

Usefulness of parametric renal clearance images in the assessment of basic risk factors for renal scarring in children with recurrent urinary tract infections

Ewa Pietrzak-Stelmasiak¹, Małgorzata Bieńkiewicz², Wojciech Woźnicki¹, Krystyna Bubińska³, Magdalena Kowalewska-Pietrzak⁴, Anna Płachcińska², Jacek Kuśmierek¹

¹Department of Nuclear Medicine, Medical University of Łódź, Poland

²Department of Quality Control and Radiological Protection, Medical University of Łódź, Poland

³Clinic of Pediatric Nephrology, Janusz Korczak Children's Hospital in Łódź, Poland

⁴Department of Pediatrics, Oncology, Hematology and Diabetology, Medical University of Łódź, Poland

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Abstract

BACKGROUND: Clinically confirmed incidents of acute pyelonephritis (APN) following recurrent infections of urinary tract (UTI) form basic risk factors for renal scarring in children. Vesico-urethral reflux (VUR) of higher grade is additional risk factor for this scarring. Opinions on diagnostic value of summed sequential images of renal uptake phase (SUM) of dynamic renal scintigraphy in detection of renal scars are diverse. However, several publications point to higher diagnostic efficacy of clearance parametric images (PAR) generated from this study.

The aim of the study. To establish a clinical value of parametric renal clearance images in detection of renal scarring.

MATERIAL AND METHODS: A prospective study was performed in a group of 91 children at the age of 4 to 18 years with recurrent UTI. Clinically documented incidents of APN were noted in 32 children: in 8 cases — one and in the remaining 24 — 2 to 5 (mean 3) incidents. In the remaining 59 patients only infections of the lower part of urinary tract were diagnosed. Static renal ^{99m}Tc-DMSA SPECT study and after 2-4 days dynamic renal studies (^{99m}Tc-EC) were performed in every patient not earlier than 6 months after the last documented incident of UTI. PAR images generated from a dynamic study by in-house developed software and SUM images were compared with a gold standard SPECT study.

RESULTS: Percentages of children with detected renal scar(s) with SPECT and PAR methods amounted to 55% and 54%, respectively and were statistically significantly higher ($p < 0.0001$) than with SUM method — 31%. Scars in children with history of APN detected with SPECT and PAR methods were significantly more frequent than with infections of only lower part of urinary tract (72% vs. 46%; $p = 0.017$ and 69% vs. 46%; $p = 0.036$, respectively). A SUM method did not reveal statistically significant differences between frequencies of detection of scars in groups specified above — 38% vs. 27% ($p = 0.31$). Both SPECT and PAR methods showed also that frequencies of occurrence of renal scars in children with higher grades of VUR were higher than without or with lower grades of VUR: 79% vs. 50% ($p = 0.048$) and 79% vs. 49% ($p = 0.04$). A SUM method did not reveal higher frequency of renal scars in children with high VUR grades: 36% vs. 30% ($p = 0.44$).

CONCLUSION: Results obtained with PAR and SPECT methods were similar. An advantage of PAR over SUM images obtained from a dynamic renal scintigraphy in detection of renal scars in children with UTI was confirmed.

KEY words: pyelonephritis, parametric clearance images, renal scarring, urinary tract infections

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Background

Recurrent urinary tract infections (UTI) are relatively frequent health problems in children. Clinically confirmed incidents of acute pyelonephritis (APN) in the course of these infections form

Correspondence to: Jacek Kuśmierek
Department of Nuclear Medicine, Medical University of Łódź
E-mail: jacek.kusmierek@umed.lodz.pl

basic risk factors for renal scarring, a condition that may lead to impairment of a physiological growth of a kidney and cause such long-term complications as arterial hypertension or chronic disease of kidneys leading to their failure [1–3]. Higher tendency to renal parenchyma infections and formation of renal scarring is also correlated with urine outflow disturbances. Vesico-urethral reflux (VUR) of higher grade forms a documented risk factor for this scarring [4, 5].

One of fundamental diagnostic aims in children with UTI is to detect renal scarring early. Children with such abnormalities should be diagnosed and treated particularly thoroughly to prevent development of further scarring and avoid long-term serious complications [2, 6, 7].

Static renal scintigraphy (planar or SPECT) using ^{99m}Tc -DMSA is considered a gold standard in detection of renal scars. Animal model studies (on white piglets) revealed its higher diagnostic efficacy, especially sensitivity, in comparison with ultrasonography and urography [8–10]. A static study presents a renal uptake function of this radiopharmaceutical and does not provide information on a transport function through kidneys and urinary tract. Both specified above functions can be obtained from a dynamic renal scintigraphy. However, results of studies on diagnostic efficacy of conventional dynamic images in detection of renal scars are diverse. Some authors, applying a static scintigraphy as a referential method, appreciate a high diagnostic value of summed sequential images of renal uptake phase of a radiopharmaceutical (SUM) in dynamic scintigraphy and assess its sensitivity to be even above 90% [11–13]. Other authors consider sensitivity of this method too low — 49–60% [14]. However, communications on high diagnostic efficacy of parametric clearance images (including our own) can be found, showing that those images improve sensitivity of the method to nearly 90% and their interpretations are highly reproducible [11, 14, 15].

The aim of the work was to establish a clinical value of parametric renal clearance images (PAR) in detection of renal scarring. This objective was achieved by comparative analysis of relationships, revealed by parametric dynamic renal scintigraphy and static (SPECT with ^{99m}Tc -DMSA) study, between frequencies of occurrence of renal scars and basic risk factors for renal scarring in children with UTI — APN and high VUR.

Material and methods

A prospective study was performed in a group of 91 children (63 girls and 28 boys) at the age of 4 to 18 years (mean value 11.5) remaining under a specialist care during 2 to 16 years (mean 6.2) because of recurrent UTI. Criteria of the episode of UTI were: clinical symptoms of lower and/or upper UTI with pure growth of $> 10^5$ cells/mL on clean catch or catheter specimen of urine. APN was defined as febrile UTI (fever of 38.5° or higher) with concomitant abnormal laboratory test results: white blood count (WBC) above $10.000/\text{mm}^3$ and elevated C-reactive protein (CRP) concentration [16, 17].

In 59 children recurrent (at least 3) incidents of infection of the lower part of urinary tract were diagnosed. In 32 children also clinically documented incidents of APN were noted: in 8 cases — one and in the remaining 24 — 2 to 5 (mean 3) incidents.

In 44 out of 91 children VUR was diagnosed with a X-ray cystourethrography during a clinical observation — in 30 children of low grade (I–II $^\circ$) and in 14 — of higher grade (III–V $^\circ$). In some patients VUR was reduced or absolved during observation period. Children were referred for scintigraphic studies (static renal SPECT study and after 2–4 days a dynamic renal scintigraphy) not earlier than 6 months after a last incident of UTI [18, 19].

A static SPECT scintigraphy was acquired 4 hours after intravenous injection of 56–185 MBq (depending on patient age) of Tc-^{99m} -dimercaptosuccinic acid (DMSA) on an Infinia Hawkeye 4 (GE Medical System) with low-energy high resolution collimator. One hundred and twenty projections (each lasting 30 seconds) in the 360° angle of rotation were acquired in a matrix 128×128 pixels with a zoom factor at least 2, adjusted to patient age. After reconstruction of SPECT images (with FBP, Metz filter 3;3.8), slices were presented along axes of every kidney.

A dynamic renal scintigraphy was performed after intravenous injection of 37–111 MBq of Tc-^{99m} ethylenedicycysteine (EC). For sufficient hydration all patients drank 10 mL of water per kilogram of body weight before radiopharmaceutical injection. Posterior views of patients in a supine position were acquired with a Nucline AP (Mediso Medical Imaging System) using a low energy high resolution collimator. A sequence of sixty 20 sec. images was acquired in every patient, with zoom factor depending on a patient age (at least 1.5). There was no need to apply a motion correction software. Time-activity curves were generated from regions of interest of both kidneys, heart and extra-renal background (a region located between kidneys). A summation of images (SUM) acquired between 40 and 140 seconds of study was accepted as a conventional method for detection of renal scars in kidneys. Additionally, parametric images (PAR) were generated, presenting regional values of a clearance function, on a pixel by pixel basis, using an in-house developed software applying a Rutland-Patlak analysis method [14].

A renal scar was defined as a cortical defect of ^{99m}Tc -DMSA uptake visible in at least two planes in SPECT study, also a defect in a summed ^{99m}Tc -EC image as well as a regional defect of function in a clearance image.

Images were evaluated in 3 segments of each kidney: upper, middle and lower, by a consensus of 2 experienced nuclear medicine specialists. Dependences between incidences of detected scars and APN or high VUR were assessed after a binary division of studied group into patients without scars and with at least one renal scar.

The study was approved by a Medical University Bioethics Committee and all subjects (or their parents) signed a written informed consent.

Statistical analysis

Data were described and analyzed with methods appropriate for qualitative variables. Statistical significance of differences between frequencies of scar detection with different diagnostic methods was evaluated with McNemar's test. Sample fractions of characteristics of interest were compared with use of Pearson's χ^2 test (for small size Fisher exact test was applied). Statistical significance was achieved when $p \leq 0.05$. Calculations were performed with Statistica 12.0 software.

Results

Percentages of children with detected renal scar(s) with SPECT and PAR methods were similar and amounted to 55% (50/91) and 54% (49/91), respectively. They were statistically significantly higher ($p < 0.0001$) than percentage of children with detected scar(s) with SUM method — 31% (28/91 children). In a reference SPECT method scars were detected in 106 renal segments (in a PAR method — in 111 and in SUM — in 59 segments). Scars were detected most often (in 87%) in renal poles (upper and lower segments) and only in 13% in middle segments. Eighty four per cent (89/106) of scars were located in the same segments in PAR and SPECT methods. However, agreement between

Table 1. Frequencies of detection of renal scarring in children with UTI and APN incidents in comparison with children without APN ($n = 91$ children)

	SPECT	PAR	SUM
With APN	23/32 (72%)	22/32 (69%)	12/32 (38%)
Without APN	27/59 (46%)	27/59 (46%)	16/59 (27%)
p	0.017	0.036	0.31

Table 2. Frequencies of detection of renal scarring in children with UTI and high grade VUR (III°–V°) vs. low grade (I°–II°) or absence (“–”) of VUR ($n = 91$ children)

	SPECT	PAR	SUM
VUR III°–V°	11/14 (79%)	11/14 (79%)	5/14 (36%)
VUR I°–II° or “–”	39/77 (50%)	38/77 (49%)	23/77 (30%)
p	0.048	0.04	0.44

locations of scars detected with SUM and SPECT methods was statistically significantly lower — 48% (50/106 segments, $p < 0.0001$)

Both SPECT as well as PAR methods revealed similar and significantly higher incidence of scars in children with history of APN incident(s) as compared with patients with infections of only lower parts of urinary tract — 72% vs. 46% ($p = 0.017$) and 69% vs. 46% ($p = 0.036$). A SUM method did not reveal statistically significant differences between incidences of scars in specified above groups of patients — 38% vs. 27% ($p = 0.31$) (Table 1).

Both SPECT and PAR methods showed also that frequencies of occurrence of renal scars in children with higher grades of VUR were higher than without or with lower grades of VUR: 79% vs. 50% ($p = 0.048$) and 79% vs. 49% ($p = 0.04$). A SUM method did not reveal higher frequency of renal scars in children with high VUR grades: 36% vs. 30% ($p = 0.44$) (Table 2).

Figure 1 presents examples of SPECT, PAR and SUM images of a patient without scars and a patient with a scar in one kidney.

Discussion

A static study of kidneys using ^{99m}Tc -DMSA, considered a gold standard in detection of renal scars, can be performed using planar or SPECT methods. No unequivocal guidelines pointing to higher usefulness of one of these methods for this purpose are available at present. In this work a ^{99m}Tc -DMSA SPECT imaging was used because this imaging has advantage over the planar method in presenting the whole kidney parenchyma. Planar studies acquired in three typical projections, visualize only 2/3 to 3/4 of kidney parenchyma in a satisfying way [20]. SPECT imaging also provides better image contrast than a planar method.

Dynamic renal scintigraphy enables not only assessment of uptake of a radiopharmaceutical in renal cortex, but also provides information, like a static renal study, on split function of both

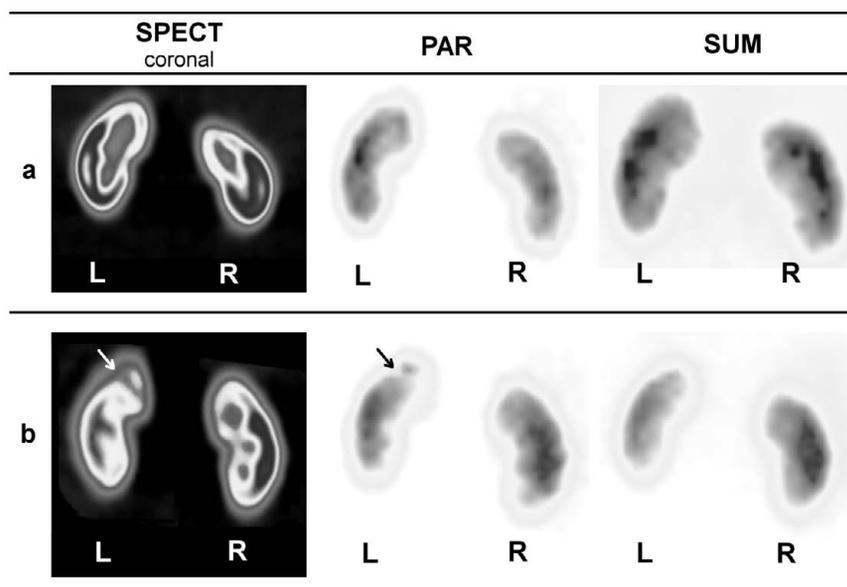


Figure 1. Examples of SPECT coronal slices, PAR and SUM images in children: **A.** without renal scars; **B.** with a scar in the upper pole of a left kidney visible only in SPECT and PAR images (arrows). L — left kidney, R — right kidney

kidneys. It also enables assessment of excretory function of a kidney together with detection of urine outflow disturbances. This study also allows, in an indirect way, to detect vesicoureteral reflux, especially of higher grades [18]. The following features of this method are considered drawbacks: planar study is routinely acquired in only one (posterior) projection, sequential images consist of low counts as a result of acquisition in short time intervals (10 to 20 seconds), a summed image of initial study phase presenting uptake of a radiopharmaceutical by a renal parenchyma is disrupted not only by extra-renal background, but is also blurred by the movement of radiopharmaceutical through a renal cortex.

However, parametric clearance images generated by a software created in our department present, on a pixel by pixel basis, relative distribution of a quantitative parameter characterizing clearance of blood from a nephrotropic radiopharmaceutical (in the present work it was $^{99m}\text{Tc-EC}$) by small parts of renal cortex. Definition of this quantity accounts for a decrease of a radiopharmaceutical content in blood (in every pixel of a kidney image), so those images are free of extra-renal background. Neither are they blurred by radiopharmaceutical flow through a renal cortex.

In our previous publications we proved that diagnostic accuracy of PAR images (close to SPECT study) is higher than accuracy of SUM images in detection of renal scars (88% vs. 73%, $p = 0.002$). SUM images provided lower (unacceptable) sensitivity than PAR images (49% vs. 89%, $p = 0.0001$), while specificities of both methods were comparable [14, 15].

Those results are confirmed in the present work by higher percentages of scars detected with SPECT and PAR studies that with SUM method — 55% and 54% vs. 31% ($p < 0.0001$) and higher agreement between localization of renal scars in segments, detected with SPECT and PAR methods than with SPECT and SUM methods — 84% vs. 48%, $p < 0.0001$).

Incidence of renal scars in children with UTI, according to the literature, varies between about 20% and 80% [2, 4, 21, 22]. This fact should be probably attributed to various methodological assumptions, different structures of studied material of patients in relation to race, age, sex, duration time of UTI, and above all incidence and number of clinically documented APNs — a basic etiological factor of cortical scars. A relatively high (about 70%) incidence of renal scars detected with parametric and SPECT methods in the group of children with a history of APN should be probably attributed to the fact that as many as 24 out of 32 patients (75%) have had more than one fully symptomatic incident of APN (on average 3) during a long-standing observation (on average 6.2 years). It can be expected that numbers of renal parenchyma infections were in fact higher but consecutive recurrences of APN may have been mildly symptomatic.

Oligosymptomatic nature of renal infections may explain a relatively high (46%) frequency of renal scars detected with SPECT and PAR methods in groups of patients with diagnosed infections of only lower part of urinary system. It should be noted that as many as 60% of UTI taking place with raised body temperature, changes in urine and symptoms specific for infection of a lower part of urinary tract affect also renal parenchyma [1, 23].

It has been shown in numerous publications that a high degree VUR stimulates infections of renal parenchyma in children, followed by scars. It is believed, however, that low degree VUR does not provide a significant risk factor for renal scarring [4, 24–26].

In our study a significantly higher frequency of renal scarring in children with high degree VUR in comparison with low degree or absence of VUR was confirmed with SPECT and PAR methods — 79% vs. 50% ($p = 0.048$) and 79% vs. 49% ($p = 0.04$), respectively. A SUM method did not show such a difference (39% vs. 30%, $p = 0.44$). The fact that study material did not include infants and 2–3 year old children forms a limitation of the study. This was due to logistic problems (i.a. necessary sedation of such patients because of a long SPECT study acquisition).

Conclusion

Frequencies of detection of renal scars in children with UTI using SPECT and PAR methods did not differ significantly and were higher than with SUM method. A PAR method, similarly to a SPECT study, confirmed a higher incidence of renal scarring in children with UTI and a history of APN incident(s), also in children with higher VUR grades (III^o–V^o). This dependence could not be revealed with a SUM method. An advantage of PAR over SUM images obtained from a dynamic renal scintigraphy in detection of renal scars in children with UTI was confirmed.

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