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Technetium-99m-*N*,*N*-ethylenedicysteine and Tc-99m DMSA scintigraphy in the evaluation of renal parenchymal abnormalities in children

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Technetium-99m dimercaptosuccinic acid (Tc-99m DMSA) as a static renal agent is currently the most frequently used agent in the detection of renal scarring, and allows accurate calculation of differential renal function (DRF). But this agent has some disadvantages such as relatively higher radiation dose and time consumption. ***Methods:*** The purpose of this study was to evaluate the potential of summed image that obtained from parenchymal phase of the dynamic technetium-99m-*N*,*N*-ethylenedicysteine (Tc-99m EC) scintigraphy in the detection of renal parenchymal defects and in the estimation of DRF, and to compare the results of this method with those of Tc-99m DMSA scintigraphy. The uptake ratios of the kidney to body background were also calculated for these two methods. Twenty-nine children with various renal disorders underwent both static Tc-99m DMSA and dynamic Tc-99m EC scintigraphy. The cortical analysis of Tc-99m EC scintigraphy was performed on the summed image obtained from dynamic images using the time interval between the first 45–120 sec. ***Results:*** There was a very close correlation between these two methods with respect to DRF (r = 0.99). In the detection of renal parenchymal lesions, scintigraphy with Tc-99m DMSA detected more lesions, and the sensitivity and specificity of the summed Tc-99m EC images were calculated as 92.6% and 100%, respectively. In addition, the ratios of mean uptake values for Tc-99m DMSA and Tc-99m EC images were 7.59 ± 2.17 and 2.95 ± 0.91, respectively. This ratio of Tc-99m EC seems to be acceptable and allows good delineation of the kidneys. But, the main disadvantages of the summed Tc-99m EC images in comparison with static Tc-99m DMSA images are the use of only posterior projection that may be an important drawback in patients with abnormal kidney positions, lower image counts and higher pixel size because of dynamic acquisition. ***Conclusion:*** These results show that summed Tc-99m EC images with an acceptable high image contrast provide an accurate DRF calculation in patients without abnormal kidney positions and allow the detection of most renal parenchymal abnormalities. However, Tc-99m DMSA scintigraphy remains the gold standard method because of its well known advantages.

Key words: technetium-99m-*N*,*N*-ethylenedicysteine, technetium-99m-dimercaptosuccinic acid, differential renal function

INTRODUCTION

Tc-99m DMSA is currently the agent of choice for renal parenchymal imaging because of its high cortical accumulation.[1–3] Tc-99m DMSA scintigraphy is the most sensitive method to detect a renal parenchymal abnormalities, and this agent concentrates principally in the proximal convoluted tubules for a sufficiently long time to enable detailed scintigraphic evaluation.[4–6] Approximately 90% of Tc-99m DMSA is bound to the plasma proteins which limits glomerular filtration.[7,8] The main disadvantages of this agent are its slightly higher radiation dose in comparison with other renal agents because of tubular fixation of DMSA and time consumption which may require a delay of 24 hours.[9–11]

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Tc-99m-ethylenedicysteine (Tc-99m EC), renal tubular agent, is a metabolite of the brain perfusion agent ethyl cysteinate dimer and has been developed as an alternative to both orthoiodohippurate (OIH) and Tc-99m-mercaptoacetyltriglycine (Tc-99m-MAG3).[12–16]

This promising agent with characteristics comparable to those of Tc-99m MAG3 and OIH provides high-quality images and low radiation dose to the patient.[16–19] The labeling procedure is easy at room temperature from a lyophilized kit, since the radiochemical purity is high and the complex remains stable for at least 8 h.[12,20]

It is excreted from the kidney principally via active transport and has a lower protein binding than both MAG3 and OIH.[20–22] In both healthy volunteers and patients, plasma clearance of Tc-99m EC has been reported to be around 0.75 of OIH clearance.[14,16,21] The plasma clearance rate in normal individuals is 473 ± 22 ml/min/1.73 m^2.[14]

The very close correlation between Tc-99m EC and OIH clearance makes it possible to estimate OIH clearance from Tc-99m EC clearance and several algorithms are available for this purpose.[23–26] After the development of technetium-99m labeled tubular agents like Tc-99m MAG3 and Tc-99m EC, the use of OIH and even Tc-99m diethylene triamine penta-acetic acid (Tc-99m DTPA) for renal studies was declined in many clinical centers. In the literature, the use of Tc-99m EC has been reported more widely in adults than children. Since the administered dose of the two agents is similar and Tc-99m EC has no tubular fixation, the absorbed radiation dose is lower in Tc-99m EC than that of Tc-99m DMSA scintigraphy. The radiation exposure is significantly lower in Tc-99m MAG3 scintigraphy (whole body dose, 0.25 mGy/MBq) than with Tc-99m DMSA (whole body dose, 1.60 mGy/MBq).[26] Moreover, because of the similarity of the administered dose and biologic behavior between Tc-99m EC and Tc-99m MAG3, the radiation-absorbed dose to the patient for Tc-99m EC may be considered to be as low as that for Tc-99m MAG3.[27]

In this study, the cortical phase images of dynamic Tc-99m EC scintigraphy were evaluated with respect to the image quality and whether or not it could be comparable with Tc-99m DMSA scintigraphy both in the estimation of DRF and in the detection of renal parenchymal abnormalities in children.

MATERIALS AND METHODS

Subjects

Twenty-nine children (12 boys and 17 girls) ranging in age from 4 months to 14 yr (mean 7.1 ± 3.6 yr) were studied with Tc-99m DMSA and dynamic Tc-99m EC scintigraphy. These two scintigraphies were performed within a period of 2–7 days. Ten patients had unilateral hydronephrosis caused by the presence of ureteropelvic junction stenosis (n = 7), prevesical ureteral stenosis (n =

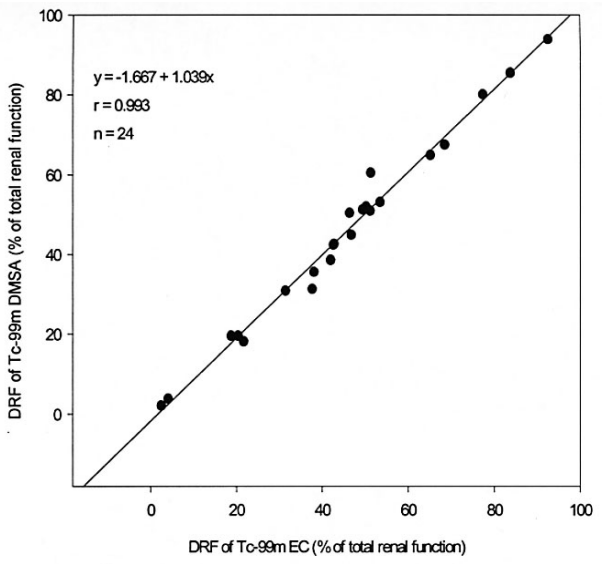

Fig. 1 Plot of differential renal function (DRF) of the left kidney of each patient with Tc-99m DMSA versus Tc-99m EC in children (n = 24).

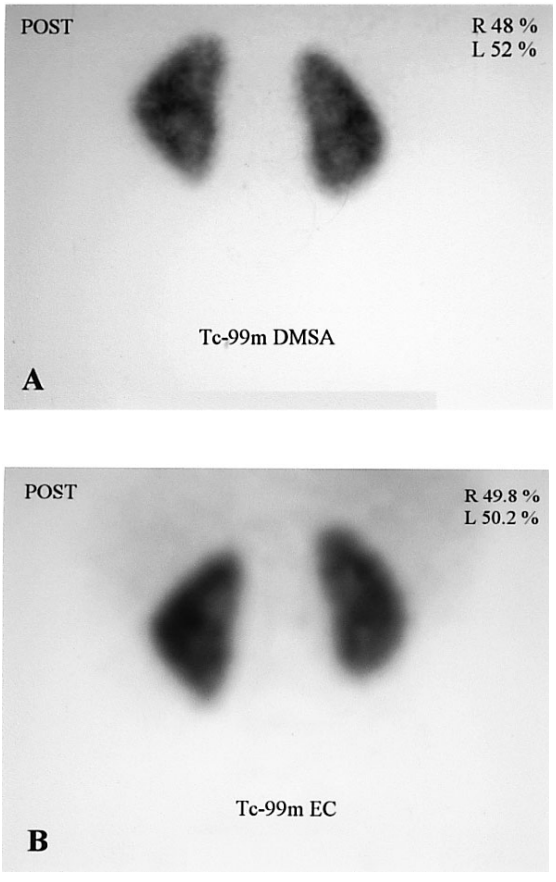

Fig. 2 A 7-year-old girl with reflux nephropathy. Tc-99m DMSA and Tc-99m EC summed images show normal kidneys. DRF values are very similar for both agents.

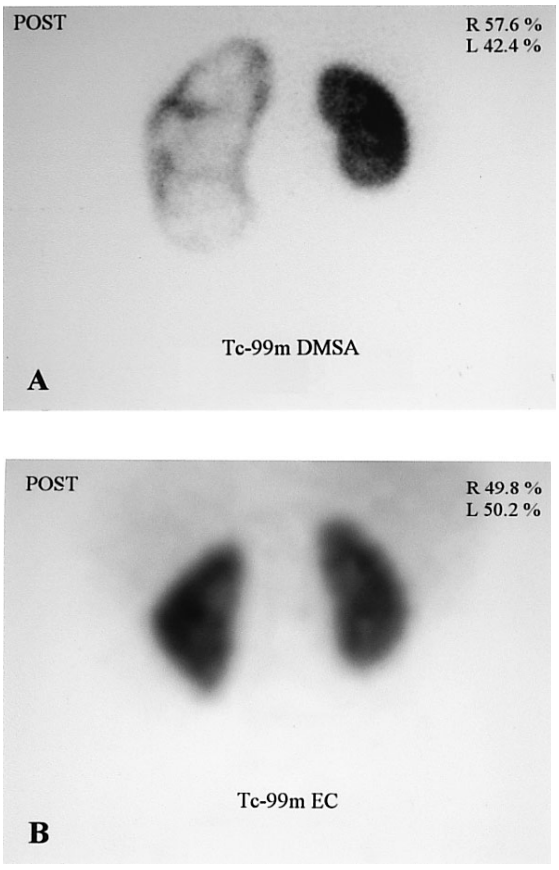

Fig. 3 An 8-year-old boy with unilateral hydronephrosis in the left kidney caused by the presence of ureteropelvic junction stenosis. Tc-99m DMSA and Tc-99m EC summed images show the same scintigraphic appearance concordant with hydronephrotic left large kidney.

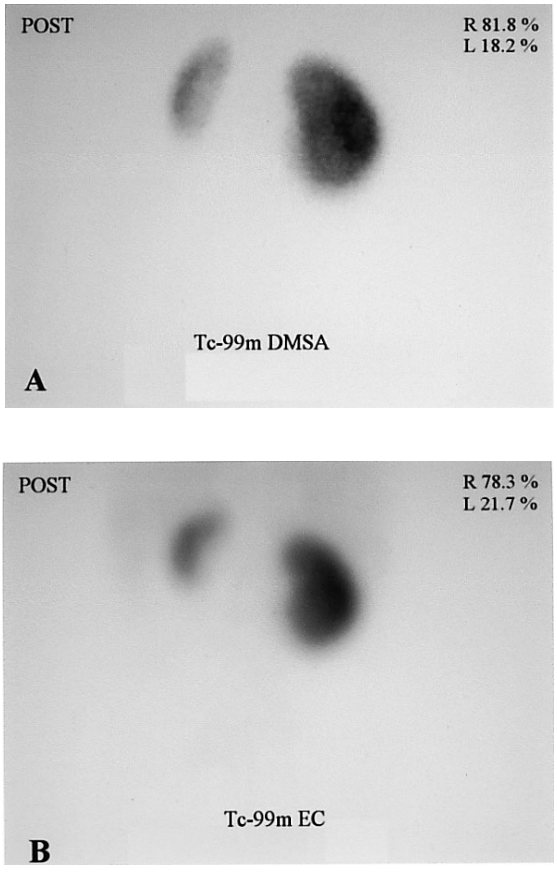

Fig. 4 A 6-year-old boy with left hypoplastic kidney. Tc-99m DMSA and Tc-99m EC summed images show excellent matching indicating left hypoplastic kidney.

2) and pelvic stone (n = 1). Of the remaining patients, five had a renal malformation (one horseshoe kidney, three renal agenesia, and one hypoplasia), five had a unilateral pyelonephritic atrophic kidney, two had a unilateral nephrectomized kidney, five had reflux nephropathy, and two had neurogenic bladder. There was no patient with abnormal positions of the kidneys.

Tc-99m DMSA Scintigraphy

Commercially available DMSA kit was prepared according to manufacturers' recommendations using 370–555 MBq (10–15 mCi) Tc-99m pertechnetate. Tc-99m DMSA was administered intravenously with a usual dose of 0.04 to 0.05 mCi/kg (1.5–1.9 MBq/kg), (minimum 0.3 mCi and maximum 3.0 mCi). The patient was examined in the supine position, and a posterior and two posterior oblique views (300 kcounts/view) were acquired by the gamma camera (Camstar 4000, GE Medical Systems) fitted with a low-energy high resolution collimator, in a 256 × 256 matrix format, at 4 to 5 hours after the injection of Tc-99m DMSA. The spatial resolution (FWHM) of the system is 3.8 mm. Actual pixel size used for DMSA (256 × 256 matrix) imaging is 1.56 mm. Static images were recorded on a dedicated computer and visually analyzed for focal renal parenchymal abnormalities. Perirenal ROI's were drawn for both kidney uptake and body background, and the DRF and the kidney to body background ratios were calculated quantitatively.

Tc-99m EC Scintigraphy

Tc-99m EC kit (Institute of Isotopes, Budapest, Hungary) was prepared by reconstitution of a labeling kit using 555–1300 MBq (15–35 mCi) freshly eluted Tc-99m pertechnetate. For a sufficient hydration, all patients were drunk 10 m*l* of water per kilogram of body weight prior to the radiopharmaceutical injection, and next, an intravenous infusion of normal saline was maintained during the entire examination. The patient was placed in the supine position, and the detector was beneath the patient using the same gamma camera equipment. Tc-99m EC (50–100 MBq) was injected as a bolus, followed by a flush of 10 m*l* saline. As soon as the bolus injection of the tracer, dynamic images were recorded in a 64 × 64 matrix for 45 frames/1 sec and 77 frames/15 sec. Actual pixel size used

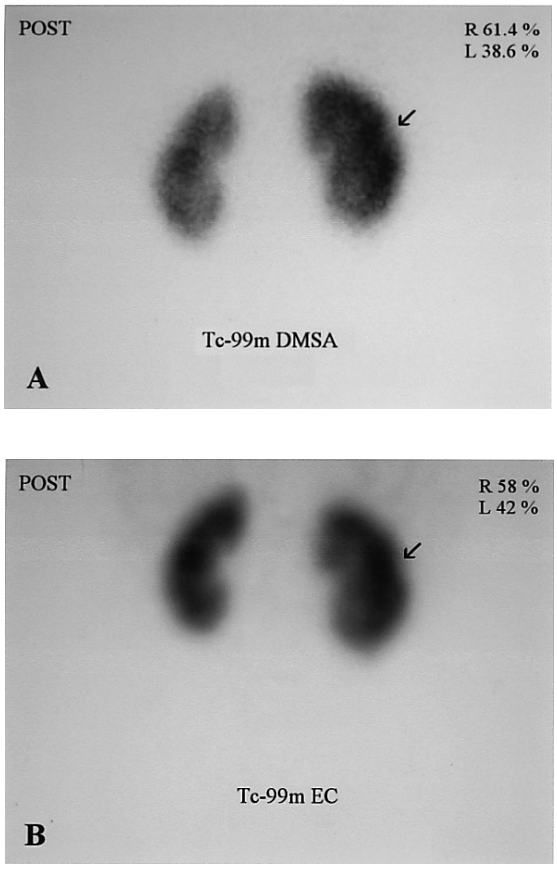

Fig. 5 A 5-year-old girl with reflux nephropathy. Tc-99m DMSA and Tc-99m EC summed images reveal a focal decreased uptake in the lateral portion of the right kidney.

for EC (64 × 64 matrix) imaging is 6.25 mm. First 45–120 sec images of Tc-99m EC were summed to obtain a static accumulation image. For tubular agents, the optimum time interval has been reported to be the first 60–120 sec in the guideline of EANM for "Guidelines for standard and diuretic renogram in children."[28] But, we prefered a slightly lower limit (45 sec) to improve the count statistics. The total renal counts and body background were determined using the regions of interest (ROIs) drawn around the kidneys on the parenchymal phase (45–120 sec). Results were expressed as percentage of the administered dose in the kidneys during the parenchymal phase that provides information about DRF.

Image Analysis

Tc-99m DMSA and Tc-99m EC images were evaluated visually and quantitatively. Visual analysis was used to define renal parenchymal abnormalities by dividing each kidney into three parts (upper, medium and lower). Quantitative analysis was used in the calculation of DRF and target to background ratios. The evaluation was performed twice by two readers without knowledge of the other investigation. A kidney was considered abnormal if the differential function on Tc-99m DMSA was < 43% and/or if a focal defect was seen.

Statistical analysis was performed using simple linear regression analysis.

Table 1 The mean uptake ratio of kidney to body background on Tc-99m DMSA and Tc-99m EC summed images

	Ratio of kidney to body background (mean ± SD)		
	right	left	both kidney
DMSA	7.59 ± 1.69	7.58 ± 2.51	7.59 ± 2.17
EC	3.05 ± 0.89	2.87 ± 0.94	2.95 ± 0.91

RESULTS

Quantitative Analysis

Relative function of the left kidney in each patient has been calculated and compared to each other for both agents. In 24 patients except five patients (two renal agenesia and three nephrectomy), a close correlation (r = 0.993) was found between the DRF values of each kidney obtained by two different methods, Tc-99m DMSA and Tc-99m EC scintigraphy (Fig. 1). The comparative image examples with the two agents are seen on Figures 2–5.

The ratios of mean uptake value of the kidney to body background using perirenal ROI's drawn around the kidneys on both posterior Tc-99m DMSA and Tc-99m EC summed images were 7.59 ± 2.17 and 2.95 ± 0.91, respectively (Table 1).

Visual Analysis

All kidneys that present (n = 53) were visualized by two agents. Of these kidneys, six atrophic kidneys were excluded from regional relative renal parenchymal analysis.

The images obtained from both Tc-99m DMSA and Tc-99m EC techniques revealed 27 and 25 focal defects, respectively (Table 2). Only two focal defects in the upper pole of the one kidney (patient 28) that detected on Tc-99m DMSA image were not able to be detected on Tc-99m EC summed image because of the high body background uptake level of this agent. The sensitivity and specificity of Tc-99m EC summed images in the detection of parenchymal focal abnormalities were calculated as 92.6% and 100%, respectively.

DISCUSSION

Technetium-99m-*N*,*N*-EC, a tubular renal imaging agent, has recently been introduced as an alternative to OIH and Tc-99m MAG3. The image quality of this agent is essentially similar to that obtained from Tc-99m MAG3, except for less prominent hepatic uptake for Tc-99m EC than those for Tc-99m MAG3.[18,27] Kabasakal et al.[21] also reported that the higher clearance rate of Tc-99m EC as compared with that of Tc-99m MAG3 is mainly due to

Table 2 The results of DRF and renal scarring

Patient no.	Renal scarring localizations					
	DRF (%)		DMSA		EC	
	DMSA	EC	R kidney	L kidney	R kidney	L kidney
1	38.6	42.0	MP, LP	N	MP, LP	N
2	51.3	49.4	N	N	N	N
3	52	50.2	N	N	N	N
4	51.5	50.4	N	N	N	N
5	60.5	51.3	MP, LP	N	MP, LP	N
6	80.1	77.3	N	N	N	N
7	—	—	agenesia	N	agenesia	N
8	53.2	53.5	N	N	N	N
9	44.9	46.8	N	LP	N	LP
10	—	—	agenesia	N	agenesia	N
11	51.0	51.2	N	N	N	N
12	67.5	68.5	UP (2 lesions)	N	UP (2 lesions)	N
13	30.9	31.5	LP	UP, MP, LP	LP	UP, MP, LP
14	19.6	20.4	N	LP	N	LP
15	2.2	2.5	N	atrophy	N	atrophy
16	93.9	92.5	atrophy	N	atrophy	N
17	3.9	4.1	N	atrophy	N	atrophy
18	64.9	65.2	MP	N	MP	N
19	85.5	83.7	atrophy	N	atrophy	N
20	42.6	42.8	UP, MP	UP, MP, LP	UP, MP	UP, MP, LP
21	19.6	18.8	N	atrophy	N	atrophy
22	35.6	38.1	N	UP, LP	N	UP, LP
23	18.2	21.7	N	hypoplasia	N	hypoplasia
24	—	—	nephrectomy	N	nephrectomy	N
25	42.4	42.6	N	UP, MP, LP	N	UP, MP, LP
26	—	—	agenesia	atrophy	agenesia	atrophy
27	—	—	nephrectomy	N	nephrectomy	N
28	31.3	37.7	UP	UP (2 lesions), LP	UP	LP
29	50.4	46.4	N	N	N	N

DRF = Differential renal function of the left kidney; UP = upper pole; MP = middle part; LP = lower pole; N = normal.

higher renal extraction ratio of the former agent. In several studies, the plasma protein-bound fraction of Tc-99m EC (30%) has been found to be significantly lower than those of Tc-99m MAG3 (90%) and also those of OIH (60%).[14,16,21]

Piepsz[29] has reported that the main tool of radionuclide techniques applied to pediatric uro-nephrology is the quantitation of function, which is an information not easily obtained by other diagnostic modalities. Tc-99m DMSA scintigraphy is an accurate method for evaluation of regional cortical impairment during acute pyelonephritis and later on, for detection of permanent scarring.

Verbruggen et al.[13] have demonstrated that Tc-99m EC has negligible uptake in the liver and intestines in animal studies. Ozker et al.[27] have reported that high body background and hepatic uptake were observed in Tc-99m MAG3 images because of high protein binding and blood pool activity in addition to the hepatobiliary excretion of Tc-99m MAG3. The delineation of the kidneys is better in Tc-99m EC images because of its lower hepatobiliary localization and lower body background.[18] It was also reported that the behavior of Tc-99m EC was closer to that of OIH than is the case with Tc-99m MAG3.[12] The labeling procedure of Tc-99m EC is easy and rapid at room temperature. Tc-99m EC images allow excellent delineation of the kidneys with high target to background ratios, even with significantly impaired renal function.[30] The plasma clearance of Tc-99m EC was found about 75% of the OIH.[21,30] The protein binding of Tc-99m EC is lower than that of OIH (33% versus 62%).

In clinical practice, Tc-99m DMSA is an excellent renal parenchymal imaging agent that 50% of the injected dose is located in the kidneys at 1 hr after the injection.[7] The main objective of renal parenchymal scintigraphy is to visualize foci of acute pyelonephritis. Whitear et al.[31] reported that Tc-99m DMSA scintigraphy was significantly more sensitive than intravenous urography and ultrasonography in the detection of renal parenchymal diseases. The previous studies showed that Tc-99m MAG3 studies could give the similar information on renal parenchymal abnormalities as Tc-99m DMSA scintigraphy.[32,33] According to these studies, the sensitivity and specificity

of the Tc-99m MAG3 technique in detecting renal parenchymal abnormalities were calculated as 88–89% and 88–100%, respectively. For this reason, Bair et al.[33] reported that Tc-99m DMSA was more accurate in renal parenchymal lesions and preferable for the evaluation of DRF in patients who had abnormal positions of the kidneys. Recently, the utility of Tc-99m EC was investigated for early diagnosis of certain cytostatics induced nephrotoxicity. Caglar et al.[34] has evaluated the toxic effects of ifosfamide and cisplatin in relation to Tc-99m DMSA and Tc-99m EC renal scintigraphy in pediatric patient group.

In the literature, there was no comparative study between Tc-99m EC scintigraphy and Tc-99m DMSA scintigraphy evaluating the renal cortical abnormalities. In this study, both Tc-99m DMSA and Tc-99m EC scintigraphies showed good matching by visual analysis in demonstrating cortical abnormalities. Tc-99m DMSA scintigraphy showed slightly more parenchymal defects than Tc-99m EC which is probably due to the higher spatial resolution and image contrast, and the possibility of obtaining images from different projections of Tc-99m DMSA scintigraphy. But, we have no patient with abnormal kidney positions that are important to take images from different projections. Technetium-99m EC scintigraphy allows nearly the same information on relative renal function of each kidney as Tc-99m DMSA scintigraphy without position abnormality, but also provides more informations about perfusion, excretion, and collecting system.

In conclusion, these results show that summed Tc-99m EC images with an acceptable high image contrast provide an accurate DRF calculation in patients without abnormal kidney positions and allow the detection of most renal parenchymal abnormalities, but Tc-99m DMSA scintigraphy remains the gold standard method because of the major advantages of this method such as the availability of different acquisition projections and better delineation of the kidneys.

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