IN THE NAME OF GOD

Determination of kidney function in cancer patients

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How to determine kidney function in cancer patients?

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KEYWORDS
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Glomerular filtration;
GFR formula;
BSA indexing

Abstract A precise and efficient method for estimating kidney function in cancer patients is important to determine their eligibility for clinical trials and surgery and to allow for appropriate dose adjustment of anti-cancer drugs, especially toxic drugs with a narrow therapeutic index. Since direct measurement of glomerular filtration rate (GFR) is cumbersome, several formulae have been developed to estimate kidney function. Most of these are based on serum creatinine concentration. Though the CKD-EPI formula is recognised as being the most accurate, there is an ongoing debate on which is the optimal formula for cancer patients. In this review, we provide an overview of different GFR estimating equations for kidney function and the advantages and disadvantages of each method and compare their performance in cancer patients. We discuss the importance of body surface area-indexing and propose a framework for evaluating kidney function in cancer patients.

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Abstract

- ✓ A precise and efficient method for estimating kidney function in cancer patients is important to determine their eligibility for clinical trials and surgery and to allow for appropriate dose adjustment of anti-cancer drugs, especially toxic drugs with a narrow therapeutic index.
- ✓ Since direct measurement of glomerular filtration rate (GFR) is cumbersome, several formulae have been developed to estimate kidney function.
- ✓ Most of these are based on serum creatinine concentration.

- ✓ Though the CKD-EPI formula is recognised as being the most accurate, there is an ongoing debate on which is the optimal formula for cancer patients.

- In this review, we provide an overview of different GFR estimating equations for kidney function and the advantages and disadvantages of each method and compare their performance in cancer patients.
- We discuss the importance of body surface area-indexing and propose a framework for evaluating kidney function in cancer patients.
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- ✓ For the cancer patient who is being evaluated for inclusion in a clinical trial, the method chosen to estimate kidney function is of particular importance.
- ✓ The current FDA classification of mild kidney impairment is a CrCl of 50e79 mL/ min, and most phase 1 trials disqualify patients from enrolment at CrCl < 60 mL/min.
- ✓ Since the CG formula systemically underestimates kidney function to a higher degree than either CKD-EPI or MDRD, it may unnecessarily exclude patients with mild kidney impairment from clinical trials.

1. Introduction

1.1. Importance of evaluating kidney function in cancer patients

- ✓ Precise estimation of kidney function is important in haematology and oncology to determine eligibility for clinical trials and surgery and to facilitate dose adjustments of chemotherapy, antibiotics, opioid analgesics and other medications, especially for toxic medications with a narrow therapeutic index.

- ✓ Since many cancer drugs are eliminated by the kidney, dose adjustments are necessary in patients with decreased kidney function to avoid both under-dosing and over-dosing.
- ✓ Kidney dysfunction is common among cancer patients and significant losses of kidney function often occur during cancer therapy [1].

[1] Launay-Vacher V, Oudard S, Janus N, Gligorov J, Pourrat X,Rixe O, et al. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. Cancer 2007;110:1376e84.

- ✓ A cross-sectional study evaluating cancer patients found a reduction in estimated glomerular filtration rate (eGFR) of 13 mL/min/1.73 m2 after 2 years, and 17.7% of patients changed from chronic kidney disease (CKD) Stage 2 to CKD stage 3 or 4 at follow-up [2].

[2] Janus N, Oudard S, Beuzeboc P, Gligorov J, Ray-Coquard I, Morere JF, et al. Prevalence of renal insufficiency in cancer patients: data from the IRMA-2 study [Abstract]. J Clin Oncol 2009; 27:9559.

- Since it is neither practical nor feasible to determine serum drug concentrations or to directly measure GFR repetitively in daily clinical practice, it is important to determine the most precise and feasible method for evaluating kidney function (e.g. estimate GFR).

- ✓ Several methods are available to directly measure GFR (Table 1).
- ✓ However, all these methods are labor-intensive, complex and time-consuming making it impossible to perform these assays in all cancer patients on a regular basis.

- ✓ Inulin clearance is the gold standard but it is only rarely used in clinical practice [3].

[3] Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by cystatin C among different clinical presentations. Kidney Int 2006;69:399e405.

- Alternative and simpler methods have been developed such as ethylenediaminetetraacetic acid, iohexol, iothalamate and diethylenetriaminepentaacetate clearance methods [4,5].

[4] Levey AS, de Jong PE, Coresh J, El NM, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;80:17e28.
[5] Soveri I, Berg UB, Bjork J, Elinder CG, Grubb A, Mejare I, et al. Back SE: measuring GFR: a systematic review. Am J Kidney Dis 2014;64:411e24.

- ✓ The only method routinely used in clinical practice to measure kidney function is creatinine clearance calculation, which is based on serum creatinine and urine creatinine concentration in a 24- h collection of urine.
- ✓ This method is problematic as creatinine clearance measurement has not been validated in cancer patients [5] and urine collections are known to be cumbersome and subject to error, especially in the outpatient setting.

[5] Soveri I, Berg UB, Bjork J, Elinder CG, Grubb A, Mejare I, et al. Back SE: measuring GFR: a systematic review. Am J Kidney Dis 2014;64:411e24.

- ✓ There are currently no randomised trials supporting the need to systematically perform direct measurement of GFR in oncology.
- ✓ However, direct measurement of GFR should be considered to guide drug dosage adjustment for chemotherapeutics with potentially severe nephrotoxicity and with a narrow therapeutic index, such as cis- or carboplatin, or in patients where the available equations exhibit low accuracy [6].

[6] Launay-Vacher V, Chatelut E, Lichtman SM, Wildiers H, Steer C, Aapro M. Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations. Ann Oncol 2007;18:1314e21.

- ✓ Currently, there is no consensus regarding the optimal means of estimating GFR to allow for adjustments of chemotherapeutics (Table 2) and to define a patient's eligibility for novel cancer drug trials.
- ✓ Historically, patients with impaired kidney function have been excluded from phase 1 studies of anticancer drugs because of a perceived increased risk for major dose limiting toxicity.

- ✓ A recent study demonstrated that 85% of clinical drug trials for the five most common malignancies published in high-impact factor journals excluded the vast majority of patients with CKD [7].

[7] Kitchlu A, Shapiro J, Amir E, Garg AX, Kim SJ, Wald R, et al. Representation of patients with chronic kidney disease in trials of cancer therapy. J Am Med Assoc 2018;319:2437e9.

- ✓ A retrospective analysis of over 10,000 patients from 373 single-agent phase 1 clinical trials found no clinically meaningful increase in grade 3 or 4 non-haematologic, grade 4 haematologic or any clinically relevant toxicities in patients with mild kidney impairment (defined according to the FDA as CrCl 50e79 mL/min) compared with those with normal kidney function [8].

[8] Beumer JH, Ding F, Tawbi H, Lin Y, Viluh D, Chatterjee I, et al. Effect of renal dysfunction on toxicity in three decades of cancer therapy evaluation program-sponsored single-agent phase I studies. J Clin Oncol 2016;34:110e6.

- In recent years, some have advocated that clinical trials be more inclusive of patients with mild to moderate kidney impairment [9].

[9] Sprangers B, Jhaveri KD, Perazella MA. Improving cancer care for patients with chronic kidney disease. J Clin Oncol 2020;38(3): 188e92. epub ahead of print

Table 1
Assessing kidney function with radiopharmaceuticals.

Renal handling	Radiopharmaceutical	Clinical use	Notes
Glomerular filtration	^{99m}Tc-DTPA	GFR	Only radiopharmaceutical that can be used to measure GFR in the USA
	^{51}CR-EDTA	GFR	Not available in the USA
	^{125}I-Iothalamate	GFR	Insufficient photon emission energy to be useful for kidney imaging
Tubular secretion	^{99m}Tc-MAG3	ERPF	Preferred over ^{99m}Tc-DTAP when obstruction is suspected or with impaired kidney function
	^{123}I- and ^{131}I-orthoiodohippurate	ERPF	Not available in the USA
Cortical retention	^{99m}Tc-DMSA	Cortical imaging	To evaluate relative function, pyelonephritis and kidney scarring

Abbreviations: ERPF, effective renal plasma flow; GFR, glomerular filtration rate; USA, United States of America.

Table 2
Common cancer drugs that require dose adjustment based on kidney function.

Drug class	Individual drugs
Alkylating agents	Bendamustine, cyclophosphamide, ifosfamide, melphalan, nitrosoureas, temozolomide, trabectedin
Antimicrotubule agents	Taxanes, vinca alkaloids, eribulin
Antitumour antibiotics	Anthracyclines, bleomycin, mitomycin
Platinum agents	Cisplatin, carboplatin
Antimetabolites	Capecitabine, cladribine, clofarabine, cytarabine, gemcitabine, hydroxyurea, methotrexate, pemetrexed, pentostatin, pralatrexate
Immunomodulatory agents	Thalidomide, lenalidomide, pomalidomide
Proteasome inhibitors	Bortezomib, carfilzomib, ixazomib
Miscellaneous cytotoxic agents	Arsenic trioxide, etoposide, irinotecan, topotecan

1.2. Importance of the assay used to estimate kidney function

- ✓ Kidney function is composed of both glomerular and tubular function.
- ✓ It is important to realise that all commonly used methods to estimate kidney function only evaluate GFR.
- ✓ The assay that is used to estimate GFR is important since there can be important interassay variability.
- ✓ This variability is exemplified by applying the different estimating formulae to determine a patient's eligibility to receive cisplatin.

- ✓ When compared to eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the Cockcroft Gault (CG) formula estimated that creatinine clearance (CrCl) results in 20% more patients being excluded from eligibility for cisplatin.

- ✓ This difference is even more pronounced among Caucasians, elderly and female patients [10e15].

[10] Raj GV, Iasonos A, Herr H, Donat SM. Formulas calculating creatinine clearance are inadequate for determining eligibility for Cisplatin-based chemotherapy in bladder cancer. J Clin Oncol 2006;24:3095e100.
[11] Tsao CK, Moshier E, Seng SM, Godbold J, Grossman S, Winston J, et al. Impact of the CKD-EPI equation for estimating renal function on eligibility for cisplatin-based chemotherapy in patients with urothelial cancer. Clin Genitourin Canc 2012;10:15e20.
[12] Horn T, Ladwein B, Maurer T, Redlin J, Seitz AK, Gschwend JE, et al. The method of GFR determination impacts the estimation of cisplatin eligibility in patients with advanced urothelial cancer. World J Urol 2014;32:359e63.
[13] Dash A, Galsky MD, Vickers AJ, Serio AM, Koppie TM, Dalbagni G, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer 2006;107:506e13.
[14] Canter D, Viterbo R, Kutikov A, Wong YN, Plimack E, Zhu F, et al. Baseline renal function status limits patient eligibility to receive perioperative chemotherapy for invasive bladder cancer and is minimally affected by radical cystectomy. Urology 2011;77: 160e5.
[15] Niwa N, Kikuchi E, Masashi M, Tanaka N, Nishiyama T, Miyajima A, et al. Are the formulas used to estimate renal function adequate for patients treated with cisplatin-based chemotherapy after nephroureterectomy for upper tract urothelial carcinoma? Clin Genitourin. Canc 2016;14:e501e7.

- Whether the CG or CKD-EPI eGFR formula is used will change a patient's eligibility for cisplatin in approximately 15% of cases [11,12,14].

[11] Tsao CK, Moshier E, Seng SM, Godbold J, Grossman S, Winston J, et al. Impact of the CKD-EPI equation for estimating renal function on eligibility for cisplatin-based chemotherapy in patients with urothelial cancer. Clin Genitourin Canc 2012;10:15e20.

[12] Horn T, Ladwein B, Maurer T, Redlin J, Seitz AK, Gschwend JE, et al. The method of GFR determination impacts the estimation of cisplatin eligibility in patients with advanced urothelial cancer. World J Urol 2014;32:359e63.

[14] Canter D, Viterbo R, Kutikov A, Wong YN, Plimack E, Zhu F, et al. Baseline renal function status limits patient eligibility to receive perioperative chemotherapy for invasive bladder cancer and is minimally affected by radical cystectomy. Urology 2011;77: 160e5.

- ✓ Moreover, in a study of Bennis et al., cisplatin dose adjustments were necessary in 9.7% using the CG formula, but only in 4.8% using the Modification of Diet in Renal Disease (MDRD) study formula [16].

[16] Bennis Y, Savry A, Rocca M, Gauthier-Villano L, Pisano P, Pourroy B. Cisplatin dose adjustment in patients with renal impairment, which recommendations should we follow? Int J Clin Pharm 2014;36:420e9.

- ✓ Compared to direct measurement of CrCl based on 24-h urine specimens, more patients are classified as ineligible for cisplatin when CrCl or GFR is estimated [15].

[15] Niwa N, Kikuchi E, Masashi M, Tanaka N, Nishiyama T, Miyajima A, et al. Are the formulas used to estimate renal function adequate for patients treated with cisplatin-based chemotherapy after nephroureterectomy for upper tract urothelial carcinoma? Clin Genitourin. Canc 2016;14:e501e7.

- ✓ This effect is most pronounced in patients over 65 years old with 24e53% of these patients being denied cisplatin when estimated CrCl or GFR is compared to measured CrCl [10].

[10] Raj GV, Iasonos A, Herr H, Donat SM. Formulas calculating creatinine clearance are inadequate for determining eligibility for Cisplatin-based chemotherapy in bladder cancer. J Clin Oncol 2006;24:3095e100.

- ✓ These differences are obviously clinically important.
- ✓ Furthermore, there is evidence that measured CrCl correlates with a patient's ability to complete three full cycles of chemotherapy whereas estimated CrCl and GFR do not [10].

[10] Raj GV, Iasonos A, Herr H, Donat SM. Formulas calculating creatinine clearance are inadequate for determining eligibility for Cisplatin-based chemotherapy in bladder cancer. J Clin Oncol 2006;24:3095e100.

- ✓ For carboplatin, the assay used to determine kidney function is also an important determinant of dosage.
- ✓ The Calvert formula is used to determine the dose of carboplatin
- ✓ (Calvert : total dose [mg] = [target area under the curve] * [GFR + 25]).

- ✓ Shord et al. retrospectively studied the dose of carboplatin given to a patient using the CG formula [17].

[17] Shord SS, Bressler LR, Radhakrishnan L, Chen N, Villano JL. Evaluation of the modified diet in renal disease equation for calculation of carboplatin dose. Ann Pharmacother 2009;43: 235e41.

- ✓ If MDRD was used instead, a discrepant dose of carboplatin (defined as a difference of more than 20%) would have occurred in 48% of patients.
- ✓ This begs the question whether the thresholds used for drug selection are appropriate and, even more importantly, what is the most useful method to estimate kidney function in patients with cancer.

- ✓ There are several methods for measuring or estimating GFR in the general population, and each has its attendant limitations.

- ✓ There is no consensus on which of the available methods is ideal in the general population, and even less so in cancer patients [6,18].

[6] Launay-Vacher V, Chatelut E, Lichtman SM, Wildiers H, Steer C, Aapro M. Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations. Ann Oncol 2007;18:1314e21.
[18] Matzke GR, Aronoff GR, Atkinson Jr AJ, Bennett WM, Decker BS, Eckardt KU, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80:1122e37.

1.3. Estimating kidney function using serum creatinine

- ✓ For multiple reasons, serum creatinine concentration is an imperfect surrogate for kidney function.
- ✓ Nonetheless, it is the most commonly used method to estimate GFR.
- ✓ Creatinine is produced by muscles and removed from the body via glomerular filtration and tubular secretion (Fig. 1).

- ✓ It is important to realise that cancer patients constitute a heterogeneous population and that weight, nutritional status and muscle mass can vary significantly within a single patient over the course of their treatment.

- ✓ Muscle wasting is common among cancer patients and is frequently progressive during cancer therapy, especially among those with advanced disease undergoing chemotherapy [19].

[19] Stene GB, Helbostad JL, Amundsen T, Sorhaug S, Hjelde H, Kaasa S, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. Acta Oncol 2015;54:340e8.

- ✓ Importantly, the relationship between serum creatinine and GFR is not linear but is rather hyperbolic, meaning that at low serum creatinine concentrations, a small change in serum creatinine concentration corresponds to a large change in GFR.
- ✓ Conversely at high serum creatinine concentrations, a big change in serum creatinine corresponds to a relatively small change in GFR.

- ✓ There are also analytical issues associated with serum creatinine measurements.
- ✓ Historically, two techniques are employed to measure serum: the classical Jaffe reaction and the enzymatic method.
- ✓ In the Jaffe method, a reaction between picrate and creatinine in an alkaline milieu produces a red-orange product that can be quantified.

- ✓ Endogenous components (glucose, proteins, ketonic acids, ascorbic acid, acetoacetate and pyruvate) are also picked up in this assay and these pseudo-chromogens account for 15e20% of the Jaffe reaction if the serum creatinine is in the normal range.

- ✓ Different enzymatic methods have been described, but they all have higher specificity for serum creatinine than the Jaffe assays and are thus considered more accurate and precise than the Jaffe method.
- ✓ Until recently, there was significant heterogeneity among the different enzymatic assays [20].

[20] Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple! Nephron 2017;136:302e8.

- ✓ The isotope dilution mass spectrometry (IDMS)-traceable method was introduced to improve standardisation [21].

[21] Pieroni L, Delanaye P, Boutten A, Bargnoux AS, Rozet E, Delatour V, et al. A multicentric evaluation of IDMS-traceable creatinine enzymatic assays. Clin Chim Acta 2011;412:2070e5.

- ✓ For all the aforementioned limitation, serum creatinine concentrations alone should not be used to monitor kidney function in cancer patients.
- ✓ Of note, the study of Kithclu et al. demonstrated that of clinical drug trials that excluded the vast majority of patients with CKD, serum creatinine threshold values were the exclusion criteria in 62% of patients [7].

[7] Kitchlu A, Shapiro J, Amir E, Garg AX, Kim SJ, Wald R, et al. Representation of patients with chronic kidney disease in trials of cancer therapy. J Am Med Assoc 2018;319:2437e9.

1.4. Estimated creatinine clearance and eGFR

- ✓ The most frequently used formulae to estimate kidney function using serum creatinine are the CG equation, which estimates creatinine clearance, and the MDRD formula and the CKD-EPI equations, which both estimate GFR [4].

[4] Levey AS, de Jong PE, Coresh J, El NM, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;80:17e28.

- ✓ Several additional formulae have been developed to estimate GFR.
- ✓ In general, the results of these formulae will be within 30% of the results of measured GFR by a reference method (nuclear medicine studies) in 85e90% of subjects [22].

[22] Delanaye P, Pottel H, Botev R, Inker LA, Levey AS. Con: should we abandon the use of the MDRD equation in favour of the CKD-EPI equation? Nephrol Dial Transplant 2013;28:1396e403

- ✓ Since all these formulae use serum creatinine to estimate GFR, based on the prior discussion on the limitations of creatinine measurements and the fact that anorexia, weight loss and muscle wasting are common findings in cancer patients, these formulae may not provide accurate estimates of kidney function in this population [23].

[23] Delanaye P, Mariat C. The applicability of eGFR equations to different populations. Nat Rev Nephrol 2013;9:513e22.

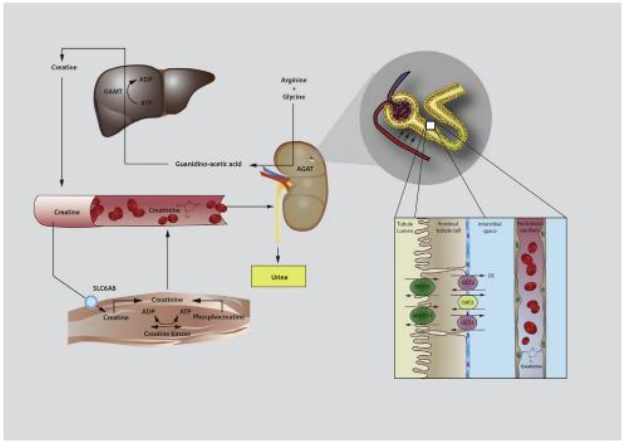


Fig. 1. Metabolism of creatinine. Creatinine is a product of the degradation of creatine that can be derived from dietary sources and *de novo* synthesis. *De novo* biosynthesis of creatine accounts for ~50% of the daily requirement and is controlled by the enzymes L-arginine-glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT). In a first step, guanidinoacetate is formed from arginine and glycine precursors by AGAT, which is highly expressed in the kidney. The second step includes a GAMT-mediated transfer of a methyl group from S-adenosyl-methionine to produce creatine mainly in the liver. Creatine synthesis is balanced with dietary intake through feedback inhibition of AGAT. Once synthesised, creatine is released into blood circulation, where it is taken up predominantly into muscles by the Na^{+}-Cl^{-}-dependent creatine transporter SLC6A8. Approximately 1.7% of the total creatine pool dehydrates to creatinine per day and permeates through the cell plasma membrane into the blood circulation. Creatinine is eliminated via the kidney by a combination of glomerular filtration and active tubular transport. Approximately ~10–40% of creatinine is actively secreted by the proximal tubule cells through transporter-mediated active uptake and efflux. Creatinine can be taken up into renal proximal tubule cells by the basolaterally localised organic cation transporter 2 (OCT2, and possibly OCT3) and the organic anion transporter 2 and effluxed into the urine by the apically localised multidrug and toxin extrusion protein 1 (MATE1) and MATE2K.

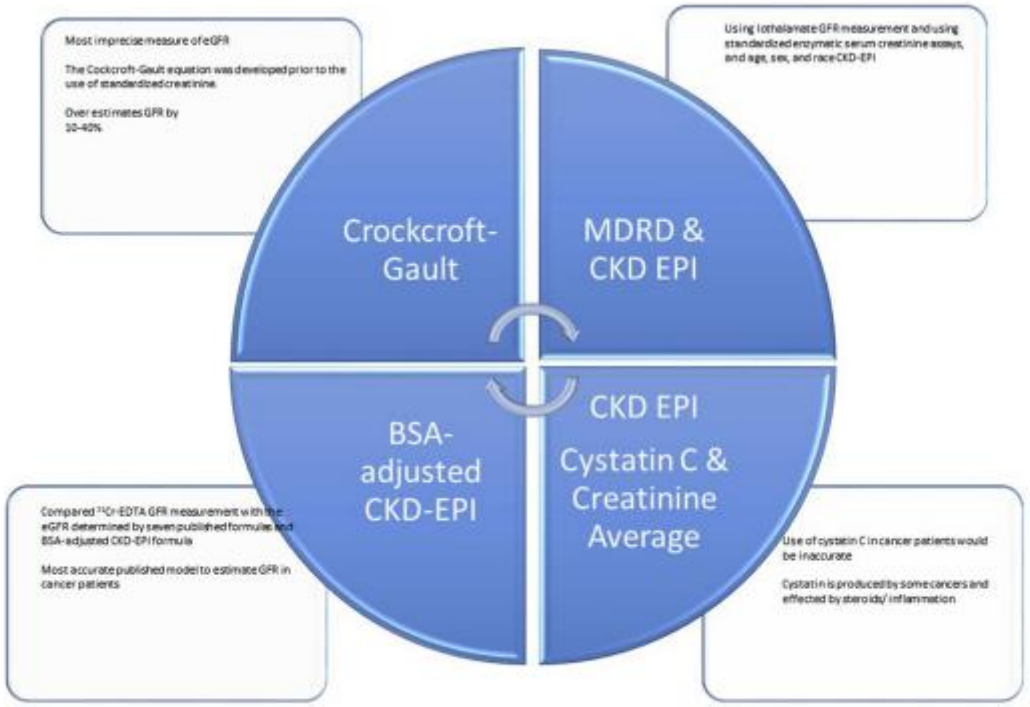
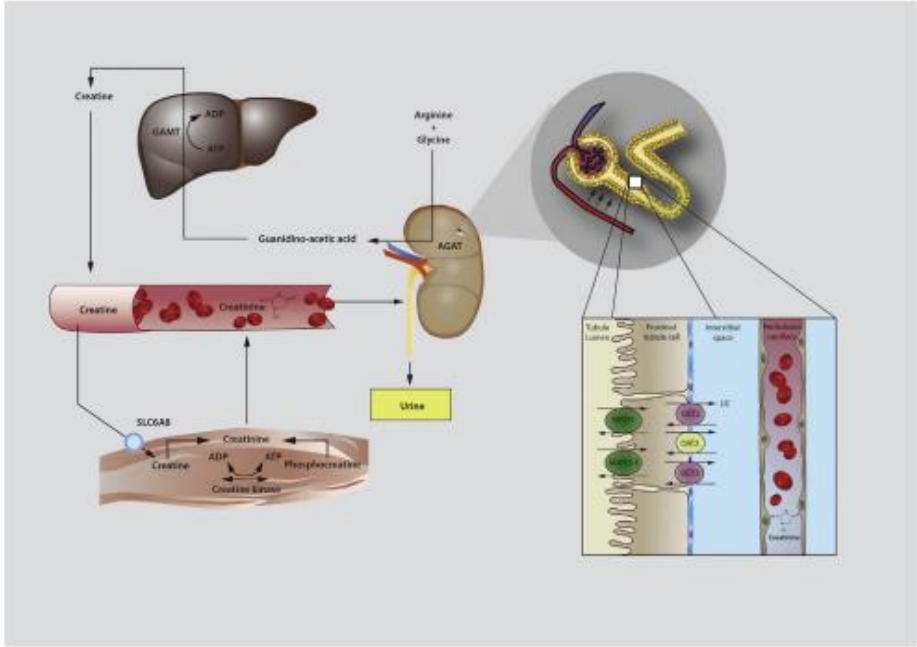


Fig. 2. Comparison of commonly used formulae to estimate kidney function (e.g. GFR).



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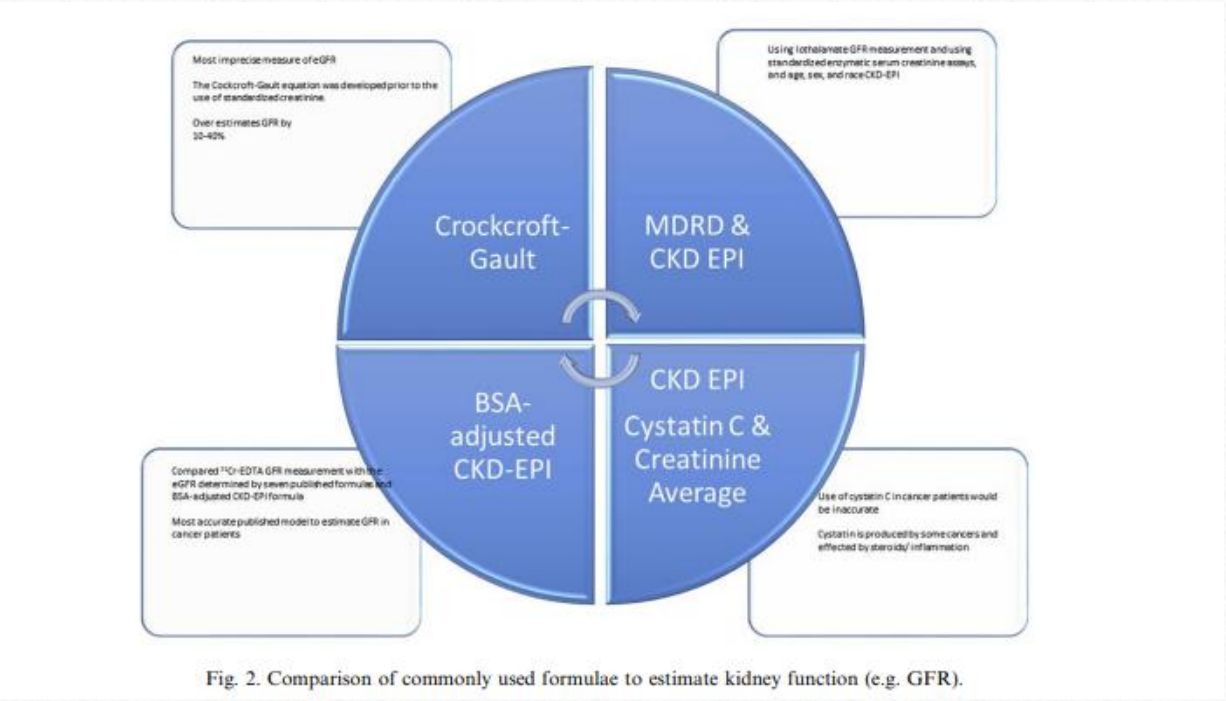

Fig. 2. Comparison of commonly used formulae to estimate kidney function (e.g. GFR).

1.5. CG formula

- ✓ The CG formula uses serum creatinine in combination with age, weight and gender to estimate creatinine clearance.
- ✓ The formula does not compensate for nonkidney function determinants of serum creatinine such as race, diet, tubular secretion and extrarenal elimination of creatinine.

- ✓ Furthermore, the formula was developed using measured creatinine clearance from 24- h urine collections as surrogate for true GFR and at a time when non-standardised non-enzymatic assays for serum creatinine measurement were employed.
- ✓ Consequently, the CG formula is an imprecise estimate of true GFR.

- ✓ Despite these significant shortcomings, the CG formula has become the most commonly used assay for kidney function-based drug dosing and for determination of drug eligibility since its incorporation into the 1998 Federal Drug Administration (FDA) guidelines on pharmacokinetics for patients with impaired kidney function.

1.6. MDRD and CKD-EPI

- ✓ Both the MDRD and CKD-EPI equations were developed using iothalamate GFR measurement, standardised enzymatic serum creatinine assays, and they incorporate readily available non-kidney function determinants of serum creatinine such as age, sex and race.

- ✓ Compared to the CG formula, the MDRD and CKD EPI formulae result in GFR estimates closer to the true GFR, especially among the elderly and in patients with a large body surface area (BSA) [24].

[24] Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter JL, Delaney MP, et al. Accuracy of the MDRD (modification of diet in renal disease) study and CKD-EPI (CKD Epidemiology collaboration) equations for estimation of GFR in the elderly. Am J Kidney Dis 2013;61:57e66.

- ✓ Although both the Kidney Disease Improving Global Outcomes (KDIGO) and the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines recommend the use of the CKD-EPI formula in clinical practice, this recommendation has not yet been fully adopted by the medical community [25].

[25] Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. Am J Kidney Dis 2014;63:820e34.

- ✓ Not surprisingly, cancer patients were not well represented in the original studies from which the MDRD and CKD-EPI formulae were developed.
- ✓ There are few studies that have compared performance of the different kidney function estimating equations among cancer patients.

- ✓ In a study by Redal-Baigorri et al. [26], the performance of MDRD and CKD-EPI was evaluated in 185 cancer patients with relatively well-preserved kidney function.
- ✓ Only 17% had a measured GFR below 60 mL/ min/1.73 m2 .

- ✓ When 51Cr-EDTA was used to measure GFR and IDMS-traceable serum creatinine measurements were obtained, the MDRD and CKD-EPI performed similarly and acceptably, around 89% for both equations [26].

[26] Redal-Baigorri B, Stokholm KH, Rasmussen K, Jeppesen N. Estimation of kidney function in cancer patients. Dan Med Bull 2011;58:A4236.

- ✓ In another study, Lauritsen et al. [27] compared the performance of the CG, MDRD and CKD-EPI formulae in germ cell cancer patients with preserved kidney function who received treatment with bleomycin, etoposide and cisplatin.
- ✓ 51Cr-EDTA was used to measure GFR and IDMS-traceable serum creatinine measurements were obtained before chemotherapy and at multiple time points during treatment.
- ✓ The performance of CG, MDRD and CKD-EPI equations were acceptable.

- ✓ However, among patients with increasing cycles of chemotherapy, the accuracy (defined as within 30% of measured GFR) decreased quickly from 85e90% to 76% for CG, 80% for MDRD and 50%, for CKD-EPI [27].

[27] Lauritsen J, Gundgaard MG, Mortensen MS, Oturai PS, FeldtRasmussen B, Daugaard G. Reliability of estimated glomerular filtration rate in patients treated with platinum containing therapy. Int J Canc 2014;135:1733e9.

- ✓ Similar findings were reported by Funakoshi et al. [28] who reported declining accuracy for all formulae after administration of cisplatin to 60% for CKD-EPI and 56% for CG.

- ✓ Before cisplatin therapy and in patients with measured GFR (mGFR) over 50 mL/min, the performance of the CKD-EPI was superior to the CG formula (accuracy of 92% versus 78%) [28].
- ✓ After chemotherapy, the accuracy of the CKD-EPI formula decreased.
- ✓ One-quarter of patients with CKDEPI values over 60 mL/min actually had a mGFR below 50 mL/min [28].

[28] Funakoshi Y, Fujiwara Y, Kiyota N, Mukohara T, Shimada T, Toyoda M, et al. Validity of new methods to evaluate renal function in cancer patients treated with cisplatin. Canc Chemother Pharmacol 2016;77:281e8.

- ✓ Hingorani et al. [29] compared mGFR (by iohexol plasma clearance) with CG (nonindexed for BSA), MDRD and CKD-EPI (both indexed for BSA) in 50 patients undergoing haematopoietic cell transplant before and 100 days after transplantation [29].
- ✓ At baseline, CKD-EPI and MDRD underestimated the GFR and CG overestimated it.

[29] Hingorani S, Pao E, Schoch G, Gooley T, Schwartz GJ. Estimating GFR in adult patients with hematopoietic cell transplant: comparison of estimating equations with an iohexol reference standard. Clin J Am Soc Nephrol 2015;10:601e10.

- ✓ The accuracies were low for patients with mean normal GFR values.
- ✓ Indeed, accuracy within 30% at baseline was 79% for CKD-EPI, 70% for MDRD and 57% for CG.
- ✓ After 100 days, the accuracy observed was similar for CKD-EPI and MDRD and slightly better for CG [29].

[29] Hingorani S, Pao E, Schoch G, Gooley T, Schwartz GJ. Estimating GFR in adult patients with hematopoietic cell transplant: comparison of estimating equations with an iohexol reference standard. Clin J Am Soc Nephrol 2015;10:601e10.

1.7. Other formulae

- ✓ While several formulae specific for cancer patients have been developed, these equations are not widely used because of the lack of any clear benefit over the more established MDRD and CKD-EPI formulae [30,31].

[30] Wright JG, Boddy AV, Highley M, Fenwick J, McGill A, Calvert AH. Estimation of glomerular filtration rate in cancer patients. Br J Canc 2001;84:452e9.
[31] Holweger K, Bokemeyer C, Lipp HP. Accurate measurement of individual glomerular filtration rate in cancer patients: an ongoing challenge. J Canc Res Clin Oncol 2005;131:559e67.

- ✓ In an interesting recent report, Janowitz et al. assessed the most accurate and least biased method to estimate GFR in a population of 2,471 Caucasian adult cancer patients receiving carboplatin chemotherapy [32].

[32] Janowitz T, Williams EH, Marshall A, Ainsworth N, Thomas PB, Sammut SJ, et al. New model for estimating glomerular filtration rate in patients with cancer. J Clin Oncol 2017;35:2798e805.

- ✓ The authors compared 51Cr-EDTA GFR measurement with the eGFR determined by seven published formulae with their newly developed formula.
- ✓ They found that the BSA-adjusted CKD-EPI formula was the most accurate published model to estimate GFR in cancer patients.

- ✓ The author's newly developed model (including serum creatinine, age, gender and BSA) improved the accuracy of eGFR estimation and carboplatin dosing.
- ✓ The new formula reduced the fraction of patients with a carboplatin dose with an absolute percentage error >20% (14.17% versus 18.62% for the BSA-adjusted CKDEPI and 25.51% for the CG formula).
- ✓ Of note, this study had some important limitations including the use of non-IDMS standardised creatinine measurements, lack of actual carboplatin dose measurements and an almost exclusive Caucasian population.

- ✓ We suggest that this new model be further examined, along with the BSA adjusted CKD-EPI, in clinical onco-nephrology practice [33].

[33] Beumer JH, Inker LA, Levey AS. Improving carboplatin dosing based on estimated GFR. Am J Kidney Dis 2018;71:163e5.

1.8. BSA or not-BSA adjusted

- An often neglected but important issue is whether BSA indexed or non-BSA-indexed estimates of kidney function should be used when dosing chemotherapy drugs.

- ✓ This is not a theoretical or trivial discussion as this choice will significantly affect drug dosing and possibly clinical outcomes [34,35].

[34] Takimoto CH, Remick SC, Sharma S, Mani S, Ramanathan RK, Doroshow J, et al. Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. J Clin Oncol 2003;21:2664e72.

[35] Shepherd ST, Gillen G, Morrison P, Forte C, Macpherson IR, White JD, et al. Performance of formulae-based estimates of glomerular filtration rate for carboplatin dosing in stage 1 seminoma. Eur J Canc 2014;50:944e52.

- ✓ The goal of BSA indexing is to make GFR results comparable between subjects with different body sizes.

- ✓ For example, differences in carboplatin dosing are dependent both on the method used to calculate GFR and whether the BSA-indexed or absolute eGFR are incorporated into the Calvert formula.

- ✓ When eGFR indexed for BSA is calculated by the CKDEPI equation, it is less likely to be associated with drug overdosing but more likely to under-dose a drug in patients as compared with non-BSA indexed eGFR calculated by the same method [35].
- ✓ BSA indexing will particularly impact GFR in cancer patients with extreme weight and/or height values.

[35] Shepherd ST, Gillen G, Morrison P, Forte C, Macpherson IR, White JD, et al. Performance of formulae-based estimates of glomerular filtration rate for carboplatin dosing in stage 1 seminoma. Eur J Canc 2014;50:944e52.

- ✓ It has been observed that cancer patients with a large BSA are frequently undertreated because oncologists will often empirically reduce the dose of chemotherapy based on the belief that using lean body mass is preferable to total body mass for dose calculation [36].

[36] Lyman GH, Sparreboom A. Chemotherapy dosing in overweight and obese patients with cancer. Nat Rev Clin Oncol 2013;10: 451e9.

- ✓ However, in the context of drug dosage adaptation, the goal is to get a precise estimate of the individual's capacity to excrete a particular drug or drug metabolite.

- ✓ The FDA and the European Medicines Agency (EMA) recommend drug dosage adaptation to be based on non-indexed GFR.
- ✓ Even though many cancer drugs are dosed according to BSA, the most commonly used method to estimate GFR in oncology is the CG formula, which yields an absolute kidney function metric (millilitres per minute) that is not indexed to BSA.

- ✓ Using an absolute kidney function estimate to prescribe anticancer drugs that are dosed according to BSA will likely alter the dose compared with dosing decisions on the basis of BSA-indexed kidney function estimates.
- ✓ So, in general non-indexed GFR estimates should be used to calculate cancer drug dosages.
- ✓ However, when drugs are dosed absolutely or based on non-BSA parameters, estimates of kidney function in millilitres per minute should be used.

1.9. Other methods to evaluate kidney function

- ✓ Large studies in the general population have established that measurement of cystatin C in combination with creatinine provides more precise GFR estimates [37].

[37] Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20e9.

- ✓ Recently, Stabuc et al. demonstrated that GFR estimates using cystatin C with 24-h creatinine clearance performed better than eGFR formulae using serum creatinine in patients with solid tumours receiving cisplatin-based chemotherapy [38].

[38] Stabuc B, Vrhovec L, Stabuc-Silih M, Cizej TE. Improved prediction of decreased creatinine clearance by serum cystatin C: use in cancer patients before and during chemotherapy. Clin Chem 2000;46:193e7.

- ✓ In contrast, Hingorani et al. also evaluated cystatin C-based formulae and demonstrated that the combined equation showed a slightly better accuracy within 30% (at 89%) compared to creatinine-based equations, only at baseline, but not at day 100 after transplantation [29].
- ✓ These conflicting findings suggest that it is too early to recommend cystatin C-based assays to estimate kidney function in cancer patients.

[29] Hingorani S, Pao E, Schoch G, Gooley T, Schwartz GJ. Estimating GFR in adult patients with hematopoietic cell transplant: comparison of estimating equations with an iohexol reference standard. Clin J Am Soc Nephrol 2015;10:601e10.

- ✓ There are additional potential limitations to cystatin C-based assays.

- ✓ First, currently the data in cancer patients are limited, lack a reference method for measuring GFR and/or include too few patients [39e41].

[39] Bretagne M, Jouinot A, Durand JP, Huillard O, Boudou RP, Tlemsani C, et al. Estimation of glomerular filtration rate in cancer patients with abnormal body composition and relation with carboplatin toxicity. Canc Chemother Pharmacol 2017;80: 45e53.
[40] Cavalcanti E, Barchiesi V, Cerasuolo D, Di PF, Cantile M, Cecere SC, et al. Correlation of serum cystatin C with glomerular filtration rate in patients receiving platinum-based chemotherapy. Anal Cell Pathol 2016:4918325. 2016.
[41] Schmitt A, Gladieff L, Lansiaux A, Bobin-Dubigeon C, EtienneGrimaldi MC, Boisdron-Celle M, et al. A universal formula based on cystatin C to perform individual dosing of carboplatin in normal weight, underweight, and obese patients. Clin Canc Res 2009;15:3633e9.

- ✓ Moreover, theoretically cancer cells might also produce cystatin C [42,43].

[42] Bodnar L, Wcislo GB, Smoter M, Gasowska-Bodnar A, Stec R, Synowiec A, et al. Cystatin C as a parameter of glomerular filtration rate in patients with ovarian cancer. Kidney Blood Press Res 2010;33:360e7.
[43] Kos J, Werle B, Lah T, Brunner N. Cysteine proteinases and their inhibitors in extracellular fluids: markers for diagnosis and prognosis in cancer. Int J Biol Markers 2000;15:84e9.

- ✓ Finally, cystatin C production is also affected by other GFR-independent factors that are not uncommon among cancer patients, such as corticoid exposure, thyroid dysfunction, inflammation and obesity [44e46].

[44] Kimmel M, Braun N, Alscher MD. Influence of thyroid function on different kidney function tests. Kidney Blood Press Res 2012; 35:9e17.
[45] Knight EL, Verhave JC, Spiegelman D, Hillege HL, De ZD, Curhan GC, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int 2004;65:1416e21.
[46] Stevens LA, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int 2009;75:652e60.

1.10. Available guidelines

- ✓ Several scientific societies, including the International Society of Geriatric Oncology (SIOG) and the National Comprehensive Cancer Network (NCCN), recommend an assessment of kidney function to allow for cancer drug dose adjustment to reduce toxicity before chemotherapy, even when serum creatinine concentration is within the normal range.
- ✓ In contrast, there are few guidelines that provide any specific recommendations regarding the preferred method to estimate kidney function in cancer patients.

- ✓ The SIOG suggests using the MDRD study equation for cancer patients older than 65 years [6,47].

[6] Launay-Vacher V, Chatelut E, Lichtman SM, Wildiers H, Steer C, Aapro M. Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations. Ann Oncol 2007;18:1314e21.

[47] Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Canc 2007;43:14e34.

- ✓ The NCCN suggests using CrCl in elderly patients and "GFR calculations" in adolescents and young adults [48,49].

[48] NCCN NCCN. Clinical practice Guidelines in oncology: older adult oncology version 1. 2018.
[49] NCCN NCCN. Clinical practice Guidelines in oncology: Adolescent and young adult version 2. 2017.

- ✓ The current FDA guidelines recommend the CG formula for determining kidney function.

- ✓ However, a draft revision of the guidelines for assessing pharmacokinetics in kidney impairment suggests that the eGFR formula also should be used to estimate kidney function without stating a preference as to which formula to be used.

2. Conclusion

- ✓ There is an ongoing debate whether to use the CG formula or CKD-EPI formula to guide drug dose adjustments for cancer drugs in patients with CKD (Fig. 2).

- ✓ Arguments favouring the use of the CKD-EPI equation are as follows.

- ✓ First, in the general population, the CKD-EPI is superior over the CG equation to estimate GFR [50,51].

[50] Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol 2005;16:763e73.
[51] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro III AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604e12.

- ✓ Second, the CKD-EPI formula estimates GFR, whereas the CG formula estimates CrCl, which is a poor estimation of true GFR.

- ✓ Third, the CG equation was developed using non-calibrated and non-IDMS traceable serum creatinine values [21].

[21] Pieroni L, Delanaye P, Boutten A, Bargnoux AS, Rozet E, Delatour V, et al. A multicentric evaluation of IDMS-traceable creatinine enzymatic assays. Clin Chim Acta 2011;412:2070e5.

- ✓ On the other side, historically the CG formula has been widely used to determine drug dosage adjustments for most drugs [52,53] and it has been demonstrated to predict the risk of drug-induced adverse events [54].

[52] 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;23:1845e53.
[53] Nyman HA, Dowling TC, Hudson JQ, Peter WL, Joy MS, Nolin TD. Comparative evaluation of the cockcroft-gault equation and the modification of diet in renal disease (MDRD) study equation for drug dosing: an opinion of the nephrology practice and Research Network of the American college of clinical pharmacy. Pharmacotherapy 2011;31:1130e44.
[54] Dufour B, Toussaint- Hacquard M, Kearney-Schwartz A, Manckoundia MD, Laurain MC, Joly L, et al. Glomerular filtration rate estimated by Cockcroft-Gault formula better predicts anti-Xa levels than modification of the diet in renal disease equation in older patients with prophylactic enoxaparin. J Nutr Health Aging 2012;16:647e52.

- ✓ For the cancer patient who is being evaluated for inclusion in a clinical trial, the method chosen to estimate kidney function is of particular importance.
- ✓ The current FDA classification of mild kidney impairment is a CrCl of 50e79 mL/ min, and most phase 1 trials disqualify patients from enrolment at CrCl < 60 mL/min.
- ✓ Since the CG formula systemically underestimates kidney function to a higher degree than either CKD-EPI or MDRD, it may unnecessarily exclude patients with mild kidney impairment from clinical trials.

- ✓ Any definitive recommendations regarding the best method for estimating kidney function in cancer patients would require performing a prospective randomised trial where chemotherapy dosage is calculated using both mGFR and eGFR and then collecting data on subsequent cancer and adverse outcomes among the different groups.

- ✓ For many reasons, there is low likelihood that such a study would be undertaken.
- ✓ The data that are available generally show differences in chemotherapy dosages when using mGFR and eGFR calculations.
- ✓ Uniformly, these studies have demonstrated differences in dose calculations when these two methods are used.

- ✓ Whether these dosing differences would result in different outcomes is not firmly established.
- ✓ There is only limited data available regarding the performance GFR estimating formulae in cancer patients.

- From this, one can conclude that the formulae are at best suboptimal for estimating GFR in cancer patients and their inaccuracy becomes more pronounced during or after cycles of chemotherapy.

- ✓ One approach includes using different eGFR formulae and calculating the absolute and relative difference between different formulae.
- ✓ If results are concordant (difference < 10 mL/min of <10%)), drug dosage recommendations available in the literature can be used.
- ✓ However, when significant discrepancies are noted, clinicians should consider the patient and their drug profile.

- ✓ For highly effective concentration dependent drugs with low risk of nephrotoxicity, the equation that gives the higher eGFR results (and thus higher dosage of the chemotherapeutic) could be considered.

- ✓ Conversely, for a drug with significant nephrotoxicity, a narrow therapeutic range or in vulnerable patient populations, it may be advisable to adjust the dosage based on a formula giving the lower eGFR result.
- ✓ The CG formula is known to give systematically lower eGFR values compared to CKD-EPI, particularly in the elderly.
- ✓ As such, the use of the CG formula will thus result in a more protective behavior in terms of drug dosage.

- ✓ In our opinion, in addition to deciding on which formula to use, it is important to consider whether BSA indexed versus non-BSA-indexed estimates of kidney function should be employed to determine dosing and eligibility for anticancer drugs.
- ✓ It is important to emphasise that the assumption that estimates of kidney function are numerically equivalent across incongruent units is incorrect.

- ✓ In the future, guidelines should be developed to improve consistency and advocate for the use of the absolute or BSA-indexed measure of kidney function (millilitres per minute) for drugs dosed absolutely or on the basis of any non-BSA parameter versus BSA-indexed measure of kidney function (millilitres per minute per 1.73 m2).


Thank You
For Your
Attention