Nuclear Imaging in Pediatric Kidney Diseases

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Renal scintigraphy is a useful tool in diagnosis and management of various nephro-urological conditions. Tc-99m dimercaptosuccinic acid renal scintigraphy (Tc-99m-DMSA), Tc-99m mercaptoacetyltriglycine (Tc-99m-MAG3) or Tc-99m diethylenetriaminepentaacetic acid (Tc-99m-DTPA) dynamic renal scintigraphy, and Radionuclide micturating cystography are the common scans used in children with kidney diseases. These studies are minimally invasive, easily available, and offer both anatomic details and functional information required for thorough evaluation. At the same time, it is essential to have appropriate knowledge to interpret these studies and be aware of their limitations and pitfalls. The advent of Positron emission tomography-computed tomography/magnetic resonance imaging (PET-CT/MRI) has broadened the scope of nuclear medicine. This article focuses on the technique, interpretation, indication and recent practice guidelines of renal scintigraphy in children with kidney diseases.

Keywords: *DMSA, DTPA, Radionuclide cystography, Renal scintigraphy.*

Nuclear medicine has played an important role in the management of various renal diseases in children. A wide variety of nephro-urological conditions can be diagnosed and evaluated using renal scintigraphic methods. Common scans used in children with kidney disease include Tc-99m dimercaptosuccinic acid renal scintigraphy (Tc-99m-DMSA), Tc-99m mercaptoacetyltriglycine (Tc-99m-MAG3) or Tc-99m diethylenetriaminepentaacetic acid (Tc-99m-DTPA) dynamic renal scintigraphy, and radionuclide micturating cystography. These methods can be safely used in children. Most of them do not require sedation or sophisticated equipment. Besides giving structural and functional information, these can be used for assessment of glomerular filtration rate. In this article, we review the technique, interpretation, indications and current practice guidelines of renal scintigraphy in children with renal diseases.

STATIC CORTICAL RENAL SCINTIGRAPHY

Both North American and European guidelines are available for the use of static cortical renal scintigraphy [1,2]. The most common radiopharmaceutical used for imaging the renal cortex is Tc-99m-DMSA; Tc-99m-glucoheptonate (GH) is also available for assessing integrity of the renal parenchyma but not routinely used. Dynamic tracers such as Tc-99m-MAG3 provide less accurate information on regional cortical abnormalities due to rapid transit time.

Tc-99m-DMSA is filtered bound to a1-microglobulin. It accumulates in the kidneys by megalin/cubilin-mediated endocytosis of the Tc-99m-DMSA protein complex [3]. Renal uptake of Tc-99m-DMSA is dependent on peritubular extraction by the tubular cells [4]. Usually no preparation is required for the procedure; sedation may be required for younger children or when the procedure is done along with Single-photon emission computed tomography (SPECT). As per North American consensus guidelines 2010, recommended administered activity for Tc-99m-DMSA is 1.85 MBq/kg (0.05 mCi/kg) and minimum administered activity is 18.5 MBq (0.5 mCi) [5]. The European Association of Nuclear Medicine (EANM) dosage card calculator can also be used for calculating the dose of the radiopharmaceutical [6]. The dose of renal scintigraphy with Tc-99m-DMSA in children aged 1-15 years varies between 0.68 to 1.22 mSV (depending on guidelines used), whereas the effective radiation dose from plain chest radiography in neonates and pediatric patients varies from 0.016 to 0.02 mSv [7,8].

The child should be placed in supine position close to the collimator. Images should be acquired 2 to 3 hours after tracer injection. Anterior, posterior and posterior oblique views are taken for planar renal scintigraphy. Anterior view should be performed in the case of horseshoe kidney or ectopic pelvic kidney. European and North American guidelines suggest obtaining 300,000–500,000 counts for posterior and posterior oblique views, and 100,000-150,000 counts for pinhole views. Pinhole collimation imaging provides better detection of small cortical defects. SPECT provides excellent image detail

with better contrast resolution. However, SPECT is not routinely used in children due to the increased imaging time required and the unclear clinical significance of additional small cortical defects detected by it.

Interpretation: Homogeneous distribution of tracer occurs throughout the renal cortex in normal Tc-99m-DMSA. The split function normally varies from 45% to 55%. Due to liver and spleen, upper poles may appear less intense. The central collecting system and medullary regions are photon deficient because of significant cortical binding of Tc-99m-DMSA. The columns of Bertin may appear quite prominent due to radiopharmaceutical uptake. Interpretation criteria as described by the Society of Nuclear Medicine has been shown in ***Box* I** [2]. ***Web Fig.* 1** shows a DMSA scan with cortical scar.

DYNAMIC RENAL SCINTIGRAPHY

Standard renography allows estimation of differential renal function and excretion. Diuretic renography is useful in assessing drainage of collecting system and differentiation between obstructive and non-obstructive causes of dilation. Tracers used are 123 I-hippuran, Tc-99m-MAG3, Tc-99m-ethylenedicysteine (Tc-99m-EC) and Tc-99m-DTPA [9]. Tc-99m-MAG3 (100% tubular secretion) is the most common radiopharmaceutical used for dynamic renal scintigraphy. It is preferred over Tc-99m-DTPA because of its rapid renal clearance and primary excretion by the tubules [8]. Tc-99m-LLEC (L,L, Ethylenedicysteine) may also used as it is more suited and close to ideal agent Hippuran [10].

BOX I INTERPRETATION OF STATIC CORTICAL RENAL SCINTIGRAPHY

Acute pyelonephritis

- May appear as single or multiple defects.
- The cortical defect may have reduced or absent localization of tracer with indistinct margins that do not deform the renal contour.
- A localized increase in volume of a single affected area or a diffusely enlarged kidney with multiple defects may occur

Chronic pyelonephritis/ mature scar

- May have relatively sharp edges with contraction and reduced volume of the affected cortex.
- Scarring can manifest as cortical thinning, flattening, or an ovoid or wedge-shaped defect.
- The defect may become more obvious with growth of normal surrounding cortex.

The child should be well-hydrated for both the standard and diuretic renogram. Bladder catheterization is not always necessary but may be required to evaluate patients with bladder pathology. In some children, the diagnosis of obstruction may be more reliable with bladder- or pelvic-drainage catheterization [11]. Children who are not catheterized should void completely before the study. The recommended administered dose of Tc-99m-MAG3 is 1.9 MBq (50 µCi) per kilogram of body weight (minimum, 19 MBq [0.5 µCi]) [11], and the dose for Tc-99m-DTPA is 3.7 MBq (100 µCi) per kilogram of body weight (minimum, 37 MBq [1 µCi]). The patient is placed in supine position with the back facing the camera. The effective dose of radiation is 0.010-0.032 mSv/MBq for 99mTc-MAG 3 and 0.0081-0.034 mSv/MBq for 99mTc-DTPA scan [12].

Dynamic renal scintigraphy is acquired in two parts. Images are acquired at a rate of 1 to 3 seconds per frame for 60 seconds to assess renal perfusion. Then images are acquired at 60 seconds per frame for 25 to 30 minutes to evaluate parenchymal radiotracer uptake and clearance [13]. Dose of furosemide is 1 mg/kg with a maximum dose of 40 mg. There are three variations based on time of administration of the diuretic furosemide. In the method endorsed by the American Society of Fetal Urology, the diuretic is injected at 20 min or later after the radiopharmaceutical, when the entire dilated system is filled with the tracer (F+20). In the method developed in Europe (F–15), the diuretic is injected 15 min before the injection of the radiopharmaceutical. In the F–0 method, there is simultaneous injection of the radiopharmaceutical and the diuretic [11]. Furosemide induced diuresis hastens the rate of tracer washout in normal non-obstructed kidney.

Interpretation: Dynamic visual presentation of changes during the study is provided by computer-generated Time-activity curves (TACs). Numerous values provided by these curves include time to peak activity, uptake slope, rate of clearance, and percent clearance at 20 minutes [13]. Regions of interest (ROIs) are drawn around the dilated pelvicalyceal system for curve analysis and calculation of the half-time (T1/2) [11]. The diuretic effect usually begins within few minutes after the administration of the diuretic. A normal curve will show an early peak within a few minutes (2-5 min), followed by complete emptying either spontaneously or after furosemide. Interpretation criteria as per Society of Nuclear Medicine are shown in the ***Box* II** [11]. A T1/2 with a value between 10 and 20 min is an equivocal result. Since T1/2 values refer to kidneys with normal or near-normal function, kidneys with reduced function may have prolonged T1/2 values without obstruction [11]. ***Web Fig.* 2** depicts a

BOX II INTERPRETATION OF DYNAMIC RENAL SCINTIGRAPHY IN VARIOUS CONDITIONS

Non obstructed drainage system

- Rapid and almost complete washout of the radiotracer occurs before injection of diuretic.
- There may be slow emptying of the kidneys, if function is decreased.
- A T1/2 less than 10 min usually means the absence of obstruction.

Obstructed hydronephrosis

- An obstructed system will not respond to the diuretic challenge.
- The curve rises continuously over 20 minutes or appears as a plateau, despite furosemide and post micturition.
- T1/2 greater than 20 minutes usually points towards obstruction.

Acquired obstruction (tumour, renal stone)

- Complete obstruction is characterized by non-visualization of the collecting system, associated with a rising curve from the parenchyma; blood flow is often decreased.
- Partial obstruction is characterized by delayed and persistent visualization of the drainage system and cortical retention of the activity, associated with decreased blood flow.

DTPA scan of a child with hydronephrosis. The relative function of each kidney is expressed as percentage of the sum of right and left kidneys. A summed image of all the frames during the clearance or uptake phase is created, which reflects the regional parenchymal function. There are two methods for calculation of differential function – Integral method and Patlak Ruthland plot method; detailed discussion of these methods is beyond the scope of this article.

Though, intra-arterial angiography remains the gold standard for identification and quantitative assessment of renovascular lesions, Angiotensin converting enzyme inhibitors (ACEI) renography remains widely available tool for assessment of perfusion and function [14] with guidelines laid down in 1998 by Society of Nuclear Medicine [15].

ACEI should be withheld for 2-5 days (depending on half-life) before the study. ACEI renography has a sensitivity and specificity of about 90% for diagnosis of renal artery stenosis. The dose of captopril is 25-50 mg by mouth. The dose of enalapril at is 40 µg/kg administered intravenously over 3-5 min with maximum dose of 2.5 mg. Radiopharmaceutical administration should be delayed for at least 60 min after captopril administration and 15 min after intravenous enalaprilat administration. The most specific diagnostic criterion for renovascular hypertension is an ACEI-induced change in the renogram. Normal findings on ACEI renography indicate a low probability for renovascular hypertension. The probability is considered high (>90%) when marked change of the renogram curve occurs after ACE inhibition compared to the baseline findings. The general interpretive criteria associated with renovascular hypertension include worsening of the renogram curve, reduction in relative uptake, prolongation of the renal and parenchymal transit time, increase in the 20 mm/peak ratio and prolongation of the Tmax [15].

RADIONUCLIDE CYSTOGRAPHY

Radionuclide cystography (RNC) and radiological micturating cystogram (MCU) are the imaging tools for evaluation of vesicoureteric reflux (VUR). Both procedures have similar sensitivity for detection of VUR; though, RNC has significantly less radiation exposure compared to MCU [16]. It is estimated that there is at least a 50- to 100-fold reduction in radiation dose to the gonads with radionuclide cystography in contrast to roentgenographic techniques [17].

RNC has not been widely used at many centers across the globe. First, the grading system for VUR as provided by MCU is commonly used by urologists for evaluation and management of children with VUR [18]. Second, MCU provides more accurate anatomical information about the urethra and bladder. Direct radionuclide cystography (DRC) requires catheterization of the bladder and administration of Tc-99m-pertechnetate with saline into the bladder. Instillation is done until full bladder capacity is reached and then the child is allowed to void. The bladder may be filled with radiotracer solution using suprapubic puncture also [19].

Tc-99m-sulfur colloid and Tc-99m-DTPA are recommended for use in the evaluation of augmented bladder [18]. The recommended administered activity for Tc-99m-pertechnetate is 18.5–37 MBq (0.5–1.0 mCi) [16]. The radiation exposure is approximately 0.048 mSv per 20 MBq of 99mTc [19].

The infant is placed supine during both filling and voiding phases. The older co-operative child voids preferably sitting on a bed pan in front of the camera, which is placed vertically. Posterior views are taken with maximum frame rate of 5 seconds per frame and 64 × 64 or 128 × 128 matrix [16].

Indirect cystography (IRC) allows detection of VUR without bladder catheterization. Tc-99m-MAG3 and Tc-99m-DTPA are the radiopharmaceuticals used for the procedure. Indirect radionuclide cystography can be performed as a part of routine dynamic renal scintigraphy. The minimal administered activity for Tc-99m-MAG3 and TC-99m-DTPA is about 20 MBq (0.5 mCi) [16]. As per procedure guidelines from the Society of Nuclear Medicine, the patient lies supine and the camera is placed under the table. A pre-void image is taken once the bladder is full. Then the child is positioned in the sitting position with the gamma camera placed posteriorly over the region of the bladder and kidneys. Images are acquired during and after voiding.

Interpretation: In a normal study, no radiotracer should be seen in the collecting system or kidneys. Interpretation criteria as described in the Society of Nuclear Medicine guidelines are: (*i*) RNC grade 1, with activity limited to the ureter (Radiographic grade I); (*ii*) RNC Grade 2, with activity reaching the collecting system with none or minimal activity in ureter (Radiographic grades II and III); and (*iii*) RNC Grade 3, with a dilatation of the collecting system and dilated tortuous ureter (Radiographic grades IV and V).

ESTIMATION OF GLOMERULAR FILTRATION RATE

Renal function is evaluated by estimation of glomerular filtration rate (GFR). Different methods are available for estimation of GFR, but Inulin clearance remains the gold standard. The radiopharmaceuticals used for the purpose of measuring GFR are Tc-99m-DTPA and Chromium-51 labelled ethylenediaminetetraacetic acid (51Cr-EDTA).

The patient should be well hydrated prior to the study. As per guidelines by Pediatric Committee of the European Association of Nuclear Medicine, the minimal and maximal dose for 51Cr-EDTA are 0.074 MBq and 3.7MBq, respectively. The administered dose for Tc-99m-DTPA is based on body surface with maximal dose of 37 MBq [20].The effective dose is approximately 0.1mSv/ examination for Tc-99m-DTPA [21].

GFR calculation using the bi-exponential fitting method requires multiple blood sampling. Thus Slope-intercept method and Distribution volume method are more commonly used. The former is based on at least two blood samples around 2 and 4 hours after intravenous injection of the tracer [22-24], and the latter is based on a single blood sample taken at 2 hours [25]. Estimated normal values corrected for body surface have been published by Piepsz and colleagues [26]. Renal uptake of Tc-99m-DTPA during renography can be used to estimate GFR. This is a less invasive procedure and does not require frequent blood- or urine-sampling [8].

CLINICAL IMPLICATIONS

Urinary tract infection (UTI): Different guidelines are available for management of children with febrile UTI as shown in ***Table* I** [27-29]. Though not routinely practiced, DMSA can be performed during acute phase of UTI to confirm the presence of acute pyelonephritis in patients with equivocal symptoms.

Vesicoureteric reflux (VUR): Radionuclide voiding cystography and MCU are used for the detection of VUR. Common indications for use of radionuclide voiding cystography as per Society of Nuclear Medicine [16] are:

- Initial evaluation of females with urinary tract infection for reflux.
- Diagnosis of familial reflux.
- Evaluation of vesicoureteral reflux after medical management.

TABLE I GUIDELINES FOR MANAGEMENT OF CHILDREN WITH FEBRILE UTI

Guidelines	*Recommendations*
NICE guidelines [27]	Perform DMSA 4-6 mo after infection in children <3 y with atypical symptoms or recurrent UTI and only for recurrent UTI in children ≥3 y. MCU is recommended in children <6 mo of age only with atypical or recurrent UTI, and children between 6 mo to 3 y of age if has dilatation on ultrasound, poor urine flow, non *E.coli* infection and family history of VUR.
American Academy of Pediatrics (AAP) guidelines [28]	DMSA not to be done as a part of routine evaluation of infants with their first febrile UTI. MCU is recommended only if renal ultrasound reveals hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy, as well as in other atypical or complex clinical circumstances in children 2-24 mo of age with first febrile UTI.
Indian Society of Pediatric Nephrology (ISPN) guidelines [29]	DMSA to be done 2-3 mo after treatment of first episode of febrile UTI in all children less than 5 y of age, and in children >5y if USG is abnormal. MCU is recommended for all infants with first febrile UTI and in children 1-5 years of age only if ultrasound or DMSA is abnormal. All patients with recurrent UTI need detailed evaluation with MCU and DMSA.

- Assessment of the results of antireflux surgery.
- Serial evaluation of bladder dysfunction (*e.g.*, neurogenic bladder) for reflux.

Antenatal hydronephrosis: Important causes for antenatal hydronephrosis are VUR and pelviureteric junction obstruction (PUJO). Therefore, MCU and diuretic renography are performed in these patients to ascertain the etiology. Since antenatal hydronephrosis may resolve spontaneously not all patients require regular imaging. As proposed by ISPN guidelines [29], MCU should be performed in patients with unilateral or bilateral hydronephrosis with renal pelvic anteroposterior diameter (APD) >10 mm, Society for Fetal Urology (SFU) grade 3-4 or ureteric dilatation. MCU is done at 4-6 weeks of age unless lower urinary tract obstruction is suspected. Infants with moderate to severe unilateral or bilateral hydronephrosis (SFU grade 3-4, APD >10 mm) who do not show VUR should undergo diuretic renography. Renography is done at 6-8 weeks of life but may be performed earlier in patients with severe hydronephrosis and cortical thinning [30].

Renovascular disease: Renovascular disease is an important cause of hypertension in children. DMSA scintigraphy can diagnose scarring or infarction as a result of renal vessel thrombosis or disease. It can also assess the cortical function post revascularization procedures [31]. Dynamic renal scintigraphy before and after administration of captopril is used in the evaluation of renovascular hypertension.

Congenital renal anomalies: DMSA is often required to evaluate renal parenchymal integrity and confirm the diagnosis of crossed renal ectopia, renal hypoplasia and multicystic dysplastic kidneys. Anterior view with DMSA is recommended for assessing the function of ectopic or horseshoe kidney. These congenital anomalies may be associated with VUR or PUJO, thus may further require MCU and diuretic renography. Dynamic renography also helps in evaluation of vesicoureteric junction (VUJ) anomaly, duplex kidney and megaureters.

Renal transplant: Renal scintigraphy plays an important role in assessment of function and complications post renal transplant. DMSA can assess damage to the renal parenchyma of transplanted kidney in case of rejection. MAG3 renography can effectively detect the presence of obstruction, urinary leak and urinoma, and also differentiate urinoma from lymphocele or seroma [32].

Other indications: Voiding dysfunction, neuropathic bladder and overactive bladder are associated with recurrent UTI and VUR and thus need evaluation for both. In case of trauma and injury to kidneys, DMSA scan can be done to assess viability of renal parenchyma before performing any surgery and can be later repeated after several months to assess extent of recovery. Diuretic renography is also performed in cases of acquired hydronephrosis. Role of FDG-PET/CT and PET/MRI has also been proposed in evaluation of genitourinary tumors in children [33,34].

PITFALLS IN INTERPRETATION

It is essential to be aware of limitations and pitfalls of renal scintigraphic methods. There can be normal variations in a study, which should be interpreted with caution. Significant motion can also alter the image quality. High background activity may be seen in chronic kidney disease and immature kidneys of infants. The cortical defects on DMSA scans are not specific for scar or acute pyelonephritis; cysts, masses, hydronephrosis or infarcts can also cause defects but can only be identified on anatomic imaging exams (*e.g.,* ultrasound). Patient should be well hydrated for the dynamic renography else there will be progressive tracer accumulation within the collecting system, with little or no activity within the bladder throughout the dynamic acquisition [35]. A timeframe of 4-6 months is advisable for reassessment dynamic renography post pyeloplasty as drainage can still be slow if done soon after surgery. Bladder status (volume, capacity and drainage), poor renal function and dilated renal pelvis also interfere with interpretation of radionuclide renography. Child has to be placed in proper position for dynamic scan else evaluation of the split renal function can be difficult. Failure of child to hold his urine until requested will affect the indirect radionuclidecystography. 99mTc-DTPA tends to over-estimate in patients with low GFR and underestimate in patients with high GFR compared to inulin [36-38].

CONCLUSIONS

Renal scintigraphy continues to play an important role in the management of genitourinary disorders especially in the pediatric age group. However, proper guidelines and protocols need to be followed for accurate interpretation. Clinico-radiological correlation is also essential for the optimum interpretation. Finally, PET-CT/MRI is bound to play a key role and aid in the diagnosis and management of genitourinary conditions in children.

Contributors: AS: conceived the idea; RSD: literature search and drafted the manuscript; AS, AJ: critically reviewed the manuscript and helped in drafting the manuscript.
Funding: None; *Competing interest*: None stated.

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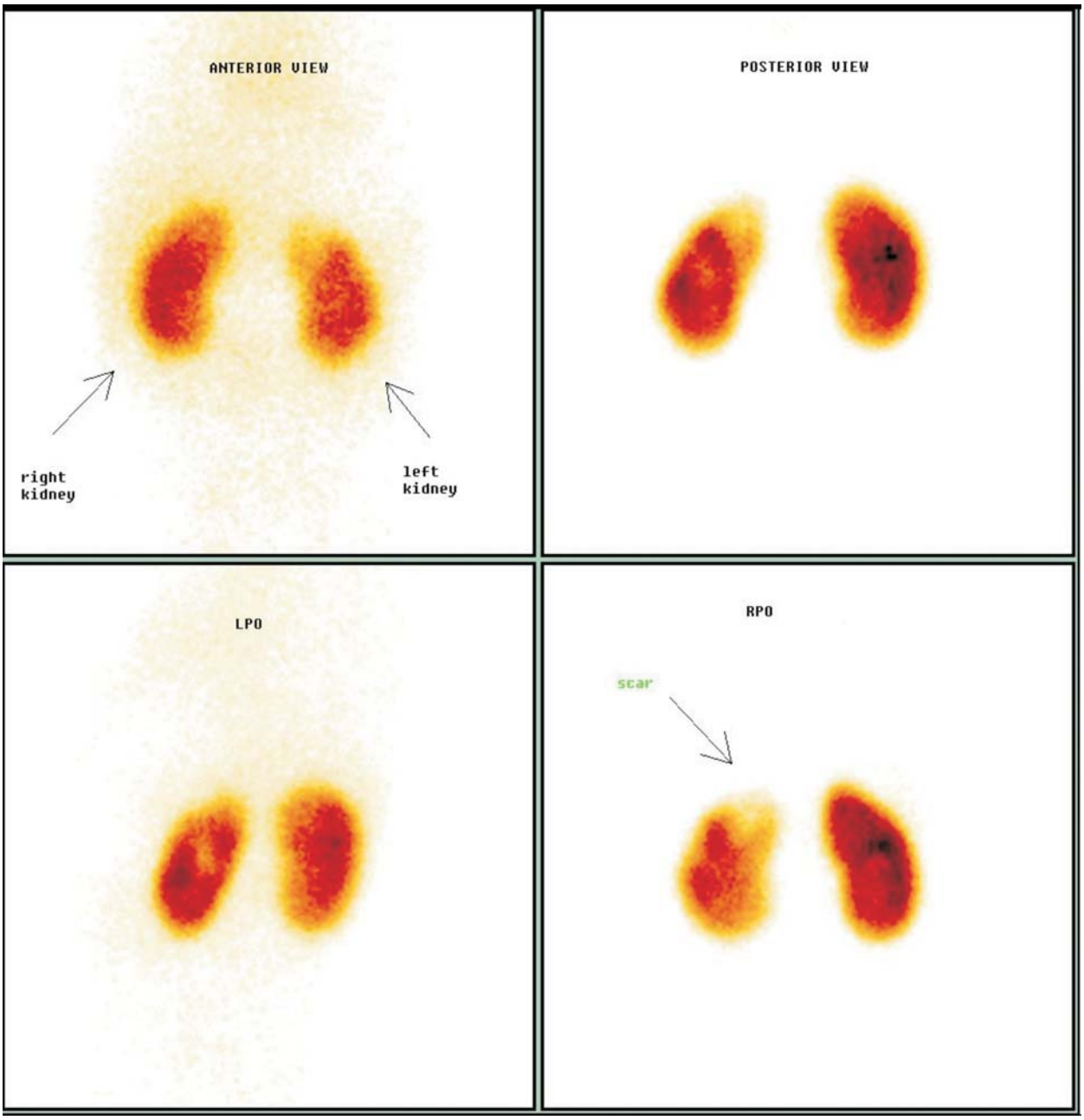
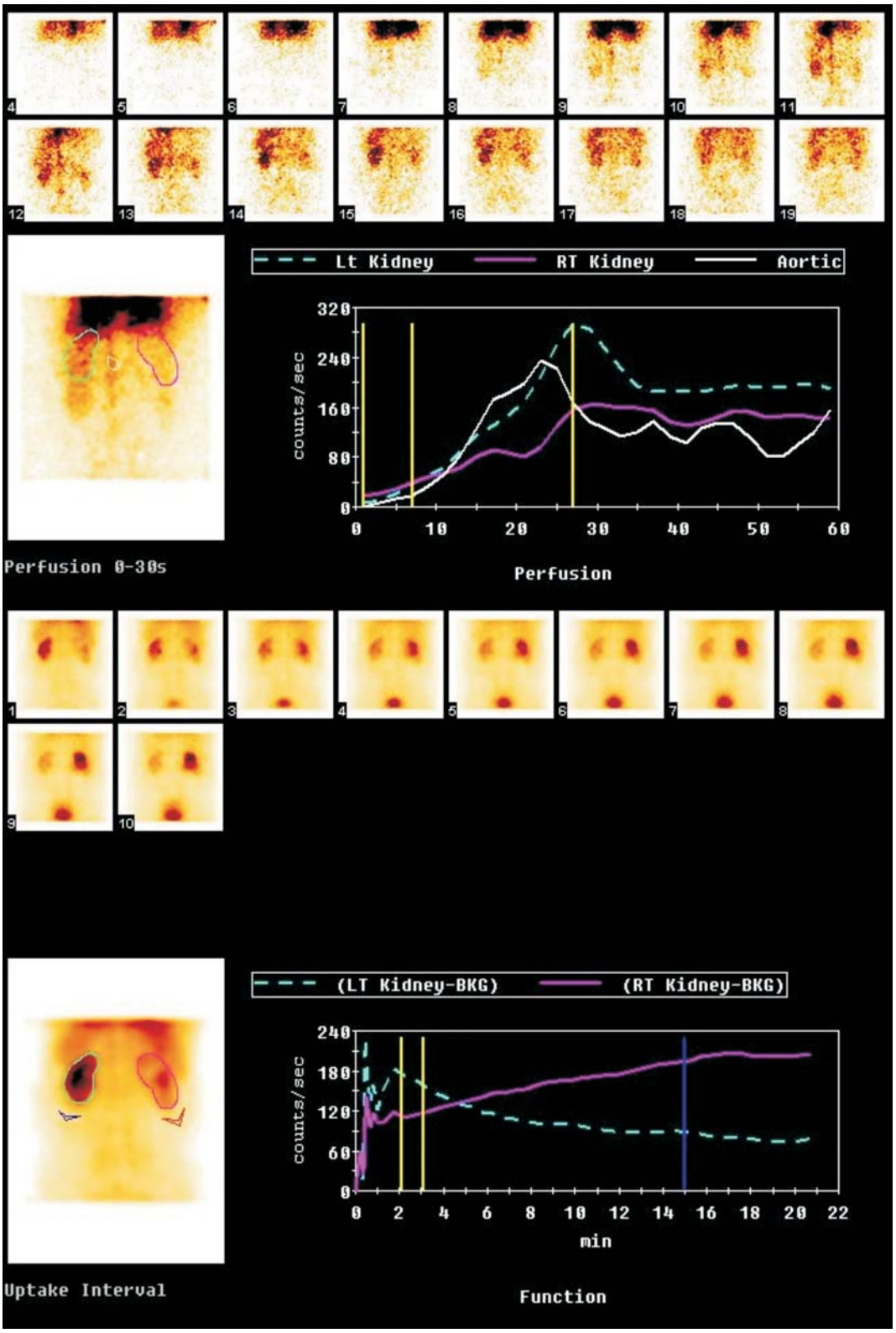


WEB FIG. 1 *Right kidney: Normal sized right kidney with normal cortical function and no definite scan evidence of cortical scar; Left kidney: Normal sized left kidney with preserved cortical function and photopenic area in upper polar region suggestive of cortical*



WEB FIG. 2 *Right kidney: Hydronephrotic with mildly impaired function and features of obstructive PCS clearance suggestive of PUJO. (Differential function 40%); Left kidney: Normal function with non-obstructive upper outflow tract (Differential function 60%).*