

Role of calculated glomerular filtration rate using percutaneous nephrostomy creatinine clearance in the era of radionuclide scintigraphy

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Abstract

Context: Gates method tends to over-estimate glomerular filtration rate (GFR) in borderline functioning kidneys. We study the role of calculated GFR in these cases in decision-making regarding performing kidney-sparing surgery or nephrectomy.

Aims: The aim of this study is to find the correlation between GFR calculated by percutaneous nephrostomy (PCN) urine creatinine clearance in obstructed kidneys and GFR by radionuclide scintigraphy. It also studies the role of this calculated GFR in borderline functioning kidneys.

Settings and Design: Single tertiary care center; retrospective.

Materials and Methods: A total of 46 patients in whom PCN was inserted as an emergency measure in an obstructed kidney and for whom diethylene-triamine-penta-acetic acid/ethylene-di-cysteine (DTPA/EC) scan was also done (Gates method) were analyzed retrospectively. PCN creatinine clearance was calculated for 3 consecutive days, and the mean value was used.

Statistical Analysis Used: Pearson's correlational analysis; Chi-square test.

Results: Overall strong correlation was found between the two GFR values (Pearson's $r = 0.540692$, $P < 0.001$). Totally 26 patients (56.52%) had comparable GFR values ($P > 0.05$). Among the 36 patients with borderline functioning kidneys, DTPA/EC scan significantly over-estimated GFR in one-third of the patients. The management plan was changed in 7 out of those patients (46.67%), with nephrectomy performed in all instead of kidney-sparing procedure. When the highest value of calculated GFR was compared, 28 patients had comparable GFRs (60.87%).

Conclusions: GFR based on radionuclide scintigraphy may be insufficient for evaluation of residual renal function to determine the management of obstructed kidney with borderline function. For adequate decision-making, other factors including creatinine clearance via PCN should also be considered. Gates method tends to overestimate GFR as compared to calculated creatinine clearance at low GFR levels.

Key Words: Creatinine clearance, diethylene-triamine-penta-acetic acid scan, glomerular filtration rate, percutaneous nephrostomy, percutaneous nephrostomy creatinine clearance

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INTRODUCTION

Radionuclide scintigraphy is considered the most widely used method for estimation of glomerular filtration rate (GFR) in clinical use.^[1,2] It is also the only noninvasive method that can estimate differential renal function, which is more relevant to urologists. Although computerized tomography (CT) volumetry has also been described for estimating the split renal function,^[3] unlike radionuclide scanning, it does not estimate the absolute GFR of each kidney. Although plasma clearance method of radionuclide scanning is considered the most accurate method, the Gates method (gamma camera) is more commonly used due to technical simplicity^[1] and being less expensive. The plasma clearance method gives only the global GFR estimate and not the differential function. However, the accuracy of Gates method has been frequently debated.^[1,2] The Gates method has limitations in some situations particularly relevant to urology like grossly hydronephrotic or borderline functioning kidney.^[2,4] In developing countries, radionuclide scintigraphy is available only in major cities. Creatinine clearance method is the most commonly used method for estimating global GFR,^[2,5] despite its inaccuracies, as it is easy to perform and gives results adequate for clinical purposes. In urology, many patients require percutaneous nephrostomy (PCN) insertion for emergency management of various disease conditions (e.g., pyonephrosis, acute kidney injury with distal obstruction, iatrogenic trauma, etc.). The creatinine clearance calculated from this PCN urine output provides GFR of that unilateral kidney of the side of PCN. This study was conducted to find out the correlation between GFR calculated by creatinine clearance of PCN urine (cGFR) and the GFR measured by technetium-99m diethylene-triamine-penta-acetic acid (DTPA) scan or technetium-99m ethylene-di-cysteine (EC) scan (mGFR). We also studied the role of this calculated GFR in borderline functioning kidneys (GFR <15 ml/min).

MATERIALS AND METHODS

A total of 46 patients (29 males, 17 females) with age ranging from 14 to 70 years (mean 39.04 years) were retrospectively analyzed from medical records from January 2012 to June 2016 in a single tertiary care center. Prior institutional ethics committee approval was taken for the same (IEC/77/15). All patients with kidney disease for whom PCN was inserted for various indications were evaluated.

Inclusion criteria: The patients in whom DTPA/EC scan was done, and for whom cGFR was also calculated.

Exclusion criteria:

- Patients with unresolved acute kidney injury/obstructive uropathy/unresolved infection
- Patients with reflux disease

- Patients with solitary functioning kidney
- Age <12 years
- Patients with ectopic kidney
- Patients with nil output from PCN.

The mGFR and cGFR estimation was done after complete stabilization of the patient and resolution of the indication for which PCN was inserted (e.g., complete drainage of pyonephrosis and resolution of sepsis, complete resolution of acute kidney injury with attainment of baseline/nadir creatinine value) and after stabilization of PCN output. The DTPA/EC scan was performed by Gates method from a single center with high volume load of radionuclide scintigraphy scans. All patients were adequately hydrated before the procedure. PCN was clamped during the procedure whenever required (Pelvi-ureteric junction obstruction). DTPA scan was performed for patients with serum creatinine up to 1.8 mg/dl, as per the protocol of the nuclear medicine department. EC scan was performed for rest of the patients. As EC scan gives only effective renal plasma flow (ERPF) values, approximate GFR estimate was calculated by dividing ERPF by 3.5, which is calculated as follows:

ERPF is given by the formula:^[6] $ERPF = \text{renal plasma flow (RPF)} \times \text{extraction ratio}$.

The GFR is related to RPF as follows:^[7] $GFR = RPF \times \text{filtration fraction}$.

The value of filtration fraction in humans is 0.2.^[7] The extraction ratio of EC is 0.7.^[8]

Hence after substitution of the above values, we derive: $GFR = ERPF/3.5$.

For cGFR estimation, 24 h PCN output was collected for 3 consecutive days, measured from 8 am of 1 day to 8 am of next day. The total PCN output was measured (V) (milliliters) and sent for urine creatinine estimation (U) (mg/dl). Blood sample was also drawn and sent for serum creatinine (P) (mg/dl) measurement at the same time. The GFR was calculated using the formula:

$$GFR \text{ (ml/min)} = (U \times V) / (24 \times 60 \times P)$$

The mean value of GFR calculated for the 3 days was considered for statistical analysis (cGFR). In this study, gross hydronephrosis was considered as grade 4 hydronephrosis using classification by Beetz *et al.*,^[9] with kidney size >15 cm in greatest dimension and paper thinning was considered maximum parenchymal thickness <3 mm.

The statistical analysis was performed using Microsoft Excel 2013. The overall correlation between mGFR and cGFR was

calculated using Pearson's correlation analysis. The age and gender variation were also calculated using Chi-square test. The Bland-Altman analysis plot was prepared by plotting mean of mGFR and cGFR on X-axis, and difference of mGFR and cGFR on Y-axis. The mGFR and cGFR values for an individual patient were converted into percent function of that unilateral kidney, by considering 60 ml/min as 100% function of each unilateral kidney. The resultant percent mGFR and cGFR functions were compared using Chi-square test. The two GFRs were defined as "comparable" if no significant difference was found between the two GFR values using Chi-square test ($P > 0.05$). If not then the GFR values were considered "noncomparable."

RESULTS

The demographic data of patients is shown in Table 1. The data of renal function and final management of patients is shown in Table 2. The result of statistical analysis of mGFR and cGFR values of the patients, as well as mGFR and highest calculated GFR, is shown in Table 3. DTPA scan was done in 33 patients and EC scan in 13 patients. In one patient, the mGFR (by DTPA scan) could not be measured due to severe hydronephrosis. Hence, cGFR value was used for decision-making and was managed with kidney-sparing surgery eventually. This patient was excluded from the comparative statistical analysis. Rest 45 patients were considered for comparative analysis.

A strong overall correlation was found between the two methods of GFR estimation (Pearson's $r = 0.540692$, $P < 0.001$) [Table 3]. The Bland-Altman plot of the same is shown in Figure 1. The mean bias was -4.16 , and mean standard deviation was 9.55 . Hence, the upper and lower limits of agreement (95%) were found to be 14.57 and -22.88 , respectively. The comparison of mGFR and cGFR in individual patient showed 26 patients (56.52%) having comparable GFRs ($P > 0.05$). 19 patients showed noncomparable GFRs ($P < 0.05$) by the two methods.

A total of 24 patients had gross hydronephrosis and paper thinning on imaging (52.2%), which were equally distributed between patients of comparable and noncomparable GFRs (15 vs. 9; $P = 0.4929$). A total of 36 patients had borderline functioning kidneys (mGFR < 15 ml/min) on DTPA/EC scan, which were also equally distributed between patients of comparable and noncomparable GFRs (21 vs. 15; $P = 0.88$). The final management was conservative (kidney-sparing) in 24 patients (52.2%) and nephrectomy in the rest 22 patients (47.8%). There was no difference in the distribution of patients with comparable and noncomparable GFRs among DTPA and EC scan groups ($P = 0.3215$).

Table 1: Demographic data of patients

Observation	Value
Total patients	46
Sex	
Male	29
Female	17
Age (years)	
Mean	39.04
Range	14-79
Type of scan done	
DTPA scan	33
EC scan	13
Diagnosis (%)	
Calculus disease	31 (67.4)
Pelvi-ureteric junction obstruction	9 (19.6)
Genito-urinary Koch	3 (6.5)
Iatrogenic genito-urinary tract injury causing stricture formation	2 (4.3)
Primary ureteric stricture	1 (2.2)
Indication for PCN (%)	
Pyonephrosis	36 (78.3)
Obstructive uropathy with raised creatinine	8 (17.4)
Temporary diversion of urine (urinary tract injury)	2 (4.3)

DTPA: Diethylene-triamine-penta-acetic acid, EC: Ethylene-di-cysteine, PCN: Percutaneous nephrostomy

Table 2: Data of renal function and final management of patients

Observation	Value
Mean mGFR (on the side of PCN), ml/min	11.54 (0-51.1)
Mean cGFR (ml/min)	7.46 (0.007-38.67)
Mean highest calculated GFR (ml/min)	8.77 (0.01-45.7)
Calculated GFR SD	1.42 (0.002-10.36)
Mean split function of the side of PCN on DTPA/EC scan (%)	27.18 (0-94.79)
Gross hydronephrosis and paper thinning on imaging (%)	24 patients (52.17)
Categorisation based on mGFR values (%)	
mGFR < 15 ml/min (borderline functioning kidney)	36 patients (78.26)
mGFR = 15-30 ml/min	6 patients (13.04)
mGFR > 30 ml/min	3 patients (6.52)
mGFR could not be calculated	1 patient (2.17)
Final management (%)	
Conservative (kidney-sparing)	24 patients (52.17)
Nephrectomy	22 patients (47.83)

mGFR: Measured glomerular filtration rate using DTPA/EC scan, DTPA: Diethylene-triamine-penta-acetic acid, PCN: Percutaneous nephrostomy, cGFR: Calculated glomerular filtration rate, EC: Ethylene-di-cysteine, SD: Standard deviation

Table 3: Results of comparative statistical analysis

Observation	Comparison with cGFR	Comparison with highest cGFR
Overall correlation (Pearson's correlation coefficient)	$r = 0.540692$ $P < 0.001$	$r = 0.544385$ $P < 0.001$
Patients with comparable GFR ($P > 0.05$)	26 (56.52%)	28 (60.87%)
Patients with noncomparable GFR ($P < 0.05$)	19 (41.30%)	17 (36.96%)
GFR could not be calculated on DTPA	1 (2.17%)	1 (2.17%)

cGFR: Calculated glomerular filtration rate, DTPA: Diethylene-triamine-penta-acetic acid

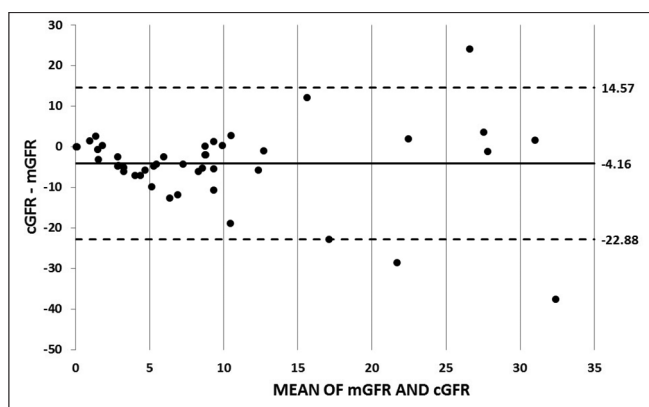


Figure 1: The Bland-Altman plot of glomerular filtration rate measured by diethylene-triamine-penta-acetic acid/ethylene-di-cysteine scan and glomerular filtration rate calculated by percutaneous nephrostomy creatinine clearance

Among the 19 patients with noncomparable GFRs [Table 4], the management plan was changed in 9 patients (47.37%) based on the above findings ($cGFR < mGFR$) combined with the imaging findings of loss of functioning parenchyma in these patients. The plan was changed from kidney-sparing surgery to nephrectomy in all these 9 patients. Among these 9 patients, 7 patients each had gross hydronephrosis with paper-thinning and borderline functioning kidneys. The other 2 patients also had paper-thinning of parenchyma and borderline functioning kidney but did not fit into the criteria of gross hydronephrosis. Our criteria for nephrectomy in borderline functioning kidney patients was a split function of less than 10%. The ratio of cGFR and DTPA/EC scan GFR of the opposite kidney was calculated for decision-making in these patients. In rest of the ten patients, the plan which was kidney-sparing in nine patients (90%) and nephrectomy in one patient (10%), did not change. The reason for no change in management plan was chronic kidney disease (CKD) status with split function $>10\%$ on the side of PCN necessitating kidney-sparing surgery (five patients), the underlying obstructive pathology (calculus disease) was easier to clear (e.g., small distal ureteric obstructive calculus) (one patient), the function was better by cGFR (two patients), split function was $>10\%$ by both methods (one patient), poor function by both methods requiring nephrectomy (one patient).

Among the 36 patients with borderline functioning kidneys [Figure 2], the GFRs by the two methods were noncomparable in 15 patients (41.67%), of which 12 patients (80%) had $mGFR > cGFR$. Hence, it can be derived that DTPA/EC scan significantly over-estimated GFR in one-third of the patients (12 out of 36) with borderline functioning kidneys. The management plan was changed in 7 out of those 15 patients (46.67%). All seven

Table 4: Data of patients with noncomparable glomerular filtration rates

Observation	Value (%)
Total patients	19
Gross hydronephrosis and paper thinning mGFR	9 (47.37)
<15 ml/min (borderline functioning kidneys)	15 (78.95)
15-30 ml/min	2 (10.53)
>30 ml/min	2 (10.53)
Borderline functioning kidneys with gross hydronephrosis and paper thinning	7 (36.84)
Type of scan (%)	
DTPA scan	15 (78.95)
EC scan	4 (21.05)
mGFR greater than cGFR	
All patients with noncomparable GFRs	16 (84.21)
Borderline functioning kidney patients	12 (80)
Plan of management changed	9 (47.37)
Gross hydronephrosis and paper thinning	7 (out of 9) (77.7)
Borderline functioning kidneys	7 (out of 9) (77.7)
Plan of management not changed	10 (52.63)
CKD status	5 (out of 10) (50)
Calculus easier to clear	1 (out of 10) (10)
Function better by cGFR	2 (out of 10) (20)
Split function $>10\%$	1 (out of 10) (10)
Poor function by both methods requiring nephrectomy	1 (out of 10) (10)

CKD: Chronic kidney disease, mGFR: Measured glomerular filtration rate using DTPA/EC scan, DTPA: Diethylene-triamine-penta-acetic acid, cGFR: Calculated glomerular filtration rate, EC: Ethylene-di-cysteine

patients had $mGFR > cGFR$ as well as gross hydronephrosis and paper thinning of parenchyma. Hence, the initial kidney-sparing (conservative) management plan was changed to nephrectomy in all of those seven patients.

The male:female distribution in patients with comparable and noncomparable GFRs was 15:12 and 14:5, respectively. No differences in gender distribution of males and females ($P = 0.2088$) was found in both the groups. When age-wise distribution of patients between the two groups was studied (age groups <20 , $20-30$, $30-40$, $40-50$, >50 years) significant difference between the distribution was observed only in the $20-30$ years' age group, where the group with comparable GFRs had significantly greater number of patients (12 vs. 2; $P = 0.00016$). However, the clinical significance of this finding cannot be commented on due to smaller sample size of our study.

If the highest value of calculated GFR from the 3 days was considered for comparative analysis, then the number of patients with comparable GFRs went up to 28 patients (60.87%) and the overall correlation was also increased ($r = 0.544385$, $P < 0.001$) [Table 3]. Furthermore, the significance level of comparison in patients with comparable GFRs also increased in the majority of the patients if highest calculated GFR value was considered for comparison (P value further increased).

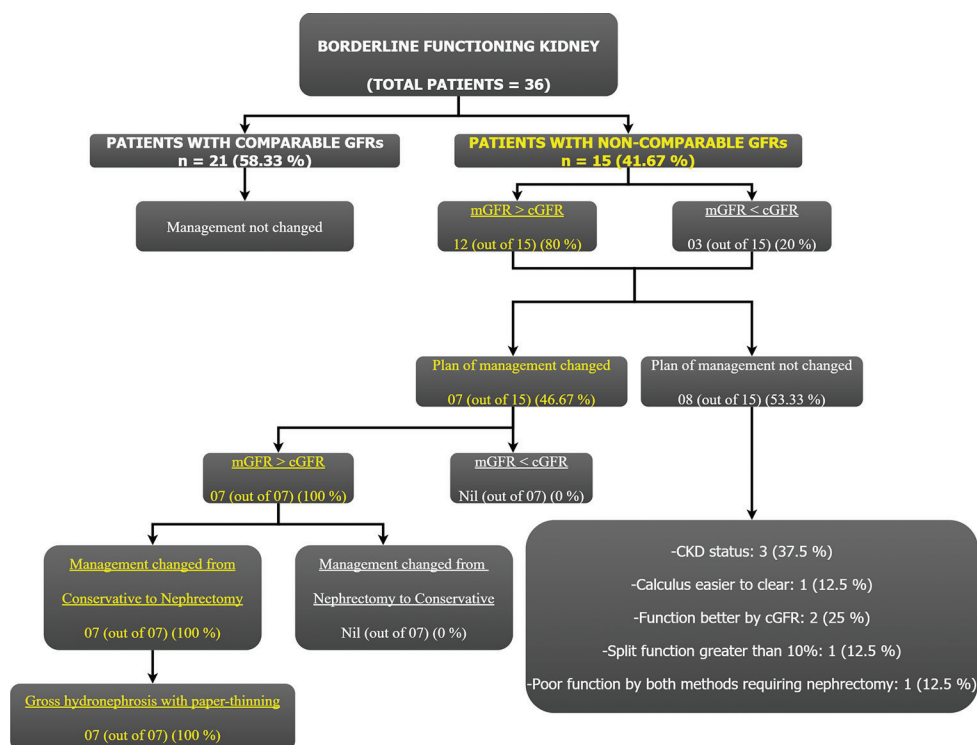


Figure 2: Management of patients with borderline functioning kidneys (glomerular filtration rate <15 ml/min), showing the role of calculated glomerular filtration rate in changing the final management plan

DISCUSSION

The PCN procedure was first described by Goodwin *et al.* in 1955.^[10] The various indications of PCN insertion include relief of urinary obstruction, urinary diversion, access for endourological procedures and for diagnostic studies.^[10] Although GFR calculation using inulin clearance is the most accurate method (gold standard), it is not easy to perform and not used in daily clinical practice,^[1] and needs exogenous administration of insulin. Hence, creatinine clearance is more commonly used as it is produced endogenously and hence easier to perform.^[2,5] Creatinine, however, is not entirely excreted by glomerular filtration.^[2,11] Approximately, 10% is excreted by tubular secretion.^[11] Hence, GFR by creatinine clearance tends to overestimate GFR.^[4,11-13] However, this method of GFR estimation is still widely preferred in routine clinical use^[5] and gives acceptable results. Trimethoprim and cimetidine can be used to block tubular secretion of creatinine, facilitating more accurate GFR calculation using creatinine clearance based methods.^[14,15]

Other methods of GFR estimation that have been described and used in daily clinical practice include equation based GFR estimation. These equations include CKD-Epidemiology Collaboration, Cockcroft–Gault formula, Modified Diet in Renal Disease-4 (MDRD-4) and MDRD-6, Schwartz equation (for pediatric patients), etc. Among these, combined

creatinine and cystatin-based CKD-EPI equation is the most accurate for global GFR estimation.^[16,17]

Hamed^[3] had described CT-based renal parenchymal volume assessment using renal arterial phase images to reconstruct a three-dimensional image of the enhancing renal cortex and estimate the renal cortical volume of both sides using volume estimation software. He found a significant correlation between this estimated differential volume and the differential function estimated by DTPA scan in unilateral obstruction. However, this method can only be used in patients with normal creatinine values as it requires contrast enhanced CT images. It also has a higher radiation exposure risk.

The Gates method, although most commonly used in DTPA/EC scan, is also inaccurate when compared with the plasma sampling method.^[1,4] It tends to underestimate GFR in Stage I and II CKD, and overestimate GFR in stage IV and V CKD.^[2,4,18] The plasma sampling method itself overestimates GFR as compared to inulin clearance method which has been quantified to be 3.5 ml/min on an average.^[19] The Gates method further overestimates GFR as compared to plasma sampling method at low GFR values.^[2] The reason for this has been proposed to be insufficient background correction in the kidney,^[1,2] which is particularly important for hugely hydronephrotic and borderline functioning kidneys. Gates method is operator dependent in these cases, which can further

increase inaccuracy. In hugely hydronephrotic kidneys, the selection of only the cortical region of interest (ROI) and exclusion of dilated pelvicalyceal system from the ROI is operator dependent. This leads to the introduction of error in the estimated GFR by Gates method. The inclusion of part of pelvicalyceal system into ROI can lead to overestimation of GFR. Rarely, it becomes very difficult to estimate and report GFR with fair accuracy in these patients, as was the case in one of our patient. In these patients, plasma sampling method could be the alternative method to estimate GFR. But as this method is not available at all places, GFR by PCN creatinine clearance can serve as a reasonable alternative in these patients. Gates method also depends on the hydration status of the patient, unlike creatinine clearance method. Many other sources of errors in the measurement of GFR by scintigraphy are well recognized and include: Decay statistics, attenuation correction, estimation of arterial plasma activity, system dead time, volume measurements, and radiopharmaceutical quality.^[2,20]

In our study, in the group with noncomparable GFRs, majority of them had mGFR > cGFR. The majority of them also had borderline functioning or hugely hydronephrotic kidneys. Hence, this GFR over-estimation could be well explained by the reasons mentioned above. As DTPA over-estimated GFR in these cases, the initial management plan was kidney-sparing. However, the cGFR served as an adjunct to the imaging findings mentioned before for changing the management plan to nephrectomy. The DTPA scan and EC scan showed similar results in this comparative study with cGFR. Hence, GFR calculated from ERPF of EC scan is as valid as GFR calculated from DTPA scan.

As evident from the study among borderline functioning obstructed kidney patients on DTPA/EC scan, if the mGFR is significantly greater than cGFR, it is likely that mGFR is over-estimated if the imaging findings also show gross hydronephrosis and/or paper thinning. This is supported by the fact that cGFR itself tends to be over-estimated as compared to true GFR by inulin clearance due to 10% tubular secretion of creatinine if the quality of urine collection is adequate. The highest calculated value of GFR correlated better with mGFR as mGFR was higher than cGFR in the majority of the patients. Hence, the difference between mGFR and cGFR was less when highest calculated GFR value was considered.

The fallacies involved in measuring cGFR using PCN include incomplete drainage of urine produced by that kidney through the PCN, as small fraction of the urine tends to drain down the ureter, leading to underestimation of GFR. However, in our study, all the patients had obstructive pathology, which prevented loss of urine down the ureter, as urine tends to drain via the path of lesser resistance, that is, via PCN. Hence, the

above fallacy was minimal. The other fallacy of this method is in patients with reflux disease, which can cause overestimation of GFR due to reflux of urine from urinary bladder to the kidney, leading to falsely increased PCN output. In this study, this fallacy was eliminated as all patients with reflux disease were excluded from the study. The obstructive pathology would have prevented the reflux of urine into pelvis if it was present.

In the developing countries, radionuclide scintigraphy available only in major cities. Hence, the majority of patients residing there do not have access to it. Hence, this calculated GFR using PCN creatinine clearance can be used as an adjunct to renal parenchymal thickness on imaging studies for decision-making for these obstructed kidney patients. Hence, PCN insertion for cGFR calculation should be allowed when the benefits outweigh the risks. The results from the study could not be compared with any other study as no other similar study has been published yet, to the best of our knowledge.

CONCLUSION

GFR based on radionuclide scintigraphy may be insufficient for evaluation of residual renal function to determine the management of obstructed kidney with borderline function. For adequate decision-making, other factors including creatinine clearance via PCN should also be considered. It is especially useful in patients with unilateral obstructed borderline functioning kidney and a functioning opposite kidney, where the decision to do kidney-sparing surgery or nephrectomy is difficult to make, especially when plasma sampling technique is not available. DTPA/EC scan by Gates method tend to overestimate GFR as compared to calculated creatinine clearance at low GFR levels.

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Conflicts of interest

There are no conflicts of interest.

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