGy fractions.[11] A recent clinical trial showed that median survival was about the same for patients given 7000 cGy (30.5 months) given over seven weeks (35 once daily treatments) compared to twice daily treatment to 4500 cGy (28.7 months), supporting the use of higher dose once daily radiation treatments for patients with limited stage small cell lung cancer.[12]

As mentioned in the section on surgery, due to the extensive nature of small cell lung cancer and the fact that spread to the lymph nodes in the middle of the chest is so common, SBRT (stereotactic body radiation therapy) is not typically offered, but is a viable option for Stage I-IIA patients who are either too frail for surgery or who refuse surgery.[13]

Radiation Side Effects

Side effects of chest radiation in small cell lung cancer is similar to chest radiation in non-small cell lung cancer.

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.[14] 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.

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. Excerpted from Chapter 5: *Radiation Therapy for Non-Small Cell Lung Cancer*.

Prophylactic Cranial Irradiation (PCI)

Because the risk of brain metastases in small cell lung cancer is so high, MRI of the brain with contrast is part of the staging workup for limited stage small cell lung cancer. About 20% of small cell lung cancer patients will already have brain metastases when they are diagnosed.[15] Prophylactic cranial irradiation (PCI) is giving radiation therapy to the entire brain (also called whole brain radiation therapy, WBRT) for patients without brain metastases on MRI to lower the risk of developing brain metastases (59% without PCI to 33% with PCI over 3 years in patients with limited stage small cell lung cancer).[16] The standard dose has been 2500 cGy given in 250 cGy fractions over 10 treatments. PCI includes the entire brain (like whole brain radiation) but also includes the spinal cord down to the level of the C2 vertebra. PCI is currently recommended for all patients with limited stage small cell lung cancer who have a good response to chemotherapy and radiation. Nevertheless, your radiation oncologist should thoroughly discuss the benefits and risks of whole brain radiation with you before making a decision on this (see the section on palliative radiation to the brain in Chapter 5: *Radiation Therapy for Non-Small Cell Lung Cancer*). If you choose not to receive PCI, then an MRI of the brain should be done every 3 to 4 months to monitor you closely.

Follow Up

After therapy is completed, patients are followed regularly to make sure they recover from side effects and also for surveillance to monitor for signs of disease recurrence.

The majority of side effects usually start to improve about four weeks after completing chemotherapy with more energy and increased appetite. However, prophylactic cranial irradiation, which starts about a month after chemotherapy is complete, may delay recovery. Late side effects from radiation to the chest may occur such as inflammation of the lungs (pneumonitis) or difficulty swallowing from

narrowing of the esophagus, both of which can be effectively treated. 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. Your radiation oncologist will want to see you one to three months after completing your treatment and subsequently at longer intervals in coordination with your medical oncologist. At every visit the doctor will review symptoms and perform a physical examination. A CT scan of the chest and blood work may be done every three to four months initially, every four to six months later, and annually after three years. An MRI (preferred) or CT of the brain will be done every three to four months during the first year, then every six months. Regular follow-up and routine CT/MRI scans are part of surveillance, which is scheduled monitoring for early signs of disease recurrence.

Prognosis

The intention of treatment for limited stage small cell lung cancer is to cure the cancer. It is expected that 70-90% of patients who receive therapy will have a response with the cancer showing shrinkage. However even after completing treatment, there is a high risk of recurrence and only 25-30% of patients are alive at five years. For patients who do not wish to receive treatment or are unable to receive treatment, the expected survival is lower.

Treatment for Extensive Stage Small Cell Lung Cancer

Patients with extensive stage small cell lung cancer have cancer that has spread either within or beyond the lungs. For the first time in three decades we have seen progress in the treatment of patients with extensive stage disease with a combination of chemotherapy and immunotherapy. Radiation therapy may be used for consolidation or for symptom control during or after chemotherapy. Surgery is generally not recommended.

Chemotherapy

Similar to patients with limited stage disease chemotherapy consists of a platinum doublet cisplatin or carboplatin with etoposide in combination with immunotherapy for patients in North America and Europe. Treatment is given over 3 days with platinum and etoposide given on the first day along with the atezolizumab and then etoposide alone on day 2 and 3 for four cycles, with each treatment being 21 days apart. After four cycles the atezolizumab is continued as a maintenance therapy for as long as the treatment remains effective. Treatment is given through a vein using either a needle inserted into the arm or a PICC or PORT as described above. Treatment is generally given as an outpatient and may take 4-6 hours the first day and then about two hours on day two and three. Prior to treatment on the first day blood work is done to make sure it is safe to give chemotherapy and you will likely meet with your medical oncologist or a member of the healthcare team. In between each cycle the

body recovers from the side effects of chemotherapy and immunotherapy and gets ready for the next treatment. Chemotherapy for extensive stage disease is usually given for 4 cycles with immunotherapy, followed by maintenance immunotherapy every 3 weeks with imaging performed every 2-3 cycles.

Immunotherapy

Immune checkpoint inhibitors have been approved for the treatment of multiple different tumor types including patients with small cell lung cancer. These agents work very differently from chemotherapy acting on proteins expressed on cancer cells and T cells that normally prevent the body from recognizing cancer cells as foreign. When these proteins are blocked the T cells are activated and able to kill cancer cells. Currently, atezolizumab is approved in combination with chemotherapy as a first-line option for patients with small cell lung cancer.[17] Durvalumab has also shown promise in combination with platinum-based chemotherapy but is not yet approved. Nivolumab and Pembrolizumab are also approved in the third-line setting for patients who have progressed on platinum-based chemotherapy as well as a second-line chemotherapy regimen. Not all patients are candidates for treatment with immunotherapy. These agents are generally not recommended for patients with a history of autoimmune disease, organ transplant or certain paraneoplastic syndromes.[18-19]

Chest Radiation

The combination of chemotherapy and radiation therapy is not typically given to patients with extensive stage small cell lung cancer. However, radiation may be given to help relieve symptoms, such as pain, shortness of breath, difficulty swallowing, and/or blockage of a bronchus, while a patient waits to get started with chemotherapy. Small cell lung cancer is the most common cause (75 to 80%) of superior vena cava (SVC) syndrome, a condition caused by a large tumor compressing the superior vena cava causing swelling of the face, neck, and upper arms; shortness of breath; and coughing.[20] Chest radiation in extensive stage small cell lung cancer is given on a case by case basis, and when given, can sometimes be given after a few courses of chemotherapy to treat any tumor that is left. Despite the fact that chest radiation is not used routinely in extensive stage small cell lung cancer, clinical studies analyzing the benefits of chest radiation in extensive stage small cell lung cancer patients have been promising and have suggested that patients may live longer if chest radiation is added to chemotherapy.[21]

Prophylactic Cranial Irradiation (PCI)

MRI of the brain with contrast is also part of the staging workup for extensive stage small cell lung cancer. Prophylactic cranial irradiation (PCI, 2500 cGy given in 250 cGy fractions over 10 treatments as in limited stage small cell lung cancer) was a standard treatment for extensive stage small cell lung cancer patients without brain metastases on MRI to lower the risk of developing brain metastases (40.4% to 14.6% over 1 year in extensive stage), as mentioned in *Lung Cancer Choices*, 4th Edition.[22] However, another clinical trial in extensive stage small cell lung cancer patients who responded well to chemotherapy, showed no increased survival in patients getting PCI.[23] Because of the side effects to the brain and the limited survival benefit, **patients with extensive stage small cell lung cancer can choose to omit PCI.** Whether or not PCI is given, you should get an MRI (preferred) or CT of the brain every three to four months to monitor for appearance of any brain metastases. It must be emphasized that PCI is still recommended for patients with limited stage small cell lung cancer.

Management of Metastases with Radiation

When patients with small cell lung cancer *actually develop* brain metastases, whole brain radiation (WBRT) is the recommended radiation treatment method, for a total dose of 3000 cGy given in 300 cGy fractions over 10 treatments. If patients have a good performance status and have an estimated survival of 6 months or more, some patients can be treated with a longer fractionation dose of 3750 cGy in 250 cGy fractions over 15 treatments. Memantine, a drug FDA approved to treat Alzheimer's dementia, has been shown to reduce the rate of decline in memory, executive function, and processing speed in patients receiving WBRT.[24]Ask your radiation oncologist about a prescription for memantine if you are going to receive PCI or WBRT.

Even when only 1 to 3 masses are detected on MRI, it is understood that in small cell lung cancer, there may be many additional masses that are too small to be detected on MRI. Because of this, focused treatments such as surgical removal or stereotactic radiosurgery (SRS) are not routine, as it is felt that the entire brain is at risk. Nevertheless, up front SRS for brain metastases in small cell lung cancer has been studied and shows promise as an alternative to whole brain radiation.[25]

In patients that develop brain metastases after PCI, repeat WBRT can be given safely but with more cognitive side effects. As an alternative to repeat WBRT, SRS can also be done with potentially less side effects provided there are a limited number of metastases.[26]

Small cell lung cancer can also spread to the liver, adrenal glands, bones (including vertebra). In these cases, radiation therapy (either conventional radiation or SBRT) can be used to treat these sites to relieve pain and prevent fracture (in cases of bone metastases). (SRS and SBRT are discussed in detail in Chapter 5: *Radiation Therapy for Non-Small Cell Lung Cancer* in the section "Palliative Radiation Therapy for Sites of Metastases in Stage IV Non-Small Cell Lung Cancer".

Prognosis

Patients with extensive stage small cell lung cancer are generally not cured with chemotherapy or radiation therapy. The purpose of treatment is to improve quality of life and symptoms as well as prolong survival. Approximately 60-70% of patients will respond to chemotherapy the first time with their cancer shrinking or disappearing. Unfortunately, responses may not last for long and additional chemotherapy or radiation may be needed. For patients who get treated, less than 5% of patients are alive at 5 years. Life expectancy is usually less than 2-3 months and often only a few weeks for patients who choose not to have any treatment.

Clinical Trials

Given the limited number of drugs currently approved for small cell lung cancer, not due to lack of studies but due to lack of success, clinical trials remain critical to advance therapy for this disease.

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A clinical trial is a research program designed to evaluate whether a new drug is effective in the treatment of a particular disease. Some trials may compare a new treatment to the current standard of care or add a treatment to the standard of care. Some people may not wish to participate in a clinical trial for fear of not receiving adequate treatment for their disease, however this is not the case in clinical trials involving cancer patients.

Patients may speak with their doctor about a clinical trial, ask questions, and make a decision if the trial is a reasonable choice for their disease. Sometimes a patient may not be able to participate in a trial because of other comorbid illnesses and the doctor would know if this was the case.

Patient participation in a clinical trial is critical to advancing the care for patients with lung cancer. See Chapter 7: *Clinical Trials and Emerging Therapies for Lung Cancer*

Notes

Lung Cancer
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5th Edition

Chapter 7

Clinical Trials and Emerging Therapies for Lung Cancer

Emily Duffield, MPH, MSN, ANP-BC

Introduction

Clinical research continues to identify and develop novel treatment options for lung cancer patients. Multiple new treatments have been made commercially available over the past few years, while others still in the developmental pipeline remain available only to patients who participate in clinical trials. There are several different classes of systemic therapy used to treat lung cancer, including chemotherapy, targeted therapy, and immunotherapy. Although traditional chemotherapy remains an important tool for lung cancer treatment, both targeted therapies and immunotherapies are playing an increasingly important role in treatment, particularly for patients diagnosed with advanced stages of the disease.

Instead of attacking all rapidly dividing cells the way chemotherapy does, targeted therapies concentrate on specific genetic abnormalities unique to some tumors, often resulting in fewer side effects and the potential for improved cancer control. Targeted therapies can pinpoint specific DNA mutations in the tumor and utilize them to prevent cancer cells from growing and dividing out of control. Targeted therapies may be used alone or in combination with other treatments to improve overall survival. The drawback to targeted therapies is that they can only be utilized by a select group of patients who have tumors with unique DNA mutations. As a result, these therapies are not indicated for all patients.

Immunotherapy is a newer type of targeted therapy that is appropriate for many lung cancer patients.

Immunotherapy is a newer type of targeted therapy that is appropriate for many lung cancer patients. Immunotherapy medications interact with certain receptors on tumor cells and immune cells to change the way the body reacts to a tumor, often allowing the immune system to recognize and attack tumors. In some cases, turning on the immune system with the help

of immunotherapy can even cause the body to completely eliminate the tumor. Immunotherapies are showing great promise in lung cancer as well as in many other types of advanced malignancies.

While many of the recently approved therapies appear to be very promising, chemotherapy remains an important part of the treatment plan for many lung cancer patients, and researchers continue to evaluate the effect of combining chemotherapy with immunotherapies and targeted therapies in an effort to further improve outcomes for patients diagnosed with lung cancer. Other areas of research include the utilization of targeted agents and chemotherapy for lung cancer maintenance therapy (prevention of relapse) and medications to prevent lung cancer (chemoprevention) in patients at high risk for developing this disease. The recently approved targeted and immunotherapies are already improving progression-free and overall survival rates for lung cancer patients, but there is more work to be done. Research and clinical trials continue to evaluate the best use of novel therapeutic agents in an effort to improve the quality of life and longevity of patients with lung cancer.

Clinical Trials

Drug development begins with the identification of new substances that show anti-cancer activity in research laboratories. Following extensive laboratory testing, clinical trials are done to establish whether these substances are safe and effective at fighting cancer in people. The purpose of clinical trials is to identify new agents that can improve survival or quality of life compared to currently available treatments.

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 a larger group of people to continue to evaluate efficacy and safety, and to identify the range and severity of side effects.

Phase 3: the drug is tested in an even 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. FDA approval for drugs is typically based on the results of Phase 3 trial data.

Phase 4: after approval by the United States Food and Drug Administration (FDA), the drug is available for use in the general population and further monitored for safety, efficacy, and long-term side effects.

The purpose of clinical trials is to identify new agents that can improve survival or quality of life compared to currently available treatments.

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 specialty pharmacies. Clinical trials have historically been available only 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). The treating oncologist may recommend trials that are available locally, as well as at regional medical centers.

Sometimes new drugs that demonstrate a major increase in efficacy compared with older therapies are granted FDA Breakthrough Therapy or Fast Track status. The status expedites the development and FDA review process with the goal of making these exciting new treatments available to patients in the shortest possible time while still preserving the research process and maintaining patient safety. Drugs with Fast Track Status or Breakthrough Therapy designation are initially available only in clinical trials, but typically move through the clinical trial process and become widely available through commercial dispensing pharmacies much more quickly than if they had followed traditional approval pathways. Certain targeted therapies have shown such improvement in efficacy and tolerability compared to standard therapies that they have moved from Phase 1 "first in human trials" to FDA approval in under four years. Shortening the timeline for moving novel drugs from the laboratory into the clinic for patient use has clear benefit for improving patient outcomes, particularly in lung cancer where for many years, there has been a clearly documented need for new and improved treatments.

Targeted Therapy

Chemotherapy drugs work by killing 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, minimizing damage to normal cells. Targeted therapy consists of either monoclonal antibodies (drug names ending in "-ab") that target the outside surface of the cancer cell or small molecules (drug 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 development, growth, and

spread to other organs (metastasis). The wider availability of full genome sequencing of tumor DNA is opening up the opportunity for truly 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 mutations, EML4-ALK gene rearrangements, and KRAS mutations. Newer targets being researched in lung cancer include ROS1, BRAF, HER2, MET, PIK3CA, RET, MEK, and NTRK. Several drugs used to target these mutations have been approved by the FDA for either lung cancer or other types of cancer, while many of the novel agents listed below are available only through clinical trials.

The technique that allows researchers to read and decipher the genetic information found in the DNA of anything from bacteria to plants to animals is call genomic sequencing.

Monoclonal Antibodies

Monoclonal antibodies are one type of signaling molecule that binds to receptors on the cell surface. When these signaling molecules stimulate cell surface receptors, they initiate a cascade of messages inside the cell that promotes cellular growth and development. The normal cellular controls for this process are absent in malignant cells, and cellular replication proceeds uncontrolled. Antibodies are 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. Identification of tumor-specific antigens allows novel drugs to use the immune response to recognize and fight cancer cells. This class of drugs, known as monoclonal antibodies, are produced in a laboratory and are designed to bind with a very specific target, such as a cell surface receptor or other defects unique to cancer cells.

Monoclonal antibodies fight cancer cells through several mechanisms, including:

- Blocking cell surface receptors to turn off the downstream cell signaling cascade.
- Targeting specific defects in the cancer cells or labeling the cancer cells, making them more vulnerable to destruction by the body's immune system.
- Delivering other drugs or substances directly to the cancer cells.

It should be noted that many of the recently approved immunotherapies used in treating lung cancer patients are monoclonal antibodies. See Chapter 4: *Systemic Therapy for Non-Small Cell Lung Cancer*

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 or joint aches.[1] Cardiac toxicity can be a serious complication, and warrants close monitoring.[2] Allergic reactions 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.

Tiragolumab is an anti-TIGIT antibody that is being evaluated in combination with atezollizumab. Overall response rate was 37% in an unselected cohort, but when PD-L1 expression was over 50%, the response rate was 66%.[3] Side effect profile was similar to what has been demonstrated with atezolizumab alone, suggesting very little added toxicity associated with Tiragolumab dosing. This combination has been granted breakthrough status by the FDA,[4] and the Phase III SKYSCRAPER-01trial (NCT04294810) is ongoing.

Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates are formed when an antibody is fused with a drug via a linking structure. The antibody portion serves to identify and target cancer cells, allowing for delivery of the cytotoxic "payload" directly to the tumor. This technique has the potential to improve therapeutic response while minimizing the risk for side effects. Resistance to these types of therapies can develop when either the cell decreases expression of the antibody target, when there is decreased internalization of the drug payload, or when there is increased export of the therapeutic compound out of the cell before it can have an anti-tumor effect.

Ado-trastuzumab emtansine (T-DM1) is an ADC directed against HER 2. Although it appeared to be quite effective in breast cancer, the impact in lung cancer has been less significant. In a trial with 49 patients, there were only 4 partial responses, and these were seen only in those patients 7 with the highest level of HER2 overexpression. Median progression free survival was 2.7 months. The TDM1 was well tolerated with fatigue being the only grade 3 adverse event reported in more than one patient. Also noted were risks of infusion related reactions and thrombocytopenia.[5]

U3-1402 is an ADC directed against HER3. Its toxic therapy is DC 8951, which is a topoisomerase 1 inhibitor. It is currently being evaluated in a phase 1 clinical trial for patients whose metastatic NSCLC has an EGFR mutation and whose disease has progressed on an oral EGFR directed targeted therapy. Initial trial results are not yet available, but are expected to be published in 2022.[6]

Sacituzumab govitecan (IMMU-132) is an ADC targeting Trop-2 that is combined with a toxic payload of SN-38, the active metabolite of irinotecan and a topoisomerase 1 inhibitor. Fifty four heavily pretreated NSCLC patients were evaluated in a phase 1 expansion cohort with a demonstrated response rate of 17%, with median PFS of 5.2 months and median OS of 9.5 months.

However, 67% of patients were seen to have a reduction of tumor size from baseline. Side effects included neutropenia, GI upset (diarrhea, nausea) and fatigue.[7]

Telisotuzumab Vedotin (ABBV-399) is a c-Met–targeted antibody-drug conjugate. Results of the Phase 1b study of telisotuzumab vedotin in combination with erlotinib in patients with lung cancer harboring an EGFR mutation and c-Met amplification showed a response rate of up to 35%. Side effects included rash, diarrhea, nausea, vomiting, fatigue, neuropathy, and loss of appetite. An increased risk of blood clots was seen as well.[8]

Small Molecules

Small molecule drugs are a large class of medications that work by entering the cell and blocking 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 additional mutations that confer resistance to first-line therapy. Identification of second and third-line therapies that continue to exploit the underlying driver mutation but also block resistance mutations has become increasingly important. EGFR and ALK are two well established therapeutic targets for small molecule inhibitors. However, multiple newer targets continue to be identified, offering patients a chance at treating their disease while maintaining better quality of life with fewer side effects than they might have with chemotherapy.

EGFR inhibitors

Multiple EGFR targeting drug therapies have been developed for lung cancer over the past 10 years. The challenge now is to identify which therapies will allow patients to remain on targeted therapy for longer, and maximize clinical benefit either by blocking resistance mechanisms from the outset, or by adding in additional therapies to address resistance mechanisms as they develop over time.

BLU-945 is a fourth generation EGFR inhibitor that has activity against both "double mutants" with EGFRm and T790m, as well as "triple mutants" with EGFRm, T790m and C797s.[9] Both T790m and C797s mutations have been well documented as resistance mechanisms to EGFR TKI drugs. Fourth generation compounds such as BLU-945 seek to block not only the original EGFR mutation, but also the more common resistance mechanisms which may develop, thereby prolonging a patients response and extending the time to progression on first line therapy. Although there are only pre-

clinical data available at this time, a phase 1 clinical trial is planned to start enrollment in the summer of 2021.[10]

Nazartinib (EGF816) is a third generation EGFR inhibitor with activity against exon 19 deletion, L858R and T790m mutations. It is currently being evaluated in Phase III trials in the first-line setting. Common side effects included rash, diarrhea, itching, mouth sores, and fatigue. Response rate in the Phase 2 trial was 64%, The 6-month duration of response rate was 91%, and the median duration of response was not estimable. Nazartinib also demonstrated good intracranial efficacy, with 53% of patients with baseline brain metastasis experiencing resolution of their intracranial disease. Currently this drug is available only through clinical trials.[11]

Because of the higher prevalence of EGFR mutations in Asian patients, there are several trials being conducted exclusively in Asia to evaluate the safety and tolerability of novel EGFR directed compounds. Unfortunately, all patients on EGFR targeted therapies will eventually progress, and much effort is being focused on how to extend time to progression on first line therapy, as well as how best to identify and treat resistance mechanisms that can arise. In the front line setting osimertinib is being combined with earlier generation EGFR TKIs (NCT03122717), with chemotherapy such as carboplatin and pemetrexed, as well as with VEG-F inhibitors including bevacizumab and ramucirumab. It is critical to obtain additional molecular profiling after progression of first line therapy to try to identify the nature of the acquired resistance mechanism as that can guide the selection of subsequent therapy. For example, if a MET alteration is identified then trial combining osimertinib with a MET inhibitor such as tepotinib[12] or savolitinib[13-15] could be considered. Alternatively, if a C797S mutation is identified, then changing to a first generation ERGFR TKI such as erlotinib or gefitinib may be appropriate. Additional cell signaling pathways and drug combinations being evaluated include blocking MEK (osimertinib + selumetinib) and Aurora Kinase A (osimeritnib + alisertib).

ALK inhibitors

Since its identification as a therapeutic target in NCSLC, multiple drugs have been FDA approved for use in patients with an ALK rearrangement (aka mutation). Similarly to what is observed in the EGFR mutant patient population, despite initial excellent response rates to TKI therapies, essentially all patients will eventually develop resistance and progress. Much effort is being dedicated into understanding the ideal sequencing of ALK inhibitors to obtain the best clinical response for patients, as certain resistance mechanisms are more likely to develop after some of the drugs than others. The G1202R mutation is identified as a resistance mechanism in up to 43% of patients who progress on ALK targeted therapies.[16] It can only sometimes be overcome by treatment with the third generation drug lorlatinib. In addition to the single agent therapies being evaluated for use in ALK mutation positive patients described below, multiple trials are looking at combinations of ALK TKIs with other drugs, including MEK, VEGF and mTOR inhibitors.[17]

TXP-0131 is a novel ALK inhibitor that demonstrated potent activity against many known ALK resistance mutations in pre-clinical studies, most excitingly it was active against G1202R as well as all the known compound or "double" resistance mutations which have been challenging to target previously. A phase 1/2 trial (FORGE-1) evaluating TXP-0131 is expected to open and begin enrollment in 2021.[18]

Ensartinib (X-396) is a potent ALK inhibitor with anti-cancer activity against both treatment naïve tumors and those that developed resistance to first-line therapy with Crizotinib. In the Phase 1 trial over 80% of patients responded to therapy, with observed activity in the brain.[19] Response lasted for a median duration of more than 20 weeks with some responses lasting for over 50 weeks. Common side effects included rash, fatigue, nausea, vomiting and swelling. Responses were also observed in the central nervous system, with an intracranial response rate of 64%. Phase 3 data from the eXalt3 trial comparing TKI treatment naïve patients randomized to crizotinib vs ensartinib showed improved PFS in the ensartinib arm and time to treatment failure at 12 months was 4.2% for ensartinib vs 23.9% for crizotinib.[20] Ensartinib also conferred improved disease control in the brain, with an intracranial ORR of 64% on the ensartinib arm compared to 21% with crizotinib. Safety data was consistent with earlier trials, with ensartinib being well tolerated. One unique AE was a sunburn like rash that was typically mild. However, it is unclear how this agent would fit into the treatment paradigm, as it does not appear to have unique properties when compared to current ALK-inhibitors that are already FDA approved.

ROS-1 Inhibitors

Because the ROS1 signaling receptor target is conformationally quite similar to that of ALK and TRK, Lorlatinib (FDA approved for use with ALK rearrangements) is also being evaluated for efficacy against ROS1 in Phase 2 trials, with promising results.[21] Although not FDA approved, Lorlatinib is recommended by NCCN guidelines for second-line therapy in patients with ROS1 rearrangement after they progress on Crizotinib.

Taletrectinib (AB-106 / DS-6051b) is a new selective ROS1/NTRK inhibitor that showed promising pre-clinical data and is currently undergoing Phase 1 testing in both the US and Japan.[22] In the pooled analysis of US and Japanese patients, the ORR was 33% with a median PFS of 14.2 months.[23] The compound is exciting to researchers as it has been shown to have activity against the secondary resistance mutation G2032R, which commonly develops after first-line ROS directed targeted therapies such as crizotinib, and also confers resistance to the next-generation inhibitors Lorlatinib and Entrectinib.

Foritinib (SAF-189s) is a potent oral TKI with activity against both ALK and ROS. Importantly, in pre-clinical studies it has demonstrated activity against the G2032R resistance mutation that often develops after initial ROS-1 directed TKI therapy.[24] It is currently being studied in a phase I/II trial enrolling both TKI naïve as well as pre-treated patients.[25]

Ceritinib has been shown to have activity in the front-line setting for lung cancer patients whose tumors have a ROS-1 rearrangement. Unlike for those patients with ALK rearrangement, Ceritinib does not seem to have second-line activity after progression on Crizotinib for ROS1-rearranged tumors. A Phase 2 trial with 32 patients showed a 62% response rate and 81% disease control rate. Activity in the brain was demonstrated, with a 63% disease control rate, although the sample size was small at only 5 patients with brain metastases.[26] Common side effects include diarrhea, nausea, vomiting, loss of appetite, and lab value changes including increased liver function enzymes and low phosphate levels.[27] Currently Ceritinib is recommended in the NCCN guidelines for first-line use in ROS1rearranged NSCLC, but it does not yet have FDA approval in this indication.

Cabozantinib is a multi-kinase inhibitor with activity against several cell signaling targets including ROS-1 rearrangement. It is being evaluated in lung cancer following progression on Crizotinib and Ceritinib. In particular, it has shown efficacy against the G2032R and L2026M resistance mutations found in ROS-1 rearranged tumors.[28-29] Safety and efficacy of Cabozantinib continues to be evaluated in lung cancer, but common side effects when used in other types of cancer included nausea, diarrhea, fatigue, mouth sores, and hand-foot syndrome (redness, pain, tingling and numbness to hands and feet).[30]

Repotrectinib has demonstrated safety and activity in clinical trials (TRIDENT-1) for patients with advanced ROS-1 fusion NSCLC, with response rates of 91% in the TKI-naïve patient population and 40% in patients who had received previous ROS-1 targeted therapy.[31] Repotrectinib also showed a potential to overcome TKI resistance mutations after treatment with Crizotinib. It is generally well tolerated, with dizziness, fatigue, contipaiton, taste changes, dyspnea and hypoxia seen in some patients. It was granted fast track status by the FDA in August 2020.[32]

BRAF Inhibitors

BRAF mutations are present in 4-5% of NSCLC patients. They are divided into three main classes – Class I are the V600 mutations, for which dabrafenib and trametinib are approved. Class II and III do not yet have FDA approved targeted therapies. Several combination therapies have appeared promising in the pre-clinical setting, and are just entering human clinical trials. Some of these include Lifirafenib (a RAF dimer inhibitor) plus mirdametinib (a MEK inhibitor) (NCT03905148) as well as combinations of LXH254 with either LTT462 or trametinib or ribociclib in melanoma patients (NCT04417621). Because these compounds are in early stages of clinical trial evaluation little safety, efficacy and response data are available. Encorafenib (Braftovi) is a BRAF inhibitor currently being studied in clinical trial in combination with Binimetinib (a MEK inhibitor) in patients with advanced NSCLC whose tumors have a BRAF V600E mutation. Trial enrollment began in June 2019, no results in lung cancer patients have been published to date. The combination was approved for melanoma patients with this mutation in 2018. Side effects have been shown to include fatigue, nausea, diarrhea, vomiting, abdominal pain, and arthralgia. This combination may be less likely to cause fevers than other BRAF targeted therapies.[33]

MEK inhibitor

Selumetinib is a small molecule drug that is currently approved for pediatric patients 2 years of age and older who have neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN). It inhibits the mitogen-activated protein kinases MEK-1 and MEK-2. It stops cellular proliferation and induces apoptosis in some cell lines.[34] Common side effects include rash, diarrhea, nausea, vomiting, hypertension, visual disturbance, and decreased liver function. It has been evaluated in combination with chemotherapy for KRAS mutant lung cancer, and unfortunately was not found to improve progression free survival when combined with docetaxel in the second-line setting. The TATTON trial showed that when combined with Tagrisso for EGFR-mutant patients Selumetinib does appear to have benefit, with 34-42% of patients having partial response, and disease control rate up to 81%.[35] Selumetinib continues to be evaluated in combination with immunotherapy in ongoing clinical trials.[36]

Bimetinib (MEK162) is being evaluated in combination with other therapeutic agents for lung cancer, including standard of care chemotherapy agents as well as other targeted therapies. Common side effects include diarrhea, fatigue, elevated lipase levels, and rash.[37] It continues to be evaluated in Phase 2 clinical trial for BRAF mutant NSCLC in combination with Encorafenib, as well as for ALK-rearranged NSCLC in combination with Brigatinib. It remains available through clinical trials only.

NTRK Inhibitors

NTRK 1/2/3 are oncogenic driver mutations that are present in many types of solid tumors. They are identified in approximately 1% of NSCLC patients.

Selitrectinib (LOXO-195) is a selective TRK inhibitor evaluated in an ongoing phase 1 clinical trial. Early results form 29 patients showed an overall response rate of 34%, with 45% of patients harboring an acquired NTRK mutation that developed during prior TRK directed therapy having a response to LOXO-195. Comon side effects included dizziness, ataxia, nausea, fatigue, lab abnormalities and abdominal pain. The estimated trial completion date is July 2024.[38]

Repotrectinib (TPX-005) is a TRK inhibitor that was granted fast-track status by the FDA for NTRK + cancers after prior first line TRK inhibitor. It continues to be evaluated in the TRIDENT-1 clinical trial for patients with either NTRK 1-3, ALK or ROS1 gene rearrangements. In the NTRK mutated cohort 6 patients were evaluable, with an overall reponse rate of 50%. It is generally well tolerated, with dizziness, fatigue, constipation, taste changes, dyspnea and hypoxia seen in some patients.[32]

Additional Small Molecule Inhibitors

Multiple other targets continue to be discovered for NSCLC as science advances and the ability to test patients for multiple gene targets becomes a reality. These additional gene targets include HER2, MET amplification, MET exon 14 mutation, KRAS, RET, PIK3CA, AXL and MAP2K1 (also

known as MEK1). Numerous drugs are currently being investigated that show activity against one or more of these targets. Interestingly, many of these drugs have more than one intra-cellular target and are being evaluated for application in different types of cancer as well as potentially being useful for multiple different tumor mutations. As the science of tumor genetic sequencing progresses more drug-gene targets will be established in an effort to truly personalize treatment to the genetic fingerprint of an individual patient's cancer, with continued improvement in treatment options and therapeutic outcomes for lung cancer patients.

MET

Savolitinib is a MET inhibitor currently being evaluated in combination with Osimertinib for use in patients who progress on first-line EGFR TKI therapy and demonstrate a MET exon 14 deletion as a resistance mechanism. In the TATTON trial the safety and efficacy of the combination of Savolitinib with Osimertinib was established. Results showed a response rate of 28% - 52%, depending on what treatment the patient had received in the front-line setting.[13-14] Side effects were somewhat more severe than observed with single agent dosing, with the most frequent side effects being nausea, diarrhea, fatigue, fevers, decreased appetite, and decreased blood cell counts (white blood cells and platelets). The combination of Savolitinib with Osimertinib continues to be evaluated in the Phase 2 SAVANNAH trial which began enrollment in early January 2019.[15]

RET

TPX-0046 is a next-generation RET inhibitor. Pre-clinical data demonstrated that this compound has the ability to overcome some of the more common resistance mechanisms identified following treatment meth currently available RET inhibitors. A phase I/II clinical trial (NCT04161391) is currently enrolling, but data from human studies are not yet available.[39] Several additional compounds are in early stages of development, including TAS0953/HM06 (NCT04683250) and BOS172738 (NCT03780517). No safety or efficacy data have been published at this time.[40-41]

KRAS

KRAS mutations are among the most commonly found oncogenic drivers of tumorigenesis in lung cancer, however KRAS has historically been considered an "undruggable" mutation due to a lack of a traditional small-molecule binding pocket on the protein. Sotorasib was approved in the spring of 2021 for patients with KRAS G12C mutations. However, this is only one of the multiple oncogenic KRAS mutations that have been identified.

Adagrasib (MRTX849) is an inhibitor of KRASG12C that irreversibly and selectively binds to KRASG12C, preventing downstream cell signaling. The KRYSTAL-1 trial evaluated 51 patients with previously treated KRAS G12C mutated NSCLC, and 45% had at least a partial response to adagrasib therapy. In those patients with a concomitant STK11 mutation, the response rate was 64%.[42] Side effects included GI upset (nausea, vomiting, diarrhea) fatigue and lab abnormalities.[42]

Additional trials are ongoing to better understand the efficacy of this drug, including combining it with immunotherapy and other targeted therapies.[43]

EGFR / HER2 Exon 20 insertion

EGFR exon 20 insertion are a unique group mutations. Unlike the majority of EGFR mutations which are "sensitizing" mutations, exon 20 insertions tend to confer resistance to the typical first generation EGFR TKIs. Thus, addressing this unique oncogenic target has required development of its own set of therapies. Amivantamab is an infusion therapy that was approved in May 2021 for this mutation subtype, but several additional agents continue to be evaluated in clinical trials. CLN-081 is an oral EGFR inhibitor with high selectivity to mutant form of EGFR with exon 20 mutations. Although the overall response rate is not yet available, preliminary trial data showed a reduction in tumor size in 76% of patients. The safety data suggest that CLN-081 is better tolerated than some of the other exon 20 targeting therapies, with fewer than 20% having grade 3 or severe side effects. Typical side effects were rash, diarrhea, lab abnormalities and stomatitis.[44]

Poziotinib is an oral tyrosine kinase inhibitor that is being evaluated in the Phase II ZENITH20 trial for lung cancer patients with EGFR or HER2 Exon 20 insertion mutations. Poziotinib irreversibly blocks signaling through the HER family of receptors, including HER1 (ErbB1/EGFR), HER2 (ErbB2), and HER4 (ErbB4). Response rates were encouraging, with tumor reduction seen in up to 28% of patients treated. Unfortunately, side effects have been problematic, with over 50% of patients experiencing moderate to severe symptoms, including rash, diarrhea, paronychia, mucositis, and fatigue. These side effects often require dose reduction or treatment discontinuation. Splitting the dose into twice daily dosage appears to decrease the risk for severe toxicity by up to 52% while maintaining response rates of approximately 30%. The ZENITH20 trial continues enrolling patients to better understand the efficacy of the twice daily dosing schedule.[45]

Mobocertinib (TAK788) is an oral inhibitor of tumors with EGFR/HER2 exon 20 insertion mutations. In a phase 1/2 clinical trial it demonstrated a response rate of 43%, and PFS of 7.3 months.[46] The extent of CNS penetration is not yet well characterized, and additional data is needed to better understand the degree to which this compound can cross the blood brain barrier. Common side effects reported were diarrhea, nausea, vomiting, decreased appetite and rash. Mobocertinib was granted breakthrough status designation by the FDA in April 2020, and the Phase 3 EXCLAIM-2 trial continues to evaluate efficacy and safety in the first line setting.

Pyrotinib is another TKI with irreversible binding and pan-HER activity (i.e. it has activity against HER1 (EGFR), HER2 and HER4. It has been evaluated in several Phase 2 trials, in one case after patient had received at least one prior line of chemotherapy, with almost 60% having had at least 2 prior lines of chemotherapy.[47] Overall response rate was 30% with a median PFS of 6.9 months.[48] Side effects were reported to be diarrhea as well as lab abnormalities.

Tarloxotinib is a pan-ErbB kinase inhibitor that was shown in pre-clinical studies to have activity against EGFR exon 20 and HER2 mutant NSCLC. The RAIN-701 study showed positive results in

their first presentation of initial data analysis in September of 2020. At the time 23 patients (of a planned 60) had been enrolled onto the trial with evaluable results. Two patients had a partial response, with a demonstrated disease control rate of 60% (at least stable disease). Side effects seen included changes to heart rhythm, rash, diarrhea, nausea and lab abnormalities.[49]

AXL

AXL is a cell membrane receptor that has been identified new drug target in lung cancer. High AXL expression is thought to suppress the body's immune response to cancer cells, and promotes resistance to anti-PDL1 immunotherapies.[50] Further, high AXL expression is thought to confer a poor prognosis in most cancers. Currently there are no FDA approved therapies targeting AXL.

Bemcentinib (BGB324) is a novel AXL inhibitor which seemed to enhance anti-PD1 therapy in pre-clinical studies. A phase 2 trial involving 38 patients have been dosed dwith the combination of bemcentinib and pembrolizumab, with 29 evaluable for response to treatment. 28% of patients showed a partial response, and 40% of the AXL-positive patient responded to therapy.[51] The FDA has granted bemcentinib fast track status, and clinical trial enrollment is ongoing.[50]

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 or "non-self" by the immune system, enabling natural immune defense mechanisms to eliminate the cancer. With immunotherapy, side effects are typically 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. However, in some cases the immune system may become over-engaged, creating auto-immune inflammatory side effects. These side effects can be severe and may require treatment with immune suppressant medications.

Several antibodies have been developed that target immune checkpoints, which play a role in cell signaling and driving cancer growth. Some of the most promising developments in treating lung cancer have been seen with drugs that target the Programmed Death 1 (PD-1) receptor pathway, including Opdivo (Nivolumab), Keytruda (Pembrolizumab), Tecentriq (Atezolizumab), and Imfinzi (Durvalumab). Currently all four of these have been approved by the FDA for at least one indication in lung cancer treatment.

Ipilimumab and Tremelimumab are monoclonal antibodies that inhibit the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoint pathway. Although these agents 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.[52-53]

NKTR-214 (Bempegaldesleukin) is a CD122-preferential IL-2 pathway agonist that was designed to enhance the patient's own immune response in order to fight their cancer. In the PIVOT-02 trial BEMPEG showed an overall response rate of 60% in the NSCLC cohort.[54] It is currently being evaluated in clinical trials in combination with Nivolumab or with Nivolumab and Ipilimumab, as well as with Pembrolizumab. Common side effects are fatigue, fevers, chills, and flu-like symptoms. Enhancing the immune response is felt to be particularly important for those patients whose tumors do not express PD-L1.

APX005M is a CD40 Agonistic Antibody being studied in combination with Nivolumab and Cabiralizumab. This drug was designed to stimulate the immune system and enhance the anti-cancer immune response. There is limited data for NSCLC, however a Phase 1 trial reported on four patients of whom one had a partial response, two had stable disease and the fourth progressed. [55] Side effects include fatigue, malaise, nausea, fevers, chills and flu like symptoms. The Phase 2 trial continues to enroll patients, with results forthcoming.

NC318 is a novel monoclonal antibody targeting Siglec-15. It was designed to function in the tumor microenvironment and enhance t-cell function, thereby restoring the ability of the immune system to recognize and fight off cancer cells. Currently only pre-clinical data have been published and suggest a tolerable safety profile with less risk of serious immune-related toxicity than the anti-PD-1 and anti-CTLA4 targeted antibodies have previously demonstrated.[56] The initial Phase1/2 clinical trial is currently enrolling patients and has an expected completion date 2021.

In an effort to try to both improve first line response rates to immunotherapy as well as to overcome resistance to first line immunotherapies, multiple trials are being conducted evaluating novel combinations of immunotherapy with targeted therapies. Some of these include PARP inhibitors, VEGF inhibitors, novel anti-CTLA-4 antibodies, anti-CD137 antibodies, ICOS agonists and antagonists

While the compounds noted above and the majority of lung cancer clinical trials continue to be designed to help patients diagnosed with stage IV disease, many immunotherapy drugs are also being tested for use in patients diagnosed with earlier stage lung cancers because of their potential for considerable clinical benefit. In stage III unresectable disease Durvalumab was FDA approved for use as maintenance therapy and other immunotherapies are now being used in combination with chemotherapy and radiation. In stage Ib, II and resectable stage III patients, the LCMC3 trial is investigated the use of 2 cycles of atezolizumab prior to surgery. This approach has demonstrated major pathologic response with less than 10% viable tumor remaining after 2 cycles of atezolizumab in 21% of patients, and complete response in 7% of patients.[57] Another trial evaluating response to combination immunotherapy prior to surgery is the NEOSTAR trial, which is enrolling stage I – IIIA patients and is using a combination of Nivolumab and Ipilimumab. In this trial major pathologic

responses were seen in 22% of patients in the nivolumab arm and 50% of patients in the Nivolumab plus ipilimumab arm following resection.[58]

Another type of cancer treatment that has received a lot of attention recently is CAR-T therapy. It is currently approved for several types of blood cancers, but its utility in solid tumors, and in lung cancer in particular remains unclear. Part of the challenge in lung cancer is identifying a target unique to the cancer cells that is not present elsewhere in the body. Too much overlap between the presence of the target in the tumor and healthy tissues will result in the patient suffering severe side effects due to off target impacts of the treatment. Rather than CAR-T cells, a perhaps more promising avenue in solid tumor is to develop specific tumor infiltrating lymphocytes (TILs) that are unique to a particular patient and will recognize and eliminate their specific cancer cells. Trials are currently enrolling patients where researchers collect a tumor specimen from a patient and then isolate the active TILs, increase their number exponentially in a lab, and then infuse them back into the patient. The TIL therapy regimen is quite intense, almost like a mini bone marrow transplant. First the patient undergoes a biopsy to collect tumor tissue. If adequate tissue is obtained, then the patient is admitted to the hospital for several weeks of chemotherapy. During this time the TILs are being isolated and grown in the lab. If the patient is clinically stable after the chemotherapy, they will then receive the infusion of TILs along with other immune stimulatory agents, after which they a monitored closely for potentially severe side effects.

Tumor Mutational Burden

Immune Checkpoint Inhibitors have become a mainstay of lung cancer treatment. In patients without targetable mutations immunotherapy continues to show improved efficacy either as monotherapy or in combination with chemotherapy in comparison with chemotherapy alone in the first- and second-line setting. Unfortunately, only about 20% of patients demonstrate durable long-term responses to these drugs, while a significant proportion of patients experience disease progression within the first months of treatment. PD-L1 expression level is currently the only biomarker approved by the FDA, yet it is not perfect, and seems to correlate with treatment response in some but not all patients. One cannot ignore the high cost of these immunotherapy medications (as much as $150,000/year), and from a purely economic perspective a better marker to identify response is needed to avoid wasteful spending of healthcare dollars. For these reasons, a new set of biomarkers must be developed that will better guide clinicians and help identify those patients who will benefit from immune checkpoint inhibitors.

> *We may encounter many defeats, but we must not be defeated.*
>
> *- Maya Angelou*

Tumor mutational burden (TMB) is one potential marker of response to immunotherapies. TMB is defined as the number of mutations per DNA megabase. It continues to be studied as a potential biomarker to predict response to immune checkpoint inhibitors in NSCLC. To date, responses from clinical trials have been mixed, with some trials showing a predictive association between high TMB and treatment response, while others not finding the same predictive relationship.[59-60]

Because of the potential for long-term durable responses with immunotherapies, any marker selected to guide treatment selection will have to be well validated with extensive clinical support. Limiting treatment options and potentially preventing patients from the benefit of these novel therapies needs to be considered with the utmost caution.

Corticosteroids and ICI

Recent research has brought into question whether or not steroid use affects clinical outcomes during treatment with immunotherapies. Some studies have demonstrated that patients who received corticosteroids prior to starting ICI therapy experienced lower overall response rates, worse progression free survival, and poorer overall survival.[61]

One large retrospective study looked to determine the effect of corticosteroid use specifically in the treatment of immune-related adverse effects and found that there was no significant difference in overall survival (median; 14.5 vs 30.0 months), progression-free survival (median; 7.8 vs 9.6 months), and objective response rate (46% vs 41%) in patients who required steroids (>10mg per day) vs those who did not. They concluded that steroids should not be avoided in patients with moderate to severe immune-related adverse effects due to concerns over reduced efficacy.[62]

Gut Microbiome and Cancer Treatment

Another avenue of research in cancer treatment is the effect of the gut microbiome on overall health, promotion of pathogenic conditions including tumor development and treatment outcomes. A recent report documented stark differences in gut flora of patients following cancer treatments compared to their healthy peers. It has long been understood that antibiotics can change the gut microbiome, and it has become clear that use of antibiotics can impact response to immune checkpoint inhibitor therapy. Several studies have demonstrated significant reduction in progression free and overall survival when antibiotics are administered in the 30 days prior to initiation of immunotherapy treatment.[63-65] Methods for how best to restore gut balance and enhance the positive effects of the microbiome on health are currently under investigation.

Vaccines

Vaccines are also being used to treat lung cancer and as maintenance therapy with the goal of decreasing or preventing the risk of recurrence.

Vaccines are also being used to treat lung cancer and as maintenance therapy with the goal of decreasing or preventing the risk of recurrence. Analogous to vaccines that may prevent the spread of communicable diseases, these cancer vaccines stimulate the immune system to identify and attack cancer cells without damaging normal cells.

CIMAvax-EGF is also known as the "Cuban Vaccine" and is currently available in the US through clinical trials. Multiple trial have shown that it is safe and does elicit an immune response.[66] Side effects have been reported to include fevers, injection site irritation, vomiting, and headache.[67] A phase III trial evaluating use of the vaccine after completion of platinum chemotherapy did not find overall survival benefit.[67] Further studies are needed to determine whether this vaccine can benefit lung cancer patients.

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.[68] Common side effects include injection site reaction and flu-like symptoms.[69] TG4010 continues to be evaluated in Phase 2 and 3 clinical trials, and is now being combined with chemotherapy as well as Opdivo (Nivolumab).[70] Additional data on this combination of drugs is expected to be published in late 2021.

BI 1361849 (CV9202) is a vaccine that is made up of six mRNAs that code for six different NSCLC-associated antigens. Phase 1 trials have demonstrated safety and tolerability of the compound, as well as an enhanced anti-tumor effect when combined with radiation.[71] Collection of survival data remains ongoing. The most common side effects were injection site reactions and mild to moderate flu like symptoms. As it is thought that this compound may increase tumor infiltrating lymphocytes, a trial combining it with an immunotherapeutic agent targeting Anti-PD-1 was performed with modest responses seen in the 26 enrolled patients, including one partial response and 46% of patients with stable disease.[72]A trial is ongoing combining BI1361849 with both Anti-PD-L1 and Anti-CTLA-4 antibodies.[73]

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.

Chemoprevention

Multiple studies have been conducted 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.[74] Antioxidants and anti-inflammatory drugs like COX-2 inhibitors did not ultimately 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.[75] A better understanding of features of pre-malignant lesions continues to develop, and a personalized "cocktail" may ultimately offer the best protection against developing lung cancer in high risk individuals.[76] Unfortunately no compound has been identified that has protective effects against lung cancer. Smoking cessation remains the best approach available to prevent an individual from developing lung cancer.

Lung Cancer Screening Programs

Because 1 in 9 smokers will go on to develop lung cancer, avoiding exposure to tobacco smoke and smoking cessation remain the best defense against lung cancer.[76] See Chapter 13: *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 both the options for treatment of this disease as well as patient outcomes. Chemotherapy has been the mainstay of treatment for most advanced lung cancers for many years. However, new targeted therapies and immunotherapies are changing the treatment landscape for lung cancer, with several new drugs demonstrating remarkable improvement in patient outcomes in terms of both progression free and overall survival. Additional novel agents used both alone and in combination with existing agents are being studied in clinical trials, with the goal of further improving patient outcomes and survival. More therapies will become available in the near future. With advances in lung cancer treatment, patients will benefit from treatments that have fewer side effects and provide long term responses to treatment, such that even if lung cancer remains incurable, it may be treated as a chronic disease and managed for many years.

With advances in lung cancer treatment, patients will benefit from treatments that have fewer side effects and provide long term responses to treatment, such that even if lung cancer remains incurable, it may be treated as a chronic disease and managed for many years.

Questions to Ask Your Doctor about Treatment Clinical Trials

If you are thinking about taking part in a clinical trial, be sure to ask your doctor, "Is there a clinical trial that I can join?" If your doctor offers you a trial, here are some questions you may want to ask.

Questions about the Trial

What is the purpose of the trial?

Why do the researchers believe that the treatment being studied may be better than the one being used now? Why may it not be better?

How long will I be in the trial?

What kinds of tests and treatments are involved?

How will the doctor know if the treatment is working?

How will I be told about the trial's results?

How long do I have to make up my mind about joining this trial?

Who can I speak with about questions I have during and after the trial?

Who will be in charge of my care?

Is there someone I can talk to who has been in the trial?

How does the treatment I would receive in this trial compare with the other treatment choices?

Questions about Risks and Benefits of Clinical Trials

What are the possible side effects or risks of the new treatment?

What are the possible benefits?

How do the possible risks and benefits of this trial compare to those of the standard treatment?

Questions about Your Rights

How will my health information be kept private?

What happens if I decide to leave the trial?

Questions about Costs

Will I have to pay for any of the treatments or tests?

What costs will my health insurance cover?

Who pays if I'm injured in the trial?

Who can help answer any questions from my insurance company?

Will I be paid for participating in the trial?

Will I be reimbursed for expenses during the trial? If yes, what type of expenses?

Questions about Daily Life

How could the trial affect my daily life?

How often will I have to come to the hospital or clinic?

Will I have to stay in the hospital during the clinical trial? If so, how often and for how long?

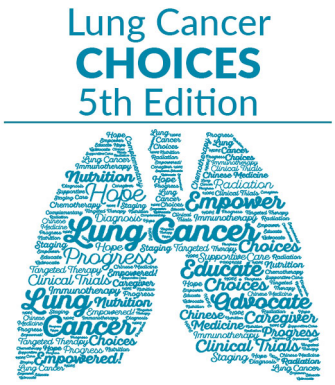
Will I have to travel long distances?

Will I have check-ups after the trial?

Questions about Comparing Choices

What are my other treatment choices, including standard treatments?

How does the treatment I would receive in this trial compare with the other treatment choices?



Chapter 8

Supportive Care

Christie Lynn Pratt, MA, DHSc

Introduction

Advances in early detection and the development of new treatment options such as targeted combination therapies and immunotherapies have increased survival rates for lung cancer patients over the last decade. However, many of these advances have associated known side effects that can present during the course of the disease and even after active treatment. It is important to address the longitudinal effects of treatment and recognize the need for and value of early 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 the 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.

Supportive care is a term that refers to treatment that aims to decrease or eliminate symptoms associated with cancer.

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. A high symptom burden can have direct negative impact on one's quality of life. The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN)'s clinical practice guidelines recommend implementing supportive care interventions early in routine oncology care.[2] Supportive care interventions can improve well-being and survival for cancer patients.[3] Intervening early may decrease unnecessary suffering and enable patients to feel strong enough to be active participants in their 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.[4] 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.[5] However, physical symptoms may become an immediate concern during treatment.[6] 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.[5] The management of these symptoms and psychological distress is important to optimize quality of life.

Symptom Management

Interdisciplinary 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 cancer itself. The primary treatment team includes a physician (medical

oncologist, radiation oncologist, or thoracic surgeon, depending on the course of treatment), advanced practice professional (physician assistant or nurse practitioner), and a primary nurse or nurse navigator. As supportive care needs emerge, a patient may be referred to additional members of the healthcare team, such as social workers, behavorial medicine professionals like psychiatrists or psychologists, palliative care/supportive care clinicians, dietitians or physical therapists, 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 individual and require self-reporting and monitoring. Open communication with the clinical team 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 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 and therapies are continuing to evolve.

There can be side effects associated with lung cancer and treatment. Symptoms and side effects vary between patients and treatments during the course of the disease. Some side effects are well documented and associated with common therapies but with newer treatments or those being researched in the setting of clinical trials not all side effects are known. 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, caregivers, and members of the healthcare 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 the treatment options outweigh the potential effect on their quality of life.

Questions to Ask Your Doctor about Potential Side Effects

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., swimming, running, traveling)?

How will this impact my ability to work?

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 to recognize and handle when side effect occurs. While the side effect profiles for the 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. If hair loss is important to you, 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 communicate this information effectively can have a major effect on the success of treatment. (See Figure 1 at the end of the chapter) 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 open communication about any symptoms or changes in function to ensure the best quality of life and active participation in decisions during and after treatment.

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.[7-8] 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% of patients receiving treatment.[9-10] 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.[9] 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.[9] 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.[5, 11-12] Fatigue can also linger for multiple years after cancer treatment has been completed.[12] 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.

An underlying psychosocial issue could cause fatigue. Depression and fatigue may be concurrent symptoms, 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).[9] 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 healthcare 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 levels can vary from patient to patient and can fluctuate throughout the course of cancer. Fatigue is subjective, and patients must 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 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. 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.

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 the fatigue progressed since the onset?

What makes the fatigue worse?

What makes the fatigue better?

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. See Chapter 9: *Nutrition in the Patient with Lung Cancer*

Patients participating in moderate activity may have better outcomes of cancer care and may experience fewer side effects.

Fatigue symptoms usually decrease, and energy levels improve after treatment has been completed, but some patients experience prolonged fatigue Intervention must begin early in treatment 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, a decline in functional ability, and withdrawal from therapy.[12-13] 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, the 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% of 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.

Bowel Changes

Depending on the course of treatment, patients may experience a change in their bowel habits to include both constipation and diarrhea. The most frequently reported symptom in patients on immunotherapy is diarrhea. The incidence of diarrhea is greater on anti-PD-1 and PDL-1 agents.[14] Patients also report that diarrhea can occur months after discontinuing an immunotherapy treatment. Monitoring and self-reporting of the frequency of symptoms to the clinical team is critical. They will determine the level of severity and the impact or changes in the treatment regimen.

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 the duration of constipation and alleviating factors, this helps 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

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 in developing a diet that meets the patient's individualized needs. Earlier determination of the cause of weight loss may provide a better outcome and overall better tolerability. If the weight loss is caused by difficulty in swallowing, nausea, vomiting, or mouth sores, the underlying causes must be 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 better 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 9*: Nutrition in the Patient with Lung Cancer*.

Respiratory Symptoms of Lung Cancer

Cough

Cough is a very common symptom of lung cancer. A 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. A 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 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.[15] 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, perceived 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. Evidence based pharmacological management of dyspnea also includes the use of systemic opioids in addition to non-pharmacological interventions to help breathing efficiency and capacity. These techniques include breathing from the diaphragm, positioning, pacing techniques. Research has shown that teaching patients breathing retraining in combination with psychosocial or behavioral interventions to address the associated and related anxiety has been successful.[16] If dyspnea is related to a pleural effusion, surgery (pleurodesis) may be an option to remove the excess fluid. Approximately 50% to 70% of 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

Immunotherapy is one of the latest advances in lung cancer. It is a treatment that is driven by stimulating the body's immune response, leveraging that response to attack the tumor. These drugs often have adverse effects triggering other immune responses impacting the skin.[14-15] 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,[15] 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, and the management of cancer-related pain can be complex. Pain is the most common cause of disability and associated with sleep disturbances, anxiety, and dyspnea, all impacting quality of life when not controlled.[17] Pain is often associated with emotional distress in cancer patients. 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. Reporting pain early and referral to supportive cancer services are crucial for the management of any pain. Pain is experienced in more than half of patients undergoing treatment, 65% of patients with advanced-stage disease, and in about a third of patients after curative treatment.[18-20]

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. The pain scale is an effective way to describe the magnitude of pain experienced (mild, 1 to 3; moderate, 4 to 7; severe, 8 to 10).[18] 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 discuss expectations and goals associated with symptom management openly.

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.[21]

Chemotherapy-induced peripheral neuropathy is a subset of neuropathic cancer 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.

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

On a scale of 0 (no pain) to 10 (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 you are experiencing?

Strategies for Pain Management

After a thorough evaluation, interventions can help decrease pain. The goals of pain management are to optimize the effects and tolerability of treatment. These goals are referred to as the 5 A's and include: Analgesia (pain relief), Activities (optimizing the ability to carry out daily activities), Affect (improve relationship between pain level and mood), Adverse Effects (reduce) and Aberrant drug use (avoid addiction).[18] 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, oxycontin, or fentanyl. Pain medications come in varied forms and delivery systems (tablets, liquid, transdermal patches, suppositories, and injections). For patients with difficulty swallowing, a liquid may be prescribed. In addition, pain pumps and devices can be implanted to provide continuous delivery of medication.

Opioids can cause new side effects or can make existing side effects worse. Opioids cause constipation, nausea, and skin itchiness (pruritus). Pruritus occurs in 10% to 50% of patients taking opioids.[23-25] 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.[21-22] 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.[23] See Chapter 11: *Integrative Medicine, Complementary Therapies, and Chinese Medicine in Lung Cancer* for more information.

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.[3] 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 cancer at diagnosis and the heavy burden of symptoms frequently associated with lung cancer.[26]

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.[24] 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-existing psychological factors.[25-27] 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 the effects of cancer treatment. Symptoms include levels of forgetfulness, difficulty concentrating, and difficulty with multitasking. This can become a very distressing and a 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.[28] The prevalence of distress varies by cancer type and ranges from 35% to 43% in lung cancer.[25] 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%) of cancer survivors continue to suffer from sadness, often severe enough to require intervention.[26] 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 the 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 too 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% of patients receive support for distress.[26]

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.[28-30] 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. [30-31]

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 peer support calls, telehealth/virtual connections, 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 the experience. 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 strong support system can ensure patients feel comfortable openly discussing symptoms and may help in 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.[32] 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.[30] 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 or addictive substances.[33]

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.[34] 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.

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 and early detection tools to manage lung cancer symptoms better.

My Symptom Management Journal

Date: Time: AM/PM

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?

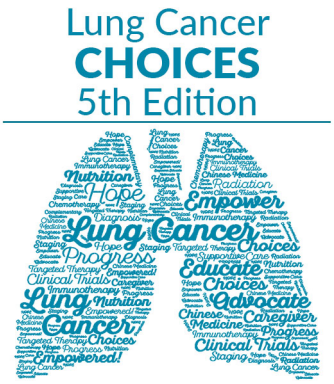
Because of this symptom, I have been unable to engage in the following activities:

Questions or instructions from my health care team:

Spoke to: Time: AM/PM

Suggested strategies for symptom management:

-
-
-



Chapter 9

Nutrition in the Patient with Lung Cancer

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Introduction

Nutrition is vital in cancer treatment and survivorship. Food provides the building blocks needed by the body to repair and heal from cancer therapy. The benefits of proper nutrition during cancer treatment include improved quality of life, decreased discomfort from side effects, reduced frequency of complications and treatment breaks, and improve quality of life.

Lung cancer treatment can create a burden of healing that can overwhelm even a healthy patient's nutritional reserve. Cancer itself can affect appetite, digestion, and use of nutrients. Treatment regimens such as surgery, chemotherapy, immunotherapy, and radiation can cause side effects that interfere with eating and drinking. A patient's nutritional status can deteriorate throughout treatment, reducing their ability to tolerate treatment. Decisions about treatment regimen may be determined based on general health performance status scores.[1] Weight loss and decreased ability to consume adequate nutrition can negatively influence those performance scores and alter treatment options.[2]

Many people that begin lung cancer treatment have already experienced some decreased appetite (anorexia) and may have noticed an early sense of fullness when eating (early satiety). Anorexia is often described as a disinterest in food. The effects of anorexia and early satiety can lead to unintentional weight loss and possibly even malnourishment.

Among patients with advanced lung cancer, more than half will become malnourished during treatment. Malnourishment is associated with worse outcomes in patients treated for cancer because nutritional deficiencies can decrease treatment tolerance, 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 support the healing process. In this chapter, we review the factors that affect nutrition and healing; the common barriers to eating, effective strategies to manage the side effects that limit nutritional intake; and resources to use during treatment and survivorship.

The goal of nutrition in treatment is to support the healing process.

Protecting Lean Body Mass

During recovery from cancer treatment, it is important to maintain muscle or "lean body mass" to help maintain optimal health and allow you to participate in usual activities. Muscle wasting can result in debilitation, decreased functional status, and reduced quality of life.[4] Maintenance of lean body mass during treatment may even improve response to cancer treatment.[5-6]

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". 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 that occurs when dieting. Both underweight and overweight people are at risk for malnourishment during lung cancer therapy.[5-6]

Involuntary weight loss may occur in about half of the people with lung cancer, even a weight loss of 5% may influence 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.[7]

Cancer cachexia is a syndrome that results in a progressive loss of muscle mass and fat stores and leads to progressive functional impairment. It is associated with a lack of appetite and negative energy and protein balance. It is important to identify these symptoms, called "pre-cachexia", and take action to treat any side effects or barriers to eating.[8] Medications, such as appetite stimulants, may help manage cancer cachexia, and this option may be discussed with the physician.[9]

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Nutritional counseling which focuses on food choice and behaviors related to eating is effective in addressing lung cancer malnutrition. Medical Nutrition Therapy, a technique used by a Registered Dietitian/Nutritionist (RDN), can help patients to increase protein and calorie intake, improve weight status, enhance energy and strength, and protect quality of life in people undergoing cancer treatment.[7, 10-12] Many cancer centers have specially trained RDNs who are dedicated to the nutritional care of cancer patients. If the cancer center does not have an Oncology RDN, a referral may be obtained from the doctor. Contact the Commission on Dietetic Registration to find a board-certified specialist in oncology nutrition – who has the credential "CSO".

Nutrition and Healing

Each time a patient receives treatment for cancer - surgery, chemotherapy, targeted therapy, immunotherapy, or radiation therapy – the body responds to the treatment with healing. The healing process requires specific nutrients, extra calories, and additional protein. People receiving treatment for lung cancer may require more energy and protein than when they were not sick; this state of increased demand for calories and protein is termed "hyper-metabolic."[13-15]

Total daily caloric content should be considered in addition to total daily protein intake. If weight loss continues despite higher protein intake, the protein will be utilized for calories and will not be available for structural repair. It is useful to have a general expectation for the number of calories and protein required each day. (Table 1) Your individual needs may differ, ask your healthcare team about your specific needs.

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

Body Weight (pounds)	Calories needed (calories/day)	Protein needed (grams of protein/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[15]
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

Staying hydrated is important to feeling well during treatment. Hydration balance is cumulative, and it can take several days to become dehydrated or to re-acquire adequate hydration status.

Fluid needs may be increased due to chemotherapy, fever, perspiration, diarrhea, use of oxygen, or the presence of chronic obstructive pulmonary disease (COPD). Symptoms of dehydration include: fatigue, thirst, dry mouth, decreased urine output, concentrated or darker colored urine, decreased skin turgor (elasticity of the skin), headache, and dizziness. Mild chronic dehydration may also increase fatigue and contribute to constipation. A fluid deficit of 1% body weight may decrease metabolic function by 5%.[16]

Patients may consider tracking daily fluid intake to ensure adequate hydration. It may help 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, such as: drink 1 cup per hour, throughout the day. Most liquids may be included as part of daily hydration, including flavored waters, milk, juice, smoothies, milkshakes, and soda. Caffeinated beverages may be included as part of daily fluid intake

if caffeine consumption is moderate (less than 300 mg per day which is 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 hydrating fluids. Fluids intended for rehydration, called "sports drinks," have a small amount of carbohydrates and electrolytes to help them absorb more effectively. Oral rehydration salt solutions (or "ORS" products) are effective at improving hydration status and are now readily available in pharmacies. Ask your healthcare team if ORS would be appropriate for you. Daily fluid requirements may be estimated using the chart below. (Table 2) Add 1 cup for each episode of diarrhea. Your individual needs may differ, ask your doctor about your specific needs.

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

The nutrition focus during lung cancer treatment is to get enough calories and protein to support the healing process. Oncologists recommend that "all calories are good calories in lung cancer therapy." The aim is to make eating as tolerable and interesting as possible and remove any unnecessary diet restrictions. Information found on the television, in magazines, and on the internet regarding "good nutrition" may not apply to people going through cancer treatment. Ask your healthcare team's advice if you have been following a heart-healthy, low-fat, low-cholesterol, or low-carbohydrate diet.

Be Flexible

Cultural traditions regarding "what makes a meal" may need to be modified in treatment, such as changing expectation 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. Snacking has been found to increase

total intake without affecting meal intake, especially if snacks are timed approximately two hours before the next meal.[17]

A quality snack may be created by combining any two of the following food groups: Breads/starches; meats/nuts/beans/eggs; milk/cheese/yogurt 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 appetite is poor. 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
Avocado on Toast
Hard boiled eggs on crackers
Tortilla chips and salsa
Cheese and crackers
Chicken salad on a piece of toast
Yogurt (full fat) with fruit topping
Apple slices and peanut butter
Cookies and milk
Smoothie made with orange sherbet and milk

Making Every Bite Count

Many foods and beverages are available in full fat or high-calorie option (for example choosing whole milk instead of skim milk). Some can be enhanced to increase nutrient density by adding protein powder supplements 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). 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, avocado, nut,

or oily fish, 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 any fat, oil or butter contains about 45 to 50 calories. By adding one teaspoon of fat to each meal and snack, caloric intake is increased by approximately 250 calories per day without having to eat a larger volume of food. Another strategy is to add one to two tablespoons of heavy cream to any milk-containing food or beverage, thus increasing the calorie content of that food by approximately 50-100 calories. These additions are almost invisible to the person who is trying to maximize caloric intake.

Diabetic Concerns

Many people are required to follow a diabetic diet that limits carbohydrate intake. When appetite is decreased, and meal size is reduced, diabetic diets may be liberalized to allow the addition of carbohydrates. Carbohydrate counting or substitution may help increase caloric intake. Eating carbohydrates may be an uncomfortable idea for patients who have followed their doctor's advice for many years to avoid simple sugars and starches. 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 food item with full carbohydrate content may be used. If consumption is close to usual portion sizes and frequency, the lower carbohydrate version may be used. An example of food substitution can be made regarding yogurt: choose a full carbohydrate version when it is the only food eaten for lunch but choose a low sugar yogurt if it is consumed with a sandwich and bowl of soup.

Be aware of the symptoms of low blood glucose in patients who take some diabetic medications, as decreased oral intake while continuing to take insulin 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, blood glucose level should be tested immediately, 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 your healthcare team. Diabetic patients may also consider carrying glucose tablets or hard candy and keeping some fruit juice at home to drink if blood sugar drops.

Vitamins and Mineral Supplements

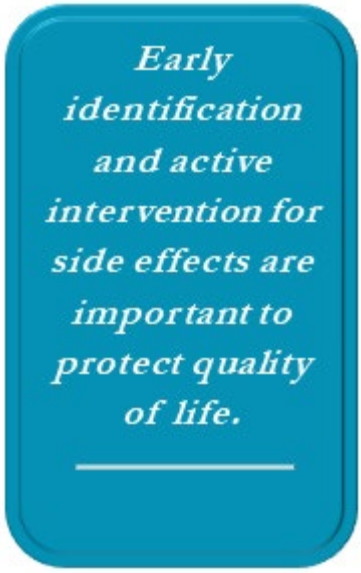
Several studies have examined the use of supplemental antioxidants, vitamins, and minerals in patients with advanced non-small cell lung cancer receiving chemotherapy. Most studies have not shown the protective benefit of antioxidants during treatment, nor reduction in cytotoxic side effects.[18] The 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.[19] Another study, focusing on the mineral selenium, found that people deficient in selenium benefited by supplementation. However, an increased rate of lung cancer occurred in people taking selenium who were not deficient.[20] Use of antioxidant nutrient supplementation (i.e., Vitamin C, Vitamin E, Selenium, and others) are not recommended during radiation therapy or alkylating chemotherapies. The Academy of Nutrition and Dietetics 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.[21]

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 fatty acid supplementation may improve global quality of life.[15] Omega-3 oils can be found in fish such as salmon, halibut, fresh tuna, as well as flaxseed and walnuts.[22-23]

Bioactive compounds of interest being studied in relation to lung cancer include: Fish oil; tea (Camellia sinesis); Isothiocyanates and Indole-3-Carbinol (present in cruciferous vegetables such as cabbage, broccoli, brussels sprouts, kale and cauliflower); Genistein isoflavones (present in soybean); Curcumin (Curcuma longa); pomegranate polyphenols (Punica granatum); Fisetin flavonoid (present in strawberry, persimmon, grape, apple, cucumber and onion).[24] If tolerated, it is appropriate to include these nutrients into a healthy diet. 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 Registered Dietitian/Nutritionist.[15, 20]

Managing Side Effects and Complications

Early identification and active intervention for side effects are important to protect quality of life. A significant component of cancer treatment support is geared to manage symptoms and side effects. Effective use of medication may facilitate symptom control and side effect management. The patient should routinely speak with the health care team members about medicines that may help control symptoms. Nutritional intervention may focus on lifestyle changes and behavior modification that address symptoms or side effects.[11, 15]



Anorexia and Early Satiety

Some patients with lung cancer may experience anorexia, also called loss of appetite. People with anorexia may describe their lack of appetite as "searching for foods that interest the taste buds" or "not being able to find anything to eat that sounds good to eat." How does a patient eat if there is no sensation of appetite or feeling of hunger? Anorexia must be addressed because although the patient may not feel natural appetite, the body experiences hunger, which may reveal as weakness, fatigue, excessive sleeping, and/or inability to concentrate.

Early satiety is often described as "feeling full after only a few bites". 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 cycle can be interrupted purposefully. 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 a schedule for meals and snack times (even small portions count), can provide fuel adequate to improve weakness and fatigue. The anorectic patient should consciously think about eating as a way to provide vital nourishment to the muscles and immune system. 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.

Instead of asking the patient, "Are you hungry?" or "What do you want to eat?" try asking "What could you eat (or drink) right now? Or, "what can you tolerate right now?" Patients should consider eating and drinking more frequently, such as every 2 to 3 hours during the day. Or, if eating is impossible, a patient may consider getting most of their nutrition from beverages. Many people experiencing anorexia for solid food still feel thirst and can use nutritious beverages to provide calories, protein, as well as fluid. For example: 2 ounces of a milkshake taken each hour provides at least 1500 calories over a day. Some patients use a kitchen timer, cell phone alarm, or watch to cue themselves to eat and drink.

Patients who do not have much appetite, may be unable to eat the same food repeatedly or tolerate leftovers. Therefore, it is advisable to make small batches and rotate through tolerated menu items. Consider keeping a record of flavor profiles that taste good (for example: fruit flavors). These taste preferences may change based on the day of the treatment cycle, fatigue, or other factors. Creating a list of tolerated foods reassures the patient that some foods are acceptable and appealing may help stimulate ideas for other menu options.

Anorectic patients may be unable to eat the same food repeatedly or tolerate leftovers. Therefore, it is advisable to make small batches and rotate through tolerated menu items. 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 try another type of food. Creating a list of tolerated foods reassures the patient that some foods are acceptable and appealing may help stimulate ideas for other menu options.

Taste Changes

Taste alterations may be the side effect of cancer itself, the chemotherapy regimen, infection, or certain medications. Most taste changes develop and dissipate depending during the treatment cycle. Taste changes may negative effect appetite, patient's describe food flavor resembles; "flat taste" or is like "cardboard" , a metallic , food is super-salty , or "sickly sweet". It is important to address the particular taste alteration, as described below.[22, 25-26] (Table 4)

Table 4. Specific Suggestions for Managing Taste Changes in Patients with Lung Cancer[25-26]

1.	Identify flavors that come through as "true" or accurate; consider similar foods to develop a greater number of tolerated food items. Often watermelon, cantaloupe, and other fruit will maintain a pleasant flavor.
2.	If tart or sour flavors are appealing, drink a small glass of fruit juice, cranberry juice or lemonade 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. Try a sample of the herb Gymnema sylvestre to temporarily deaden the taste buds to sweet flavors (professional wine tasters use it, and the effect lasts about 20 minutes). Available at local pharmacies or online.

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 sources 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 a 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.	Clean the mouth and tongue after each meal.
13.	Use sugar-free mints, candies, and gums to refresh the mouth.
14.	A metallic taste may be managed with plastic or bamboo cutlery.
15.	Synsepalum dulcificum is a fruit supplement (also called "miracle fruit") which may enhance sweet flavors and help reduce bitter, acidic or metallic taste sensations. Available online.
16.	Examine the mouth for red or white patches that may indicate an infection and report any signs of thrush to the doctor.

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 nausea. Distinguish and note what triggers nausea or queasiness to 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.[25, 27](Table 5)

Table 5. Specific Suggestions for Managing Nausea and Vomiting in Patients with Lung Cancer[25, 27]

1.	Eat and drink small volumes at frequent intervals throughout the day. Imagine "trickling" the food and beverages. For some people, nausea is worse when the stomach is empty or when they become overly hungry.
2.	Identify good times of day to eat.
3.	Choose bland, starchy foods that will digest quickly: potato, toast, pancakes, waffles, couscous, noodles, rice, dry cereal, oatmeal, pretzels, crackers, applesauce, bananas.
4.	Eat and drink clear liquids that digest rapidly: broth-based soups, juice, soda, gelatin, Popsicles.
5.	Sour and tart flavors may 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.
6.	Use cold plates to decrease exposure to odors. Avoid being around cooking odors, or exposure to fast food odors in an enclosed environment (like the car).
7.	Foods and beverages made with ginger are a natural way to soothe the stomach: ginger tea, ginger snaps, ginger ale, ginger candies.
8.	Avoid foods that are greasy, fried, pungent, or strongly spiced.
9.	Review medication use with your medical provider: Optimize use of anti-nausea medications, and address reflux, and constipation.

Sore Mouth and Throat

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 help minimize symptoms and nutritional deficiencies resulting from these conditions.[25, 27](Table 6) Foods that are recommended if diarrhea is occurring due to the side effects of immunotherapy.[25, 27](Table 7) Fatigue and food safety are issues that warrant special considerations.[28-29](Tables 8 and 9)

Table 6. Specific Suggestions for Managing Mucositis and Radiation Esophagitis in Patients with Lung Cancer[25, 27]

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 achieved 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 thoroughly.
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 the 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 pills 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 Diarrhea in Patients with Lung Cancer[25, 27]

1.	Eat and drink small volumes at frequent intervals throughout the day. Imagine "trickling" the food and beverages. Avoid eating large portions as this may trigger diarrhea.
2.	Eat and drink clear liquids that digest rapidly: broth-based soups, juice, soda, gelatin, Popsicles.
3.	Choose bland, starchy foods that will digest quickly: rice, potato, white toast, pancakes, waffles, couscous, noodles, dry oat cereal, oatmeal, pretzels, and crackers.
4.	Include beverages and foods that contain electrolytes (potassium): banana, inside of a baked potato, orange juice (small portions), tomato juice (small portions).
5.	Include beverages and foods that contain electrolytes (sodium): canned soups, crackers, pretzels.
6.	Substitute low lactose items for dairy such as milk, yogurt, cheese, and ice cream. Consider using a lactase enzyme or tablet when consuming dairy.
7.	Avoid beverages that contain caffeine, carbonation, or alcohol. Avoid sugar substitutes found in sugar-free candy and gum (ingredients that end in "OL").
8.	Avoid foods that are high fiber, greasy, fried, pungent, or strongly spiced.
9.	Report frequent loose stools to your health care team, as an infection may cause diarrhea. Do not use anti-diarrheal medications until instructed by your healthcare team.
10.	Review medication use with your medical provider. Ask if you should stop taking medications intended to treat constipation.

Table 8. Specific Suggestions for Managing Fatigue in Patients with Lung Cancer[28-29]

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, canned green beans, potato salad, and ice cream.
2.	To maximize the energy provided from food schedule meals and snacks at frequent intervals. Plan your more substantial 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 various 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. Stay well hydrated. Avoid drinking liquids in the evening to avoid interrupting sleep at night.
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 maintain muscle, strength, and promote bowel health.

Example menu if the patient has fatigue:

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 iced tea
Snack:	Ice cream bar
Dinner:	Baked chicken (already prepared at a grocery store), salad mix (bagged), instant mashed potato, gravy (out of a jar), green beans (canned), a glass of chocolate milk
Snack:	Graham crackers, vanilla pudding (single-serve container)

Table 9. Food Safety Suggestions for Patients with Lung Cancer[28-29]

1.	**The 4 Basic Steps of food safety: Clean, Separate, Cook, and Chill**. Safety practices are especially important when the immune system is weakened, such as during chemotherapy or periods of neutropenia.
2.	**Clean:** Wash hands in warm soapy water for at least 20 seconds before food preparation and before eating.
3.	**Clean:** Food preparation surfaces should be cleaned thoroughly with dish soap and water and allowed to air dry.
4.	**Clean:** Wash canned goods lids before opening. Use clean utensils and food platters.
5.	**Clean:** Wash raw fruits and vegetables under running tap water, including those with skins and rinds. Ask the doctor if you should use only cooked or canned fruits and vegetables.
6.	**Separate:** Avoid cross-contaminating foods and food contact surfaces with raw meats.
7.	**Separate**: Use separate cutting boards, for meat and produce, and for raw versus cooked meat.
8.	**Cook:** Avoid eating pink or undercooked meat. **Cook** raw pork, eggs and ground beef to an internal temperature of 160 degrees F. **Cook** poultry, hot dogs, lunch meats, bologna, and deli meats, sauces, soups and gravies to an internal temperature of 165 degrees F. **Cook** steaks, roasts, and fish to in internal temperature of 145 degrees F. Use a food thermometer to ensure proper temperatures.
9.	**Chill:** Keep cold food at 40 degrees F or cooler.
10.	**Chill:** Promptly refrigerate perishable groceries and meal leftovers. Do not let hot food sit on the counter to cool down before refrigeration.
11.	**Chill:** Divide up large batches of food into smaller containers, so they cool quicker in the refrigerator.
12.	**Chill:** Thaw frozen foods in the refrigerator; do not thaw foods on the counter at room temperature. If you thaw food in the microwave, cook it immediately to 185 degrees F.
13.	**Discard** leftovers stored at room temperature more than 2 hours, and discard leftovers that are more than two days old. When in doubt, throw it out.

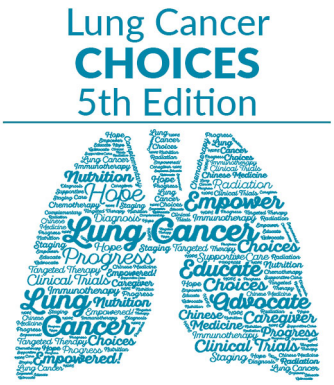
Resources for Treatment and Survivorship

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.[25] It can be accessed online, and downloaded or printed at: https://www.cancer.gov/publications/patient-education/eating-hints It is also available in Spanish. Other resources are available on the website of the National Cancer Institute www.cancer.gov.

The American Cancer Society (ACS) offers helpful information: Nutrition for People with Cancer: Survivorship during and after cancer treatment and Living well during treatment.[29] It is available online at http://www.cancer.org/acs/groups/cid/documents/webcontent/002903-pdf.pdf. and https://www.cancer.org/treatment/survivorship-during-and-after-treatment.html Support information is also available in Spanish as well as other languages. Other resources are available on the website of the American Cancer Society www.cancer.org.

The American Institute for Cancer Research (AICR) offers a comprehensive guide for nutrition, physical activity, weight management, and cancer prevention information. They also provide recommendations for cancer survivors. The 3rd Expert Report Diet, Nutrition, Physical Activity, and Cancer: A global perspective includes reviews of thousands of nutrition and cancer studies, to help develop public policy and personal prevention recommendations.[30] 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 www.aicr.org also offers updates on new research as it occurs, recipes and links to reputable resources.

Notes



Chapter 10

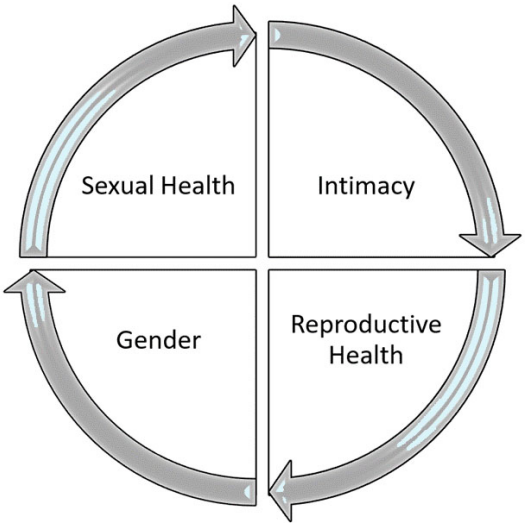
Sexuality and Lung Cancer

Jenna Kahn, MD and Loise W. Wairiri, MD

Introduction

Sexuality is defined as a central aspect of being human throughout life which encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy, and reproduction. (Figure 1) It is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviors, practices, roles, and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, legal, historical, religious, and spiritual factors.[1]

Figure 1. Components of Sexuality



Sexuality-related concerns such as sexual health, intimacy, reproductive health, and gender are prevalent among cancer patients from diagnosis, during treatment, and can even extend years after primary management.[2] In this chapter, we will discuss sexuality concerns, mechanisms, how they relate to cancer, and interventions.

Defining Sexual Health in Cancer Survivorship

Sexual health is an important aspect of quality of life that requires a positive and respectful approach to sexuality and sexual relationships.[3] Often, sexuality in cancer management suffers thus affecting the quality of life in these patients.

Reduced sexual function is a common distressful consequence of lung cancer diagnosis and treatment. The estimated prevalence of sexual dysfunction in cancer patients ranges from 40% to 100% depending on the type of cancer, treatment modality, and methods of assessment.[4] In lung cancer patients, the prevalence has not been well documented, however studies show that sexual function progressively worsens over the lifetime of the patients.[5] Lung cancer patients and their partners suffer significant physical and psychological distress as a result of cancer diagnosis and management. Data suggests that substantial disruptions in the psychological well-being impacts patient's sexual functioning, social well-being, and quality of life.[6] In addition to the effects of cancer diagnosis and treatment, older age and comorbidities such as diabetes, arthritis, congestive heart failure worsen and increase concerns on sexuality.[7]

Lung cancer management has often minimized sexual health and remained focused on the short-term quality of life improvement and palliative care. Conversations surrounding sexual health in cancer patients have been largely reserved.[8] A research study that examined the effects of lung cancer treatment in sexuality reported that 51.7% of patients had self-reported sexual concerns and of these patients, 24.7% had moderate to severe sexual concerns.[9] Despite these numbers, cancer care providers and patients express that sexual health issues are not well addressed or adequately treated in the course of cancer management.[10-12] Poor patient-provider communication is a major barrier to sexual health management in oncology as patients may feel unsupported and uncomfortable discussing their sexuality concerns openly.[13-14] Patient's interactions with health care providers during cancer management and follow-up are great opportunities to discuss quality of life issues including sexuality and sexual health. An interactive cancer management approach ensures the patient feels supported at all times during care.

Intimacy in Cancer Patients

According to the American Psychological Association (APA), intimacy is defined as an interpersonal state of emotional closeness and characterizes familiar, close, and usually affectionate or loving personal relationships that require parties to have detailed knowledge or deep understanding of each other.[15] Intimate relationships are vital to human beings but often suffer when partners suffer from significant or chronic illnesses such as cancer.

Cancer diagnosis and treatment is stressful and causes significant distress on the physical and psychological well-being of cancer patients and their partners and as a result, a significant strain on the intimate relationships between cancer patients and their partners. Fatigue, pain, body image concerns, self-esteem and worth, depression, anxiety are some of the reasons why intimacy in relationships can be affected.[16]

Patients and partners have unique experiences and valid concerns in the course of cancer diagnosis and management. Communication, assessment, and evaluation by the cancer care team can help tailor interventions best suited to the patient and their partner. Briefly, some of the ways to manage intimacy issues and concerns include; patients and partners seeking professional help from their cancer care team, establish open communication with each other, make necessary adjustments to accommodate for physical and emotional symptoms such as fatigue, pain, shortness of breath, low energy or moods, validating each other's feelings, and setting time when appropriate for closeness and reacquaintance with each other.[16]

Reproductive Health Concerns in Lung Cancer Patients

Cancer diagnosis and treatment are often a threat to fertility to reproductive-aged patients. Although statistically majority of patients with lung cancer are past childbearing age, a few patients are diagnosed with lung cancer during the reproductive age group.

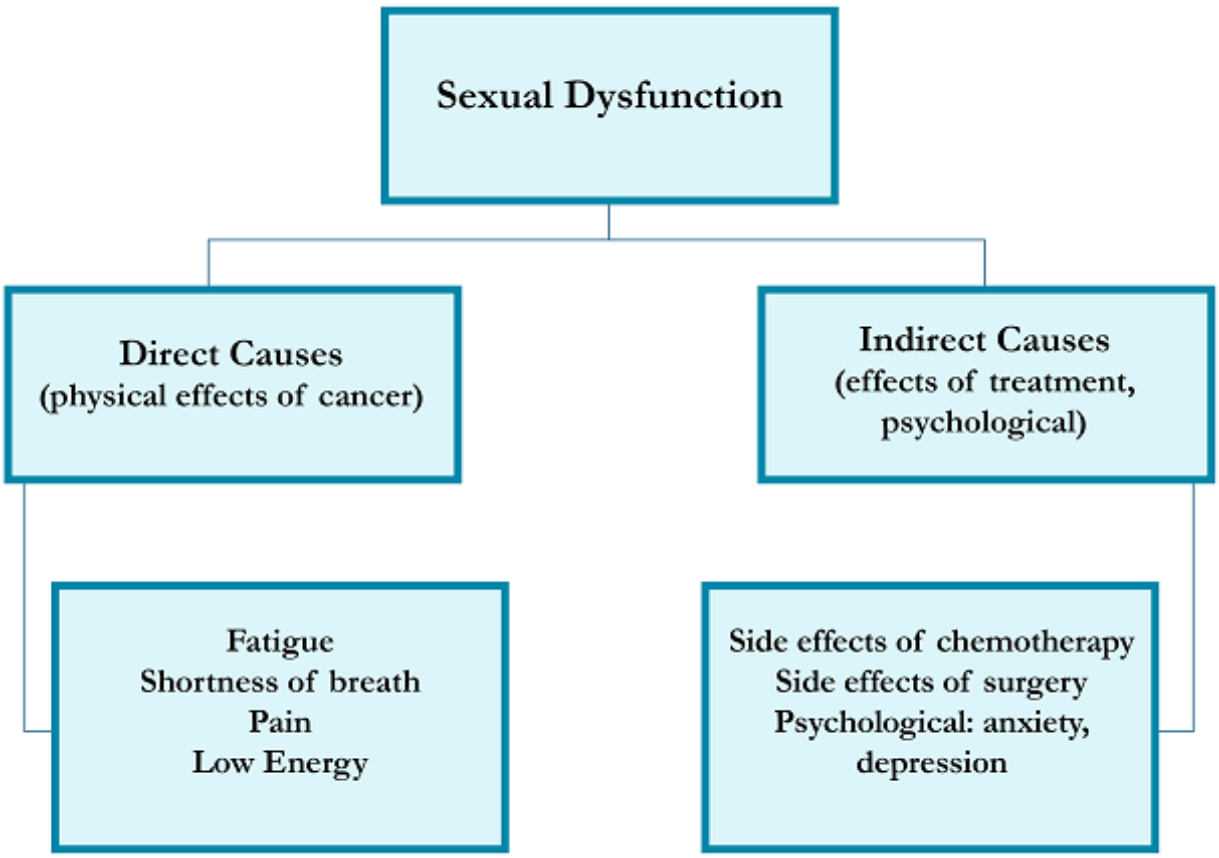
Infertility is defined as failure to conceive after 1 year of intercourse without contraception and may be permanent or transient. Causes of compromised fertility vary and include side effects of cancer treatment (chemotherapy, radiation therapy), age, psychological effects of the disease, and treatment.[17]

Depending on the patient, different methods to restore/preserve fertility exist and should be discussed by the primary care and cancer care team at diagnosis or before treatment starts such as chemotherapy and radiation therapy. There are evidence-based guidelines on fertility preservation options for men and women and guidance regarding these options from oncologists and cancer care providers.

Mechanisms of Sexual Dysfunction in Cancer Patients

The patient's ability for intimacy and sexuality can be affected by a variety of factors that directly or indirectly stem from the disease. Symptoms of lung cancer independently contribute to a decrease in sexual function among patients and include pain, fatigue, and shortness of breath. The functional status of lung cancer patients correlates to sexual concerns in these patients.[10] Factors that contribute indirectly include psychological stressors and adverse effects of cancer treatment (surgery, chemotherapy, radiation therapy).[18] A summary of the causes of sexual dysfunction is shown in Figure 2.

Figure 2. Causes of sexual dysfunction in cancer patients



Psychological distress
Depression and anxiety are prevalent among cancer patients with studies reporting rates of up to 43.4% in lung cancer patients.[19] Anxiety and depression are associated with a decline in sexuality. As a result of the high rates of psychological distress in cancer patients, reduced sexuality is prevalent in this population.[20]

Anticancer therapies
Chemotherapy and surgery are significantly associated with decreased sexual function in lung cancer patients.

Surgery for lung cancer can decrease the sexual functioning of patients due to its invasive nature and increased physiological demands. Increased fear and anxiety post-operatively also contributes to the decreased sexual functioning among patients undergoing surgery for lung cancer. Depression and anxiety are especially prevalent in patients with lung cancer post-operatively.[21]

Chemotherapy for lung cancer is associated with fatigue, psychosocial and physical symptoms, and increased distress, all of which can reduce sexual function in these patients.[22]

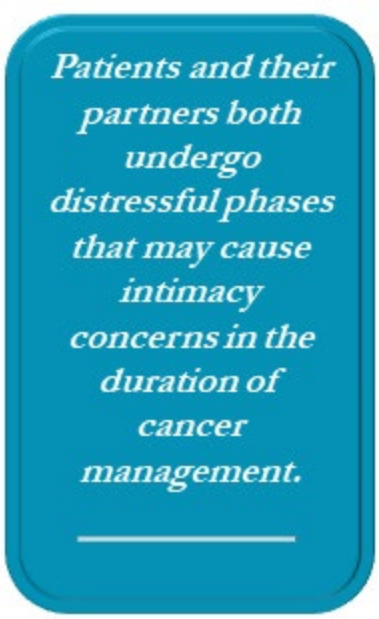
Management of Sexual Dysfunction in Cancer Patients

The first step towards the management of the concerns in intimacy and sexuality is holding discussions on the same throughout treatment and follow-up. Issues with intimacy and sexuality are important medical conditions just as any other medical conditions that need to be addressed. Health care providers are not bothered or too busy to handle such issues and according to the American Society of Clinical Oncology (ASCO) should initiate discussions on sexual health and dysfunction to the patients.[4] We encourage patients to have a discussion openly with their health care provider at any time during cancer management. The choice to include the partner in the conversation should be made if the patient so wishes. Sometimes patients may feel uncomfortable bringing up sexual concerns with the cancer care team and in that case, should bring them up to the primary care physicians. Below are some phrases that can be used to bring up discussions on sexuality.[23]

Management and Evaluation of Sexual Health

Pre-treatment counseling and routine assessment
It is important to understand before and during cancer treatment that reduced sexual function is among the adverse effects encountered during treatment. This varies from patient to patient and the degree of dysfunction also varies throughout cancer management. Providers having baseline information on your pre-treatment/pre-diagnosis sexuality allows for easier follow-up and addressing any sexual concerns as soon as they arise. As discussed earlier, the causes of declining sexual function are varied and include; psychological stressors (anxiety, depression), physical stressors (fatigue, shortness of breath, pain), and psychosocial stressors (financial, familial, occupational, marital). They

all affect individuals differently and addressing these causes with your health care provider is important in management.[18]



Communication and involving the partner

Patients and their partners both undergo distressful phases that may cause intimacy concerns in the duration of cancer management. Communication with health care providers is important to establish goals and treatment outcomes for sexuality function. Including partners in these discussions when the patients are willing and comfortable may offer better perspectives on expected course and outcomes during cancer management.[24]

Specific management

Information on the management of sexual problems and concern below has been sourced from the ASCO recommendations. Access to sexual health resources and referral information for the patient and partner is available from the health care providers. (Figure 3)

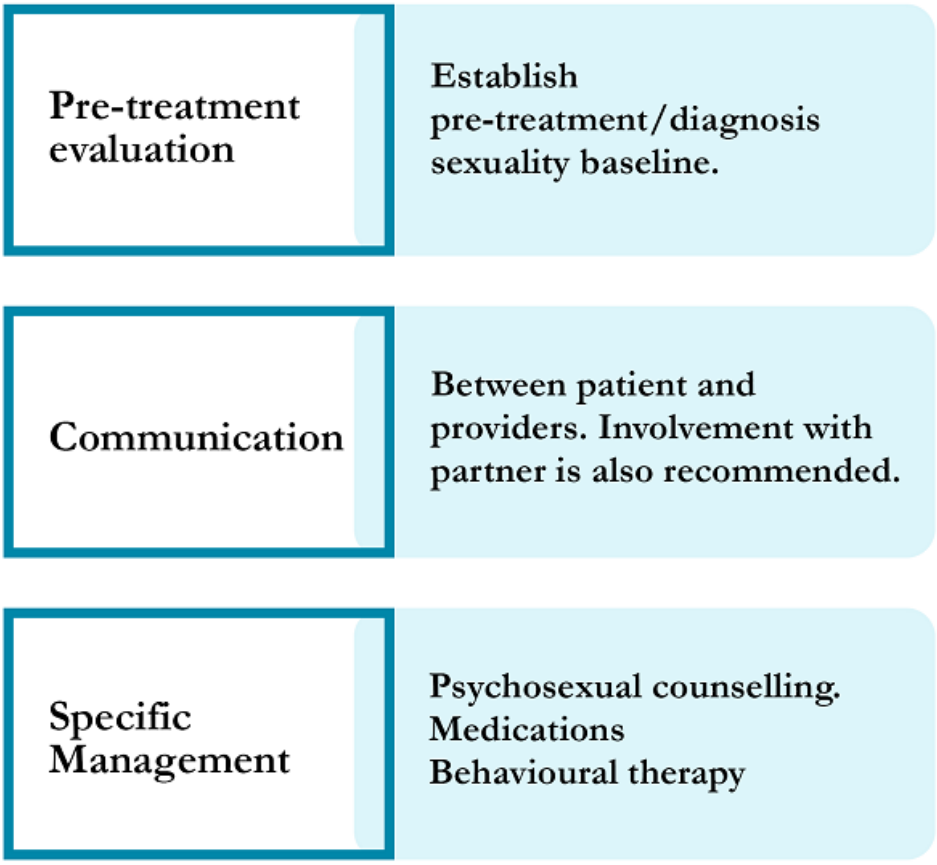
Psychosocial/psychosexual counseling should be offered to all cancer patients to improve sexual functioning. Current evidence does not support any type of counseling over the other. Counseling is especially helpful for cancer patients who are experiencing body image issues, patients looking to improve intimacy and sexuality issues, and also to improve overall sexual functioning and satisfaction.[4] Regular stimulation may also be helpful for patients experiencing sexual difficulties.

Specific medications can also be used to reduce symptoms and improve sexual function. These medications are tailored to men and women depending on their symptoms and after careful evaluation. For women, these include: lubricants, vaginal moisturizers used as the first option for vaginal dryness and used at higher frequency as needed, low dose vaginal estrogen are a second option for those who do not respond to lubricants, lidocaine used for introital pain and dyspareunia, and dehydroepiandrosterone for women with vaginal/vulval atrophy.

For men; phosphodiesterase type 5 inhibitors may be beneficial for erectile dysfunction. Men who do not respond to these may consider alternative interventions such as erectile devices, medicated urethral system, or intracavernosal injections.

Behavioral therapy such as cognitive behavioral therapy, hypnosis, and medications such as Serotonin Reuptake Inhibitors (SNRI) such as venlafaxine are other options that are considered for the treatment of sexual dysfunction.[4]

Figure 3: Summary of the management of sexual dysfunction



Conclusion

- Sexuality is an important aspect of the quality of life in cancer patients. It encompasses sexual health, intimacy, reproductive health, and gender identity.
- Cancer diagnosis and treatments affect sexual function and sexuality.
- It is normal for patients to feel uncomfortable to bring up sexual health concerns to their health care providers; however, patients should understand that these concerns are valid and are a significant aspect of their quality of life.
- Quality of life is a general sense of well-being and addresses multiple dimensions of life such as physical well-being, psychological well-being, social well-being, and spiritual well-being.
- Both patients and health care providers should be advocates for the patient's best care and quality of life. This can be done through open communication on every aspect of life that the patient may not be performing optimally.

- Communication between the patient, provider, and partner (if the patient so wishes) remains the cornerstone for optimal management of sex and reproductive health concerns.
- Evidence-based interventions exist that can help address and alleviate these concerns.
- Patients should feel free to address any sexual concerns with their health care providers at any time during cancer management. Partners are welcomed into these discussions if the patient so wishes.
- There are numerous resources and support available throughout cancer care to alleviate sexuality concerns. Clinicians offer appropriate sexual counseling and treatment as necessary to improve patient's quality of life.[25]

Questions to Ask About Sexuality

Sometimes patients may feel uncomfortable bringing up sexual concerns with the cancer care team and in that case, should bring them up to the primary care physicians. Below are some phrases that can be used to bring up discussions on sexuality:[23]

"I'm curious about sexual health issues in patients with lung cancer. Could you speak more to this?"

At the start of a new treatment, "How may my sexual health be affected by this new treatment?"

"In my research, I have found that sexual health issues are common in patients with lung cancer, I would like to talk more about this."

"I want to discuss how my cancer may affect my sexual intimacy as my sexual drive and libido have decreased. Can we discuss how this relates to my cancer?"

How will this treatment affect my hormones?

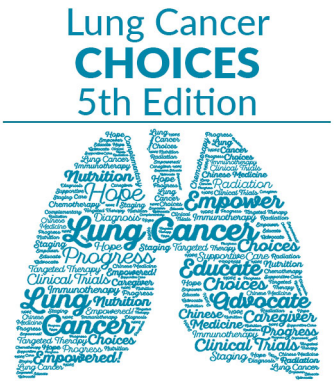
Will this treatment affect my fertility? What can I do about it?

What changes are likely to be temporary? How long are they likely to last? Are any changes likely to be permanent?

Should we take any precautions when having sex? "

What kind of contraception should we use and for how long?

Notes



Chapter 11

Integrative Medicine, Complementary Therapies, and Chinese Medicine in Lung Cancer

Misha Ruth Cohen, OMD, LAc

Introduction

The terms "integrative medicine" and "integrative oncology" are now widely accepted as the terminology to describe complementary therapies that are used as supportive treatment as part of multidisciplinary and interdisciplinary conventional cancer care.

The National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH) redefined integrative medicine as integrative health. Integrative health is described as medicine that "combines mainstream medical therapies and complementary and alternative medicine therapies for which there is some high-quality scientific evidence of safety and effectiveness."

In the 2013 guidelines published in Chest on complementary therapies and integrative medicine for lung cancer, integrative oncology "refers to the study and use of complementary modalities that are not traditionally part of modern Western medical practices but can be used as adjuncts to mainstream medicine to control the symptoms associated with cancer and cancer treatment."[1]

Integrative medicine and complementary therapies 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 integrative medicine and Western medicine for supporting people diagnosed with lung cancer.

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 therapies are being used, Chinese medicine can relieve adverse side effects and improve the treatment outcome.

Chinese medicine is a system of medicine that has been used for thousands of years in the treatment of health imbalances and disease.

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.[1-3]

In 2018, a review was published in the Journal of Alternative and Complementary Medicine that may provide a basis for discussion that can enhance patient-doctor dialogue regarding the use of Complementary and Alternative Integrative Medicine (CIM) during and after treatment for lung cancer.[4]

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.[5] 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 individualization makes double-blind controlled studies challenging to develop because each 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 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.

Western cancer therapies focus on killing 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 should be evaluated on its 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 complicated and take many years to complete. These studies are needed to understand the efficacy of Chinese medicine fully.

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 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.

"Mindfulness isn't difficult. We just need to remember to do it.

- Sharon Salzberg

Synergy between Western and Chinese Medicine

The simultaneous use of traditional Chinese medicine therapies may improve Western medicine. In China, and 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.

Chinese Herbal Medicine

There are many Chinese and Western herbs used by people with cancer. A qualified, certified practitioner of herbal medicine should prescribe herbs. 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, give diplomas based on professional qualifications (example - 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). Licensed practitioners 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 the effectiveness of platinum-based chemotherapy.[3] 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.[3]

Formulas based on *Ji Xue Teng (Spatholobus)* are used to help support people with cancer during and after chemotherapy and radiation treatments. Support includes improving levels of fatigue, improving blood counts and decreasing anemia and neutropenia, allowing for fewer 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.

New research in 2018 of 6,939 lung cancer patients in Taiwan investigated the frequencies and patterns of Chinese herbal medicine treatment for lung cancer patients and its effect on their survival probability. The conclusion was that the use of Chinese herbal medicine as adjunctive therapy might increase survival of lung cancer patients.[6]

Herbal formulas based on the Chinese herb *Ji Xue Teng (Spatholobus)* may decrease bone marrow suppression and may enable the 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.[7]

Timothy Ross, DAOM has documented possible supportive Chinese herbal medicine therapies for reducing radiation damage in his presentation: "Strategies to Increase Treatment Efficacy, Reduce Harm of Ionizing Radiation, Potentiate Chemotherapy, Protect Normal Cells, Potentiate the Immune System".[8]

Dr. Ross reported on an article published in 2021 "Review of the Efficacy and Mechanisms of Traditional Chinese Medicines as a Therapeutic Option for Ionizing Radiation Induced Damage in Frontiers in Pharmacology", Zhang et al 2021 has found evidence for reducing damage from radiation in mice and cell studies by common Chinese herbs ginseng, American ginseng, astragalus, dang gui, Siberian ginseng and ginger along with a host of other herbs used by traditional Chinese herbalists. He also reported on studies of common complex herbal prescriptions such as Si Wu Tang and Bu Zhong Yi Qi Tang.

Dr. Ross stated that the mechanisms of action of Chinese herbal medicines in preventing radiation injury include:

1. Reduce DNA damage
2. Promote DNA repair
3. Regulate cell cycle arrest
4. Prevent excessive accumulation of ROS and inhibits oxidative damage
5. Suppress extrinsic and intrinsic apoptotic pathways via reduction of P53, caspase, BAX/Bcl2 activation
6. Regulation of inflammatory response
7. Participate in the regulation of multiple abnormally activated signaling pathways.

Dr. Ross also presented a review published in 2014 by Mehta et al in Targeted Oncology "Curcumin and lung cancer—a review". Curcumin was shown to potentiate the antitumor effect of some anti-cancer medications. Curcumin reduces side effects such as gastrointestinal effects of chemotherapies,

exerts a cytotoxic effect on the NSCLC cell line, can be used as an adjunct along with standard chemotherapeutic agents, and can prevent carcinogenesis.[9]

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.

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 providers 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 the 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, although there is a recent move in that direction within the United States. The guidelines require attention to manufacturing processes, including cleanliness of buildings 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 appropriate herbs given in the correct doses but are caused by the inclusion of the wrong herb or supplement in a formula. Therefore, herb identification and authenticity is an important aspect of herb manufacturing.

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.[10] Acupuncture may stimulate serotonin levels within the brain, resulting in a sense of well-being and pain relief.[11] 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).[12]

Acupuncture and acupressure as adjunctive cancer treatment have been studied for postoperative nausea and vomiting, chemotherapy-related nausea and vomiting, and pain relief.[11] An observational study of acupuncture in lung cancer showed significant improvements in pain, appetite, nausea, nervousness, and well-being.[13] 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 a 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 a 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.[14] 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.[15]

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.

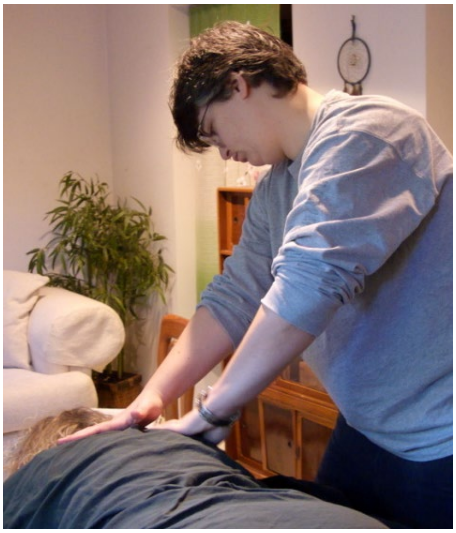
People with allergies to metal should not use acupuncture. Some people with cancer have increased autoimmune reactions.

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

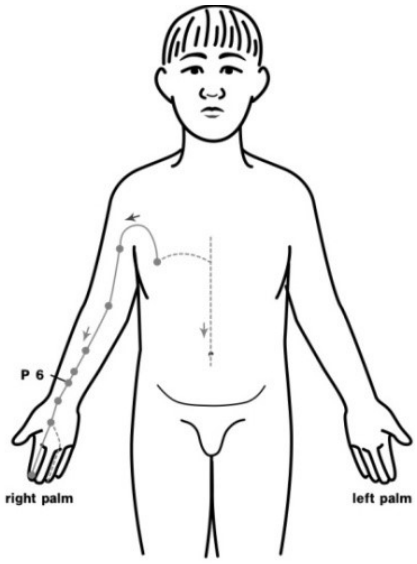
Acupressure and Massage

Many forms of massage and bodywork 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 a massage, symptom scores were decreased by 50%.[16]

Several studies in the use of the acupuncture point Pericardium 6 (P6) in women with breast cancer showed that nausea and vomiting from chemotherapy might 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.[14]



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. A Western healthcare practitioner should check lumps and areas of swelling 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. Consultation is especially important in immunocompromised individuals, including people having chemotherapy, patients with HIV infection, and others with low immunity.



The Pericardium Channel

The Society for Oncology Massage states:

"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."[17]

Food Therapy

In Chinese thought, the digestion must be kept healthy or a person can easily become ill.

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 damaging 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 harmful 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.

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.

While there are different approaches to food therapy currently used in the West, traditional methods that have been used in Chinese medicine are still used today. For example, we now know that the type and amount of carbohydrates in the diet is very important in maintaining good health. It is especially important to focus on the glycemic index of carbohydrates to improve insulin sensitivity. In our clinic, we combine traditional methods with modern understandings of using food to promote health, including reducing cancer risk. This is discussed more fully in *The New Chinese Medicine Handbook*.[18]

Taking this into account, traditionally, rice is the basic food used for healing in Chinese medicine, although other grains may be used, including quinoa, barley, rye, and buckwheat. Some people will need to avoid grains with gluten, such as barley and rye, due to gluten sensitivity. Congee is a special grain porridge that is considered traditionally to be a very therapeutic food and used 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. Cooking can be done overnight, and it is ideal to use a slow cooker such as a crockpot or any cooking pot. Herbs with or without meat or vegetables are added as directed by the Chinese medicine practitioner for the patient's specific condition. In our clinic, we highly recommend that the glycemic index and load of the grains be offset by using a substantial amount of protein and vegetables in order to have the best healing properties.

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.

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 or diarrhea associated with the medication.

Qi Gong is the traditional Chinese discipline that focuses on breathing and movement of Qi ("life force").

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") to increase physical harmony and strength and establish spiritual and emotional peace.[19] 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.[19] Furthermore, *Qi Gong* in cancer patients may improve quality of life and mood status and decrease inflammatory markers and side effects of cancer treatment.[5]

A systematic review published in 2018 in The Journal of Cancer Survivorship concluded that Tai Chi and Qigong show promise in addressing cancer-related symptoms and quality of life in a variety of cancer survivors.[20]

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 of 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.

Conclusion

In conclusion, people diagnosed with lung cancer and other cancers has a wide range of integrative and complementary modalities to choose from, including a wide breadth of Chinese traditional medicine practices. These can often be used as adjunctive therapies to support Western conventional treatments. Side effects frequently can be ameliorated using various forms of integrative and Chinese medicine. It is best to seek out qualified – licensed when necessary - practitioners and teachers who have knowledge of cancer support in your quest to use these practices. It important to discuss and confirm any therapies you might be considering with your Western conventional treatment team.

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 or more servings of steamed or cooked dark leafy greens daily, such as kale, collard greens, or broccoli (cruciferous veggies). 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.

Notes

Lung Cancer
CHOICES
5th Edition

Chapter 12

Lung Cancer in People who have Never Smoked

Jessica A. Hellyer, MD and Heather A. 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 third leading cause in women.[1-2] 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 and Asian populations globally, Hispanic populations and in women.[1] The causes of lung cancer in people who have never smoked are not well understood. Lung cancer treatment is similar for patients with early stage disease regardless of whether they smoked. However, for patients with advanced (stage IV) disease, many people who have never smoked who develop lung cancer will have mutations in their tumor which allow the tumor to respond to specific targeted treatments.

***Never smoker:** An adult who has never smoked, or who has smoked less than 100 cigarettes or cigars in his or her lifetime.*

Frequency

The information about how many people develop cancer each year comes from cancer registries. These databases compile information about the type of cancer and age of the person, but often lack information about smoking history. Therefore, it is difficult to know how many cases of lung cancer are attributable or caused by tobacco use. Separate registries on smoking patterns are often used to estimate how many people in a population use tobacco. This information can be loosely correlated

to the trends in lung cancer incidence from cancer registries to make estimates about how many people with lung cancer have develop 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.[3]

It is unknown whether the incidence of 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.[4] In the United States, more women who had never smoked died of lung cancer in the 1980s and 1990s than in the 1960s.[5] Moreover, although lung cancer incidence rates have been declining overall due to the success of tobacco cessation programs, recent data show that lung cancer rates have declined quicker among non-Hispanic men than women, reversing a long-observed trend that more men develop lung cancer than women. Correlation with data from tobacco registries suggests that the relative increase in lung cancer among women in the US is not due to increase in tobacco use.[6-7] However, these 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 and other reports have shown no increase in lung cancer in people who have never smoked.[8-9] There is a sense among doctors who treat lung cancer that the number of people with lung cancer who have never smoked is increasing and this area is being actively investigated. In Taiwan, for example, the majority of patients (53%) diagnosed with lung cancer do not have a smoking history and the type of cancer (adenocarcinoma) and tumor characteristics tend to be different in the lung cancer of people who have never smoked compared to those that have.[10] Studies are ongoing to better understand this important issue.

The Causes

The causes of lung cancer in people who have never smoked are unknown, but several factors may increase the risk.[11] (Table 1)

Environmental exposures

Many environmental toxins have been implicated in increasing the lung cancer risk. Second hand smoke may cause approximately 20% of the lung cancers in people who have never smoked.[12] Air pollution is thought to be responsible for 5% of cases of lung cancer but it may be higher.[13] Indoor air pollution, such as fumes from cooking oil and smoke from burning coal, may increase lung cancer risk, especially in Asia.[14]

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.[15-16] Jobs that expose people to toxic substances, such as uranium, asbestos, chromium, and arsenic, may increase the risk of developing lung cancer.[17-18] Arsenic may be present in drinking water in some areas such as Taiwan and Chile.[19-20] 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.[21-22]

Medical History

Chronic inflammatory diseases of the lung, such as pulmonary fibrosis or interstitial lung disease, can increase the risk of developing lung cancer.[23] Lung damage from prior radiation therapy (for example, people who received chest radiation for Hodgkin's Disease (a type of Lymphoma) or other cancers of the chest) also increases the risk of developing lung cancer.[24] In addition, lung cancer risk may be increased in people who have the human papilloma virus, but not everyone agrees with that risk.[25] At this time there is no proof that human papilloma virus causes lung cancer.

Genetics

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.[11, 26-27] 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.

"Surrender to what is. Let go of what was. Have faith in what will be.

- Sonia Ricotti

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

Secondhand 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 papillomavirus (controversial)
Other family members with lung cancer
Differences in ability to fix DNA damage

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 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, 28] 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 there are racial/ethnic and gender disparities in non-smoking lung cancer. Non-smoking lung cancer is more common in people of Asian ancestry and Hispanics as well as in women.[29-31] 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, and rising.[3, 6] The reason for these differences is not known although theories include a difference in biologic susceptibility to toxins or unequal reduction in workplace exposures.[7] Recently we learned more about the risks of lung cancer in Hispanic populations and some evidence of lung cancer susceptibility.[32]

In about half of the cases of lung cancer in people who have never-smoked, we are able to detect a genetic difference in the tumor which not only caused the cancer, but also serves as a target for therapy. 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. For example, tumors from patients who have never smoked are more likely to have mutations in a protein known as the epidermal growth factor receptor (EGFR).[33-34] Tumors with specific changes in the EGFR protein are more likely to shrink when treated with drugs that attack the EGFR protein, such as osimertinib, erlotinib, gefitinib, dacomitinib and afatinib. Another mutation that is more common in the tumors of people with no smoking history is in the Anaplastic Lymphoma Kinase (ALK) gene.[35-36] The drugs alectinib, brigatinib, crizotinib, lorlatinib and ceritinib are used to treat lung cancer patients who have the ALK gene rearrangement.

There are other, less common, DNA mutations that are found more frequently in the tumors of patients with non-smoking lung cancer. In addition to EGFR, ALK and ROS1 we now can look for changes in BRAF, RET, MET, HER2 and NTRK and can offer specific "targeted" therapy when identified in tumors of patients with metastatic disease. In general, patients will have only a single major change in the DNA (for example, a patient with a change in the EGFR gene usually does not also have an ALK gene rearrangement). It is important that testing is done to look for EGFR, ALK, ROS1, BRAF and NTRK at a minimum in lung cancer patients who have never-smoked, though there are many other gene changes in tumors of patients who have never smoked which have been identified such as RET, MET and HER2. As more "targeted" treatments are developed it becomes even more important that a tumor is tested for all the mutations that could allow for other treatment options. See Chapter 2: *Comprehensive Biomarker Testing*

Treatment of Lung Cancer in People who have Never Smoked

Early-Stage Lung Cancer (Stage I-III)

Treatment for people who have never smoked who have early stage non-small cell lung cancer is the same as treatment for smoking-associated lung cancer. For patients with tumors that can be removed with surgery, surgery is preferred therapy, followed by chemotherapy in some cases (depending on tumor characteristics). For people with stage III lung cancer that cannot be removed with surgery, treatment is a combination of chemotherapy plus radiation therapy, followed by a year of immunotherapy. The latest research now shows that EGFR targeted drugs may help prevent the return of cancer in people early stage lung cancer that has been removed with surgery if the cancer has the EGFR mutation. Recently published data on the use of osimertinib in patients with stage IB-IIIA lung cancer following completion of surgery showed an improvement in the length of time prior to the cancer recurring compared with patients who did not receive osimertinib.[37] Though we do not yet know if that approach will change cure rates, the delay in return of cancer is very significant and osimertinib is now a treatment option in this setting.

Advanced Stage Lung Cancer (Stage IV)

People who have never smoked and who have lung cancer are more likely to have changes in specific genes such as EGFR, ALK or ROS1. These gene changes are not seen in the normal cells from a person with lung cancer, only in the cancer cells. In recent years, other genetic changes have been discovered including alterations in BRAF, RET, MET, NTRK, HER2 and others. For most people diagnosed with stage IV non-small cell lung cancer, the first treatment is chemotherapy plus immune therapy or immune therapy alone. 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 have never smoked, to have their tumor tested for genetic changes. This is also called biomarker testing. See Chapter 2: *Comprehensive Biomarker Testing*

Treatment for people with early-stage non-small cell lung cancer who have never smoked is the same treatment for smoking-associated lung cancer.

EGFR

Patients with metastatic lung cancer who have specific EGFR gene changes should receive osimertinib as the initial treatment as this has been shown on average to control the tumor longer than chemotherapy and may even lead to living longer compared to starting with other treatments.[38] For patients who are unable to receive osimertinib, treatment with erlotinib, gefitinib, dacomitinib or afatinib is preferred over chemotherapy based on studies that have shown that they have a higher chance of shrinking the tumor than chemotherapy for these patients.[39-40] In the patients who start on one of the earlier EGFR treatments such as erlotinib, gefitinib, dacomitinib or afatinib, but who have tumor progression, testing for a resistance mutation called T790M is done to see if they would benefit from osimertinib prior to going on to chemotherapy.

The EGFR-targeted drugs are not generally added to chemotherapy, although this is an area of active investigation. A study looking at gefitinib alone versus gefitinib plus chemotherapy showed patients who received gefitinib plus chemotherapy had a longer time on treatment and improvement in overall survival compared with gefitinib alone.[41] However, gefitinib is rarely used as first line therapy in the US anymore so it is unclear how to apply this information. Studies looking at osimertinib plus chemotherapy are ongoing. Other studies have looked at whether to add chemotherapy to the targeted drug once it has stopped working. The IMPRESS trial showed that it is not beneficial in the majority of patients to continue the targeted drug when chemotherapy is started when the drug gefitinib was used in this trial.[42]

Adding other targeted agents to EGFR drugs has also been examined. For example, bevacizumab, a drug that reduces blood vessel formation in tumors, was investigated in combination with erlotinib. On average, patients who received both drugs together had their tumor controlled almost twice as

long as patients who received erlotinib alone. Despite this, there was no difference between in the two groups in how long patients lived with cancer.[43] Another blood vessel targeted therapy, ramucirumab, was also looked at in combination with erlotinib and showed that when given together patients had longer tumor control compared to erlotinib alone. Based off of this data, this is a reasonable initial treatment option, although we are still waiting to see whether this combination will result in an increase in survival.[44] Trials looking at osimertinib in combination with bevacizumab are underway although the preliminary data from a study looking at osimertinib in combination with bevacizumab in patients with a tumor containing a specific EGFR mutation (T790M) failed to show a benefit.[45] Most of the information above is for the most common mutations in EGFR (the del19 and L858R mutations). There are other less common EGFR mutations that are treated similarly. However other mutations in EGFR, especially those known as "exon20" mutations make tumors less likely to respond and newer treatments are being developed.

ALK

There are many targeted drug options for patients who have the ALK gene rearrangement (most common in lung cancer patients who have never smoked). Crizotinib was the only clinically available ALK+ targeted agent for several years but is no longer the preferred front line therapy. There are three recommended options for first line treatment of ALK+ lung cancer. First, is alectinib based off data from the ALEX trial showing improved disease control (almost three times longer) on alectinib compared to crizotinib and found that alectinib had fewer side effects.[46] In addition, alectinib does a better job of controlling and preventing cancer metastases to the brain compared with crizotinib. Other options for front line treatment include brigatinib based off of data that showed that brigatinib did a better job controlling tumors (both in and out of the brain) than crizotinib.[47] Lorlatinib was the most recent agent to be approved as a front line option after results from the CROWN trial showed a doubling of the number of patients alive and without disease progression in the group that was treated with lorlatinib compared with crizotinib.[48] Finally, Certinib, an older ALK targeted agent is also an option for front line treatment. Ceritinib has not been compared to crizotinib, but was studied against chemotherapy in the ASCEND-4 study that showed that ceritinib did a better job of controlling disease compared with chemotherapy.[49]

After progression, treatment with another ALK targeted agent is preferred prior to chemotherapy. Options in the second line setting depend in part on which drug was given first and is tailored to each patient. Alectinib is the most common drug used in this setting but the other ALK drugs may also be appropriate depending on each patient's treatment history.

ROS1

ROS1 rearrangements are also more common in patients who have never smoked. In early studies of crizotinib in patients with previously treated ROS1 positive lung cancer, the majority of patients had their tumor respond to crizotinib and this response lasted on average about a year and a half. For this reason, crizotinib is approved as a first treatment of ROS1 lung cancer.[50] More recently, entrectinib was also approved for up front treatment of ROS1 positive lung cancer. This was based off of information from three small studies that showed that about three quarters of patients treated with

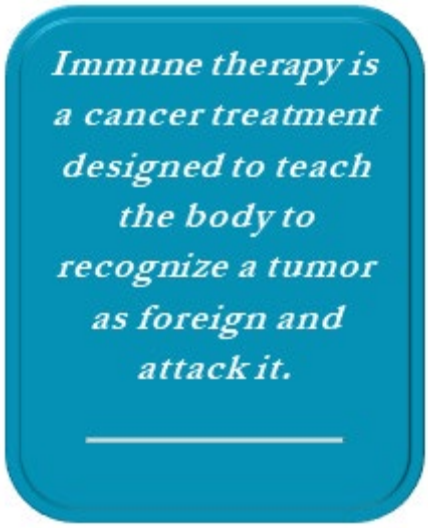
entrectinib had a response in their tumor. Importantly, entrectinib also seems to work well in patients whose lung cancer has grown in the brain.[51] Ceritinib also has some activity in ROS1 mutant tumors and is another option for first line treatment.[52] There are multiple options when the first line treatment stops working and this includes other ROS1 "targeted" drugs, chemotherapy or clinical trial.

Other genetic changes

In addition to EGFR, ALK and ROS1 we now can look for changes in BRAF, RET, MET, NTRK and HER2 and can offer specific "targeted" therapy when identified in tumors of patients with metastatic disease. BRAF inhibitors approved for use in lung cancer are the combination of dabrafenib/trametinib. HER2 active drugs include TDM-1, afatinib and trastuzumab. Multiple drugs are active for RET including selpercatinib, pralsetinib, cabozantinib and vandetinib. Cabozantinib is also active for METexon 14 splice site variations, as are tepotinib, capmatinib and crizotinib. Larotrectinib and entrectinib were both recently approved for treatment of tumors with NTRK fusions.

Chemotherapy and Immune therapy

One theory as to how cancer is able to develop and grow is that it acquires mechanisms to evade the body's immune system. Immune therapy is a cancer treatment designed to teach the body to recognize tumor as foreign and attack it. Those drugs have been shown to work in lung cancer regardless of smoking history, but perhaps less so in patients with no smoking history. Patients with mutations in EGFR or ALK were excluded from many of the early immune therapy trials, so it is unknown how well this group benefits from immune therapy and there is some evidence to suggest their tumors do not respond as well. Efforts to get immune therapy to work in patients with limited smoking history are ongoing with multiple combination drug studies. For patients without targetable mutations, preferred first line treatment is a combination of chemotherapy plus immunotherapy. This has been shown to work in some patients regardless of smoking status.[53]

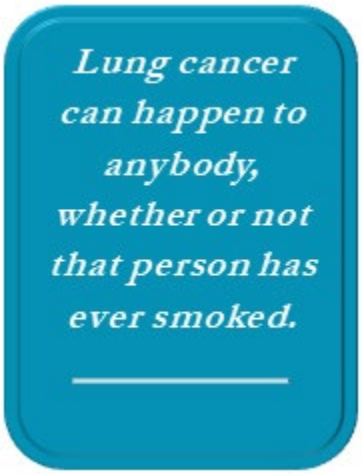


For patients with mutations in EGFR or ALK who have had growth of their cancer on targeted therapy, a 4-drug combination of chemotherapy plus bevacizumab (target against blood vessels) plus immunotherapy was found to have a small benefit in tumor control and the suggestion of possible improvement in survival.[54] However, the number of patients in the study with EGFR or ALK mutations who received this combination was small (111 patients) so additional data is needed to understand how to best use these treatments in patients who develop molecularly targeted mutations. Chemotherapy alone is another good option for patients with non-smoking lung cancer that has grown on targeted therapy (in the case of having a targetable mutation) or on a chemo-

immunotherapy combination. The combination of targeted therapy plus immunotherapy has been examined in a number of trials but unfortunately this combination has not been very effective and notably has a high rate of toxicity.[55] The most important point is that the best treatment cannot be chosen until all the information about a tumor is known. The results for immune therapy (PD-L1) often come back sooner than the results about EGFR, ALK and the other potential tumor mutations. But when lung cancer develops in someone with a limited history of smoking the chance of a tumor having a mutation that can be treated is very high. So it is critical to wait to get the tumor mutation results back before starting treatment, unless there is a medical reason that treatment must start sooner. Starting immune therapy (even with chemotherapy) can increase the risk of toxicity from some of the targeted treatments (like osimertinib), which can be a problem if that treatment is started before knowing about the tumor mutations.

Conclusion

Lung cancer can happen to anybody, whether or not that person has ever smoked. Although 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 (lung cancer in people who have never smoked happens more often in women and in people from different ethnic groups including Asian or Hispanic. It is also seen more often if someone develop cancer very young. When lung cancer develops in someone who has never smoked it is more likely to be the adenocarcinoma type.



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 have never smoked are more likely to have tumors with 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 osimertinib or erlotinib, and patients with the ALK gene rearrangement usually respond well to alectinib, brigatinib 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.[28, 56]

Notes

Lung Cancer
CHOICES
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Chapter 13

How to Quit Smoking Confidently and Successfully

Joelle Thirsk Fathi, DNP, RN, ARNP, CTTS, NCTTP

Introduction

Smoking cessation (quitting smoking) is one of the best things to 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, but only 7.5% are successful likely because they attempt to quit without help.[1] There are many reasons people want to quit smoking, and better health is often at the top.[2] Unfortunately, many people who actively smoke have had many unsuccessful quit attempts; this can be discouraging and prevent people from trying to quit again.

If you smoke, the most important thing that you can do is to stop smoking. Smoking before surgery puts people at risk of severe complications.

The chances of quitting smoking are 2-3 times greater with cessation treatment and therapeutic support.[3] Knowing how to approach quitting smoking, find the necessary support, and be successful in quitting for good can be challenging. The content in this chapter provides the critical information needed to understand how nicotine dependence occurs, what happens when quitting 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.[4] 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.[5] These gases and chemicals circulate throughout the body and cause damage to the body's cells. Additionally, cigarettes contain nicotine (the potent substance from the tobacco plant). Nicotine is the notable ingredient in all tobacco products, including cigarettes, that causes physical, mental, and behavioral dependence and makes it hard to quit smoking.[6]

How Nicotine Affects the Brain

When a cigarette is smoked, the combustible gases and chemicals are inhaled into the lungs and quickly travel from the lungs into the arterial blood and to the left side of the heart. The left side of the heart, with each beat, moves this oxygenated arterial blood, including the contents of the cigarette, out to the body's tissues, organs, and straight to the brain. The transfer of nicotine, from the time a puff from a cigarette is inhaled to the time it is delivered to the brain, occurs quickly, within three to ten seconds.

How Nicotine Withdrawal Happens

Nicotine is clever in how it works in the brain; it easily attaches to receptors in the brain specifically responsive to nicotine, called the nicotinic acetylcholine receptors. Everyone has these receptors in the brain, but for smokers, these receptors are specifically stimulated by nicotine and respond in a way that the non-smoker does not experience. When the nicotine attaches to the receptor, the receptors are stimulated to release neurotransmitters (chemicals that your body makes) from that receptor. Dopamine is the most dominant neurotransmitter released when nicotine attaches to these nicotinic acetylcholine receptors, but other neurotransmitters are also released at this time. These neurotransmitters stimulate the reward center in the brain, creating a pleasurable experience that many people describe as a "brain buzz". Dopamine and other neurotransmitters also enhance energy and concentration, elevate mood, and suppress appetite. The instant gratification and other physiologic responses to nicotine are all reasons why people continue to smoke, and dependence on cigarettes occurs and persists.[6]

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 is quickly metabolized, begins losing its stimulating effects soon after it is inhaled, and is gone within two hours. Once nicotine metabolizes and disappears in the body, tissues, and brain, the receptors are empty and stop expressing dopamine, and the dopamine levels drop. It is at this point that the receptors start begging for more nicotine, and withdrawal symptoms are experienced, which result in an increased 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.

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 nicotine use, including missing just one cigarette, cutting back on the typical intake of nicotine, or stopping the use of nicotine altogether. These symptoms, intensity, and frequency vary from person to person and directly correlate with the amount of nicotine that is routinely consumed and the concentration of nicotine levels in the body.[5]

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.[5] These symptoms are unpleasant and, for many intolerable. If not prevented or treated, these symptoms lead to a powerful urge to smoke again. Replenishing nicotine by having just one cigarette will ease or eliminate these symptoms. This is why people often revert to smoking because it makes withdrawal symptoms go away almost instantly.

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

What it Takes to Quit Successfully

There are many ways to quit smoking and stay quit. People can quit on their own, but it can be a challenge to do this alone. There is a much higher chance of success when smokers can secure support and counsel from a health care professional or a specialist trained in quitting smoking. Using nicotine replacement therapy with or without 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.[6-8]

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.[9]

Nicotine Replacement Therapy

Nicotine replacement therapy has been utilized for many years, is readily available, and can be a very effective approach to quitting smoking. Similar to the use of nicotine products, like cigarettes, the body absorbs the nicotine in the bloodstream and finds its way to the brain but the difference with nicotine replacement therapy is that toxic chemicals are not inhaled into the lungs. When nicotine from the replacement therapy reaches the brain, it attaches to the nicotinic acetylcholine receptors, which stimulates the release of dopamine and other neurotransmitters. Nicotine replacement therapy mimics nicotine delivery by a cigarette but delivers nicotine to the brain by another mode, thus preventing and treating withdrawal symptoms.[6]

Getting enough nicotine with a combination of the long-acting patch and a short-acting method will prevent withdrawal symptoms, make quitting smoking much easier, and provide a smoother transition off cigarettes.

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 to prevent withdrawal symptoms. Often people feel that the patch, gum, or lozenge did not work for them. This can occur 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 prevent withdrawal symptoms, make quitting smoking much easier, and provide a smoother transition off cigarettes.

Transdermal Nicotine Patch, A Long-acting Nicotine Replacement

Nicotine replacement is available in a patch that delivers nicotine continuously over 24 hours.[8] The patch is a long-acting delivery method that delivers a steady amount of nicotine to pass, from the patch, through the skin, directly to the blood with immediate transport to the brain. It is important to dose the patch according to how many cigarettes are smoked in a day so that enough nicotine is available to prevent withdrawal symptoms. One cigarette contains about 1 mg of nicotine. The patch should be dosed 1 mg for every cigarette smoked in a typical day. Choosing the right dosed patch will give an optimal nicotine delivery to the brain and minimize or prevent withdrawal symptoms.[7, 9-10]

Patch Dosing Recommendation[9]

less than10 cigarettes/day (less than a ½ pack per day)	14 mg patch
10 or more cigarettes/day (½ pack per day or more)	21 mg patch
more than 20 cigarettes/day	Dose patch to the number of cigarettes smoked per day with the guidance of your health care provider

The patch needs to 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 1 pack per day (20 cigarettes) is routinely smoked, start the patch regimen at 21 mg on the quit date. Use this dose every day for 4 weeks, then step down to a 14 mg patch for 2-4 weeks, then step down to a 7 mg patch for 2-4 weeks, and then stop the patch.[9-10]

In this example, the nicotine replacement patch would be used for a total of 8-12 weeks (2-3 months) following the quit date; this ensures a safe and effective transition off nicotine. This is longer than many people think they need to use patches. Remember, the key is to be successful in the long run so, wean off as slowly as needed; there is no rush!

The patch delivers relatively steady levels of nicotine, but breakthrough urges to smoke can occur. This is where short-acting nicotine replacement therapy can be beneficial in further shutting down the cravings to smoke.

Tips on Using the Patch

1. The patch is a long-acting medication formulation. For safe, effective, and continual delivery of the medication (nicotine) the patch should NOT be cut.
2. Similar to cigarettes, the nicotine in the patch is stimulating and can cause active or vivid dreaming and/or wakefulness at bedtime. Unless you are accustomed to waking up to smoke throughout the night, you may want to consider taking the patch off an hour before bedtime to ease these symptoms and avoid disruption of sleep. Start a new patch as soon as you wake up in the morning.
3. Remember that it takes at least an hour for the nicotine in the new patch to deliver a steady concentration of nicotine in the blood stream, so it is important to use a short-acting nicotine replacement, in combination with the long-acting patch, for urges to smoke.

Short-acting Nicotine Replacement

Nicotine replacement is available in several forms of short-acting delivery methods. These short-acting doses of nicotine are essential in the success of using nicotine replacement therapy in quitting smoking. Even if the transdermal patch is used continuously for nicotine replacement, break-through urges to smoke could occur and lead to withdrawal symptoms. Think of short-acting nicotine replacement as a quick-acting, rescue medication. Treating these cravings with one of the following four options of nicotine replacement in combination with the long-acting patch is one of the most effective ways to avoid lapsing or relapsing with a cigarette and returning to regular smoking patterns.

Nicotine Gum

Nicotine gum is available in 2 and 4 mg doses. It is important to know that the gum only works if it is absorbed through the mucosal lining of the mouth (between the gum and cheek). 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 (about a minute) and park it. Continue this pattern for about five cycles (approximately 30 minutes total) to get the full dose of nicotine the gum has to offer. Chewing for a minute is necessary to activate and release more nicotine in the gum, then park it for optimal absorption. It is safe to chew up to 20 pieces of gum a day for breakthrough cravings and withdrawal

symptoms.[7, 9-10] This product is available over the counter for purchase. Many insurance companies are now covering this when prescribed by a health care provider.

Getting the Most out of the Nicotine Gum

Nicotine gum is ineffective when wearing dentures but can be chewed and effective if the dentures are out of the mouth. Chewing the nicotine gum like a regular stick of gum may cause ingestion/swallowing of the nicotine and cause nausea, indigestion, or even hiccups. Swallowing nicotine also disrupts the proper absorption of the nicotine because of the acid in the stomach. Avoid carbonated drinks and acidic foods and beverages before and during use of the gum because these too will destroy the action of the nicotine in the gum.[10]

Nicotine Lozenge

The nicotine lozenge is similar to the gum. It is available in 2 and 4 mg doses and, like the gum, needs to be parked between the gum and cheek to be optimally absorbed. The standard starting dose is the 2 mg lozenge, which delivers the equivalent of nicotine in one cigarette. Like the gum, avoid eating and drinking acidic foods and beverages right before and while a lozenge is in the mouth. This product is also available over the counter and by prescription.[7, 9-10] These lozenges vary in size and dissolvability by the manufacturer. Although some are cheaper over the counter, these products are often reported by people to be too big and bulky and take too long to dissolve in the mouth. There is a "mini" lozenge on the market that is the size of a Tic-Tac, is easily tucked between the gum and cheek, and dissolves readily while delivering nicotine quicker to the brain.

Nicotine Nasal Spray

The nicotine nasal spray contains nicotine that has the quickest onset of action in treating nicotine cravings and is delivered through the mucosal wall of the nose. When instilling this nicotine, it is important to spray it against the nasal wall while plugging one nostril (side of the nose) and (while looking at the floor) inhale while spraying. Avoid tipping the head back and sniffing it into the upper region of the nasal passages or sinuses. One spray in each nostril delivers a similar dose of one cigarette (two sprays total). This product is available by prescription only.[7, 9-10]

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, but many people and health care

providers do not know about it. 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 puff it into the mouth (as if you are sucking on a straw) for optimal absorption. This product is available by prescription only.[7, 9-10] which is different from an E-cigarette, which is discussed later in this chapter. **A dispensing pharmacist can teach how to load and use the inhaler.** The inhaler is not effective if dentures are in place.

Long-acting transdermal nicotine patch + Short-acting nicotine (gum, lozenge, inhaler, or nasal spray) = Quitting Successfully!

How to Know if you are Getting too Much Nicotine Replacement

It is possible to use/take in more nicotine in the nicotine replacement than you are accustomed to when regularly smoking or using other tobacco products. Symptoms associated with getting too much nicotine are feeling anxious, jittery, headache, nausea, excessive wakefulness, and chest pain or heart palpitations. If you develop these symptoms or any others that you think are associated with nicotine delivery, stop using all nicotine products, including taking the patch off, and call your health care provider for further advice as soon as possible. Remember to avoid smoking cigarettes or using other manufactured tobacco products (chewing tobacco, snus, snuff, electronic cigarette, etc.) while using any nicotine replacement therapy to reduce the chances of overdosing on nicotine. This will provide the best opportunity for you to quit.

Non-Nicotine/Prescription Medication Therapy Options

Bupropion Sustained Release

Bupropion Sustained Release (SR) is a long-acting prescription medication commonly used to help people quit smoking. It has been shown to increase the chance of quitting smoking by 52% to 77% and is as effective as nicotine replacement therapy.[11] Bupropion SR may also be combined 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". This is true; bupropion is used for depression because it allows more neurotransmitters, like dopamine and norepinephrine to circulate in the brain.

Remember that nicotine drives the dopamine levels up, which is why the brain experiences a mood elevation when smoking. When the dopamine levels drop with nicotine withdrawal, the brain can experience agitation, anxiety, and depressive mood changes. Bupropion helps transition off

cigarettes/nicotine because it allows more dopamine to circulate and prevents the brain from experiencing an abrupt withdrawal of 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.[5-7, 10] Talk to your health care provider to determine if bupropion is the right medication for you.

Varenicline

Varenicline (also known as "Chantix") is a prescription medication commonly used to help people quit smoking. Varenicline has shown an increased success rate in quitting smoking of up to fourfold[10] and is more effective than bupropion[11] and nicotine replacement therapy.[12]

This medication works by attaching to the same receptors in the brain and causes the same release of dopamine that nicotine does. Varenicline mimics the presence and action of nicotine and tricks the brain into thinking it has nicotine onboard.[5-7, 10] Because of the way this medication mimics the presence of nicotine and attaches to the nicotinic acetylcholine receptors in the brain, it is not designed to be used in combination with nicotine replacement therapy unless directed otherwise by a health care provider.This medication greatly reduces the craving for nicotine and reduces withdrawal symptoms. Talk to your health care provider to determine if varenicline is the right medication for you.

Tips on Taking Bupropion SR and Varenicline

Always take these medications with food to avoid nausea. If you take these medications twice a day, be sure to take the second dose closer to dinnertime to prevent the disruption of sleep and vivid dreams. Like nicotine from cigarettes, varenicline stimulates the central nervous system, and because of this action, it is more activating than sedating, taking it with dinner is ideal. Sometimes a dose adjustment is necessary, to tolerate the medication and optimize your opportunity to quit smoking.

Bupropion (aka Wellbutrin or Zyban) and varenicline are more activating than sedating. If you experience agitation or even anxiety that does not go away, it might mean you need to reduce the dose of the medication or even stop it.

Cutting back on the dose may reduce these symptoms and allow you to benefit from its action in helping you quit.

If you experience any symptoms that persist or include disturbing thoughts or changes in your mood, you should stop the medication immediately and call your health care provider.

Vaping/Electronic Nicotine Delivery Systems (e-Cigarettes)

Many people are asking about the use of electronic cigarettes, also known as e-cigarettes or "vapes", as a replacement for conventional cigarettes or as aids in quitting smoking. Vaping and electronic cigarettes are battery-operated devices that deliver nicotine and other chemicals to the body through an inhaled vapor or aerosol rather than a combustible gas, as cigarettes do. Some people feel that vapes and electronic cigarettes may be safer for their health because they do not "light up" or create combustible gases while using them. Recent research demonstrates a higher quit rate for people who use electronic cigarettes **with nicotine** than people who use electronic cigarettes **without nicotine**.[13] However, there is no clinical research to suggest that vaping and electronic cigarettes are effective in quitting smoking long-term; in fact, they may have higher addictive potential compared to conventional cigarettes in younger people[14] and contribute to relapse and sustained dependence on nicotine products, including the electronic cigarettes and combustible cigarettes, making it difficult to quit smoking.[15-17] Furthermore, national health authorities and agencies advise against the use of such products, especially those purchased on the street (bootlegger). This is due to increasing national clinical reports of serious respiratory illness known as "e-cigarette or vaping product use-associated lung injury" or EVALI and even death directly related to these products.[18] The long-term effectiveness and safety of electronic cigarettes or vapes are not known, and using them is not recommended at this time.

Individual and Behavioral 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 good scientific evidence that individual and behavioral counseling sessions, as a stand-alone therapy or when combined with nicotine replacement therapy or non-nicotine medication therapy, significantly improve the sustained success rates of quitting smoking.[7, 19-20] The more counseling support provided can further increase rates of smoking cessation by 10 to 20%.[21]

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 an excellent 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.

Complementary and Alternative Medicine Approaches to Quitting

There are many complementary and alternative therapies available that may be helpful to quit smoking. Some of the more common and popular methods are acupuncture or acupressure, hypnosis, massage, and herbal preparations or medicines. These approaches have not been widely studied, and current research does not show these methods are effective in long-term success in quitting smoking. However, some have contributed to long-term quit success when combined with other evidence-based therapies, as discussed in this chapter.[22-23]

Technology Based and Remote Cessation Support

Web-based/Online support

There are web-based smoking cessation resources on the internet. These online resources provide support and counseling options. There is not much existing evidence that these resources are highly effective when used as the only approach to quitting smoking.[24] However, using them in combination with nicotine replacement and non-nicotine therapy likely adds benefit in quitting smoking.[25]

American Lung Association/Freedom from Smoking

www.freedomfromsmoking.org

U.S. Department of Health and Human Services

www.smokefree.gov

Become An EX

www.becomeanex.org

Quitlines

There are telephone quitlines 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, for free. With a prescription, some can offer medications like bupropion (Zyban or Wellbutrin) and varenicline (Chantix) at a reduced cost.

The quitline 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 visiting their

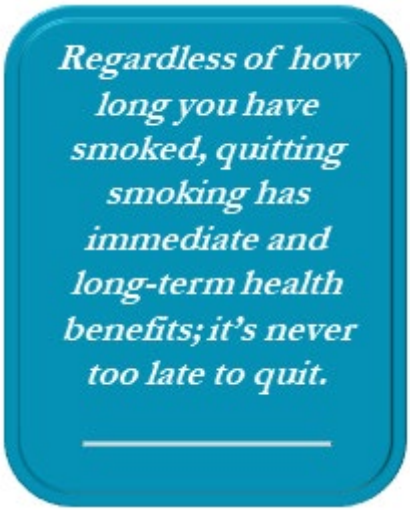
website www.naquitline.org. You can also find out about local resources through your local public health department or search online using your specific state or city and "quit smoking" as keywords.

Many employers, especially large employers, have contracts with a professional quitline service that employees, and even family members of employees, can benefit from. The services and resources they provide are similar to the public quitlines. Call your Human Resources department at your job to see if they provide this benefit and cover smoking cessation medications, including over-the-counter nicotine replacement therapy.

How to Deal with Lapse and Relapse

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.[5] This can also occur if treatment is disrupted or stopped too soon.

Lapses and relapses are sometimes part of the road to success in quitting long-term.[7] 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 resume the quit attempt successfully. This can be done by returning to the approaches and methods that helped quit in the first place and reach out to your health care provider and other support systems. 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 Smoke

When quitting smoking, it is important to address your lifestyle, rituals, and behaviors associated with and trigger 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 daily routines and intentionally develop new rituals in your life that do not include cigarettes. It can be helpful to tell people close to you or those you frequently encounter that you are quitting smoking; this will help them support you in your efforts.

Conclusion

Quitting smoking is one of the best actions you can take to protect your health. Quitting also helps your body prepare for and optimally respond to medical treatment and enhances your ability to avoid complications and heal following surgery.[26] Regardless of how long you have smoked, quitting

smoking has immediate and long-term health benefits; it's never too late to quit.[5] It can be challenging to quit, but with the right tools and knowledge about the best and most effective approaches to quitting smoking, quitting is a more realistic and obtainable goal.

Notes

Notes

Lung Cancer
CHOICES
5th Edition

Resource Directory

Organizations

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
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
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
www.cancercare.org/get_help/assistance/cc_financial.php

GoodDays
GoodDays 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) 608-7141
www.mygooddays.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
www.healthwellfoundation.org

Patient Access Network Foundation (PAN Foundation)
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)
www.panfoundation.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
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 (nephrology)

1-888-427-7478 (oncology)
1-888-762-6436 (The Safety Net Foundation)
http://www.amgen.com/responsibility/access-to-medicine/

AstraZeneca
AZ&ME Prescription Savings Program. Helping patients access their AstraZeneca medicines
1-800-AZandME
https://www.azandmeapp.com/

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.
www.rxassist.org/pap-info/company-detail?CmpId=7

Boehringer Ingelheim Patient Assistance Program
The BI Cares Patient Assistance Program is a charitable program provided by the Boehringer Ingelheim Cares Foundation (BI Cares), an independent nonprofit organization, to improve patients' health and lives. The program provides Boehringer Ingelheim medicines free of charge to uninsured and underinsured US patients who meet our eligibility requirements.
https://www.boehringer-ingelheim.us/our-responsibility/patient-assistance-program

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
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:
LillyPatientOne: www.lillypatientone.com/patient/index.html
Alimta: www.alimta.com/financial-assistance.html

Celgene
Celgene Patient Support® can help you and your loved ones understand the programs and services available to you.
https://celgenepatientsupport.com/

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
www.genentech-access.com/patient.html

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
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: 1-888-669-6682
www.pharma.us.novartis.com/our-products/patient-assistance/patient-assistance-foundation-enrollment

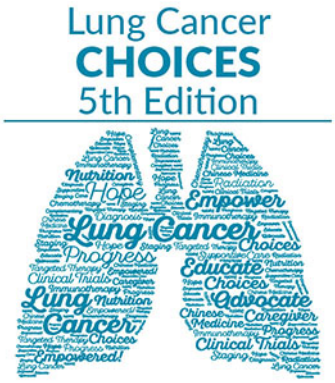
Pfizer
Pfizer RxPathways connects eligible patients to a range of assistance programs that offer insurance support, co-pay help, and medicines for free or at a savings.
Pfizerrxpathways.com

Health and Pharmaceutical Resources
https://www.rxresource.org/index.html

Government Resources

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
www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm107434.htm

National Cancer Institute (NCI)
The National Cancer Institute (NCI) is part of the National Institutes of Health (NIH), which is one of 11 agencies that comprise the Department of Health and Human Services (HHS). NCI, established under the National Cancer Institute Act of 1937, is the Federal Government's principal agency for cancer research and training. The National Cancer Act of 1971 broadened the scope and responsibilities of NCI and created the National Cancer Program.
https://www.cancer.gov/types/lung



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.

Arrythmias (uh-rith-mee-uh): Any disturbance in the rhythm of the heartbeat.

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.

arthralgia (ahr-thral-juh): Pain in a joint.

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.

biomarkers (bahy-oh-mahr-ker) (molecule marker, signature molecule): A biological molecule (the basis for all human cells), found in blood or other bodily fluids or tissue, which is a sign of normal or abnormal process or of a condition or disease.

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.

cardiomyopathy (kahr-dee-oh-mahy-op-uh-thee): Any disease of the heart muscle, leading to decreased fundtion: usually of unknown cause.

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 (rey-dee-oh-graf, -grahf): 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.

conjunctivitis (kuh-n-juhngk-tuh-vahy-tis): Inflammation of the conjunctiva; the mucous membrane that lines the exposed portion of the eyeball and inner surface of the eyelids.

D

diarrhea (dahy-uh-ree-uh) Loose, water stools.

Dosimetrists (do·sim·e·trist): 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)

dyspareunia (dis-pə-ˈrü-nē-ə, -nyə): difficult or painful sexual intercourse

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.

epistaxis (ep-uh-stak-sis): Nosebleed.

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.

genetic mutation: a change in the structure of a gene

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

Hazard Ratio: A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.

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.

hyperglycemia (hy·per·gly·cae·mi·a): An abnormally high level of glucose in the blood.

hypophysitis [hī-pŏfĭ-sī'tĭs]: Inflammation of the pituitary gland.

hyperthyroid [hahy-per-thahy-roid]: Of, relating to, or having hyperthyroidism.

hypothyroidism [hahy-puh-thahy-roi-diz-uh m): Deficient activity of the thyroid gland.

I

immune system (ih-MYOON SIS-tim): The complex group of organs and cells that defends the body against infections and other diseases.

infusion (in-fyoo-zhuh n): 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.

Introital (in-ˈtrō-ət-ᵊl)**:** of or relating to an introitus; the *introital* opening of the vagina

K

keratitis (ker-uh-tahy-tis): inflammation of the cornea.

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.

Kyphosis (kī-ˈfō-səs): Exaggerated outward curvature of the thoracic region of the spine resulting in a rounded upper 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.

molecular testing: Also called assays or profiles, can help your treatment team identify specific biomarkers in a tumor.

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.

mucositis: Inflammation of the mucous membranes lining the digestive tract from the mouth to the anus.

myocarditis: Inflammation of the heart muscle.

N

neoadjuvant therapy (NEE-oh-ADD-joo-vent THAIR-uh-pee): treatment given before the main treatment to help cure a disease.

nephritis (nuh-frahy-tis): inflammation of the kidneys.

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.

occult (uh-kuhlt, ok-uhlt): Of a disease or process, not accompanied by readily discernible signs or symptoms.

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.

occultpericarditis: 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.

phlebitis (fle-BYE-tis): Inflammation of a vein.

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.

proteinuria (proh-tee-n*oo* r-ee-*uh*, -ny*oo* r-, -tee-*uh*): The presence of abnormally large amounts of protein in the urine, usually resulting from kidney disease but sometimes from fever, excessive exercise, or other abnormal condition.

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 (steyj): 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.

Stomatitis (stow·muh·tai·tuhs)**:** Inflammation of the mouth and lips.

Systemic therapy (sis-TEH-mik THAYR-uh-pee):Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body.

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.

U

Uveitis (yoo·vee·ai·tuhs): inflammation of the uvea.

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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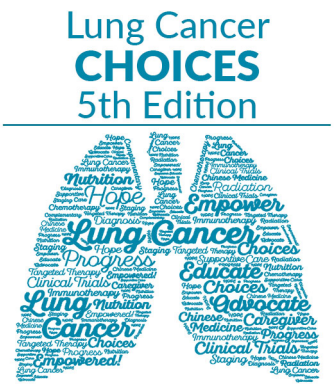

About the Editors

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*, 4th 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 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. 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 2017, Ms. Sandt received recognition by the Economist Intelligence Unit as a "2017 HCV Change Maker" for Caring Ambassadors significant contribution to the elimination of hepatitis C.

Cindy Langhorne joined the Caring Ambassadors Program, Inc. in August of 2007 as the Lung Cancer Program Director. Ms. Langhorne brings over twenty-one 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 (25+) 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.

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Chapter 2: Comprehensive Biomarker Testing

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Chapter 7: Clinical Trials and Emerging Therapies for Lung Cancer

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Chapter 8: Supportive Care

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Chapter 13: How to Quit Smoking Confidently and Successfully

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