Lung Cancer and Mesothelioma

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Summary and Key Points

1. Tobacco is the leading cause of lung cancer. Radon exposure in the air over time is a second, but distant leading cause. Asbestos exposure, especially when combined with tobacco use, is a cause of mesothelioma.
2. The two major pathology categories of lung cancer are non-small cell lung cancer and small cell lung cancer. Common types of non-small cell lung cancers are adenocarcinoma, squamous cell and large cell carcinoma. Mesothelioma is a cancer of the pleura.
3. Treatment of lung cancer and mesothelioma requires a multidisciplinary approach to care involving Medical Oncologists, Radiation Oncologists, Thoracic Surgeons, Pulmonologists, Palliative Care Physicians, Pathologists, Radiologists, and Primary Care Physicians.
4. The foundation for the curative treatment of early stage non-small cell lung cancer and mesothelioma is surgery.
5. The foundation for the curative treatment of early stage small cell carcinoma of the lung is combination chemoradiotherapy, although a few patients with very early small cell lung cancer may benefit from resection of the primary.
6. The goal of treatment for early stage non-small cell lung cancer and some presentations of limited stage small cell lung cancer is cure.
7. Small cell lung cancers and advanced stage non-small cell lung cancers are treated with systemic therapy (such as chemotherapy or biologic therapy).
8. Chemotherapy with or without radiation therapy is used to treat unresectable or advanced stage mesothelioma.
9. When cure is not possible, improvement in quality of life is the important goal regardless of whether there is an increase in the quantity of life gained from treatment (although sometimes, the latter is achieved).

Introduction

Lung cancer (non-small cell and small cell carcinomas) includes malignancies that arise within the lung parenchyma or bronchi. The pleural surface of the lungs gives rise to mesothelioma. Lung cancers are pathologically categorized into non-small cell and small cell carcinoma. Surgery, chemotherapy, and radiation therapy all play important roles in the treatment of lung cancer. There is an exciting and developing understanding of the wide variety of biologic characteristics and behaviors of lung cancers and new biologic and molecular tests have enabled clinicians to better tailor individualized treatment strategies.

Epidemiology

The American Cancer Society has estimated that in 2009, there were 219,440 new diagnoses of lung cancer and 159,390 deaths from the disease in the United States. Lung cancer is the second most common form of cancer in both men and women. It remains the most common cause of cancer-related death. Lung cancer incidence in the United States climbed throughout the 20th century as tobacco smoking became increasingly popular. Rates of smoking among men began to fall in the 1960's and, beginning in the early 1990's, the incidence rate of lung cancer in men also began to fall. Rates of smoking among women were never as high as those in men. However, decline in smoking rates among women did not begin until the 1970's. The lung cancer incidence

rate among women peaked in the 1990's and there has been little reduction in the rate since then.

There are about 2500 cases of mesothelioma diagnosed each year in the United States. The Surveillance, Epidemiology, and End Results (SEER) data base reports that the incidence of mesothelioma peaked in the early 1990's, and has been gradually declining since. The peak and decline in mesothelioma incidence is believed to be due to the widespread use of asbestos in construction during the 20th century. Since the early 1970's however, federal regulations have sharply limited the use of asbestos.

Etiology

In the United States and around the world, cigarette smoking is the strongest and most prevalent risk factor for the development of lung cancer. The risk is related not only to the amount of cigarette use (usually expressed as packs per day) but to the cumulative duration of such use (usually expressed as pack years). Cigarette use is estimated to account for approximately 90% of all lung cancers. Thus, it is a readily targeted life style risk factor. Second hand smoke exposure (and some people believe even third hand exposure from carcinogens that deposit on clothing) is a real risk factor, albeit nowhere near as significant as first hand exposure.

The role that genetics play in the etiology of lung cancer is not clear. There are people who develop lung cancer without any known cigarette use or other risk factors. In addition, not all people who smoke cigarettes develop lung cancer. There are some familial genetic syndromes, but these are not common.

In the last half century, the relative incidence of squamous cell carcinoma has fallen compared to adenocarcinoma. It is believed that this change in histology is in large part due to the wide-spread introduction of filtered cigarettes in the 1950's. Though the overall risk of lung cancer from filtered cigarettes is the same as from unfiltered cigarettes, filters alter the type of carcinogens and location of carcinogen deposition resulting from smoking. Filters force smokers to inhale more deeply, increasing the likelihood that carcinogens will be deposited deep in alveoli or terminal bronchioles. This altered pattern of carcinogen deposition has been hypothesized to be the reason why the usually peripherally-based adenocarcinomas have been increasing in frequency as compared to the usually centrally-based squamous cell carcinomas in the last two decades. Deeper inhalation also results in hotter and more complete combustion of the cigarette.

Risk factors for the development of mesothelioma include asbestos exposure and cigarette smoking. The combination of the two multiplies the risk. Shipyard workers, plumbers, construction-workers and asbestos miners were at significant risk of asbestos exposure. Occupational history is an important part of the workup for mesothelioma.

Screening

Recently, the National Lung Screening Trial (NLST) demonstrated decreased mortality in high risk patients (patients 55-74 years of age with a 30 pack-year smoking history who were currently smoking (or quit within the previous 15 years) who underwent low dose chest CT scan to screen for lung cancer. These results are encouraging and low dose radiation CT screening of patients at high risk for lung cancer has now been endorsed by a number of national organizations. However, associated harms include radiation exposure, false positive results, and unnecessary interventions (Figure 1).

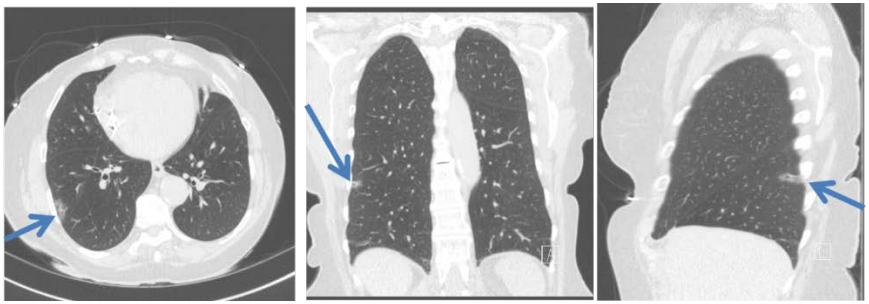


Figure 1. 74 year old woman with a 50 plus tobacco year history quitting in 2007. PFT's in 2013 revealed a moderate-severe obstructive ventilatory defect. CT shows a suspicious 2.3 cm ground glass opacity in the right lower lobe. This may represent a small focus of pneumonia or a primary lung cancer such as minimally invasive adenocarcinoma. This lesion persisted on follow-up imaging favoring the diagnosis of a carcinoma. Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

Recommendation

The United States Public Health Service Task Force on Prevention recommendations are summarized below:

- Asymptomatic adults aged 55 to 80 years who have at least a 30 pack-year smoking history and currently smoke or have quit smoking within the past 15 years. Screen annually for lung cancer with low-dose computed tomography.
- Discontinue screening when the patient has not smoked for 15 years (Figure 2).

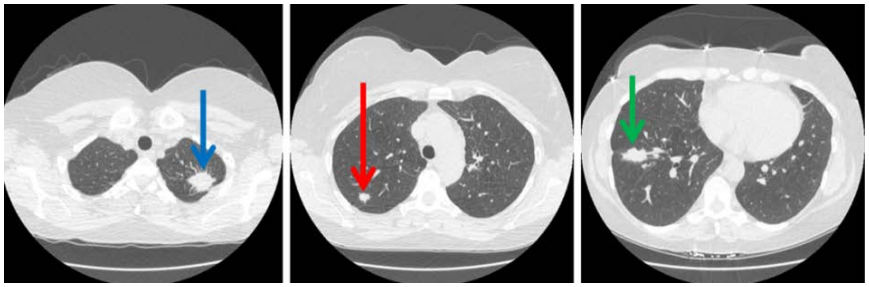


Figure 2. 53 year old woman, with significant tobacco history, referred for screening. 3.1 cm left upper lobe mass (blue arrow), 1.2 cm right upper lobe nodule (red arrow), and 2.6 cm right lower lobe nodule (green arrow) were found, concerning for malignancy. The spiculated appearance of all 3 lesions suggests synchronous primary lung cancers. Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

It is important to appreciate that the vast majority of lung nodules identified by CT screening are not cancer. The costs and risks to patients of evaluating many benign lung nodules will have to be weighed against potential benefits of screening for each patient. Additionally, the NLST was conducted in a limited number of centers with a well-defined protocol for evaluating lung nodules. Any screening program based on the NLST should incorporate the same rigorous standards that were used in the study.

Clinical Presentation

A majority of lung cancers are diagnosed at advanced stages. This is due in part to the limitations of screening for lung cancer and to lung cancer developing in a stealthy manner, often being asymptomatic at early stages of the disease. In addition, a number of presenting symptoms (cough, shortness of breath, weight loss, decreased appetite, and fatigue) are nonspecific and can be caused by a variety of other non-malignant etiologies, most often pneumonia (Figures 3a & b).

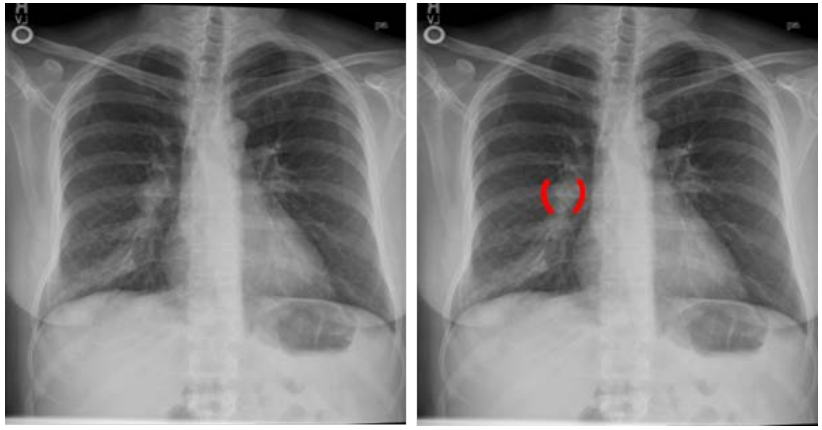


Figure 3a. Chest X-ray demonstrates an opacity in the right lower lobe. The right hilum is biconvex & masslike in shape. This finding is suggestive of post-obstructive pneumonia versus pneumonia with reactive lymphadenopathy Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

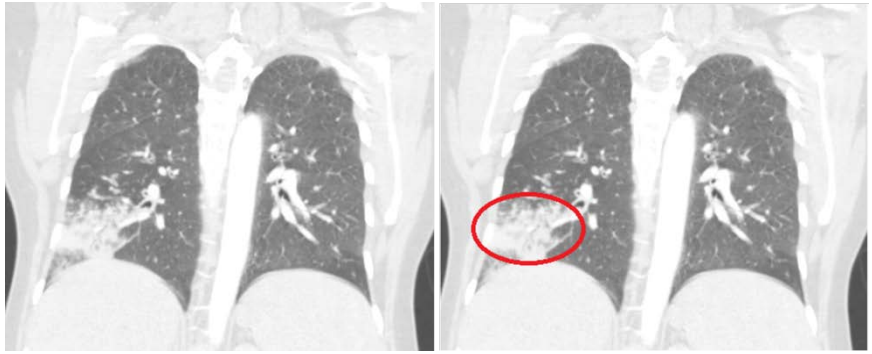
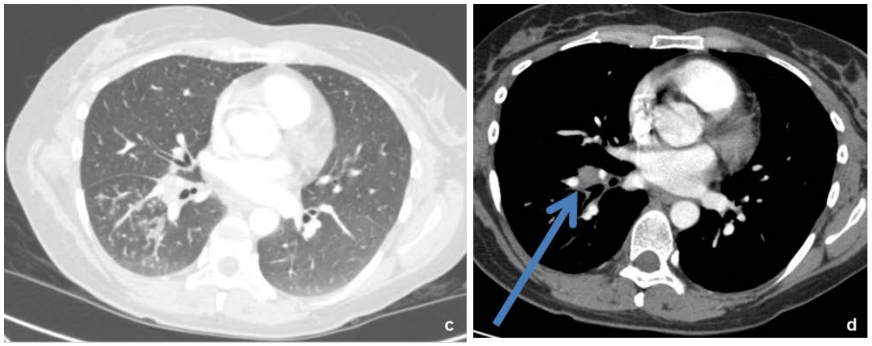


Figure 3b. AP Digital Reconstructed Radiograph (DRR) (from CT scan) Lung window, better defines the consolidation in the right lower lobe than the chest xray. Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

Sometimes hemoptysis (coughing up of blood), pain, hoarseness, dysphagia (difficulty swallowing), and other systemic symptoms are present at the time of diagnosis.

In any person who smokes cigarettes, has been a cigarette user, or has other identifiable risk factors, the above symptoms should indicate the need to obtain imaging of the lungs (usually one begins with a chest x-ray (Figure 6a) and then subsequently can employ more detailed imaging studies such as computed tomography (CT) (Figures 3c & d; 4a & b) and positron emission tomography (PET) scans (Figure 5).



Figures 3c & 3d. Lung window **(3c)**- Shows the pneumonia in the right lower lobe. Mediastinal window **(3d)**- Demonstrates a nodule as the cause of the post-obstructive pneumonia (arrow). Further work up confirms lymphoma in this patient. Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

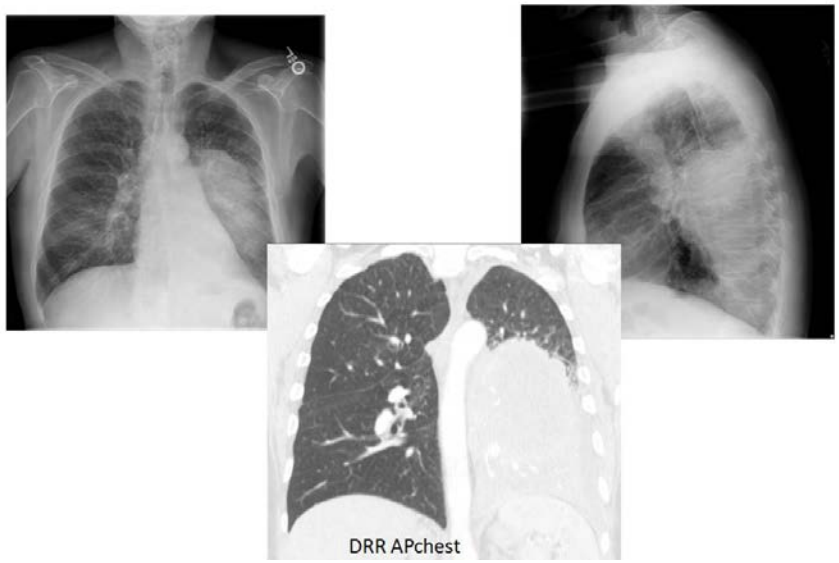


Figure 4a. Adenocarcinoma. AP and lateral views of the chest demonstrates a large mass-like opacity occupying the left lower lobe Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

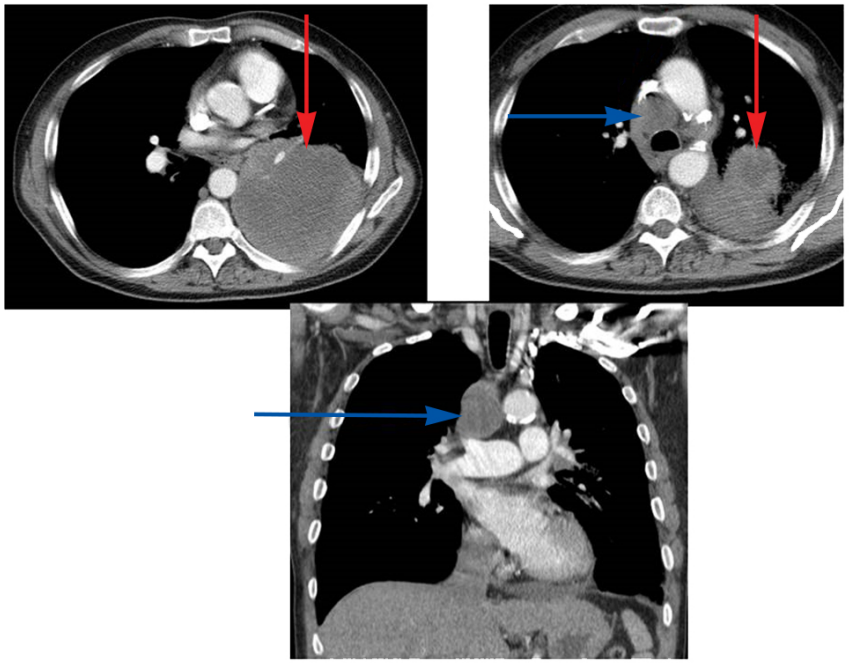


Figure 4b. Adenocarcinoma. Axial and coronal images of chest CT confirm the presence of a large mass within the left lung (red arrow). A large necrotic contralateral lymph node was noted (blue arrow). Biopsy proved the mass to be adenocarcinoma. This patient has Stage T3 N3 disease by chest CT criteria. Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

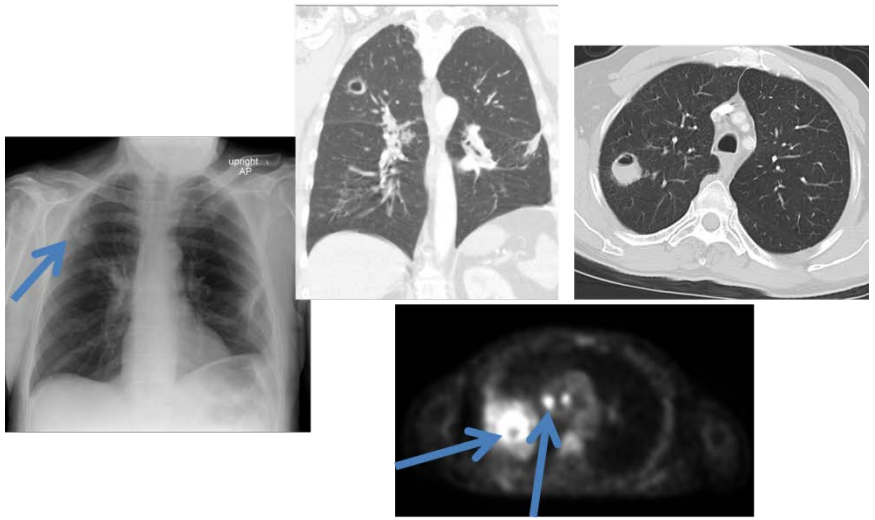


Figure 5. Squamous cell carcinoma. Frontal view of the chest demonstrates round lesion with lucency in the right upper lobe concerning for a cavitary tumor which is better seen on the coronal and axial views of the contrast enhanced CT of the chest. PET shows intense tracer uptake correlates with the right upper lobe cavitary lesion and is consistent with biopsy proven squamous cell carcinoma. Squamous cell carcinomas tend to cavitate. Notice 2 smaller areas of increased PET positivity consistent with hilar and mediastinal nodal disease. So this patient has T2a N2 disease by PET criteria. Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

Pathology

There are two major pathology categories of lung cancer (excluding mesothelioma): non-small cell and small cell. Within the non-small cell category, the common pathology designations include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma (Figure 6) accounts for approximately 40% of lung cancers, squamous cell carcinoma (Figure 7) approximately 25%, large cell (Figure 9) approximately 10% and small cell cancer (Figure 8) approximately 15%. Miscellaneous other pathologies make up about 10% of cases.

Adenocarcinoma

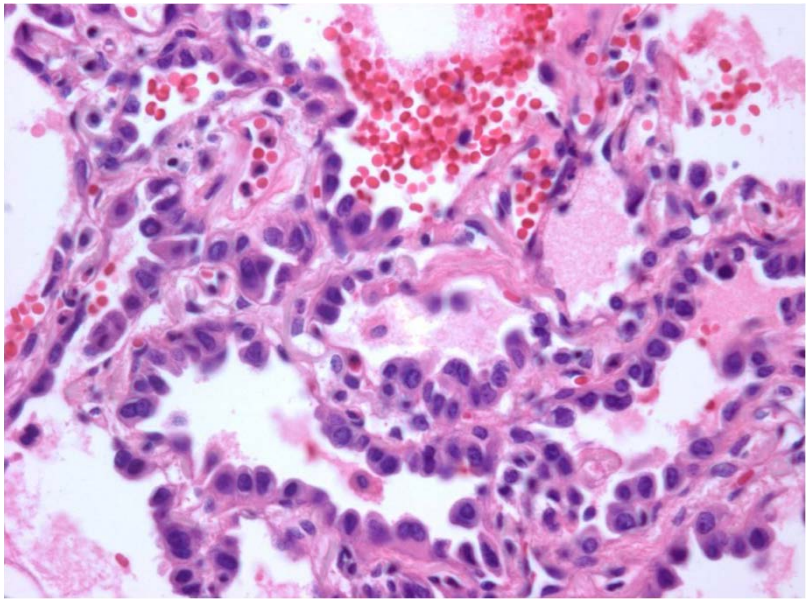


Figure 6. The malignant cells in adenocarcinoma are composed of cuboidal or columnar shaped cells either growing along the alveolar walls (as illustrated here) or showing glandular proliferation. The malignant cells have hyperchromatic nuclei with prominent nucleoli and eosinophilic cytoplasm with or without mucin. Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

Squamous Cell Carcinoma

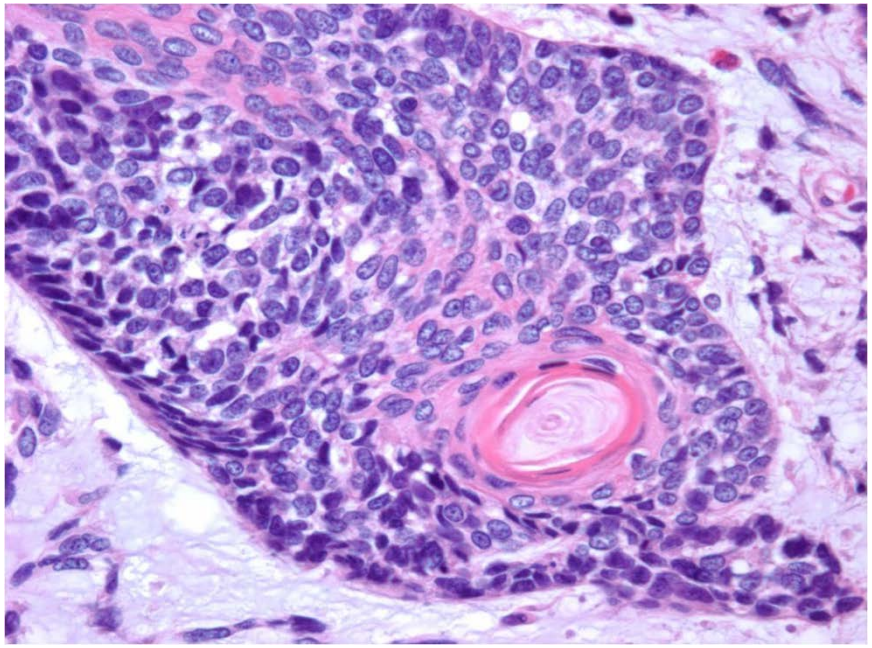


Figure 7. The malignant cells in squamous cell carcinoma show keratinization and /or intercellular bridges. Keratinization could be manifested as either keratin pearl formation (as illustrated here) and/or individual cells with markedly eosinophilic dense cytoplasm. Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

Small Cell Carcinoma

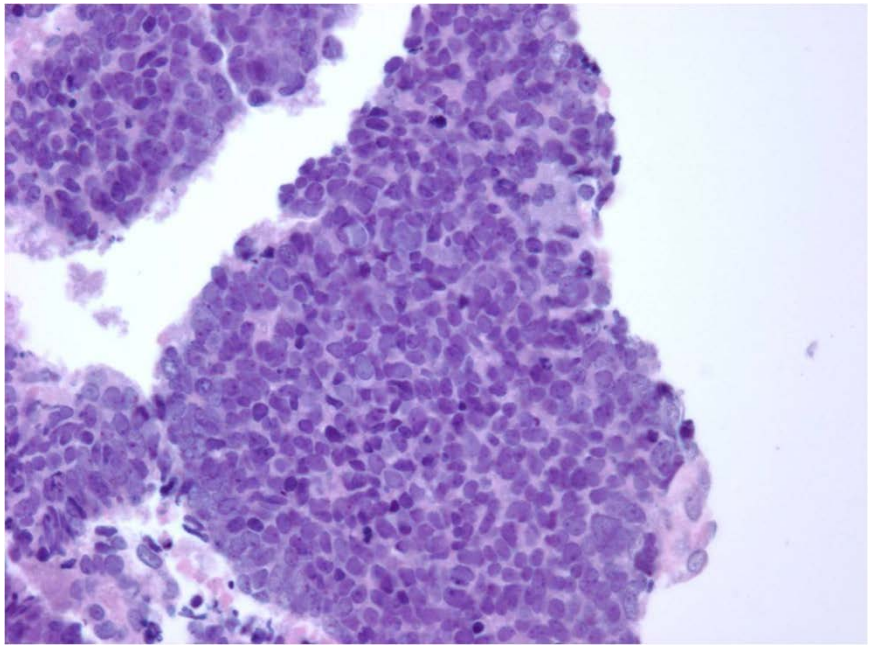


Figure 8. The malignant cells in small cell carcinoma are small and densely packed with scant cytoplasm, indistinct cytoplasmic borders, finely granular nuclear chromatin and absent or inconspicuous nucleoli. Hematoxylin has a deep blue-purple color and stains nucleic acids whereas Eosin stains proteins, which are mostly found in the cytoplasm. The malignant cells in small cell carcinoma have very little cytoplasm and are densely packed. Therefore, they would look more purple on Hematoxylin and Eosin stains Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

Large Cell Carcinoma

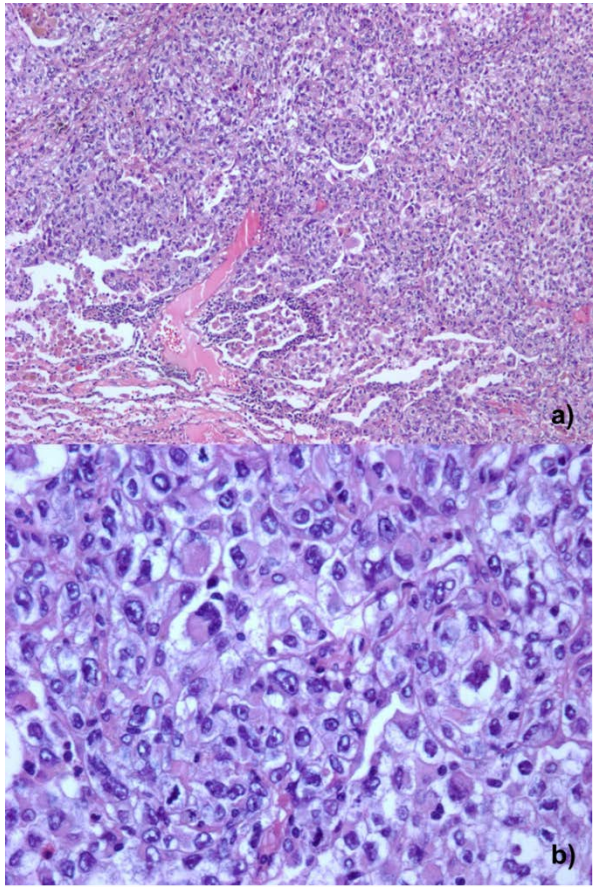


Figure 9. a). Large cell carcinoma 100X: The neoplasm is comprised of diffuse sheets of malignant cells without morphologic evidence of squamous and glandular differentiation. Portion of normal lung parenchyma is also present in the lower left corner of the picture.

b). Large cell carcinoma 400X: Large vesicular nuclei with prominent nucleoli and abundant clear or eosinophilic cytoplasm are noted on malignant cells. No keratin pearls, intercellular bridges, mucin or gland formation are seen. A few mitotic figures are also present in this field. Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

Mesothelioma

Mesothelioma (Figure 10a, b & c) is distinct from parenchymal lung cancer. It arises from the pleural surface that surrounds the lungs, whereas lung cancer arises from either the parenchymal tissues or the airways (although lung cancer can invade into or spread to the pleural surfaces). Three histologic types of malignant mesothelioma exist: epithelioid, sarcomatoid and biphasic (mixed epithelioid and sarcomatoid).

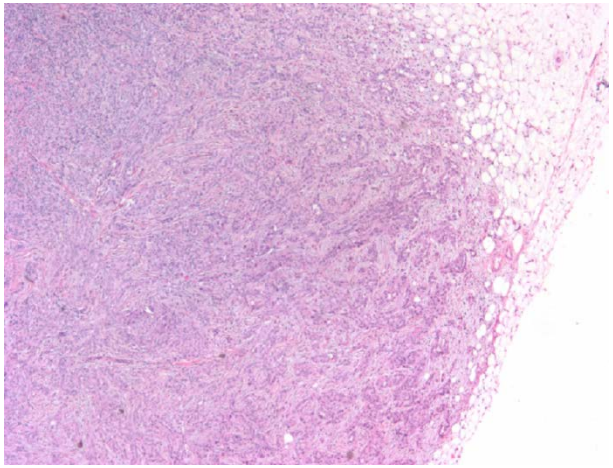


Figure 10a. Epithelioid mesothelioma 40x magnification. The tumor is comprised of epithelioid cells that form nests and tubule-like structures infiltrating the subpleural adipose tissue (on the right). Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

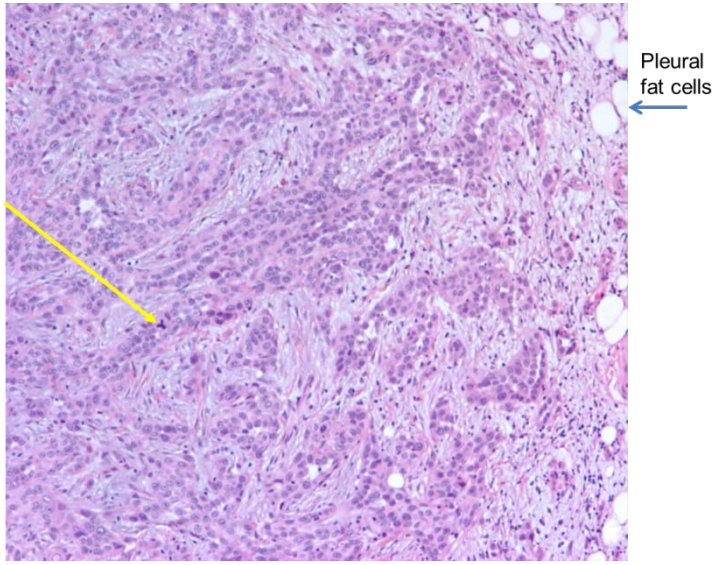


Figure 10b. Epithelioid mesothelioma 100x magnification. Individual tumor cells have round vesicular nuclei with irregular borders and prominent nucleoli and esonophilic cytoplasm. Increased number of mitotic figures, including an atypical one (arrow), are seen within the tumor. The tumor cells are positive for mesothelial differentiation markers such as calretinin and WT-1 by immunohistochemistry. Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

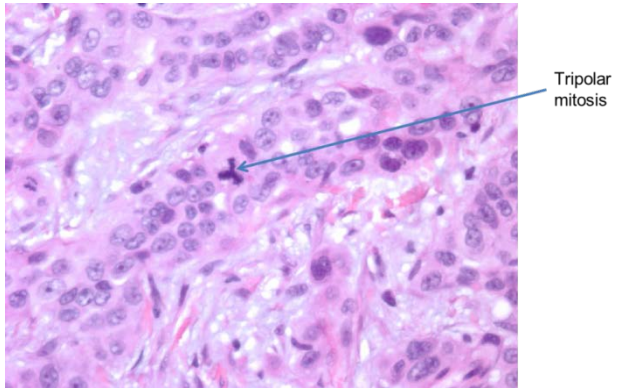


Figure 10c. Epithelioid mesothelioma 400x magnification. Image ccourtesy of the University of Massachusetts Medical School, Department of Pathology.

Prognostic Factors, Staging and Natural History

Lung cancer is staged with the American Joint Committee on Cancer (AJCC) tumor, lymph node, and metastasis (TNM) system, seventh edition. As with all cancers, staging is based on prognostic grouping and predicted natural history of the disease. So stage is a measure of an individual patient's prognosis. The other important prognostic factor is the individual patient's overall condition, referred to as Performance Status.

Small cell lung cancer has a higher propensity to spread to distant parts of the body (metastasize) early in the course of the disease than does non-small cell lung cancer. However, any lung cancer can metastasize. The common anatomic locations for metastases include, but are not limited to, other parts of the lungs, regional lymph nodes, liver, adrenal glands (Figure 11), brain (Figure 12), and bones. Lung cancer can spread to the lymph nodes that are within and outside of the lungs, such as to the lung hilar areas, the mediastinum (the area in between the lungs), and to the supraclavicular regions (above the collar bones). Lung cancer can also grow by direct extension into nearby anatomic structures, such as the airways, the major blood vessels, the heart, and the chest wall.

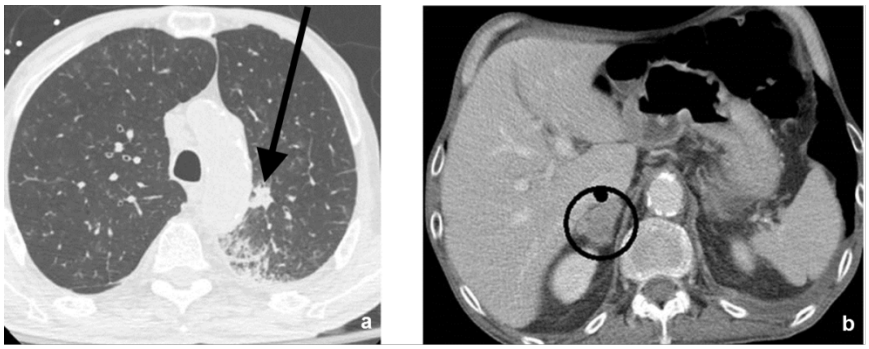


Figure 11. Metastasis to adrenal. **11a**. Small spiculated mass (arrow) in the left upper lobe concerning for a primary lung cancer. **11b**. Axial image at the level of right adrenal gland demonstrates a large soft tissue mass consistent with metastatic disease to the adrenal gland. Patient has Stage IV, T1 Nx M1 disease. Images courtesy of University of Massachusetts Medical School, Department of Radiology.

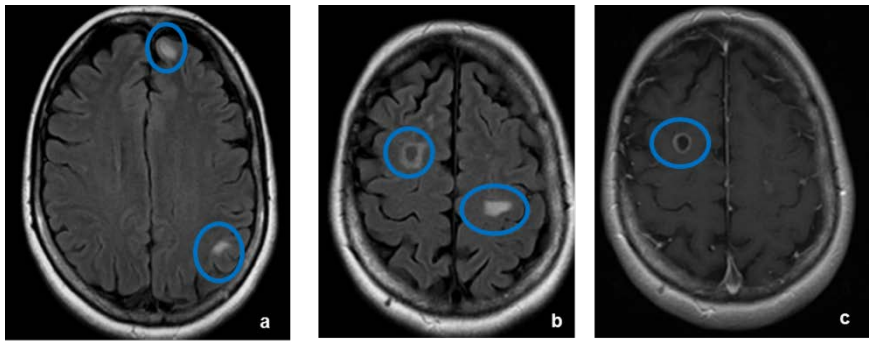


Figure 12. 55 year old woman with 30 pack year smoking history was found to have a 3 cm right middle lobe carcinoma with spread to mediastinal lymph nodes and metastasis to the adrenal gland. No neurologic symptoms, but on routine staging brain MRI multiple small brain metastases are noted.

12a. Axial FLAIR image shows abnormal foci of hyperintensity at the grey-white junctions of the left frontal and left parietal lobes (blue circles) representing edema from tumor metastasis in these regions.

12b. Axial FLAIR image shows another abnormal focus of hyperintensity in the left superior frontal lobe representing edema related to a tiny metastasis in this region. In the right superior frontal lobe, there is another lesion with central hypointensity representing an area of central necrosis of a tumor.

12c. Post contrast axial T1 image demonstrates ring-enhancement of the right frontal tumor. Lack of internal enhancement is due to central necrosis. The left parietal metastasis is identified as a tiny punctate focus of enhancement indicating the actual size of the microscopic metastasis. Images courtesy of the University of Massachusetts Medical School, Department of Radiology.

Mesothelioma has a lower tendency to metastasize than do most lung cancers. It is more apt to grow along the pleural surfaces and to extend directly into the lung parenchyma and the chest wall. It can also grow into the diaphragms, which sit underneath the lungs (Figures 13 & 14).

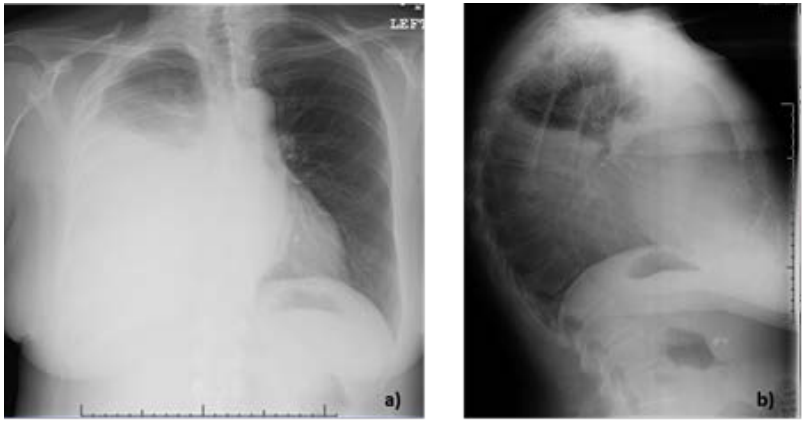


Figure 13. Chest x-ray demonstrating mesothelioma. Large mass in the right chest compressing the remaining pneumotized right upper lung with mild displacement of mediastinal structures to the left. Images courtesy of the University of Massachusetts Medical School, Department of Radiology.

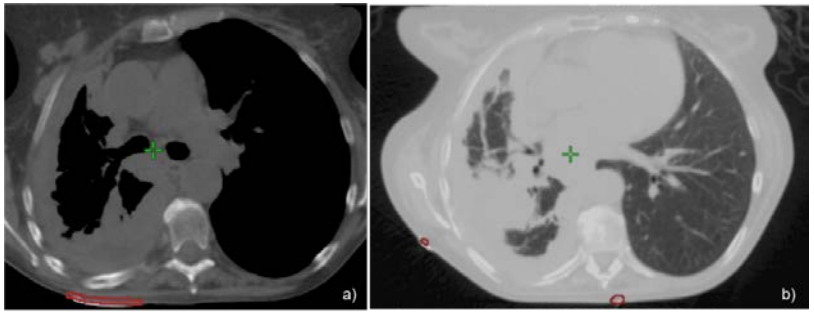


Figure 14. CT scan demonstrating mesothelioma. **14a**. Mediastinal window **14b**. Lung window. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology**.**

Both lung cancer and mesothelioma can cause pleural effusions, which are collections of fluid within the pleural space that separates the lungs from the chest walls. As this pleural fluid expands, it compresses the lungs, adversely affecting lung function (producing shortness of breath). Pericardial fluid can also develop within the space between the heart and its surrounding lining (the pericardium). As this pericardial effusion grows, it compresses the rhythmic contraction of the heart and thereby diminishes cardiac function. This is referred to as cardiac tamponade, which can be life threatening.

The presence of lymph node involvement by lung cancer (Figure 15) and the presence of any distant metastases are very important in staging lung cancer. The staging of lung cancer not only helps to identify appropriate treatment options, but also provides meaningful prognostic information as to the benefits of available therapies and prognosis. Non-small cell lung cancer is staged based on the role that surgery may have in its treatment: early stage (surgery has a role), locally advanced stage (surgery may or may not have a role), and advanced stage (surgery does not have a role except for palliation). Starting in 2010, small cell cancers are staged with the same system as non-small cell cancers. The current lung staging systems can be found at The American Joint Committee on Staging and the revised TNM Staging System.

Drawing a sketch of the extent of disease on a diagram of the body or the chest helps students learn staging systems and oncologists conceptualize the patient's disease to plan appropriate treatment. These staging diagrams make the staging systems much clearer to physicians, by illustrating the extent of disease often clarifying treatment decisions and assist in learning the AJCC staging system for each disease site.

An interactive series of staging diagrams are available here.

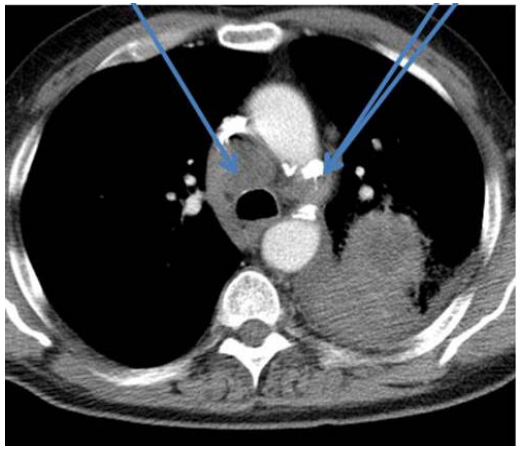


Figure 15. Lymph node metastases. Double arrow- AP window node (ipsilateral, N2) Single arrow- Contralateral paratracheal node (N3) Image courtesy of the University of Massachusetts, Department of Radiology.

Small cell lung cancer (Figures 16 & 17) now is staged with the same system as non-small cell cancer. The staging system previously used for this disease revolved around the role that radiation therapy could have in its treatment. If the extent of the tumor could be safely encompassed within a standard radiation field, then the small cell lung cancer was termed *limited* stage. Otherwise, the disease was called *extensive* stage, usually metastatic. This terminology is still found in older charts and academic papers, and in the minds of many oncologists.

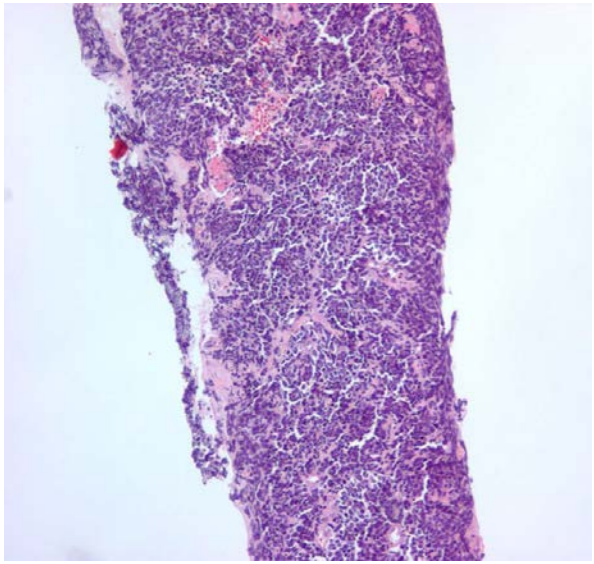


Figure 16. Small cell lung cancer 100X: Small cell carcinoma of lung showing diffuse sheets of small blue cells completely replacing lung parenchyma. Image courtesy of the University of Massachusetts, Department of Pathology.

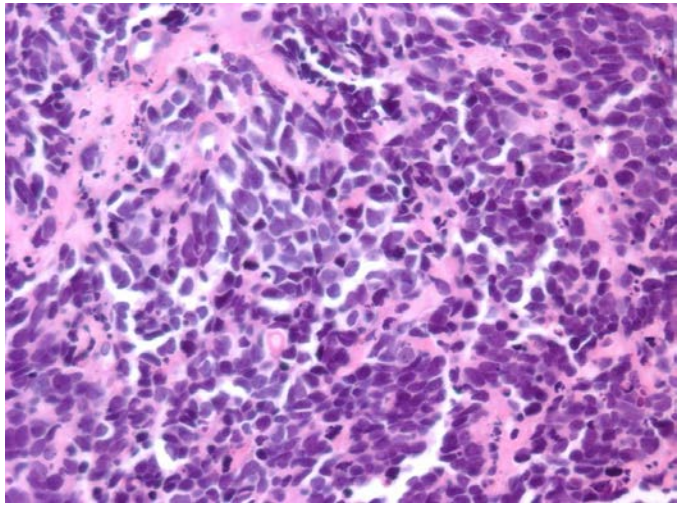


Figure 17. Small cell lung cancer 400X: On high magnification, the tumor is comprised of neoplastic cells showing nuclear molding, nuclei with salt-pepper chromatin and inconspicuous to absent nucleoli. There is a very high nuclei to cytoplasm ratio with only very scant rim of eosinophilic cytoplasm. The tumor reveals very high proliferative index as demonstrated with several mitotic figures in this field. Image courtesy of the University of Massachusetts, Department of Pathology.

Imaging

Common imaging studies used in the staging of lung cancer include CT, fluorodeoxyglucose positron emission tomography (FDG-PET), (Figures 18a - c & Movie 1) magnetic resonance imaging (MRI), and radiolabeled technetium bone scan (Figure 19). There is no standard serum blood test used to diagnose lung cancer or mesothelioma. A number of serum markers have been identified, such as carcinoembryonic antigen (CEA), but as of now, they are not routinely used to screen for or to diagnose lung cancer. The key to proper diagnosis remains obtaining adequate tissue through a biopsy or from an operation for detailed pathology testing. There is a developing array of molecular and histochemical tests being used to aid in the diagnosis of lung cancer and mesothelioma. Increasingly, some molecular tests are also affecting treatment choices.

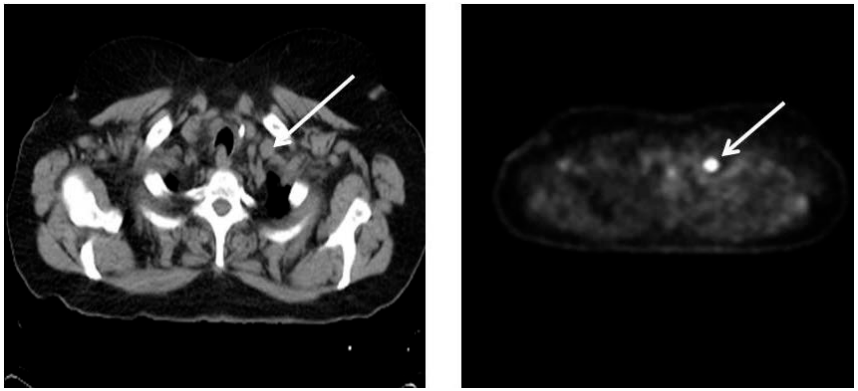


Figure 18a. CT and PET slice demonstrating a hypermetabolic lymph node in the left supraclavicular region representing a metastasis. Image courtesy of the University of Massachusetts, Department of Radiology.

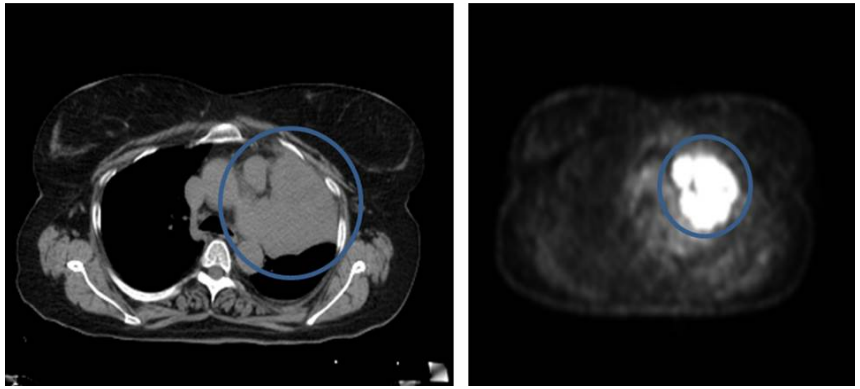


Figure 18b. CT and PET slice demonstrating a large mass in the left upper lobe. Pathology confirmed the diagnosis as adenocarcinoma. Image courtesy of the University of Massachusetts, Department of Radiology.

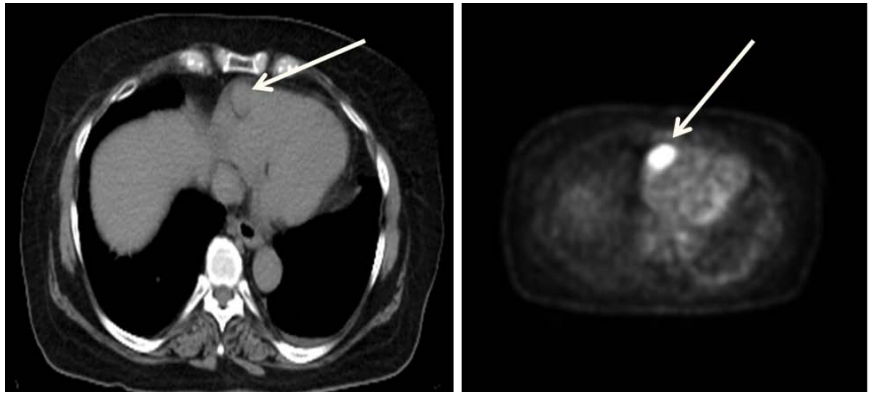
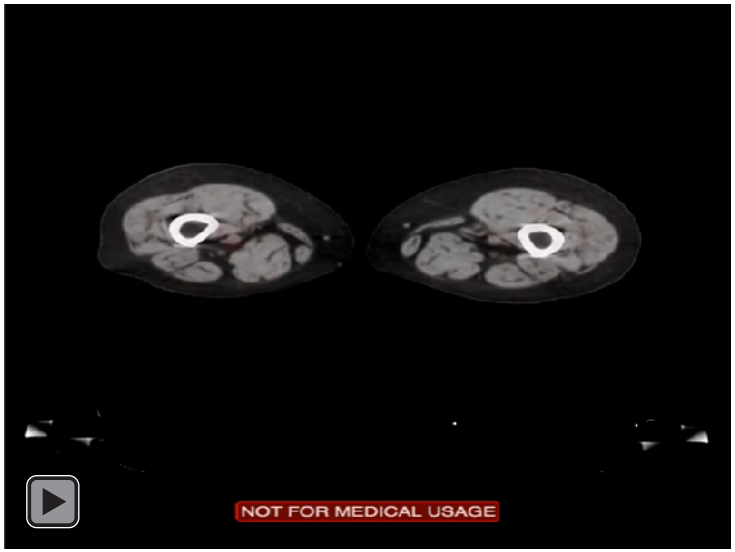


Figure 18c. Matched CT and PET scan slices demonstrates a mass adjacent to the right ventricle, which does have increased uptake on the PET, representing either an enlarged lymph node or a myocardial appendage. Image courtesy of the University of Massachusetts, Department of Radiology.



Movie 1. Axial slices of a PET scan of a lung cancer patient from cephalad to caudad, presented as a movie. Movie courtesy of the University of Massachusetts, Department of Radiology, Division of Nuclear Medicine.

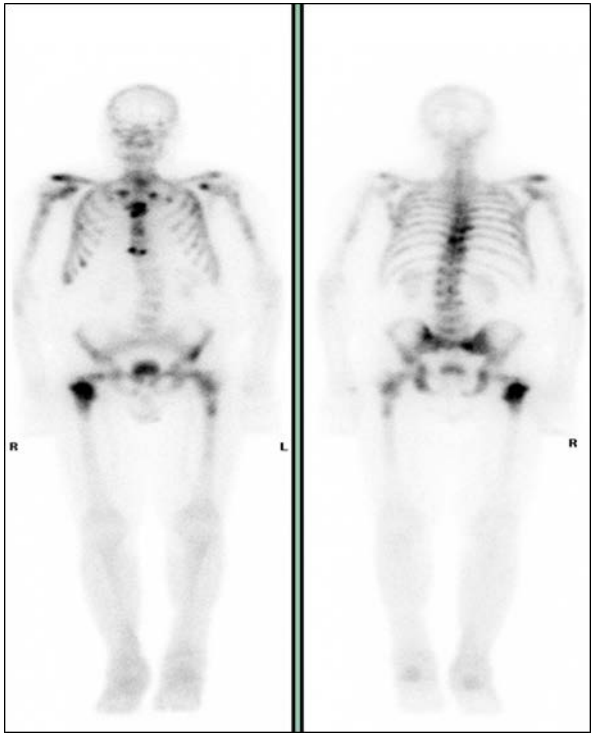


Figure 19. Positive bone scan, showing metastases from lung cancer. Notice increased uptake of radiotracer in right proximal humerus, left acetabulum, sternum, multiple vertebrae, left scapula and sacrum. Image courtesy of the University of Massachusetts, Department of Radiology Division of Nuclear Medicine.

Principles of Treatment

A thorough history and physical examination are important to help identify the panoply of presenting problems and to identify any anatomic findings suggestive of cancer spread or anatomic compromise. Because most people who develop lung cancer have a cigarette smoking history, one needs to identify any other tobacco-related problems, such as coronary heart disease, diabetes mellitus, peripheral vascular disease, other cancers, emphysema, and central nervous problems (such as strokes). These medical issues can complicate and limit the treatment options available.

Surgery

For non-small cell lung cancer, surgical resection is the only reliable curative modality for patients who present at an early enough stage, which is unfortunately the minority. Lobectomy (Figures 20 and 21) is the surgery of choice for small to medium-sized tumors while pneumonectomy is done for larger or centrally located tumors.

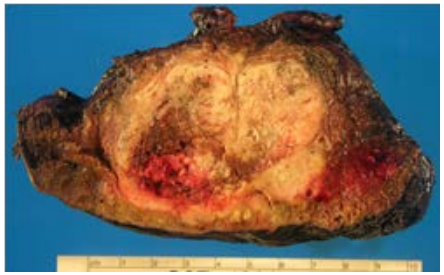


Figure 20. Lobectomy specimen. Courtesy of the University of Massachusetts, Department of Pathology.

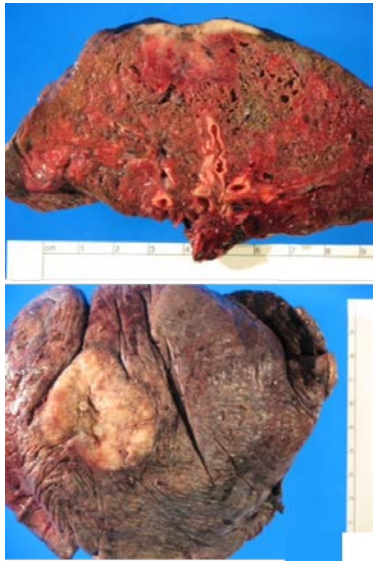


Figure 21. Lung adenocarcinoma in a lobectomy specimen forming a mass (4.7 cm) and invading pleura. Courtesy of the University of Massachusetts, Department of Pathology.

Sublobar resection, either wedge resection, (Figure 22) or segmentectomy (Figure 23) is an acceptable alternative for peripheral Stage 1A tumors less than 2cms if a lobectomy (Figure 24) cannot be tolerated or is declined.

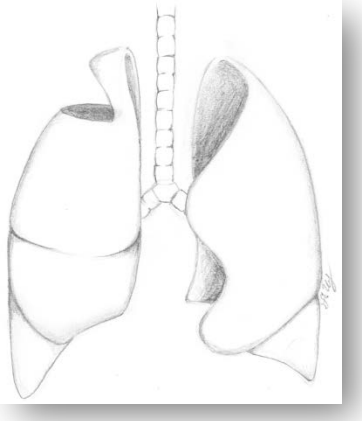


Figure 22. Lung Wedge Resection, Right Upper Lobe. Illustration by Sarah Alyssa Uy.

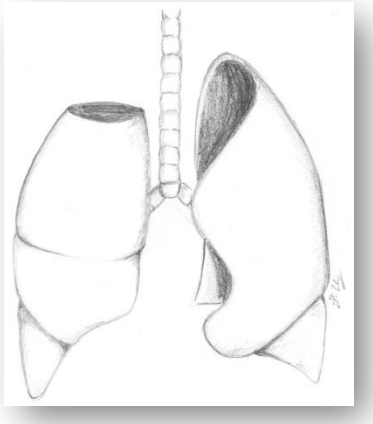


Figure 23. Apical Segmentectomy, Right Upper Lobe. Illustration by Sarah Alyssa Uy.

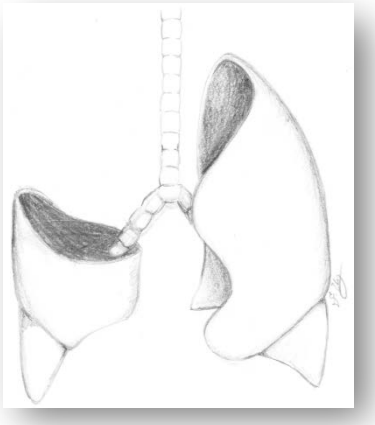


Figure 24. Right Upper Lobectomy. Illustration by Sarah Alyssa Uy.

An operation treats only localized disease, so if there is a higher likelihood of systematic metastases, chemotherapy is added after surgery. This is the case after selected Stage 1B and all Stage 2 patients. For Stage 3 patients, there is a very high likelihood of systemic metastases in addition to extensive local disease so the foundation of treatment is a combination of radiation and chemotherapy, and in selected patients surgical resection is done afterwards to remove residual disease. The role of surgery in advanced or overtly metastatic disease is palliation, such as drainage of pleural effusion or relief of airway obstruction.

For small cell lung cancer, surgical resection is not standard and is done only for selected patients with tumors smaller than 2cms with no lymph node metastases, and either preceded or followed by chemotherapy because of the great tendency of small cell cancer to metastasize early. The only form of surgery acceptable for these patients is lobectomy. The currently preferred treatment method, however, even for these very early stage patients is combined chemoradiation.

When mesothelioma is removed surgically, an attempt is made to remove the entire pleural surface of the affected lung and the chest wall (pleurectomy- PL). Surgery that involves the removal of the ipsilateral pleura, the ipsilateral diaphragm and pericardium, the entire involved

lung, and frequently part of the chest wall is called extra-pleural pneumonectomy (EPP) (Figure 25).

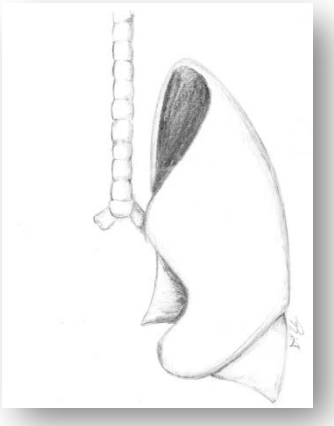


Figure 25. Right Pneumonectomy. Illustration by Sarah Alyssa Uy.

The current standard method of attempting cure for mesothelioma involves administering chemotherapy first to eliminate possible metastases (neoadjuvant chemotherapy), EPP to remove the bulk of the tumor, and post-operative radiation to the ipsilateral hemithorax to attempt to eradicate residual disease. Many patients with mesothelioma do not have the cardiopulmonary reserve to tolerate an EPP, and even after undergoing this treatment regimen the recurrence rate is still high.

However, not every person with early stage non-small cell disease is medically able to withstand a major thoracotomy or the loss of lung parenchyma. Therefore cardiopulmonary and other medical assessment is appropriate before embarking on such major procedures. Pulmonary function tests are performed on major lung resection candidates, and predict the probability of major postoperative pulmonary-related complications. Regardless of the type of lung resection done (lobectomy, pneumonectomy etc.), patients should have at least 40% of their ideal FEV1 (forced expiratory volume in 1 second) and DLCO (diffusion capacity for carbon monoxide) left at the end of their lung surgery. Since major lung resections are quite stressful on the heart because of the acute increase in pulmonary vascular resistance which accompanies lung removal, in selected patients a cardiac evaluation in the form of either an exercise or pharmacologic cardiac stress test is done.

Some people decide they do not want surgery. It is not yet known to what degree patients may still be cured if they medically cannot tolerate or choose not to undergo an operation but receive other types of treatments, such as newer radiation therapy techniques that focally target the tumor with high doses (Movie 2). Even if such people cannot achieve a cure of their cancer, they may enjoy long term survival.

Chemotherapy

For localized small cell carcinoma, clinical studies over the years have shown that there is an improvement in clinical outcome, including survival, if limited stage small cell lung cancer is treated with a combination of chemotherapy and radiation therapy. This therapy needs to start as rapidly as possible.

When a non-small cell lung cancer has spread to nearby lymph nodes or has spread to other nearby anatomic structures (such as the chest wall) but has not overtly been found to have metastasized elsewhere, chemotherapy with radiation therapy can be used initially to treat the cancer. This is called neoadjuvant treatment. Some patients whose tumors respond well to concurrent chemotherapy and thoracic radiation may be candidates for thoracic surgery to remove any residual cancer. As the cancer becomes bulky, such neoadjuvant treatment is less and less successful.

When either non-small cell or small cell cancers have spread to distant sites (metastatic, or Stage IV disease), then the foundation of treatment is systemic chemotherapy. The goal of such treatment is palliative, not curative. Randomized trials have shown about a six to eight-month improvement in median overall survival with the use of current chemotherapy in metastatic lung cancer compared to no anti-cancer treatment. However, patients who respond to treatment can enjoy significant relief of symptoms caused by the cancer, such as pain, fatigue, shortness of breath, loss of appetite, and weight loss. It has recently been documented that early involvement of a palliative care service in the care of patients with advanced lung cancer can extend survival as well as enhance quality of life.

A small percentage of patients with non-small cell lung cancer, particularly with adenocarcinoma, may have a specific acquired gene

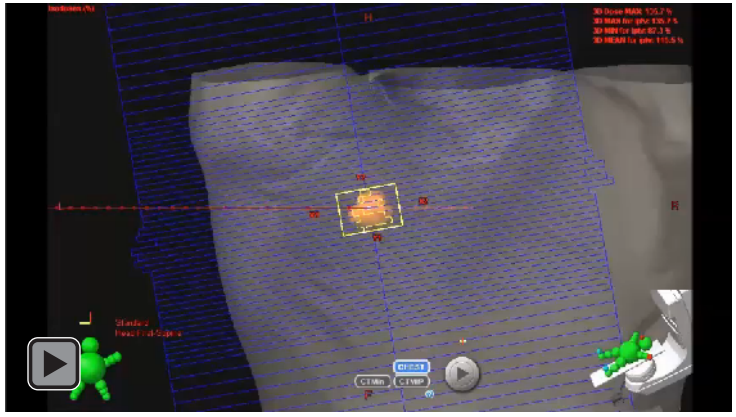
mutation in their cancer that can serve as a target for therapy. Mutations in the epidermal growth factor receptor (EGFR) gene can cause activation of the EGFR tyrosine kinase (TK). Erlotinib and gefitinib are inhibitors of the EGFR TK and treatment with these drugs, will produce a tumor response in 75% of these patients. Similarly, the fusion gene, echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) results in activation of the ALK oncogene. Crizotinib is a specific inhibitor of ALK TK and can produce a tumor response in about 60% of patients whose tumors have the EML-ALK fusion gene.

Recently the antibodies nivolumab and pembrolizumab have been approved for treatment of recurrent metastatic non-small cell lung cancer after previous treatment with chemotherapy. These antibodies target the programmed death 1 (PD-1) receptor on T cells. PD-1 activation is one mechanism used by the immune system to down regulate an immune response. Anti-PD-1 antibodies are able to block this immune checkpoint and represent a novel immune therapy of lung cancer. It is anticipated that the use of these antibodies, and others that work via a similar mechanism, will increase significantly in the near future.

Radiation Therapy (RT)

Radiation therapy is regional treatment, used to treat the primary and draining lymphatic volumes, with curative intent (as primary treatment, hoping to achieve long term control), as neoadjuvant or adjuvant therapy (in each case, with or without sensitizing chemotherapy), with prophylactic intent or with palliative intent.

Recently, stereotactic radiation therapy (2-5 treatments) or radiosurgery (a single treatment) has been used in an attempt to ablate small tumors in the chest or the brain (Movie 2).



Movie 2. Stereotactic radiation treatment of a small lung cancer. Movie courtesy of the University of Massachusetts, Department of Radiation Oncology.

In addition, fractionated radiation therapy is often utilized in an attempt to prevent the development of brain metastases in patients with small cell carcinoma, referred to as prophylactic cranial irradiation (PCI).

In the palliative treatment of advanced stages of lung cancer and mesothelioma, radiation therapy may be used to target a painful bone metastasis or to help keep open a lung airway that is becoming obstructed or compressed by the cancer. It is important to remember that when a patient reaches a point in the course of cancer that anti-cancer treatment is no longer possible, the responsibility to still care for the person remains. In particular, hemoptysis is effectively and quickly reduced or eliminated in patients receiving palliative radiotherapy.

Conclusion

Management of all forms of lung cancer and of mesothelioma requires a multidisciplinary approach to care involving Medical Oncologists, Radiation Oncologists, Thoracic Surgeons, Pulmonologists, Palliative Care Physicians, Pathologists, Radiologists, and Primary Care Physicians.

Prevention is the most effective means of decreasing mortality from these diseases; this requires protection from exposure to asbestos and tobacco.

Thought Questions

1. If cigarette smoking magically disappears tomorrow, what impact would you expect that to have on lung cancer incidence? Would lung cancer be expected to disappear altogether?

   Your answer:

Expert Answer

2. Why is it important to distinguish between small cell and non-small cell lung cancer histologies?

   Your answer:

Expert Answer

3. Why is it less important to distinguish between the various histologic types that make up non-small cell lung cancer?

   Your answer:

Expert Answer

4. How could molecular profiling of cancers affect the clinical importance of distinguishing between the different kinds of non-small cell lung cancer?

   Your answer:

Expert Answer

5. Why has the incidence of undifferentiated large cell carcinoma declined to the point that it is rarely diagnosed anymore?

   Your answer:

Expert Answer

Glossary

Bulky disease- Large volume of cancer in primary nodes or metastatic sites. Bulky disease in Hodgkin disease is defined differently.

Effusion- Fluid in pericardial sac or pleural space

Metastasize- Spread to distant parts of the body

Other tobacco-related problems- Coronary heart disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, peripheral vascular disease, emphysema, and central nervous problems (such as strokes)

Packs per day- Amount of cigarette use at any individual time

Pack years- Cumulative duration of cigarette use. (Maximum number of packs per day) x (Number of years smoking)

Thoracotomy- Surgical operation of cutting through the chest wall into the pleural space

References

1. Higashiyama M, Oda K, Okami J, Maeda J, Kodama K, Imamura F. Malignant pleural mesothelioma with long-term tumor disappearance of a local relapse after surgery: a case report. J Med Case Reports. 2009;3:6800.
2. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.

Staging Diagrams

AJCC staging consists of the disease (cancer site/type), the type of staging or timing of the staging: clinical (c) versus pathologic (p) versus post-neoadjuvant therapy (yp), the stage group (I-IV) and the T (primary site), N (nodal involvement), and M (metastasis) stage categories.

Oncologists draw tumor deposits on outlines of body regions, usually with red ink, during the staging of a cancer. The process of drawing helps physicians remember the patient's stage; drawing a series of stages for a given disease site helps learn the staging system, and makes the AJCC staging table meaningful for visual learners.

In this packet are:

1. Blank staging diagrams to assist with staging the patients you see. Printing out these blank diagrams and staging patients on the diagrams would be a valuable exercise.

2. Case-based interactive staging diagrams to provide a self-assessment of your staging knowledge. A patient's extent of disease is described in each case. Write the Type of Staging, Stage Group, T stage, N stage, and M stage in the corresponding blank fields. Clicking on the Expert Answers and Diagrams link will trigger the correct stage and annotated diagram to appear.

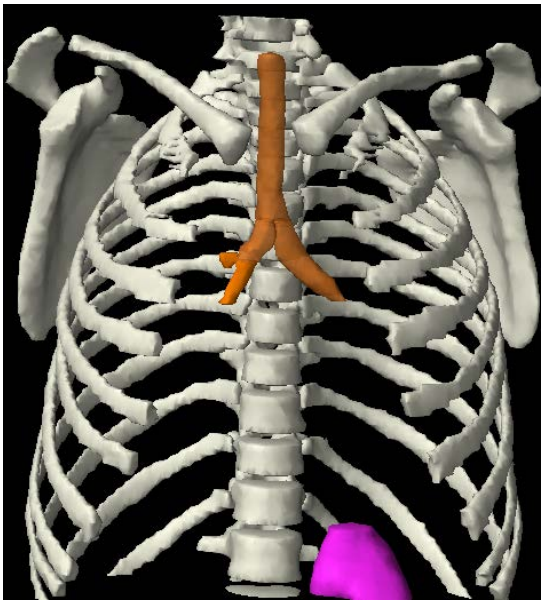
The blank diagrams below were created using a CT image set on the Varian Aria Radiation Therapy Treatment Planning System. Images Courtesy of University of Massachusetts Medical School, Department of Radiation Oncology.

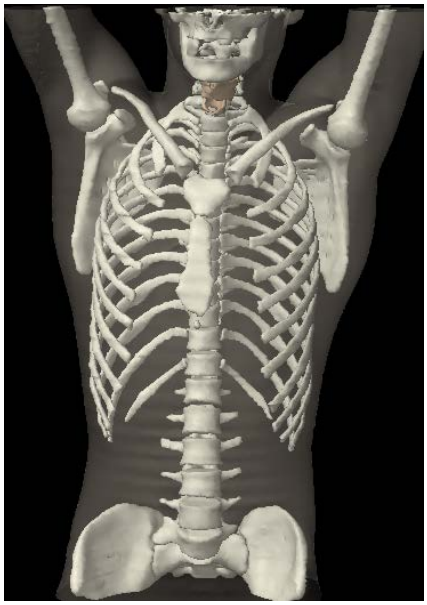
Blank Staging Diagram Form for Thoracic Malignancies

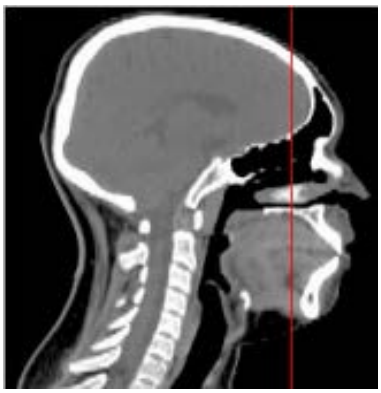
AJCC Lung Cancer Staging, 7th Edition is available here.

Disease: *Thoracic Malignancy*

Type of Staging _____ **Stage** _____ **T** _____ **N** _____ **M** _____







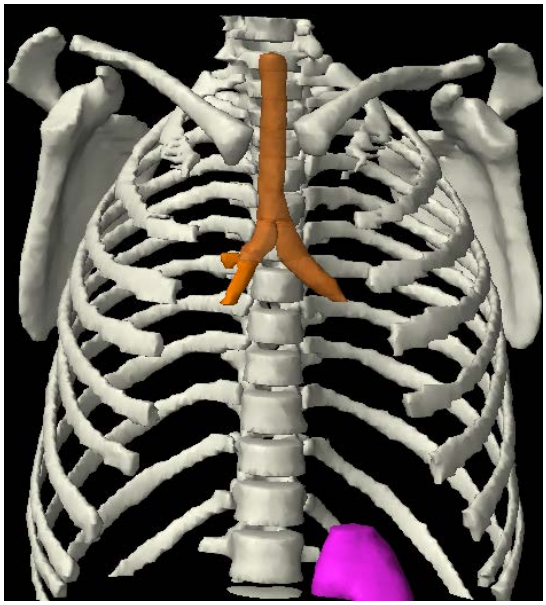
Interactive Staging Diagram Form for Thoracic Malignancies

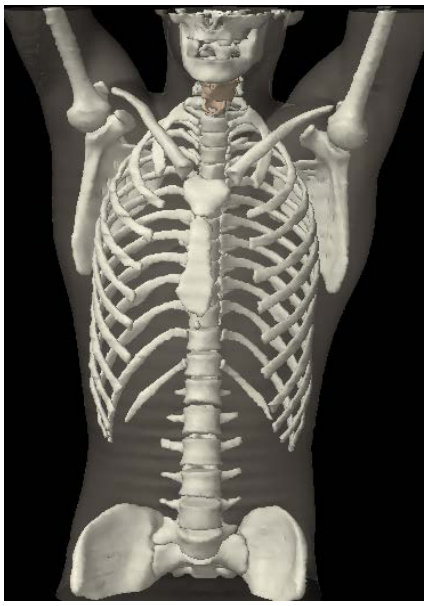
A1. Chest radiograph demonstrates a 2 cm mass in right upper lung field. Brain MRI is negative, and PET/CT scan shows a 1.4 cm mass in the right upper lobe, which is PET avid, but no other evidence of PET uptake.

Disease: *Lung Cancer*

Type of Staging _____ **Stage** _____ **T** _____ **N** _____ **M** _____

Click here to reveal Expert Answers and annotated diagram



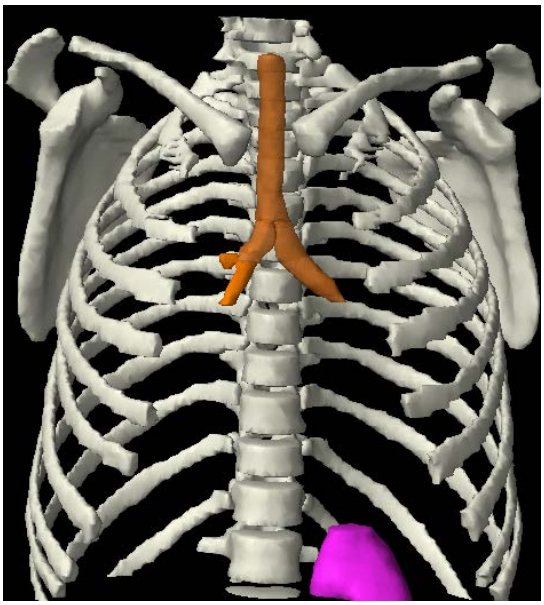


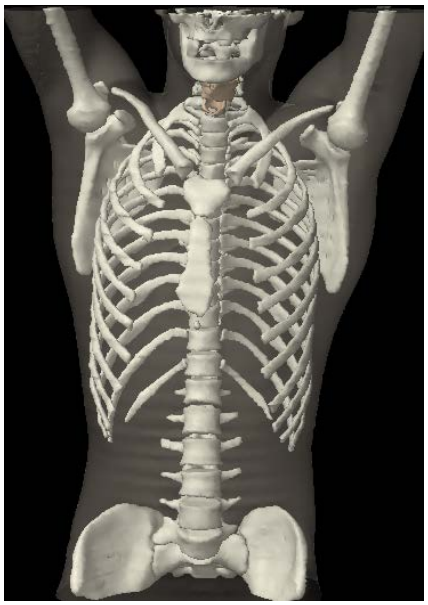
A2. After thoracotomy on the patient described in A1, pathology report shows 1.6 cm nodule of squamous cell carcinoma and 12 negative lymph nodes.

Disease: *Lung Cancer*

Type of Staging _____ **Stage** _____ **T** _____ **N** _____ **M** _____

Click here to reveal Expert Answers and annotated diagram



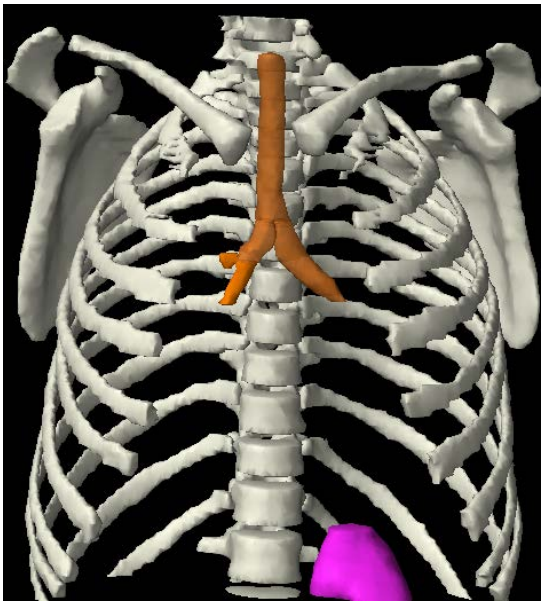


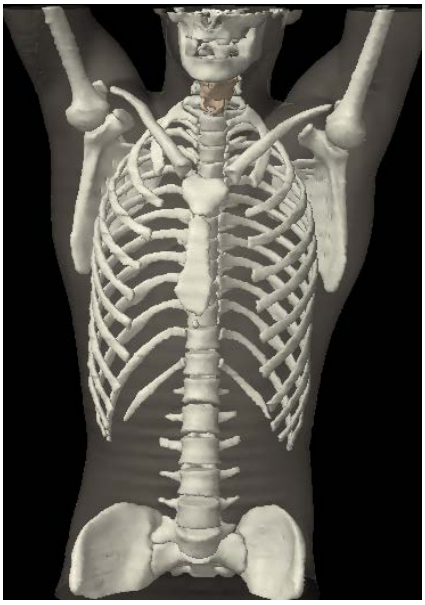
B. After chemotherapy for biopsy proven adenocarcinoma of the right lower lobe of the lung, CT shows 6 cm mass in right lower lung; & right hilar mass which is negative on PET scan. PET/CT and Brain MRI show no evidence of spread beyond the chest. So resection proceeds. Both masses seen are resected; both contain tumor.

Disease: *Lung Cancer*

Type of Staging _____ **Stage** _____ **T** _____ **N** _____ **M** _____

Click here to reveal Expert Answers and annotated diagram



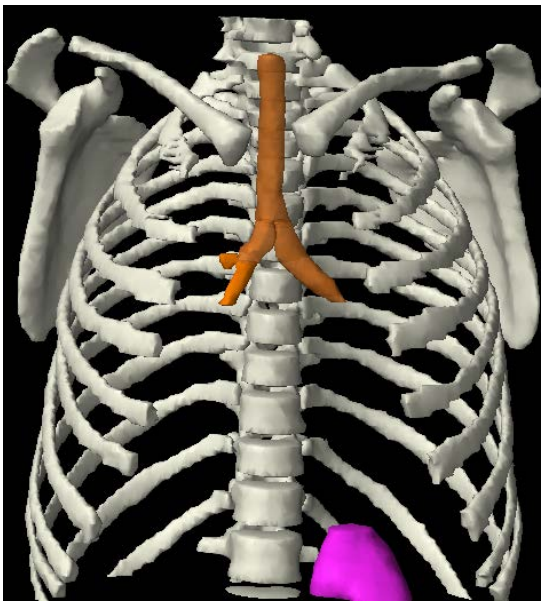


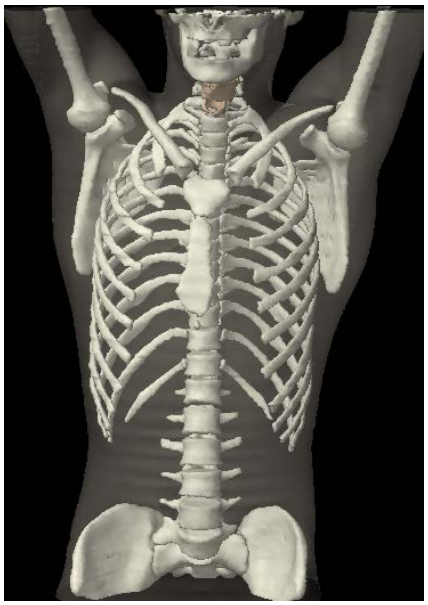
C. 8 cm mass in right lower lung, ipsilateral paratracheal and hilar nodes and needle biopsy of level 7 (subcarinal) node read as small cell carcinoma. Brain MRI is negative, and PET/CT shows no evidence of disease outside the thorax.

Disease: *Lung Cancer*

Type of Staging _____ **Stage** _____ **T** _____ **N** _____ **M** _____

Click here to reveal Expert Answers and annotated diagram



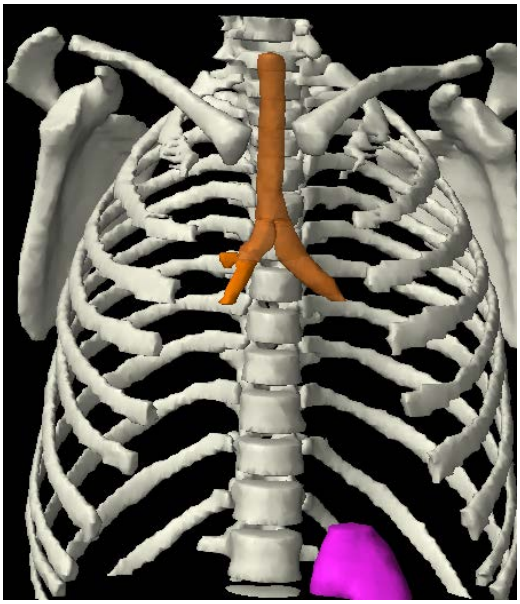


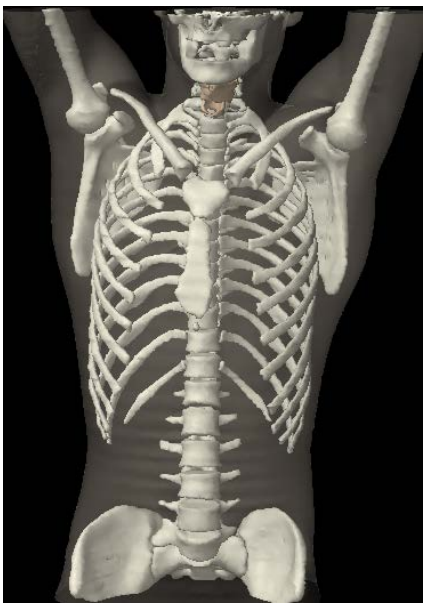
D. 2 cm mass in right lower lobe; needle biopsy of contralateral paratracheal mass performed under endobronchial ultrasonic guidance read as consistent with carcinoma, consistent with squamous cell carcinoma. Brain MRI is negative, and PET/CT shows no evidence of disease outside the thorax.

Disease: *Lung Cancer*

Type of Staging _____ **Stage** _____ **T** _____ **N** _____ **M** _____

Click here to reveal Expert Answers and annotated diagram



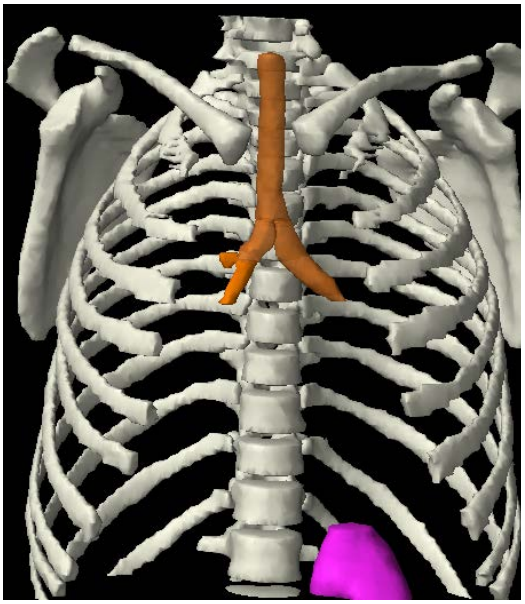


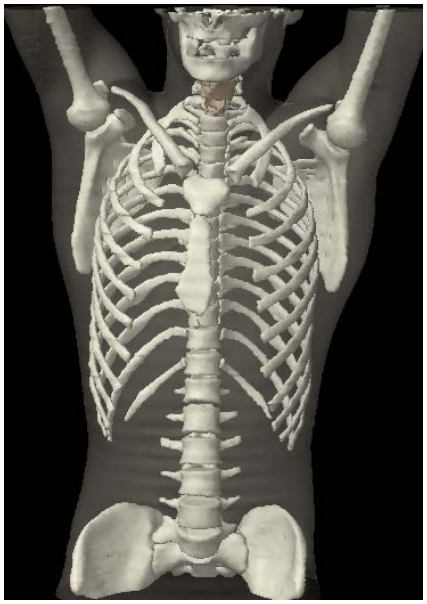
E. Screening CT shows a new 2.5 cm right lower lobe nodule and bilateral supraclavicular masses; the left one, Virchow's node, is palpable and needle biopsy of this mass was read as malignant cells consistent with adenocarcinoma.

Disease: *Lung Cancer*

Type of Staging _____ **Stage** _____ **T** _____ **N** _____ **M** _____

Click here to reveal Expert Answers and annotated diagram





F. Screening CT of a heavy smoker reveals a 1 cm mass in the left upper lobe of the lung, and an enlarged adrenal gland, consistent with metastasis. Needle biopsy of the adrenal gland read as small cell carcinoma. Brain MRI demonstrates many small enhancing lesions in the brain; the largest is the cerebellum, with surrounding edema. And bone scan is positive in the right scapula.

Disease: *Lung Cancer*

Type of Staging _____ **Stage** _____ **T** _____ **N** _____ **M** _____

Click here to reveal Expert Answers and annotated diagram