PI Session: 2021.08.13_FDT_Radiology Overview: Imaging of Lymph Nodes and Lymphoma Preparatory_Marcus John Julius, M.D.

Objectives: At the end of this session, students will be able to:
1. Describe the components of an x-ray imaging system and their contribution to the creation of radiographs.
2. Differentiate normal mediastinal and hilar appearance from mediastinal widening and hilar enlargement.
3. Discuss the most important interaction of ultrasound waves with matter (along with the principles necessary for image creation).
4. Compare and contrast the sonographic appearance of normal and abnormal lymph nodes.
5. Classify the CT appearance of different types of matter in order from hypodense to hyperdense (using this information to differentiate cystic and calcified lymph nodes).
6. Explain the physiologic mechanism essential to the production of a PET scan (and its role in the assessment of lymphoma).

Overview: Good news! This preparatory document serves, in part, to review the essential concepts of a multitude of imaging modalities (first introduced in M1 year). Your M2 imaging lectures will also introduce the appearance of a variety of pathologic conditions on multiple imaging modalities.

Note: Please use the differential diagnoses (D/D) included in your imaging lectures as a ***reference*** upon which to build throughout M2 year. There is no need to memorize D/D for any given PI imaging session. Rather, it is my goal to help you create and expand your imaging differentials as you gain experience throughout your M2 year.

-**Imaging modalities**: Vital to the practice of radiology. These modalities are based on a wide variety of energy sources (including x-rays, radionuclides, ultrasound, and nuclear magnetic resonance).
- -General radiology (and its subsets): uses x-rays to image tissues and organs
  - -*Radiographs* (commonly referred to as 'x-rays').
  - -*Fluoroscopy*: use of x-rays to obtain real-time moving images of internal structures
  - -*Angiography*: radiography of blood vessels
    - -*Arteriography*: images of arteries
    - -*Venography*: images of veins
  - -*Arthrography*: radiography of joints
- -Ultrasonography: uses of high-frequency sound waves to produce images of tissues and organs
- -Nuclear medicine: uses radioactive isotopes to image anatomic and physiologic processes
- -Computerized axial tomography (CT): uses x-rays (taken at different angles around the body) and computer processing to create cross-sectional images of the body
- -Magnetic resonance imaging (MRI): uses a large magnet and radio waves to create multi-planar images of the body

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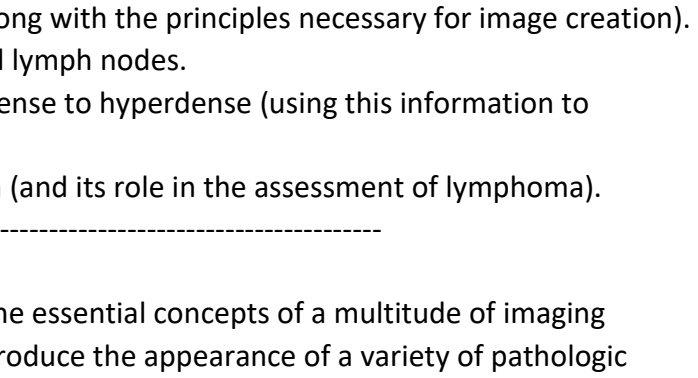
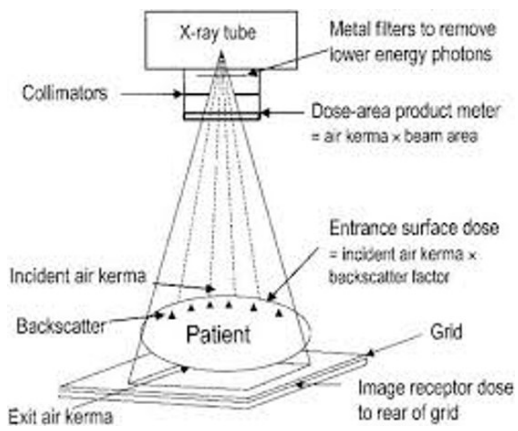
General radiology

-**PHYSICS**: X-ray production involves the use of an x-ray tube.



- -**X-ray tube**: Works as a *converter*:
  - -Receives electrical energy…Produces heat (99%) and x-rays (1%)
  - -*Cathode*: Source of electrons for x-ray generation. Often tungsten (W) filament
  - -*Anode*: Conversion of electron energy into x-rays-AND-Dissipation of heat. Commonly tungsten (W) or tungsten/rhenium alloy (W/Re)
  - -Electrons are accelerated from cathode to anode across high voltage (kV)
  - -Two different types of x-rays may be produced
    - -Bremsstrahlung x-rays
    - -Characteristics x-rays

-**Additional components of x-ray imaging**



- -*Filter*: Aluminum, copper, or other absorber placed in an x-ray beam path to preferentially absorb low-energy x-rays.
- -*Collimation*: Restriction of an x-ray beam (limits area of exposure)
- -*Grid*: Strips of lead (in a radiolucent matrix) used to reduce scatter radiation prior to its arrival at an image receptor
- -*Image receptor*: Site of capture, display, and storage of image
  - -Analog: film/screen; Digital: Detectors which convert x-ray input into digital signal

X-RAY INTERACTION WITH MATTER

Production and Appearance of Images

-'*Film Blackening'*: The more readily x-rays pass through matter, the more they reach the detector/film (and the more they 'darken' the film).

-X-rays pass most readily through *gas* (i.e., gas is the 'darkest' density on film, *BLACK*)

-*The converse*: The more readily x-rays are removed from a beam as they pass through matter (i.e. attenuated by photoelectric effect and scatter), the less they reach the detector/film (and the less they 'darken' the film)

-Dense materials and materials of higher atomic number attenuate the x-ray beam

-*Metals* are the 'brightest' density on film, *WHITE*)

-**Spectrum from black…to…white on film or detector:**

- Gas (black) > Fat (Dark gray) > Water/soft tissue (Gray) > Bone (Off White) > Metal (White)

TERMINOLOGY

-*Radiolucent*: Black.

-*Radiopaque*: White

-*Contrast*: The ability to differentiate tissues based on their different radiographic densities (i.e. shades of gray)

-*Contrast media*: Substances administered to enhance the body's inherent density difference

-Intravenous (IV). Intra-arterial. By mouth (PO). By rectum (PR). Intra-articular. Intra-thecal

ADVANTAGES OF GENERAL RADIOGRAPHY

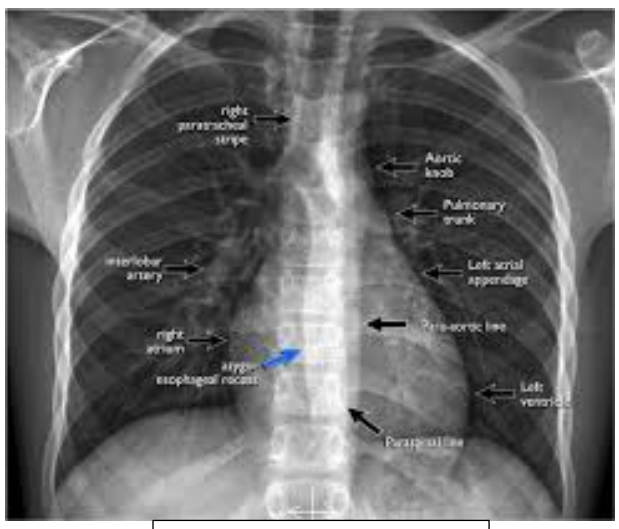
-Cost-effective

-Useful starting point (i.e. may direct further testing)

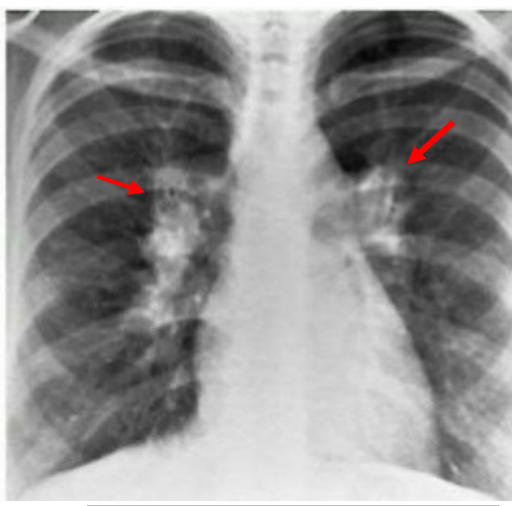
DISADVANTAGES OF GENERAL RADIOGRAPHY

-Exposure to ionizing radiation

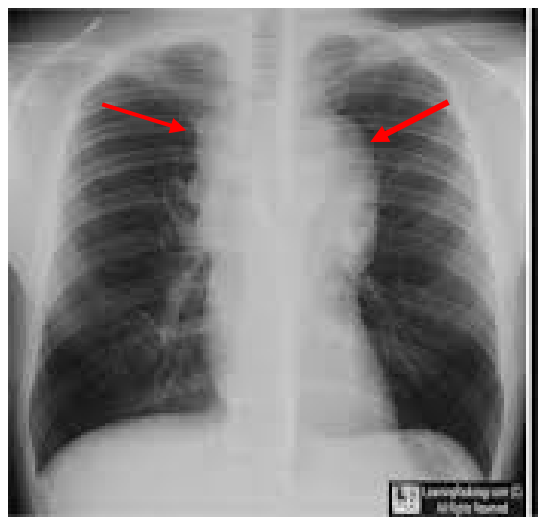
-Limited assessment of soft tissue detail



Normal CXR



Bilateral hilar enlargement (Learningradiology.net)



*Mediastinal widening (*Slideshare.com)

Differential diagnosis of bilateral hilar enlargement

-Sarcoidosis

-Infection (tuberculosis, mycoplasma, histoplasmosis)

-Malignancy (**lymphoma**; carcinoma)

-Inorganic dust disease (silicosis)

-Pulmonary arterial hypertension

Differential diagnosis of mediastinal widening

-Lymph node enlargement (see next D/D)

-Traumatic aortic injury/thoracic aortic aneurysm/Vascular anomalies

-Mediastinal masses (anterior, middle, posterior compartments): Discussed in Pulmonary Module

-Lipomatosis

-Pneumomediastinum

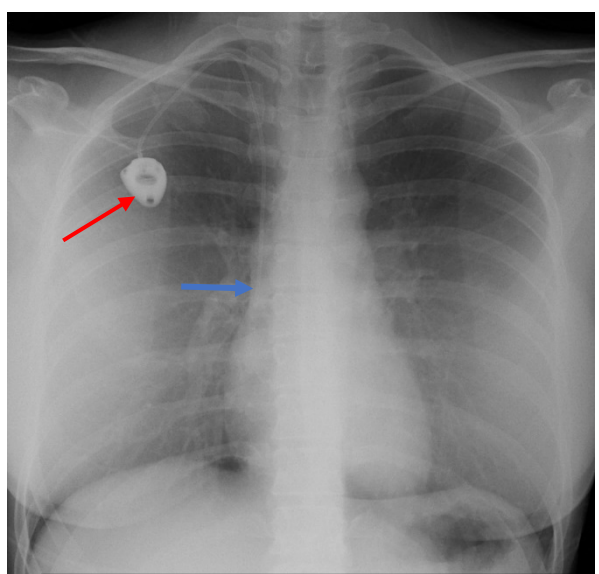
Differential diagnosis of mediastinal lymph node enlargement

-Sarcoidosis

-Malignancy (primary lung cancer; metastatic esophageal/breast/thyroid cancer; **lymphoma**)

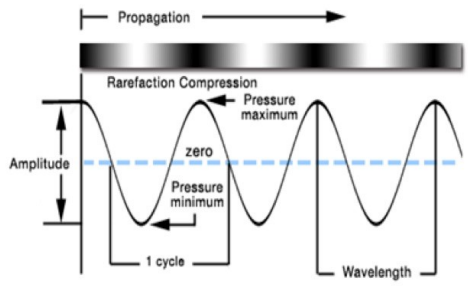
-Infection (tuberculosis; histoplasmosis)

-Occupational lung disease (silicosis, coal worker's pneumoconiosis



Right internal jugular central line (port at red arrow), tip in superior vena cava (blue arrow) (Radiopaedia.org)

Ultrasonography



Ultrasound waves

-Mechanical disturbance traveling through a medium

-*Wavelength*: distance between successive waves

-*Frequency*: number of oscillations per second (in hertz, Hz)

-Ultrasound frequency is higher than audible sound

-Audible sound frequencies: 15Hz-20,000Hz

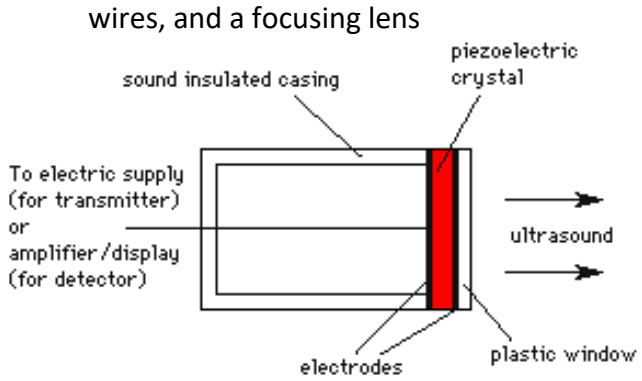
-Ultrasound frequencies: greater than 20,000Hz

-*Velocity* of sound (in medium) = Frequency x wavelength

Production of ultrasound

-*Transducer*: device that converts one form of energy to another form of energy

-*Ultrasound transducer* (**see below**) is comprised of high-quality crystals, a backing material, electrode wires, and a focusing lens



-Converts electrical energy into ultrasound waves via the '**piezoelectric (i.e. 'pressure electricity') effect**

-High frequency voltage oscillations cause a high-quality crystal to change shape, which alters the pressure in front of the transducer (producing ultrasound waves)

-Electricity…to…pressure (as a '*transmitter*')

-Returning echoes (i.e. reflected sound) subject the crystal to changes in its shape. These pressure changes are then converted to electrical signals (and ultimately an image)

-Pressure…to…electricity (as a '*receiver*')

ULTRASOUND INTERACTION WITH MATTER

-***Reflection*** *(most important interaction of US with matter)*

-Sound *reflected* at a tissue interface forms an echo, which is used to create an image

-Degree of reflection is based on both *angle of incidence* and *acoustic impedance* of tissues

-Angle of incidence equals angle of reflection

-Acoustic impedance = density of medium x velocity of sound in medium

-*The greater the degree of acoustic impedance difference at a tissue-tissue boundary, the greater the degree of wave reflection*

-*Refraction*, *Attenuation* (i.e. *Scatter* and *Absorption*) also contribute to the creation of the sonographic image

TERMINOLOGY

– '*Echoic*': root word

-Prefixes describe the underlying echogenicity (from 'black' to 'white')

– '*an*', '*hypo*', '*iso*' (better yet, intermediate), and '*hyper*.

ADVANTAGES OF ULTRASONOGRAPHY

-No ionizing radiation

-Infinite imaging planes

-Dynamic imaging (i.e. vascular assessment; fetal assessment)

DISADVANTAGES OF ULTRASONOGRAPHY

-User-dependent

-Limited assessment of osseous structures. Bowel gas often obscures detail

SONOGRAPHIC FEATURES OF A NORMAL LYMPH NODE

-Oval (short axis-to-long axis ratio, S/L, <0.5)

-Size depends on region of body

-Mediastinal lymph nodes: 10mm short axis (upper limit of normal)

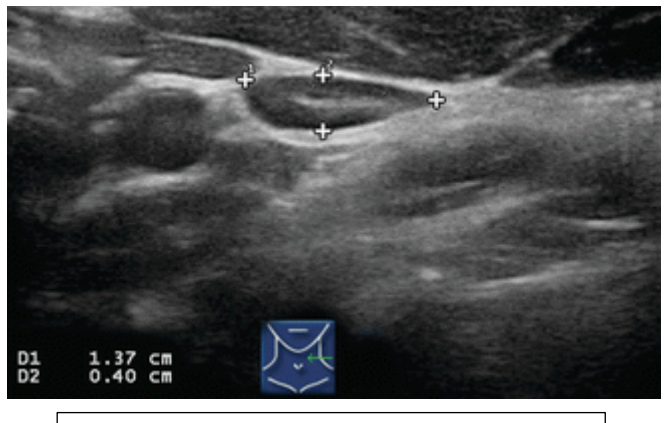
-Mesenteric lymph nodes: 5mm short axis (upper limit of normal)

-*Hypoechoic* to adjacent muscles

-Concentric outer cortex (<3mm)

-*Echogenic* (fatty) hilum, with central vascularity

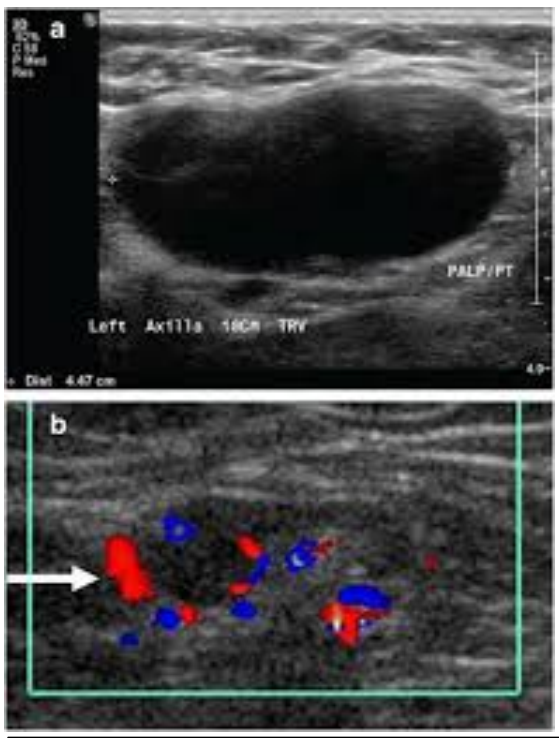
-Well-defined margins



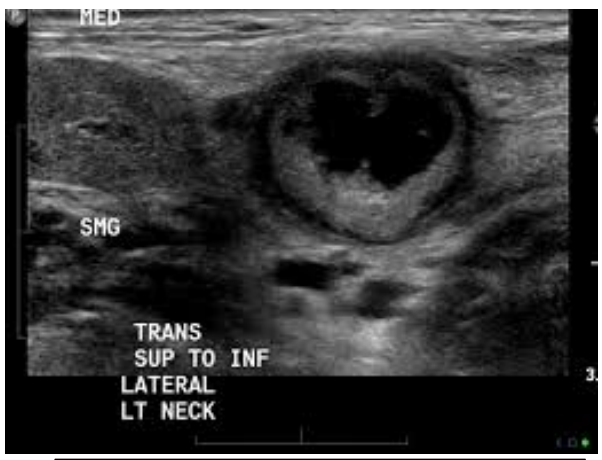
Normal lymph node (RadiologyKey.com)

SONOGRAPHIC FEATURES ASSOCIATED WITH AN ABNORMAL LYMPH NODE:

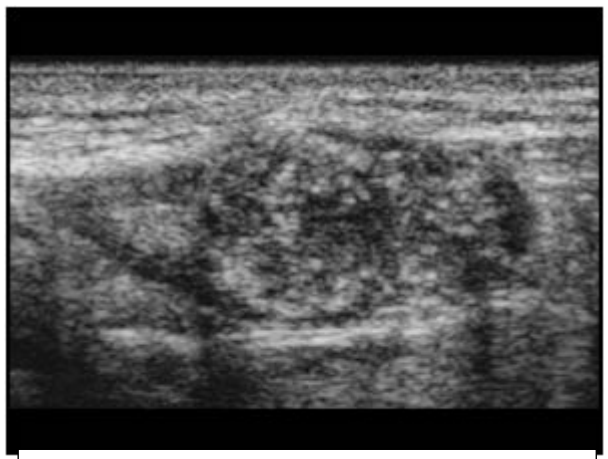
-Round (short axis-to-long axis ratio, S/L, >0.5)
-Enlargement (>10mm short axis, depending on location)
-May be more hypoechoic than normal
    -Cystic necrosis, however, can occur (with sites of *anechogenicity*)
    -Microcalcifications and heterogeneous echogenicity may also occur (with sites of *hyperechogenicity*)
-Eccentric, thickened cortex (>3mm)
-Loss of fatty hilum
-Ill-defined margins
-Prominent non-hilar, cortical blood flow
Note: Reactive/hyperplastic lymph nodes are associated with infection/inflammation
    -Enlarged lymph nodes (often with surrounding edema)
    -More prominent hilar blood flow than normal



Hypoechoic; Loss of fatty hilum;
Mixed peripheral/central vasculature (in axillary lymph node, secondary to metastatic breast cancer)
(Researchgate.com)

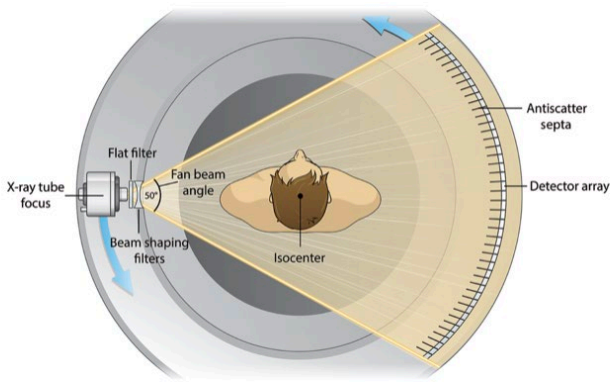


Cystic necrosis (in cervical lymph node), secondary to squamous cell carcinoma
(Radiopaedia.org)

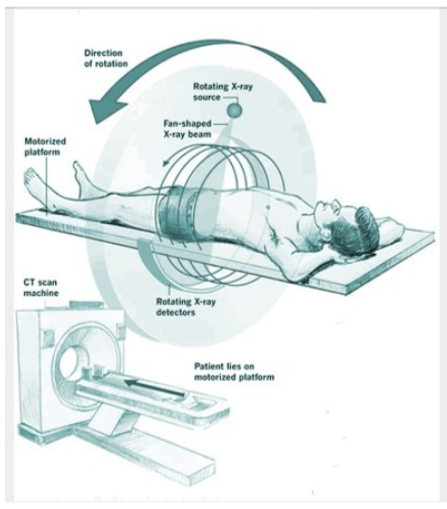


Heterogeneously, hyperechoic lymph node (with punctate calcification), secondary to papillary thyroid carcinoma
(Ultrasoundcase.info)

COMPUTERIZED AXIAL TOMOGRAPHY



-Components of X-ray tube and detector array (in a CT unit)
    -*X-ray tube*: source of x-rays
    -*Filters*: tailors the beam quality (by absorbing low energy x-rays)
        shapes the beam (which is referred to as 'fan-shaped' beam)
    -*Anti-scatter septa*: positioned between detector elements
    -*Detector array*: scintillators (produce light when x-ray photons are absorbed)



-*Image acquisition*
    -Axial scanning: table and patient are stable, while x-ray tube rotates through 360 degrees (then table moves an increment…followed by another tube rotation)
    -Helical/spiral scanning: table/patient move linearly, while x-ray tube rotates thorough 360 degrees

CT IMAGING INTERACTION WITH MATTER

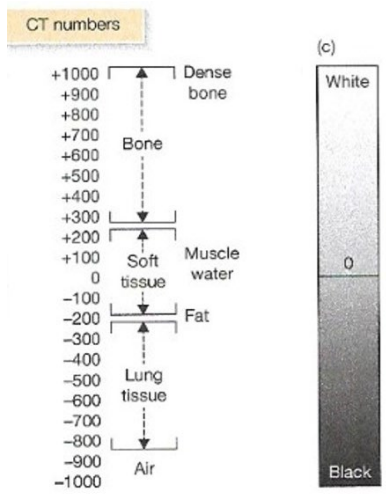
-Since CT imaging utilizes x-rays, the very same concepts involving x-ray interaction with matter hold true for CT imaging.

- *The more readily x-rays pass through matter, the less than are attenuated.*

-*Gas permits x-rays to pass through most readily*

-*The more readily x-rays are removed from a beam as it passes through matter (i.e. by photoelectric effect and scatter), the more they are attenuated.*

-Dense materials and materials of higher atomic number attenuate the x-ray beam



-Hounsfield units (HU) or CT numbers: the attenuation of a material relative to the attenuation of water (0 HU)

-Negative HU: matter attenuates x-rays LESS THAN water

-Air: (-1000 HU)

-Fat: (-100 HU)

-Positive HU: matter attenuates x-rays MORE THAN water

-Soft tissue: (+ 50 HU)

-Bone (+1000 HU)

-CT spectrum from negative HU to positive HU: *Objective*

Gas (-1000 HU) <Fat (-100 HU) < Water (0 HU) <Soft tissue (+50 HU) <Bone (1000 HU) < Metal (>1000HU)

TERMINOLOGY

-Density

-hypodense (or of decreased density): lower HU

-hyperdense (or of increased density): higher HU

LYMPHADENOPATHY

-'Disease of lymph nodes' (by strict definition)

-abnormal number

-abnormal internal architecture (i.e. infiltration, necrosis, calcification)

-*enlargement* (although, *technically*, this is termed *lymphadenomegaly)*

-Abnormal lymph nodes are not always enlarged (micrometastases)

-Enlarged lymph nodes may be reactive (representing an inflammatory response, not pathology in the lymph node itself)

CT IMAGING OF LYMPH NODES

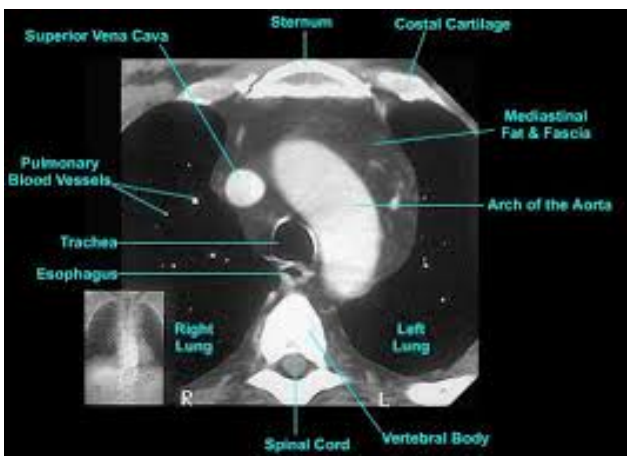
-Size assessment (of individual nodes and conglomerations of nodes)

-Density, measured in Hounsfield units (HU): HU values are estimates

-Normal lymph nodes have soft tissue density: Average 70 HU

-Low density (cystic or necrotic nodes: Less than 50 HU)

-High density (calcified and enhancing nodes: Greater than 100 HU)



Normal mediastinal CT
(Aboutcancer.com)

ADVANTAGES OF CT IMAGING

-Optimal soft tissue differentiation

-Excellent osseous detail

-Submillimeter imaging with potential for multiplanar reconstruction

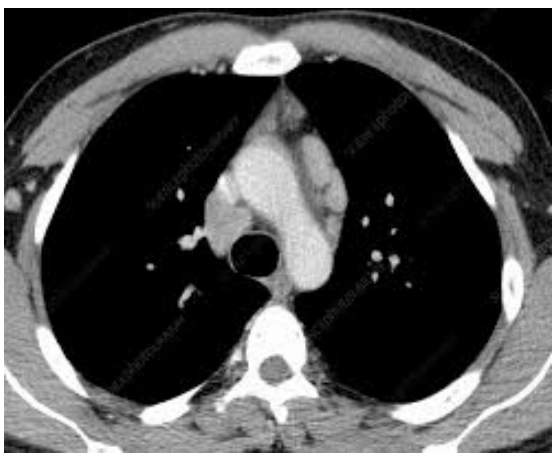
-3-dimensional imaging

-Fast scanning techniques

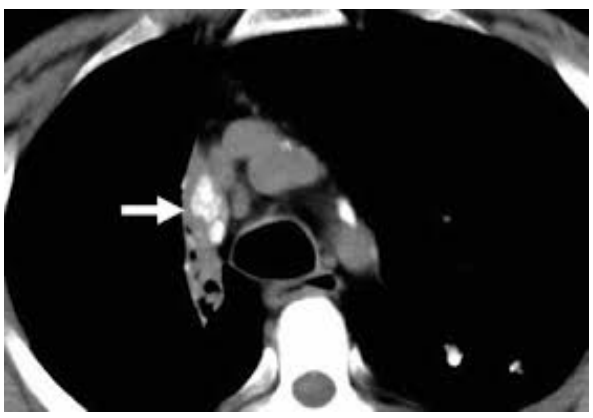
DISADVANTAGES OF CT IMAGING

-Exposure to ionizing radiation

-Cost

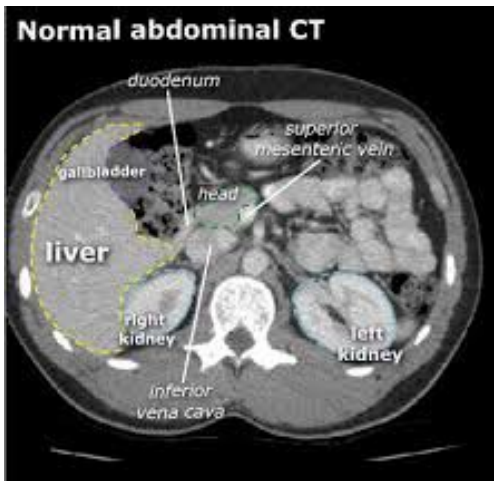


Hodgkin Lymphoma
(Sciencephoto.com)



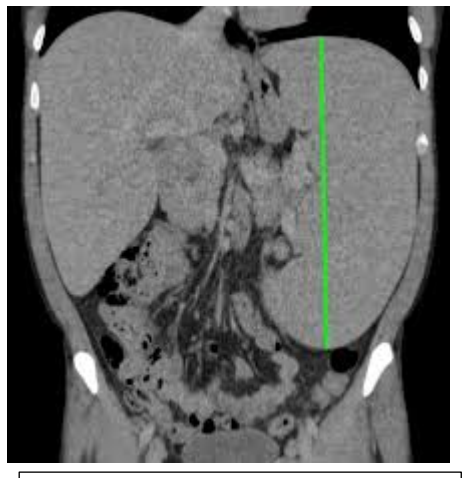
Calcified mediastinal lymph nodes
(secondary to tuberculosis)
(Insightsintoimaging.com)

Necrotic mediastinal LAP (secondary to metastatic squamous cell carcinoma)



Normal abdominal CT
(AnatomyNote.com)

Non-Hodgkin Lymphoma (with splenomegaly)
(ResearchGate.com)



Splenomegaly
(Radiopaedia.org)

Differential Diagnosis of Lymphadenopathy

-Infection (acute, chronic)
-Neoplasia (lymphoma, metastases)
-Autoimmune
-Drug-induced
-Idiopathic

Differential Diagnosis of Low Density (Cystic/Necrotic) Lymph Nodes

-Metastatic carcinoma (SCC)
-Lymphoma
-Infection (TB, fungus)

Differential Diagnosis of High Density (Calcifications/Inorganic material) Lymph Nodes

-Granulomatous infection (TB, histoplasmosis)
-Sarcoidosis
-Amyloidosis
-Treated lymphoma
-Inhalation lung disease (coal worker's pneumoconiosis, silicosis)
-Metastases (papillary thyroid, bronchogenic, breast, mucinous ovarian/colonic, osteosarcoma)

Splenomegaly

Greater than 12cm in length on imaging

Differential diagnosis

-Hematologic
-Hemodynamic
-Infection
-Storage diseases
-Neoplasia
-Trauma

NOTE: The Lugano classification system for staging of lymphoma includes lesion measurement guidelines (i.e. eligible lymph node and extranodal lesions). Detailed discussion of lesion selection and measurement is beyond the scope of this document.

Nuclear Medicine

Nuclear medicine utilizes the introduction of radioactive substances into the body to assess structure and function. It can assist with the diagnosis and potential treatment of disease.

INTERACTION WITH MATTER (PET scan)

-*Metabolism*: F^{18} fluorodeoxyglucose (FDG), a positron-emitting isotope (T ½ of F^{18}: 110 minutes)

-F-18 fluorodeoxyglucose (FDG) is administered via IV

-Cells with high metabolic rate (i.e. tumor cells) take up and metabolize F-18 FDG

-FDG is metabolized to FDG-6-phosphate (which cannot be further metabolized by tumor cells)

-FDG-6-phosphate accumulates in tumor cells (and is detected and quantified)

-Nuclear medicine images may be 'fused'/merged with CT or MRI images (for more optimal structural/functional assessment): **See images below**

- Beta plus (B+) decay or positron emission

-A proton inside the nucleus is converted into a neutron; a positron (positively-charged electron) is emitted

-Positron loses its kinetic energy and annihilates with an electron

-Mass of positron and electron (511 keV each) are converted into two 511 keV photons that are emitted in opposite directions (i.e. 180 degrees apart) in an annihilation reaction.

NORMAL PET SCAN

-Standardized uptake value (SUV): Calculation that determines the activity (or uptake) of radiopharmaceutical (i.e. F-18 FDG)

-Ratio of tissue radioactivity concentration at a point in time [C(T)] and the injected dose of radioactivity (MBq) per kilogram of patient's body weight

-SUV=C(T)/Injection dose (MBq)/patient's body weight (kg)

-Sites of physiologic uptake exist

-High uptake: **Brain**, **heart**, **GU system**

-Moderate uptake: **Liver**, stomach, large bowel, tonsils

-Low uptake: **Mediastinum**, spleen, adrenal glands, pancreas, esophagus, small bowel, salivary glands, thyroid, lung (low/absent)

-Absent uptake: Gallbladder, lung (low/absent)

-Note: Muscular activity (including tongue and larynx) can be increased with exercise, anxiety, insulin administration/release

-Delineation between benign and malignant lesions falls within the **SUV range of 2.0 to 2.5.**

-Infectious and inflammatory processes often demonstrate high SUV (potential False Positive, FP, for malignancy)

-PET sensitivity/specificity is diminished for lesions smaller than 7mm (potential False Negative, FN)

TERMINOLOGY

'Activity'

-'Increased activity': Sites of elevated uptake of radiopharmaceutical

-'Decreased activity': Sites of diminished uptake of radiopharmaceutical

ADVANTAGES OF NUCLEAR MEDICINE

-Functional assessment (i.e. physiology)

-High sensitivity for detecting abnormalities

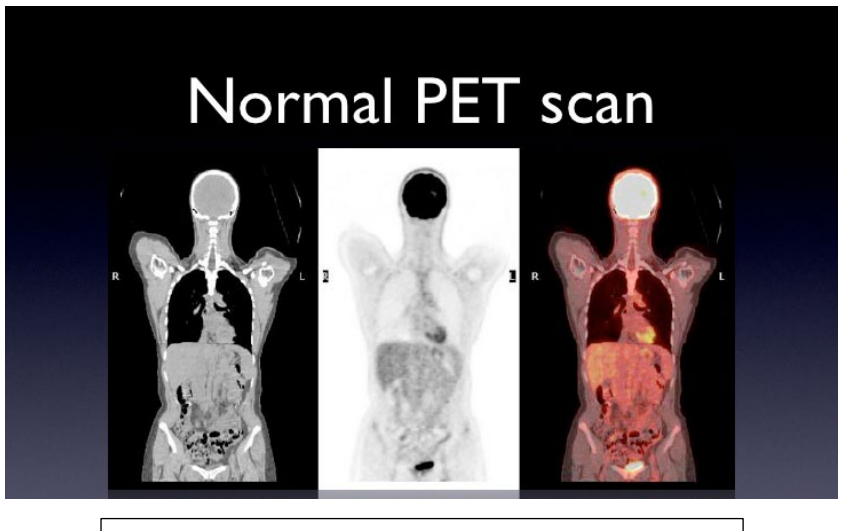
DISADVANTAGES OF NUCLEAR MEDICINE

-Low specificity in characterizing abnormalities

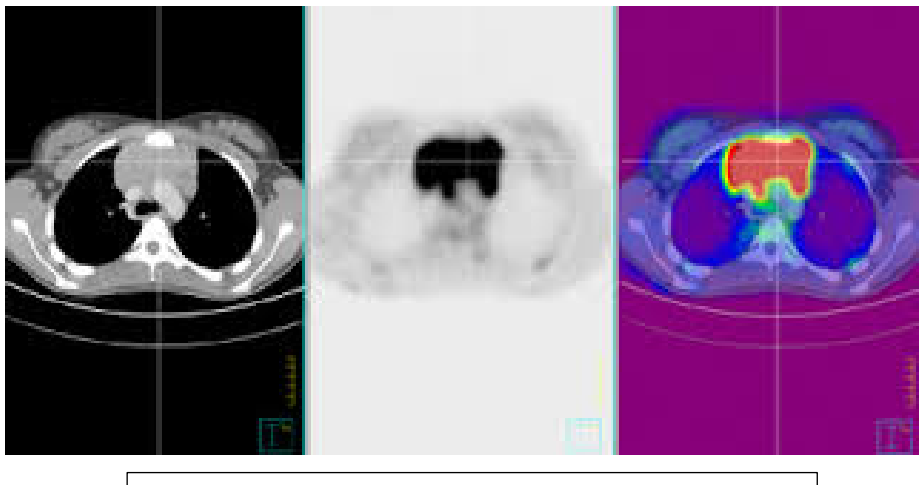
-Somewhat limited anatomic detail

-Cost

-Exposure to ionizing radiation



Greatest physiologic activity on FDG-PET scan:
Brain, heart, GU system



CT/PET/Fused PET-CT images (Hodgkin Lymphoma)
(CedarsSinai.com)

STAGING OF LYMPHOMA: Clinical and pathology lecture topic

-FDG PET-CT is utilized for staging and treatment response assessment in Hodgkin lymphoma and FDG-avid Non-Hodgkin lymphomas (i.e. DLBCL, follicular lymphoma)

-For non-avid NHL subtypes, CT staging is performed

CRITERIA FOR TREATMENT RESPONSE: For reference only (**NOT for memorization).**

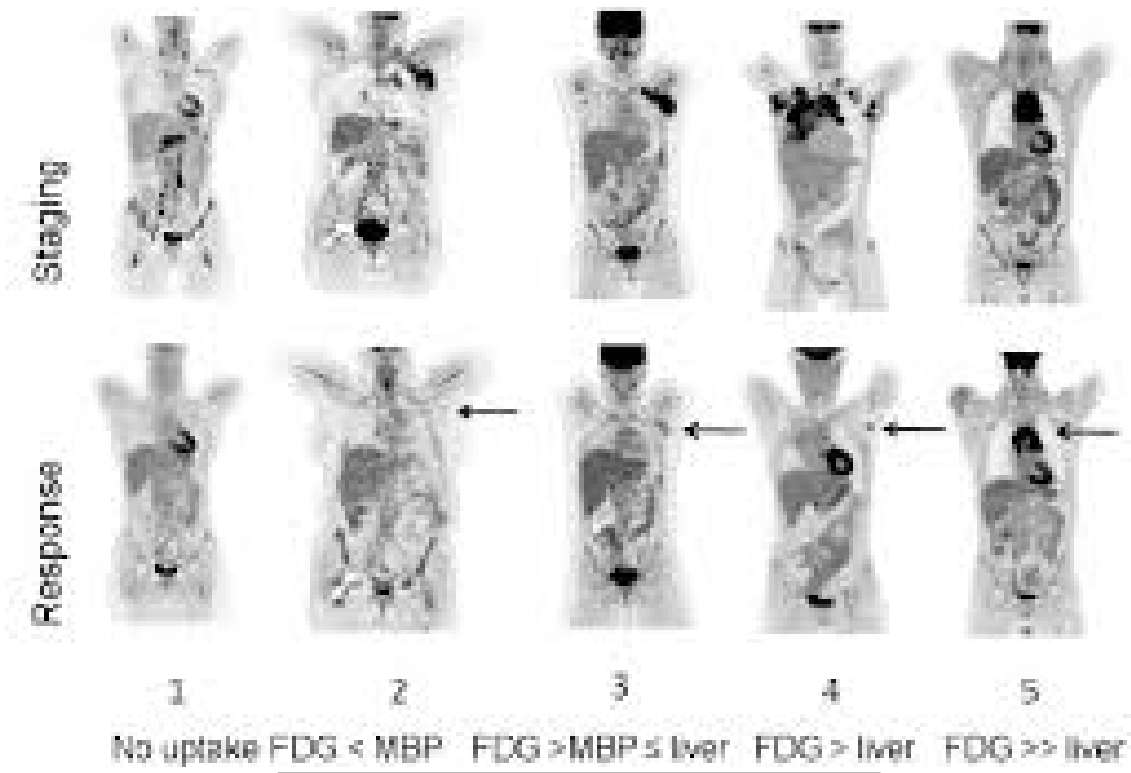
-Separate PET-CT and CT based criteria exist. (Only PET-CT criteria will be presented here)

-Recall, however, that PET-CT criteria utilize the **liver and mediastinal blood pool** for comparison

-Lugano classification system recommends the **Deauville five-point scale** for reporting treatment response (bottom row of images, below)

-Deauville five-point scale utilizes the mediastinal and liver FDG uptake on PET scans for comparison with nodal/extra-nodal foci

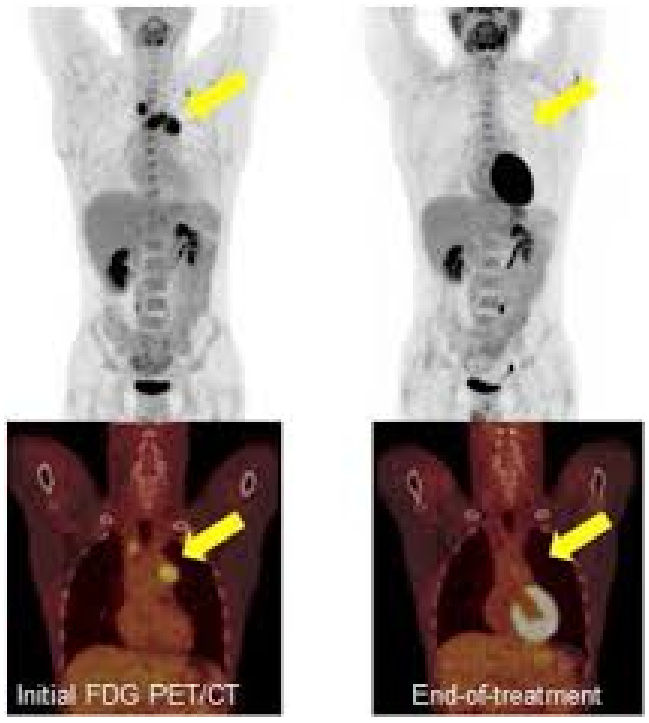
1. No uptake or residual uptake (when used as interim examination)
2. Slight uptake, but below mediastinal blood pool (MBP)
3. Uptake above mediastinal blood pool but below/equal to liver
4. Uptake slightly to moderately greater than liver
5. Markedly increased uptake (or any new lesion on response evaluation)



Example of Deauville Five-point scale (5PS)
(ResearchGate.net)

Modality	Complete Response	Partial Response	Stable Disease	Progressive Disease
FDG PET-CT	Scores 1, 2 ,3 in nodal or extranodal sites with or without a residual mass	Scores 4 or 5 with ↓ uptake compared with baseline and residual mass(es)	Scores 4 or 5 with no obvious change in FDG uptake	Scores 4 or 5 in any lesion with ↑ uptake from baseline and/or New FDG-avid foci

Lugano FDG PET-CT Treatment Response Criteria
(Radiopaedia.org)



Example of Complete Metabolic Response (CMR) at site of mediastinal lymph node involvement (NHL) (Scienceprint.com)

Magnetic Resonance Imaging

Note: MRI is available for imaging assessment of lymphoma. MRI topics (physics, advantages/disadvantages, and terminology) will be fully reviewed later in M2 year.

COMPETELY OPTIONAL: Links to Dr. Julius' MRI video from M1 year:

https://neomed.mediasite.com/Mediasite/Play/b21170b4267041cf89e83e73ed8f5fee1d

https://neomed.mediasite.com/Mediasite/Play/056f489e7d0b4a0d8cb285ee538a42b91d

https://neomed.mediasite.com/Mediasite/Play/8c8e8d35c6934d6192431de368f1cce11d

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References:

-Clinical Radiology: The Essentials. Daffner et al. 4th ed. (Chapters 1, 2, 4).

-Primer of Diagnostic Imaging. Weissleder et al. 4th ed. (Chapters 1, 13, and 14).

-PET and PET/CT: A Clinical Guide. Lin et al. 1st ed. (Chapters 1, 2, 4, 5, and 17).

Note: Medical images are from anonymized patient and online archives (as detailed)

OPTIONAL: Want to know more?

https://www.med-ed.virginia.edu/courses/rad/

www.auntminnie.com

www.acr.org

www.rsna.org