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ORIGINAL ARTICLE

Comparison of ^{51}Cr-EDTA and ^{99m}Tc-DTPA for glomerular filtration rate measurement

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Abstract

Purpose The production of ^{51}Cr-labelled ethylenediaminetetraacetic acid (^{51}Cr-EDTA), a validated and widely used radioisotopic tracer for glomerular filtration rate (GFR) measurement in Europe, was recently halted by the manufacturer. Technetium-99m-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) clearance has so far mostly been restricted to assessment of separate renal function by scintigraphy, but scarcely used and validated for GFR measurement. We compared the performances of ^{51}Cr-EDTA and ^{99m}Tc-DTPA for GFR and extracellular fluid measurement.

Methods In a multi-centre prospective study, ^{51}Cr-EDTA and ^{99m}Tc-DTPA were simultaneously injected into 88 patients, and their urinary and plasma clearances, as well as their volumes of distribution, were measured during seven 30-min periods after a 90-min equilibrium time.

Results Mean age was 52.2 ± 14.5 years, 59% were men. Urinary clearances of ^{51}Cr-EDTA and ^{99m}Tc-DTPA were 64.1 ± 27.6 and 66.1 ± 28.0 mL/min, respectively, with a mean bias of 2.00 ± 2.25 mL/min, an accuracy within 10% of 95% [95% CI 91–99], and a coefficient of determination (R^2) of 0.994. Plasma clearances of ^{51}Cr-EDTA and ^{99m}Tc-DTPA were 66.1 ± 25.8 and 68.1 ± 26.6 mL/min, respectively, with a mean bias of 1.96 ± 3.32 mL/min, an accuracy within 10% of 91% [95% CI 85–97] and a R^2 of 0.985. Distribution volumes were 17.3 ± 4.6 L for ^{51}Cr-EDTA and 16.6 ± 4.6 L for ^{99m}Tc-DTPA (R^2 0.930).

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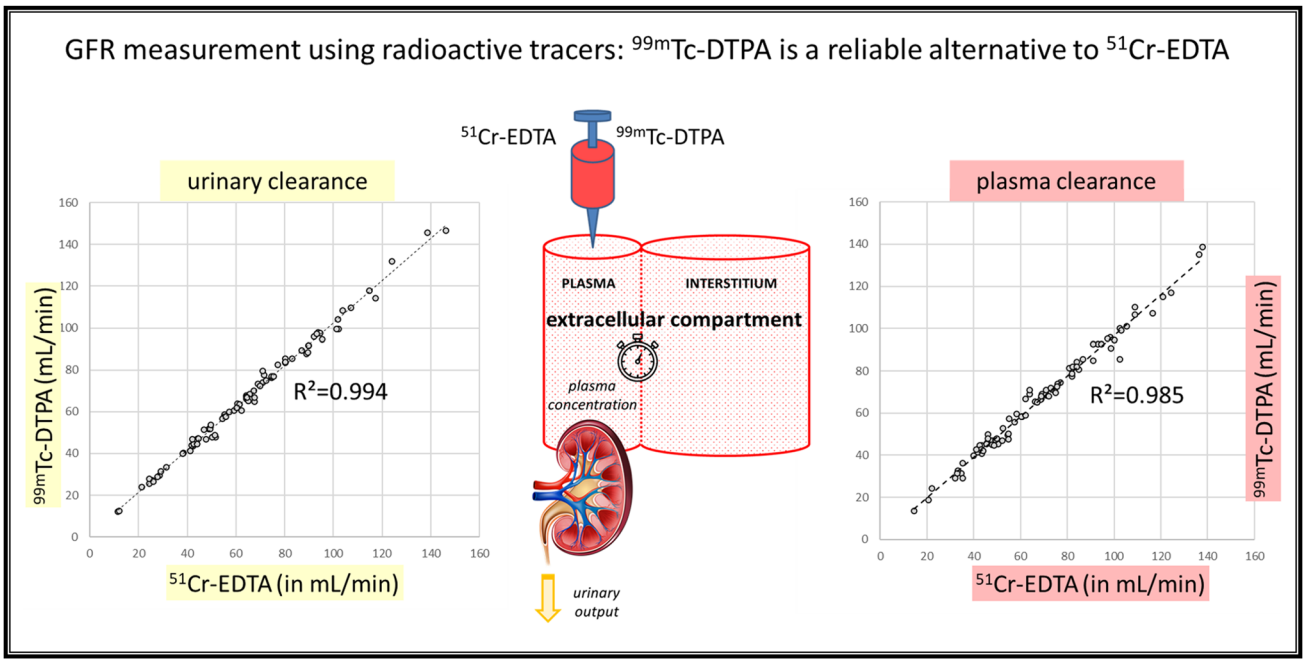
Conclusion The accuracy and precision of ^{99m}Tc-DTPA clearance, compared to ^{51}Cr-EDTA clearance, was excellent for both urinary and plasma clearance methods, despite an approximate 2 mL/min overestimation, showing that the tracer is a reliable alternative to ^{51}Cr-EDTA for GFR measurement.

Graphic abstract



Keywords Glomerular filtration rate measurement · ^{51}cr-EDTA · ^{99m}tc-DTPA · Radio-labelled tracers · Plasma clearance · Renal clearance

Introduction

Glomerular filtration rate (GFR) measurement using exogenous markers is indicated in clinical practice when medical decision requires an accurate GFR value, or in situations where the expected precision of estimators is insufficient for clinical decision-making [1]. Urinary clearance of inulin is considered the gold standard method [2], but inulin was recently withdrawn from the market due to cases of severe immune-allergic reactions. Plasma clearance of the contrast agent iohexol is a convenient and routinely used GFR measurement method [3, 4]. Iothalamate is another convenient tracer but its accuracy is less validated than iohexol [2]. ^{51}Cr-labelled ethylenediaminetetraacetic acid (^{51}Cr-EDTA) has been largely used and validated as a radio-isotopic GFR measurement tracer method in Europe [1, 2, 5–7]. Although its use is limited by the need for nuclear medicine facilities to manipulate radioactive tracers, the precision of radioactive sample measurement is extremely high, and the simultaneous urinary and plasma clearance allows very accurate GFR measurement since factors of imprecision of both procedures do not overlap [1]. Unfortunately, the manufacturer discontinued ^{51}Cr-EDTA production at the end of 2018, compelling nephrologists to urgently consider alternative radio-isotopic methods, both for initial GFR measurements and for longitudinal follow-up of patients.

Technetium-99m-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) clearance was developed a few decades ago, and was compared to inulin in series of less than 50 subjects [8–10], using a no-longer commercially available compound, with inconsistent results in part attributed to a short half-life of the radionuclide and a possibly higher protein binding than other tracers. ^{99m}Tc-DTPA was therefore scarcely used for GFR measurement and was mostly restricted to assessment of split renal function by scintigraphy.

In three renal physiology units in which GFR was routinely measured using ^{51}Cr-EDTA, we prospectively evaluated the performance of the new commercially available ^{99m}Tc-DTPA, with the $CaNa_3$-DTPA compound (Technescan® DTPA, Curium France), while ^{51}Cr-EDTA was still available, using a simultaneous bolus injection of both tracers in 88 patients. Urinary and plasma clearances, as well as volumes of distribution of both tracers,

were assessed in order to compare their renal and extra-renal handling.

Methods

Study design and participants

Eighty-eight adult patients referred to the physiology units of three Parisian university hospitals (Bichat, Tenon, and Georges -Pompidou European Hospitals) for routine GFR measurement were included in the study. Patients were recruited between January 15th and March 11th, 2019. Patients were recruited according to the following schedule; one patient per day per centre in the first week, then two patients per day per centre per week over the following weeks for the whole time that both tracers were available in each centre. These patients were selected among the first referred patients who arrived in the unit, regardless of their indication for GFR measurement.One patient refused to participate and was not included. Pregnancy and dialysis were exclusion criteria. Past medical history, treatment, and anthropometric data were collected. All measurements started in the morning between 08:00 a.m. and 09:00 a.m. Fasting was not required.

The study was classified as non-interventional by the DRCI (*Délégation à la recherche Clinique et à l'Innovation*) of Assistance Publique-Hôpitaux de Paris. All patients received oral and written information before inclusion, and signed informed consent to participate in the study which was approved by our local Ethics Committee. Research was conducted in accordance with good clinical practices and the Declaration of Helsinki.

GFR and extracellular water measurements

Bolus injections of ^{51}Cr-EDTA (GE Healthcare, Vélizy, France, 1.8 or 3.7 MBq depending on expected renal function according to estimated GFR) and ^{99m}Tc-DTPA (Technescan® DTPA, Curium France, 3.7 MBq) were administered simultaneously (^{99m}Tc-DTPA immediately after ^{51}Cr-EDTA) in the same vein, followed by an injection of 10 mL of saline. Each syringe was weighed before and after injection, in order to calculate the injected amount of the tracer. After a 90-min resting period to allow equilibrium of the tracer in its distribution volume, urine was collected every 30 min for seven consecutive periods, hence for a total of 5 h after injection. Seven blood samples were collected from the arm contralateral to the injection at the mid-time of each period.

Activity of urinary and plasma samples together with standards were measured with the following gamma counters: Wallac Wizard 3″1480 (PerkinElmer) in Bichat hospital, Wallac Wizard 1470-005 (PerkinElmer) in Tenon hospital and Cobra II® 5003 (Packard) in Georges -Pompidou European Hospital. ^{99m}Tc radioactive decay was taken into account by applying a correction factor depending on when radioactivity of each sample was counted.

Urinary clearance was calculated for each tracer as the average of the seven clearances. All urine samples were considered, with no selection. Blood samples drawn at mid-time of each of the seven urinary periods (from 105 to 285 min after injection) were used to plot the late plasma disappearance curve of the tracer as a function of time. Plasma clearance was calculated for each tracer from the late disappearance curve using the slope-intercept method with the Bröchner-Mortensen correction [11].

We also performed sensitivity analyses for comparison of both tracers in which only the first three periods were considered for urinary clearance, and in which the period analysed was shorter for plasma clearance (up to 225 min, or up to 165 min only).

The volume of distribution was calculated after the equilibrium period, as the remaining quantity of the tracer (difference between injected and excreted amount) divided by the plasma concentration of the tracer at the corresponding time, calculated from the equation of the plasma disappearance curve of the tracer. The volume of distribution obtained at 90 min after injection was reported, unless the calculated value was lower at 120 min (a sign of incomplete bladder voiding at the equilibrium time). Values of plasma clearance and volume of distribution were missing in two patients due to errors in assessing the injected quantity of ^{99m}Tc-DTPA, and volume of distribution was missing in a third patient due to urine loss during equilibrium time.

As these analyses relied on paired comparisons of values obtained in the same patient, neither GFR values nor volumes of distribution were indexed to body surface area.

Statistical analyses

Precision and accuracy of GFR and volume of distribution of ^{99m}Tc-DTPA, compared with those of ^{51}Cr-EDTA (reference), were evaluated using bias (difference between values obtained by both tracers), relative bias (bias divided by value obtained using ^{51}Cr-EDTA, expressed in percentage), intrinsic precision (also called precision around mean bias, absolute difference between individual bias and mean bias, divided by reference value and expressed in percentage), Pearson's correlation coefficients, coefficients of determination, accuracy within 10 and 30% (AW10 and AW30, percentage of ^{99m}Tc-DTPA-derived values within 10 or 30% of ^{51}Cr-EDTA-derived values, respectively), and root mean square error (RMSE, calculated from the difference of the logarithmic estimated and reference values). The 95% confidence intervals (CI) for RMSE, and AW10 and AW30 were

calculated using 200 bootstrap iterations. Measured GFR and volumes of distribution of both tracers were compared using paired *t* tests. To compare agreement between plasma clearances versus agreement between urinary clearances, paired t-tests were used for intrinsic precision and RMSE, and McNemar tests were used for AW10 and AW30. Performances of the tracers were also compared graphically using linear correlation and Bland–Altman plots [12]. All tests were two-sided using a significance level of 0.05.

Results

A total of 88 patients (53 from Bichat Hospital, 20 from Georges Pompidou European Hospital and 15 from Tenon hospital) were included in the study. Characteristics of the patients are reported in Table 1. Mean age was 52.2 ± 14.5 years, mean body mass index was 26.6 ± 8.6 kg/m^2, and 52 (59%) were men. Mean estimated GFR (using the creatinine-derived chronic kidney disease Epidemiology Collaboration [CKD-EPI] equation [13]) was 65 ± 26 mL/min. Three patients were being evaluated for kidney donation and had normal renal function, while 11 (12.5%), 35 (39.8%), 19 (21.6%), 13 (14.8%) and 7 (8.0%) had chronic kidney disease stage 1, 2, 3b, 3b and 4, respectively.

Linear correlations and Bland–Altman plots for urinary clearances, plasma clearances and volumes of distributions of both tracers are shown in Fig. 1.

Table 1 Characteristics of the study population

Parameter	Total population ($n = 88$)
Age (years)	52.2 ± 14.5
Men	52 (59%)
Body Mass Index (kg/m^2)	26.0 ± 5.4
History of hypertension	56 (64%)
Systolic blood pressure (mm Hg)	130 ± 17
Diastolic blood pressure (mm Hg)	72 ± 13
Heart Rate (beats/min)	71 ± 12
Creatinine (µmol/L)	117 ± 45
eGFR	65.1 ± 26.1
Protein-to-creatinine ratio (mg/mmol)	15.2 [7.9–26.4]
Indication for referral	
Follow-up of chronic kidney disease	43 (50%)
Kidney transplant recipient	27 (31%)
Potential kidney donor	3 (3%)
Drug nephrotoxicity	13 (15%)

Data are in *n*(%), mean ± SD, or median [25th–75th percentile], as appropriate. Some percentages do not add up to 100 because of rounding

eGFR estimated glomerular filtration rate, using the CKD-EPI equation

GFR and volumes of distributions measured with both tracers, as well as metrics of precision and accuracy of values obtained with ^{99m}Tc-DTPA versus those obtained with ^{51}Cr-EDTA, are indicated in Table 2. The intra-individual coefficients of variation of the seven fractionated urine clearances were 19% for both tracers. Urinary clearances of ^{51}Cr-EDTA and ^{99m}Tc-DTPA were 64.1 ± 27.6 and 66.1 ± 28.0 mL/min, respectively ($p < 0.001$), with a mean bias of + 2.00 ± 2.25 mL/min, a mean intrinsic precision of 2.7 ± 2.8%, a Pearson's correlation coefficient of 0.997, an AW10 of 95% (95% CI 91–99), and an AW30 of 100%. Very similar results regarding agreement between tracers were found when considering only the first three urine samples, with a mean bias of + 2.34 ± 2.82 mL/min, a mean intrinsic precision of 3.5 ± 3.4%, a Pearson's correlation coefficient of 0.996, an AW10 of 93% and an AW30 of 100% (Table 3a).

Plasma clearances of ^{51}Cr-EDTA and ^{99m}Tc-DTPA were 66.1 ± 25.8 and 68.1 ± 26.6 mL/min, respectively ($p < 0.001$), with a mean bias of 1.96 ± 3.32 mL/min, a mean intrinsic precision of 3.9 ± 3.9%, a Pearson's correlation coefficient of 0.992, an AW10 of 91% (95% CI 85–97) and an AW30 of 100%. Metrics of agreement between plasma clearances did not differ significantly compared with those of urinary clearances, except for a slightly higher intrinsic precision (reflecting less dispersion around the bias) for urinary clearances (2.7 ± 2.8%, versus 3.9 ± 3.9% for plasma clearances, $p = 0.02$). Results were in the same range order when only 5 points of the plasma disappearance curve, from 105 to 225 min, were considered, whereas agreement between both methods was weaker when the slope was calculated using only three points from 105 to 165 min after injection (Table 3b).

For ^{51}Cr-EDTA, the difference between plasma and urinary clearance was defined by a mean bias of 1.95 ± 7.02 mL/min, an intrinsic precision of 8.4 ± 10.8%, and AW 10 and AW 30 of 67 and 94%, respectively. For ^{99m}Tc-DTPA, the difference between plasma and urinary clearance was defined by a mean bias of 1.86 ± 7.39 mL/min, an intrinsic precision of 8.5 ± 10.7%, and AW 10 and AW 30 of 69 and 95%, respectively (*p* value non-significant compared to ^{51}Cr-EDTA for all metrics).

Of note, the mean bias of GFR estimated by the CKD-EPI equation was 1.01 ± 15.70 and − 0.99 ± 16.07 mL/min compared to urinary clearances of ^{51}Cr-EDTA and ^{99m}Tc-DTPA, respectively, and − 1.07 ± 13.71 and − 3.03 ± 14.31 mL/min compared to plasma clearances of ^{51}Cr-EDTA and ^{99m}Tc-DTPA, respectively.

The volumes of distribution of the tracers were 17.3 ± 4.6 L (22.3 ± 5.9% of body weight) and 16.6 ± 4.6 L (21.5 ± 5.8% of body weight), for ^{51}Cr-EDTA and ^{99m}Tc-DTPA, respectively. Mean bias was − 0.65 ± 1.08 L, AW10 and AW30 were 81% (95% CI 73–90) and 99% (95% CI

95–100), respectively, and Pearson's correlation coefficient was 0.972 (Table 2).

Discussion

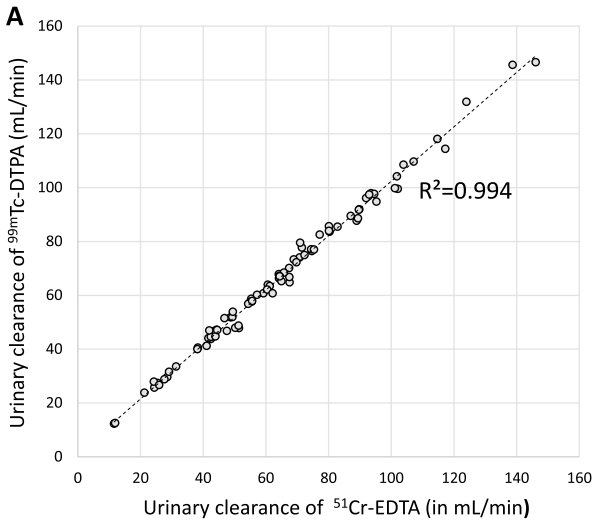
Accuracy and precision of GFR measurement using ^{99m}Tc-DTPA, compared with ^{51}Cr-EDTA, were excellent for both urinary and plasma clearance methods, despite an approximate 2 mL/min overestimation. These results, combined with the closely related volumes of distribution of the tracers, suggest similar plasma protein binding, extra-renal handling, glomerular filtration and tubular handling of the currently commercialized ^{99m}Tc-DTPA compared to ^{51}Cr-EDTA.

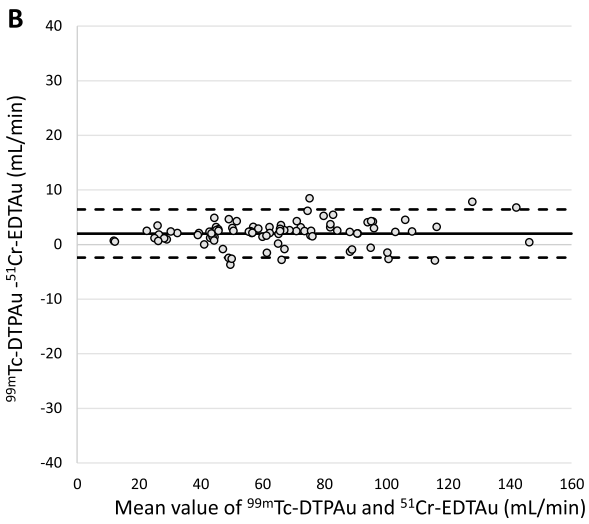
A few previous studies had compared both tracers for GFR measurement and found good agreement, however they were conducted in small series of patients [9, 14–17]. One study, published in 1984, had compared plasma and renal clearances, as well as volumes of distribution of ^{99m}Tc-DTPA, ^{51}Cr-EDTA and inulin in 20 patients, and had reported no difference in either measurement for the two radioactive tracers and therefore concluded that the two tracers could replace each other for the measurement of GFR [9]. A relatively larger study, performed in 56 patients, recently compared ^{99m}Tc-DTPA ($CaNa_3$-DTPA compound) with ^{51}Cr-EDTA for GFR measurement [18], and also found very good agreement between both tracers, with a mean bias of 1.4 mL/min for plasma clearance, in agreement with our results showing slightly higher values when using ^{99m}Tc-DTPA. However, urinary clearance was not measured in this study. In addition, most patients had preserved or moderately altered renal function, and only three patients had GFR < 30 mL/min, whereas our study included patients over a wide range of renal function. Our study is the largest to date to compare both tracers, and it relied on both urinary and plasma clearance methods and included measurement of the volumes of distribution of the tracers, allowing a detailed and complete comparison of the tracers and their physiological behaviours. Although the GFR values measured by ^{99m}Tc-DTPA are significantly higher than those measured with ^{51}Cr-EDTA (2.00 ± 2.25 mL/min for urinary clearance and 1.96 ± 3.32 mL/min for plasma clearance), this difference is not clinically relevant, and intrinsic precision was excellent, so that both tracers can be used interchangeably in clinical practice. Importantly, the difference between plasma and renal clearance, reflecting extra-renal clearance of the tracer, was approximately 1.9 mL/min for both tracers, in favour of a similar extra-renal handling of ^{99m}Tc-DTPA and ^{51}Cr-EDTA. The slightly lower volume of distribution of ^{99m}Tc-DTPA compared with that of ^{51}Cr-EDTA may reflect a higher—although limited—protein binding, as suggested by previous studies [17, 19–21].

Sensitivity analyses yielded similar, very high agreement between both tracers when using only the first three urine samples, or when restricting the plasma clearance study period to five points (from 105 to 225 min), showing that the agreement between both tracers is not the result of multiple sampling. Further restricting the plasma disappearance curve to three points from 105 to 165 min was, as expected, too short to properly estimate the slope of the late plasma decay as illustrated by lower agreement between both tracers.

Overall, our findings obtained in a multi-centre prospective study, combined with the above-mentioned recently published Danish study in a completely independent setting, and with older small-scaled studies, demonstrate that ^{99m}Tc-DTPA and ^{51}Cr-EDTA yield very similar GFR values, which is of major clinical relevance in the context of the discontinued production of ^{51}Cr-EDTA. To our knowledge, the official reason for the discontinuation of ^{51}Cr-EDTA was not released, but financial motivations are likely. Of note, although radiolabelling kits of DTPA are cheaper than ^{51}Cr-EDTA, the overall cost of the procedure is mainly due to operating expenses, thus the overall cost of both procedures is similar. These results are all the more important as the previous gold standard GFR measurement tracer inulin was withdrawn from the market. ^{51}Cr-EDTA was not available in Northern America but it was used in Europe and internationally recognized as a reference tracer [1, 2]. Not only did ^{51}Cr-EDTA have ideal properties as a GFR tracer, but since its measurement was radioactive, it was very accurate, and in addition, the simultaneous urinary and plasma measurement of GFR provided highly trustworthy results through the confrontation of both methods, which do not share the same sources of imprecision. Iohexol is widely used with the plasma clearance method and is much easier to implement than radioactive compounds, which makes it a very useful tracer. However, continuing the expertise of radioactive GFR measurement along with the routine use of non-radioactive tracers is very important as these different methods are complementary due to different strengths and limitations. Some patients may be allergic to iodine contrast agents, and being able to confront methods when the clinical issue requires major precision is important. Noteworthy, ^{99m}Tc-DTPA is commercially available worldwide, which makes our results relevant beyond Europe; in addition, it allows scintigraphy assessment of separate renal function. Overall, this radioisotope is one of the few key remaining GFR measurement tracers.

Importantly, the excellent correlation between the measurements obtained with both tracers will not circumvent the limitations related to the much shorter physical half-life of ^{99m}Tc (6 h) compared to that of ^{51}Cr (27.7 days). For instance, ^{99m}Tc-DTPA is not compatible with the late blood sampling which is required to improve the precision


A
Urinary clearance of 99mTc-DTPA (mL/min)
Urinary clearance of 51Cr-EDTA (in mL/min)
R²=0.994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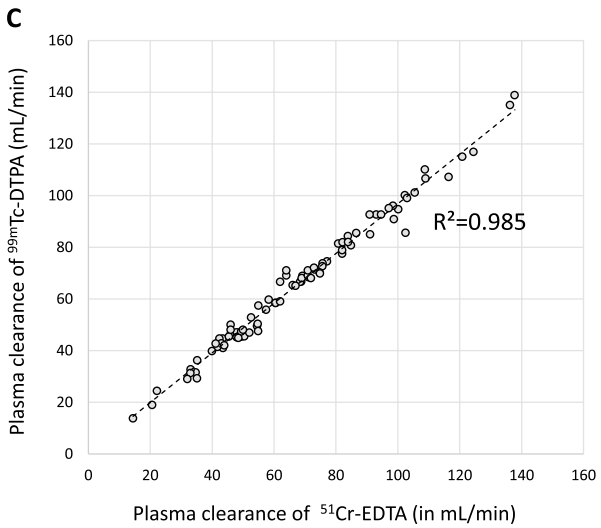
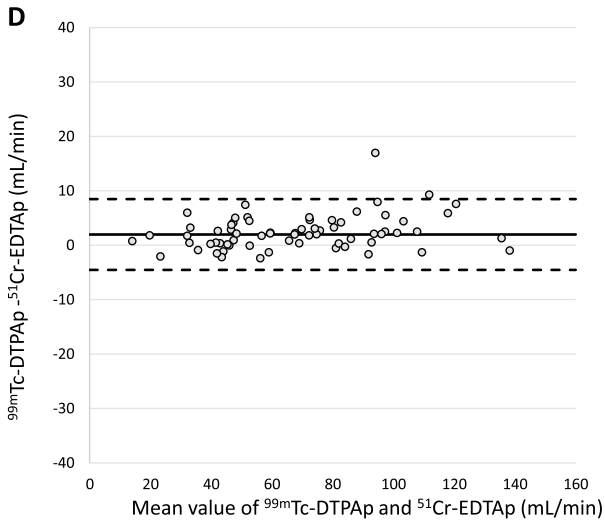
99mTc-DTPAu -51Cr-EDTAu (mL/min)
Mean value of 99mTc-DTPAu and 51Cr-EDTAu (mL/min)


C
Plasma clearance of 99mTc-DTPA (mL/min)
Plasma clearance of 51Cr-EDTA (in mL/min)
R²=0.985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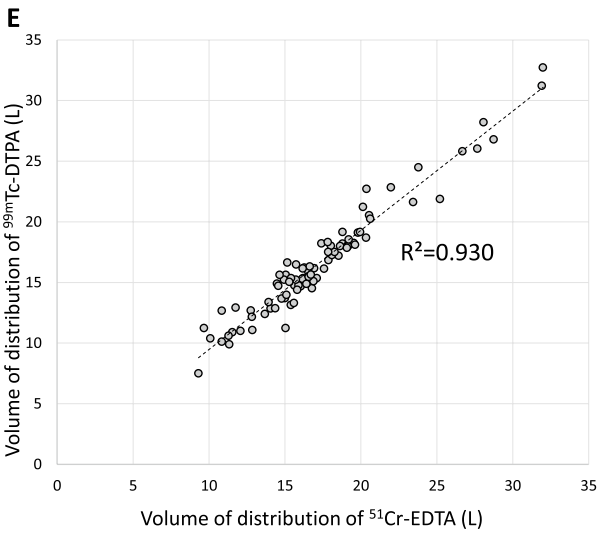
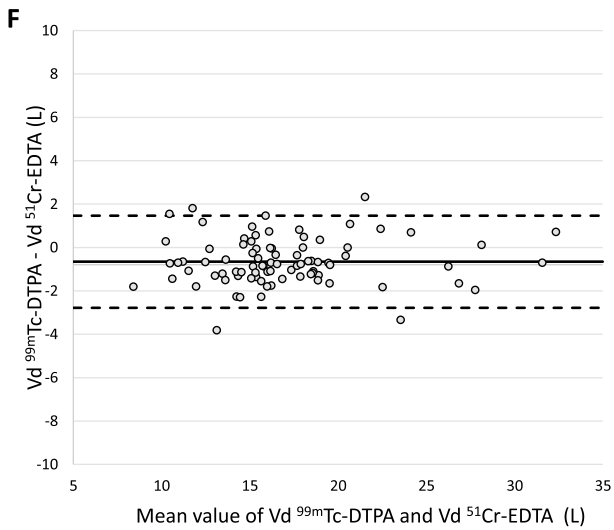
99mTc-DTPAp -51Cr-EDTAp (mL/min)
Mean value of 99mTc-DTPAp and 51Cr-EDTAp (mL/min)


E
Volume of distribution of 99mTc-DTPA (L)
Volume of distribution of 51Cr-EDTA (L)
R²=0.930


F
Vd 99mTc-DTPA - Vd 51Cr-EDTA (L)
Mean value of Vd 99mTc-DTPA and Vd 51Cr-EDTA (L)

◂**Fig. 1** Graphical comparison of values measured with ^{99m}Tc-DTPA versus those measured with ^{51}Cr-EDTA. For urinary clearance (top panels, **a**, **b**), plasma clearance (middle panels, **c**, **d**) and volumes of distribution (bottom panels, **e**, **f**), left panels represent linear correlation between metrics obtained by ^{99m}Tc-DTPA versus those obtained with ^{51}Cr-EDTA, while right panels represent Bland–Altman plots (value obtained with ^{99m}Tc-DTPA minus that obtained with ^{51}Cr-EDTA in function of average value obtained with both tracers). In left panels, the dotted lines represent identity line. In Bland–Altman plots, the full line represents mean bias while the dotted lines represent bias ± 1.96 × standard deviation. *^{51}Cr-EDTAu* urinary clearance of ^{51}Cr-EDTA, *^{99m}Tc-DTPAu* urinary clearance of ^{99m}Tc-DTPA, *^{51}Cr-EDTAp* plasma clearance of ^{51}Cr-EDTA, *^{99m}Tc-DTPAp* plasma clearance of ^{99m}Tc-DTPA, *Vd ^{51}Cr-EDTA* volume of distribution of ^{51}Cr-EDTA, *Vd ^{99m}Tc-DTPA* volume of distribution of ^{99m}Tc-DTPA

of plasma clearance when the expected GFR value is low. Because of this limitation, GFR measurement in patients with severe renal failure should preferably rely on urinary clearance. For the same reason, unlike ^{51}Cr-EDTA, counting of the plasma and urine samples must be performed shortly after the procedure and cannot be delayed or repeated during the following days.

Amongst the strengths of our study, the prospective multi-centre design reinforces the robustness of our results obtained in three different centres with independent procedures and handling of the samples. In addition, all three centres carried out both urinary and plasma clearance methods,

Table 2 Precision and accuracy of ^{99m}Tc-DTPA compared to ^{51}Cr-EDTA for the measurement of GFR (urinary and plasma clearances) and volumes of distribution of the tracers

Parameter	*n*	Mean ± SD (mL/min)	Mean bias (mL/min)	Relative bias (%)	*r*	Intrinsic precision (%)	AW10 (%)	AW30 (%)	RMSE
EDTAu	88	64.1 ± 27.6	–	–	–		–	–	–
DTPAu (vs EDTAu)	88	66.1 ± 28.0*	2.00 ± 2.25*	3.6 ± 3.7*	0.997	2.7 ± 2.8	95 [91–99]	100 [100–100]	0.050 [0.044; 0.056]
EDTAp	86	66.1 ± 25.8	–	–	–		–	–	–
DTPAp (vs EDTAp)	86	68.1 ± 26.6*	1.96 ± 3.32*	3.1 ± 5.4*	0.992	3.9 ± 3.9	91 [85–97]	100 [100–100]	0.060 [0.051; 0.067]
p value vs urinary methods			0.82	0.40		0.02	0.39	1	0.14
Vd EDTA	85	17.3 ± 4.6	–	–	–		–	–	–
Vd DTPA (vs Vd EDTA)	85	16.6 ± 4.6*	− 0.65 ± 1.08*	− 3.9 ± 7.0*	0.972	5.1 ± 4.4	81 [73–90]	99 [95–100]	0.084 [0.069; 0.095]

Data are mean ± SD or value [95% CI]

EDTAu urinary clearance of ^{51}Cr-EDTA, *DTPAu* urinary clearance of ^{99m}Tc-DTPA, *EDTAp* plasma clearance of ^{51}Cr-EDTA, *DTPAp* plasma clearance of ^{99m}Tc-DTPA, *Vd EDTA* volume of distribution of ^{51}Cr-EDTA, *Vd DTPA* volume of distribution of ^{99m}Tc-DTPA, *SD* standard deviation, *AW 10* accuracy within 10%, *AW 30* accuracy within 30%, *RMSE* root mean square error, *r* Pearson's correlation coefficient, *n* number of available values

*$p < 0.001$ versus value measured with ^{51}Cr-EDTA or versus null bias. 95% CI were determined by 200 bootstrap iterations

Table 3 Sensitivity analyses for comparison of urinary and plasma clearances of ^{51}Cr-EDTA and ^{99m}Tc-DTPA (a) sensitivity analysis for urinary clearances using only the first three urine samples and (b) sensitivity analyses for plasma clearances restricting the plasma disappearance curve time-period

Parameter	Mean bias (mL/min)	Relative bias (%)	*r*	Intrinsic precision (%)	AW10 (%)	AW30 (%)
(a) DTPAu vs EDTAu						
7 samples (main analysis)	2.00 ± 2.25	3.6 ± 3.7	0.997	2.7 ± 2.7	95	100
3 samples (sensitivity analysis)	2.34 ± 2.82	4.0 ± 4.4	0.996	3.5 ± 3.4*	93	100
(b) DTPAp vs EDTAp						
105–285 min (main analyis)	1.96 ± 3.32	3.1 ± 5.4	0.992	3.9 ± 3.9	91	100
105–225 min	2.01 ± 3.62	3.0 ± 5.8	0.991	4.3 ± 4.3	92	100
105–165 min	2.58 ± 5.59	4.8 ± 14.2	0.977	8.1 ± 10.8**	71*	96

EDTAu urinary clearance of ^{51}Cr-EDTA, *DTPAu* urinary clearance of ^{99m}Tc-DTPA, *SD* standard deviation, *r* Pearson's correlation coefficient, *AW 10* accuracy within 10%, *AW 30* accuracy within 30%, *EDTAp* plasma clearance of ^{51}Cr-EDTA, *DTPAp* plasma clearance of ^{99m}Tc-DTPA, *r* Pearson's correlation coefficient, *AW 10* accuracy within 10%, *AW 30* accuracy within 30%

*$p < 0.05$ versus main analysis (seven urine samples). Data are mean ± SD or %

*$p < 0.05$, **$p < 0.001$ versus main analysis (105 to 285 min). Data are mean ± SD or %

and measured volumes of distribution of the tracers, so that the very high precision and accuracy of GFR measured by the two clearance methods, which rely on different assumptions, and the closely correlated volumes of distribution, demonstrate similar behaviour of the tracers and make our results extremely robust.

The main limitation of our study is the relatively limited number of patients due to the short overlap between implementation of ^{99m}Tc-DTPA-based GFR measurement method in each centre and to the discontinuation of ^{51}Cr-EDTA. However, to our knowledge, this is still the largest study comparing ^{99m}Tc-DTPA with any other GFR tracer, and the robustness of the results over the entire range of GFR values allows to draw a clear conclusion with regard to the use of ^{99m}Tc-DTPA in clinical practice. Another limitation of our study is that only clearances based on a single bolus injection were tested. The performances of ^{99m}Tc-DTPA for GFR measurement using continuous infusion of the tracer, required in specific clinical situations such as in patients with oedema, were not evaluated in the present study.

In conclusion, this multi-centre prospective study shows that ^{99m}Tc-DTPA is a reliable alternative to ^{51}Cr-EDTA for GFR measurement based on plasma or urinary clearance after a single bolus injection.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no financial or non-financial competing interests according to the subject and matter of the presented article. Dr. Balouzet reports non-financial support from Curium, outside the submitted work; Dr. Courbebaisse reports grants from Biohealth (Italy), grants from Advicenne (France), grants from Kyowa Kirin (Japan), and personal fees from Alnylam (France), outside the submitted work; Dr. Rouzet reports personal fees from GE Healthcare and grants from Spectrum Dynamics, outside the submitted work. Other authors have no relevant conflicts of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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