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# Current Status of Radionuclide Renal Cortical Imaging in Pyelonephritis

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**Brief Title:** Renal cortical imaging

**ABSTRACT**

Pyelonephritis is an infection of the kidneys which is seen more commonly in children than the adults. Technetium-99m-dimercaptosuccinic acid ($^{99m}$Tc-DMSA) scan is a radionuclide imaging study to detect renal scarring after acute pyelonephritis (late DMSA scan) and also helps to diagnose acute pyelonephritis in febrile urinary tract infections (acute DMSA scan). Planar imaging in multiple views (posterior and bilateral posterior oblique views) is generally used. Pinhole imaging with a high-resolution collimator magnification of each kidney allows detection of smaller cortical defects. Single-photon emission computed tomography (SPECT) is optional. SPECT/Computed tomography (SPECT/CT) is not recommended in children due to higher radiation exposure than routine DMSA scan. The main limitations of DMSA scan includes relatively long waiting time after radiotracer injection, long acquisition time and high radiation dose which is particularly important in repeated studies in children and limited spatial resolution of gamma cameras. $^{99m}$Tc-glucoheptonate is an alternative radiotracer when $^{99m}$Tc-DMSA is not available. Dynamic renal functional imaging radiotracers can grossly assess renal cortex in the first few minutes of the dynamic imaging. Gallium‑68 prostate‑specific membrane antigen ligand ($^{68}$Ga-PSMA ligand) positron emission tomography (PET) has ability to provide images of normal renal cortex and demonstrate renal cortical defects from cysts. In this article, we wanted to assess the current status of renal cortical imaging and present $^{68}$Ga-PSMA ligand renal cortical PET images. We would like to further emphasize that $^{68}$Ga-PSMA ligand provides excellent renal cortical images and studies should be done to compare $^{68}$Ga-PSMA ligand PET to DMSA scan in renal diseases, particularly in pyelonephritis.

**Key words:** Renal cortical imaging, $^{99m}$Tc-DMSA, pyelonephritis, $^{68}$Ga-PSMA ligand, PET

## INTRODUCTION

Pyelonephritis is a bacterial infection of the kidneys. The estimated annual incidence of pyelonephritis is 10.5 million to 25.9 million cases globally (*1*-*3*). It is more commonly seen in children, particularly in infants and females. Young sexually active women, elderly and pregnant women are also at risk.

Pyelonephritis can be acute or chronic. In acute pyelonephritis, kidney infection is sudden whereas in chronic pyelonephritis kidney infection is recurrent or persistent. The main cause of acute pyelonephritis is gram-negative bacteria, the most common being Escherichia coli. Vesicoureteral reflux is the most common underlying etiology in febrile urinary tract infections (UTIs) or pyelonephritis in children (*4*). Signs and symptoms of acute pyelonephritis usually include fever, flank pain, burning on urination, increased frequency and increased urgency. Patients also experience nausea and vomiting. Common symptoms of acute pyelonephritis can be absent in children (*5*). Early diagnosis of pyelonephritis allows early treatment with antibiotics and reduces the risk of renal and non-renal complications. Pyelonephritis can complicate with sepsis, septic shock, death, hypertension and renal scarring/renal failure.

A detailed history and physical examination is the mainstay of evaluating patients with pyelonephritis. Laboratory studies such as urinalysis, urine culture and blood work (complete blood cell count and complete metabolic panel) should be performed. Imaging studies such as renal ultrasound, Technetium-99m-dimercaptosuccinic acid ($^{99m}$Tc-DMSA) scan and abdominal/pelvic computed tomography (CT) with contrast, and magnetic resonance (MR) imaging are helpful in detecting acute pyelonephritis and renal scarring. The mainstay of treatment of acute pyelonephritis includes antibiotics, analgesics and antipyretics.

## $^{99m}$Tc-DMSA scan

$^{99m}$Tc-DMSA is a widely used radiotracer for renal cortical imaging. $^{99m}$Tc-DMSA binds to proximal tubular cells (pars recta) with 40%-65% of the injected dose present in the renal cortex 2 hr after the injection (*6,7*). DMSA scan is used to detect renal parenchymal defects due to acute pyelonephritis and renal sequelae (scars) 6 months after acute infection. It also helps detecting renal abnormalities such as abnormal duplex kidney, small kidney, dysplastic tissue and horseshoe kidney, ectopic kidney and confirmation of non-functional multicystic kidney (*6,7*).

The most common clinical indication of DMSA scan is pyelonephritis (*8-14*). DMSA scan is mainly used to detect scarring sequel following acute pyelonephritis (late DMSA scan). It is recommended to wait at least 6 months to obtain DMSA scan to demonstrate the scarring (*7*). It is also used to diagnose acute pyelonephritis in patients with febrile UTIs and called as acute DMSA scan (*7,10,12,14*). Single or multiple defects are seen in the renal cortex in pyelonephritis. In acute pyelonephritis, renal cortical defects are seen as reduced or absent uptake and do not deform the renal contour. There may be increase in the volume of the affected area or whole kidney (*6*). Renal cortical defects are with volume loss in the affected cortex in cases with scarring sequel following acute pyelonephritis and with chronic pyelonephritis (*6*). Acute and chronic pyelonephritis cannot always be distinguished on DMSA scan (*6*).

In routine $^{99m}$Tc-DMSA studies, planar images of the kidneys with high or ultra-high resolution collimators are obtained in posterior and bilateral posterior oblique projections (*6,7*). Additional planar images from bilateral anterior oblique and lateral and anterior projections can also be obtained if there is no patient motion or discomfort. Pinhole imaging with a high-resolution collimator magnification of each kidney allows detection of smaller cortical defects (*6*). Single-photon emission computed tomography (SPECT) imaging is optional and various results have

been reported comparing sensitivity of SPECT to planar and pinhole imaging. SPECT was reported to be superior to planar imaging for demonstrating renal cortical defects (*15,16*). However, Brenner et al. reported that DMSA SPECT using dual-head SPECT camera offers no statistically significant diagnostic advantage over planar imaging for detection of cortical defects (*17*). Rodriguez et al. stated that contour defects are seen more frequently on tomographic slices, whereas reduced uptake defects are seen more frequently on planar images (*18*). Due to slightly vertical tilted anatomic position of the kidneys, interpretation of tomographic slices may be difficult but 3D maximum intensity projection image may help better demonstrating contour defects. SPECT/CT is not recommended in children due to higher radiation dose as compared to routine DMSA scan.

Studies have shown that a DMSA scan is more sensitive for detecting acute and chronic pyelonephritis than renal ultrasound (*19-21*). Intravenous pyelography has low sensitivity in detecting acute pyelonephritis (*22,23*). DMSA scan detected more defects as compared to ultrasound and intravenous pyelography (*24,25*). There were changes in the DMSA scan in 92% of the children with acute pyelonephritis as compared to renal ultrasound which showed changes in 69% of the children (*24*). At follow-up, 68% of the children showed changes in the DMSA scan, 47% by renal ultrasound and 48% by intravenous pyelography (*24*). DMSA scan was abnormal in 78% of the children with acute pyelonephritis and renal ultrasound was abnormal in 11% (*25*). Parenchymal defects seen on Tc-99m DMSA scan are not specific to pyelonephritis and can also be seen in renal abscess, cyst, duplex kidney and hydronephrosis. Hence, a combination of an ultrasound and a DMSA scan allows a better differentiation between these clinical situations (*7*). Doppler sonography (color and power) and DMSA results were concordant in 81% of kidneys with acute pyelonephritis (*26*). In another study, power Doppler was found to

be superior to color Doppler in defining extent of hypoperfusion which is seen in most pyelonephritic lesions (*27*). Studies have demonstrated that CT is more accurate or has a similar sensitivity and specificity to DMSA scan for the detection of acute pyelonephritis but it has the risk of intravenous contrast reaction and higher radiation exposure (*28-30*). Studies comparing magnetic resonance urography/MR imaging to DMSA scan have shown that magnetic resonance urography/MR imaging is equivalent or superior to DMSA scan in the detection of pyelonephritis and renal scarring (*31-33*).

Per American College of Radiology appropriateness criteria for acute pyelonephritis, DMSA scan, color Doppler ultrasound, CT with or without contrast, MR imaging and other radiological studies are usually not appropriate for initial evaluation of acute pyelonephritis in the uncomplicated patient (*19*). In complicated patients with acute pyelonephritis (diabetes or immunocompromised or history of stones or prior renal surgery or not responding to therapy), CT abdomen and pelvis with and without IV contrast is usually appropriate and DMSA scan, ultrasound and MR imaging may be appropriate (*19*).

***Limitations of DMSA scan***

One of the main limitations of DMSA scan is relatively high radiation dose, particularly when multiple studies are needed in pediatric patients with recurring UTIs. The effective dose estimate range is 1-10 mSv for adults and 0.3-3 mSv for children (*19*). Radiation dose to the kidney is 0.45 mGy/MBq and effective dose is 0.039 mSv/MBq for children (5 year-old) (*6*).

The other limitations of DMSA scan includes relatively long waiting time after radiotracer injection which is usually 2-3 hr and relatively long image acquisition time which is minimum of 15-30 min (5-10 min per view, minimum 3 views). A long acquisition time can cause motion artifacts. Patient sedation may be needed, particularly in infants or uncooperative children, to

prevent motion artifacts. Patient sedation procedure is inconvenient for the patient and families and laborious for the physicians and staff involved in performing DMSA scan. Patient sedation procedure requires patient preparation, presedation evaluation, obtaining informed consent and performing the sedation as well as post-sedation assessment. It also carries certain risks and side effects. Immature renal function in newborns may cause reduced kidney to background ratio and reduce the detection of renal cortical defects (*6*). A smaller percentage of lesions are detected in children less than one year of age than children more than 1 year of age (*34*). Physicians should also be aware of normal variations of kidneys (*7*). High normal background activity in the renal cortex may obscure small parenchymal defects.

***Other radiotracers for renal cortical imaging***

Technetium-99m-glucoheptonate ($^{99m}$Tc-glucoheptonate) is another radiotracer used to image the renal cortex when $^{99m}$Tc-DMSA is not available. $^{99m}$Tc-glucoheptonate is partially concentrated and excreted in the urine. It is partially bound to the renal tubules with 10%-20% of the injected dose present in the proximal convoluted tubules of the cortex 2 hr after injection (*6*). Approximately 40%-65% of this radiopharmaceutical is handled by glomerular filtration (*6*).

Dynamic renal imaging tracers such as Technetium-99m Mercapto-acetyl-triglycine ($^{99m}$Tc-MAG-3) and Technetium-99m diethylene-triamine-pentaacetate ($^{99m}$Tc-DTPA) can grossly assess renal cortex in the first few minutes of the dynamic study and can demonstrate moderate or large cortical defects. Dynamic $^{99m}$Tc-MAG-3 scintigraphy can show a region of decreased activity at 2 minutes, which develops into an area of focal parenchymal retention at 10 to 20 minutes (regional parenchymal dysfunction) (*35*). Sfakianakis et al. also used MAG-3 SPECT to image renal parenchyma (*36*).

***Potential radiotracers***

Gallium‑68 prostate‑specific membrane antigen ligands ($^{68}$Ga-PSMA ligand) are relatively new positron emission tomography (PET) radiotracers for prostate cancer which are used for initial staging in high-risk disease and for localization of prostate cancer in the setting of biochemical recurrence (*37-40*). Physiological biodistribution of $^{68}$Ga-PSMA ligand includes uptake/activity in various normal tissues which is highest in the kidneys. Assessing kidneys in low intensity settings shows that this radiotracer demonstrates high uptake in renal cortex with high resolution images (*41*). Figure 1 shows normal $^{68}$Ga-PSMA ligand PET images of renal cortex as compared to DMSA scan. Figure 2 shows renal cortical defects due to cysts seen on Ga-68 PSMA ligand PET/CT images. $^{68}$Ga has shorter half‑life (68 min) than $^{99m}$Tc (6 hr). Effective and kidney radiation doses with $^{68}$Ga-PSMA ligand appear to be comparable to $^{99m}$Tc-DMSA but this should be further studied (6*,42,43*). The CT part of PET/computed tomography (PET/CT) imaging further increases radiation dose but CT images may not be needed as non-attenuation corrected PET also provides good quality images of the kidneys due to high renal cortical uptake *(41)*. Waiting time after radiotracer injection (30-60 min versus 2-3 hr) and image acquisition time (2-6 min versus 15-30 min) is less with $^{68}$Ga-PSMA ligand PET as compared to DMSA scan. PET scanners offer higher efficiency for detecting gamma photons and higher spatial resolution over gamma cameras (*44*). Although $^{68}$Ga-PSMA ligand is costlier than $^{99m}$Tc-DMSA and not available at every institute, it would be worthwhile to compare PSMA PET to DMSA scan in renal diseases, particularly in pyelonephritis, to understand whether this PET radiotracer could be used to image renal cortex in various renal diseases.

## CONCLUSION

Pyelonephritis is a common infection of the kidneys, particularly in children. Early diagnosis and treatment is important to avoid complications. Currently, $^{99m}$Tc-DMSA scan is a commonly used radionuclide renal cortical imaging study with certain limitations. $^{68}$Ga-PSMA PET shows excellent images of normal renal cortex and demonstrates renal cortical defects from cysts. In this article, we wanted to assess the current status of renal cortical imaging and present $^{68}$Ga-PSMA ligand renal cortical PET images. We would like to further emphasize that $^{68}$Ga-PSMA ligand provides excellent renal cortical images and studies should be done to compare $^{68}$Ga-PSMA ligand PET to DMSA scan in renal diseases, particularly in pyelonephritis.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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**FIGURE LEGENDS**

**FIGURE 1.** Selected **c**oronal CT, PET and PET/CT fusion images of $^{68}$Ga-PSMA ligand (normal size and magnified) (top and middle row images) and coronal CT, SPECT and SPECT/CT fusion images of $^{99m}$Tc-DMSA (bottom row image) in two different patients with normal renal profile. $^{99m}$Tc-DMSA images were obtained from a 32-year-old average size male with microscopic hematuria and CT showing small size right kidney and no parenchymal abnormalities in both kidneys. DMSA scan was performed 3 hours following intravenous injection of 185 MBq (5 mCi) $^{99m}$Tc-DMSA using GE Discovery 670-16 slice SPECT/CT camera (GE Medical Systems, Waukesha, USA) equipped with high resolution parallel hole collimator and with following acquisition and reconstruction parameters: a low-dose CT, SPECT acquisition:20 second per view, 60 views in 360° rotation, 128x128 matrix, no zoom, 20% window centered at 140 keV and iterative reconstruction (2 iterations and 10 subsets). $^{99m}$Tc-DMSA images show small size right kidney and no parenchymal defects in both kidneys. $^{68}$Ga-PSMA ligand PET/CT image was obtained in a 59 year-old average size patient with prostate cancer, 60 min following intravenous injection of 185 MBq (5 mCi) $^{68}$Ga‑PSMA ligand using Philips Time of Flight PET/CT camera (Philips Medical Systems, Best, Netherlands) with a low-dose CT (120 kVp and 40 mAs) and 3 min/bed PET acquisition from skull base to mid thighs. $^{68}$Ga-PSMA ligand PET images show high resolution images of the kidneys with high uptake and excellent separation of renal columns as compared to DMSA scan. Maximum standardized uptake value (SUVmax) in $^{68}$Ga-PSMA ligand PET study was 50.7 in the left renal cortex.

RC: Renal cortex, RM: Renal medulla, R-col: renal column, Clx: Calyceal structures, P: Pelvis (with mild pelvic activity).

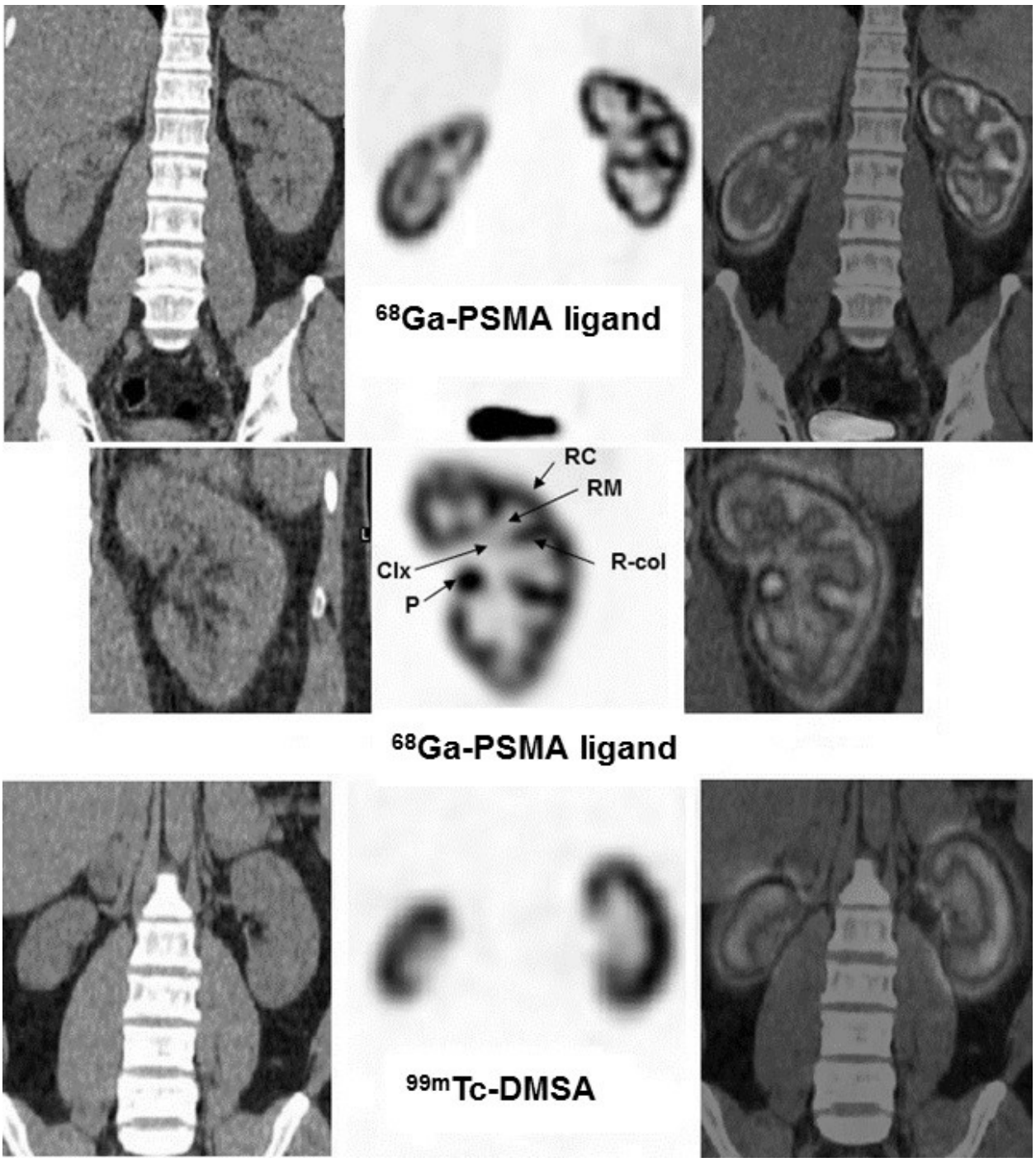
68Ga-PSMA ligand
RC
RM
Clx
R-col
P
68Ga-PSMA ligand
99mTc-DMSA

**FIGURE 2.** Selected transaxial CT and PET images of $^{68}$Ga-PSMA ligand PET/CT study in a 67 year-old patient with prostate cancer and normal renal profile with the same parameters and equipment used in figure 1. PET image shows cortical defects in both kidneys corresponding to low attenuation areas/cysts in both kidneys which measure 32 mm x 34 mm on the right and 8 mm x 10 mm on the left (arrows). SUVmax was 74.7 in right renal cortex and 67.4 in right renal column.