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Summary and Key Points

1. Radiology is important in the detection, diagnosis and staging of cancer. Diagnostic imaging is integral to guide treatment planning, assess for residual disease and response to the treatment, and monitor recurrence and progression of most malignancies.
2. Commonly used modalities for oncologic imaging include Computed Tomography, Magnetic Resonance Imaging, Positron Emission Tomography/Computed Tomography, mammography, and ultrasound.

Introduction

Imaging is an integral part of the multidisciplinary management of cancer.[1] Radiographic techniques are indispensable for proper staging of cancers and evaluation of the response of tumors to treatment. A wide variety of imaging modalities is available to clinicians. This chapter will introduce the role of radiology in the diagnosis and treatment of cancer.

Radiology in Staging

Staging of cancer is a way to describe the extent of spread of a tumor throughout the body. Each malignancy has a unique staging system; however the TNM classification is the most widely used staging system. Radiology is integral to staging the various malignancies using noninvasive techniques. Tumor (T) size, location, and regional involvement can be assessed radiographically. Nodal (N) and metastatic (M) disease may also be staged.

Radiologic staging becomes especially important to guide treatment planning. As an example, cervical cancer staging by ultrasound or MRI can determine whether a patient's tumor is operable. MRI, in particular, demonstrates exquisite soft tissue detail (Figures 1a- c). For example, when parametrial invasion from a cervical cancer is identified, patients are classified as Stage IIB for which radiation and chemotherapy are the treatment of choice over primary resection.

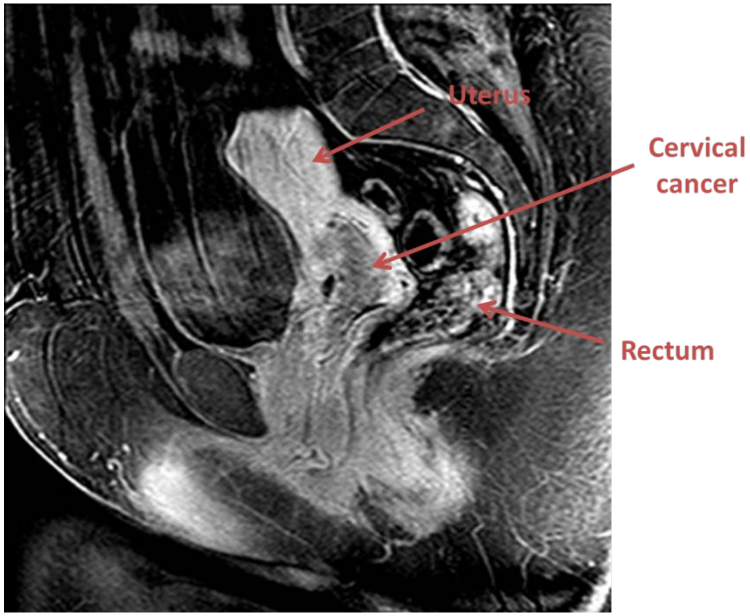


Figure 1a. Sagittal contrast MRI. University of Massachusetts Medical School, Department of Radiology.

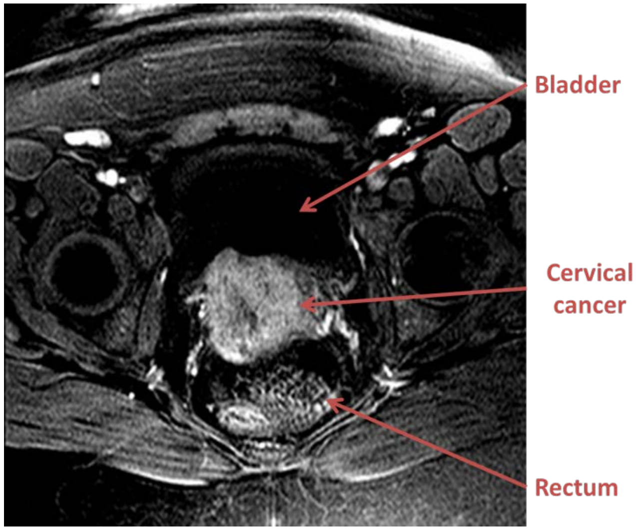


Figure 1b. Axial contrast MRI. Stage IVa with bladder involvement resulting in hydroureter (not shown). University of Massachusetts Medical School, Department of Radiology.

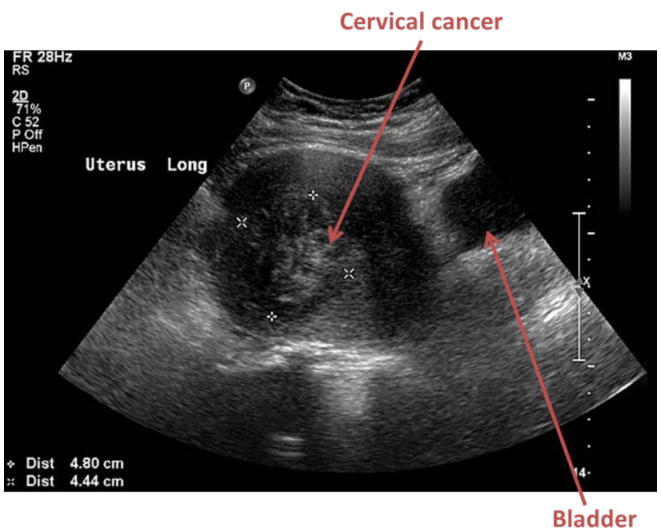


Figure 1c. Pelvic ultrasound. University of Massachusetts Medical School, Department of Radiology.

Functional imaging with PET/CT, and dynamic contrast enhanced CT/MRI are being used to assess tumor response to therapy. The Response Evaluation Criteria In Solid Tumor (RECIST) provides guidelines for the categorization of treatment responses into four groups:[2]

Treatment Response	Definition
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	≥ 30% decrease in the sum of the longest diameter (SLD) of target lesions
Stable Disease (SD)	Persistence of non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progression of Disease (PD)	> 20% increase in the SLD (min 5mm increase) OR the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Tumor assessment early in the course of treatment can be very helpful. If tumor growth (progression) is seen despite treatment, then it will be necessary to discontinue potentially toxic therapies that are not working and/or to switch to therapies that may be more effective.

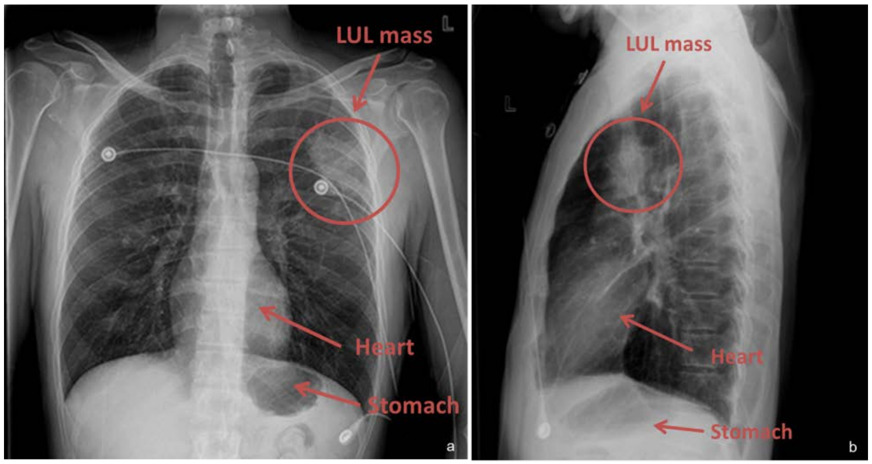
Modalities

X-ray/ Fluoroscopy/ Mammography

X-ray

Plain film radiography (X-ray) (Figures 2a-d) is rarely used in cancer imaging. Plain X-rays offer the benefit of an inexpensive, low radiation modality and may be used for:

- bone tumor characterization
- screening for tumor[3]
- interval surveillance of tumor



Figures 2a-b. Left upper lobe (LUL) mass. **Figure 2a**: AP x-ray. **Figure 2b**: Left lateral x-ray. University of Massachusetts Medical School, Department of Radiology.

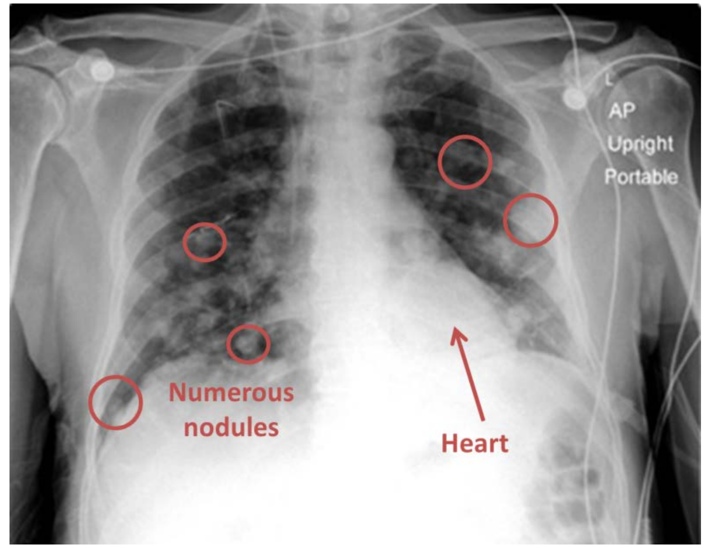


Figure 2c. AP x-ray demonstrating leiomyosarcoma metastasis to lung. University of Massachusetts Medical School, Department of Radiology.

Figure 2d. Well-defined lytic lesion in 2nd proximal phalanx consistent with benign enchondroma. University of Massachusetts Medical School, Department of Radiology.

<u>Fluoroscopy</u>

Fluoroscopy incorporates rapid or continuous imaging with an x-ray beam to dynamically image patients. These studies include the esophagram, upper GI series, and barium enema. Fluoroscopy is rarely used as the primary method of diagnosis due to more advanced imaging modalities. However, it still maintains value in assessing physiologic function over a period of time, such as the severity of stenosis from a mass at the gastroesophageal junction (Figures 3-4).

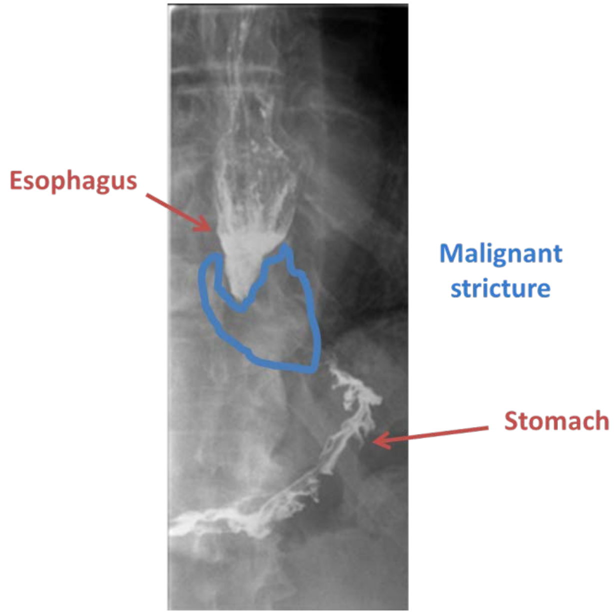


Figure 3. Esophogram with malignant mass effect extending up from GE junction. University of Massachusetts Medical School, Department of Radiology.

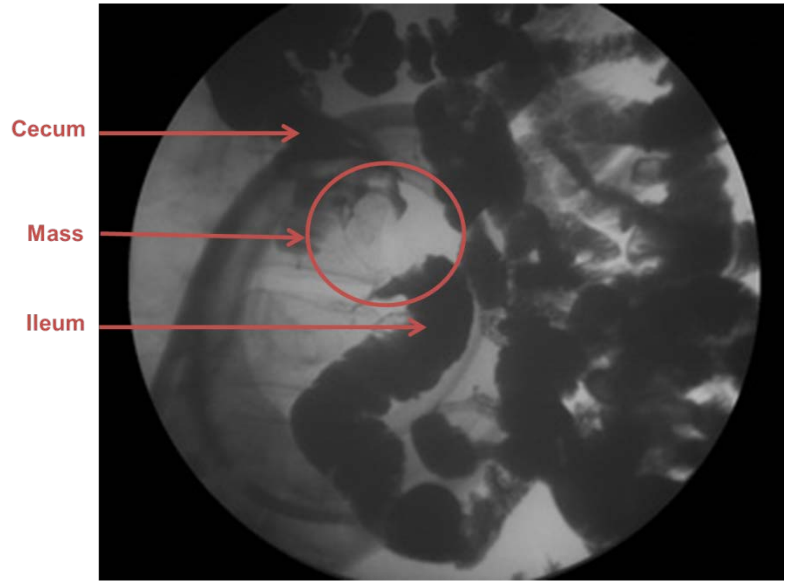
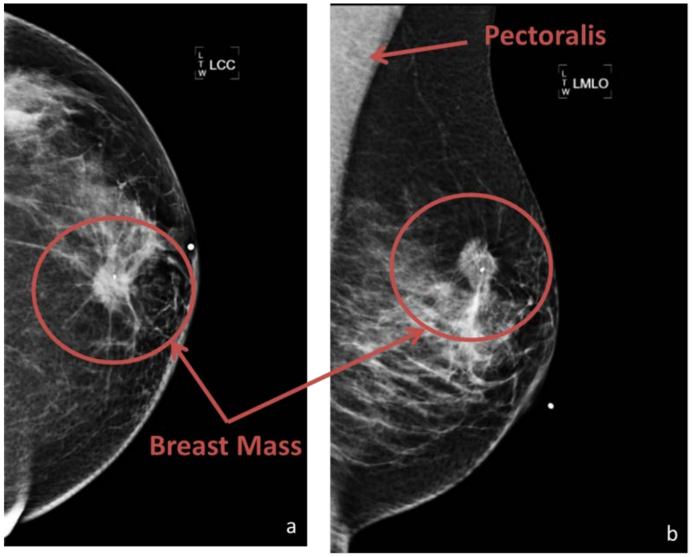


Figure 4. Screen capture of a fluoroscopic examination demonstrating a mass lesion causing narrowing of ileocecal valve. Diagnosis: carcinoid. University of Massachusetts Medical School**,** Department of Radiology.

Mammography

Mammography is an essential modality for the screening and management of breast cancer.[4] With relative low radiation exposure, high resolution images of the breast parenchyma can be studied for soft tissue masses or microcalcifications which can be associated with ductal carcinoma (Figures 5a-b). MRI is a very useful adjunct to mammography in diagnostically challenging cases such as in patients with dense glandular tissues or from scar tissue due to prior surgery.



Figures 5a-b. Left breast mass with spiculated margins. University of Massachusetts Medical School, Department of Radiology.

Ultrasound

In ultrasonography, a small transducer with a piezoelectric ceramic element rapidly vibrates up to 20 million times per second creating sounds waves that pass through the body. The sound waves are reflected back to the transducer dependent on the acoustic characteristics of the tissue; these reflections are used to create the sonogram. Although comprehensive staging cannot be performed with ultrasound alone, ultrasound has high spatial resolution for superficial structures. It lacks ionizing radiation and allows for continuous imaging that makes it the modality of choice for image guided biopsies.

Ultrasound works best for structures located next to the probe. Such areas include superficial structures such as the thyroid gland, breasts, liver, and kidneys. Transvaginal ultrasound is routinely used for detailed assessment of the female pelvic structures. Additionally, small transducers have been fitted onto endoscopes for detailed imaging of esophageal, pancreatic, and colorectal malignancies. Doppler ultrasound also allows the radiologist to obtain blood flow characteristics of an organ or tumor.

Figure 6. US of the right breast with a 5 cm mass. University of Massachusetts Medical School, Department of Radiology.

Computerized Tomography (CT)

In the late 1970's, CT scanning was developed using a rotating x-ray source and detector, allowing for the creation of cross-sectional imaging. Intravascular and oral contrast may be used with CT to provide better definition of vascular structures, organs, and the digestive tract.

Advances in technology, sub-millimeter pictures, and rapid acquisition techniques have enabled us to create high resolution images, reformat the images in different cross-sectional planes, create 3D images (Figure 7a-b), and develop new techniques such as Virtual Colonoscopy.

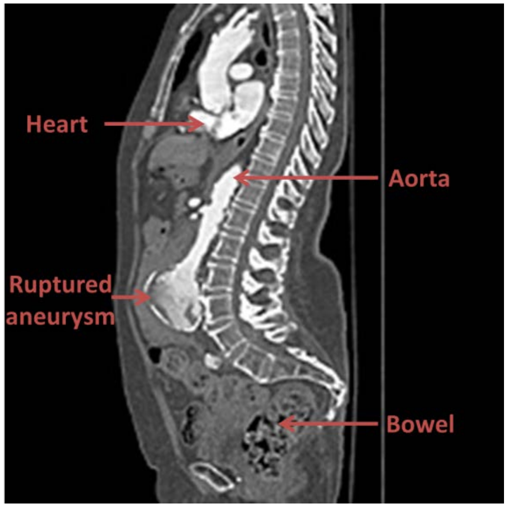


Figure 7a. CT study timed at the arterial phase of the contrast bolus (CT angiography) demonstrates a ruptured abdominal aortic aneurysm (AAA). Static sagittal reformatted contrast enhanced CT. University of Massachusetts Medical School, Department of Radiology.

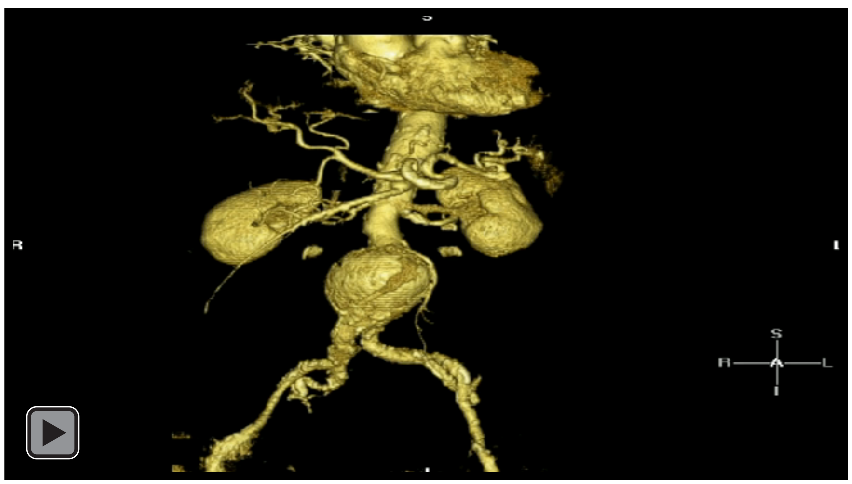


Figure 7b (movie). CT angiography of a ruptured AAA. 3D MIP (maximum intensity projection) images demonstrating only selected structures. University of Massachusetts Medical School, Department of Radiology.

Interpreting the images generated from a CT scanner requires a basic understanding of the physics involved. CT acquires images by passing x-rays circumferentially through the body. Attenuation of the x-rays as they pass through varying densities is recorded. This information is converted by the scanner into Hounsfield units (HU) which is a standardized method for measuring linear attenuation. At standard pressure and temperature, the density of distilled water is defined as zero HU, while the density of air is defined as -1000 HU. These standards were chosen as they are universally available references.[5]

By convention, the less dense objects are displayed as black and higher density such as bone and intravascular contrast are displayed as white (Figure 8).

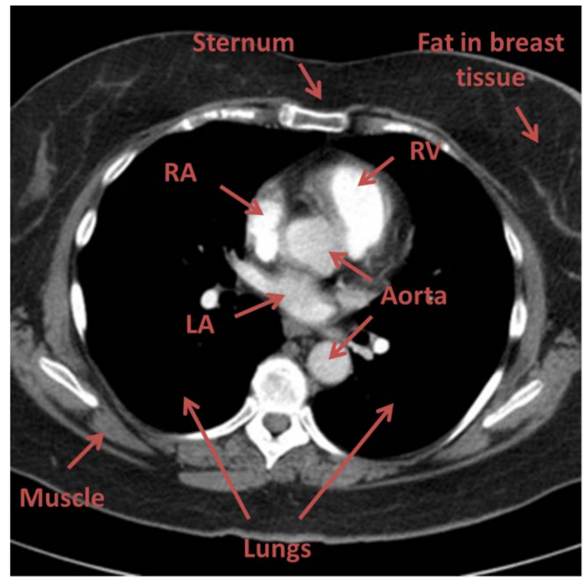


Figure 8. Structures from the least dense (black) to the most dense (white):
Air < Fat < Muscle < Contrast (heart and vessels) < Bone

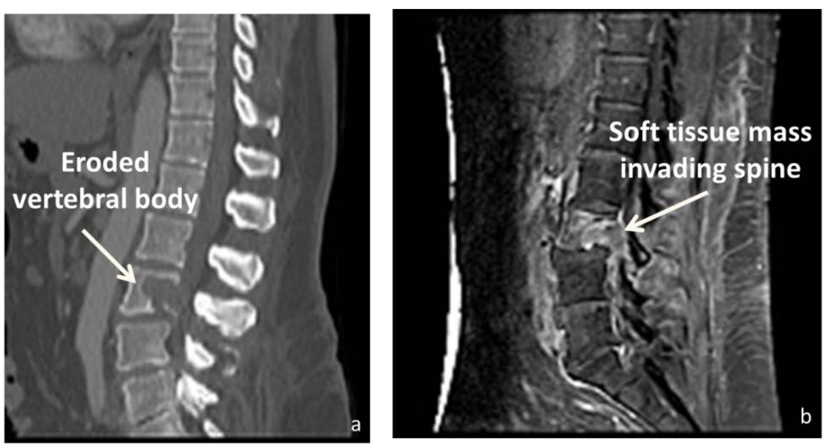
Right Atrium (RA), Left Atrium (LA) Right Ventricle (RV)
University of Massachusetts Medical School, Department of Radiology.

One practical application in CT evaluation of tumors is in the diagnosis of a lipoma, where the density of the tumor is purely fat. Another example is with the evaluation of adrenal tumors where an average density of less than 10 HU indicates a predominately fatty composition, diagnostic of a benign adrenal adenoma.

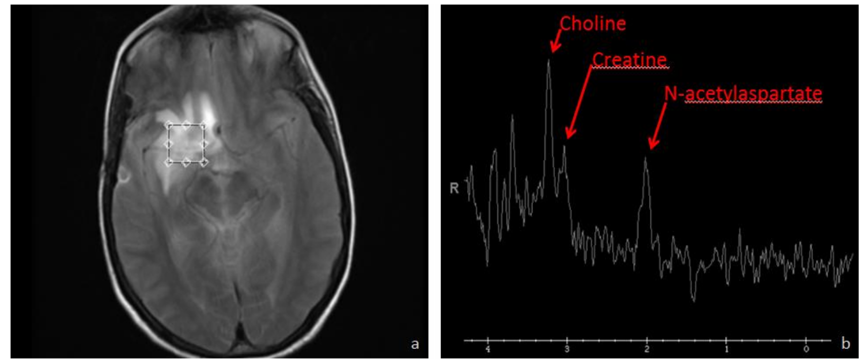
The drawback to CT imaging is the use of x-ray (ionizing) radiation in much higher doses (150 - 1,100 times) than seen with plain radiographs. Recent technical innovations have lowered the radiation dose from CT imaging; however, the ordering physicians must be aware of the small, but real, risk for medically induced cancers. The decision for the use of CT needs to weigh the risks versus benefits as well as the cumulative effect from multiple CTs over a lifetime.

Magnetic Resonance Imaging (MRI)

MRI provides superb contrast resolution (tissue differentiation) at the cost of lower spatial resolution (image clarity) compared with CT. Patients are placed within a large magnetic field created either by a permanent magnetic or liquid nitrogen cooled superconductor. Radiofrequency pulses generate signal based on the different tissue characteristics, which is then interpreted into images by the scanner. Images can be provided from various angles and constructed into a three dimensional image. Imaging of the brain/spine, liver, and pelvis heavily rely on MR imaging for the increased sensitivity and specificity compared with CT (Figures 9a-b). Advances with functional MRI and MR Spectroscopy are continually being explored with clinical and research applications (Figures 10a-b).



Figures 9a-b. **Figure 9a:** CT of the lumbar spine show a lytic tumor eroding through the posterior vertebral body of the L3 vertebrae. **Figure 9b:** MR of the lumbar spine allows much better assessment of the soft tissues. In this case, the posterior extent of this tumor invades the spinal canal and compresses the adjacent nerve roots. University of Massachusetts Medical School, Department of Radiology.



Figures 10a-b. **Figure 10a:** MRI of the brain demonstrates a new lesion in the inferior right frontal lobe in a patient with a history of brain tumor resection. This may represent residual tumor or post-surgical/radiation change. **Figure 10b**: The addition of MR Spectroscopy shows abnormally reduced creatine and N-acetylaspartate indicating that this lesion represents progression of tumor. University of Massachusetts Medical School, Department of Radiology.

Contraindications to MRI are related to the strong magnetic field (10,000 to 300,000 times the field strength on the Earth's surface). This excludes patients with ferromagnetic material implanted in the body (pacemaker, certain aneurysm clips, deep nerve stimulators, endoscopy capsules, Swan-Ganz catheters, etc). Even certain tattoo inks contain elements of iron that have been reported to be a cause of thermal injury from electromagnetic induction. A comprehensive list of these items is found at http://www.mrisafety.com.

Contrast agents

Contrast agents increase the sensitivity of conventional imaging by improving visibility of internal body structures. These agents distribute proportional to blood flow allowing better visualization of hypervascular lesions. Radiocontrast for X-ray based imaging, MRI contrast and microbubbles (ultrasound) are used in order to enhance their respective imaging modalities.

Radiocontrast agents are used in X-ray based imaging such as CT, fluoroscopy, and radiography. These agents take advantage of a difference in density between the contrast agent and adjacent structures. Iodine and barium agents are commonly used agents. Modern intravenous contrast agents are based around iodine. Iodine may be administered as an ionic compound or non-ionic (organic) compound. The ionic form was initially developed and widely used, but fell out of favor due to potential complications such as renal failure. The organic form which covalently binds iodine has fewer complications and is now the primary contrast enhancing agent for CT. In addition to evaluation of the soft tissues for tumor, infection, and inflammation, iodine is used in angiography (arterial investigation), venography (venous investigation), voiding cystourethrography (VCUG), hysterosalpingogram (HSG), intravenous urography (IVU), and myelography.

Contrast-induced nephropathy (CIN) is a major side effect of iodinated intravascular contrast. This is defined as renal injury as a consequence of radiocontrast resulting in either a greater than 25% increase of serum creatinine or an absolute increase in serum creatinine of 0.5 mg/dL. These agents should be avoided in patients with poor renal function.

Barium is mainly used in the imaging of the digestive system. Barium is administered as barium sulfate, a water-insoluble compound. Typical studies that utilize barium include, barium swallow (oro-esophageal investigation), barium upper GI (stomach investigation), barium upper GI and follow through (stomach and small bowel investigation), barium enema (large bowel investigation).

MRI contrast agents improve visibility of internal structures in magnetic resonance imaging. Most commonly used agents are gadolinium-based. The primary mechanism through which MRI functions is in the evaluation of the spin of protons- the most predominate form in the body– the water molecule. Molecular rotational oscillations of the water molecule behave differently in different tissues, which are used to generate MR images. Gadolinium based agents alter the spin of adjacent protons resulting in enhancement. Effectively, more gadolinium within a tissue equates to more enhancement. Like CT contrast, higher concentrations of MR contrast are seen in pathology that has greater vascularity and permeability such as tumors, infection, and inflammation. This is particularly effective in evaluation of brain tumors where disruption of the blood-brain barrier allows enhancement of these lesions where the intact blood-brain barrier prevents passage of the gadolinium chelate.

Gadolinium contrast agents have not proven safer than radiocontrast agents. The free solubilized gadolinium ion is toxic and its deposition in tissues is thought to be the primary cause of nephrogenic fibrosing dermopathy, also known as nephrogenic systemic fibrosis (NSF). This systemic disease most closely resembles scleromyxedema. Patients with poor renal function are at more risk for NSF. Dialysis has not been proven effective in the removal of free gadolinium ions and gadolinium based contrast should be avoided in patients on dialysis. Gadolinium is administered as a chelated compound. The stronger the chelating agent bond, less likely to have free ions, hence less risk for NSF. In addition, different characteristics of the chelating agent have been shown to alter the pharmacokinetics. Such novel research in altering the pharmacokinetics has proven effective in differentiating benign versus malignant liver lesions.

Perfusion imaging is also a novel technique to help differentiate tumor from radiation-induced changes, as both may enhance. Neoangiogenesis seen with tumor growth results in an abnormal increase in vascular flow and permeability. This alteration in vascularity can be detected by perfusion imaging either by contrast enhanced CT or MRI, thus differentiating tumor from radiation necrosis. This has been shown to be particularly helpful in the management of brain tumors where radiation is often used to treat tumors.

Radiologic contrast media are considered among the most heavily studied medications when it comes to allergic reactions. While rare, anaphylactoid reactions can occur and are potentially life threatening. Pretreatment with corticosteroids has been shown to decrease the incidence of adverse events.

Microbubble contrast agents may be used in ultrasound. These bubbles are composed of agitated saline solution ranging in size, typically between 1-4 micrometers. It is not currently used in oncologic imaging, but has been shown to be helpful in echocardiograms for the detection of cardiac shunts.

Nuclear Medicine

The division of nuclear medicine uses physiologic/functional imaging to provide valuable information that may not be obtained through the anatomic imaging discussed above. The basis of nuclear medicine is to inject radioactive isotopes bound to specific radiopharmaceuticals, and image the resultant radioactive decay based on physiologic localization.

Unlike CT, ultrasound, or MRI, the multitude of radiopharmaceuticals involved in each exam create a unique image and address very specific issues in diagnosis and treatment. Examples of nuclear medicine studies used in oncologic imaging include bone scans (Technetium 99m-MDP) (Figure 11), neuroendocrine tumor imaging (Indium-111 pentotreotide, Iodine-123 metaiodobenzylguanidine), and CD20 antibody imaging (Indium-111 Zevalin). Lymphoscintigraphy (Technetium 99m– sulfur colloid) is another commonly ordered study to aid in sentinel lymph node biopsy. New molecular markers are being studied for future clinical use, and show considerable promise in the field of oncologic imaging. Additional information about the mechanism of uptake and uses for these scans can be found at [AuntMinnie.com.](AuntMinnie.com)

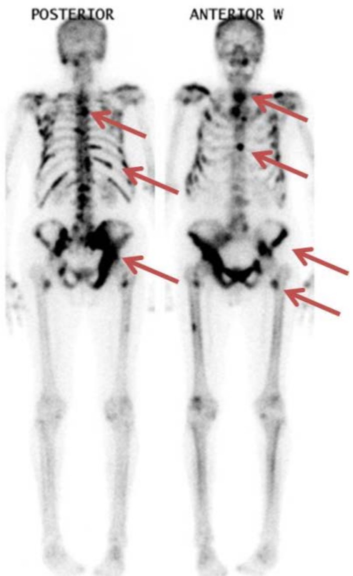


Figure 11. Bone scan demonstrating superscan with prostate metastases. University of Massachusetts Medical School, Department of Radiology.

Positron Emission Tomography (PET)

Positron emission tomography is a functional imaging technique that detects gamma rays emitted by the annihilation reaction of a positron-emitting radionuclide (tracer). The most common and widely used PET agent is fluoro-18-deoxyglucose (FDG). This glucose analog can be administered intravenously and has an identical physiologic distribution as its parent molecule.

FDG accumulation occurs in normal glucose-avid organs like the brain, salivary glands, liver, and bowel. A large percentage of malignancies are hypermetabolic with increased tracer uptake. This is helpful for diagnosis, staging, and monitoring for disease recurrence (Figures 12 & 13). Examples include non-small cell lung cancer, breast cancer, colorectal cancer, pelvic malignancies, lymphoma, sarcomas, and head/neck cancer. Many ongoing clinical trials are evaluating whether FDG can also be used to predict treatment response and help refine therapy planning.

Figure 12a (movie). Normal FDG PET rotating MIP. Physiologic bowel uptake. University of Massachusetts Medical School, Department of Radiology.

Figure 12b. PET scan of diffuse breast cancer metastases. University of Massachusetts Medical School, Department of Radiology.

Figure 13a, b, c. Normal patient. PET and CT are commonly acquired together. **Figure 13a**. PET allows evaluation of metabolic activity, but tends to have poor resolution. **Figure 13b**. CT has high spatial resolution. **Figure 13c**. Merging PET and CT allows for more accurate evaluation of the anatomical structures and their metabolic activity. University of Massachusetts Medical School, Department of Radiology.

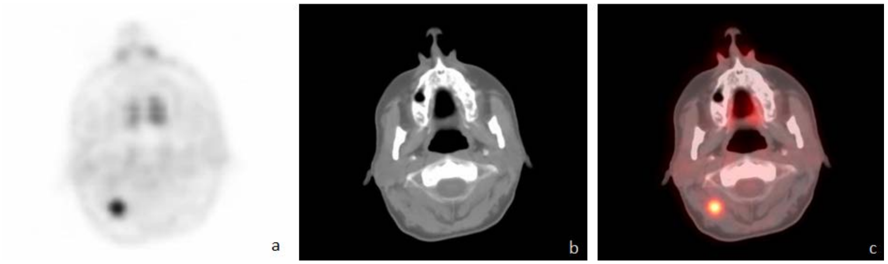


Figure 14a, b, c. Melanoma metastasis. **Figure 14a**. Abnormal increase in metabolic activity is seen in the posterior right upper neck. **Figure 14b**. Detection of subtle metastasis can be challenging by CT. **Figure 14c**. Fusion of PET and CT images better identifies the anatomic structures around this metastasis. University of Massachusetts Medical School, Department of Radiology.

As with other nuclear medicine agents, patient preparation can be an important part of getting accurate results. Recent glucose ingestion will act as a competitive inhibitor, decreasing the sensitivity for malignant disease. Insulin (endogenous or exogenous) can alter glucose dynamics and also decrease sensitivity for oncologic imaging. Because the biodistribution of the FDG molecule is dependent on where glucose is being metabolized, exercise prior to the study will drive uptake into the skeletal muscles and again decrease sensitivity. Guidelines for proper patient preparation can be found at the National Cancer Institute FDG PET Guidelines.

Conclusion

Oncologic imaging is a continually evolving field with clinical applications that directly and indirectly impact the patient's outcome. Each modality has advantages and disadvantages depending on the question being answered and sometimes the evaluation may require more than one imaging modality. Radiology consultation may be helpful to determine the most appropriate imaging study. Every physician is expected to be able to, at the least, review the images ordered and compare his impression with the official diagnostic radiologist interpretation.

Thought Questions

1. A 68 year old man with a T1, N0 (Stage I) squamous cell carcinoma of the lung undergoes a left upper lobectomy. Four months later, a chest CT shows no evidence of tumor. He continues with regular check-ups consisting of physical exams and periodic chest CTs. 18 months after his surgery another chest CT shows an enlarged right mediastinal lymph node. Biopsy of the node shows squamous cell cancer. The patient and his family wonder why the abnormality was not seen previously. They wonder why his physicians did not have him get regular MRIs or PET scans. How could you answer them?

   Your answer

   Expert Answer

2. A 22 year old woman was successfully treated for Hodgkin Disease three years ago. Her physician still wants to her to have CT scans periodically, but she is concerned about exposure to x-rays. What can you tell her about the differences in radiation exposure from chest x-rays, chest CTs, chest MRI, breast ultrasound, and PET scan?

   Your answer

   Expert Answer

3. A 52 year old woman has a routine screening mammogram that detects a mass in her right breast. An ultrasound is obtained that shows a mass that is consistent with a fibroadenoma. An MRI of the breast shows a mass that enhances with gadolinium. At this point the patient is thoroughly confused about why she had all these different imaging studies. What can you tell her about how these modes of imaging provide different information about a breast mass?

   Your answer

   Expert Answer

Glossary

CT angiography- Computerized tomography (CT) angiography or map of the blood vessels performed with computerized tomography

Endogenous- Substrate of process that occurs within the body

Exogenous- Substrate of process that occurs outside the body and can be administered to the patient

Functional imaging- Images based on physiologic distribution rather than anatomic or structural characteristics

Hounsfield units (HU)- A linear scale based for radiodensity with water defined as 0 HU

Microbubbles- Ultrasound contrast agent constructed of 1-4 µm bubbles of gas surrounded by a thin shell

Nephrogenic systemic fibrosis- Rare condition causing fibrosis of the skin, joints and internal organs associated with Gadolinium contrast in patients with renal failure

Nephropathy- Damage to the kidney

Noninvasive radiology techniques- Procedures that do not penetrate into the body. Almost all diagnostic imaging falls into this category

Piezoelectric- Process that converts electrical input into mechanical output (vibration) and vice versa

Staging- Procedure to determine where and how much cancer is in a patient

Treatment response- Effects of usually noninvasive therapies on disease burden

Virtual Colonoscopy- CT procedure using air distension to evaluate the colon similar to what would be seen during a colonoscopy

References

1. Fass L. Imaging and cancer: a review. Mol Oncol. 2008;2(2):115-52.
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

   PubMed Abstract
3. Hakama M, Hakama M, Coleman MP, Alexe DM, Auvinen A. Cancer screening: Evidence and practice in Europe 2008. Eur J Cancer. 2008;44(10), 1404-13.

   PubMed Abstract
4. Shapiro S. Evidence on screening for breast cancer from a randomized trial. Cancer. 1977;39(6): 2772–82.
5. De Vos W, Casselman J, Swennen GR. Cone-beam computerized tomography (CBCT) imaging of the oral and maxillofacial region: A systematic review of the literature. Int J Oral Maxillofac Surg 2009;38(6):609–25.

   PubMed Abstract
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer; 2013.
7. Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology. 2008;248(1):254-63.
8. American College of Radiology. ACR appropriateness criteria for palpable breast masses. 2012.