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Performance of formulae based estimates of glomerular filtration rate for carboplatin dosing in stage 1 seminoma

Running title: Formulae for carboplatin dosing in seminoma

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Abstract

Background: Single cycle carboplatin, dosed by glomerular filtration rate (GFR), is standard adjuvant therapy for stage 1 seminoma. Accurate measurement of GFR is essential for correct dosing. Isotopic methods remain the gold standard for determination of GFR. Formulae to estimate GFR have improved assessment of renal function in non-oncological settings. We assessed utility of these formulae for carboplatin dosing.

Methods We studied consecutive subjects receiving adjuvant carboplatin for stage 1 seminoma at our institution between 2007-2012. Subjects underwent 51Cr-EDTA measurement of GFR with carboplatin dose calculated using the Calvert formula. Theoretical carboplatin doses were calculated from estimated GFR using CKD-EPI, MDRD and Cockcroft-Gault (CG) formulae with additional correction for actual body surface area (BSA). Carboplatin doses calculated by formulae were compared with dose calculated by isotopic GFR; a difference <10% was considered acceptable.

Results: 115 patients were identified. Mean isotopic GFR was 96.9ml/min/1.73m^2. CG and CKD-EPI tended to overestimate GFR whereas MDRD tended to underestimate GFR. The CKD-EPI formula had greatest accuracy. The CKD-EPI formula, corrected for actual BSA, performed best; 45.9% patients received within 10% of correct carboplatin dose. Patients predicted as underdosed (13.5%) by CKD-EPI were more likely to be obese (p=0.013); there were no predictors of the 40.5% receiving an excess dose.

Conclusions Our data support further evaluation of the CKD-EPI formula in this patient population but clinically significant variances in carboplatin dosing occur using non-isotopic methods of GFR estimation. Isotopic determination of GFR should remain the recommended standard for carboplatin dosing when accuracy is essential.

Keywords: Carboplatin, glomerular filtration rate, formula, seminoma, dosing

Introduction

Stage I seminoma is the most common presentation of testicular germ cell tumour (GCT) and accounts for approximately 40% of all occurrences(1). The management of stage 1 seminoma historically included adjuvant radiotherapy, however following orchidectomy, cases can be managed by surveillance alone or single agent carboplatin adjuvant therapy(2-3). Carboplatin is a platinum based alkylating agent that interferes with DNA processes and is used in the treatment of several malignancies(4). The main therapeutic and toxic effects of carboplatin are related to its cytotoxicity. The most important dose-limiting toxicity of carboplatin exposure is myelosuppression, particularly thrombocytopaenia. Carboplatin exposure, defined as the area under the plasma concentration versus time curve (AUC), is associated with both severity of toxicity and anti-tumour effect(5). Carboplatin is mainly eliminated by the kidneys. In patients with normal renal function, approximately 60-70% of an administered carboplatin dose is excreted by the kidneys within 24 hours of administration. Carboplatin clearance is poorly associated with body surface area (BSA) but has a linear relationship with glomerular filtration rate (GFR)(5-6)

The Calvert formula is widely used for dosing carboplatin and incorporates GFR as its key variable(6). It is therefore essential to establish an accurate GFR. Clinical data are suggestive of a dose-response curve across therapeutically deliverable doses of carboplatin (4). Consistent with these data, an exploratory analysis of the MRC TE19/EORTC 30982 study, a randomized trial comparing carboplatin with radiotherapy (RT) as adjuvant treatment for stage I seminoma, found a higher risk of relapse in patients where carboplatin dose was calculated based on creatinine clearance with an arbitrary 10% dose reduction applied, in comparison to those patients dosed according to isotopic GFR (3). This highlights the importance of accurate assessment of

GFR and hence carboplatin dose in this setting. In the UK current oncological practice commonly employs isotopic methods to calculate measured GFR such as the chromium-51 EDTA clearance method (51Cr-EDTA)(7-8). 51Cr-EDTA is accurate, reproducible, is validated for prescription of chemotherapy, and is considered 'gold-standard' in this setting. However, it is relatively time consuming, requires access to specialised equipment (a gamma counter), nuclear medicine expertise and involves the handling and disposal of radioactive materials. Centres without access to a nuclear medicine department may experience logistical difficulties in obtaining estimation of renal function for accurate prescription of chemotherapy.

A number of methods of deriving GFR based on estimating equations have been developed. The most widespread in routine clinical practice in the general population is the 4-point MDRD (MDRD) formula, which calculates estimated glomerular filtration rate (eGFR)(9). This formula is widely used for the diagnosis and classification of chronic kidney disease(10). This takes into account age, gender, race (white or Afro-Caribbean) and serum creatinine. A calculated MDRD eGFR is issued with all biochemistry reports measuring the biochemical panel of urea, creatinine and electrolytes in the United Kingdom. Whilst well validated as a measure of kidney function, this formula was derived from patients with known kidney disease and has not been robustly validated in patients without renal impairment, and is generally considered inadequate for use in calculating drug dosing. In addition to kidney function, serum creatinine is influenced by other factors including diet, muscle mass (low in the elderly, cachexia and amputees) and drugs (e.g. trimethoprim impairs tubular secretion of creatinine). Whilst eGFR reporting has improved detection and management of chronic kidney disease, the MDRD formula tends to underestimate eGFR at higher levels of kidney function(11). To address the limitations of the MDRD formula

the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula has emerged to derive an eGFR, demonstrating less bias, greater accuracy and improved precision (12) and it is likely that this will be widely adopted as the standard measure of kidney function in all adult patients, following its endorsement in the most recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines(10).

The Cockcroft-Gault (CG) formula is still widely used for calculation of renal function to guide dosing for many drugs (e.g. gentamicin). Cockcroft-Gault calculates creatinine clearance (CrCl) rather than GFR(13). In general CrCl tends to overestimate GFR due to tubular secretion of creatinine, particularly at lower levels of kidney function. Moreover, with obese patients, who have a relatively lower muscle mass, if actual body weight is used, CG will overestimate GFR, whilst if ideal body weight is used (as recommended by CG), GFR may be underestimated. In the absence of access to isotopic measurement of GFR, many centres employ Cockcroft-Gault derived CrCl to calculate carboplatin dosing.

We determined to investigate the accuracy of the Cockcroft-Gault, MDRD and CKD-EPI formulae in estimating GFR compared with the gold standard measurement of GFR using the 51Cr-EDTA method in a relatively homogenous population comprising men with stage I seminoma. We also report the impact of using these formulae on carboplatin dosing in this cohort.

Methods

Patients

We retrospectively identified all men who had received adjuvant carboplatin AUC7 for stage I seminoma at our institution between January 2007 and August 2012 using chemotherapy prescribing software (Chemocare vers 5.2, CIS Healthcare, Belfast, U.K.). Patient demographics and co-morbidities were recorded from initial visit. Body Mass Index (BMI)(14), Body Surface Area (BSA using the DuBois formula)(15) and Ideal Body Weight (IBW) were calculated(16). The West of Scotland Research Ethics Committee granted a waiver as approval of this study on the basis that it represented analysis of routinely collected data to improve clinical care.

51Cr-EDTA Glomerular Filtration Rate

51Cr-EDTA clearance was performed in accordance with the method described by the British Nuclear Medicine Society(17). Briefly, following injection of 3 MBq chromium 51 EDTA, four accurately timed blood samples are taken between two and four hours post-administration. Cr-51 EDTA clearance is used to calculate measured GFR using the slope-intercept method with correction for the systematic error introduced as described by Brochner-Mortensen(18). GFR values were reported as GFR corrected for body surface area (using Haycock formula)(19) and uncorrected GFR.

Biochemistry

Routine biochemistry was performed in a standard National Health Service laboratory using a standard Jaffe method for measurement of serum creatinine (measured on Abbott Architect) The adjustment factors produced by the UK National External Quality Assessment Service were used for the creatinine assay to produce

isotope dilution mass spectrometry (IDMS)- traceable serum creatinine values (as is routine clinical practice). Only laboratory values obtained within less than one week of the ^{51}Cr-EDTA GFR measurement were used.

Estimated Creatinine Clearance and Glomerular Filtration Rate

Estimated Creatinine Clearance was calculated using the CG formula using actual body weight (ABW) and ideal body weight (IBW). Further correction was performed to correct CrCl to standardise measurements to 1.73m^2 of BSA (Table 1). The Estimated glomerular filtration rate (eGFR) was, calculated using the Management of Diet in Renal Disease (MDRD)(9) and the Chronic Kidney Disease Epidemiology (CKD-EPI)(12) formulae (Table 1).

Correction for Body Surface Area

51-Cr-EDTA assays are reported as their measured value in ml/min usually accompanied by a standardised correction for a BSA of 1.73m^2. eGFR formulae are calculated to report for a BSA of 1.73m^2. The Calvert formula (6) incorporates the measured (ml/min) GFR in calculation of carboplatin doses.

In this study, we compared 51-Cr-EDTA ml/min/1.73m^2 with eGFR (ml/min/1.73m^2) when evaluating performance of formulae and similarly 51-Cr-EDTA ml/min with eGFR ml/min (with correction for actual BSA).

As a separate analysis, we also incorporated additional correction for patient's actual BSA to the eGFR formulae (ml/min) (Table 1) to investigate whether this would improve accuracy of dosing. We refer to this as CKD-EPI uncorrected (CKD-EPI$_{UNCORR}$).

Carboplatin dosing

Using the Calvert equation (Table 1), an AUC 7mg/ml/min carboplatin dose was calculated for each patient using the GFR obtained from the 51-Cr EDTA method(6). Carboplatin dose was calculated using GFR in ml/min in accordance with clinical practice (6). Theoretical carboplatin doses were also calculated for each patient using each of the GFR estimating formulae as well as the CG formula for CrCl based on both actual and ideal body weight. For each formula, theoretical carboplatin doses were calculated for GFR ml/min and GFR corrected for 1.73m^2 BSA.

Statistical Methods

Measured and estimated GFR were compared graphically using the Bland Altman method to illustrate limits of agreement between the different estimating methods and the measured GFR(20). Bias was assessed as the mean difference, with positive values indicating an under-estimation of measured GFR. Precision was assessed as standard deviation for the differences. Accuracy was assessed using the standard error of the estimate in a linear regression analysis (root mean square error) relative to measured GFR. Accuracy was also assessed as the percent of estimates within 30% of the measured GFR (P_{30}), which takes into account higher errors at higher values and absolute values of the difference between measured and estimated GFR. Means were compared using the paired t-test. Theoretical carboplatin doses were compared with doses obtained using measured GFR in terms of percentage error (PE) and absolute percentage error (APE). An APE of >10% was considered clinically significant variation in carboplatin dosing. All analyses were performed using the SPSS 19.0 software package (IBM, Armonk, NY, USA). Figures were prepared using Minitab 15.0 (Minitab, State College, PA, USA).

Results

Patient Characteristics

We identified 115 male subjects who had received adjuvant carboplatin AUC 7 for with stage I seminoma. The baseline patient characteristics are shown in Table 2. The median age was 39.4 (range 20.8- 68.9). All patients were Caucasian. The majority of patients had no comorbidity (90.4%). 8 patients (7%) had hypertension, 2 patients (1.7%) had diabetes mellitus and 2 patients (1.7%) had Down's syndrome. The mean weight was 87.5kg (SD 18.3, range 51- 161kg). 40 patients (34.8%) were obese (BMI>30). The mean 51Cr-EDTA GFR was 116.3ml/min (SD 26.1) and 96.9ml/min/1.73m^2 (SD 17.4) when corrected for body surface area. Full data was available for 111 patients, 3 patients had missing height and weight measurements and one patient had missing biochemistry.

Performance of estimating GFR formulae

Differences between measured GFR and eGFR are shown in Table 3 and were compared graphically using the Bland-Altman Method (Fig. 1). CG tended to overestimate GFR using both ABW and IBW (134.1 and 107.1ml/min respectively) however, when corrected for 1.73m^2 BSA CG_{IBW} underestimated the GFR (90.7ml/min/1.73m^{2-})

CKD-EPI also tended to overestimate GFR (mean eGFR 101.0 ml/min/1.73m^2) whereas MDRD tended to underestimate GFR (mean eGFR 93.6ml/min/1.73m^2). Bias, the mean difference between measured and estimated GFR, was greatest using the CG_{ABW} formula (-17.6 ml) and similar using MDRD and CKD-EPI formulae (+3.1 and -4.3ml/min/1.73m^2, respectively). Based on the SD of the bias, precision was greatest using the CKD-EPI formula (±17.1ml/min/1.73m^2), whereas CG_{IBW} normalised to

1.73m^2 had the least precision (±22.4ml/min/1.73m^2). Based on the root mean square of error and $P_{30,}$ CKD-EPI had the greatest accuracy of the GFR estimating formulae, 103 (90.4%) had an eGFR within 30% of the measured value.

Effect of estimating GFR on carboplatin prescribing

Using GFR obtained from 51Cr-EDTA, mean carboplatin AUC7 dose calculated using the Calvert formula was 988.2mg. Doses calculated using eGFR formulae are summarised in Table 4. For CG, using ABW mean dose of carboplatin was 1113.7mg and 925.0mg using IBW. Mean calculated doses were 829.9 and 881.3mg for MDRD and CKD-EPI respectively (Figure 2). By uncorrecting for BSA mean calculated dose using CKD-EPI$_{UNCORR}$ was 1013.1mg. Using paired t-testing; we tested the null hypothesis that there was no statistically significant difference between the means of doses calculated using 51-Cr EDTA and eGFR formulae. There was no statistically significant difference between the mean Cr51-EDTA calculated dose and the mean dose obtained using the CKD-EPI$_{UNCORR}$ formulae ($p=0.16$). In contrast, mean dose calculated by the MDRD and all CG formulae were statistically dissimilar ($p<0.05$).

Doses calculated using estimating formulae were compared to those obtained using the gold-standard using percentage error. CGABW corrected to 1.73m2 had the lowest mean PE (-0.8%). MDRD tended to under dose patients (mean PE -13.8). CG calculated using IBW tended to overdose patients (median PE +13.4) but with correction for 1.73m^2, CG$_{IBW}$ tended to underestimate the dose of carboplatin. The CKD-EPI$_{UNCORR}$ formula had the lowest absolute percentage error (mean 8.3%) and MDRD and CG$_{IBW}$ per 1.73m^2 had the highest APE (mean 19.5 and 22.9% respectively). Patients with an APE<10% were considered to have received an equivalent dose of carboplatin; 45.9% of patients would have received equivalent dose of carboplatin using CKD-

EPI_{UNCORR} compared to just 23.7% of patients using MDRD. If the acceptable APE is increased to within 20% of the measured dose, 86.4% of patients would have received an equivalent dose.

Table 5 demonstrates the proportions of patients who would have received too-little, too-much and equivalent doses of carboplatin using the various formulae. Although CKD-EPI_{UNCORR} was the most accurate, 13.5% of patients would have received too little carboplatin and 40.5% would have received too much. Using MDRD, 67% of patients would have been under-dosed and using the CG_{ABW} formula, 55.0% of patients would have received too much carboplatin. Based on CKD-EPI_{UNCORR} eGFR, patients predicted to receive an inadequately low carboplatin dose had a larger BSA (p=0.035) and were obese (body mass index >30) (p=0.013), whilst there were no obvious predictors of the 40.5% who would have received too great a dose.

Discussion

A single dose of adjuvant carboplatin AUC7 has emerged as a standard option in the management of stage 1 seminoma. Accurate GFR estimation is essential for correct dosing and safe prescribing in this group of patients. The MRC TE19/EORTC 30982 protocol recommended isotopic measurment of GFR and this was performed in approximately 62% of enrolled patients. The remainder had a urinary 24 hour creatinine clearance measured. The use of CG or other estimating formulae was not permitted. The current gold-standard is chromium 51 EDTA GFR, however it is not always practical to perform this test prior to the initiation of chemotherapy and a formula for estimating GFR based on routinely collected clinical parameters would simplify the pathway for these patients. Various formulae have been used to estimate creatinine clearance and GFR, however, none have been validated for prescription of chemotherapy. In our study of 115 male subjects received adjuvant carboplatin AUC7 for stage one seminoma between 2007-2012 at a single tertiary oncology centre, we found that the CKD-EPI formula had most clinical utility in predicting accurate carboplatin dosing as well as closest overall correlation with measured GFR. Perhaps surprisingly, CKD-EPI, which corrects for body surface area was most closely aligned with measured GFR uncorrected for body surface area , as assessed by bias. Numerically CKD-EPI$_{UNCORR}$ was closest to measured GFR. Measured GFR is the measure used for carboplatin dosing using the Calvert method.

We assume that carboplatin dosing predicted by Cr-EDTA GFR using the Calvert formula, remains the 'gold-standard' for achieving cure with minimal risk of nephrotoxicity and myelosuppression. Whilst, the CKD-EPI or CKD-EPI$_{UNCORR}$ formula was able to predict dosing accurately in a proportion of patients, the majority would have received an inaccurate dose with both over and under dosing possible. Although

the clinical significance of such variation in carboplatin dosing is uncertain, it is relevant that an exploratory analysis of MRC TE19/EORTC 30982 raised the possibility of a clinically signficant reduction in efficacy with underdosing of just 10%. Specifically, the protocol mandated a dose reduction of 10% in those patients whose carboplatin dose was calculated using urinary creatinine clearance rather than isotope GFR although the mean GFR obtained by both methods was, in fact, similar (3). A trend (HR, 0.51; 95% CI, 0.24 to 1.07; P=0.08) towards poorer outcome was observed in the subgroup with the dose reduction. Therefore, delivery of an accurate AUC7 dose may be important in reducing recurrence rates in men with stage 1 seminoma and underdosing should be avoided. In our cohort, at a 10% margin of error, CKD-EPI$_{UNCORR}$ would calculate an equivalent, or larger, dose of chemotherapy in 86.5% of patients but 13.5% would still be underdosed.

Development of convenient, inexpensive and accurate methods for estimation of renal function for prescription of chemotherapy is extremely appealing. To date, radioisotopic methods remain the most widespread method for calculation for GFR in this setting, However, they are relatively time consuming with blood sampling required over at least a four hour period. They also require access to specialised equipment (a gamma counter) and involve the handling and disposal of radioactive materials and are relatively expensive. Usually, these issues are dealt with by the local Nuclear Medicine Department although not all centres have access to these facilities and expertise. Radiocontrast methods, e.g. iohexol clearance, offer a potential alternative for accurate assessment of renal function, and whilst these are often used in research studies, these have not translated into widespread clinical practice for chemotherapy prescribing. Inulin clearance remains the gold-standard for measurement of renal function but this is not used clinically, as this is expensive, time consuming and difficult to measure.

Other studies have examined this issue, specifically addressing the needs of oncology patients. Ainsworth *et al* studied the performance of the CG and MDRD equations in a larger oncology cohort, as well as investigating the accuracy of the Wright and Jeliffe equations, which were specifically derived from oncology cohorts(21-23). Their findings suggest that the CG formula may have merits for calculating GFR (approximated by CrCl), but only if specific adjustment is made in patients with an actual body weight 30% greater than their ideal body weight. This study did not address the potential impact on carboplatin dose prescribed which is a more important measure than the accuracy of the formula. It is clear that whilst the MDRD formula is widely used in the general population for diagnosis of chronic kidney disease, due to its systematic underestimation of GFR at normal and near-normal levels of kidney function, it has no place in the determination of GFR for prescription of carboplatin.

In order to address the limitations of the MDRD equation, the CKD-EPI formula has emerged (in truth a set of eight equations with the equation used dependent on the age, race, gender and serum creatinine in the individual patients). Unlike MDRD, which was derived in patients with chronic kidney disease, CKD-EPI was derived from a large population of patients with a range of renal function and this has resulted in an equation, which is more accurate in patients with normal renal function. This has since been recommended as the routine method for estimated GFR (eGFR) in adults in routine clinical practice(10).

The performance of the CKD-EPI equation has been examined in a small number of oncology patients. Craig *et al* found all estimating equations (MDRD, CKD-EPI, CG) to be associated with carboplatin overdosing (in 60-80% of cases) in a wide spectrum of oncology patients with the majority of subjects having gynaecological, lung, lymphoma and upper GI cancers(24). This study highlights the difficulties in using estimating

equations to calculate carboplatin doses in oncology patients. All the estimating equations depend on creatinine as the major endogenous variable representing excretory renal function. Creatinine varies widely between individuals dependent mainly on muscle mass, but also depends on dietary protein intake. Therefore, it is inappropriate, to broadly apply eGFR equations to all cancer patients, where sarcopenia is common and dietary intake may be poor. Oedema may be present, so actual body weight may not reflect muscle mass, limiting the performance of the CG equation. Although both the Wright and Jelliffe formulae were derived specifically attempted to address the needs of cancer patients, our data, combined with others(24)(Ainsworth *et al*, 2012) highlight the challenges using derived eGFR formulae in this group, which are at least as, if not more heterogeneous, as the various populations used to generate the CKD-EPI and MDRD formulae. CKD-EPI was generated from a dataset of over 8000 subjects and it would be challenging to generate a similar dataset to reliably address the prescribing needs of all oncology patients.

In contrast to these previous studies, we examined the performance of the various estimating equations in a fairly homogenous group of men being prescribed carboplatin as adjunctive therapy stage 1 seminoma. Appropriate carboplatin dose could be calculated in 45.9% of patients. Although patients who were likely to receive an inadequate dose were more likely to be obese, we did not find the overall performance of CKD-EPI formula eGFR based prescribing to increase by only studying non-obese subjects, using a BMI cut point of 30. Our homogenous study cohort represents a strength, demonstrating that in patients, with limited co morbid disease, no tumour burden and no evidence of cachexia, CKD-EPI based calculation of carboplatin dose will appropriate in nearly half of cases. By altering the threshold for accurate dosing to within 20% of that indicated by radioistopic measured GFR, CKD-EPI

will predict an appropriate carboplatin dose in 86.4.% of cases. However, caution needs to be exerted, prior to omitting isotopic GFR using these thresholds, given the risk of reduced cure rate if under dosed, and myelosuppression if overdosed.

Our study is limited by its relatively small size and retrospective nature. A prospective study in a validation cohort would be required to confirm that eGFR does lead to similar carboplatin dosing as isotopic methods. These results are unlikely to be generalisable to other oncology patients, including older patients, those with comorbid disease, cachexia and more advanced malignancy. Therefore it seems likely that eGFR based carboplatin dosing should be reserved to well defined groups of patients free of conditions likely to influence muscle mass (and hence serum creatinine).

In conclusion we have demonstrated that the CKD-EPI formula can be used to calculate an accurate dose of adjuvant carboplatin in many patients with stage 1 seminoma. Importantly, however, a majority of patients would experience incorrect-dosing of a magnitude compatible with clinical sequelae if CKD-EPI$_{UNCORR}$ were to be used. By contrast only 13.5% would have been underdosed. Other formulae, including CG, were not reliable in this cohort. Further work to identify predictors of those patients who require measurement of true, rather than estimated GFR, may allow a reduction in the use of isotopic GFR measurement whilst maintaining optimal dosing of adjuvant carboplatin.

Conflict of interest: The authors have no conflict of interest to declare

Titles and legends to figures and tables

Table 1: Calculations used. Key: Wt: weight in kg, Ht: height in cms, AUC: area under the concentration curve in mg/ml/min; GFR is glomerular filtration rate in ml/min; Modified Cockcroft and Gault (C&G) equation for estimated creatinine clearance; Modification of Diet in Renal Disease (MDRD) formulae; Chronic Kidney Disease Epidemiology (CKD-EPI). All formulae are listed for males

Table 2: Baseline Characteristics (n=115)

Table 3: Performance of eGFR compared against Cr-EDTA GFR measurements

[a] Bias is the mean difference between eGFR and isotope measured value

[b] Precision is the standard deviation of the mean differences

[c] From linear regression model, see methods for detail

[d] Percentage of estimates within 30% of the measured GFR

[e] Cockcroft-Gault calculated using actual body weight

[f] Cockcroft-Gault calculated using ideal body weight

Table 4: Carboplatin AUC7 doses calculated using the Calvert formulae and various GFR estimating methods with comparison of error with doses obtained using the 51Cr-EDTA method

[a] Paired t-test comparing mean calculated dose with mean estimated dose, $p<0.05$ indicates means are significantly different

[b] Percentage error between doses calculated with 51Cr-EDTA and those calculated with estimating formulae

[c] Absolute percentage error between doses calculated with 51Cr-EDTA and those calculated with estimating formulae

[d] Number of patients with absolute percentage error within 10% of actual dose of carboplatin

[e] Number of patients with absolute percentage error within 20% of actual dose of carboplatin

Table 5: Comparison of carboplatin doses calculated using eGFR formulae versus 51Cr-EDTA, demonstrating the number of patients who would receive the same, higher or lower dose of carboplatin using a 10 and 20% margin of acceptability

Figure 1 (a) and (b) Bland and Altman plots comparing each of the prediction equations (a) CKD-EPI and (b) MDRD studied with EDTA-measured GFR corrected to 1.73m^2. Each value of eGFR is compared to the corresponding measured value. The y axis shows the differences between these two values, and the x axis, the average of the two values, for each patient (in ml/min/1.73 m2). The resulting upper and lower limits of agreement between the 2 methods are illustrated as dotted lines, and the middle line illustrates bias.

Figure 2: Box and whisker plots showing (a) carboplatin doses calculated using Calvert method with different estimating formulae and (b) Percentage error (PE) in carboplatin dosing using different eGFR formulae, data between the two bold or dotted x-axis reference lines represent patients receiving within 10 or 20% of the correct carboplatin dose, respectively. Positive PE indicates overdosing of patients.

1. Powles TB, Bhardwa J, Shamash J, Mandalia S, Oliver T. The changing presentation of germ cell tumours of the testis between 1983 and 2002. BJU Int 2005;95(9):1197-200.
2. Schmoll HJ, Jordan K, Huddart R, Pes MP, Horwich A, Fizazi K, et al. Testicular non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v147-54.
3. Oliver RT, Mead GM, Rustin GJ, Joffe JK, Aass N, Coleman R, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol 2011;29(8):957-62.
4. Alberts DS, Dorr RT. New Perspectives on an Old Friend: Optimizing Carboplatin for the Treatment of Solid Tumors. Oncologist 1998;3(1):15-34.
5. de Lemos ML. Application of the area under the curve of carboplatin in predicting toxicity and efficacy. Cancer Treat Rev 1998;24(6):407-14.
6. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989;7(11):1748-56.
7. Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate measurement in man by the single injection methods using 51Cr-EDTA. Clin Sci 1969;37(1):169-80.
8. SIGN. Management of Adult Testicular Germ Cell Tumours. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN). (SIGN publication no. 124). 2011.
9. 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 prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-70.
10. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158(11):825-30.
11. Winearls CG, Glassock RJ. Dissecting and refining the staging of chronic kidney disease. Kidney Int 2009;75(10):1009-14.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604-12.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.
14. Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. J Chronic Dis 1972;25(6):329-43.
15. DuBois DD, EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;6(17):863-71.
16. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother 2000;34(9):1066-9.
17. Fleming JS, Zivanovic MA, Blake GM, Burniston M, Cosgriff PS. Guidelines for the measurement of glomerular filtration rate using plasma sampling. Nucl Med Commun 2004;25(8):759-69.
18. Brochner-Mortensen J. Routine methods and their reliability for assessment of glomerular filtration rate in adults, with special reference to total [51Cr]EDTA plasma clearance. Dan Med Bull 1978;25(5):181-202.

19. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. J Pediatr 1978;93(1):62-6.
20. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307-10.
21. Ainsworth NL, Marshall A, Hatcher H, Whitehead L, Whitfield GA, Earl HM. Evaluation of glomerular filtration rate estimation by Cockcroft-Gault, Jelliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae in oncology patients. Ann Oncol 2012;23(7):1845-53.
22. Jelliffe RW. Letter: Creatinine clearance: bedside estimate. Ann Intern Med 1973;79(4):604-5.
23. Wright JG, Boddy AV, Highley M, Fenwick J, McGill A, Calvert AH. Estimation of glomerular filtration rate in cancer patients. Br J Cancer 2001;84(4):452-9.
24. 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(8):1310-6.

Table 1

	Formulae
Body Surface Area (m^2) [DuBois]	$0.007184 \times Wt^{0.725} \times Ht^{0.425}$
Body Mass Index (kg/m^2)	$Wt / Height\ (m)^2$
Ideal Body Weight [Devine]	Male: 50 +(0.906 x (Ht- 152.4))
Calvert (mg)	AUC x (GFR + 25)
Cockcroft- Gault for males (ml/min)	(140—age) x weight x 1.23/sCr
Cockcroft- Gault ($ml/min/1.73m^2$)	CrCl x (1.73/BSA)
MDRD ($ml/min/1.73m^2$)	$32788 \times (sCr)^{-1.154} \times (Age)^{-0.203}$ (Multiply by 0.742 if female and additionally by 1.212 if patient is Afro-Caribbean)
CKD-EPI for males ($ml/min/1.73m^2$)	If sCr ≤ 80 µmol/L = $141 \times (sCr/0.9)^{-0.411} \times (0.993)^{age}$ If sCr> 80 µmol/L = $141 \times (sCr/0.9)^{-1.209} \times (0.993)^{age}$ (multiply answer by 0.87 if patient is Afro-Caribbean)
Correction of eGFR formulae for actual BSA ($ml/min/xm^2$)	eGFR x (*x*B.S.A/1.73)

Table 2:

n=115	Mean	SD
Age at GFR (years)	40.3	±10.1
Weight	87.5	±18.3
Height (cm)	177.5	±8.2
BSA (m^2)	2.0	±0.2
BMI (kg/m^2)	27.8	±5.8
Serum creatinine (umol/l)	82.0	±12.8
Chromium 51EDTA GFR (ml/min)	116.4	±26.1
Chromium 51EDTA GFR ($ml/min/1.73m^2$)	96.9	±17.4
Carboplatin dose (mg)	988.2	±173.3

Table 3

	GFR (mean ±SD)	Bias[a]	Precision[b]	Root mean square of error[c]	P_{30} n(%)[d]
51 Cr EDTA (ml/min)	116.3 (26.1)	-	-	-	-
51Cr EDTA per 1.73m² BSA (ml/min/1.73m²)	96.9 (17.4)	-	-	-	-
CG_{ABW}[e] (ml/min)	134.1 (35.9)	-17.6	21.1	16.3	52 (46.8)
CG_{ABW}[e] per 1.73m² BSA (ml/min/1.73m²)	112.6 (21.8)	-15.6	21.7	16.1	60 (54.0)
CG_{IBW}[f] (ml/min)	107.1 (22.6)	10.1	21.0	16.7	84 (75.6)
CG_{IBW}[f] per 1.73m² BSA (ml/min/1.73m²)	90.7 (21.5)	6.3	22.4	16.4	85 (76.6)
MDRD (ml/min/1.73m²)	93.6 (17.2)	3.1	18.9	16.1	101 (88.5)
CKD-EPI_{UNCORR} (ml/min)	119.5 (21.7)	-3.8	21.1	16.7	101 (88.5)
CKD-EPI(ml/min/1.73m²)	101.0 (15.1)	-4.3	17.1	15.7	103 (90.4)

Table 4

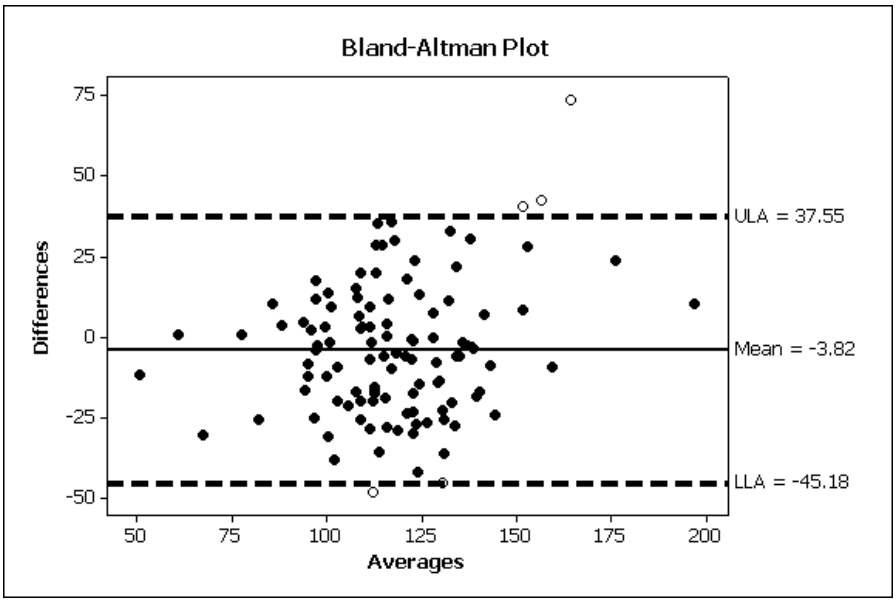
GFR measure	Carboplatin dose (mg), mean (SD)	t-test[a]	PE (%)[b], mean (SD)	APE (%)[c] mean (SD)	APE <10%[d], n(%)	APE <20%[e], n(%)
51Cr-EDTA (ml/min)	988.2 (173.3)	-	-	-	-	-
CG_{ABW} (ml/min)	1113.7 (251.3)	*P*<0.001	13.4 (17.3)	17.3 (13.4)	45 (40.5)	73 (66.3)
CG_{ABW} (ml/min/1.73m^2)	963.4 (152.9)	*P*=0.012	-0.8 (15.8)	12.9 (9.2)	46 (41.4)	87 (78.4)
CG_{IBW} (ml/min)	925.0 (158.0)	*P*=0.001	-4.5 (17.9)	14.8 (11.0)	49 (44.5)	74 (66.7)
CG_{IBW} (ml/min/ 1.73m^2)	809.9 (150.4)	*P*=<0.001	-15.5 (21.2)	22.9 (12.8)	19 (17.1)	53 (47.7)
MDRD (ml/min/1.73 m^2)	829.9 (120.5)	*P*<0.001	-13.8 (18.4)	19.5 (12.3)	27 (23.7)	61 (54.0)
$CKD\text{-}EPI_{UNCORR}$ (ml/min)	1013.1 (151.9)	*P*=0.160	4.13 (13.7)	11.6 (8.3)	51 (45.9)	96 (86.4)
CKD-EPI (ml/min/1.73 m^2)	881.3 (105.5)	*P*<0.001	-8.6 (16.8)	15.3 (11.2)	44 (39.6)	83 (74.8)

Table 5

Estimating Formula	Same dose n(%)		Overdosed n(%)		Underdosed n(%)	
	10% error	20% error	10% error	20% error	10% error	20% error
CG $_{ABW}$ (ml/min)	45 (40.5)	73 (66.3)	61 (55.0)	37 (33.4)	5 (4.5)	1 (0.9)
CG $_{ABW}$ /1.73m^2 (ml/min/1.73m^2)	46 (41.4)	87 (78.4)	28 (25.2)	12 (9.5)	37 (33.3)	12 (9.5)
CG $_{IBW}$(ml/min)	49 (44.5)	74 (66.7)	42 (37.8)	23 (20.7)	20 (18.0)	14 (12.6)
CG $_{IBW}$/1.73m^2(ml/min/1.73m^2)	19 (17.1)	53 (47.7)	15 (13.5)	8 (6.6)	77 (69.4)	50 (45)
MDRD (ml/min/1.73m^2)	27 (24.1)	61 (54.0)	10 (8.9)	5 (4.4)	75 (67.0)	48 (42.5)
CKD-EPI$_{UNCORR}$ (ml/min)	51 (45.9)	96 (86.4)	41 (40.5)	12 (10.8)	15 (13.5)	4 (3.6)
CKD-EPI (ml/min/1.73m^2)	44 (39.6)	80 (72.0)	11 (10.0)	7 (6.3)	60 (54.0)	24 (21.6)

Figure 1

a)


Bland-Altman Plot
ULA = 37.55
Mean = -3.82
LLA = -45.18
Differences
Averages
75
50
25
0
-25
-50
50
75
100
125
150
175
200

b)

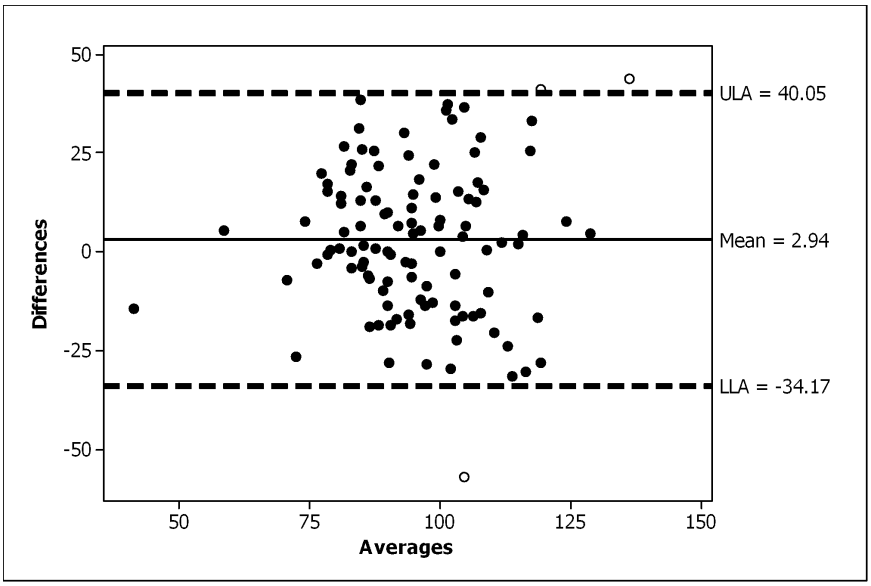
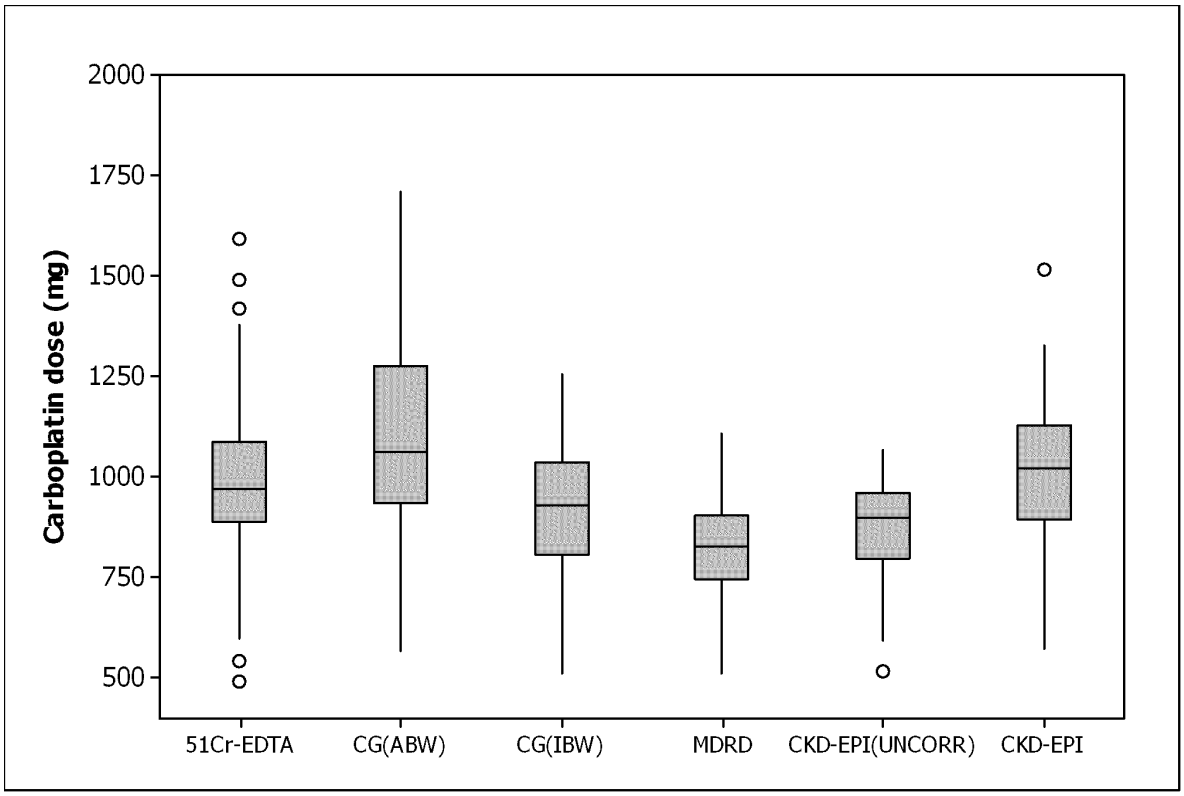
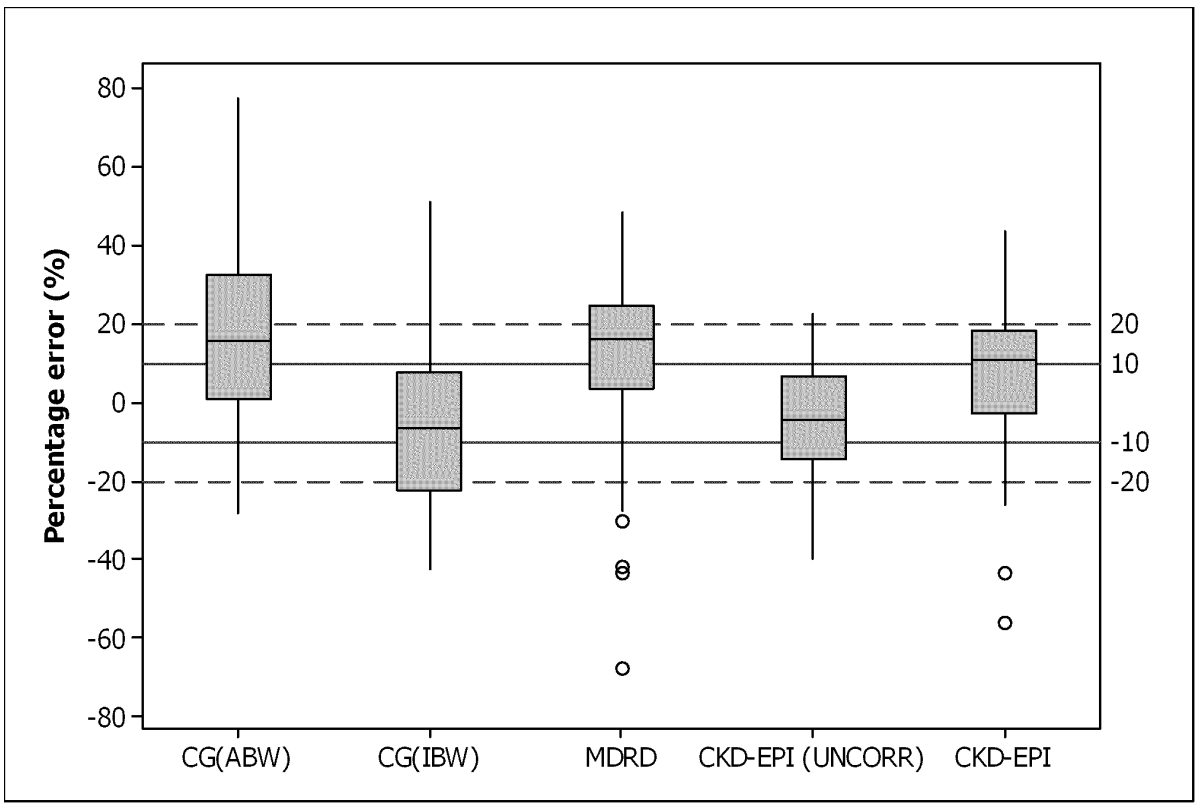

ULA = 40.05
Mean = 2.94
LLA = -34.17
Differences
Averages
50
25
0
-25
-50
50
75
100
125
150

Figure 2

a)


Carboplatin dose (mg)
2000
1750
1500
1250
1000
750
500
51Cr-EDTA
CG(ABW)
CG(IBW)
MDRD
CKD-EPI(UNCORR)
CKD-EPI

b)


Percentage error (%)
80
60
40
20
0
-20
-40
-60
-80
20
10
-10
-20
CG(ABW)
CG(IBW)
MDRD
CKD-EPI (UNCORR)
CKD-EPI