Review of the Clinical and Technical Aspects of ^{99m}Tc-Dimercaptosuccinic Acid Renal Imaging: The Comeback "Kit"

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^{99m}Tc-labeled dimercaptosuccinic acid (^{99m}Tc-DMSA) imaging is a well-established and highly sensitive method for the diagnosis of several renal cortical disorders affecting children and adults. Beginning in 2014, ^{99m}Tc-DMSA availability was severely impaired when it was added to the Drug Shortages List of the U.S. Food and Drug Administration and was commercially unavailable thereafter. The agent shortage negatively impacted practitioners' ability to evaluate renal cortical defects in children and adults and changed renal imaging practice. A survey among pediatric nuclear medicine clinicians confirmed the clinical need for ^{99m}Tc-DMSA. Finally, in early 2023 the Food and Drug Administration again approved ^{99m}Tc-DMSA in the United States. During the ^{99m}Tc-DMSA shortage, established practitioners may not have had the opportunity of using ^{99m}Tc-DMSA as they were accustomed in their experience. Also, newer imaging specialists and referring physicians and technologists may not have benefited from having ^{99m}Tc-DMSA in their training. Therefore, it is time to bring back ^{99m}Tc-DMSA into the armamentarium of imaging methods available to evaluate regional cortical renal function.

Key Words: radiopharmaceuticals; renal; DMSA; imaging; kidney; SPECT

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For the diagnosis and follow-up of several renal disorders in children and adults, ^{99m}Tc-labeled dimercaptosuccinic acid (^{99m}Tc-DMSA) renal imaging is a well-established method that is of great value (Table 1). It is safe and simple to perform and has a very high diagnostic sensitivity (>90%) for the detection of renal cortical defects (*1,2*). The renal cortex is where blood is filtered in the nephrons. The filtering unit of the nephron is the glomerulus; it is attached to the convoluted tubule, which removes waste while returning needed substances to the body. Scintigraphic defects on ^{99m}Tc-DMSA imaging indicate loss of function in the renal cortex, most commonly due to pyelonephritis or scarring.

^{99m}Tc-DMSA has been widely available for decades. Unfortunately, during the period 2014 until 2023, ^{99m}Tc-DMSA had a severely limited availability in the United States and was commercially unavailable. The supply interruption was "due to the inability of [a] proposed supplier to reliably produce one of the product's key components and the additional complexities related to the manufacturing relocation of the final product …" (*3*). In contrast ^{99m}Tc-DMSA continued to be available in Europe and many other countries around the world.

The shortage of ^{99m}Tc-DMSA in the United States significantly limited the use of this unique, highly sensitive imaging method. During the shortage of ^{99m}Tc-DMSA, only non–Food and Drug Administration–approved ^{99m}Tc-DMSA formulations were available in the United States through a very small patchwork of local suppliers. This was not sufficient to meet clinical demand (*1,4*).

This shortage created a vicious circle in which many nuclear medicine units were no longer performing ^{99m}Tc-DMSA scintigraphy due to the unavailability of the radiopharmaceutical, resulting in a significant reduction of clinical demand. Additional factors contributing to its reduced use include older practice guidelines, lack of education and experience of referring physicians about its value, concern about radiation exposure, and others. Understandably, clinicians

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TABLE 1
Indications for ^{99m}Tc-DMSA Imaging

No.	Indication
1	Detection of permanent renal parenchymal scarring
2	Detection of acute pyelonephritis
3	Detection of parenchymal damage after trauma
4	Characterization of structural renal abnormalities: for example, solitary kidney, duplex kidney, small kidney, dysplastic kidney, horseshoe kidney
5	Detection of ectopic renal tissue, including cross-fused renal ectopia
6	Quantitation of differential (split) renal function
7	Confirmation of nonfunctional multicystic dysplastic kidney
8	Evaluation of unexplained hypertension when there is clinical suspicion for renal disease such as dysplasia or scarring
9	Evaluation of renal parenchymal function in patients with renovascular hypertension before and after revascularization procedures
10	Renal parenchymal function regional assessment in patients with complex renal calculi before and after treatment
11	Surgical decision-making for ureteropelvic junction obstruction or refractory vesicoureteral reflux based on differential renal function
12	Evaluation of renal parenchyma when there is allergy to iodinated CT contrast, and MRI is unavailable/contraindicated (*18*)

faced with questions of renal cortical integrity used other imaging techniques despite their lower sensitivity (e.g., ultrasound) and in some cases greater technical complexity (e.g., MRI).

In 2019, a survey among nuclear medicine clinicians clearly demonstrated an ongoing need for the availability of ^{99m}Tc-DMSA (Fig. 1). Respondents reported unfamiliarity with how to access alternative formulations of ^{99m}Tc-DMSA that were available through several nuclear pharmacies, including both compounded and manufactured formulations. Some providers had access to ^{99m}Tc-DMSA but were reluctant to use less stringently regulated, non–Food and Drug Administration–approved compounded formulations or were not aware that a manufactured option was also available (*4*).

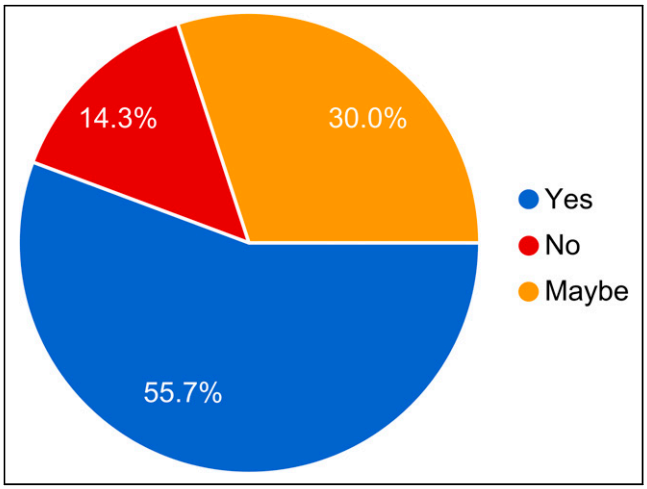

FIGURE 1. Results from 70 respondents to our 2019 survey about clinical need for ^{99m}Tc-DMSA during lack of availability of this agent: "Would your practice be performing ^{99m}Tc-DMSA scans now if ^{99m}Tc-DMSA were available?" Most respondents confirmed need for ^{99m}Tc-DMSA in their clinical practice. Survey was sent to SNMMI All Member Community via SNMMI Connect Communities discussion board (https://communities.snmmi.org). (Adapted from (*4*).)

During the diagnostic assessment of urinary tract infection, some advocate obtaining a voiding cystourethrogram to evaluate for the presence of vesicoureteral reflux, which may be followed by ^{99m}Tc-DMSA—that is, a "bottom-up" approach. Others prefer a "top-down" approach—that is, obtaining a ^{99m}Tc-DMSA scan initially, followed by a voiding cystourethrogram possibly if there is evidence of renal damage. Whether regional preference is for the top-down approach or the bottom-up approach in the evaluation of urinary tract infection, ^{99m}Tc-DMSA imaging is a helpful tool for the diagnosis of renal cortical abnormalities (*5*–*7*).

Depending on the patient's clinical question, ^{99m}Tc-DMSA imaging can be a valuable complementary test to other diagnostic procedures, or in some cases it can be useful on its own. When used early and appropriately in the evaluation process, it can shorten the time to diagnosis. A commercial source of ^{99m}Tc-DMSA is available again in the United States (NEPHROSCAN; Theragnostics Inc., www.nephroscan.com). As many clinicians seek to reinstate its use, the time is right to review and refresh our knowledge on its pharmacodynamics, biodistribution, technical aspects, and clinical value.

RADIOPHARMACEUTICAL KINETICS AND BIODISTRIBUTION

After intravenous injection, ^{99m}Tc-DMSA is principally taken up by the brush borders of the proximal convoluted tubules of the renal cortex. The renal uptake and distribution of tracer closely reflect total renal function and regional renal blood flow (*8*). In patients with normal kidney function, uptake of the injected activity is approximately 40% at 4 h and 70% at 24 h. The renal uptake gradually increases over time. In patients with normal renal function, a very small proportion of the activity is slowly eliminated into the pelvicalyceal system and the bladder. Otherwise, once the

activity reaches the renal cortex, it does not wash out or redistribute over time. By 4 h very little extrarenal activity should be present (Fig. 2) (*9*).

The administered volume and mass of the agent are rather small compared with those of MRI and CT contrast media, therefore not resulting in a pharmacologic, allergic, or toxic effect. As an example, in a 1-y-old weighing 10 kg, the administered volume is 0.03 mL and the mass is 0.22 mg in practice; the 0.03 mL is diluted with normal saline to facilitate injection. As another example, in a 10-kg, 1-y-old patient having a ^{99m}Tc-DMSA scan, the administered volume of ^{99m}Tc-DMSA solution is 0.06 mL containing only 0.64 mg of radiopharmaceutical. In comparison, for the same 1-y-old undergoing MRI, 940 mg of gadolinium-diethylenetriaminepentaacetic acid (Magnevist; Bayer) is typically administered in a volume of 2.0 mL. For a contrast-enhanced CT scan, 6,400 mg of ioversol (Optiray 320; Covidien) may be administered in a volume of 20 mL. Thus, the administered volume for ^{99m}Tc-DMSA is 20- to 200-fold less and the administered mass is more than a thousandfold less (*4,9*).

Normal split renal function (i.e., the percentage of the total renal uptake in either the right or the left kidney) assessed by ^{99m}Tc-DMSA is in the range of 45%–55%.

The total renal uptake of ^{99m}Tc-DMSA (right + left kidney) relates to the patient's total renal function (*9*). Therefore, if the patient's total renal function is diminished, the total renal uptake of ^{99m}Tc-DMSA will also be diminished. If one kidney has low function, the contralateral kidney will compensate with increased function and size to maintain normal total renal function (*10–12*).

In neonates, renal uptake of ^{99m}Tc-DMSA may be relatively low due to renal immaturity (*9,13,14*). Although structurally complete in terms of numbers of nephrons by 36 wk, the newborn kidney is still functionally immature. Renal function undergoes rapid maturation during the first weeks after birth in both term and preterm infants. This low renal uptake is usually accompanied by relatively high body background activity. With maturation, renal uptake gradually reaches a normal level. The kidney-to-background ratio gradually approaches the adult level by approximately 2–3 y of age (*15*).

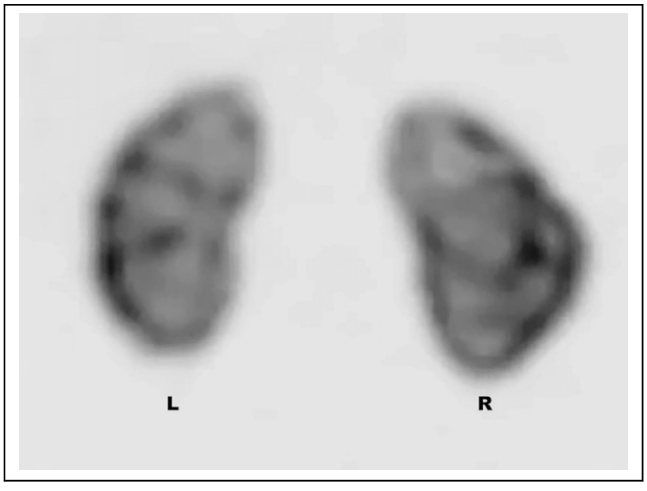

FIGURE 2. Typical ^{99m}Tc-DMSA renal SPECT. Maximum intensity projection shows distribution of renal cortex.

ADMINISTERED ACTIVITY

According to the North American Guidelines for Administered Activities in Children and Adolescents, the recommended intravenous administered activity of ^{99m}Tc-DMSA is 1.85 MBq/kg (0.05 mCi/kg) with a minimum of 11.1 MBq (0.3 mCi) and a maximum 111 MBq (3.0 mCi) (*16–18*). Ultimately, the amount of administered activity may vary depending on the nuclear medicine physician's and technologist's experience and preferences, the patient's condition, and the type of instrumentation used.

PATIENT PREPARATION

Patients are usually imaged in the normal state of hydration. There are no restrictions for foods, fluids, or physical activity, except when sedation or general anesthesia is planned. The patient and caregivers should be informed about the intravenous injection, the time interval between injection and imaging time, as well as the need for the patient to remain still for the duration of the imaging. They should be assured not to expect any reactions from the injection. Outpatients need to be informed about the need for the patient to meet discharge criteria after sedation or general anesthesia and the time commitment needed.

With the increased use of SPECT and PET, the use of sedation has increased. The use of sedation and general anesthesia may be less frequent with personnel trained and experienced in the handling and imaging of children. In contrast, some institutions use sedation and general anesthesia protocols routinely in certain age groups. Sedation or general anesthesia should be planned ahead of the patient's visit to nuclear medicine, including the assessment of the appropriateness for the particular patient. It is important to assess the appropriateness of the patient for sedation or general anesthesia before the study. Proper advance instructions about eating, diet, and any other preparation should be communicated clearly to the patient and family. Importantly, if the patient needs more than one imaging procedure in the same day, sedation scheduling should be appropriately coordinated.

TRACER INJECTION

Best results are obtained when experienced, well-trained nurses, technologists, or physicians are the personnel assigned for the intravenous injection. Ensure that appropriate injection technique and immobilization are used. The usual volume of tracer solution is 0.1–0.5 mL followed by a gentle saline flush (1–3 mL) to clear the tracer from the line (*19*).

IMAGING AND POSTPROCESSING

Typically, imaging is obtained at 2–4 h after tracer administration, and in some cases imaging at 24 h can be useful if tracer is seen in the pelvicalyceal system in 2- to 4-h imaging. The patient should void before imaging and be able to remain still for image acquisition for approximately 20 min. If that is not possible, immobilization, sedation, or, exceptionally, general anesthesia may be considered.

The patient is positioned on the imaging table supine for planar imaging and SPECT. For pinhole imaging the patient should be in the prone position. Details on image acquisition, processing, and display can be found in the Society of Nuclear Medicine and Molecular Imaging (SNMMI) procedure standard/European Association of Nuclear Medicine practice guideline (*18*).

Even though careful immobilization can be effective, patient motion can affect the quality of the images. Appropriate motion correction techniques are useful and can recover the information, thus avoiding having to repeat the study acquisition (*20*). Respiratory motion of the kidneys can affect image quality, and there are methods that can reduce the effect of respiratory motion, rendering improved renal images (*21*).

In the rare instance that the 2- to 4 h images show tracer in the pelvicalyceal system, the patient may be asked to return the next day for additional images (Fig. 3). This instance may occur in the presence of a very dilated collecting system. After the scan, the patient may resume normal activity.

The choice of imaging protocol varies depending on the physician/technologist experience and preferences as well as the available equipment and may involve both planar imaging (with either parallel-hole or pinhole collimator) or SPECT (Fig. 4). Keeping this in mind, generic descriptions of methodology are provided. The methods discussed are based on the Anger-type scintillation cameras and generally available image processing and displays. Newer and developing instrumentation and software methodology can produce clinically acceptable images at a lower radiation exposure and sometimes at a shorter imaging time (*22,23*).

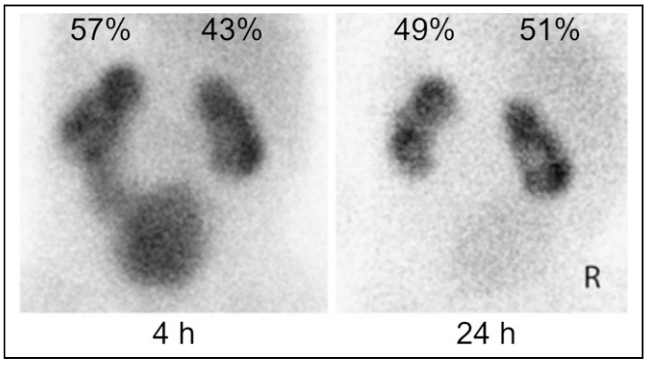

FIGURE 3. Retention of tracer principally in left pelvicalyceal system at 4 h after intravenous injection of ^{99m}Tc-DMSA, limiting assessment of split renal cortical function. At 4 h, estimated split renal function was 57% of total renal uptake in left kidney and 43% in right kidney. Repeat imaging after several hours provides more accurate determination of split renal cortical function. Tracer is taken up by sulfhydryl groups in brush borders of proximal convoluted tubules. Therefore, tracer remains in renal cortex while activity in urine drains out of renal areas and bladder. At 24 h, estimated split function was 49% of total renal function on left and 51% on right. (Adapted with permission of (*19*).)

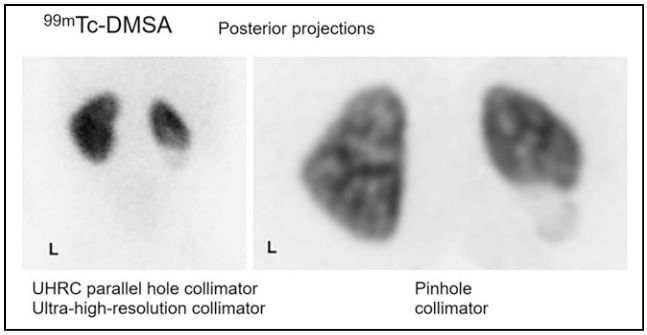

FIGURE 4. ^{99m}Tc-DMSA posterior planar images of infant with right duplex kidney. Images with ultra-high-resolution parallel-hole collimator and with pinhole collimator demonstrate superior spatial resolution with pinhole collimator.

Planar Imaging (Parallel-Hole Collimator)

Planar imaging may reveal several relevant anatomic findings including the number, size, and position of the kidneys; large cortical defects; differential/split renal function; infection; congenital abnormalities (duplex kidney upper-/lower-pole function, ectopic kidney, cross-fused renal ectopia, horseshoe kidney); infarction; and trauma. Posterior as well as left and right posterior oblique views (300,000–500,000 counts per view) should be obtained as needed. After the initial images are obtained, the physician may wish to order additional views (obliques, anterior, laterals).

Pinhole Collimation

The pinhole collimator, if available, can produce images of very high spatial resolution that may be particularly useful in discerning small renal abnormalities in infants. The pinole aperture size affects image resolution. The smaller the aperture, the higher the spatial resolution; however, the smallest aperture is not as sensitive. We recommend a small aperture (3 mm) if available, although 4 mm may also be acceptable. The highest resolution is obtained when the patient-to-collimator distance is as small as possible. Image size, spatial resolution, and sensitivity decrease with increased patient-to-collimator distance. Pinhole imaging takes more time than with a parallel-hole collimator. When using the pinhole collimator, a prone position is usually used in small children/infants. If the camera system allows, the pinhole collimator positioned under the imaging table as closely as possible to the kidneys is also acceptable.

SPECT

^{99m}Tc-DMSA SPECT may be superior to planar imaging for regional mapping of functioning renal parenchyma, providing additional sensitivity and specificity in patients suspected of having renal cortical abnormalities (Fig. 5) (*24–26*).

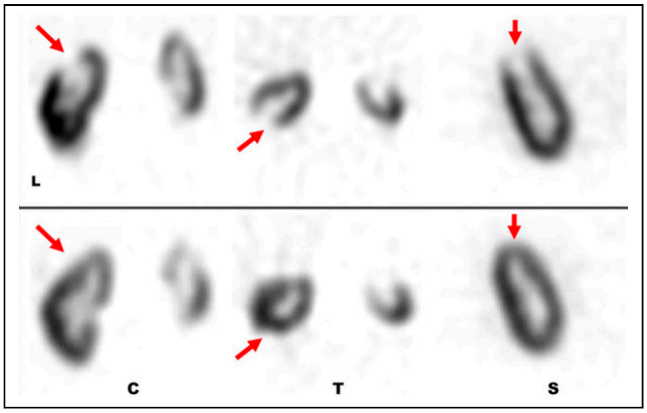

FIGURE 5. Coronal (C), transverse (T), and sagittal (S) slices of ^{99m}Tc-DMSA SPECT from patient recovering from acute pyelonephritis of upper pole of left kidney. Images were obtained 1 y apart.

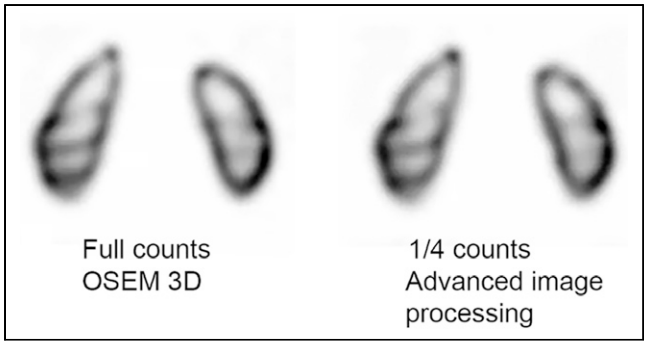

FIGURE 6. Coronal SPECT slices from same patient processed with full counts (left panel) and with one-quarter number of counts using advanced image processing (right panel). This example demonstrates that it is possible to use fewer counts (and therefore less administered activity) to obtain same diagnostic quality. OSEM 3D = 3-dimensional ordered-subsets expectation maximization.

SPECT can also provide more accurate results than planar imaging, particularly in pediatric patients and poorly functioning kidneys (*27*). SPECT permits simultaneous evaluation of images in the transverse, coronal, or sagittal plane. In addition, evaluating rotating volume-rendered images such as maximum intensity projections permits a superior gestalt view of the functional anatomy of the kidneys. ^{99m}Tc-DMSA SPECT acquisitions can take 15–20 min, requiring the patient to remain still during that time. SPECT acquisition parameters will vary depending on the equipment and software used. According to the SNMMI procedure standard/European Association of Nuclear Medicine practice guideline (*18*), SPECT imaging requires 360° of sampling, typically on a 128 × 128 matrix with a multihead camera. For most cameras, 120 views in total (3° spacing) with 15–20 s per view can be used. Alternative angular sampling/view times can be used with more advanced reconstructions.

Hybrid SPECT/CT of ^{99m}Tc-DMSA provides both functional and anatomic definition of the kidneys, broadening the scope of SPECT imaging (*28*). With appropriate automated software, ^{99m}Tc-DMSA SPECT can allow for the estimation of renal volumes, which can be compared with normal renal values as a function of age and body weight. This information can aid physicians in evaluating and monitoring renal growth (*29*).

RADIATION EXPOSURE

The use of radiopharmaceuticals such as ^{99m}Tc-DMSA in patients involves exposure to ionizing radiation; therefore, attention to patient radiation exposure must be considered. The justification and optimization of its use in the clinic are best summarized by the SNMMI's statement on dose: "The right test with the right dose should be given to the right patient at the right time." (*30*). The effective dose of radiation to patients with ^{99m}Tc-DMSA is in the range of 1.0 mSv, which is about the same as or perhaps slightly lower than that associated with pelvic CT. Therefore, if the information that can be derived from ^{99m}Tc-DMSA scintigraphy is considered of significant clinical benefit to the patient, this likely outweighs the potential (*31*) risk of the relatively small amount of radiation exposure (Fig. 6) (*32*).

COMPARISON WITH ULTRASOUND, CT, AND MRI

^{99m}Tc-DMSA SPECT provides a unique 3-dimensional image of the functioning renal cortex. Ultrasonography does not involve ionizing radiation, is generally available, is relatively inexpensive, and can provide initial useful information about the morphology and location of the kidneys. It is operator-dependent, is poorly sensitive for detection of acute pyelonephritis and renal scarring, and may not provide information about viable cortical renal cells. Abdominal CT results in an effective dose of around 5.0 mSv (*4*). CT with intravenous contrast provides detailed anatomic information, but contrast has risks including allergic reaction and further damage to already compromised kidneys. MRI does not include ionizing radiation but requires a longer imaging time that in most children requires sedation or in some cases general anesthesia, which carries real patient risks. This may be of particular concern since most patients undergoing these evaluations are under 7 y of age (*33*). MRI has high spatial resolution and high soft-tissue contrast and allows simultaneous evaluation of the collecting system and renal parenchyma. MR urography is usually available only in specialized pediatric centers and can provide dynamic and quantitative information about renal function.

CONCLUSION

^{99m}Tc-DMSA renal imaging remains a very useful and sensitive imaging modality in the evaluation of several disorders affecting the renal cortex. The agent shortage negatively impacted practitioners' ability to evaluate renal cortical defects in children and adults and changed renal imaging practice. As a result, clinical practitioners—both imaging

specialists and referring physicians—may be less familiar with the technology than they once were. Newer personnel—both physicians and technologists—may not have encountered the valuable use of ^{99m}Tc-DMSA in their training. Since the shortage of commercially available ^{99m}Tc-DMSA ended in 2023 and the radiopharmaceutical is now routinely available, it is time to bring ^{99m}Tc-DMSA renal imaging back into the fold of imaging options that should be considered to ensure early diagnosis and potentially reduce unnecessary imaging.

DISCLOSURE

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

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