
^{68}Ga -EDTA PET/CT Imaging and Plasma Clearance for Glomerular Filtration Rate Quantification: Comparison to Conventional ^{51}Cr -EDTA

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Glomerular filtration rate (GFR) can accurately be determined using ^{51}Cr -ethylenediaminetetraacetic acid (EDTA) plasma clearance counting but is time-consuming and requires technical skills and equipment not always available in imaging departments. ^{68}Ga -EDTA can be readily available using an onsite generator, and PET/CT enables both imaging of renal function and accurate camera-based quantitation of clearance of activity from blood and its appearance in the urine. This study aimed to assess agreement between ^{68}Ga -EDTA GFR (^{68}Ga -GFR) and ^{51}Cr -EDTA GFR (^{51}Cr -GFR), using serial plasma sampling and PET imaging. **Methods:** ^{68}Ga -EDTA and ^{51}Cr -EDTA were injected concurrently in 31 patients. Dynamic PET/CT encompassing the kidneys was acquired for 10 min followed by 3 sequential 3-min multibed step acquisitions from kidneys to bladder. PET quantification was performed using renal activity at 1–2 min ($\text{PET}_{\text{initial}}$), renal excretion at 2–10 min ($\text{PET}_{\text{early}}$), and, subsequently, urinary excretion into the collecting system and bladder (PET_{late}). Plasma sampling at 2, 3, and 4 h was performed, with ^{68}Ga followed by ^{51}Cr counting after positron decay. The level of agreement for GFR determination was calculated using a Bland–Altman plot and Pearson correlation coefficient (PCC). **Results:** ^{51}Cr -GFR ranged from 10 to 220 mL/min (mean, 85 mL/min). There was good agreement between ^{68}Ga -GFR and ^{51}Cr -GFR using serial plasma sampling, with a Bland–Altman bias of -14 ± 20 mL/min and a PCC of 0.94 (95% confidence interval, 0.88–0.97). Of the 3 methods used for camera-based quantification, the strongest correlation was for plasma sampling–derived GFR with PET_{late} (PCC of 0.90; 95% confidence interval, 0.80–0.95). **Conclusion:** ^{68}Ga -GFR agreed well with ^{51}Cr -GFR for estimation of GFR using serial plasma counting. PET dynamic imaging provides a method to estimate GFR without plasma sampling, with the additional advantage of enabling renal imaging in a single study. Additional validation in a larger cohort is warranted to further assess utility.

Key Words: ^{68}Ga ; EDTA; ^{51}Cr EDTA; glomerular filtration rate; GFR

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The determination of renal function as measured by glomerular filtration rate (GFR), expressed as the volume of fluid filtered by the renal glomeruli per minute, is utilized for a wide range of clinical decision making. The gold standard method for determining GFR is inulin clearance, but this is expensive, time-consuming, highly dependent on collection accuracy, and not commonly available. ^{51}Cr -ethylenediaminetetraacetic acid (EDTA) blood clearance counting is the most commonly implemented method for accurate estimation of GFR. Disadvantages include a requirement for multiple plasma samples, a significant number of manual laboratory processes, and a well counter, which is not available in many imaging facilities. It is also not possible to image ^{51}Cr -EDTA, negating use for determining split or regional renal function or possible causes of renal impairment.

One method of estimating renal function is the Cockcroft and Gault formula, which is based on serum creatinine, weight, and age. Although useful for identifying patients with renal impairment, it is too inaccurate across the full range of GFR for purposes such as determining chemotherapy dosing (1–3). More recently, the Modification of Diet in Renal Disease (MDRD) (4) and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (5) formulae have been shown to provide more accurate estimations. Radiolabeled $^{99\text{m}}\text{Tc}$ -diethylenetriaminepentaacetic acid (DTPA), a small organic molecule that is excreted solely by the glomerulus, can also be used for estimation of GFR. This is commonly performed by imaging on a γ camera but is prone to several sources of error, including attenuation of the activity by soft tissue, inaccuracy of using a geometric mean when renal geometry is asymmetric, extracellular localization of DTPA, and a variable degree of protein binding of DTPA.

PET/CT offers accurate camera-based quantification, superior to current γ camera technology (6). Although quantitative SPECT/CT is becoming more widely available, the long acquisition time renders this technology of limited utility for dynamic imaging. The 3-dimensional dynamic capability of PET/CT offers a key benefit over SPECT/CT for applications such as GFR estimation. EDTA can be labeled with ^{68}Ga , a positron-emitting isotope, which can be imaged as first described in 1960 (7,8). In that era, authors described ^{68}Ga -EDTA as having a “low radiation hazard to patient, ease of preparation, constant availability and low cost making this an excellent tracer for clinical imaging” (9). More recently, ^{55}Co -EDTA has been described in an animal study, but this technique has

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not been translated to human use and is limited by the requirement for a cyclotron (10). Our group demonstrated the excellent imaging characteristics of ^{68}Ga -EDTA as part of a high-throughput dynamic small-animal imaging study (11).

Although ^{68}Ga EDTA imaging has been performed using stand-alone PET (12), there are no data on the utility of PET/CT imaging for GFR estimation. This study aimed to compare the agreement of GFR estimated from ^{68}Ga -EDTA dynamic PET/CT and plasma sampling to ^{51}Cr -EDTA plasma sampling. As an exploratory endpoint, we also assessed the utility of PET/CT in determining split renal function.

MATERIALS AND METHODS

Patients

This prospective study aimed to recruit a total of 30 patients scheduled to undergo a GFR estimation study with ^{51}Cr -EDTA plasma sampling. The study schema (Fig. 1) was approved by the institutional clinical governance and ethics committee (trial 12613000845730 in the Australian New Zealand Clinical Trials Registry). The study included patients older than 18 y and excluded patients who were pregnant or breast-feeding. The patients were instructed to eat and drink normally before the study.

Radiotracer Production and PET/CT Imaging

^{68}Ga was eluted from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator (IDB Holland BV) and purified using a method previously described (13). This eluate was transferred to a SepPak alumina N column (Waters Corp.), washed with 10 mL of distilled water, and eluted with 10 mL of a solution of 0.05 M EDTA in 0.1 M sodium acetate, pH 6. Radiochemical purity was determined with thin-layer chromatography silica gel plates developed in a solvent system of ammonium acetate (1 M):methanol (50:50).

A peripheral intravenous line was inserted in each arm and blood taken to measure serum creatinine. One cannula was utilized for dose administration and the second for taking blood samples. The patient was positioned on the PET/CT camera (Biograph 64 with TrueV; Siemens Medical Systems) with arms raised. The extended axial field of view of 21.6 cm available on this scanner enables simultaneous imaging of both kidneys and inclusion of the cardiac blood pool in approximately half the patients. A scout scan and a low-dose CT scan

encompassing the diaphragm to the base of the pelvis were obtained and used to locate the kidneys for the PET acquisition. A median of 56 MBq of ^{68}Ga -EDTA (range, 46–95 MBq) and 2–4 MBq of ^{51}Cr -EDTA were injected intravenously, followed by a 20-mL flush with normal saline. PET imaging over the kidneys was performed for 10 min (dynamic 3-dimensional list mode) and reframed into 20×30 s frames. Subsequently, images were acquired from the kidneys to the bladder (3 bed steps, 1 min per bed step) and repeated 3 times in short succession (Supplemental Video 1, showing dynamic acquisition of ^{68}Ga -EDTA PET/CT for estimation of glomerular filtration rate, is available at <http://jnm.snmjournals.org>). The low-dose CT scan was used for attenuation correction.

GFR Estimation by Plasma Sampling

Injected dose was calculated by assaying the pre- and postinjection syringe in a dose calibrator. Blood samples were taken at 2, 3, and 4 h after injection. Blood was centrifuged at 2,000 rpm for 10–15 min to separate plasma. Two milliliters of plasma were obtained using a pipette. ^{68}Ga counting was performed within 6 h after injection (Biodex 950 well counter; Biodex Medical Systems). ^{51}Cr counting was performed between 8 and 72 h after injection (Wallac Wizard 1470 gamma counter; PerkinElmer). All counts were decay-corrected. ^{51}Cr -EDTA GFR (^{51}Cr -GFR) was calculated with 3 plasma samples using the slope-intercept method as detailed in the British Nuclear Medicine Society guidelines (14). The results were not corrected for body surface area, and Brochner-Mortensen correction was not applied.

GFR Estimation by PET/CT Imaging

For each kidney, a region of interest (ROI) within an isocontour of SUV greater than 4 was calculated to determine activity in the whole of the kidney including cortex and renal pelvis ($\text{ROI}_{\text{kidney}}$) (MARVn software, version 2.35; Peter MacCallum Cancer Centre). A second ROI within an isocontour of SUV greater than 12–20 was determined to delineate excreted urine ($\text{ROI}_{\text{urine}}$), with operator discretion permitted within this range to adapt the SUV to optimally delineate the structures. These ROIs were calculated for each kidney in each frame, and time-activity curves were produced, with the percentage of the injected dose (%ID) calculated and plotted against time (Fig. 2).

Three methods were used to analyze clearance of ^{68}Ga -EDTA. The first method was renal activity at 1–2 min ($\text{PET}_{\text{initial}}$). The second method was the rate of renal excretion at 2–10 min ($\text{PET}_{\text{early}}$), defined by subtracting $\text{ROI}_{\text{urine}}$ from whole-kidney activity with the result representing parenchymal activity, expressed as %ID. The slope of an initial linear increase phase of the %ID for each kidney $\text{ROI}_{\text{urine}}$ was used to represent accumulated excreted urinary activity, usually 3–5 min after administration. Finally, in the third method, the rate of excretion into bladder, ureters, and kidneys during imaging acquired at a later time was calculated (PET_{late}). %ID accumulated excreted urinary activity during the 3 later time-point images encompassing the kidneys, ureter, and bladder was determined and plotted against time (Fig. 3). %ID at 20 min using the line of best fit of the 3 time points defined PET_{late} .

GFR Estimation by Serum Creatinine and Split Function Calculation

Estimated GFR was calculated using serum creatinine taken just before $^{68}\text{Ga}/^{51}\text{Cr}$ -EDTA administration, using the MDRD (4) and the CKD-EPI (5) formulae. Body surface area normalization was removed by multiplying the estimated GFR by calculated body surface area/1.73.

A subset of patients also underwent $^{99\text{m}}\text{Tc}$ -dimercaptosuccinic acid (DMSA) planar imaging and SPECT/CT performed on a Symbia True-Point 6 hybrid device (Siemens Medical Solutions). For planar imaging, split function was determined using a manually drawn ROI around each kidney and the geometric mean; for SPECT/CT, a 3-dimensional

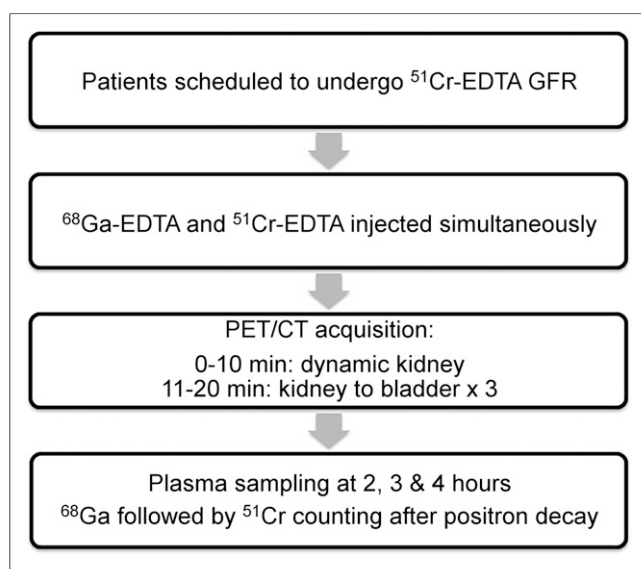


FIGURE 1. Study schema.

automated contour with a threshold of 20% of maximum counts was used. For PET/CT, %ID using the first and second methods above was used to determine split function.

Statistics

A Bland–Altman plot (15) was used to determine the level of agreement between ^{68}Ga -EDTA and ^{51}Cr -EDTA plasma sampling, between both of these and estimated GFR, and between split function derived from DMSA SPECT/CT and that derived from planar imaging and PET/CT. The Pearson correlation coefficient (PCC) was also used to correlate these measures in addition to ^{68}Ga -EDTA PET-based image measures of GFR with ^{68}Ga -EDTA. Analysis was performed with Prism, version 6 (GraphPad Software Inc.).

RESULTS

Thirty-one GFR studies were performed in 25 patients. In one episode, imaging failed to include the entire bladder, resulting in inability to perform camera-based GFR estimation. Thus, comparative ^{68}Ga -EDTA and ^{51}Cr -EDTA plasma sampling results were available for 31 patients, whereas PET/CT-based GFR estimation was available for 30 patients. Patient age ranged from 47 to 91 y (median, 75 y). ^{51}Cr -EDTA plasma GFR ranged from 10 to 220 mL/min (mean, 85 ± 48 mL/min). Renal impairment was severe in 2 patients, moderate in 8, and mild in 8, using a ^{51}Cr -GFR of less than 30, 60, and 90 mL/min, respectively, as cut-offs. Thirteen patients had normal renal function. Seventeen studies were performed in patients with neuroendocrine tumors being planned or followed for peptide receptor radionuclide therapy and 14 in patients with renal cell carcinomas being evaluated for surgery or stereotactic radiotherapy to the kidney. The latter group also underwent split renal function estimation before treatment. Four

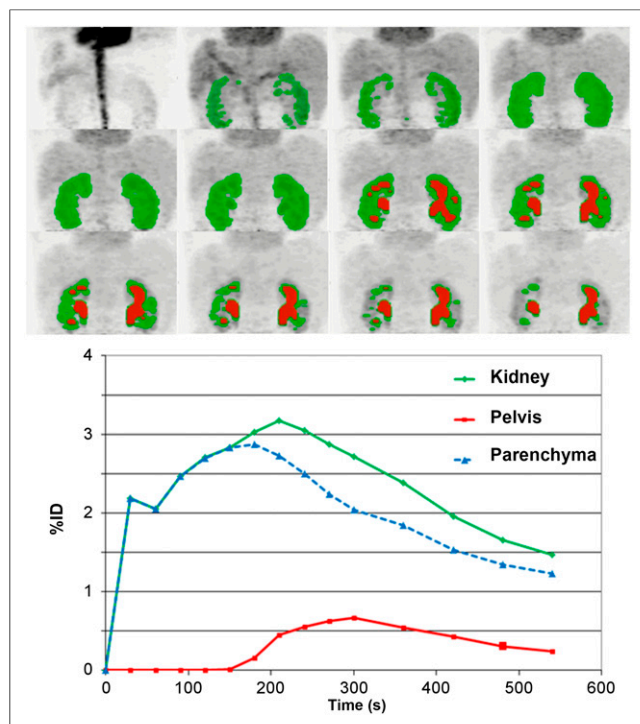


FIGURE 2. Dynamic PET/CT acquisition between 0 and 10 min showing maximum-intensity projection overlaid with renal activity (green) and excreted activity (red) defined by SUV of >4 and >15 , respectively. Time–activity curves were generated.

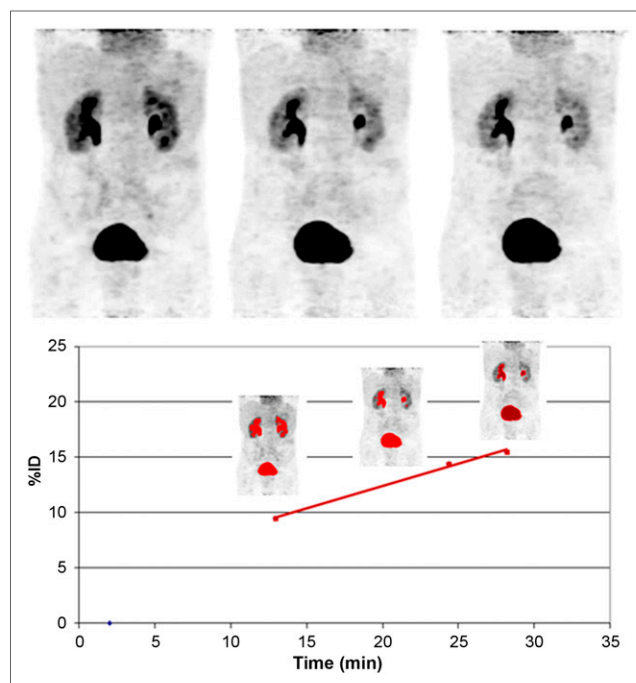


FIGURE 3. Three bed-step sequential acquisitions at later time points encompassing kidneys and bladder. Excreted activity is defined by ROI with SUV > 15 (red).

patients had 2 studies and 1 patient had 3 studies to assess effects of intervening therapy, either peptide receptor radionuclide therapy for the neuroendocrine tumor patients or stereotactic radiotherapy for the renal cell carcinoma patients. In these patients, the time between studies ranged from 27 to 338 d (median, 55 d).

Plasma Sampling

There was a near-perfect exponential fit of the 3 plasma samples, with r^2 values of 0.98 and 0.99 for ^{51}Cr -GFR and ^{68}Ga -GFR, respectively. There was a strong correlation between ^{68}Ga -GFR and ^{51}Cr -GFR plasma sampling, with a PCC of 0.94 (95% confidence interval [CI], 0.88–0.97) (Fig. 4A). There was good agreement between ^{68}Ga -GFR and ^{51}Cr -GFR plasma sampling, with a Bland–Altman bias for ^{68}Ga -EDTA of -14 ± 20 (Fig. 4B). In patients with a GFR over 150 mL, however, there was significant underestimation of ^{68}Ga -GFR compared with ^{51}Cr -GFR. The high PCC indicates a proportional bias increasing with GFR.

Camera-Based Measurement

The strongest correlation was between PET_{late} and ^{68}Ga -GFR, with a PCC of 0.90 (95% CI, 0.80–0.95) (Fig. 5). For $\text{PET}_{\text{early}}$ and $\text{PET}_{\text{initial}}$, the correlation was weaker, with a PCC of 0.81 (95% CI, 0.62–0.90, $P = 0.1$) and 0.77 (95% CI, 0.56–0.89, $P = 0.02$), respectively. In one patient, imaging was delayed, enabling calculation of PET_{late} but not $\text{PET}_{\text{early}}$ or $\text{PET}_{\text{initial}}$. Using PET_{late} , GFR can be derived with the following formula:

$$\text{GFR}(\text{mL}/\text{min}) = 7.7 \times \text{PET}_{\text{late}} - 3.9. \quad \text{Eq. 1}$$

The correlation between camera-based measurement and ^{51}Cr -GFR was also determined, demonstrating a PCC of 0.88 (95% CI, 0.76–0.94), 0.76 (0.54–0.88), and 0.72 (0.49–0.86) for PET_{late} , $\text{PET}_{\text{early}}$, and $\text{PET}_{\text{initial}}$, respectively.

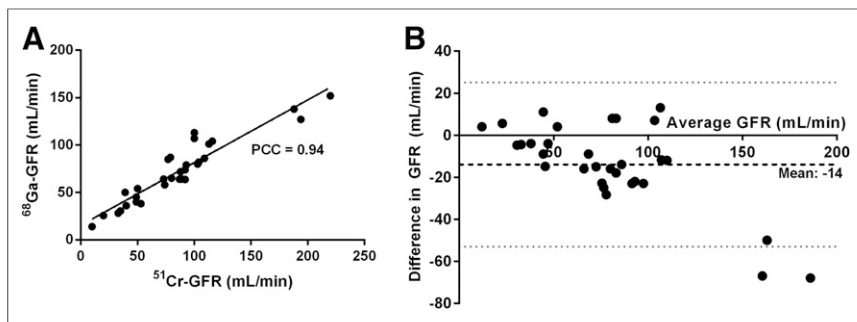


FIGURE 4. ^{68}Ga -GFR vs. ^{51}Cr -GFR by plasma sampling. (A) Correlation of ^{68}Ga -GFR and ^{51}Cr -GFR with PCC. (B) Bland–Altman plot illustrating agreement of ^{68}Ga -GFR with ^{51}Cr -GFR, mean bias (dashed line), 95% CI (dotted line).

Agreement with Estimated GFR

There was good agreement between ^{68}Ga -EDTA and ^{51}Cr -EDTA GFR derived from plasma sampling and estimated GFR, with a Bland–Altman bias of 7 ± 24 and 4 ± 30 for ^{51}Cr -GFR agreement with MDRD-estimated GFR and CKD-EPI, respectively, compared with -6 ± 14 and 18 ± 20 for ^{68}Ga -GFR.

Split Function

In 11 studies, DMSA planar imaging and SPECT/CT were also performed for evaluation of split renal function before stereotactic radiotherapy for known renal cell carcinomas. There was good agreement between planar imaging and SPECT/CT, with a Bland–Altman bias for left-to-right split function of $-1\% \pm 5$ (95% CI, -9% – 12%), but in 2 patients DMSA planar imaging differed by more than 10%. Both had severe renal dysfunction, with overlying hepatic activity contributing counts to the right kidney on planar imaging. The Bland–Altman bias for agreement between ^{68}Ga -EDTA PET/CT and DMSA SPECT/CT was $3\% \pm 7$ (95% CI, -11% – 17%). In 5 patients there was more than a 10% difference between PET/CT and SPECT/CT.

DISCUSSION

^{51}Cr -EDTA has been considered the radionuclide agent of choice for measuring GFR because its clearance is similar to that of inulin, with the first published use in humans being in

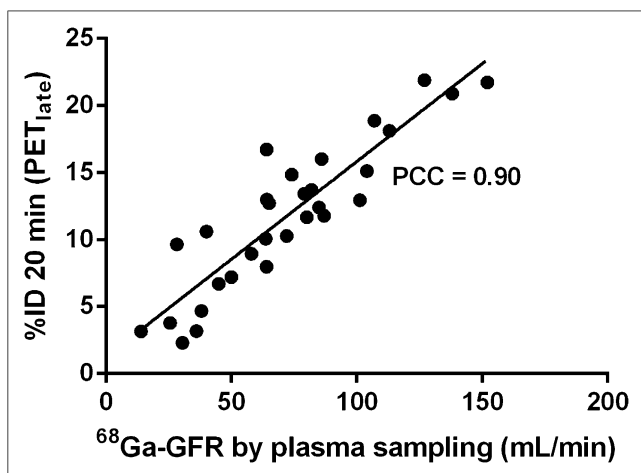


FIGURE 5. Correlation of PET imaging–derived GFR and ^{68}Ga -EDTA by plasma sampling.

1967 (16,17). A single-sample technique can be used (18), although use of 2 or 3 blood samples increases accuracy and is recommended for patients with significant renal dysfunction (19,20). ^{51}Cr -EDTA is not available in many countries, and the need for simplification has led some to adopt γ -camera GFR estimation with $^{99\text{m}}\text{Tc}$ -DTPA planar imaging, which is prone to error (21). In particular, calculation of renal activity for imaging-based approaches requires calculation of an estimate of renal depth to correct for tissue attenuation but has limited accuracy. PET/CT offers numerous advantages, including rapid and accurate 3-dimensional quantitative capability.

^{68}Ga is increasingly available because of its use for somatostatin-receptor imaging (22) and is becoming more widely available through on-site generators, which have a shelf life of up to 9–12 mo. ^{68}Ga -EDTA preparation is straightforward and potentially provides a cost-effective alternative to plasma sampling.

In this study, there was good but not perfect agreement between ^{68}Ga - and ^{51}Cr -EDTA GFR calculated using plasma sampling, despite injection of both radiotracers simultaneously and use of the same samples for positron and γ counting. In particular, in patients with a ^{51}Cr -EDTA GFR of more than 150 mL/min, the ^{68}Ga -GFR was significantly lower. Within the high reference range, however, agreement is less important because management is unlikely to be altered. The reason for this discordance is unclear but may be due to differences in plasma binding, tubular secretion, or dissociation in vivo. A recent study confirmed high labeling efficacy and low red blood cell or protein binding of ^{68}Ga -EDTA (23).

Studies have demonstrated that ^{51}Cr -EDTA systemically overestimates GFR by approximately 10% using the single-exponential method, and this overestimation is more marked at high GFRs (24, 25). A post hoc analysis after Brochner-Mortensen correction (26) of the ^{51}Cr -GFR demonstrated stronger agreement and correlation with ^{68}Ga -GFR, with a Bland–Altman bias of -1.3 (SD, 11; 95% CI, -23 to 20) and a PCC of 0.95. Our current study showed that both ^{68}Ga -GFR and ^{51}Cr -GFR agreed well with GFR estimated by MDRD or CKD-EPI.

Although plasma clearance provides a reliable estimate of renal clearance, measuring urine clearance is more direct and therefore less subject to nonrenal variations or the limitations posed by low activity in blood at late time-points. PET provides the ability to noninvasively quantify regional activity in MBq/mL with near-perfect agreement with known concentrations of activities in phantom experiments (27). The accurate and dynamic ability of PET to quantify activity in 3 dimensions makes it ideal for applications such as GFR estimation. Current camera-based quantification of GFR relies largely on using early renal cortical uptake as described by Gates (28). In this study, we have found that measurement of activity that has actually filtered into the collecting system can readily be quantified, providing a more direct means of estimating GFR. In this study, this was limited by estimating GFR at an early time point when the radiopharmaceutical is more subject to nonrenal variations. Nevertheless, our results show good agreement with plasma-based sampling at 2–4 h, particularly in impaired GFR.

In our facility, a tertiary cancer center, common clinical indications for measuring GFR include dose adjustment for kidney-excreted

chemotherapy agents such as carboplatin (1), determination of overall and split renal function before abdominal radiotherapy (29), and monitoring of renal function during radionuclide therapy if the agent is excreted by the kidneys (30). Many patients undergo both a ^{51}Cr -EDTA and a $^{99\text{m}}\text{Tc}$ -DTPA or $^{99\text{m}}\text{Tc}$ -DMSA study to determine split renal function. This study also demonstrated the potential of ^{68}Ga -EDTA PET/CT to assess both overall and differential or regional renal function, although further research is needed to validate this possibility. ^{68}Ga -EDTA PET/CT also has the potential to replace $^{99\text{m}}\text{Tc}$ -DTPA renography, including for evaluation of renal tract obstruction given its 3-dimensional dynamic capability, although MAG-3 remains the agent of choice as it is predominantly secreted (31). The short half-life of ^{68}Ga also makes it ideal for renography before and after angiotensin-converting enzyme inhibition to assess for hemodynamically significant renal artery stenosis (32).

This study was limited by a relatively small cohort of patients who were elderly and had concomitant malignancy. The field of view of a PET camera does not enable the kidneys, ureters, and bladder to be encompassed in a single field of view. Because urine excretion and transit occur, some of the activity passing from kidneys to bladder during the 3-min imaging time might therefore have been double-counted; the resultant error was considered small and minimized as the same methodology was used at all 3 delayed time-points. The study was strengthened by including patients with a broad range of GFR, including normal, mild, moderate, and severe renal dysfunction. Further optimization, including both image acquisition and processing technique, may improve results. The effective radiation dose from the ^{68}Ga -EDTA study is approximately 1.2 mSv from the PET component (33) and 0.25 mSv from ultra low dose CT used for attenuation correction.

CONCLUSION

Assessment of GFR with ^{68}Ga -EDTA is feasible, with good agreement between plasma sampling and conventional ^{51}Cr -EDTA. Camera-based GFR estimation correlates strongly with the plasma sampling technique, enabling noninvasive and rapid GFR estimation. The ability to image EDTA with PET/CT also provides additional information and may improve diagnostic algorithms in a range of renal diseases. Additional validation in a larger cohort is warranted to further assess utility.

ACKNOWLEDGMENT

Preliminary data from this study were presented orally at the 2013 annual meeting of the Society of Nuclear Medicine and Molecular Imaging, Vancouver, BC, Canada. Final data were presented orally at the 2014 annual meeting of the World Federation in Nuclear Medicine and Biology, Cancun, Mexico

REFERENCES

1. Millward MJ, Webster LK, Toner GC, et al. Carboplatin dosing based on measurement of renal function: experience at the Peter MacCallum Cancer Institute. *Aust N Z J Med*. 1996;26:372–379.
2. Shepherd ST, Gillen G, Morrison P, et al. Performance of formulae based estimates of glomerular filtration rate for carboplatin dosing in stage I seminoma. *Eur J Cancer*. 2014;50:944–952.
3. Craig AJ, Samol J, Heenan SD, Irwin AG, Britten A. Overestimation of carboplatin doses is avoided by radionuclide GFR measurement. *Br J Cancer*. 2012;107:1310–1316.
4. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new pre-

diction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.

5. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
6. Hicks RJ, Hofman MS. Is there still a role for SPECT-CT in oncology in the PET-CT era? *Nat Rev Clin Oncol*. 2012;9:712–720.
7. Yano Y, Anger HOA. Gallium-68 positron cow for medical use. *J Nucl Med*. 1964;5:484–487.
8. Gleason GI. A positron cow. *Int J Appl Radiat Isot*. 1960;8:90–94.
9. Schaer LR, Anger HO, Gottschalk A. Gallium edetate ^{68}Ga experiences in brain-lesion detection with the positron camera. *JAMA*. 1966;198:811–813.
10. Goethals P, Volkaert A, Vandewielle C, Dierckx R, Lameire N. ^{55}Co -EDTA for renal imaging using positron emission tomography (PET): a feasibility study. *Nucl Med Biol*. 2000;27:77–81.
11. Aide N, Desmots C, Beauregard JM, et al. High throughput static and dynamic small animal imaging using clinical PET/CT: potential preclinical applications. *Eur J Nucl Med Mol Imaging*. 2010;37:991–1001.
12. Yamashita M, Inaba T, Kawase Y, et al. Quantitative measurement of renal function using Ga-68-EDTA. *Tohoku J Exp Med*. 1988;155:207–208.
13. Zernosekov KP, Filosofov DV, Baum RP, et al. Processing of generator-produced ^{68}Ga for medical application. *J Nucl Med*. 2007;48:1741–1748.
14. Fleming JS, Zivanovic MA, Blake GM, Burniston M, Cosgriff PS. British Nuclear Medicine Society Guidelines for the measurement of glomerular filtration rate using plasma sampling. *Nucl Med Commun*. 2004;25:759–769.
15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(327):307–310.
16. Garnett ES, Parsons V, Veall N. Measurement of glomerular filtration-rate in man using a ^{51}Cr -edetic-acid complex. *Lancet*. 1967;1(289):818–819.
17. Favre HR, Wing AJ. Simultaneous ^{51}Cr edetic acid, inulin, and endogenous creatinine clearances in 20 patients with renal disease. *Br Med J*. 1968;1:84–86.
18. Groth S, Aasted M. ^{51}Cr -EDTA clearance determined by one plasma sample. *Clin Physiol*. 1981;1:417–425.
19. Blaufox MD, Aurell M, Bubeck B, et al. Report of the Radionuclides in Nephrology Committee on Renal Clearance. *J Nucl Med*. 1996;37:1883–1890.
20. Goates JJ, Morton KA, Whooten WW, et al. Comparison of methods for calculating glomerular filtration rate: technetium-99m-DTPA scintigraphic analysis, protein-free and whole-plasma clearance of technetium-99m-DTPA and iodine-125-iothalamate clearance. *J Nucl Med*. 1990;31:424–429.
21. Mulligan JS, Blue PW, Hasbargen JA. Methods for measuring GFR with technetium-99m-DTPA: an analysis of several common methods. *J Nucl Med*. 1990;31:1211–1219.
22. Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol*. 2012;56:40–47.
23. Lee JY, Jeong JM, Kim YJ, et al. Preparation of Ga-68-NOTA as a renal PET agent and feasibility tests in mice. *Nucl Med Biol*. 2014;41:210–215.
24. Hilson AJ. Overestimation of true renal clearance by conventional measurements of GFR using ^{51}Cr -EDTA. *Eur J Nucl Med Mol Imaging*. 2003;30:934.
25. Moore AE, Park-Holohan SJ, Blake GM, Fogelman I. Conventional measurements of GFR using ^{51}Cr -EDTA overestimate true renal clearance by 10 percent. *Eur J Nucl Med Mol Imaging*. 2003;30:4–8.
26. Brøchner-Mortensen J, Jodal L. Reassessment of a classical single injection ^{51}Cr -EDTA clearance method for determination of renal function in children and adults. Part II: Empirically determined relationships between total and one-pool clearance. *Scand J Clin Lab Invest*. 2009;69:314–322.
27. Seo Y, Teo BK, Hadi M, Schreck C, Bacharach SL, Hasegawa BH. Quantitative accuracy of PET/CT for image-based kinetic analysis. *Med Phys*. 2008;35:3086–3089.
28. Gates GF. Computation of glomerular filtration rate with Tc-99m DTPA: an in-house computer program. *J Nucl Med*. 1984;25:613–618.
29. Lopez-Gaitan J, Ebert MA, Robins P, et al. Radiotherapy of abdomen with precise renal assessment with SPECT/CT imaging (RAPRASI): design and methodology of a prospective trial to improve the understanding of kidney radiation dose response. *BMC Cancer*. 2013;13:381.
30. Kashyap R, Jackson P, Hofman MS, et al. Rapid blood clearance and lack of long-term renal toxicity of ^{177}Lu -DOTATATE enables shortening of renoprotective amino acid infusion. *Eur J Nucl Med Mol Imaging*. 2013;40:1853–1860.
31. O'Reilly P, Aurell M, Britton K, Kletter K, Rosenthal L, Testa T. Consensus on diuresis renography for investigating the dilated upper urinary tract. Radionuclides in Nephrology Group. Consensus Committee on Diuresis Renography. *J Nucl Med*. 1996;37:1872–1876.
32. Szabo Z, Xia J, Mathews WB, Brown PR. Future direction of renal positron emission tomography. *Semin Nucl Med*. 2006;36:36–50.
33. Radiation dose to patients from radiopharmaceuticals (addendum 2 to ICRP publication 53). *Ann ICRP*. 1998;28:1–126.