

Nuclear Medicine

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Last Updated:

Tuesday, February 14, 2023

Keywords:

Radiopharmaceutical, Positron Emission Tomography (PET), Renal Scintigraphy, Bone scan

Summary

- Radiopharmaceuticals are radioactive compounds used in nuclear medicine. They typically include two parts, a pharmaceutical for targeting a desired organ system and a radionuclide label for imaging or therapy.
 - Common radionuclides in urology include Fluorine-18, Gallium-68, and Technetium-99m
 - Common radiopharmaceuticals include ¹⁸F-FDG, ¹⁸F-fluciclovine, PSMA ligands (e.g., ⁶⁸Ga-PSMA-11), ^{99m}Tc-DMSA, ^{99m}Tc-MAG3, and bone imaging agents (e.g., ^{99m}Tc-MDP).
- Gamma rays emitted from radionuclides in a patient are detected using a Gamma Camera
- Co-registration of functional (PET) and anatomic (CT or MRI) improves the sensitivity and specificity of PET imaging.
- Nuclear imaging is an imaging modality that assesses function. The images have low spatial resolution and therefore look “fuzzy” compared to anatomic imaging techniques
- Common radiopharmaceuticals used in renal function imaging are MAG3 and DMSA. MAG3 is excreted by tubular secretion. DMSA is bound the renal tubules and has longer biological half-life, increasing radiation exposure.
- Of the nuclear medicine scans commonly used in urology, the bone scan has the highest radiation dose (4 mSv). This is less than half that of a typical abdominal CT (10 mSv). Radiation dose from a PET/CT study is 5-15 mSv (higher if the CT is performed as a diagnostic CT rather than a low-dose CT).
- The most suitable radionuclide for a particular nuclear medicine test is the one emits the lowest energy that is needed for a diagnostic quality study and has a short half-life.
- Nuclear cystography with ^{99m}Tc-DTPA can detect vesicoureteral reflux in children with approximately 1% of the radiation dose of VCUG.
- Renal cortical scintigraphy with ^{99m}Tc-DMSA can detect acute pyelonephritis and areas of scarring in chronic pyelonephritis.
- Tc99m methylene bisphosphonate (MDP) bone scan is widely used for staging in men with

- high risk prostate cancer (PSA >20, Gleason score ≥8, T3 or T4 cancer)
- SPECT/CT performed along with bone scan provides helpful anatomical correlation
 - ¹⁸F-NaF PET/CT has superior sensitivity to ^{99m}Tc-labeled diphosphonate bone scan
 - The sensitivity of ^{99m}Tc bone scan for metastatic kidney cancer is <50% because the lytic bone metastases in RCC may cause minimal osteoblastic reaction
 - ¹²³I-MIBG or ⁶⁸Ga-DOTATATE imaging can be used to identify and localize pheochromocytoma.
 - ¹⁸F-Fluciclovine PET was approved by the FDA in 2017 and is indicated for suspected recurrent prostate cancer when conventional imaging is negative or equivocal.
 - Two PSMA PET agents (⁶⁸Ga-PSMA-11 and ¹⁸F-DCPyl) are FDA approved as of 2021 for imaging patients with high risk prostate cancer and suspicion for metastasis prior to curative intent therapy or suspected biochemical recurrence based on elevated serum PSA.
 - Radium-223 dichloride is an α-particle emitter that is the most commonly used radiopharmaceutical for treatment of symptomatic bone metastasis in castration-resistant prostate cancer.
 - ^{99m}Tc-sestamibi SPECT can help differentiate oncocytoma (bright on sestamibi SPECT) from RCC (dark on sestamibi SPECT).

1. Technical Considerations

1.1 Radiopharmaceuticals

Diagnostic nuclear medicine utilizes trace amounts of radioactive chemicals (radiotracers) to evaluate organ function. Tracers used in general nuclear medicine, positron emission tomography (PET), and in vitro laboratory studies, as well as radioactive compounds that are used for internal radionuclide therapy, are **radiopharmaceuticals**. Many radiopharmaceuticals are currently available to assess or target various organ systems. Once a radiopharmaceutical is administered, typically by intravenous injection, it is distributed, and radioactivity is subsequently measured to evaluate specific physiologic or pathologic processes in different parts of the body.

Radiopharmaceuticals are typically composed of two parts, a pharmaceutical that has desired physiologic or pharmacologic properties for targeting and probing specific cellular or molecular mechanisms and a radionuclide label that has desired properties for imaging or therapy. Occasionally, a radionuclide such as radioactive iodine isotopes or radium-223 may itself have the required properties for targeting.

An ideal radiopharmaceutical concentrates only in the organ(s) of interest with minimal background or nonspecific activity. An ideal radiopharmaceutical for diagnostic imaging using a gamma camera (scintigraphy) emits only gamma rays with useful energies for detection. Low energy gamma rays and alpha and beta emission are too easily absorbed by the body and contribute to ionizing radiation exposure. Very high energy gamma rays can exit the body but are difficult to detect using standard gamma cameras. Although a smaller fraction of high-energy gamma rays gets absorbed by the body, due to their high energy they cause significant ionizing-radiation exposure. Most radionuclides used

in nuclear medicine are easily detected, which minimizes the amount of pharmaceutical administered to the patient.

An ideal PET radiopharmaceutical only emits short-range positrons that annihilate near the source. High-energy, long-range positrons (as with ^{68}Ga) can affect image resolution.

The half-life of most radiopharmaceuticals for gamma-imaging and PET is a few hours, long enough for them to reach the target organ(s) and imaging to be completed, but not too long to linger in the patient. Radionuclide half-lives are listed in **Table 1**. Radionuclides are chosen because of properties that help to limit radiation dose to the patient. Common radiopharmaceuticals used in urology are listed in **Table 2**.¹

Most nuclear medicine or PET centers obtain radiopharmaceuticals from a radiopharmacy. Radionuclide is generally eluted from a generator (for example, $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ or $^{68}\text{Ge}/^{68}\text{Ga}$ generator) or obtained using a cyclotron. New radiopharmaceutical production techniques achieve high radionuclide purity and specific activity, reducing the amounts needed for administration to produce diagnostic quality images and making it safer to the patient.

Table 1: Half-Life of Commonly Used Radionuclides

Agent	Symbol	Half-life	Radiation
<i>Scintigraphy</i>			
Technetium-99m	$^{99m}_{43}\text{Tc}$	6 hours	Gamma
Iodine-123	$^{123}_{53}\text{I}$	13.2 hours	Gamma
Iodine-131	$^{131}_{53}\text{I}$	8.0 day	Gamma, Beta
Xenon-133	$^{133}_{54}\text{Xe}$	5.3 day	Gamma, Beta
Indium-111	$^{111}_{49}\text{In}$	67 hours	Gamma
Thallium-201	$^{201}_{81}\text{Tl}$	3.1 day	Gamma
Gallium-67	$^{67}_{31}\text{Ga}$	78.3 hours	Gamma
<i>PET</i>			
Gallium-68	$^{68}_{31}\text{Ga}$	68 min	Positron
Carbon-11	$^{11}_{6}\text{C}$	20.3 minutes	Positron
Nitrogen-13	$^{13}_{7}\text{N}$	10 minutes	Positron
Oxygen-15	$^{15}_{8}\text{O}$	124 seconds	Positron
Fluorine-18	$^{18}_{9}\text{F}$	110 minutes	Positron
Copper-64	$^{64}_{29}\text{Cu}$	12.7 hours	Positron
<i>Radionuclide therapy</i>			
Lutetium-177	^{177}Lu	6.7 days	Beta

Radium-223

²²³ Ra

11.4 days

Alpha

Table 2: Common Radiotracer Combinations in Urology

Radionuclide	Radiopharmaceutical	Target Organ(s) / Purpose
Carbon-11	Acetate	Prostate
	Choline	Prostate
Fluorine-18	FDG (fluorodeoxyglucose)	Tumor, infection
	Sodium fluoride	Bone metastasis
	Fluorocholine	Prostate
	FACBC (fluciclovine)	Prostate cancer
	DCFPyl (piplulfolastat)	Prostate Cancer
Gallium-67	Citrate	Infection, tumor
Gallium-68	DOTATATE DOTATOC	Pheochromocytoma, Paraganglioma, Other neuroendocrine tumors
	PSMA	Prostate Cancer
Copper-64	DOTATATE	Neuroendocrine tumors
In-111	In-111 WBC	Infection
	In-111 Pentetreotide	Neuroendocrine tumors
Technetium-99m	Diphosphonate (methylene diphosphonate, hydroxymethylene diphosphonate)	Bone
	DMSA (dimercaptosuccinic acid)	Renal cortical

	DTPA (diethylenetriamine pentaacetic acid)	Renal dynamic, lung ventilation
	Glucoheptonate	Renal dynamic
	MAG3 (mercaptoacetyltriglycine)	Renal
	Pertechnetate	Testis, Meckel diverticulum
	Tilmanocept	Lymphoscintigraphy
	Sulfur colloid (filtered)	Lymphoscintigraphy
Iodine-123	MIBI (metaiodobenzylguanidine)	Pheochromocytoma, neural crest tumors
Iodine-131	MIBG	Pheochromocytoma, neural crest tumors (treatment)

1.2 Instrumentation: Gamma Camera, SPECT, PET, and hybrid imaging

A gamma camera is a device that detects individual gamma rays that are emerging from the patient and localizes them. Many gamma cameras contain a scintillation crystal coupled with an array of photomultiplier tubes (PMTs) or equivalent silicon photomultipliers (SiPM). The crystal absorbs incident gamma rays and rapidly releases the energy by emitting visible or near-ultraviolet light photons that are detected by photomultipliers generating an electrical pulse. Some cameras use crystals that directly convert gamma radiation to an electrical current pulse. The pulse height is proportional to the energy of gamma ray interaction. In general, the crystals are fragile and expensive and need to be hermetically sealed.

Three terms that describe primary operational characteristics of a gamma camera are:

- *Uniformity*: the ability of a gamma camera to produce a uniform image in response to a uniform source of gamma rays.
- *Sensitivity*: the ability of a gamma camera to use the gamma rays available to it.
- *Resolution*: the ability of a gamma camera to reproduce the details of a nonuniform source of gamma rays (this is spatial resolution, rather than energy resolution).

Because the gamma rays can be emitted from the patient in multiple directions, however, the camera must use a collimator. The collimator is made of perforated lead and is interposed between the patient and the scintillation crystal. It allows the gamma camera to localize accurately the radionuclide in the patient's body. Collimators can be made to different specifications to maximize either sensitivity or resolution. The three operational characteristics of uniformity, resolution, and sensitivity can be measured either intrinsically (without a collimator) or extrinsically (with a collimator). Most radiation striking the collimator at oblique angles is not included in the final image, and less than 1% is used to generate the desired image. Thus, the collimator is the rate limiting step in the imaging chain of gamma camera technology.¹ The three operational characteristics of uniformity, resolution, and sensitivity can be measured either intrinsically (without a collimator) or extrinsically (with a collimator).

Raw gamma camera images need processing prior to being interpretable. As a result, gamma cameras have dedicated computer processing systems. The computer collects data from the photomultipliers and helps to display it in a way that is anatomically and functionally useful to the practitioner. The gamma camera has inherent limitations that will always cause scintigraphic images to have low spatial resolution compared to anatomic imaging such as MRI or CT; thus, in order to delineate anatomy, they must be used alongside other imaging modalities. In contrast to anatomical imaging, nuclear medicine is a functional imaging modality, and its strength is in the demonstration of organ function. Single-photon emission computed tomography (SPECT) acquires images at multiple projections by rotating the gamma cameras around the patient and uses a computer algorithm such as filtered back projection or iterative reconstruction (e.g., ordered set expectation maximization) to reconstruct a 3-dimensional dataset, similar to the way that a CT scanner uses x-rays at multiple projections to produce cross-sectional images.

PET scanners use a timing circuitry (coincidence detection) to detect pairs of gamma rays emitted indirectly by a PET radionuclide. The two simultaneous photons in a pair always travel in opposite directions so their source can be localized along the line connecting the location of interaction between gamma rays and detector ring on the PET scanner. Since PET does not need collimation to localize radioactivity, it inherently has higher sensitivity than gamma cameras and SPECT.

Time-of-flight PET uses crystals and detection circuitry optimized to significantly increase time resolution of the system compared to regular PET, allowing to localize the source within a short segment of the line connecting the two detectors.

Hybrid systems combine SPECT or PET with CT. The patient is scanned in tandem without changing position between the two scans, allowing accurate co-registration between anatomic images and functional or metabolic data acquired using SPECT or PET. One of the limitations of PET or SPECT is limited **anatomical information** that anatomic imaging generally provides. Software fusion of PET with a previously acquired diagnostic CT often **lacks precise co-registration**, because patient positioning and imaging protocols are often different. Combined PET/CT or SPECT/CT allows the acquisition of spatially registered functional and anatomic data in one imaging procedure. Most PET/CT and some SPECT/CT systems also allow CT to be acquired as a full diagnostic protocol without compromising functional imaging. Hybrid scanners allow for biological characterization of morphological abnormalities seen on CT and vice versa. Combining tissue characterization and determining the exact location and the extent of disease has been shown to result in improved sensitivity and specificity. **Co-registered functional and anatomical information is particularly helpful in the evaluation of PET tracers in the abdomen and pelvis.** CT images are additionally used to estimate and correct for attenuation of gamma rays within the patient's body. Attenuation corrected PET can accurately quantify the amount of radiopharmaceutical and its radioactive metabolites within the tissue or lesions.

As an alternative to PET/CT, integrated PET/MR systems allow for simultaneous acquisition of PET and MRI. This is particularly helpful in certain applications requiring very accurate co-registration or anatomic visualization of structures not well seen on CT such as prostate cancer imaging. Another potential advantage of PET/MR is improved workflow in scenarios that the patient needs to have both PET and MRI done but CT imaging is not clinically indicated. Using MRI instead of CT significantly reduces exposure to ionizing radiation from the study. This is a particularly important consideration in pediatric imaging.

1.3 Processing Computer

Raw gamma camera images need processing prior to being interpretable. As a result, gamma cameras have dedicated computer processing systems. The computer collects data from the photomultipliers PMTs and helps to display it in a way that is anatomically and functionally useful to the practitioner. These images can have poor spatial resolution; thus, in order to delineate anatomy, they must be used alongside other imaging modalities. The gamma camera has inherent limitations that will always cause its images to look "fuzzy" compared to other imaging techniques. In contrast to

anatomical imaging, nuclear medicine is a functional imaging modality, and its strength is in the demonstration of organ function. In the arena of physiologic imaging, nuclear medicine has no equal.

1.4 Imaging modes

In static imaging, a single image (or two images with dual-head cameras) is acquired with the camera in one location, after which the camera head or patient position is readjusted prior to starting the next image. Static imaging can be combined with longitudinal motion of the gamma camera to create a whole-body image. Gamma cameras also have dynamic imaging capabilities, in which a series of images are taken sequentially, each for a set length of time. This acquisition mode allows visualization of physiologic processes that change over time, such as blood flow or organ function. The ability to demonstrate organ function through dynamic imaging is a key aspect of nuclear medicine. Gated imaging is a third acquisition mode that uses ECG signal to acquire data from different phases of the cardiac cycle.

Conventional SPECT cannot be performed dynamically, but can be combined with gating (e.g., to assess myocardial motion and systolic function). PET can be performed dynamically or with gating. However, most clinical PETs are done as multi-bed static imaging, generally covering from skull-base to upper thighs (unless there is a specific reason to image the entire body).

2. Radiation Safety and Adverse Events

Pharmacological Safety

Diagnostic radiopharmaceuticals are typically administered in picomolar or nanomolar amounts and are not expected to have a measurable physiologic or pharmacologic effect.

Metaiodobenzylguanidine (MIBG, lobenguane) is an exception and symptoms related to physiologic effects (tachycardia, pallor, vomiting, abdominal pain) can be experienced, particularly if a central line is used for administration. Adverse reactions are less common with newer high specific-activity formulations. Slow infusion can minimize adverse reaction to MIBG and is required when higher doses are administered for radionuclide therapy.

The reported frequency of allergic reaction or other adverse effects to radiopharmaceuticals in general is very low.² Serious or life-threatening events have not been reported with radiopharmaceuticals but may occur with non-radioactive interventional drugs used as a part of diagnostic procedure.³

Radiation Dose

Radionuclides are chosen for the energy they emit and their half-lives. **The most suitable agents emit the lowest energy that is needed for a diagnostic quality study and have short half-lives.** As a result, the radiation dose for a given nuclear medicine test is negligible. Table 3 lists the radiation doses of common nuclear medicine studies in urology with a chest x-ray and abdominal computed tomography (CT) scan as references. By comparison, annual background radiation exposure in an industrialized nation is approximately 2.2 millisieverts (mSv).⁴

For radiopharmaceutical such as MIBG that are labelled with radioactive iodine, thyroid uptake should be blocked (e.g., by administration of potassium iodine) to minimize radiation to the thyroid gland.

Staff, Pregnancy, and Children

For staff working in the nuclear medicine facility, normal hygiene precautions such as a rubber gloves and following radioprotection measures and good practice recommendations such as syringe shields and proper disposal are required. Staff handling radioactive material need to have adequate training and are required to use personal dosimetry devices.

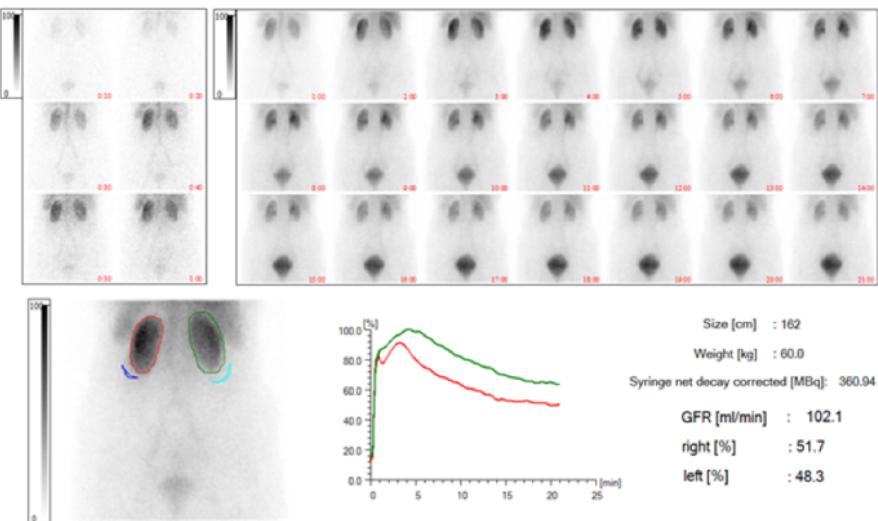
The exposure of ancillary staff and caregivers and family for diagnostic nuclear medicine procedures is very low, and no specific safety measures are needed apart from apart limiting contamination. The radiation to caregivers after radionuclide therapy, however, may exceed exposure limits for general public and written safety instructions may need to be provided to the patient.

In women of childbearing age, pregnancy and lactation status must be checked. In patients who are pregnant, the decision to delay administration of radioactive material after delivery should consider possible harm to the patient due to delayed diagnosis or risks associated with alternative diagnostic procedures. For most diagnostic procedures, radiation exposure to the fetus is considered to be low and the risk of harm is minimal. Healthy births have been reported from women who underwent nuclear medicine studies while pregnant. One caveat is that certain radionuclides, such as I-131, may cross the placenta and cause permanent damage to the developing fetus (in this case, hypothyroidism). ⁴ Radionuclide therapies are generally contraindicated during pregnancy, and most institutions require verification of absent pregnancy via a blood or urine test. In lactating women, a small amount of radioactive material may be detected in milk. For most radiotracers, excreted activity in breast milk is very low and lactation can be safely continued. Breast feeding is recommended to be briefly interrupted (12-24 hours) after certain procedures but is generally discontinued permanently after administration of I-131 or Ga-67 citrate due to the long half-life of these radionuclides; breast feeding could be resumed again for future children.

Various nuclear medicine studies have been done on children for decades safely and without proven adverse effect, due to the low dose of radiation involved. The radiation to these patients may be significantly less than alternative radiologic or fluoroscopic procedures.

3. Clinical Applications

3.1 Renal Scintigraphy



Report Created by GAMMA SCANS

Figure 1: A) DTPA scan to assess glomerular filtration

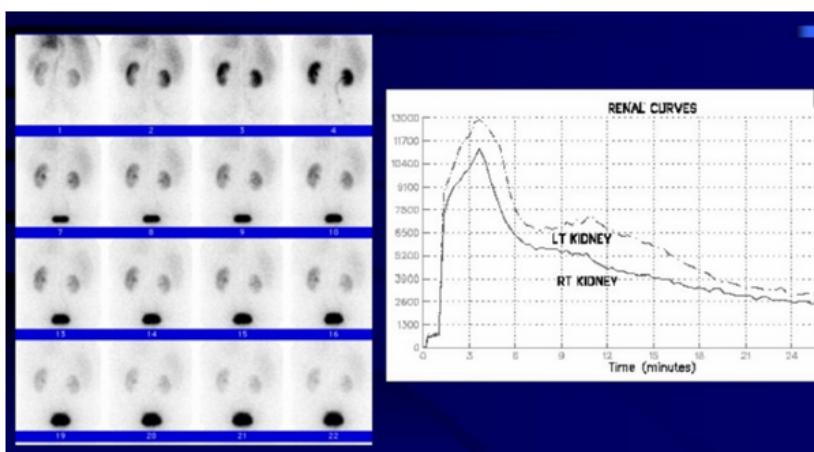


Figure 1: B) MAG3 scan to assess tubular secretion

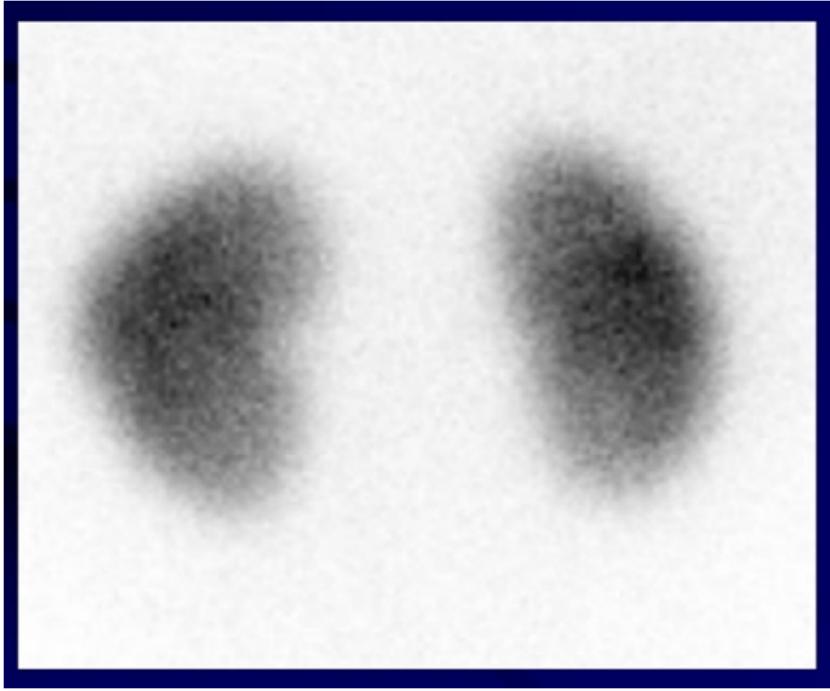


Figure 1: C) DMSA scan to assess renal tubule anatomy

Radiotracers commonly used for evaluating renal function fall into three main categories:

- Those excreted by **glomerular filtration (Figure 1A)**
 - ^{125}I -iothalamate
 - ^{51}Cr -EDTA
 - $^{99\text{m}}\text{Tc}$ -diethylenetriaminepentaacetic acid (DTPA)
- Those excreted by **tubular secretion (Figure 1B)**
 - ^{125}I -hipurran
 - ^{131}I -hipurran
 - $^{99\text{m}}\text{Tc}$ -mercaptoacetyltriglycine (MAG-3)
- Those **bound in the renal tubules (Figure 1C)**
 - $^{99\text{m}}\text{Tc}$ -glucoheptanate
 - $^{99\text{m}}\text{Tc}$ -dimercaptosuccinic acid (DMSA)



Figure 2: A) DMSA scan that demonstrates a horseshoe kidney



Figure 2: B) DMSA scan that detects photopenia on this posterior image of the kidneys suggesting scarring in the upper

pole of the right kidney.

Excreted by glomerular filtration

The most popular of these is DTPA. **DTPA is used for the evaluation of glomerular filtration function**. It can be used to visualize the kidneys, ureter, bladder, and also to measure the glomerular filtration rate (GFR). Because the nephrogram phase of the examination is brief, it is not an ideal agent for demonstrating intraparenchymal renal lesions. Also, it is not ideal for patients with obstruction or impaired renal function.¹

When ¹²⁵I-iothalamate or ^{99m}Tc-DTPA are used for measurement of GFR based on serial blood measurements (no imaging), a very small amount of activity is administered and radiation to the patient is negligible. For patients with normal or mild renal impairment, radionuclide GFR is a reliable tool for monitoring renal function (e.g., in chronic renal disease or during the course of nephrotoxic drugs).⁵

Excreted by tubular secretion

MAG-3 is one of the most used agents for renal nuclear scintigraphy. It is **cleared predominantly by the proximal tubules (95%)** with minimal filtration (less than 5%).¹ Also, because of a high extraction fraction, it is more useful in patients with renal impairment and provides better images of the kidneys. It can be used for measurement of effective renal plasma flow (ERPF).

Bound in the renal tubules

Both DMSA and glucoheptanate bind to the renal tubules to permit renal cortical imaging. There is very little excretion of either agent, although glucoheptanate does have more glomerular excretion. DMSA has a relatively long half-life, increasing radiation exposure to the kidneys. Both can be used to visualize anatomic variants and cortical abnormalities, such as scarring (**Figure 2A** and **Figure 2B**).¹

7 August, 2013

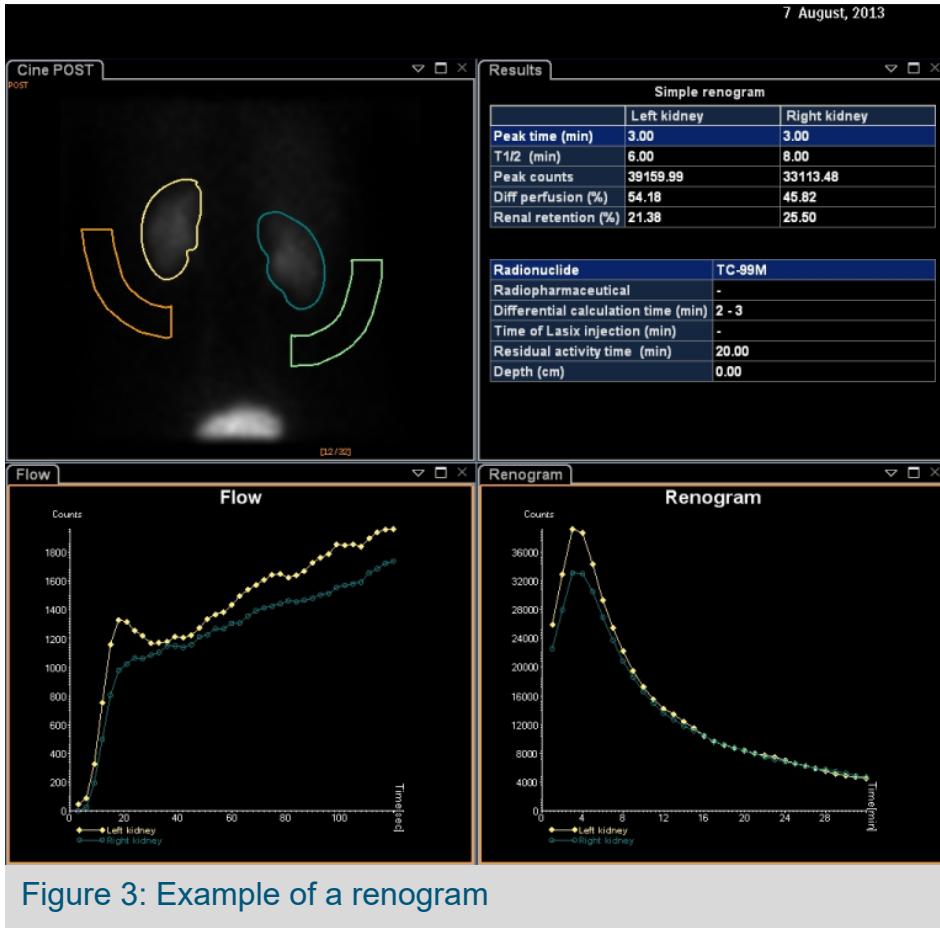


Figure 3: Example of a renogram

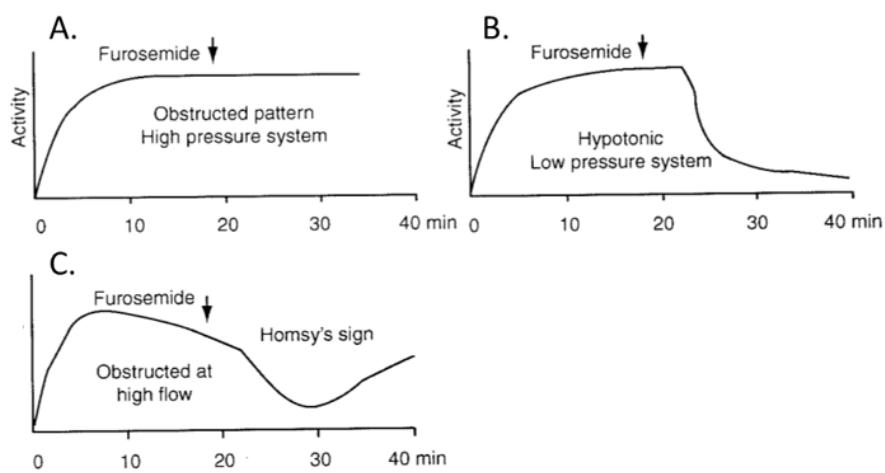


Figure 4: Patterns of clearance in diuretic renography.

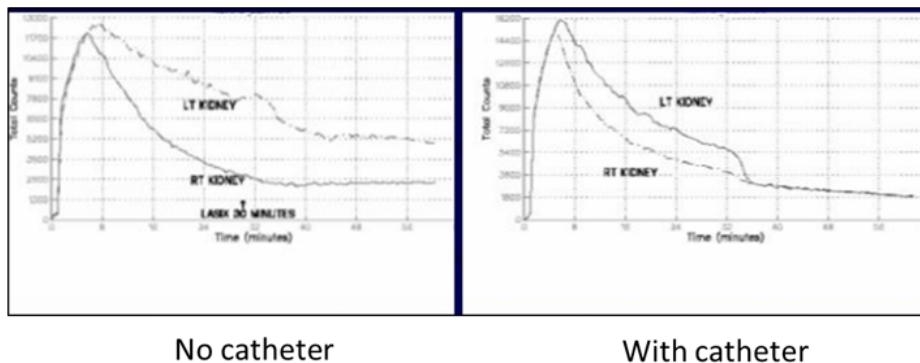


Figure 5: Effect of catheter placement on diuretic renography

It is important to obtain renal images in a standard manner. The patient should be well hydrated prior to imaging to prevent false-positive studies. In adults, oral hydration with two glasses (500 mL) of water is adequate. Patients should void just prior to the procedure. A large field-of-view camera with a low-energy, high-resolution, parallel-hole collimator is used. The patient lies supine on the imaging table with the camera under the table viewing the kidneys and bladder.

The first step of scintigraphy is **visual assessment of perfusion and function**. This is accomplished with ^{99m}Tc -labeled agents, which provide anatomic, functional, and collecting system patency information. Renal perfusion is usually begun as the radiotracer is visualized in the proximal abdominal aorta, with subsequent serial images made every 1 to 5 seconds. The activity reaches the kidneys about 1 second after the bolus in the abdominal aorta passes the renal arteries.

Time-activity curves reflecting renal perfusion during the first minute may be generated by drawing regions of interest over the aorta and each kidney. Each of the renal curves may then be compared with the time-activity curve of the abdominal aorta to assess relative renal perfusion.

After perfusion, **renal functional imaging** is the next sequence. In this series, 3- to 5-minute images are taken after administration of radionuclide. In general, maximal parenchymal activity is seen at 3 to 5 minutes, with activity usually appearing in the collecting system and bladder by about 4 to 8 minutes. Furosemide may be used to clear activity from the renal collecting systems and enhance excretion. Post-void images to enhance collecting system drainage are ideal for a complete study.

Regions of interest (ROI) measurements may be taken to create dynamic activity and excretion curves, or a renogram (Figure 3).⁴

A renogram curve is ideally obtained by using agents that are eliminated by tubular secretion (e.g. MAG3). The normal renogram curve consists of three phases: **initial renal perfusion, tubular concentration, and excretion.**⁴ The perfusion phase lasts about 30 to 60 seconds and represents the initial arrival of the radionuclide in each kidney. The tubular concentration phase occurs during minutes 1 through 5 and contains the peak of the curve. The initial uptake slope closely correlates with ERPF values. The excretion phase represents the down slope of the curve and is produced by excretion of the radionuclide from the kidney and clearance from the collecting system. There are specific quantitative data points that a renogram must possess:

- **Time to peak activity:** normally after 3-5 minutes.
- **Half-life for drainage:** the time for half of the peak activity to be cleared from the kidney. Normal is about 8 to 12 minutes.
- **Differential function:** an index of relative renal function between the two kidneys normally after 1-3 minutes. Activity in each kidney should be equal, ideally 45-55%. Usually calculated using the Rutland plot.

Diuretic scintigraphy (renography) is used to assess impairment in renal drainage. Either DTPA or MAG-3 may be used. If one or both kidneys do not appear to drain after 20 minutes, furosemide can be given intravenously at a dose of 0.5 mg/kg. Data acquisition should continue after this. Of note, a full bladder may prevent adequate drainage of upper collecting systems and can cause a false-positive study for obstruction. The bladder is catheterized routinely in diuretic renography. In adults and older children, bladder catheterization may not be necessary if there is no evidence of vesicoureteric reflux, neurogenic bladder, or lower tract obstruction. **No response to the diuretic is diagnostic of an obstructed, high-pressure system (Figure 4A).** The systems with delayed uptake that will show a good excretory response to the diuretic indicate a nonobstructed, low-pressure system (Figure 4B). If a renogram curve shows a good initial response to the diuretic, only to be followed by an upswing in the excretion curve (**Homsy's sign**), this is an intermittently obstructed system only affected at high-flow rates (Figure 4C). Quantitatively, a delayed ($T_{1/2} = 10\text{-}20$ minutes) or prolonged ($T_{1/2} > 20$ minutes) response to the diuretic should be considered a partially or completely obstructed system, respectively. If renal function is poor, the response to diuretic may be compromised and affect the veracity of the test. Additionally, a stent or vesicoureteral reflux may affect the study. **Both of these effects may be mitigated with bladder catheter placement (Figure 5).** If at the end of dynamic imaging there is high residual activity (particularly in children), gravity-assisted and postvoid drainage should be assessed.

Cortical scintigraphy using DMSA or glucoheptanate is performed for the evaluation of space-occupying lesions, functioning pseudotumors such as cortical columns of Bertin, or edema or scarring associated with acute or chronic pyelonephritis, especially in children. Planar images with low-energy, high-resolution collimators are obtained 2 to 4 hours after intravenous injection of radio-pharmaceutical. Image magnification (e.g., with pinhole collimators) may be needed in children. Standard images are posterior, right posterior oblique, and left posterior oblique views. SPECT with a multihead camera has a higher detection rate for renal lesions than conventional planar or pinhole collimator techniques.

Table 3. Radiation Dose from Common Nuclear Medicine Studies in Urology

Procedure	Patient radiation dose (mSv)
Bone Scan	4 ⁶
DTPA Renogram	1.3
MAG3 Renogram	0.7
DMSA scan	0.7 - 1.3 ⁷
DTPA GFR determination	0.0006
⁶⁸ Ga-PSMA PET (excluding radiation from CT)	3 - 5
¹⁸ F-FDG PET/CT	10 - 20
¹⁸ F-FDG PET/MRI	3.6 ⁸
Medical chest x-ray (1 film)	0.1
Abdominal CT scan	10

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The exposure of ancillary staff and caregivers and family for diagnostic nuclear medicine procedures is very low, and no specific safety measures are needed apart from apart limiting contamination. The radiation to caregivers after radionuclide therapy, however, may exceed exposure limits for general public and written safety instructions may need to be provided to the patient.

In women of childbearing age, pregnancy and lactation status must be checked. In patients who are pregnant, the decision to delay administration of radioactive material after delivery should consider possible harm to the patient due to delayed diagnosis or risks associated with alternative diagnostic procedures. For most diagnostic procedures, radiation exposure to the fetus is considered to be low and the risk of harm is minimal. Healthy births have been reported from women who underwent nuclear medicine studies while pregnant. One caveat is that certain radionuclides, such as I-131, may cross the placenta and cause permanent damage to the developing fetus (in this case, hypothyroidism). ⁴ Radionuclide therapies are generally contraindicated during pregnancy, and most

institutions require verification of absent pregnancy via a blood or urine test. In lactating women, a small amount of radioactive material may be detected in milk. For most radiotracers, excreted activity in breast milk is very low and lactation can be safely continued. Breast feeding is recommended to be briefly interrupted (12-24 hours) after certain procedures but is generally discontinued permanently after administration of I-131 or Ga-67 citrate due to the long half-life of these radionuclides; breast feeding could be resumed again for future children

Finally, nuclear medicine studies have been done on children for decades with no known adverse effect, due to the low dose of radiation involved. The radiation to these patients may be significantly less than alternative radiologic or fluoroscopic procedures.

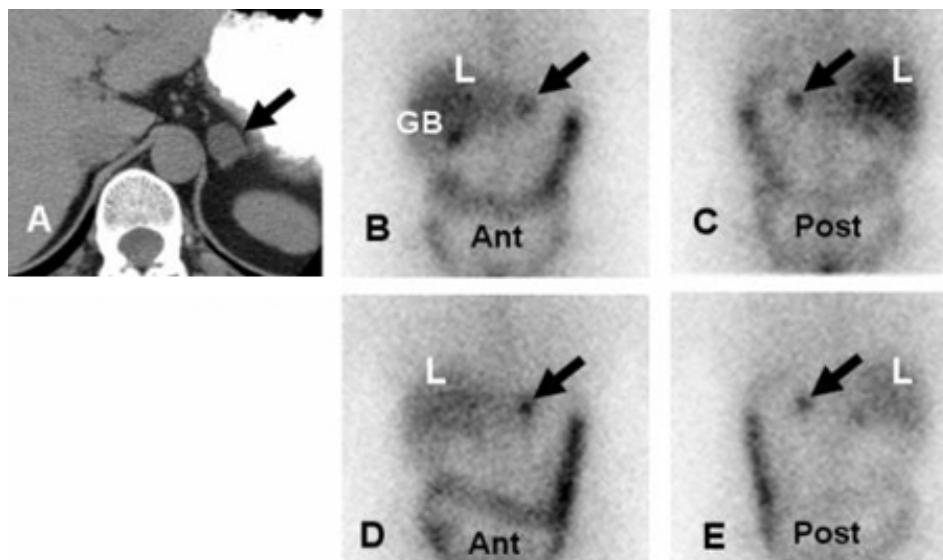


Figure 6: Left adrenal aldosteroma depicted with dexamethasone suppression NP-59 imaging: 57-year-old woman with biochemical evidence of hyperaldosteronism and a left adrenal mass. Abdominal CT (A) demonstrates a 2 cm left adrenal mass (black arrow), anterior and posterior abdominal NP-59 scans (B and C) on the third day post-injection; anterior and posterior abdominal NP-59 scans (D and E) on the fifth day post-injection; abnormal left adrenal uptake (black arrows) occurs early, before day 5 post-injection (B and C); normal uptake in liver (L), bowel (B), and gallbladder (GB).

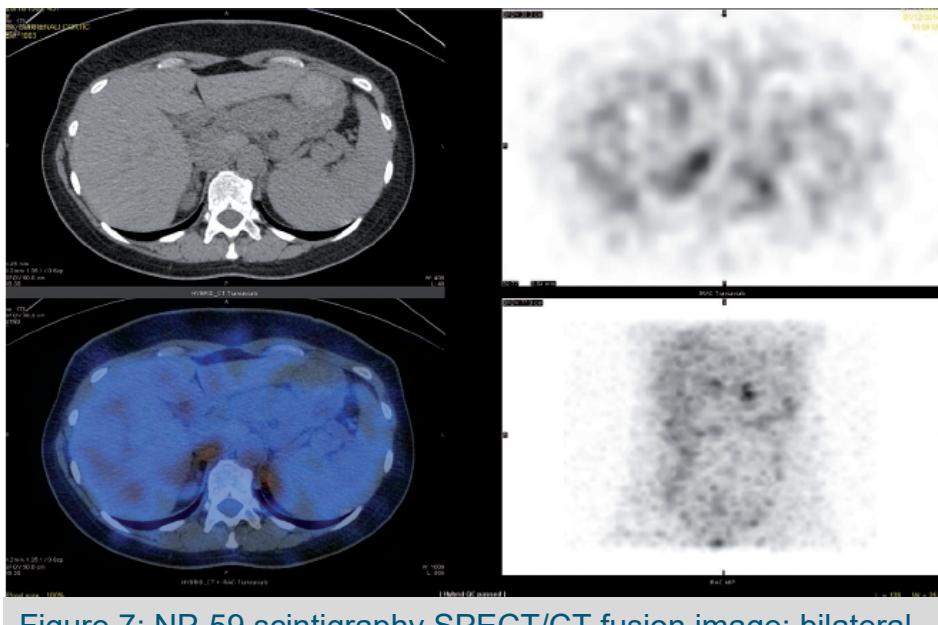


Figure 7: NP-59 scintigraphy SPECT/CT fusion image: bilateral adrenal uptake.

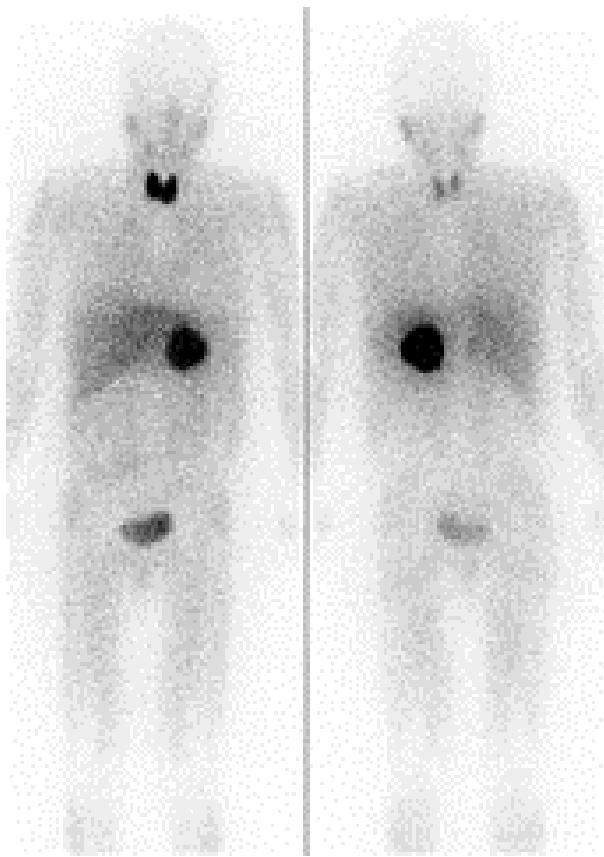


Figure 8. ^{131}I -MIBG scintigraphy shows right adrenal pheochromocytoma as a dark round lesion in the center of the body.

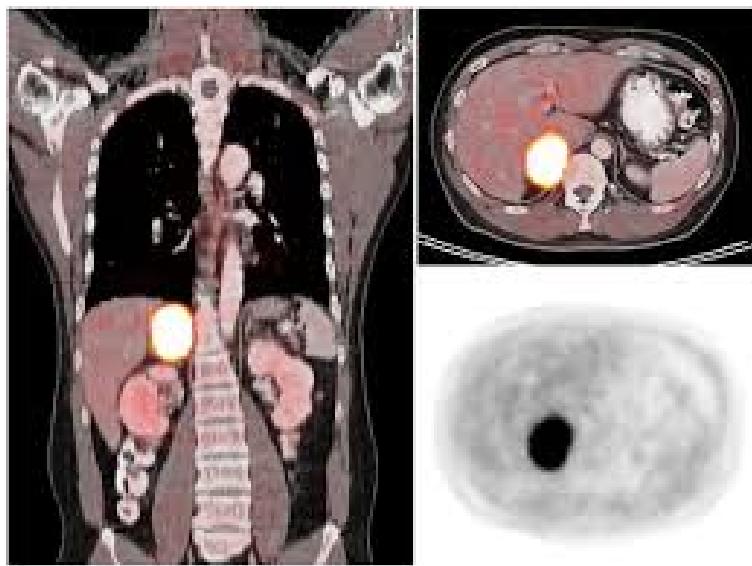


Figure 9: F-18 Flurodopamine PET-CT shows a right pheochromocytoma.

3.2 Renovascular Hypertension

Renovascular hypertension is defined as an **elevated blood pressure caused by renal hypoperfusion**, usually resulting from anatomic stenosis of the renal artery and activation of the renin–angiotensin-aldosterone system. It affects less than 1% of general hypertensive patients and up to 35% of patients with risk factors for RVH. Clues include abrupt hypertension, hypertension resistant to 3-drug therapy, abdominal or flank, unexplained azotemia or recurrent pulmonary edema in an elderly hypertensive patient, or worsening renal function during therapy with angiotensin-converting enzyme inhibitors (ACEIs). Many patients will also have a size discrepancy in their kidneys. A test to diagnose this condition is **ACEI or captopril renography**. For at least 3 days prior to the test, patients should discontinue ACEIs or angiotensin II receptor blocking agents, chronic diuretics, and calcium channel blockers, as long as clinically safe. All antihypertensive medications need not be stopped.⁹ **Radionuclides of choice are either 99mTc-DTPA or 99mTc-MAG3.**

A baseline renogram is obtained and then one is obtained after administration of a short acting ACEI, usually captopril at 25-50mg. Oral and intravenous hydration are administered during the test. **Heart rate and blood pressure should be monitored during the test, as profound hypotension can result.** The most specific diagnostic criterion for renovascular hypertension is an ACEI-induced change in the renogram.¹⁰ A normal ACEI renogram indicates a low probability (<10%) of renovascular hypertension. Renal imaging is started immediately following intravenous administration of the radionuclide and furosemide, 40 mg (for adults). Flow and functional images are obtained for 30 minutes, and time/activity curves are generated. Criteria associated with renovascular hypertension include worsening of the renogram curve, reduction in relative uptake, prolongation of the renal and parenchymal transit time, and prolongation of the time to maximum activity. ACEI renography has a sensitivity and specificity of about 90% for diagnosis of renovascular hypertension.

Reduced renal function may reduce the accuracy of the test (**Figure 10**).¹¹

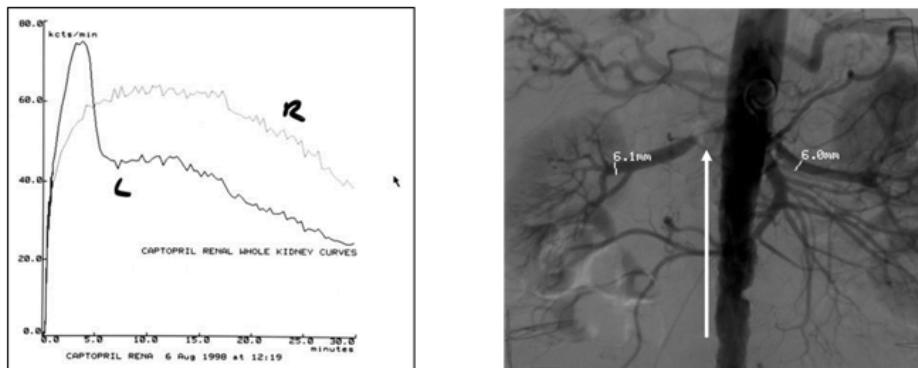


Figure 10: Captopril renogram and associated arteriogram showing functional right renal artery stenosis.

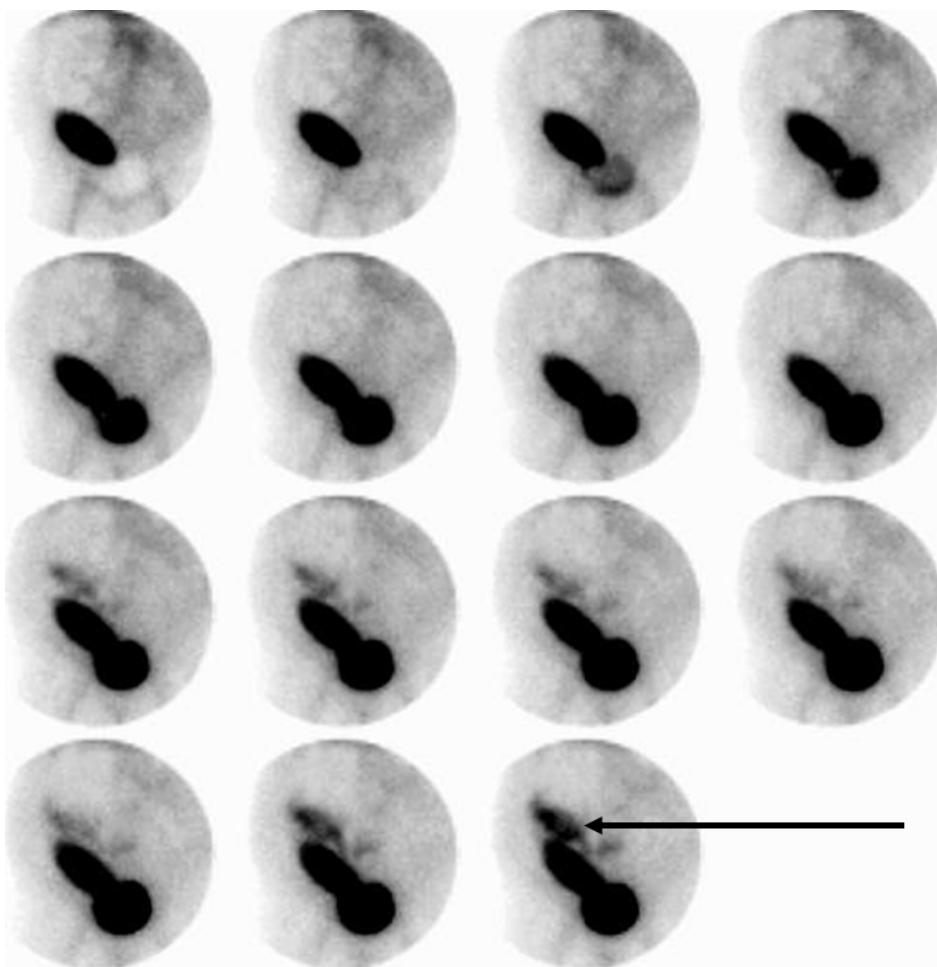


Figure 11: Renal transplant renogram demonstrating urine leak (arrow)

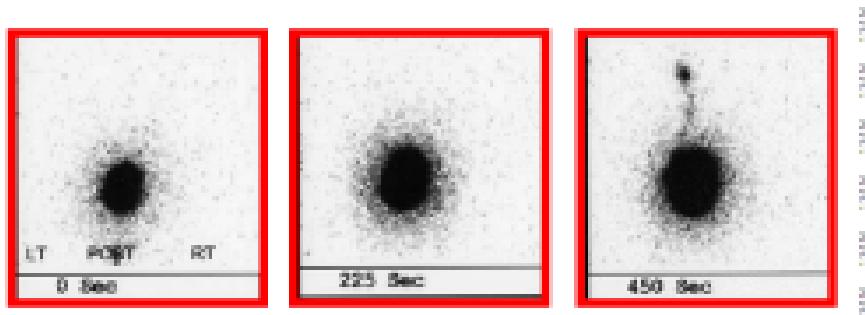


Figure 12: Static images of nuclear cystography demonstrating vesicoureteral reflux

3.3 Renal Transplantation

A transplant renogram is used to assess kidney perfusion post-transplant, especially in cases of acute tubular necrosis (ATN) with decreased urine output. It can also be used to determine a urine leak from the transplant collecting system. **$^{99m}\text{Tc-MAG3}$** is the preferred radionuclide. After administration of the radionuclide, immediate images are obtained. Within the first minute, some recommend one frame/second to determine a **first pass study**.¹⁰ This backs off to every 20 sends for 30 minutes. The bladder catheter is clamped after 30 minutes and total radionuclide in the kidney, collecting system, bladder, and any drains can be quantitated.

The first pass images can demonstrate qualitative perfusion of the transplant kidney. Kidney function can be assessed by inspection of the dynamic images of the renogram curve. Finally, total radionuclide in the system can be measured after 30 minutes and compared to subsequent studies to compare relative uptake and function.¹⁰ Urine leaks can be detected by inspection of late images.

3.4 Vesicoureteral Reflux

A radionuclide cystogram may be used to detect vesicoureteral reflux (VUR) in children with minimal radiation exposure, exposing the child to approximately **1% radiation** when compared to conventional voiding cystourethrography (VCUG). The radionuclide of choice is **$^{99m}\text{Tc-DTPA}$** . Although catheterization is not required (indirect cystography), it is generally preferred for accuracy. After catheterization of the child, the bladder is filled with a saline-radionuclide mixture over approximately 10 minutes to capacity. The infusion is stopped when the patient feels full with slight discomfort or the estimated bladder volume is reached [estimated bladder volume in milliliters = (patient's age + 2) \times 30]. After filling has ended, the child is permitted to void. Images are taken every five seconds and the ROI is the bladder and kidneys. **The diagnosis of VUR is based on an**

increase of activity in the renal pelvis viewed on static and dynamic imaging (Figure 12).¹² A post void residual can be calculated at the conclusion of the test. Although it is difficult to grade VUR according to classification guidelines because of lack of anatomic detail, nuclear cystography is nonetheless very sensitive and considered ideal to screen for VUR and monitor the natural history or surgical follow-up of reflux.

4. Urologic Infections

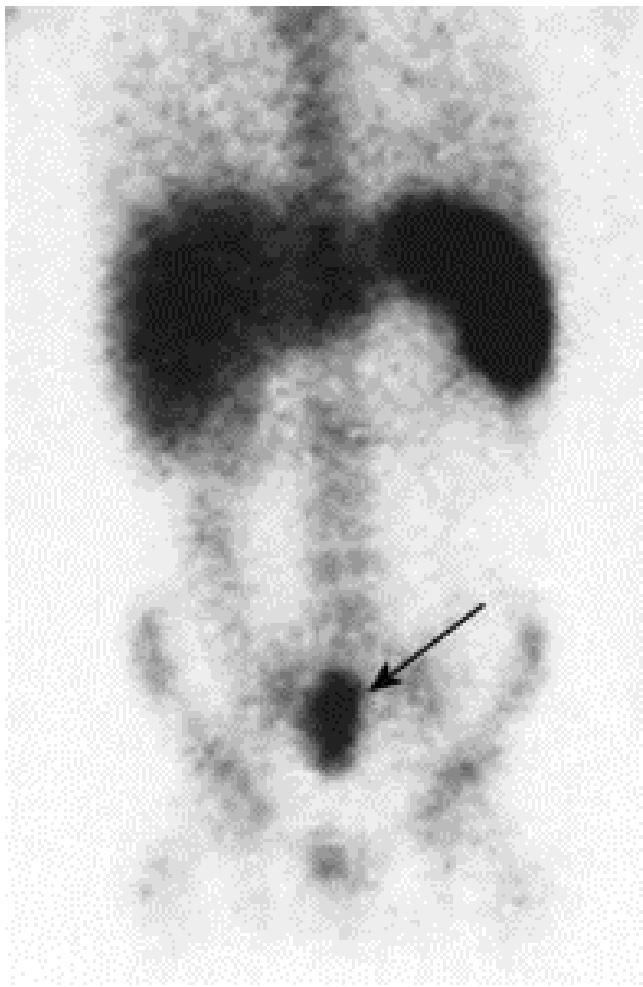


Figure 13: Pelvic abscess clearly demonstrated by ¹¹¹Indium or ^{99m}Tc white cell scan.

Radionuclide imaging can be used to identify and monitor infections encountered in urologic practice. **⁶⁷Gallium citrate and ¹¹¹indium- or ^{99m}Tc-labeled autologous white blood cells concentrate in inflamed and infected tissues.** No currently available tracers can distinguish infection from sterile inflammation. Gallium also accumulates in some tumors and cannot distinguish between benign and malignant inflammatory processes. ⁶⁷Gallium-citrate is injected intravenously and imaging of the abdomen is commenced 48 hours later. A repeat study can be obtained at 72 hours to differentiate suspected inflammatory or neoplastic lesions from physiologic gallium accumulation in the bowel. If there is clinical urgency to make a diagnosis earlier, imaging at 24 hours or even at 4 to 6 hours will

often identify a focus of infection, although detail will be suboptimal before 2 days. Also, physiologic uptake of gallium in the kidneys can persist up to 24 hours after injection and can obscure renal infection. A renal scan or colloid liver/spleen scan may be obtained in the same position as the gallium scan, for subtraction, to localize any abnormal sites of uptake more accurately. Recently, single photon emission tomography (SPECT) fused with CT has markedly improved lesion localization.

$^{111}\text{Indium}$ or $^{99\text{m}}\text{Tc}$ white cell imaging requires drawing approximately 60 mL of blood, followed by labeling with tracer, and reinjection. Imaging with $^{111}\text{indium}$ WBC commences at 24 hours, whereas $^{99\text{m}}\text{Tc}$ WBC are imaged several hours after labeling and reinjection. Neither tracer is ideal for urologic imaging because of physiologic accumulation in the kidneys and bladder, a problem not encountered with gallium as long as images are obtained more than 24 hours after injection.

Renal cortical scintigraphy with $^{99\text{m}}\text{Tc-DMSA}$ or $^{99\text{m}}\text{Tc-GHA}$ can detect acute pyelonephritis and areas of scarring in chronic pyelonephritis. It can demonstrate focal or global areas of decreased uptake of tracer with preservation of the renal contour. In acute pyelonephritis, scintigraphy shows focal areas of decreased activity or focal defects, whereas other imaging modalities may be normal or show minor anatomic changes. Scars may be the end result of reflux or infection of the renal parenchyma as in acute pyelonephritis.

Renal scintigraphy is the procedure of choice for long-term follow-up of the functional and anatomic status of the kidneys in patients who have chronic pyelonephritis. Although parenchymal or drainage system anatomy may show little change and be difficult to evaluate, scintigraphy can determine quantitatively whether the disease is stable, progressive, or resolving.

Renal abscesses usually result from ascending spread of urinary tract pathogens. Although scintigraphy may show the abscess as a focal defect, the image is not diagnostic. Gallium or WBC imaging may be capable of localizing the area of abscess, yet in most circumstances differentiation from pyelonephritis is difficult. Gallium and labeled white cells have been useful occasionally in the detection of abdominal abscesses, most notably those involving the psoas muscle.

Fanolesomab (FNB), a $^{99\text{m}}\text{Tc}$ -labeled murine anti-CD 15 IgM monoclonal antibody that specifically targets neutrophils, is a novel radiopharmaceutical designed to detect and localize infections. FNB has shown promise in detecting infectious states, such as appendicitis or other intra-abdominal infection. FNB has the advantage of imaging within minutes of injection, having a $^{99\text{m}}\text{Tc}$ label and ease and speed of preparation. FNB is likely to replace gallium and labeled white cells for scintigraphic infection detection, except in the kidneys, where physiologic uptake limits FNB's accuracy.¹³

5. Urological Malignancies

PET provides insight into the biological behavior of tumors more so than their morphological appearance. PET allows one to noninvasively determine various physiological and biochemical processes in vivo. **PET instrumentation is highly sensitive, with the capacity to detect**

subnanomolar concentrations of radiopharmaceutical, and it provides superior image resolution compared to conventional imaging with gamma cameras. PET can target several biological features of tumors including glucose metabolism, cell proliferation, tissue perfusion, and hypoxia.

In most malignancies, tumors are characterized by elevated glucose consumption and increased expression of glucose transporters and hexokinase (generally in cancer cells but sometimes in cancer-associated inflammatory cells or fibroblasts) which results in increased uptake of the **radiolabeled glucose analogue ^{18}F -fluorodeoxyglucose (FDG)**. The transport of FDG through the cell membrane via glucose transport proteins and subsequent intracellular phosphorylation by the enzyme hexokinase have been identified as key steps for subsequent tissue accumulation. Because FDG-6-phosphate is not further metabolized, it accumulates in cells and is visualized by PET imaging. The degree of uptake is closely associated with glucose metabolism which is typically high in malignant lesions but may be low in benign or indolent lesions. To minimize physiologic uptake in skeletal muscles, the patients are required to fast for a minimum of 4 hours, and are advised to avoid strenuous activity preferably for 24 hours before the study.

FDG-PET is primarily used for staging a variety of cancers, including head and neck cancer, lung cancer, breast cancer, colorectal cancer, lymphoma, and melanoma. In addition, the quantitative assessment of changes in tumor metabolic activity provided by FDG-PET allows monitoring of response to cancer treatment. Such changes are often seen before morphological changes detected by conventional imaging modalities.

FDG and most other PET tracers in clinical use have significant urinary excretion that interferes with assessment of renal parenchyma and urinary tract. Intense excreted activity may even obscure retroperitoneal and pelvic organs. Therefore, the utility of FDG PET in localized urogenital malignancies with low probability of metastasis is limited. Hydration and loop diuretics such as furosemide can reduce urinary activity and help with identification of lesions that would be otherwise obscured.

Certain cancers such as prostate carcinoma, pheochromocytoma, and low-grade renal cell carcinomas (e.g., low-grade clear cell RCC) generally have low FDG uptake. For these cancers, other radiopharmaceuticals may be used (e.g., fluciclovine or PSMA PET for prostate cancer).

5.1 Bone Scan

See [AUA Guideline on Advanced Prostate Cancer](#)



Figure 14: Technetium-99m methylene bisphosphonate (MDP) planar scintigraphy reveals multiple skeletal metastases.



Figure 15: ^{18}F -NaPET/CT images showing increased sclerotic activity within the anterior L1 vertebral body.

Radionuclide bone scan is a sensitive imaging method used to detect bone metastases in patients who have prostate cancer. Bone scans are indicated for patients with high-risk prostate cancer (PSA >20, Gleason score ≥ 8 , T3 or T4 cancer). Conversely, patients with low-risk prostate cancer should not undergo staging with bone scan because bone scans are positive in <1% of men with PSA < 20 ng/ml.¹⁴ **AUA** and **NCCN** guidelines regarding the role of staging imaging for men with unfavorable intermediate risk prostate cancer differ. A bone scan can detect bone metastases up to 18 months before evidence on plain film. Unfortunately, because bone scans image the secondary effects of prostate cancer on bone, false positives from degenerative change, inflammation, Paget disease, or trauma occur frequently. This limitation in specificity often leads to subsequent confirmatory imaging with modalities such as plain radiography, CT, MR imaging, or PET/CT scan. In **renal cell carcinoma**, bone scan is reserved primarily for patients with bone pain or elevated

alkaline phosphatase. Skeletal metastasis are seen in one-third of patients with advanced RCC and are associated with significant morbidity due to pain, pathologic fracture, or spinal cord compression. Although bone scan has generally high sensitivity of skeletal involvement in various cancers, lytic bone metastases in RCC may cause minimal osteoblastic reaction, decreasing sensitivity of bone scans to ≤50%.¹⁵ NaF PET/CT however has good sensitivity and accuracy for osseous involvement in RCC.¹⁶

In patients with muscle invasive bladder cancer or upper tract urothelial carcinoma, NCCN guidelines call for bone scan if there is clinical suspicion or symptoms of bone metastases. PET/CT may be alternatively considered if there are additionally known or suspected extra-osseous metastases. Bone metastasis in non-muscle invasive bladder cancer is unlikely, and scintigraphy is not generally recommended.

Radionuclide bone scintigraphy using radiolabeled bisphosphonates is the mainstay for the detection of skeletal metastases in patients with various tumoral entities. Bisphosphonates are organic phosphate compounds currently used as therapeutic agents for osteoporosis, due to their ability to reduce bone resorption by inhibiting human osteoblast secretion and proliferation. The rationale of using bisphosphonates for the detection of bone malignancies is that the presence of neoplastic cells usually induces increased turnover by the surrounding bone tissue; therefore, bisphosphonates primarily accumulate on the surface of crystals of hydroxyapatite around neoplastic tissue, rather than in the healthy bone. **Technetium-99m methylene bisphosphonate (MDP) and technetium-99m hydroxymethylene bisphosphonate (HMDP)** are the radiopharmaceuticals of choice to detect skeletal metastases in patients with high-risk prostate cancer at either first diagnosis or suspicion of relapse due to doubtful imaging findings and/or increased PSA value.

Bone scintigraphy can be performed by using a planar and optional tomographic (single-photon emission computed tomography [**SPECT**]) acquisition protocol: a non-contrast enhanced CT scan can be performed in addition to tomographic SPECT acquisition (**SPECT/CT**) for anatomical correlation and attenuation-correction purposes. Planar imaging of the whole body (vertex to toes) is often performed first. Additional spot planar images may be required to cover portion of the body that are incompletely or inadequately imaged on whole body images. SPECT or SPECT/CT is often performed on a limited part of body (based on location of symptoms or clinical suspicion or abnormalities noted on whole body planar images or previous imaging). A slight increase in sensitivity, yet without significant changes in specificity, when SPECT is performed as a completion of planar scan, has been reported. Since osteoblastic reaction occurs much earlier than anatomical changes in cortical bone, bone scintigraphy using MDP or HMDP is much more sensitive than such morphological modalities as CT or magnetic resonance imaging (MRI) and detects bone metastases long before anatomical changes appear. MRI, however, can potentially detect metastases from certain malignancies by directly identifying tumor in the marrow space (for example on diffusion weighted or post-contrast T1 weighted images) before it grows enough to cause reactive bone changes. Since marked osteoblastic reaction is common in bone metastases from prostate cancer, bone scintigraphy is the most sensitive, widely available, and easy-to-perform diagnostic method in

this setting, currently.

Although very sensitive, bone scintigraphy has low specificity, since both MDP and HMDP accumulate in the surrounding bone reaction, not inside the neoplastic cells, thus a higher uptake of radiopharmaceutical in a skeletal site could be ascribed to each event able to produce an increased bone apposition in that site. Overall specificity of bone scintigraphy is about 40% in prostate cancer patients. False-positive findings on bone scintigraphy are more commonly consequent to traumatic/microtraumatic injury (accidental or iatrogenic), joint degenerative or inflammatory disease (arthrosis, osteoarthritis), metabolic disorders (eg, hyperparathyroidism), or benign bone diseases (eg, benign neoplasms, Paget's disease). The overall accuracy of bone scintigraphy varies depending on the location of findings in the skeleton, being as low as 42% and 51% for pelvis and lumbar spine, respectively; conversely, higher accuracy values are shown for skull and long-bone lesions (83% and 75%, respectively). ¹³

SPECT/CT has better accuracy and specificity than planar scintigraphy or SPECT alone as many benign entities such as degenerative disease that are associated with increased radiotracer uptake have characteristic location and radiographic appearance that would exclude malignancy. On the other hand, CT may occasionally show lesions (particularly small lesions or lytic lesions) that are difficult to prospectively identify on scintigraphy.

¹⁸F-NaF PET for bone scanning was first described in 1993 for clinical use. It provides highly sensitive, 3-dimensional imaging of the skeleton, with demonstrable utility in a growing range of benign and malignant bone disorders. ¹⁸F-NaF PET has the advantages of high spatial resolution, attenuation correction, 3-dimensional tomographic images, and hybrid PET/CT imaging. PET imaging with ¹⁸F-NaF has several advantages over quantitative methods using ^{99m}Tc-MDP bone scanning. In contrast to γ -camera imaging, including SPECT, PET allows for absolute quantification of radioactivity per measured volume. ¹⁸F-NaF PET is a highly sensitive method for detection of osseous metastatic disease from a range of primary tumors, including lung, breast, prostate, thyroid, and squamous cell cancers of the head and neck. Generally, increased ¹⁸F-NaF uptake is found in sclerotic and mixed lesions and at cortical locations.

¹⁸F-NaF PET has superior sensitivity to ^{99m}Tc-labeled diphosphonate bone scanning using planar and SPECT protocols. When combined with hybrid PET/CT imaging, ¹⁸F-NaF was able to clarify many findings otherwise equivocal on conventional bone scanning. For biochemical relapse of prostate cancer, ¹⁸F-NaF appears to have greater diagnostic yield than ¹⁸F-FDG. In a comparative study between ¹⁸F-NaF PET and ¹⁸F-flurocholine PET, ¹⁸F-NaF resulted in higher numbers of detected bone metastases, although detection of additional sites of disease did not alter management.¹⁷

Conventional bone scans have **several limitations** for therapy response assessment. Unlike ¹⁸F-FDG, which targets the glucose consumption within tumors, bone-seeking radiotracers reflect the response of bone tissue to the presence of metastases. Thus, at best they represent an **indirect measurement** of tumor response. Consequently, even after successful systemic treatment of bone metastases, bone scans are known to improve very slowly. Other notable problems are **false-negative results, a flare response leading to worsening of the scan appearance despite**

a clinical response to therapy, poor interobserver agreement, subjective interpretation, and inability to grade changes in intensity and extent. Also, certain chemotherapeutic approaches may **directly interfere** with bone remodeling. For example, the anti-RANKL (receptor activator of nuclear factor κ B ligand) monoclonal antibody denosumab inhibits osteoclast function, which interferes with the ability to assess response on bone scans.

Although the ability to perform quantitative analysis in response evaluations is a key advantage of ^{18}F -NaF PET over conventional bone scanning, it has **rarely** been applied in clinical trials. Several initial studies demonstrate the potential for quantitative approaches to monitor treatment response using ^{18}F -NaF PET.

5.2 Pheochromocytoma

A pheochromocytoma is a tumor of neuroectodermal origin that produces excess quantities of catecholamines as well as numerous other physiologically active peptides. This overabundance of catecholamines causes blood pressure to increase, accompanied by a constellation of signs and symptoms that can imitate those seen with a diverse grouping of medical and surgical disorders. A pheochromocytoma is a rare cause of secondary hypertension, responsible for less than 1% of all cases of hypertension. Early recognition, precise localization, and attentive management of a benign pheochromocytoma in most instances lead to a complete cure. Pheochromocytoma and extra-adrenal paraganglioma can be malignant and 15-20% of patients can develop metastatic disease.

^{123}I -MIBG Imaging

Similar to the sympathetic nervous system, tumors of neural crest origin such as pheochromocytoma and most extra-adrenal paragangliomas express cell membrane norepinephrine transporters (NET).⁷ MIBG is a norepinephrine analogue and is taken up by the norepinephrine transporter in tumors as well as adrenergic nerve terminals in ganglia, adrenal medulla and sympathetically innervated organs such as the brown adipose tissue, heart, lungs, salivary glands, liver, and spleen. ^{131}I -MIBG and ^{123}I -MIBG have been in clinical use for several decades for diagnostic imaging in pheochromocytoma because of its high affinity and uptake by the NET and subsequent storage in the cytosol in neuro-secretory granules via vesicular monoamine transporters 1 and 2.¹⁸ Retention of MIBG in chromaffin cells is critical for MIBG scintigraphy or radionuclide therapy.¹⁹ Poorly differentiated pheochromocytoma and paragangliomas could have low uptake due to low expression of vesicular monoamine transporters.²⁰

Until recently the gold standard functional imaging method for pheochromocytoma was scintigraphy with ^{131}I -MIBG, with sensitivity of 77%-90% and excellent specificity of 95%-100%. I-131 however has suboptimal photon energies for imaging and causes significantly higher radiation to the patient and particularly thyroid gland (even with iodine blockade using SSKI) than I-123 due to longer half-life and beta emissions. As a result, ^{123}I -MIBG is currently the radiopharmaceutical of choice for diagnostic imaging and is reported to have sensitivity of 83%-100% and specificity of 95%-100% for detecting sporadic pheochromocytoma.²¹

Normal adrenal medulla shows physiological uptake of $^{123/131}\text{I}$ -MIBG. Medication use interfering with MIBG uptake in patients could result in false-negative results. Medications that should be discontinued prior to the MIBG injection (if feasible to do safely) includes labetalol, calcium channel blockers, antidepressants, tramadol, and pseudoephedrine. SPECT improves the identification of lesions in case of lesions with limited uptake or those with central necrosis. Recent use of SPECT-CT in such patients has further improved its utility with accurate anatomical localization. SPECT-CT has been shown to detect additional lesions in 81% patients for ^{123}I -MIBG and 53% patients for ^{131}I -MIBG when compared to planar scintigraphy.¹³

^{131}I -MIBG was approved in US in 2018 for treatment of patients with MIBG scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma. An open-label multicenter clinical trial showed reduced need for antihypertensive medication in a quarter of the patients and structural response in 22% of the patients treated with ^{131}I -MIBG.²² Unfortunately, hematologic adverse reactions including severe neutropenia, thrombocytopenia, and lymphopenia were common and 12% of patients had to discontinue treatment due to myelosuppression or other severe adverse effects. Despite the high specific activity of ^{131}I -MIBG and low affinity of MIBG for adrenergic receptors that minimizes side effects, worsening hypertension occurred in 11% of the patients. Similar results were previously published supporting the utility of ^{131}I -MIBG for therapy despite the possibility of serious toxicity.²³

Somatostatin Receptor (SSTR) Imaging

Ga-68 or Cu-64 somatostatin analogue PET tracers (^{68}Ga -DOTATATE, ^{68}Ga -DOTATOC, ^{68}Ga -DOTANOC, ^{64}Cu -DOTATATE) are the second choice for nuclear imaging of adrenal pheochromocytomas (after ^{123}I -MIBG and FDOPA PET) and first choice for metastatic pheochromocytoma or extra-adrenal paragangliomas, or for imaging patients with succinate dehydrogenase deficient malignancies.²⁴ In-111pentetreotide can be used when SSTR PET is not available, and has been used with variable results to detect this tumor. It has higher sensitivity for detecting metastatic pheochromocytoma than for detecting benign pheochromocytoma.

Most existing somatostatin-based tracers primarily target somatostatin receptor subtype 2 (SSTR2). Although SSTR2 is not always present on pheochromocytoma, SSTR2 and SSTR3 are frequently overexpressed in primary pheochromocytomas and paragangliomas.²⁵ ^{68}Ga -DOTANOC PET/CT has been shown to have high accuracy for detection of pheochromocytomas in patients with Multiple Endocrine Neoplasia syndrome.²⁶ The reported sensitivity of ^{68}Ga -DOTATATE PET/CT in sporadic pheochromocytoma is slightly lower than FDOPA PET (81% vs. 94%).²⁷ Lesions with internal cystic degeneration generally have low uptake causing a false negative PET.²⁸ Several studies have reported that the sensitivity and diagnostic accuracy for SSTR PET is superior to ^{123}I -MIBG.²⁹ In pheochromocytoma patients, on a per-lesion basis, the sensitivity of ^{68}Ga -DOTATOC was 91.7% and that of ^{123}I -MIBG was 63.3%. It appears that Ga-68 labeled somatostatin analogues are particularly superior to ^{123}I -MIBG for detecting extra adrenal pheochromocytoma, smaller lesions and lesions with central necrosis.³⁰

F-18 Fluorodopa and F-18 Flurodopamine PET-CT

F-18 labeled dihydroxyphenylalanine (FDOPA) has enabled PET imaging of benign pheochromocytoma. FDOPA enters the cell via the amino acid transporter based on the capability of pheochromocytomas and other neuroendocrine tumors to take up, decarboxylate, and store amino acids and their biogenic amines. Recent studies confirmed the usefulness of this technique in benign and malignant pheochromocytomas. It has been found to be superior to both $^{123/131}\text{I}$ -MIBG and FDG for these tumors. In patients with metastatic disease, a per-lesion-based analysis showed a limited overall sensitivity of FDOPA PET: less than half of the metastases detected by CT/MRI were detected by FDOPA PET. On the other hand, in 71% of patients with malignant pheochromocytomas/paragangliomas, one or more metastases were discerned by the technique. For non-metastatic pheochromocytoma FDOPA performed similarly to I-123 MIBG.³¹

Another tracer for imaging pheochromocytoma is **F-18 Flurodopamine**, Flurodopamine (FDA) PET is clearly superior to I-131 MIBG with sensitivities of 100% and 56%, respectively. FDOPA PET-CT may be better than I-131 MIBG for imaging pheochromocytoma and especially extra-adrenal lesions.

F-18 FDG PET/CT

Because of low metabolic activity of pheochromocytomas, FDG uptake in these tumors is frequently low, although high uptake is generally seen in SDHx-associated paragangliomas. FDG has been used with some success for imaging metastatic pheochromocytoma, it is nevertheless a non-specific ligand that shows uptake in various tumors as well as inflammation. **Table 4** summarizes the choice of radiopharmaceuticals for imaging pheochromocytoma and paragangliomas.

Table 4. Selection of radiopharmaceutical(s) for imaging pheochromocytoma and paraganglioma²⁴

	<i>1st choice</i>	<i>2nd choice</i>	<i>3rd choice</i>
Sporadic Pheochromocytoma	¹²³ I-MIBG	⁶⁸ Ga-DOTATATE*	FDG
Inherited PHEO (except SDHx): NF1/RET/VHL/MAX	¹²³ I-MIBG or ⁶⁸ Ga-DOTATATE*	FDG	¹¹¹ In-pentetreotide
Sporadic head and neck paraganglioma	⁶⁸ Ga-DOTATATE*	¹¹¹ In-pentetreotide	
Extra-adrenal sympathetic paraganglioma Multifocal or metastatic paraganglioma SDHx mutation	⁶⁸ Ga-DOTATATE*	FDG and ¹²³ I-MIBG or FDG and ¹¹¹ In-pentetreotide	

* ⁶⁸Ga-DOTATOC or ⁶⁴Cu-DOTATATE are equivalent options to ⁶⁸Ga-DOTATATE

5.3 Prostate Cancer

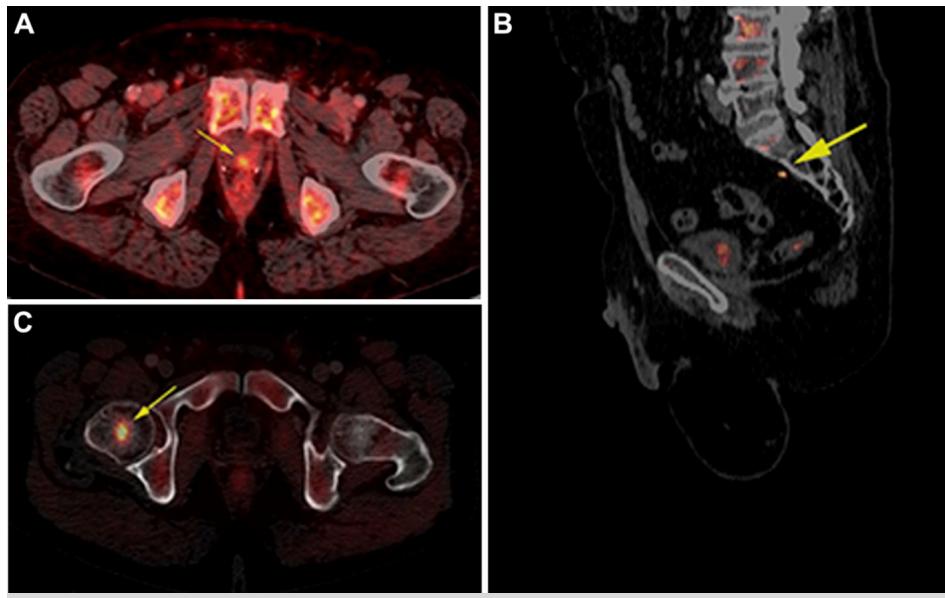


Figure 16

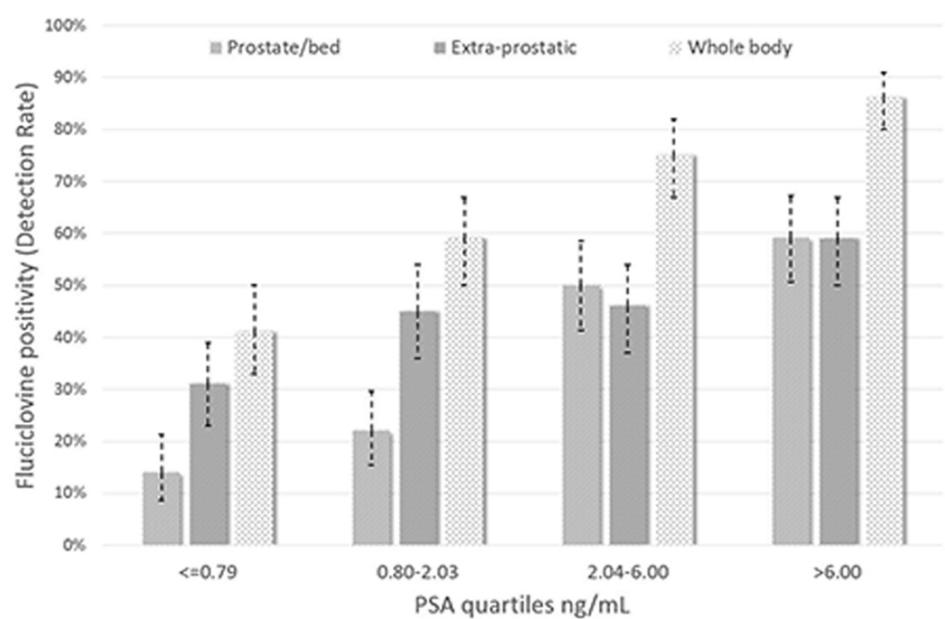


Figure 17

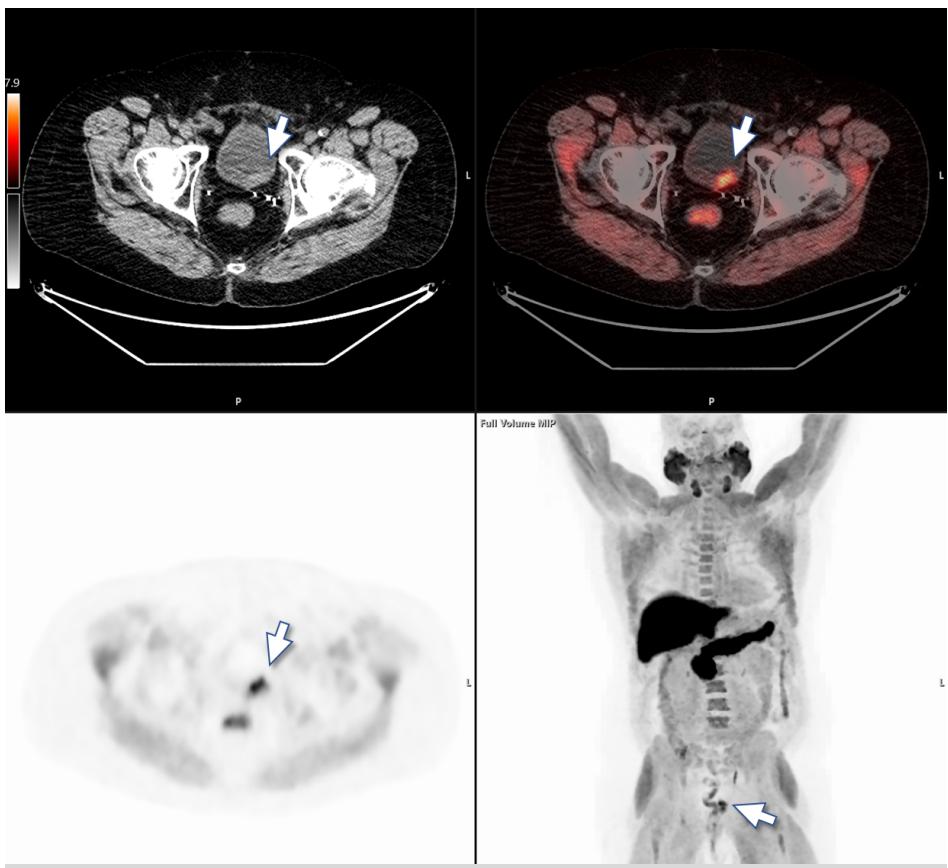


Figure 18: ^{18}F -Fluciclovine PET shows bladder wall recurrence (arrow). The maximum intensity projection (MIP, lower right) also shows biodistribution of fluciclovine with intense physiologic uptake in the liver and pancreas. Normal bone marrow uptake in the lower lumbar spine and sacrum is absent due to prior radiation therapy. Unlike FDG and many other radiopharmaceuticals, fluciclovine is not significantly excreted in the urine, making it easier to see lesions in the pelvis and prostate bed.

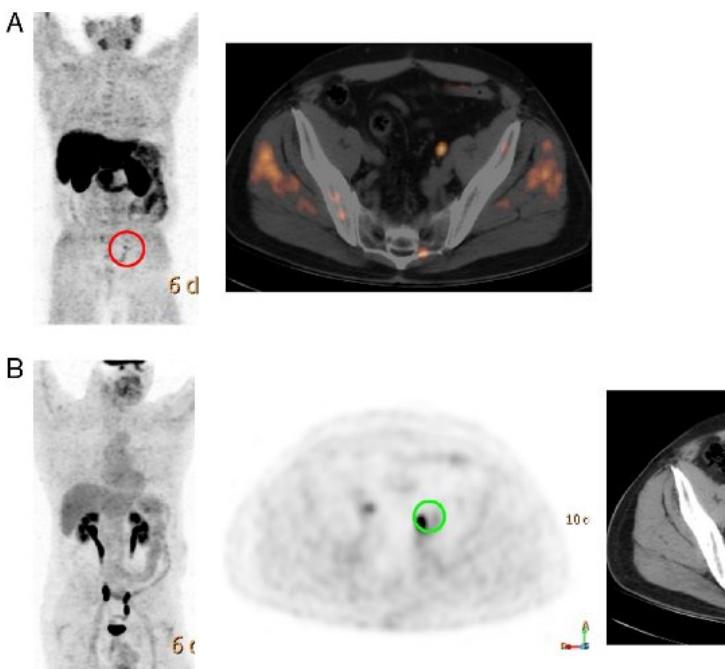


Figure 19: ^{11}C -choline PET CT shows prostate cancer recurrence within the left iliac lymph node.

FDG PET

Diagnosis and staging

Most primary prostate tumors have low-grade FDG uptake and considerable overlap between carcinoma and BPH. Furthermore, there is no correlation between increasing tumor grade and FDG uptake. For local lymph node detection at primary diagnosis, PET is not reliable enough to use in the pre-surgical assessment. Low tumor volume and limited spatial resolution of the camera have been postulated as a reason for the PET-negative studies.

Metastatic Disease

FDG-PET is generally inferior to bone scan for detection of osseous metastases, with sensitivities of 20–65%.³² As in the primary disease, the reasons for this are unclear, but it may reflect greater glycolysis in some metastases than in the primary. The type of bone lesions may also be relevant. PET was better than a bone scan for identifying osteolytic lesions, but worse in osteosclerotic lesions in patients with breast cancer. However, PET may identify soft-tissue disease in lymph nodes outside the pelvis and in the liver, which would be negative on CT.

Recurrence

FDG PET is not very useful in distinguishing fibrosis after surgery and radiotherapy from residual prostate cancer tissue. In patients with rising PSA levels, FDG cannot reliably distinguish postoperative scar and local recurrence after radical prostatectomy.

Monitoring treatment response

Although FDG accumulation may decrease in the metastatic prostate cancer lesions, the changes in PSA and FDG uptake may be of different orders of magnitude and therefore, FDG PET may be unreliable in assessing response to therapy. Neuroendocrine prostate cancers and PSMA-negative

lesions could be exceptions for which FDG PET seems to be useful for assessment and monitoring of response to treatment.

18F-Fluciclovine PET

In 2017, 18F-Fluciclovine (Axumin™) was approved for use in the US by the FDA for patients with suspected recurrent prostate cancer. Also known as trans-1-amino-3-18F-flurocyclobutanecarboxylic acid (18F-FACBC), fluciclovine is a synthetic amino acid analogue of L-leucine which is taken up by amino acid transporters which are upregulated in prostate cancer, including LAT-1 and ASCT2. Two studies were the basis for approval.³³ In the first study, 105 men with suspected recurrent prostate cancer underwent fluciclovine scanning as read by 3 independent radiologists, with confirmatory needle biopsy of suspected lesions. The second study compared fluciclovine scans with C11 choline scans, also reviewed by 3 blinded radiologists. Both studies demonstrated accuracy of fluciclovine for suspected recurrent prostate cancer. A larger prospective phase 3 study demonstrated a cancer detection rate of 68% (403/595 patients), both in the prostate fossa (39%), pelvic lymph nodes (33%) as well as distant metastatic sites (26%).³⁴ See **Figure 16**, **Figure 17**, and **Figure 18**.

18F-Fluciclovine is indicated for suspected recurrent prostate cancer as indicated by rising PSA when conventional imaging (CT, radionuclide bone scan and MRI) are negative or equivocal.

Prostate Specific Membrane Antigen (PSMA) imaging

Prostate specific membrane antigen (PSMA, folate hydrolase, or glutamate carboxypeptidase II) is a transmembrane glycoprotein enzyme that is highly expressed on the surface of prostate cancer cells. PSMA overexpression correlates with advanced, high-grade, metastatic, androgen-independent disease.

¹¹¹In-capromab pendetide scintigraphy utilizes an IgG monoclonal antibody that binds to the PSMA on prostatic epithelial cells, but not to PSA or prostatic acid phosphatase. Studies report a sensitivity of 75%, a specificity of 86% and an overall accuracy of 81% in the detection of extraprostatic disease in high-risk prostate cancer patients. ¹¹¹In-capromab scans have been shown to detect occult metastatic disease in about 25% of men who were thought to have isolated local recurrence.³⁴ Sensitivity is good even at low PSA levels, with one study identifying abnormal uptake in 85% of post-prostatectomy patients, with a median relapsed PSA level of 1.2 ng/ml (range 0.2–4.8 ng/ml).

Low-molecular-weight substrates bind with high-affinity with the catalytic domain of PSMA are superior to monoclonal antibodies such as capromab and are preferred for targeting due to faster pharmacokinetics and higher tissue penetration, and low nonspecific binding to inflammatory cells.

PSMA PET radiopharmaceuticals (⁶⁸Ga-PSMA-11 and ¹⁸F-DCPyL) are now FDA approved for imaging prostate cancer. The two indications for PSMA PET are detection of PSMA-positive lesions in men with prostate cancer and (1) suspicion for metastatic disease before initial definitive therapy, and (2) **suspicion for biochemical recurrence after treatment.**^{35,36} A recently published randomized clinical trial showed that PSMA PET changed management of ~25% of patients with high-risk prostate cancer who were candidates for curative-intent surgery or radiotherapy.³⁷ PSMA

imaging may also play an important role in differentiating local failure from metastatic recurrence after radical prostatectomy to allow for a better selection of patients for salvage radiotherapy. Both F-18 and Ga-68 labeled PSMA agents have higher positivity and tumor-to-background contrast in biochemically recurrent prostate cancer than radiolabeled choline, especially at low serum prostate-specific antigen (PSA) levels (<1 ng/mL).³⁶ In patients with biochemical recurrence and low PSA levels (<0.5 ng/mL) evaluated for potentially curative salvage treatment, PSMA PET has the highest detection rate of all existing imaging techniques.³⁸ In one study, patients with early biochemical recurrence after prostatectomy underwent both ⁶⁸Ga-PSMA-11 and ¹⁸F-fluciclovine PET/CT; the detection rate was 56% for PSMA PET compared to 26% for fluciclovine.³⁹ Even for bone involvement, PSMA PET has excellent sensitivity. ¹⁸F-DCFPyL PET localized bone lesions in 8 of 38 patients with negative bone scan or ¹⁸F-NaF PET.⁴⁰

Multiple F-18 and Ga-68 radiolabeled PSMA ligands are used throughout the world. ¹⁸F-DCFPyL and ¹⁸F-PSMA-1007 have rapid plasma clearance and low hepatic uptake and higher tumor-to-background uptake compared to first generation PSMA tracers such as DCFBC. Ga-68 labeled tracers are overall diagnostically comparable to F-18 labeled tracers although the image quality and half-life of Ga-68 is suboptimal compared to F-18. Unfortunately, intense excreted activity in the urinary tract sometimes obscures lesions around the bladder. High hepatic uptake with some PSMA tracers such as ⁶⁸Ga-PSMA-11 reduces sensitivity for hepatic involvement. Although PSMA tracers are often assumed to be specific for prostate cancer, PSMA overexpressed can occur in neovasculature in other cancers such as squamous cell carcinoma, and renal cell carcinoma. It is important to recognize that a small subset (<10%) of prostate cancers or metastatic prostate cancer lesions may not overexpress PSMA. Other PET radiopharmaceuticals including fluciclovine and FDG may play a role if there is a discrepancy between PMSA PET findings and clinical picture.^{40,41}

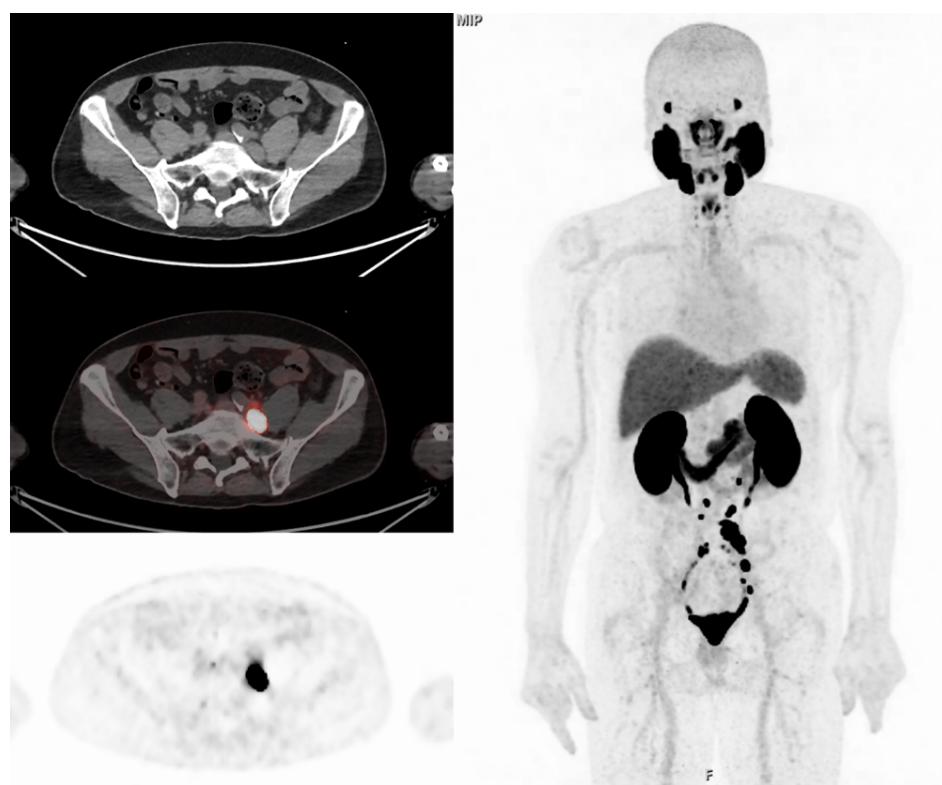


Figure 20. PSMA PET/CT (using ^{18}F -DCFPyl) in a patient with biochemically recurrent prostate cancer. Axial CT, fused, and PET images show an enlarged left iliac lymph node with intense uptake. MIP image (right) shows bilateral retroperitoneal lymph node metastases. Normal intense uptake is seen in salivary and lacrimal glands, kidneys, and along the ureters and bladder.

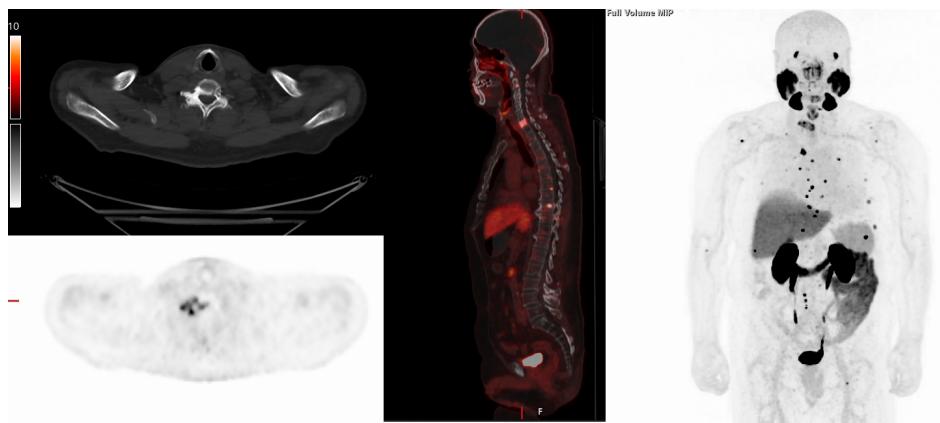


Figure 21. ^{18}F -DCFPyl PET/CT in a patient with metastatic prostate carcinoma and multifocal osseous lesions.

Alternative PET tracers in Prostate Cancer

In neoplastic cells there is up-regulation of choline uptake and phosphorylation. Attempts have been made to use choline initially labelled with ^{11}C as a PET tracer. Two initial studies found that ^{11}C -choline was better than FDG for evaluating the primary, local disease and bone metastases.

^{18}F labeled choline showed a high uptake in patients with advanced prostate cancer, with detection of bone and soft-tissue metastases. Tumor uptake was also reduced in patients scanned after androgen ablation, suggesting a role in monitoring. ^{18}F -fluorocholine-PET/CT might have a significant impact on management of prostate cancer patients, particularly if PSA levels increase to $> 4 \text{ ng/ml}$. Fluorocholine-PET/CT may be useful for detecting local recurrence and lymph node metastases as well.

^{11}C -acetate has been compared to ^{18}F -FDG and on visual analysis all primary tumors accumulated ^{11}C -acetate, compared with 15 for FDG. ^{11}C -acetate also identified intrapelvic and bone metastases.³² ^{11}C -choline-PET/CT revealed a sensitivity of 83% for localization of nodules $>5 \text{ mm}$, which was comparable to transrectal ultrasound-guided biopsy.⁴²

5.4 Renal Cell Carcinoma

FDG uptake in primary RCC lesions is variable depending on histologic subtype and grade.^{43,44} High uptake is more common in aggressive tumors⁴⁵ or certain uncommon histologies such as succinate dehydrogenase-deficient RCC, mucinous tubular and spindle cell carcinoma, or RCCs with sarcomatoid dedifferentiation. In contrast, low-grade clear cell and chromophobe carcinomas usually

have low uptake. Overall, the sensitivity and accuracy of FDG PET for detection and characterization of primary renal lesions is not high enough to justify routine use in staging. Nonetheless, FDG PET can be used to characterize equivocal findings on other modalities and helps with decision making and has 85-90% sensitivity and specificity for detecting extra-renal metastasis in high-risk patients or recurrence after nephrectomy.^{46,47}

Local recurrence in the renal bed can occur in ~5% of patients and is potentially curable. Assessing this condition with CT has always been difficult, because of the problem of separating scar tissue from tumor. PET, because of its unique metabolic activity, does not have this limitation. In one study assessing this circumstance and in the eight patients referred for this condition, PET was able to clearly differentiate tumor recurrence from fibrosis/necrosis, and thus affect the management. PET has also distinguished tumor and tumor thrombus in the renal vein after therapy. It is worth noting that FDG PET can be more sensitive than bone scan for evaluation of osseous involvement in RCC.⁴⁸

^{99m}Tc-sestamibi SPECT can help differentiate some benign solid renal masses from RCC. Sestamibi is a lipophilic cation that binds electrostatically to the mitochondria, resulting high uptake in mitochondria-rich cells such as oncocytes. Oncocytomas (the most common benign solid renal mass) and hybrid oncocytic/chromophobe tumors are rich in mitochondria. Conversely, RCCs (particularly low-grade clear cell subtype) typically have a paucity of mitochondria. As a result, oncocytomas have high uptake on sestamibi SPECT, while most RCCs have low uptake. Malignant lesions also actively transport sestamibi out of the cytoplasm, resulting further decreased uptake. A positive sestamibi SPECT has high specificity (95%) for benign tumors.⁴⁹

5.5 Bladder Cancer

Relatively little work has been done with PET in bladder cancer; the main area of concern is the excretion of tracer through the bladder, making visualization of the tumor difficult. Still, FDG PET can be useful in staging muscle invasive bladder cancer and is more accurate than conventional imaging for nodal or distant metastases⁵⁰ although early nodal involvement is frequently missed. For lymph node staging PET has a sensitivity of 67%, a specificity of 86% and an accuracy of 80%, all of which are better than CT or MRI. Persistent FDG uptake in primary tumor following neoadjuvant chemotherapy in patients with stage II or III disease is suggestive of pathologic residual disease. PET/CT can also be done after cystectomy (if metastatic disease is suspected) and is accurate for restaging and biopsy planning. As in renal cell carcinoma, it is capable of differentiating tumor recurrence from radiation fibrosis/necrosis.

5.6 Testicular Cancer

FDG-PET has 90% sensitivity for detecting residual tumor in seminoma. In patients with seminoma and residual masses of >1 cm, the reported sensitivity, specificity, PPV and NPV for PET are 89%, 100%, 100% and 97%, respectively. The effect is greatest in masses of >3 cm.

The ability of FDG-PET to predict response to chemotherapy in testicular cancer was evaluated in

patients completing two or three cycles of induction chemotherapy, but before the start of high-dose chemotherapy. All patients underwent PET and CT, as well as having markers measured. The outcome of high-dose chemotherapy was accurately predicted by PET, CT and markers in 91%, 59% and 48%, respectively. PET therefore adds information in predicting those with an unfavorable outcome and provides valuable prognostic information for those in a good or intermediate outcome group, to appropriately select patients for further treatment.³²

In seminoma PET is useful in defining the presence or absence of disease in residual masses. It has also identified disease earlier than conventional imaging in patients with raised marker levels. The studies at initial diagnosis are promising but further work needs to be done on PET in this area. At best it will enable a more appropriate use of chemotherapy/radiotherapy in those who require it, and in those who do not, enabling better overall treatment.

6. Treatment of Metastatic Prostate Cancer

The majority of patients with metastatic castrate resistant prostate cancer (mCRPC) develop bone metastases, which results in significant morbidity and mortality as a result of skeletal-related events (SREs) such as bone pain, pathologic fracture, and spinal cord compression. **Bone-seeking radiopharmaceuticals have historically been available but relegated as a palliative treatment for pain in patients with metastatic prostate cancer.** Therapeutic radiopharmaceuticals emit either alpha or beta particles. An alpha particle, which is ejected from a heavy nucleus during alpha decay, consists of two neutrons and two protons. A beta particle is an electron released from a nucleus containing excess neutrons during beta decay, in which one neutron is converted to a proton, an electron, and a neutrino. Both α- and β-particles can deliver damaging radiation locally to cancerous cells. Several β-emitting radiopharmaceuticals (strontium-89, 153Sm-EDTMP, and Re-186 HEDP) are approved for palliation of pain caused by bone metastases from prostate cancer. The most prominent limitation of these agents is myelosuppression. ⁸⁹Sr and ¹⁵³Sm are the most commonly used β-emitting radiopharmaceuticals, initially approved in the US for treatment of bone metastases are **Strontium-89 chloride or ⁸⁹Sr** (Metastron; GE Healthcare, Arlington Heights, IL) and Samarium-153 lexisronam or ¹⁵³Sm (Quadramet; EUSA Pharma, Oxford, UK). There was no demonstration of improvement in overall survival in Phase III trials, although **palliative benefits** were seen that formed the basis of US FDA approval. Pain improves in most patients^{51,52} with complete reduction in pain in some patients and no increase in analgesic use, although severe adverse effects (mainly leukopenia and thrombocytopenia) are relatively frequent.^{13,53} Palliation occurs within 4-28 days after administration and typically lasts for 3-6 months.

Ra-223 dichloride (²²³Ra) is currently the most commonly used radiopharmaceutical for treatment of symptomatic bone metastasis in castration-resistant prostate cancer. ²²³Ra dichloride (marketed as Xofigo; Bayer Health Pharmaceuticals, Wayne, NJ), is an α-particle emitter. Radium is a calcium analogue which binds to newly formed hydroxyapatite crystals in areas of increased osseous turnover. α-emitters deliver a more localized radiation with very short ranges of <100μm than do β-emitters causing disruption of tumor-stroma interaction rather than directly

radiating and damaging malignant cells.⁵⁴ They have higher mutagenic and lethality potential effects through DNA damage. Due to small track length (<0.1mm in tissue) radiation to normal bone marrow and myelosuppression is far less than beta-emitters. Radium is excreted through the gastrointestinal tract with 60-75% of the administered activity excreted within the first week. The remaining radium decays with a half-life of 11.4 days. Radium also emits a very small amount of gamma rays that have been used for dosimetry, but are not generally clinically useful. ²²³Ra administration has a dose dependent effect in reducing pain, with more than 50% of patients experienced relief or decreased need for pain medication after intravenous injection of 55 kBq/kg.⁵⁵

Multiple studies demonstrate that ²²³Ra treatment is safe and well tolerated. The ALSYMPACA trial (ALpharadin in SYMptomatic Prostate CAncer) is the first randomized phase III trial to demonstrate improved overall survival with a bone-seeking radioisotope.⁵⁶ A total of 922 patients with mCRPC across 19 countries were recruited. All patients were required to have progressed with symptomatic bone metastases with at least 2 metastatic sites on scintigraphy in the absence of visceral metastases. All recruited patients had either received previous docetaxel, refused docetaxel, or were ineligible for docetaxel. The study demonstrated a 3.6-month survival advantage (14.9 versus 11.3 months, resp., P = 0.00185, HR = 0.695). In addition, the frequency of skeletal-related events was reduced in the ²²³Ra group, and the median time to a SRE increased (15.6 versus 9.8 months). ²²³Ra is also less toxic than the previous generation of bone-seeking radionuclides. It was well tolerated with low rates of grade 3/4 neutropenia (1.8% versus 0.8%) and thrombocytopenia (4% versus 2%). This trial formed the basis of approval by the FDA of alpharadin on May 15, 2013 for patients with symptomatic mCRPC to the bones in the absence of visceral metastases. Non-bulky (<3 cm) nodal involvement is not a contraindication for ²²³Ra therapy. However, ²²³Ra is ineffective for treatment of liver or pulmonary metastases which are associated with shorter survival compared to patients with metastases limited to skeleton and lymph nodes.

The recommended dose and schedule for ²²³Ra is 55 kBq/kg administered by slow intravenous injection over 1 minute every 4 weeks for 6 doses. Given the potential for hematologic toxicity certain parameters are required prior to first administration, with absolute neutrophil count $\geq 1.5 \times 10^9/L$ and, hemoglobin \geq to 10g/dL and platelet count greater than or equal to $100 \times 10^9/L$. The ability to utilize ²²³Ra in the clinic may shift the paradigm with regard to the use of radiopharmaceuticals such that it may truly be a viable treatment option even in men before chemotherapy unlike older radiopharmaceuticals that have usually been relegated to use in the end-of-life care setting.

While there are no current guidelines that would dictate optimal sequencing strategies that incorporates the use of radiopharmaceuticals with contemporary agents, the role of radiopharmaceuticals, specifically ²²³Ra, is anticipated to increasingly gain preference especially in the setting of symptomatic or asymptomatic patients presenting with predominantly bony metastases with the feasibility of continuation of concomitant androgen-biosynthesis inhibitors or antiandrogens. Concurrent ²²³Ra therapy and chemotherapy is not well studied and is not recommended due to synergistically increased toxicities. ²²³Ra appears to be safe in patients who have adequate marrow function after chemotherapy.

Although ^{223}Ra can be given safely with abiraterone or enzalutamide⁵⁷, adding ^{223}Ra therapy to combination of abiraterone and prednisone does not improve skeletal symptoms and has been associated with increased incidence of pathologic fractures and mortality [ERA-223 trial: 806 patients, Increased incidence of fracture 28.6% vs. 11.4%].⁵⁸ The interim analysis of phase III EORTC-1333-GUCG/PEACEIII clinical trial showed that the combination of ^{223}Ra and enzalutamide can increase the risk of fractures in asymptomatic or mildly symptomatic mCRPC patients. However, fracture is rare if bone protecting agents such as zoledronic acid or denosumab are started at least 6 weeks before the first injection of ^{223}Ra .⁵⁹⁻⁶⁰ Re-treatment with ^{223}Ra in selected patient population is feasible and appears to be well tolerated.⁶¹

Utilization of targeted radionuclide therapy in metastatic prostate cancer using PSMA is emerging. Low-molecular-weight PSMA ligands bind to either folate hydrolase or glutamate carboxypeptidase catalytic domains of PSMA and form a complex that can subsequently internalize and deliver a beta or alpha-emitting radionuclide in prostate cancer cells. Safety and therapeutic effects of several ^{177}Lu -labeled PSMA ligands is being investigated in several past and on-going compassionate use clinical trials. PSA response is seen in most patients after the first treatment⁶² and often continues after each subsequent treatment.⁶³ Other reported therapeutic effects include decreased size of soft tissue lesions,⁶⁴ improved pain control and quality of life,⁶⁵ and improved progression free and overall survival.⁶⁶ Treatment is particularly effective in patients with metastatic disease limited to lymph nodes. Patients with visceral metastasis may have poor PSA response and shorter survival after treatment.⁶⁷ **PSMA-617 is the most well studied radiopharmaceutical for treatment of metastatic prostate cancer** and has particularly favorable clearance from renal parenchyma compared to other tracers reducing radiotoxicity to kidneys. Recently, the results of VISION trial were published.⁶⁸ This was a multicenter randomized clinical trial comprising 831 patients with metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor-pathway inhibitor and one or two taxane regimens. After a median follow-up of 20.9 months, ^{177}Lu -PSMA-617 plus standard care significantly prolonged both progression-free survival (8.7 vs. 3.4 months) and overall survival (15.3 vs. 11.3 months) compared to standard care alone. The treatment was well tolerated and did not affect the overall quality of life despite higher incidence of significant adverse events (grade 3 or above: 52.7% vs. 38%). It is important to note that the therapeutic effect depends on high expression of PSMA in lesions, therefore PSMA PET before therapy is used to assess patient eligibility. Patients with negative PSMA PET or one or more lesions with low uptake (i.e., less than or equal to liver) were excluded from the VISION trial (12.6% of patients in total). Similarly, a multicenter, randomized phase 2 trial showed ^{177}Lu -PSMA-617 therapy is associated with better PSA response and fewer grade 3 or 4 adverse events compared to cabazitaxel in patients with metastatic castration-resistant prostate cancer. In this study, PSMA and FDG PET were used in conjunction to assess eligibility, and patients with low PSMA uptake in FDG-avid lesions were excluded.

Videos

Presentations

Nuclear Medicine Presentation 1

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