

Assessment of clinical usefulness of parametric clearance images in diagnosis of kidney cicatrization in children with chronic infections of the urinary tract

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Abstract

BACKGROUND: Cicatrization of the renal cortex is closely related to chronic infections of the urinary system. Static renal scintigraphy is used as the method enabling detection of local defects of radiopharmaceutical uptake, and is treated as the “gold standard” in the diagnosis of renal scars.

The aim of the reported investigation was a comparison of the diagnostic efficacy of parametric clearance images and the conventional summation images — obtained from dynamic

scintigraphy — in the detection of local defects of renal function. As the “gold standard” for the above comparison, the static scintigraphy of kidneys was accepted.

MATERIAL AND METHODS: Forty-one patients (age 4–19 years), 28 girls and 13 boys, participated in the study. Altogether, 73 kidneys were analyzed (in 9 patients, only one kidney). In each patient dynamic renal scintigraphy was performed after IV administration of ^{99m}Tc EC (ethylenedicysteine) and static planar renal scintigraphy using ^{99m}Tc-DMSA (dimercaptosuccinic acid) as a reference method. From the dynamic study, summation and parametric clearance images were generated. Each kidney was divided into 3 segments (upper, middle, lower); altogether 219 segments were evaluated by modified Howard's scale. Planar and oblique projection images were compared with corresponding summation and parametric clearance images.

RESULTS AND CONCLUSIONS: Parametric clearance imaging has a higher sensitivity and accuracy for detection of regional post-inflammatory changes in the kidneys than conventional summation images ($p < 0.05$) and shows parenchymal changes similarly to static scintigraphy (high Cohen's kappa index).

Key words: urinary tract infections, renal scars, parametric clearance images

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Introduction

Chronic and repeating infections of the urinary tract are frequent among children. The frequency of urinary tract infections is only second to those of the respiratory system. They form a substantial diagnostic and therapeutic problem. Failure of

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diagnosis is linked to lack of or delayed undertaking of therapy [1]. The available statistics show that at 10 per cent of children of both sexes and 20–50 per cent of adult females are diagnosed with at least one episode of urinary tract infection in their life [2]. The frequency of infections is higher among females than males, with the exclusion of the neonatal period when boys are more frequently affected than girls [3–6].

The factor most predisposing to infection of the upper part of the urinary system is impediment of urinary flow [7]. In children the presence of vesicoureteral reflux (VUR) facilitates penetration of bacteria from the bladder to the ureters. However, the isolated retrograde vesicoureteral, non infected reflux does not produce renal scars. The acute form of pyelonephritis may be a repeating disease. However, the fact that the spectrum of clinical symptoms is reducing with each repetition of the urinary infection may lead to a delay in diagnosis. The result of acute urinary tract infection may become a chronic disease and therefore lead to scars in the renal parenchyma [8, 9]. The delayed consequence of the urinary tract infection is frequently seen in children who in early childhood had numerous episodes of acute pyelonephritis. Grabe et al. [10] and Still et al. [11] demonstrated that girls with returning urinary tract infections and renal scars develop repeat urinary tract infection in adulthood, and particularly in pregnancy [12].

The concept of reflux nephropathy has been introduced by Bailey [13]. This syndrome results from multifocal scarring of renal parenchyma and is connected with the vesicoureteral reflux [14, 15]. In addition, in the course of the chronic pyelonephritis with renal scarring the slowing of renal growth and progressive sclerotisation of renal glomeruli is observed. In subsequent years a substantial proteinuria is noted, with the loss of a few grams of protein per day. The scarring also leads to impairment of kidney physiology, disturbances of urinary flow and excretion, and impairment of renal perfusion. All these phenomena stimulate bacterial infections of the urinary system [16].

Epidemiological data indicate that urinary nephropathy is a cause of late renal insufficiency in about 15 per cent of adult patients, particularly females, and about 5–6 per cent of children qualified for renal transplantation [17].

The role of genetic predisposition to renal scarring has also been of interest to many investigators for a number of years [18–23].

The studies of Rossleight et al. [23] demonstrated that there is a strong association and concordance between static scintigraphy (^{99m}Tc DMSA) and histopathology in white piglets after experimental (artificial) infection of the urinary system in these animals [24–26].

The static scintigraphy of kidneys has been accepted as a “gold standard” in detection of renal defects induced by chronic infection of the urinary system. On the other hand, dynamic scintigraphy of the urinary system (e.g. using ^{99m}Tc EC) — renoscintigraphy — provides complex information on the secretory and excretory function of the system and permits assessment of the degree of impairment of the kidney as an organ. These two methods are used in a diagnostic algorithm for evaluation of the renal damage induced by inflammatory processes in the urinary system. Renal scars lead to manifold damage of these organs, which may lead to serious chronic disease and premature death. The basic aim of diagnosis and treatment of infection of the urinary

system is prevention of its progressive damage and reduction of premature mortality [1, 3, 27, 28].

The aim of the study reported below was a comparison of the diagnostic efficacy of parametric clearance images and conventional summation images—both derived from dynamic urinary tract scintigraphy—in the detection of regional defects of renal function (renal scars). Both alternatives have been evaluated accepting static renal scintigraphy as a standard.

The additional analysis was devoted to the question of whether two independent renoscintigraphic procedures (static and dynamic) could be reduced to one—dynamic only—providing information both on urinary transport through the system and images of renal parenchyma via parametric clearance images. This would save time, reduce the cost of radiopharmaceuticals, accelerate the diagnosis, and reduce the effective dose to the patient.

Material and methods

In accordance with the principles of the Helsinki Declaration, the study was performed after receiving acceptance from the Bioethical Commission of the Medical University of Lodz.

Forty-one patients (28 girls and 13 boys) aged 4 to 19 years were studied. Altogether 73 kidneys were evaluated (in 9 subjects only one kidney due to aplasia or substantial hypoplasia of the other one). The patients were under clinical-nephrological observation and had been in therapy for a long time period. These individuals, with diagnosed vesicoureteral reflux (VUR) of varying intensity, were investigated not earlier than 6 months and not later than 2 years after the last incident of the urinary system infection. Full nuclear medicine diagnosis required two visits in the nuclear medicine department, separated by a 2–5-day interval.

In all patients, the following procedures were performed:

- dynamic renoscintigraphy — ^{99m}Tc -ethylenodicysteine (^{99m}Tc -EC) was injected intravenously; the activity varied from 37 to 111 MBq according to the du Bois formula. The study was made on a planar gamma camera (Mediso, Nucline MB 9200). Sixty images of 20-second duration were acquired in an image matrix 64 x 64 with a zoom factor of 1.5. From this dynamic study conventional summation, images were generated in the time span from 20 to 120 seconds after injection of ^{99m}Tc -EC. The parametric clearance images were obtained according to the method of Surma and Anderson (see Appendix 35). These images are a graphical presentation (utilizing a colour scale) of the clearance rate of the nephrotropic radiopharmaceutical by very small fragments of renal parenchyma, on a pixel-by-pixel basis;
- at the next session, a static scintigraphy of the kidneys' parenchyma was obtained, using ^{99m}Tc -dimercaptosuccinic acid (^{99m}Tc -DMSA). The activity administered was calculated according to the du Bois formula (accepting activity of 185 MBq for an adult). This method is commonly accepted as the standard procedure for visualization of renal scars. Image acquisition was made from 90 to 120 minutes after injection of the radiopharmaceutical. A dual-head scintillation camera was employed (General Electric, Infinia Hawkeye). Three projections were evaluated: one posterior and two posterior oblique (in a matrix of 128 x 128 and zoom factor of 2.0).

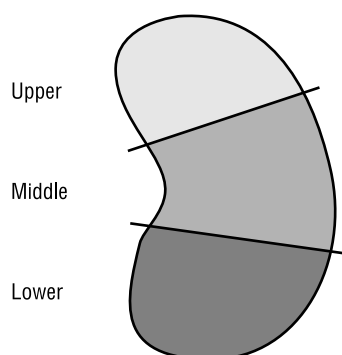


Figure 1. Schematic division of a kidney into 3 segments: upper, middle, lower.

Table 1. Contingency table presenting results of conventional summation and parametric clearance images relative to that of static scintigraphy (n = 219 segments)

		Static scintigraphy — reference method	
		Number of focal defects	
Conventional summation images	0	127	46
	1	2	44
Parametric clearance images	0	110	6
	1	19	84

Kidneys were assessed according to modified Howard's method. Each kidney was divided into 3 segments: upper, middle and lower. Regional defects of the radiopharmaceutical uptake and worsening of clearance function were classified according to the following score system: 0 — normal segment or 1 — one or more defects per segment (Figure 1). Altogether, 219 segments were evaluated. The defect was defined as a cold lesion (on clearance image) in at least half of the kidney parenchyma and/or when an obvious break of continuity of the profile of the renal cortex was seen. The scheme of renal segmentation is depicted in Figure 1.

The images were evaluated and classified by two physicians (Table 1) who were specialists in nuclear medicine. The final result was arrived at by consensus. The inter-observer agreement

was investigated earlier by two investigators [29, 30] and was found to be very satisfactory. Therefore, this analysis was not repeated in this study.

Results

Analysis of the data was based on a comparison of the diagnostic efficacy of the conventional summation images with that of the clearance parametric data (Table 1). In this comparison the posterior oblique projections were disregarded as they did not contribute to meaningful data. In the literature [31–33] there is no established opinion on the diagnostic value of oblique projection and SPECT images.

Examples of static renal scintigraphy along with summation and clearance parametric images of normal kidneys (Figure 2) and kidneys with scars have been presented in Figures 3 and 4.

The parametric clearance data had a very high sensitivity (93%), accuracy (88%), negative predictive value (95%), and Cohen's kappa index ($\kappa = 0.71$) in comparison with static images (a reference method). The results of this method were statistically significantly better than those obtained by simple summation of renoscintigraphic images: sensitivity 49% ($p < 0.01$), accuracy 78% ($p < 0.05$), negative predictive value 73% ($p < 0.05$), and kappa index 0.51 ($p < 0.05$). The conventional summation images had higher specificity and positive predictive value than clearance parametric images; however, the differences were not statistically significant (Table 2).

Discussion

The information on the diagnosis of renal involvement in urinary tract diseases by means of clearance parametric images is scarce [29, 30]. The method itself was developed by Surma and Anderson in the 1990s in London [35]. Dynamic renoscintigraphy is a well-known and established diagnostic tool, providing clinically useful information on the secretory and excretory function of the urinary system. Investigations of renal scarring have so far been a domain of static scintigraphy as the reference method. An analysis of its diagnostic efficacy, when compared with other imaging techniques, has been studied. The main interest of investigators has been concentrated on the detection and evaluation of the impairment of the renal cortex [36–39].

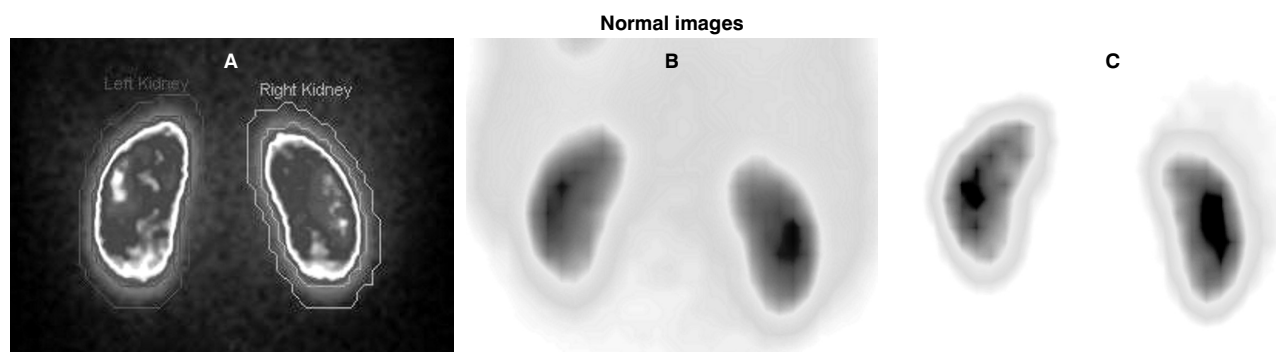


Figure 2. Planar image of kidneys in posterior view (A), summation image (B), and clearance parametric image (C) — normal images, without scars.

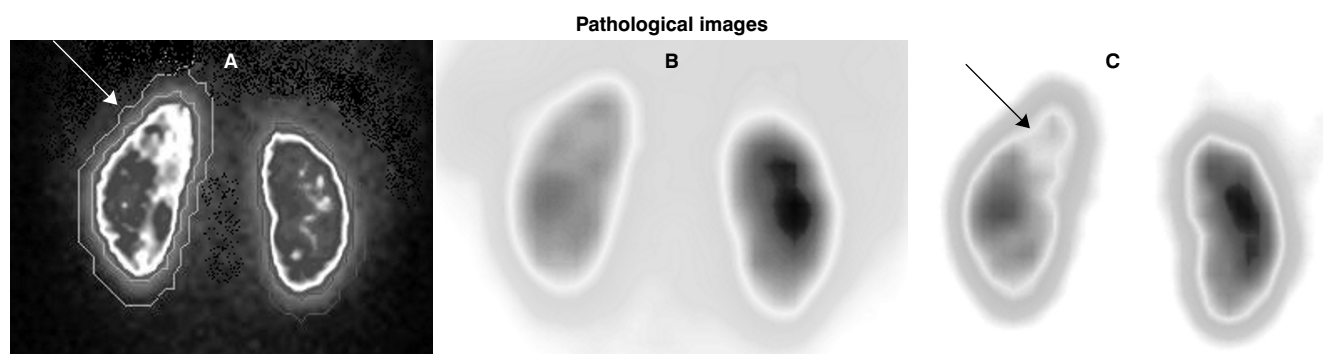


Figure 3. Planar image in posterior view (A), summation image — without defect (B), and clearance parametric image of kidneys (C) — renal scars are indicated with arrows.

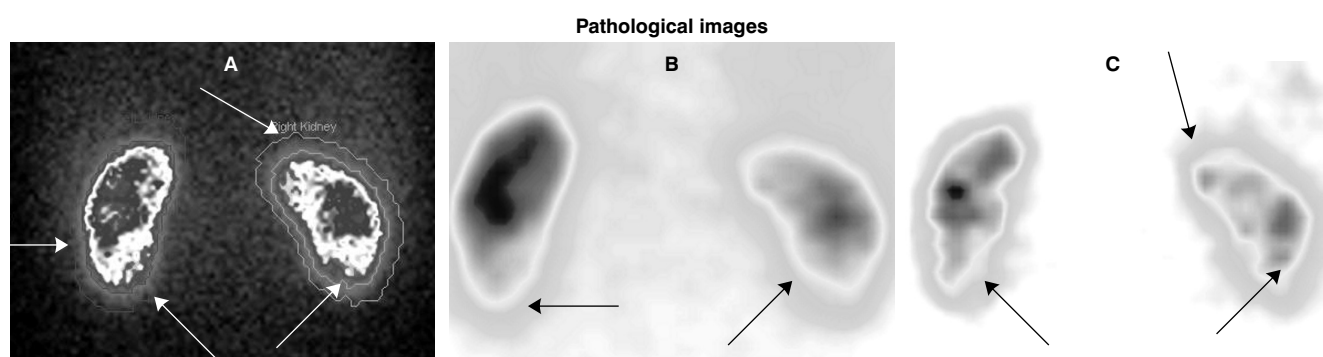


Figure 4. Planar image of kidneys in posterior view (A), summation image (B), and clearance parametric image (C) — renal scars are indicated with arrows.

Table 2. Comparison of diagnostic efficacy of conventional summation and clearance parametric images relative to static scintigraphy

	Sensitivity	Specificity	Accuracy	PPV	NPV	Kappa
Conventional summation images	49%	92%	78%	96%	73%	0.51
Parametric clearance images	93%	85%	86%	82%	95%	0.71
Significance (p)	0.01	NS	0.05	NS	0.05	0.05

PPV — positive predictive value; NPV — negative predictive value; NS — non significant

Of course, at present the static and dynamic scintigraphy of kidneys is not the only tool available to urologist and nephrologist. Urography with intravenously administered iodine-contrast medium is a well-known and useful tool for the diagnosis of disturbed function of the urinary system. Urography visualizes kidneys and excretion of urine. Detection of defects of excretion function is useful and may help in the diagnosis of retrograde vesicoureteral refluxes. It may help in the detection of scarring but cannot provide clear data on the renal cortex and its function. Moreover, it exposes the patient to contrast medium and doses of X-rays which are much higher than those from scintigraphy. Aranyo et al.[40] demonstrated that urography has a sensitivity of 66%, specificity of 94%, 90% of positive and 79% of negative predictive value, and 83% accuracy relative to ^{99m}Tc -DMSA scintigraphy [41].

Ultrasonography (conventional, colour, and Power Doppler) is a commonly available, easily accessible, safe, and low cost tool. Power Doppler ultrasound methodology seems to attain 30–80% sensitivity and 65–81% specificity in the detection of urinary tract in-

fections [42–44]. Its main advantage, however, is its ability to visualize blood flow in renal vessels, lesions of hypoperfusion or complete lack of perfusion, detection of pathologic vascularization in tumours, differentiation of blood vessels from the pyelocalyceal system, and clear visualization of the parenchyma limits. Doppler methods may substitute for other methods (e.g. nuclear medicine), particularly in acute pyelonephritis and post-inflammatory scars [45–47].

Computed tomography is, at present, a basic method for studies of the morphology of urinary systems as well as neighbouring tissues and organs. This method may be applied either with or without contrast media. A contrast medium-enhanced evaluation of the medulla and renal cortex is difficult; however, a kidney with vessels and pyelocalyceal system is easily visible. In chronic pyelonephritis this method does not properly visualize the calyx-pelvic region [48].

Nuclear magnetic resonance imaging is a valuable diagnostic tool, providing both morphological and functional information. Compared with static scintigraphy with the use of ^{99m}Tc -DMSA, MRI

(T1) shows 82% sensitivity and 91% specificity in the detection of scars. In sequence of T1-W, scars are detected with 77% sensitivity and 87% specificity (when related to static scintigraphy) [49]. An additional advantage is the speed of MRI. A single T1-W sequence takes 3 minutes while full SPECT takes 50 minutes (and may require sedation of the patient). These features may contribute to the acceptance of MRI in the future as the reference procedure in nephrology (however, at present both the cost and availability would not justify such a choice) [50, 51].

Conclusions

1. Parametric clearance imaging is a method of higher sensitivity and accuracy for detection of regional post-inflammatory changes in the kidneys (renal scars) than conventional summation images. Specificity of parametric clearance images was also high. It was lower than for summation images (but statistically non-significant).
2. Parametric clearance images present parenchymal changes similarly to static scintigraphy using renotropic radiopharmaceuticals.
3. Conventional dynamic renoscintigraphy provides both kinetic data on the function of the urinary system and parametric clearance images for the assessment of renal parenchyma, including scars. Therefore, resignation from classic static scintigraphy for evaluation of renal damage due to chronic infection of the urinary system appears justified.
4. One procedure (dynamic scintigraphy) instead of two shortens the time of diagnosis, reduces the effective dose to the patient, and the cost to the healthcare system.

Appendix

Theory of clearance calculation

Numerous techniques have been proposed to measure kidney clearance from the uptake phase of radioisotope renoscintigram. All of them are based on the assumption that no radiopharmaceutical leaves the kidney during (what is defined as) the minimum transit time (ca. 3 minutes after injection). The most comprehensive theory on the cumulation of a radiopharmaceutical in the kidneys was proposed by Rutland [52]. The theory was verified in practice for the whole kidney and is being used in routine investigations.

The $R(t)$ curve derived from the region of interest (ROI) over the kidney may be considered as the sum of two components:

- pure activity in the renal parenchyma — $CR(t)$;
- extrarenal background activity, which is proportional to the concentration of tracer in the blood — $F \times P(t)$:

$$R(t) = CR(t) + F \times P(t) \quad (1)$$

If we consider only the initial period, shorter than MTT, before elimination of urine from the kidney begins, then pure renal activity $CR(t)$ should be proportional to the integral of the curve describing the changes of the activity in blood:

$$CR(t) = K \times \int_0^t P(u) du \quad (2)$$

The resulting curve of renal activity changes could then be arranged as:

$$R(t) = F \times P(t) + K \times \int_0^t P(u) du \quad (3)$$

where F and K are unknown constants called "the blood background activity subtraction factor" and the "uptake coefficient" or "uptake constant", respectively. Integrated $P(t)$ function, presented as $P(u)$, is the function of the changes of radiopharmaceutical concentration in the plasma. F and K depend on a number of parameters, mainly on the renoscintigraphic curve $R(t)$. The radiopharmaceutical concentration curve in the plasma $P(t)$ in t moments is, in turn, related to the respective ROI, taking into account the attenuation coefficients and the presence of tissue between the kidney and the detector.

Dividing both sides of the Equation (3) by $P(t)$, we obtain:

$$\frac{R(t)}{P(t)} = F + K \times \frac{\int_0^t P(u) du}{P(t)} \quad (4)$$

which is a straight line equation of the relationship between

$$y = \frac{R(t)}{P(t)}$$

and

$$x = \frac{\int_0^t P(u) du}{P(t)}$$

F and K are line parameters. They can be determined using the least square method. The derived F value is used to determine the blood background component, and after subtracting the latter from the renal ROI curve, a curve depicting changes in the activity in renal parenchyma is obtained:

$$CR(t) = R(t) - F \times P(t) \quad (5)$$

By dividing the values of the pure renal activity by the integral of the function describing concentration of the radiopharmaceutical in the blood:

$$K = \frac{CR(t)}{\int_0^t P(u) du} \quad (6)$$

an interpretation of the coefficient K may be obtained. As can be seen, the coefficient K is similar to the definition of clearance. However, K would depict explicitly the kidney clearance only if the denominator provided an integral of the real plasma concentration of the radiopharmaceutical. Nevertheless, values of the curve over the heart are only proportional to the concentration, and therefore K is only proportional to the clearance. Consequently, determination of the clearance would be possible if the scale factor between K and the clearance were known.

This theory is applicable to the curve obtained for the whole kidney as well as to curves generated from every pixel within the ROI. F and K are determined for every pixel, and K_{ij} (i, j — pixel

indexes) is proportional to the clearance of the parenchymal fragment corresponding to the pixel. Moreover, owing to the imaging of the uptake constant K_{ij} obtained for each pixel i, j , it becomes possible to present a two-dimensional clearance distribution in the kidney.

For the whole kidney, values of the curve are relatively high and statistical fluctuations are relatively small. The values of the uptake constant obtained for the whole kidney are always positive. When the above theory is applied to a one-pixel ROI we can expect negative values, since pixel count rates may approach zero and their fluctuations may bring about negative values of K_{ij} . The latter have no physiological interpretation as this would mean that the tracer returns from the kidney parenchyma to the plasma.

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