DIAGNOSIS OF LUNG CANCER

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- Diagnosis of lung cancer can be done by

1) Clinical presentation
2) Investigations
    a) non invasive
    b) invasive

Clinical Presentation

Symptoms	Patients (%)
Cough	45–75
Weight loss	8–68
Dyspnea	37–58
Hemoptysis	27–57
Chest pain	27–49
Hoarseness	2–18

Metastatic Manifestations

- Intrathoracic metastases
  - Superior Vena Cava Syndrome
  - Malignant Pleural Effusion
  - Recurrent Laryngeal Nerve Palsy
  - Phrenic Nerve Palsy
  - Pancoast's Syndrome
  - Horner's Syndrome
  - Involvement of heart and pericardium
  - Involvement of esophagus

- Extrathoracic manifestations
  - Brain metastases
  - Skeletal metstases
  - Adrenal metastases
  - Lymph node metastases
  - Hepatic metastases

Extended Clinical Evaluation

Symptoms Elicited in History
Constitutional—weight loss >10 lb Musculoskeletal—focal skeletal pain Neurologic—headaches, syncope, seizures, extremity weakness, recent change in mental status
Signs Found on Physical Examination
Lymphadenopathy (>1 cm) Hoarseness, superior vena cava syndrome Bone tenderness Hepatomegaly (>13-cm span) Focal neurologic signs, papilledema Soft tissue mass
Routine Laboratory Tests
Hematocrit <40% in males Hematocrit <35% in females Elevated alkaline phosphatase, GGT, AST, calcium

NON INVASIVE INVESTIGATIONS

Sputum Cytology

- The sensitivity and specificity of sputum cytology are 66% and 99%, respectively
- Its accuracy depends on the expertise of the health care team in obtaining the sample (three samples are required), the preservation technique, and the size and location of the lesion. Central lesions are more likely to yield positive cytologic results than are peripheral lesions.
- Sputum cytology should be obtained in all patients with central lesions who are at risk for more invasive biopsy techniques.
- In addition, patients with hemoptysis with or without a mass on chest radiographs should have sputum cytology obtained.

- **Chest Radiography**
- The majority of lung cancers are detected initially by plain chest radiograph.
- In certain situations, the plain film may be sufficient to detect spread to the mediastinum. For example, the presence of bulky lymphadenopathy in the superior or contralateral mediastinal areas may be considered adequate evidence of metastatic disease to preclude further imaging evaluation of the chest.
- The chest radiograph is simply too insensitive a measure of mediastinal lymph node involvement with lung cancer, and thus, further noninvasive or invasive assessment is usually necessary.

- **Computed Tomography of the Chest**
- CT of the chest is the most widely available and commonly used noninvasive modality for evaluation of the mediastinum in lung cancer
- CT is helpful in defining the size, location, and characteristics of the primary mass (e.g., smooth-bordered, spiculated, calcified), the presence or absence of lymphadenopathy and, if performed through the adrenal glands, the presence of abnormalities in the liver and adrenal glands. The bony structures of the thoracic cavity can also be evaluated by chest CT.

- Numerous studies of CT have been performed comparing clinical staging by CT with the "gold standards" of mediastinoscopy or surgery. The results demonstrated that regardless of the lymph node size used as a threshold for defining malignant adenopathy, CT findings in isolation could not be considered as conclusive evidence that lymph nodes were malignant.
- The most widely accepted criterion for an abnormal lymph node is a short-axis lymph node diameter of 1 cm or greater on CT.

- Other criteria used are :

1. A long axis diameter of ≥ 1c m,
2. A short axis diameter of ≥ 1.5 cm,
3. A short axis diameter of ≥ 1 cm plus evidence of central necrosis or disruption of the capsule, and
4. A short axis diameter of ≥ 2 cm regardless of nodal morphology.

- The American College of Chest Physicians (ACCP) compiled the studies assessing the performance characteristics of CT scan for staging the mediastinum in a meta-analytic format.Thirty-five studies were identified, comprising 5111 evaluable patients. **The pooled sensitivity of CT scanning for staging the mediastinum was 51% (95% CI, 47%–54%) and the pooled specificity was 86% (95% CI, 84%–88%).**

- The corresponding positive and negative likelihood ratios were 3.4 and 0.6, respectively, confirming that CT scanning has a limited ability either to rule in or to exclude mediastinal metastasis.
- However, because CT usually guides the selection of nodes for biopsy by mediastinoscopy or needle aspiration, it remains an important diagnostic tool in lung cancer.
- Accurate noninvasive node staging is essential because the choice of individual nodes for sampling by minimally invasive techniques, including transbronchial, transthoracic, or transesophageal needle aspiration, will be directed by the findings of the CT scan.

- The limitation of CT-based mediastinal lymph node evaluation is evident in the fact that 5% to 15% of patients with clinical T1No lesions will be found to have positive lymph node involvement by surgical lymph node sampling.
- the most important message in evaluating the accuracy of CT scanning is that approximately 40% of all nodes deemed malignant by CT criteria are actually benign, depending on the patient population.Specificity can be affected by clinical factors such as the presence of obstructive pneumonitis.

- CT can also be helpful in the evaluation of pleural effusion in patients withlung cancer. The CT scan can indicate the presence or absence of fluid, the contour of the pleural space, and whether or not nodules or masses are present on the pleural surface.
- Given the limitations of the imperfect sensitivity and specificity of CT, it is usually inappropriate to rely solely on the CT scan to determine mediastinal lymph node status. Nonetheless, CT continues to play an important and necessary role in the evaluation of patients with lung cancer and is recommended as part of the evaluation of patients who present with newly diagnosed or suspected lung cancer.

Positron Emission Tomography

- PET is a metabolic imaging technique based on the function of a tissue rather than on its anatomy.
- Lung cancer cells demonstrate increased cellular uptake of glucose and a higher rate of glycolysis when compared with normal cells.
- The radiolabeled glucose analogue [^{18}F]fluoro-2-deoxy-D-glucose (FDG) undergoes the same cellular uptake as glucose but, after phosphorylation, is not further metabolized and becomes trapped in cells.

- Accumulation of the isotope can then be identified using a PET detector.
- Specific criteria for an abnormal PET scan are either a standard uptake value of greater than 2.5 or uptake in the lesion that is greater than the background activity of the mediastinum.
- It has proved useful in differentiating neoplastic from normal tissues.

- In 2865 evaluable patients, the pooled estimates of sensitivity and specificity for identifying mediastinal metastasis were 74% (95% CI, 69%–79%) and 85% (95% CI, 82%–88%), respectively.
- Corresponding positive and negative likelihood ratios for mediastinal staging with PET scanning were 4.9 and 0.3, respectively.
- These findings demonstrate that PET scanning is more accurate than CT scanning for staging of the mediastinum in patients with lung cancer, though PET is far from perfect.

- Whereas a negative mediastinal PET may obviate the need for mediastinoscopy prior to thoracotomy in certain situations, a positive mediastinal PET should not negate further evaluation or the possibility of resection.
- In the latter case, lymph node sampling should still be pursued because the possibility of a false-positive PET scan cannot be ignored.

- It should be remembered that PET is primarily a metabolic examination and has limited anatomic resolution. It is possible for PET to identify lymph node stations but not individual lymph nodes.
- CT scanning provides much more anatomic detail but lacks the functional information provided by PET.

Disadvantages

- the technique is not infallible because certain non-neoplastic processes, including granulomatous and other inflammatory diseases as well as infections, may also demonstrate positive PET imaging.
- Furthermore, size limitations are also an issue, with the lower limit of resolution of the study being approximately 7 to 8 mm depending on the intensity of uptake of the isotope in the abnormal cells. One should not rely on a negative PET finding for lesions less than 1 cm on CT scan.

- Newer technology includes CT/PET fusion, a single machine that incorporates CT and PET during the same scan.
- This allows the clinician to obtain anatomic (CT) and functional (PET) images simultaneously. Early work suggests improvement in the number of patients correctly staged with this modality over CT or PET alone.
- The future of PET in lung cancer may also include its use to evaluate response to treatment.

Magnetic Resonance Imaging

- There are very few circumstances in which magnetic resonance imaging (MRI) is a useful tool in staging lung cancer.
- However, MRI can be useful in evaluating superior sulcus tumors, especially for possible invasion of the brachial plexus, and for evaluating vertebral invasion.

Adrenal and Hepatic Imaging

- For adrenal masses, CT, MRI, percutaneous biopsy, and even adrenalectomy can be used to help delineate benign from malignant disease.
- Well-defined, low-attenuation (fatty) lesions with a smooth rim on unenhanced CT are more likely to be benign adenomas,but the CT appearance of many lesions is insufficiently distinctive.

- Follow-up scanning with repeat CT, serial ultrasonography, MRI (especially with chemical shift and dynamic gadolinium-enhanced techniques), or 6-β-iodo-^{131}I-methyl-norcholesterol scanning can sometimes help with the critical distinction between metastatic disease and adenoma.
- Percutaneous adrenal biopsy is a relatively safe and effective means of achieving a definitive diagnosis in doubtful cases and is especially important when the histology of the adrenal mass will dictate subsequent management.

- Most liver lesions are benign cysts and hemangiomas, but contrast CT (or ultrasound) is often required to establish a likely diagnosis.
- Percutaneous biopsy can be performed when diagnostic certainty is required.

INVASIVE TECHNIQUES

Mediastinoscopy

- Mediastinoscopy remains the gold standard for invasively staging the mediastinum in patients with known or suspected lung cancer.
- Mediastinoscopy is most often used to sample nodes of the paratracheal (station 4), and anterior subcarinal (station 7) region.
- The subcarinal area is more difficult to sample and thus has a lower yield.

- An extended cervical mediastinoscopy can be carried out to reach aortopulmonary and para-aortic lymph nodes (stations 5 and 6) by using the same cervical incision as mediastinoscopy but dissecting into a different fascial plane.
- Alternatively, an anterior mediastinotomy (the so-called Chamberlain procedure) may be needed to sample lymph nodes in these aortopulmonary and para-aortic locations (stations 5 and 6).

- Overall, mediastinoscopy has a reported sensitivity of 78%, with a specificity of 100%.
- Mediastinoscopy may also be able to differentiate between stage IIIA and IIIB mediastinal involvement.
- As with any surgical procedure, mediastinoscopy has risks and limitations. It requires general anesthesia, with a morbidity of 2% and a mortality of 0.08%

Transthoracic Needle Aspiration

- Transthoracic needle aspiration (TTNA), usually under CT or fluoroscopic guidance, is an expedient and relatively safe way to diagnose the primary tumor mass and establish a diagnosis of lung cancer.
- As a general rule, if a lesion is less than 3 cm in size and lateral to the midclavicular line, bronchoscopy would not be the diagnostic procedure of choice. TTNA should be considered under such circumstances if tissue diagnosis is necessary.
- The sensitivity and specificity of TTNA are 90% and 97%, respectively

- TTNA may be essential only in certain situations:

1. patients who are poor surgical candidates but who require tissue diagnosis prior to treatment,
2. patients in whom a noncancerous lesion is strongly suspected,
3. patients who request that a diagnosis of cancer be confirmed prior to considering surgery, and
4. patients with high likelihood of metastatic disease.

- One drawback of TTNA is the risk of pneumothorax. Several investigations have reported a 22% to 45% risk of pneumothorax for CT-guided TTNA.
- Although pneumothorax may lead to hemodynamic compromise without therapeutic tube thoracostomy, in most cases of pneumothorax secondary to TTNA, treatment is not required.
- The primary factors shown to increase the risk or incidence of pneumothorax are the presence of emphysema, a smaller lesion size, and a greater depth of needle penetration from the pleural surface to the edge of the lesion.

Fiberoptic Bronchoscopy

- Patients with known or suspected lung cancer may have symptoms due to endobronchial involvement that require airway inspection with bronchoscopy: shortness of breath, unilateral wheezing, hemoptysis, and cough.
- Endobronchial lesions can be visualized easily and biopsied through a flexible bronchoscope.
- The yield with three or more biopsies should approach 100% for centrally located lesions.

- Data from 4507 patients revealed that central endobronchial biopsies provide the highest sensitivity (74%), followed by brushings brushing (61%) and washings (47%). The combination provides a diagnosis in 88% of cases.

- When lung cancer presents with submucosal infiltration or extrinsic compression from peribronchial disease, endobronchial forceps biopsy has a lower yield (55%) than transbronchial needle aspiration (TBNA) (71%).
- In these situations, normal mucosal markings are often obscured and the surface is replaced with bronchial collateral vessels and firmer surface tissue, which may have to be penetrated to reach malignant cells.
- In addition, peribronchial tumor may be inaccessible to biopsy forceps. TBNA can be more effective if the lesion is close enough to the tracheobronchial tree to be encountered with a 1.3- to 1.5-cm-long needle.

Transbronchial needle aspiration (TBNA)

- The use of TBNA in staging lung cancer has been reported to be both sensitive and specific in diagnosing spread of cancer to lymph nodes.
- The overall sensitivity of TBNA for NSCLC is 78%, and the specificity is 99%.

- The standard method of performing TBNA starts with a CT scan of the chest to guide needle aspirations toward the most involved group of lymph nodes.
- Lesions localized by a CT scan can be accessed with bronchoscopy by measuring the number of CT slices above or below the carina (or other airway landmarks) and placing the needle the required distance above or below the landmark corresponding to that number of CT slices.

- It has been shown that a plateau in yield for malignancy is achieved after seven passes with the needle through a lymph node.
- The importance of having a qualified and experienced cytopathologist on site cannot be overemphasized. Thorough interpretation by such individuals who are available for rapid on-site evaluation has been shown to enhance yield from TBNA.

- All samples should contain a preponderance of lymphocytes to define true nodal sampling. Specimens without lymphocytes should be deemed unsatisfactory, and the presence of respiratory epithelium should raise concerns about contamination.
- TBNA allows for minimally invasive sampling of the mediastinum and hilar lymph nodes and potentially avoids more invasive procedures such as mediastinoscopy, mediastinotomy, and open thoracotomy.

Endoscopic Ultrasound

- Endoscopic ultrasound (EUS) is another modality that has significantly impacted lung cancer staging, primarily due to its superior ability to sample the posterior mediastinum through the esophageal wall.
- Currently, EUS with fine-needle aspiration is performed using real-time ultrasound.
- In pooled analysis of more than 1000 patients with lung cancer and mediastinal adenopathy, EUS has a sensitivity and specificity of 84% and 99.5%, respectively

- In patients with lung cancer who have no adenopathy seen on CT scan, EUS has been shown to sample nodes as small as 3 mm in diameter. This is useful given the high incidence of metastasis found in normal-sized lymph nodes in lung cancer.

- Lymphatic pathways favor spread to aortopulmonary window nodes from left upper lobe tumors and to subcarinal nodes from left and right lower lobe lesions.
- EUS has been studied in patients with known lung cancer without enlarged mediastinal lymph nodes on CT, and it has detected mediastinal involvement (stage III or IV disease) in up to 42% of cases.

- In addition, EUS has the advantage of being able to stage lung cancer from locations outside the mediastinum.
- The left lobe of the liver, a substantial part of the right lobe of the liver, and the left (but not the right) adrenal gland can be identified and sampled in 97% of patients.
- In addition, left pleural effusions can be visualized and sampled during an EUS procedure.
- EUS is increasingly being combined with endobronchial ultrasound (EBUS) for minimally invasive staging of lung cancer

Endobronchial Ultrasound

- Perhaps the greatest addition in the armamentarium for staging lung cancer is endobronchial ultrasound with fine-needle aspiration (EBUS-TBNA).
- EBUS-TBNA is indicated for the assessment of mediastinal and hilar lymph nodes and diagnosis of lung and mediastinal tumors.

- It can be used to sample the highest mediastinal (station 1), the upper paratracheal (station 2R, 2L), the lower paratracheal (station 4R, 4L), the subcarinal (station 7), as well as the hilar (station 10), and the interlobar (station 11) lymph nodes.
- The para-aortic (station 6), aortopulmonary window or subaortic (station 5), paraesophageal (station 8), and pulmonary ligament (station 9) lymph node stations are usually not accessible by this technique.

- Pooled analysis of nearly 1000 patients shows that EBUS-TBNA has a sensitivity and specificity of 90% and 100%, respectively.
- The combination of EUS and EBUS has shown better yield than either technique alone and may provide near-complete access to the mediastinum for staging, even in the radiologically normal mediastinum.

2015 WHO Classification of Lung Tumors

Histologic Type and Subtypes :

Epithelial tumors

1. Adenocarcinoma

a) Lepidic adenocarcinoma*e*
b) Acinar adenocarcinoma
c) Papillary adenocarcinoma
d) Micropapillary adenocarcinoma*e*
e) Solid adenocarcinoma
f) Invasive mucinous adenocarcinoma*e*

- Mixed invasive mucinous and
- nonmucinous adenocarcinoma

a) Colloid adenocarcinoma
b) Fetal adenocarcinoma
c) Enteric adenocarcinoma
d) Minimally invasive adenocarcinoma

- Nonmucinous
- Mucinous

a) Preinvasive lesions

- Atypical adenomatous hyperplasia
- Adenocarcinoma in situ
  - Nonmucinous
  - Mucinous

2. Squamous cell carcinoma

- Keratinizing squamous cell carcinoma
- Nonkeratinizing squamous cell carcinoma
- Basaloid squamous cell carcinoma
- Preinvasive lesion

a) Squamous cell carcinoma in situ

3. Neuroendocrine tumors

- Small cell carcinoma
- Combined small cell carcinoma
- Large cell neuroendocrine carcinoma
- Combined large cell neuroendocrine carcinoma

4. Carcinoid tumors
   - Typical carcinoid tumor
   - Atypical carcinoid tumor
5. Preinvasive lesion
   - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
6. Large cell carcinoma
7. Adenosquamous carcinoma
8. Sarcomatoid carcinomas
   - Pleomorphic carcinoma
   - Spindle cell carcinoma
   - Giant cell carcinoma
   - Carcinosarcoma
   - Pulmonary blastoma

9. Other and Unclassified carcinomas

- Lymphoepithelioma-like carcinoma
- NUT carcinoma*e*

10. Salivary gland-type tumors

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Epithelial-myoepithelial carcinoma
- Pleomorphic adenoma

11. Papillomas

- Squamous cell papilloma
  - Exophytic
  - Inverted
- Glandular papilloma
- Mixed squamous and glandular papilloma

12. Adenomas

- Sclerosing pneumocytoma
- Alveolar adenoma
- Papillary adenoma
- Mucinous cystadenoma
- Mucous gland adenoma

Mesenchymal tumors:

- Pulmonary hamartoma
- Chondroma
- PEComatous tumors
  - Lymphangioleiomyomatosis
  - PEComa, benign
  - Clear cell tumor
  - PEComa, malignant
- Congenital peribronchial myofibroblastic tumor
- Diffuse pulmonary lymphangiomatosis

- Inflammatory myofibroblastic tumor
- Epithelioid hemangioendothelioma
- Pleuropulmonary blastoma
- Synovial sarcoma
- Pulmonary artery intimal sarcoma
- Pulmonary myxoid sarcoma with *EWSR1–CREB1 translocation*
- Myoepithelial tumors
  - Myoepithelioma
  - Myoepithelial carcinoma

Lymphohistiocytic tumors:

- Extranodal marginal zone lymphomas of mucosa-associated
- Lymphoid tissue (MALT lymphoma)
- Diffuse large cell lymphoma
- Lymphomatoid granulomatosis
- Intravascular large B cell lymphoma
- Pulmonary Langerhans cell histiocytosis
- Erdheim–Chester disease

Tumors of ectopic origin

- Germ cell tumors
  - Teratoma, mature
  - Teratoma, immature
- Intrapulmonary thymoma
- Melanoma
- Meningioma, NOS

Metastatic tumors

THANK YOU