British Journal of Cancer (2012) 107, 1310–1316

www.bjcancer.com

Overestimation of carboplatin doses is avoided by radionuclide GFR measurement

AJ Craig*[,1], J Samol[2], SD Heenan[3], AG Irwin[4] and A Britten[4]

[1]Joint Department of Physics, Royal Marsden NHSFT, Downs Road, Sutton, Surrey SM2 5PT, UK; [2]Department of Medical Oncology, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT, UK; [3]Nuclear Medicine Department, Lanesborough Wing, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT, UK; [4]Medical Physics and Bioengineering Department, Knightsbridge Wing, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT, UK

BACKGROUND: Glomerular filtration rate (GFR) is used in the calculation of carboplatin dose. Glomerular filtration rate is measured using a radioisotope method (radionuclide GFR (rGFR)), however, estimation equations are available (estimated GFR (eGFR)). Our aim was to assess the accuracy of three eGFR equations and the subsequent carboplatin dose in an oncology population.

PATIENTS AND METHODS: Patients referred for an rGFR over a 3-year period were selected; eGFR was calculated using the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Cockcroft-Gault (CG) equations. Carboplatin doses were calculated for those patients who had received carboplatin chemotherapy. Bias, precision and accuracy were examined.

RESULTS: Two hundred and eighty-eight studies met the inclusion/exclusion criteria. Paired *t*-tests showed significant differences for all three equations between rGFR and eGFR with biases of 12.3 (MDRD), 13.6 (CKD-EPI) and 7.7 ml min^{-1} per 1.73 m^2 (CG). An overestimation in carboplatin dose was seen in 81%, 87% and 66% of studies using the MDRD, CKD-EPI and CG equations, respectively.

CONCLUSION: The MDRD and CKD-EPI equations performed poorly compared with the reference standard rGFR; the CG equation showed smaller bias and higher accuracy in our oncology population. On the basis of our results we recommend that the rGFR should be used for accurate carboplatin chemotherapy dosing and where unavailable the use of the CG equation is preferred.

British Journal of Cancer (2012) **107,** 1310–1316. doi:10.1038/bjc.2012.393 www.bjcancer.com
Published online 30 August 2012

Keywords: carboplatin; glomerular filtration rate; EDTA

Carboplatin is an alkylating chemotherapy agent (Souhami and Tobias, 2005) belonging to the group of platinum cytotoxics and is mainly used not only in combination with other cytotoxic drugs but also as a single agent to treat common malignancies, such as lung cancer, gynaecological, gastrointestinal, urological cancers, and many other cancers including curative malignancies, such as Hodgkin's and non-Hodgkin's lymphomas. Myelosuppression is carboplatin's dose-limiting toxicity and the pre-treatment renal function affects the severity of this. The renal clearance of carboplatin is closely related to the glomerular filtration rate (GFR) and to this end the dose is adjusted using the GFR in the Calvert formula (Calvert *et al*, 1989).

The Calvert formula was developed using ^{51}Cr-EDTA as the GFR measurement method, but equations may be applied to calculate an estimated GFR (eGFR). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) (National Kidney Foundation, 2002) recommends the use of the eGFR along with markers of kidney damage for staging chronic kidney disease (CKD). These estimation equations are now commonly used in clinical practice for various clinical applications (Lamb *et al*, 2005; Thomsen, 2007; Craig *et al*, 2011; National Kidney Disease Education Program, 2012).

*Correspondence: AJ Craig; E-mail: allison.craig@rmh.nhs.uk
Received 18 April 2012; revised 6 August 2012; accepted 6 August 2012; published online 30 August 2012

The eGFR is an estimate of the GFR using a combination of variables such as serum creatinine, gender, age, weight and ethnicity, and offers the advantage of being a cheaper, easier and faster alternative to the ^{51}Cr-EDTA. There are several estimation equations available for clinical use. The MDRD eGFR equation was introduced by the Modification of Diet in Renal Disease study group in 1999 (Levey *et al*, 1999, 2000) and re-expressed for use with standardised serum creatinine values in 2005 (Levey *et al*, 2005, 2006). It was derived based on a patient group with CKD and is recommended by K/DOQI (National Kidney Foundation, 2002) and the UK Guidelines for CKD (National Collaborating Centre for Chronic Conditions, 2008) for classifying CKD. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR formula was developed in 2009 (Levey *et al*, 2009; Stevens *et al*, 2010) to be more accurate than the MDRD equation for a GFR >60 ml min^{-1} per 1.73 m^2. The Cockcroft-Gault (CG) equation has been in use in clinical practise for many years (Cockcroft and Gault, 1976; Rostoker *et al*, 2007) and is often used when prescribing anticancer drugs, although in our cancer centre at St George's it is more commonly used between chemotherapy cycles for monitoring renal function.

At our cancer centre it is standard to use ^{51}Cr-EDTA as the baseline renal function measurement before the start of chemotherapy, especially when using carboplatin. There are centres (Hematology/Oncology Pharmacy association, 2010) that are using estimation equations such as the MDRD equation for calculating carboplatin doses. The CG equation is widely used for calculating carboplatin doses.

There have been few studies investigating the use of estimation equations in oncology patients (De Lemos *et al*, 2006; Seronie-Vivien *et al*, 2006; Barry *et al*, 2009; Shord *et al*, 2009; Jennings *et al*, 2010; Redal-Baigorri *et al*, 2011; Ainsworth *et al*, 2012). Some of these studies investigated the use of the MDRD and CG equations to calculate the carboplatin dosage (De Lemos *et al*, 2006; Barry *et al*, 2009; Shord *et al*, 2009; Ainsworth *et al*, 2012) and other non-carboplatin chemotherapy agents (Jennings *et al*, 2010). None of these studies have investigated the use of the CKD-EPI equation in calculating carboplatin dosing compared with ^{51}Cr-EDTA as the gold standard. In this single-centre analysis of retrospective data, we have compared the GFR results from the ^{51}Cr-EDTA with those calculated from the MDRD, CKD-EPI and CG equations in oncology patients treated for a wide range of cancer types. The carboplatin doses calculated from the radionuclide GFR (rGFR) and the eGFR equations were then compared.

PATIENTS AND METHODS

This study was approved by our local Research Office as clinical audit and informed consent was waived due to the retrospective nature of the study.

Subjects

Records of all patients referred for an rGFR between September 2005 and September 2008 were reviewed retrospectively, in total 1352 studies.

Inclusion criteria were as follows: patients referred from Oncology who were treated with chemotherapy following their rGFR (if multiple studies were available for the same patient the first was chosen); serum creatinine measurement within 7 days of the rGFR; serum creatinine of 60 μmol l^{-1} and over; and patients aged over 20 years (the corrected GFR ranges for adults start at 20 years (Fleming *et al*, 2004)).

Exclusion criteria were as follows: patients with missing information and patients with a creatinine level of under 60 μmol l^{-1}, which is the lower limit of our laboratory normal range. The Food and Drugs Administration released guidance (Food and Drug Administration, 2012) on the use of isotope dilution mass spectrometry (IDMS) standardised serum creatinine values for calculating carboplatin doses as they appeared to underestimate low serum creatinine values compared with older methods – they recommended the capping of doses for low serum creatinine values. To avoid any dose capping or rounding of serum creatinine values, we have excluded these low serum creatinine values (<60 μmol l^{-1}) from our study.

rGFR measurement and eGFR calculation

^{51}Cr-EDTA (3 MBq) was administered by intravenous injection and plasma samples taken at approximately 120 and 240 min post-injection. Plasma samples were counted in a Wallac Wizard 1480 automatic gamma counter (Wallac, Turku, Finland) for 600 s per sample.

The rGFR was calculated using the slope-intercept method, ,as recommended by the UK national guidelines (Fleming *et al*, 2004) with the Brochner-Mortensen correction (Brochner-Mortensen, 1972). The Haycock formula was used for body surface area (BSA) estimation for all studies to allow the calculation of the corrected rGFR and the absolute rGFR. The kinetic Jaffe method, which is calibrated against IDMS values, was used for measuring the serum creatinine for all studies. The eGFR were calculated for all patients using the four-variable MDRD equation (Levey *et al*, 1999, 2000, 2005, 2006), the CKD-EPI equation (Levey *et al*, 2009; Stevens *et al*, 2010) and the modified CG equation (Cockcroft and Gault, 1976; Rostoker *et al*, 2007) to calculate BSA corrected eGFR values (Table 1).

The patients were split into two groups – those who received carboplatin chemotherapy and those who received non-carboplatin-based chemotherapy. For those who had received carboplatin chemotherapy the dosing was calculated using the Calvert formula (Calvert *et al*, 1989) (Table 1). The eGFR values were BSA corrected to get absolute values for use in the Calvert equation. It is normal practice to round the carboplatin dose to account for the degree of accuracy possible with ampoules and vials (Plumridge and Sewell, 2001), at our cancer centre doses are rounded up to the nearest 10 mg.

Statistical analysis

The rGFR results were plotted against the eGFR results and least squares linear regression performed to calculate R^2. Bland-Altman analysis (Bland and Altman, 1986) was performed for the rGFR *vs* the eGFR. The means ± s.d. were given and paired *t*-tests were carried out. The bias was given as the mean difference between the eGFR and rGFR values and the precision as the s.d. of the differences. The biases were also calculated over four rGFR ranges: <30 ml min^{-1} per 1.73 m^2, 30–59 ml min^{-1} per 1.73 m^2, 60–89 ml min^{-1} per 1.73 m^2, and $\geqslant 90$ ml min^{-1} per 1.73 m^2. A *P*-value of <0.05 was considered statistically significant. The maximum differences between the rGFR and eGFR were examined. Accuracy was described as the number of studies within 10, 30 and 50% of the rGFR values.

For carboplatin dosing, the means and range for each GFR method were investigated and Bland-Altman analysis was performed. The accuracy was examined as the number of studies within 5, 10, 20, 30 and 50% of that calculated from the rGFR values. All statistical analyses were performed using Analyse-it for Microsoft Excel (2008).

RESULTS

Study demographics

Applying the study criteria resulted in 288 rGFR studies, 24% of the patients were inpatients. The range of corrected rGFR values

Table 1 Equations used for calculation of eGFR and carboplatin dosing

MDRD	$\mathrm{eGFR}(\mathrm{ml\ min^{-1}\ per\ 1.73\ m^2}) = 175 \times \mathrm{SCr}^{-1.154} \times A^{-0.203} \times 0.742\ (\text{if female}) \times 1.212\ (\text{if black})$
CKD-EPI	$\{\mathrm{eGFR}(\mathrm{ml\ min^{-1}\ per\ 1.73\ m^2}) = 141 \times \min(\mathrm{SCr}/\kappa, 1)^{\alpha} \times \max(\mathrm{SCr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018\ (\text{if female}) \times 1.159\ (\text{if black})$
Modified CG	$\mathrm{eGFR\ (ml\ min^{-1}\ per\ 1.73\ m^2)} = \frac{(140-A)\times \mathrm{weight}}{72\times \mathrm{SCr}} \times \frac{1.73}{\mathrm{BSA}} \times 0.85\ (\text{if female})$
Calvert	$\mathrm{Dose\ (mg)} = \mathrm{AUC(mg\ ml^{-1}\ min)} \times [\mathrm{GFR(ml\ min^{-1})} + 25]$

Abbreviations: A = age; AUC = prescribed area under curve; $\alpha = -0.329$ for females, -0.411 for males; BSA = body surface area (m^2); eGFR = estimated glomerular filtration rate; $\kappa = 0.7$ for females, 0.9 for males; max = maximum of SCr/κ or 1; min = minimum of SCr/κ or 1; SCr = serum creatinine (mg dl^{-1}); weight = patient weight (kg).

Table 2 Study demographics and clinical data

	Study data Range (mean ± s.d.)
Male : female (%)	56 : 44
Age range at rGFR measurement (years)	21–93 (66 ± 12)
Weight (kg)	31–131 (72 ± 17)
Height (cm)	143–196 (169 ± 10)
BSA (m^2)	1.1–2.6 (1.8 ± 0.3)
BMI	13–45 (25 ± 5)
Serum creatinine ($\mu mol\,l^{-1}$)	60–637 (89 ± 48)
rGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	5–128 (63 ± 20)
MDRD eGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	8–149 (76 ± 23)
CKD-EPI eGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	7–138 (77 ± 23)
CG eGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	9–153 (71 ± 24)
Days between rGFR and serum creatinine	0–7 (2 ± 2)

Abbreviations: BMI = body mass index; BSA = body surface area; CG = Cockcroft-Gault; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; rGFR = radionuclide glomerular filtration rate. Data are presented as ranges or percentage.

Table 3 Ethnicity of patients in study, data obtained from the hospital electronic patient record system (patients classify their own ethnicity)

Ethnicity	% Of patients
White British	47.6
White	5.1
White Irish	3.5
Indian	1.3
Black Caribbean	4.8
Black African	2.2
Bangladeshi	0.3
Pakistani	0.5
Mixed White + Black Caribbean	0.5
Mixed ethnic group	0.3
Any other Black background	0.3
Any other ethnic group	0.5
Any other White background	4.0
Asian other	2.7
Other	0.8
Patient unwilling to disclose	0.8
Unknown	2.2

were 5–128 $ml\,min^{-1}$ per $1.73\,m^2$. Full study demographics and clinical data can be found in Table 2.

The gender and ethnicity of the patients were obtained from hospital records. The ethnicity term in the estimation equations was used for black patients (9% of studies) as stated (Levey *et al*, 1999, 2009; Stevens *et al*, 2010) (Table 3).

Comparison of MDRD, CKD-EPI and CG eGFR with rGFR

All eGFR equations showed significant correlation with the rGFR (MDRD: $R^2 = 0.57$, $P < 0.0001$; CKD-EPI: $R^2 = 0.59$, $P < 0.0001$; CG: $R^2 = 0.52$, $P < 0.0001$) (Figure 1). Bland-Altman plots of the eGFR data *vs* the rGFR are shown (Figure 2), none of the biases calculated were significant (Table 4). Precisions of 15.3 $ml\,min^{-1}$ per $1.73\,m^2$ (MDRD), 14.6 $ml\,min^{-1}$ per $1.73\,m^2$ (CKD-EPI), and 16.8 $ml\,min^{-1}1.73\,m^2$ (CG) were found. The maximum differences in rGFR and eGFR values were 88.3 $ml\,min^{-1}$ per $1.73\,m^2$ for the MDRD eGFR, 87.1 $ml\,min^{-1}$ per $1.73\,m^2$ for the CKD-EPI eGFR and $-88.0\,ml\,min^{-1}$ per $1.73\,m^2$ for the CG. All equations showed significant differences in the means from the paired *t*-test ($P < 0.0001$). The GFR population accuracies for the eGFR equations can be seen in Table 5.

Of the 288 studies, 175 patients received carboplatin-based chemotherapy and 113 received non-carboplatin-based chemotherapy, no significant differences were found in the mean biases between these two groups of patients.

The studies were split up into groups depending on the cancer type: gynaecological, lung, lymphoma, upper GI, urological, melanoma, breast, colorectal, and anal cancer; merkel and germ cell tumour, leukaemia and three studies with unknown primaries. The four largest groups (gynaecological, lung, lymphoma and upper GI cancer) were examined. No differences could be seen between these four groups for the CKD-EPI eGFR, the MDRD eGFR showed a lower bias in the group with gynaecological cancer and the CG eGFR showed a higher bias for the lymphoma group.

Comparison of carboplatin dosing using the different GFR methods

The maximum prescribed dose with the rGFR was 790 mg – this was 1150, 1020 and 1120 mg for the MDRD, CKD-EPI and CG, respectively (Table 6). The MDRD eGFR overestimated the carboplatin dosing in 81% of cases whereas the CKD-EPI overestimated in 87% of cases and the CG overestimated in 66% of cases. In all, 30, 35 and 26% (MDRD, CKD-EPI, CG) of cases had an increase in dose of more than 20%; 1, 1 and 2% (MDRD, CKD-EPI, CG) had a reduction in dose of more than 20%. Figure 3 shows the Bland-Altman plots for the carboplatin dosing. Table 7 shows the accuracy of the calculated carboplatin doses. The average absolute percentage error found was 18%, 19% and 15% for the MDRD, CKD-EPI and CG, respectively.

DISCUSSION

We compared the MDRD, CKD-EPI and CG eGFR equations for a general oncology population treated at St George's cancer centre to a reference standard of ^{51}Cr-EDTA rGFR; comparing GFR values and the carboplatin doses calculated from the Calvert equation (Calvert *et al*, 1989). The MDRD, CKD-EPI and CG estimation equations showed overestimations in GFR values, resulting in overestimations of carboplatin dosing, and limited accuracy both for the GFR value and the carboplatin dose.

Two studies (Froissart *et al*, 2005; Redal-Baigorri *et al*, 2011) showed similar precision to our study for both the MDRD and the CKD-EPI; and the CG showed a lower precision than the MDRD as seen previously (De Lemos *et al*, 2006). However, our study found an overestimation in the GFR from all three of these estimation equations, with the CKD-EPI demonstrating no better performance at high GFR values as previously demonstrated (Levey *et al*, 2009). Other studies have shown both an underestimation of GFR values (De Lemos *et al*, 2006; White *et al*, 2010) and an overestimation (Kukla *et al*, 2010, Poge *et al*, 2011). Likewise, some studies (Froissart *et al*, 2005; Redal-Baigorri *et al*, 2011) showed better accuracies in the GFR values than our study whereas Poge *et al* (2011) showed similar accuracies to ours for these equations. The CG equation showed the smallest mean bias and higher accuracy; the accuracy was similar to that found by Seronie-Vivien *et al* (2006).

In our study, no clinically significant differences in the GFR values were noted for patients receiving carboplatin-based chemotherapy regimens compared with non-carboplatin-based chemotherapy regimes. Also no clinically significant differences were noted for the four largest cancer groups in our study for the CKD-EPI equation. However, a difference was noted in the gynaecological cancer due to the all female cohort where the gender term in the MDRD equation causes a reduction in the GFR value. A higher bias was noted for lymphoma patients for the CG eGFR equation, this is thought to be the lower age range in this group.

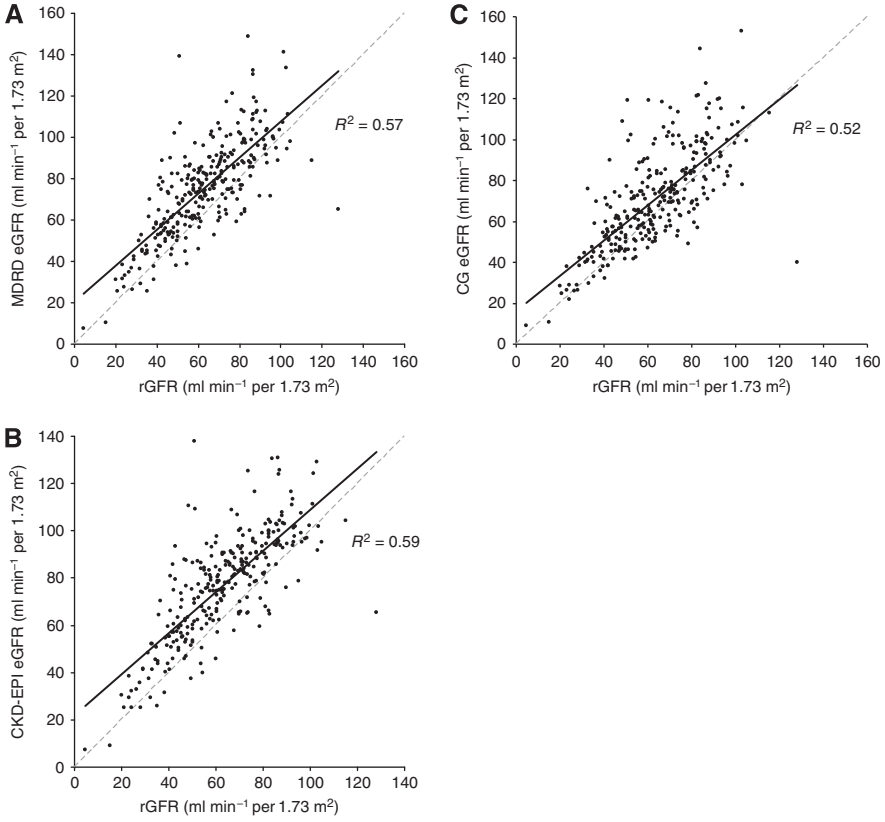

Figure 1 Scatter plots of rGFR plotted against (**A**) the eGFR calculated from the MDRD equation, (**B**) the eGFR calculated from the CKD-EPI equation and (**C**) the eGFR calculated from the CG equation. The linear regression lines are shown as solid lines, the lines of identity are shown as dashed lines.

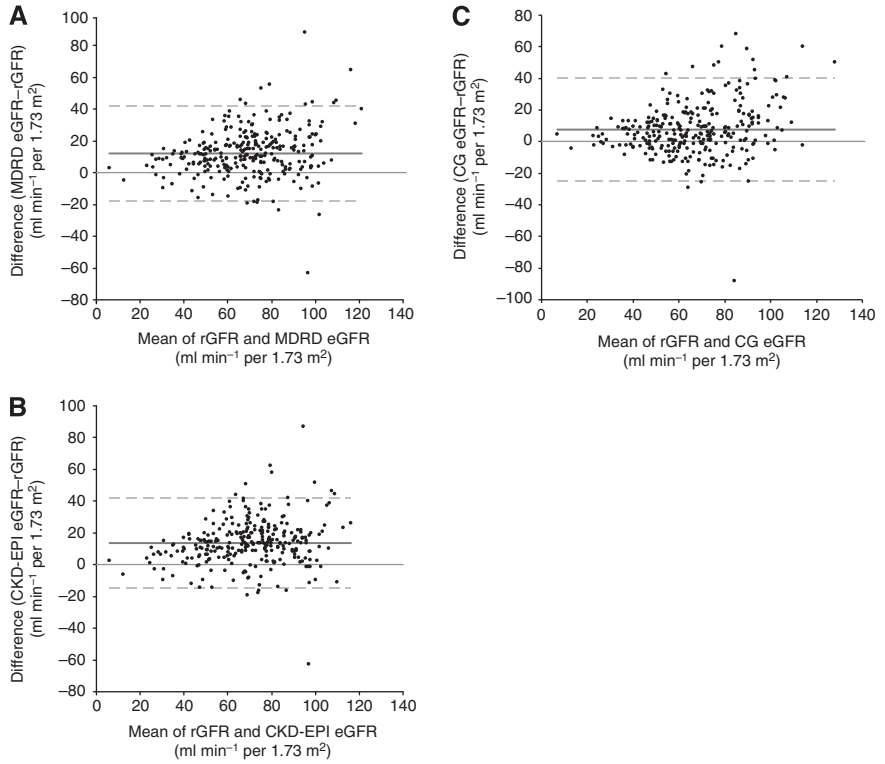

Figure 2 Bland-Altman plots of the difference of the eGFR and the rGFR against the mean of the eGFR and the rGFR. The 95% limits of agreement are represented by the dashed lines, the lines of bias are represented by the solid lines. These are shown for (**A**) the MDRD eGFR (bias 12.3 ml min^{-1} per 1.73 m^2; 95% confidence limits −17.8 : 42.3 ml min^{-1} per 1.73 m^2), (**B**) the CKD-EPI eGFR (bias 13.6 ml min^{-1} per 1.73 m^2; 95% confidence limits −15.0 : 42.2 ml min^{-1} per 1.73 m^2) and (**C**) the CG eGFR (bias 7.7 ml min^{-1} per 1.73 m^2; 95% confidence limits −25.2 : 40.6 ml min^{-1} per 1.73 m^2).

Table 4 Absolute bias (ml min^{-1} per 1.73 m^2) calculated over the entire range of studies and for various rGFR classes for the eGFR equations (*P*-values are in brackets)

		(ml min^{-1} per 1.73 m^2)			
eGFR	**Mean bias**	**rGFR < 30**	**30 < rGFR < 59**	**60 < rGFR < 89**	**rGFR ⩾ 90**
MDRD	12.3 (*P* = 0.4237)	7.0 (*P* = 0.2263)	15.7 (*P* = 0.2937)	12.0 (*P* = 0.4009)	0.9 (*P* = 0.9681)
CKD-EPI	13.6 (*P* = 0.3524)	6.1 (*P* = 0.3271)	17.1 (*P* = 0.2627)	13.5 (*P* = 0.2846)	2.2 (*P* = 0.9045)
CG	7.7 (*P* = 0.6456)	4.2 (*P* = 0.4778)	11.0 (*P* = 0.4532)	6.9 (*P* = 0.6818)	−0.7 (*P* = 0.9760)

Abbreviations: CG = Cockcroft-Gault; CKD-EPI = chronic kidney disease epidemiology collaboration; MDRD = modification of diet in renal disease; rGFR = radionuclide glomerular filtration rate.

Table 5 Percentage of studies with an eGFR within 10, 30 and 50% of the rGFR

	% Within 10% of rGFR	**% Within 30% of rGFR**	**% Within 50% of rGFR**
MDRD	24	66	87
CKD-EPI	19	65	86
CG	35	75	89

Abbreviations: CG = Cockcroft-Gault; CKD-EPI = chronic kidney disease epidemiology collaboration; MDRD = modification of diet in renal disease; rGFR = radionuclide glomerular filtration rate.

Table 6 Means and range of carboplatin doses (mg) as calculated by the rGFR, MDRD eGFR, CKD-EPI eGFR and CG eGFR

	Carboplatin doses (mg)			
rGFR (ml min^{-1} per 1.73 m^2)	**rGFR**	**MDRD**	**CKD-EPI**	**CG**
Overall (*n* = 175)	458 (230–790)	519 (280–1150)	529 (270–1020)	503 (250–1120)
< 30 (*n* = 7)	258 (230–290)	310 (280–360)	307 (270–360)	295 (250–370)
30–59 (*n* = 84)	383 (270–500)	464 (280–700)	472 (290–700)	445 (300–790)
60–89 (*n* = 85)	511 (350–720)	563 (380–1150)	575 (380–1020)	545 (330–1120)
⩾90 (*n* = 13)	645 (550–790)	637 (340–860)	660 (340–830)	667 (260–960)

Abbreviations: CG = Cockcroft-Gault; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; rGFR = radionuclide glomerular filtration rate. Data presented as mean (range).

Calvert *et al* (1989) state that ^{51}Cr-EDTA (or similar techniques) is the method of choice for the determination of GFR for carboplatin dose determination. The GFR value has an obvious effect on the carboplatin dosing and we found an overestimation like Shord *et al* (2009) for the MDRD equation whereas others demonstrated an underestimation of carboplatin dosing (De Lemos *et al*, 2006) for the MDRD and CG equations. The overestimation found was not as marked in those studies with a higher GFR for all equations. Previous studies differ on what is a clinically significant difference in carboplatin dose with some (Plumridge and Sewell, 2001; De Lemos *et al*, 2006), favouring 5% while some (Shord *et al*, 2009; Ainsworth *et al*, 2012) deeming this too low and favouring 20%. De Lemos *et al* (2006) found an error of larger than 5% in 85% of studies if a formula was used, similar those found in our study: 82% (MDRD), 87% (CKD-EPI) and 74% (CG). Ainsworth *et al* (2012) found dosing differences of larger than 20% for 32% of patients from the MDRD and 22% of patients from the CG equation compared with 31% (MDRD), 36% (CKD-EPI) and 28% (CG) for our study – with most of these being overestimations. The CG equation showed the greatest accuracy in agreement with Ainsworth *et al* (2012). A study of the Bland-Altman plots showed a high number of the outliers for the MDRD and CKD-EPI equations were patients where the ethnicity term in the equation had been used; there were no other common criteria in the outliers.

The choice of reference standard used varies across the many different studies including ^{51}Cr-EDTA (Froissart *et al*, 2005, Redal-Baigorri *et al*, 2011; Ainsworth *et al*, 2012), Iohexol (Levey *et al*, 2009), ^{125}I-Iothalamate (Levey *et al*, 1999, 2009), ^{99m}Tc-DTPA (White *et al*, 2010; Poge *et al*, 2011), imaging (De Lemos *et al*, 2006), creatinine clearance (Barry *et al*, 2009) and carboplatin clearance (Seronie-Vivien *et al*, 2006). Different forms of the MDRD equation have been used: some studies have concentrated on the six-variable formula (Shord *et al*, 2009); some have used the four-variable equation (De Lemos *et al*, 2006; Seronie-Vivien *et al*, 2006; Jennings *et al*, 2010); and some the 4 variable equation re-expressed for standardised creatinine (Barry *et al*, 2009; Redal-Baigorri *et al*, 2011). In this study, we have used the four-variable standardised formula as the four-variable formula is simpler to use than the six-variable and has been shown to have similar accuracy (Levey *et al*, 2000). Different forms of the CG equation have also been used (De Lemos *et al*, 2006). Another variable between studies is the method with which to measure the serum creatinine levels. The MDRD equation was updated in 2006 (Levey *et al*, 2006) for use with serum creatinine levels standardised to IDMS to allow for comparison between laboratories, and the CKD-EPI was

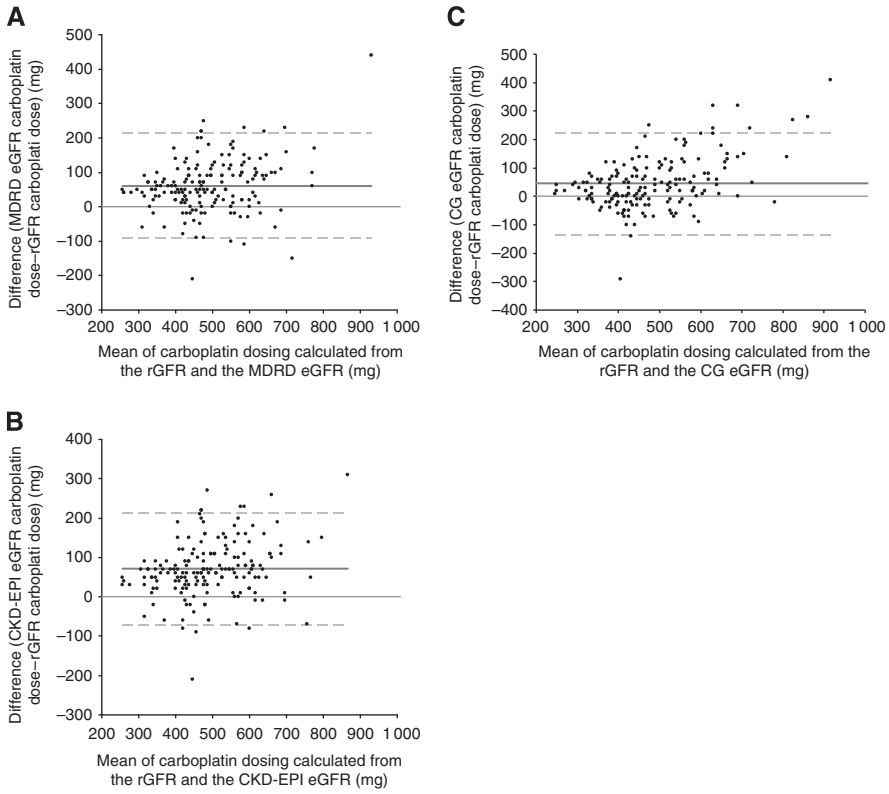

Figure 3 Bland-Altman plots of the difference of the carboplatin dosing against the mean of the carboplatin dosing calculated from the eGFR and the rGFR. The 95% limits of agreement are represented by the dashed lines, the lines of bias are represented by the solid lines. These are shown for (**A**) the MDRD eGFR (bias 61.0 mg; 95% confidence limits −92.4 : 214.4 mg), (**B**) the CKD-EPI eGFR (bias 70.7 mg; 95% confidence limits −71.1 : 212.6 mg) and (**C**) the CG eGFR (bias 45.1 mg; 95% confidence limits −133.6 : 223.8 mg).

Table 7 Percentage of carboplatin doses, calculated using the eGFR, within 5, 10, 20, 30 and 50% of the carboplatin dose calculated using the rGFR

	% Within certain percentage of rGFR carboplatin dose				
eGFR	**5**	**10**	**20**	**30**	**50**
MDRD	18	32	69	86	96
CKD-EPI	13	25	64	82	95
CG	26	43	72	86	97

Abbreviations: CG = Cockcroft-Gault; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; rGFR = radionuclide glomerular filtration rate.

developed using values calibrated to IDMS; all of our serum creatinine values are standardised to IDMS. The standardised serum creatinine values are known to underestimate serum creatinine at lower levels compared with older methods, and capping of doses for low serum creatinine values is recommended (Food and Drug Administration, 2012). Other studies (Dooley *et al*, 2004; Kaag and Steins, 2011) examining low creatinine values recommend rounding up low serum creatinine values for use in estimation equations. A brief look at serum creatinine values below $60\,\mu\text{mol}\,\text{l}^{-1}$ in our initial patient group gave abnormally high results; these were higher for the MDRD equation than the CKD-EPI equation which takes into account the serum creatinine levels within the terms of the equation. Glomerular filtration rate values of up to $875\,\text{ml}\,\text{min}^{-1}$ per $1.73\,\text{m}^2$ were calculated by the MDRD equation translating into carboplatin doses of 4060 mg. Doses of such magnitude would only be used in oncology patients treated with curative intent and followed by a stem cell autograft to allow recovery of the bone marrow (Rick *et al*, 2001; De Giorgi *et al*, 2003). When comparing the MDRD equation with the creatinine clearance calculated, Barry *et al* (2009) found large differences in the GFR and the calculated carboplatin dosage at low serum creatinine values. The MDRD equation was based on a patient population with CKD and this makes its usage outside this patient population questionable.

When the MDRD equation was developed (Levey *et al*, 1999), 88% of the patients were identified as ethnically white with under representation of ethnic minorities being a clear limitation. In our study, the patient population is ethnically much more diverse and this may well be a source of potential error. Another source of potential error is that serum creatinine measurements are not reliable in certain clinical situations including acute renal failure, pregnancy, oedematous states, muscle-wasting disease states, amputees and malnourished patients (National Collaborating Centre for Chronic Conditions, 2008), and these could not all be confidently excluded from our study.

In conclusion, we have shown that both the MDRD and the CKD-EPI estimation equations performed poorly compared with the reference standard rGFR using ^{51}Cr-EDTA in a heterogeneous oncology patient population that is also ethnically diverse. We have also shown that both equations are poor across the range of common cancer types and less common cancer types treated with carboplatin-based or non-carboplatin-based chemotherapy regimens. The large inaccuracies seen in carboplatin dosing by the use of eGFR values lead us to recommend that an exogenous filtration marker, such as rGFR, should be used for accurate carboplatin chemotherapy dose calculation, however, if no rGFR is available then the use of the CG equation is preferred.

REFERENCES

Ainsworth NL, Marshall A, Hatcher H, Whitehead L, Whitfield GA, Earl HM (2012) Evaluation of glomerular filtration rate estimation by Cockcroft-Gault, Jeliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae in oncology patients. *Ann Oncol* **23**(7): 1845–1853

Analyse-it for Microsoft Excel (version 2.11), Analyse-it Software, Ltd (2008). http://www.analyse-it.com/

Barry A, O'Cearbhaill R, Griffin D, Donnellan P, Keane M, Grimes H (2009) Evaluation of carboplatin dosage based on 4-variable modification of diet in renal disease equation. *Ir J Med Sci* **178**(3): 301–307

Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* **327**(8476): 307–310

Brochner-Mortensen J (1972) A simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Invest* **30**(3): 271–274

Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* **7**(11): 1748–1756

Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum –creatinine. *Nephron* **16**(1): 31–41

Craig AJ, Britten A, Heenan SD, Irwin AG (2011) Significant differences when using MDRD for GFR estimation compared to radionuclide measured clearance. *Eur Radiol* **21**(10): 2211–2217

De Giorgi U, Papiani G, Severini G, Fiorentini G, Marangolo M, Rosti G (2003) High-dose chemotherapy in adult patient with germ cell tumours. *Cancer Control* **10**(1): 48–56

De Lemos ML, Hsieh T, Hamata L, Levin A, Swenerton K, Djurdjev O, Vu T, Hu F, Conklin J, Malfair Taylor SC (2006) Evaluation of predictive formulae for glomerular filtration rate for carboplatin dosing in gynecological malignancies. *Gynecol Oncol* **103**(3): 1063–1069

Dooley MJ, Singh S, Rischin D (2004) Rounding of low serum creatinine levels and consequent impact on accuracy of bedside estimates of renal function in cancer. *Br J Cancer* **90**(5): 991–995

Fleming JS, Zivanovic MA, Blake GM, Burniston M, Cosgriff PS, British Nuclear Medicine Society (2004) Guidelines for the measurement of glomerular filtration rate using plasma sampling. *Nucl Med Commn* **25**(8): 759–769

Food and Drug Administration (2012) Carboplatin Dosing. www.fda.gov/AboutFDA.CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm (accessed 24 January 2012)

Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P (2005) Predictive performance of the modification of diet in renal disease and cockcroft-gault equations for estimating renal function. *J Am Soc Nephrol* **16**(3): 763–773

Hematology/Oncology Pharmacy association (2010) Newsletter, Fall 2010. www.hoparx.org/uploads/files/newsletterfall_2010.pdf (accessed 24 January 2012)

Jennings S, De Lemos ML, Levin A, Murray N (2010) Evaluation of creatinine-based formulas in dosing adjustment of cancer drugs other than Carboplatin. *J Oncol Pharm Practice* **16**(2): 113–119

Kaag D, Steins M (2011) Impact of rounding low serum creatinine concentration on the accuracy of carboplatin AUC dosing. *EJHP Sci* **17**(1): 13–20

Kukla A, El-Shahawi Y, Leister E, Kasiske B, Mauer M, Matas A, Ibrahim HN (2010) GFR-estimating models in kidney transplant recipients on a steroid-free regimen. *Nephrol Dial Transplant* **25**: 1653–1661

Lamb EJ, Tomson CRV, Roderick PJ (2005) Estimating kidney function in adults using formulae. *Ann Clin Biochem* **42**(5): 321–345

Levey AS, Bosch JP, Breyer Lewis J, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* **130**(6): 461–470

Levey AS, Coresh J, Greene T, Marsh J, Stevens L, Kusek JV (2005) Expressing the MDRD study equation for estimating GFR with IDMS traceable (gold standard) serum creatinine values. *J Am Soc Nephrol* **16**: 69A

Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F (2006) Using standardised serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* **145**(4): 247–254

Levey AS, Greene T, Kusek JW, Beck GJ (2000) A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol* **11**: 155A

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, Kusek JW, Eggers P, Vann Lente F, Greene T, Coresh J (2009) CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* **150**(9): 604–612

National Collaborating Centre for Chronic Conditions (2008) *Chronic Kidney Disease: National Clinical Guideline for Early Identification and Management in Adults in Primary and Secondary Care*. Royal College Physicians: London. http://www.renal.org/Libraries/Other_Guidlines/NICE_73_Chronic_Kidney_Disease_2008.sflb.ashx (accessed 10 February 2011)

National Kidney Disease Education Program (2012) Chronic Kidney Disease and Drug Dosing: Information for Providers. http://nkdep.nih.gov/professionals/drug-dosing-information.htm (accessed 10 January 2012)

National Kidney Foundation (2002) K/DOQI clinical practise guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* **39**(Suppl 1): S1–S266

Plumridge RJ, Sewell GJ (2001) Dose-banding of cytotoxic drugs: a new concept in cancer chemotherapy. *Am J Health Syst Pharm* **58**(18): 1760–1764

Poge U, Gerhardt T, Stoffel-Wagner B, Sauerbruch T, Waitas RP (2011) Validation of the CKD-EPI formula in patients after renal transplantation. *Nephrol Dial Transplant* **26**: 4104–4108

Redal-Baigorri B, Heine Stokholm K, Rasmussen K, Jeppesen N (2011) Estimation of kidney function in cancer patients. *Dan Med Bull* **58**(2): A4236

Rick O, Bokemeyer C, Beyer J, Hartmann JT, Schwella N, Kingreen D, Neureither S, Metzner B, Casper J, Wandt H, Hartmann F, Schmoll HJ, Derigs G, Gerl A, Berdel WE, Kanz L, Siegert W (2001) Salvage treatment with Paclitaxel, ifosfamide, and cisplatin plus high-dose carboplatin, etoposide, and thiotepa followed by autologous stem-cell rescue in patients with relapsed or refractory germ cell cancer. *J Clin Oncol* **9**(1): 81–88

Rostoker G, Andrivet P, Pham I, Griuncelli M, Adnot S (2007) A modified Cockcroft-Gault formula taking into account the body surface area gives a more accurate estimation of the glomerular filtration rate. *J Nephrol* **20**(5): 576–585

Seronie-Vivien S, Toullec S, Malard L, Thomas F, Durrand V, Chatelut E (2006) contribution of the MDRD equation and of cystatin C for renal function estimates in cancer patients. *Med Oncol* **23**(1): 63–73

Shord SS, Bressler LR, Radhakrishnan L, Chen N, Villano JL (2009) Evaluation of the Modified Diet in renal disease equation for calculation of carboplatin dose. *Ann Pharmacother* **43**(2): 235–241

Souhami R, Tobias J (2005) *Cancer and its Management*. 5th edn. Blackwell Scientific Publications: Oxford

Stevens LA, Schmid CH, Zhang YL, Coresh J, Manzi J, Landis R, Bakoush O, Contreras G, Genuth S, Klintmalm GB, Poggio E, Rossing P, Rule AD, Weir MR, Kusek J, Greene T, Levey AS (2010) Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant* **25**(2): 449–457

Thomsen HS, European Society of Urogenital Radiology (ESUR) (2007) ESUR guideline: gadolinium-based contrast media and nephrogenic systemic fibrosis. *Eur Radiol* **17**(10): 2692–2696

White CA, Akbari A, Doucette S, Fergusson D, Knoll GA (2010) Estimating glomerular filtration rate in kidney transplantation: is the new kidney disease epidemiology collaboration equation any better? *Clin Chem* **56**(3): 474–477