Clin Exp Nephrol (2015) 19:1107–1113
DOI 10.1007/s10157-015-1115-1

ORIGINAL ARTICLE

Renal function evaluation in patients with cancer who were scheduled to receive carboplatin or S-1

Kanako Shibata[1,2] · Yoshinari Yasuda[1,3] · Ryo Kobayashi[4] · Yuichi Ando[5] · Tomoya Shimokata[5] · Hideki Kamiya[6] · Mutsuharu Hayashi[7] · Shoichi Maruyama[3] · Seiichi Matsuo[3] · Makoto Nakao[8] · Teruo Tsuchiya[2] · Hitomi Teramachi[2]

Received: 12 January 2015 / Accepted: 8 April 2015 / Published online: 19 April 2015

Abstract
Background Accurate glomerular filtration rate (GFR) evaluation is significant for drug dosing of carboplatin, anticancer drug excreted mainly from kidney. Serum cystatin-C (sCys-C) is a GFR marker with little affected by body muscle mass volume. And GFR equations based on serum creatinine (eGFRcreat) and sCys-C (eGFRcys) were developed; however, accuracy of eGFRcys has not been elucidated fully among patients with cancer. Therefore, we analyzed the performance of GFR equations among patients with cancer whose GFR values were measured by inulin clearance (Cin).
Methods Study design was a cross-sectional study. Subjects were 41 patients with cancer whose GFR values were measured by Cin for drug dosing studies of carboplatin or S-1 in Nagoya University Hospital from 2007 to 2010 and 29 non-cancer patients. Correlation with Cin and slope of regression line were evaluated in eGFRcreat and eGFRcys. Single and multiple regression analyses were analyzed to identify associating factors with eGFRcreat/Cin or eGFRcys/Cin.
Results Age, body weight, body mass index (BMI) and sCr were different between cancer patients and non-cancer patients, but sCys-C and Cin were consistent in 2 groups. The slope of the regression line for Cin vs. eGFRcys with zero intercept in cancer patients was 1.10 (95 % CI: 1.02–1.17), which was significantly different from 1.0. In multiple regression analysis revealed that BMI and urinary creatinine excretion were significantly associated with eGFRcreat/Cin, and cancer was only associating factor with eGFRcys/Cin.
Conclusion eGFRcys should not be used for evaluation of renal function in patients with cancer because it underestimates GFR.

Keywords Cancer · Cystatin C · Creatinine · GFR equation · Japanese

✉ Yoshinari Yasuda
yyasuda@med.nagoya-u.ac.jp

1 Department of CKD Initiatives Internal Medicine, Nagoya University Graduate School of Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

2 Laboratory of Clinical Pharmacy, Gifu Pharmaceutical University, Gifu, Japan

3 Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

4 Department of Pharmacy, Gifu University Hospital, Gifu, Japan

5 Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan

6 Division of Diabetes, Department of Internal Medicine, Aichi Medical University, Nagakute, Aichi, Japan

7 Department of Cardiology, Fujita Health University Second Hospital, Nagoya, Japan

8 College of Pharmacy, Kinjo Gakuin University, Nagoya, Japan

Introduction

Carboplatin is an anticancer drug used to treat many types of solid cancer. Since carboplatin is mainly eliminated from the kidneys, the administrated dosage of carboplatin is adjusted based on renal function, not by body surface area. The Calvert formula is widely used for carboplatin dosing [1], glomerular filtration rate (GFR) is required to achieve the target area under the plasma drug concentration–time curve (AUC) for each patient.

Calvert formula: Carboplatin dose (mg)
= target AUC (mg/mL × min) × [GFR(mL/min) + 25].

Acute kidney injury (AKI) and bone marrow suppression are major side effects of carboplatin. Thrombocytopenia is reported to be strongly associated with AUC [2]. Therefore, accurate renal function evaluation is essential to determine carboplatin dosing to improve its efficacy and safety.

Renal function is evaluated by GFR. Inulin clearance (Cin) is the gold standard for measuring GFR. However, Cin is cumbersome and inconvenient as a routine measurement. Thus, in clinical practice, renal function is usually evaluated as estimated GFR (eGFR) using a GFR equation. In general, a GFR equation based on serum creatinine (sCr) is used, but it has been rarely validated among patients with cancer.

Since sCr is a marker for renal function and body muscle mass volume, a GFR equation based on sCr theoretically overestimates GFR in subjects with low muscle mass [3]. It is well known that patients with cancer lose muscle mass volume as the disease advances, so there is serious concern whether a GFR equation based on sCr is applicable for patients with cancer, especially those who have low body muscle mass volume.

Serum Cystatin C (sCys-C) has been highlighted as a GFR marker with little affected by body muscle mass volume. Recently, calibration of sCys-C to the standardized value of ERM-DA472/IFCC has been completed [4]. Several GFR equations based on sCys-C and combinations of sCr and sCys-C were developed, including the chronic kidney disease epidemiology collaboration (CKD-EPI), Japanese and Grubb's GFR equations [5–7]. The kidney disease: improving global outcomes (KDIGO) guideline recommends methods based upon sCys-C or direct measurement of GFR in patients with CKD for administration of drugs with narrow therapeutic or toxic range [8]. On the other hand, several lines of evidences reveal that the sCys-C level is elevated in patients with cancer, for example malignant melanoma [9] and colorectal cancer [10]. But the clinical significance of the effect of cancer on sCys-C among patients who need accurate renal function evaluation for carboplatin dosing has rarely been analyzed. Very recently, Chew-Harris JS demonstrated better accuracy in sCr and sCys-C-based CKD-EPI equation among patients with cancer [11], but there is no previous study to validate these GFR equations among Japanese patients with cancer. Since the CKD-EPI equation was not accurate for Japanese, it is mandatory to evaluate the clinical value of Japanese GFR equations in Japanese patients with cancer [12].

Since our group measured Cin in patients with cancer for drug dosing studies of carboplatin [13] and S-1 [14], and sCys-C values were measured, the accuracy of Japanese GFR equations based on sCr and sCys-C was investigated in this study.

Materials and methods

Study population and design

Study design was a cross-sectional study. Study subjects were 41 consecutive patients with cancer from 2007 to 2010, all of whose GFR values were measured by Cin for chemotherapy dosing of carboplatin or S-1 at Nagoya University hospital. Among 41 cancer patients in this study, 24 and 12 patients were previously reported in pharmacokinetic studies of carboplatin [13] and S-1 [14], respectively. As a non-cancer patient, 29 consecutive patients without cancer were included, whose Cin was measured using exactly the same method. Patients with CKD G5, Cin under 15 mL/min/1.73 m^2 were excluded from the study. Out of 29 non-cancer patients, 16 patients were renal transplant donor candidates, and 13 were CKD with the following causative diseases; 3 IgA nephropathy, 3 diabetic nephropathy, 2 membranoproliferative glomerulonephritis, 1 anti-neutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis, 1 renal transplant recipient, 1 chronic glomerulonephritis, 1 membranous nephropathy, and 1 obese-related nephropathy. Among 29 non-cancer patients, 25 patients could be followed up for more than 2 years, and none of them was diagnosed any kinds of cancer. One patient died of cardiovascular event. And remaining 3 patients were transferred to different clinic within 2 years; however, there was no one who was diagnosed cancer diseases before transfer.

sCr and sCys-C measurement

sCr was measured using the IDMS (isotope dilution mass spectrometry) traceable enzymatic method at Nagoya University Hospital. sCys-C was measured using a colloidal gold immunoassay (Nescoat GC Cystatin C; Alfresa Pharma, Osaka, Japan) and calibrated to the standardized value to ERM-DA472/IFCC.

Cin and creatinine renal clearance

Cin and creatinine clearance (Ccr) were measured simultaneously in 70 participants. The method for measuring Cin and Ccr was described in the previous study [15]. In brief, Cin and Ccr were calculated from serum and urine concentrations and urine flow rate. Inulin (1 %) was administered by means of a continuous intravenous infusion for

2 h under overnight fasting and hydrated conditions. During the inulin infusion, serum samples were collected 4 times at 0 (blank), 45, 75, and 105 min for creatinine and inulin, and urine samples were collected between 30 and 60, 60 and 90, and 90 and 120 min for inulin and creatinine after completely emptying the bladder at 30 min from the start of the inulin infusion. Inulin samples were assayed by means of an enzymatic method using a kit (Diacolor Inulin; Toyobo Co, Osaka, Japan). The mean value of 3 measurements was used for the Cin and Ccr study.

Calculation of eGFR based on sCr or sCys-C

eGFR was calculated using the Japanese GFR equations based on sCr (eGFRcreat) and sCys-C (eGFRcys) [12, 15].

$$\text{eGFRcreat (mL/min/1.73m}^2\text{)} = 194 \times \text{sCr}^{-1.094} \times \text{Age}^{-0.287} \ (\times 0.739 \text{ if female})$$

$$\text{eGFRcys } (\text{mL/min/1.73m}^2) = [104 \times \text{sCys-C}^{-1.019} \times 0.996^{\text{Age}} (\times 0.929 \text{ if female})] - 8$$

Statistical analysis

Difference between cancer patients and non-cancer patients was evaluated using an independent t test. Values of $P < 0.05$ were considered statistically significant. Statistical analysis was performed using SPSS version 22 (SPSS, Inc., Chicago, IL, USA).

This study was approved by the Ethics Committee of Nagoya University Hospital, Nagoya and written informed consents were obtained in all patients.

Results

Clinical characteristics of the study population are shown in Table 1. The cancer patients were significantly older than non-cancer patients ($P < 0.01$). Body weight and body mass index (BMI) in the cancer patients were significantly lower than the non-cancer patients ($P < 0.01$). There was no significant difference in gender, albumin, and urinary creatinine excretion. Although sCr was significantly higher in patients without cancer, no significant difference was shown in Cin, sCys-C, eGFRcreat, and eGFRcys between cancer patients and non-cancer patients (Table 1).

Figure 1 shows the relationship between Cin and estimations of GFR and Ccr. Correlation coefficients between eGFRcreat and Cin were 0.85 and 0.90 in cancer patients and non-cancer patients. Correlation coefficients between eGFRcys and Cin were 0.74 and 0.93 in cancer patients and non-cancer patients. Ccr overestimated Cin in all patients. Ccr correlated significantly with Cin at correlation coefficients 0.81 and 0.94 in patients with and without cancer, respectively. But bias between Ccr and Cin varied in each patient (Fig. 1c).

Table 1 Characteristics of the subjects

	Cancer	Non-cancer	P
Number	41	29	
Gender (M/F)	26/15	23/6	0.15
Age (years)	66.0 ± 7.3	55.4 ± 13.8	<0.01*
Height (cm)	161.8 ± 7.2	163.7 ± 7.7	0.30
Weight (kg)	55.1 ± 10.1	66.4 ± 15.8	<0.01*
BMI (kg/m^2)	21.0 ± 2.9	24.7±4.7	<0.01*
Creatinine (mg/dL)	0.8 ± 0.2	1.2 ± 1.0	<0.01*
Cystatin C (mg/L)	1.1 ± 0.3	1.4 ± 0.8	0.05
albumin (g/dL)	3.5 ± 0.8	3.7 ± 0.7	0.06
Ucre (mg/day/kg)	19.1 ± 4.3	17.7 ± 4.1	0.19
Cin (mL/min/1.73 m^2)	76.3 ± 26.4	66.6 ± 35.7	0.20
eGFRcreat (mL/min/1.73 m^2)	77.9 ± 18.7	66.7 ± 32.7	0.07
eGFRcys (mL/min/1.73 m^2)	69.5 ± 18.6	69.1 ± 32.1	0.95
eGFRcreat/Cin	1.1 ± 0.3	1.1 ± 0.4	0.84
eGFRcys/Cin	1.0 ± 0.3	1.1 ± 0.2	0.05*
Cancer type			
Lung	25		
Head and neck	15		
Cervical	1		

Data were expressed mean ± SD

BMI body mass index, *Ucre* urinary creatinine excretion, *Cin* inulin clearance, *eGFRcreat* estimated GFR based on serum creatinine, *eGFRcys* estimated GFR based on serum Cystatin C

* $P < 0.05$

The slope of the regression line for Cin vs. eGFRcys with zero intercept in cancer patients was 1.10 (95 % CI: 1.02–1.17), which was significantly different from 1.0 (Table 2).

Factors affecting eGFRcreat/Cin and eGFRcys/Cin were analyzed using single and multiple regression analyses with eGFRcreat/Cin and eGFRcys/Cin as dependent variables, and BMI, albumin, cancer, urinary excretion of creatinine and gender as independent variables in total subjects ($N = 70$). Single regression analysis showed BMI, albumin, and urinary creatinine excretion were significant factors associated with eGFRcreat/Cin, but no factor was statistically significant in eGFRcys/Cin (Tables 3, 4). Multiple regression analysis showed that low urinary creatinine excretion and low BMI are associated with high level of eGFRcreat/Cin (Table 3). And only cancer was independently and negatively associated with eGFRcys/Cin ($P = 0.02$) (Table 4).

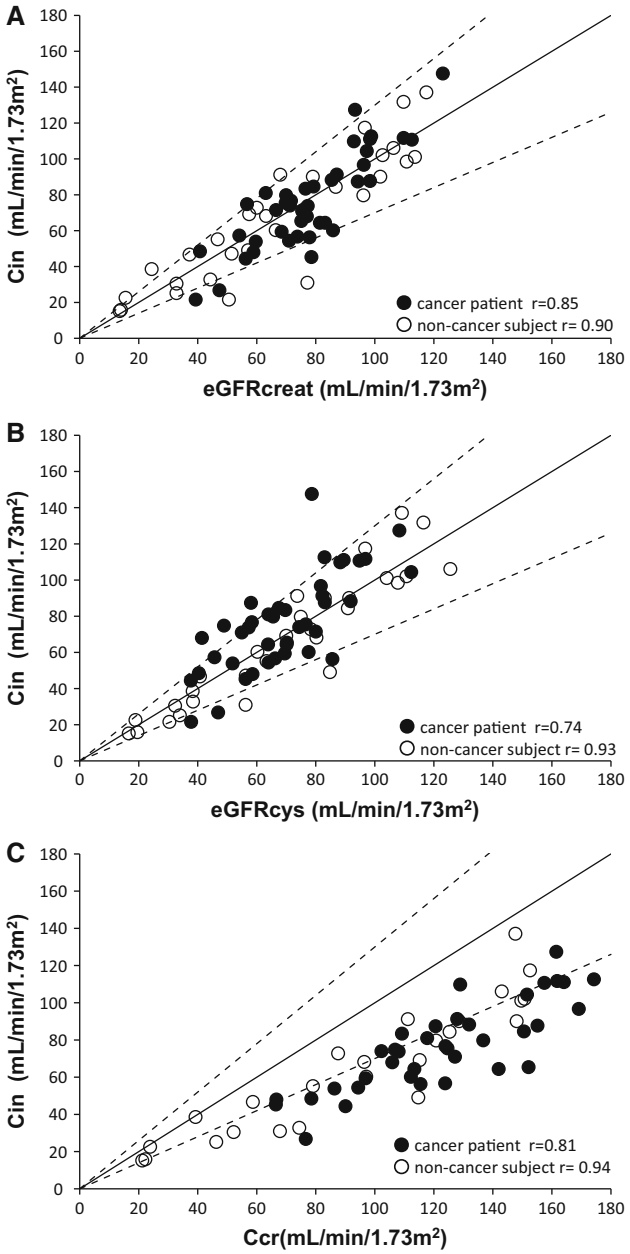

Fig. 1 Relationship between Cin and eGFRcreat (**a**), eGFRcys (**b**) and Ccr (**c**). *Solid lines* show the line of identity. *Dashed lines* represent 30 % difference of identity. Patients with cancer were plotted by *closed circle*, non-cancer patients were plotted by *open circle*

Discussion

In this study, we measured GFR by Cin, sCr, and sCys-C among 41 Japanese patients with cancer and 29 non-cancer patients. And we demonstrated that eGFRcys underestimated Cin and that is only cancer was associated with eGFRcys/Cin.

There were several strong points in this study. First, renal function was evaluated by Cin via the same protocol to develop Japanese GFR equations [15]. Second, factors influencing the difference between Cin and eGFR were analyzed among 70 patients with or without cancer in both eGFRcreat and eGFRcys. Third, all patients with cancer were included in this study, whose GFR values were measured by Cin for drug dosing studies analyses using carboplatin or S-1 [13, 14]. And all patients without cancer and with GFR $\geq$15 mL/min/1.73 m^2 by Cin measurement using the same protocol were eligible as non-cancer patients.

Table 2 Slopes of the regression lines of eGFRcreat and eGFRcys in cancer and non-cancer patients

	Cancer ($N = 41$)	Non-cancer ($N = 29$)
Slope (95 % CI)		
eGFRcreat	0.99 (0.93−1.05)	1.00 (0.92−1.08)
eGFRcys	1.10 (1.02−1.17)	0.98 (0.91−1.04)

Data of slope were slopes of the regression lines with zero intercepts (95 % CI)

eGFRcreat estimated GFR based on serum creatinine, *eGFRcys* estimated GFR based on serum Cystatin C

Our results were consistent with the previous study. Funakoshi Y and colleagues measured Cin in 45 Japanese patients with cancer and with eGFR $\geq$50 mL/min/1.73 m^2. Cin values were compared with eGFRcreat by the Japanese GFR equation, Cockcroft-Gault Formula (CGF), 24 h-Ccr, modification of diet in renal disease (MDRD) equation and CKD-EPI equations, and it was demonstrated that eGFRcreat correlated most accurately with Cin [16]. However, the previous study did not analyze in sCys-C nor associating factors. In the present study, eGFRcreat and eGFRcys were analyzed in slope with Cin in comparison to non-cancer patients, and significant associations were demonstrated between BMI, albumin or urinary creatinine excretion and eGFRcreat/Cin, and between cancer and eGFRcys/Cin. These results were in substantial agreement with many other studies [5–7, 15, 17]. Moreover, there was no limitation on eGFR in this study, so 3 patients (7.3 %) with eGFR <50 mL/min/1.73 m^2 and 6 patients (14.6 %) with Cin <50 mL/min/1.73 m^2 were included. In Funakoshi's paper, Cin was measured among patients with cancer who were scheduled to receive cisplatin. Patients with low GFR were not eligible due to nephrotoxicity of cisplatin. Our study was the first study to analyze GFR equations in comparison to Cin among Japanese patients with cancer and with GFR <50 mL/min/1.73 m^2. However, the number of patients was insufficient to validate GFR equations, and no patient in CKD G5 categories was included. Therefore, 8 patients whose GFR values were <15 mL/min/1.73 m^2 were excluded from non-cancer patients in the present study. The accuracy of GFR equations among patients with cancer and low GFR should be

Table 3 Simple and multiple regression analyses of factors affecting eGFRcreat/Cin

	Single regression		Multiple regression	
	β	P	β	P
BMI (kg^2/m)	−0.26	0.03*	−0.03	0.01*
Albumin (g/dL)	−0.24	0.04*	−0.12	0.06
Cancer	0.03	0.80	−0.09	0.30
Ucre (mg/day/kg body weight)	−0.41	<0.01*	−0.04	<0.01*
Gender	−0.09	0.45	0.15	0.09

eGFRcreat estimated GFR based on serum creatinine, *Cin* inulin clearance, β standardized regression coefficient, *BMI* body mass index, *Ucre* urinary creatinine excretion

* $P < 0.05$

Table 4 Simple and multiple regression analyses of factors affecting eGFRcys/Cin

	Single regression		Multiple regression	
	β	P	β	P
BMI (kg^2/m)	−0.08	0.50	−0.02	0.08
Albumin (g/dL)	0.03	0.82	<0.01	1.00
Cancer	−0.23	0.05	−0.30	0.02*
Ucre (mg/day/kg body weight)	−0.22	0.06	−0.21	0.12
Gender	−0.13	0.29	0.04	0.72

eGFRcys estimated GFR based on serum Cystatin C, *Cin* inulin clearance, β standardized regression coefficient, *BMI* body mass index, *Ucre* urinary creatinine excretion

* $P < 0.05$

analyzed in another study with a large sample size including various GFR categories.

In the present study, eGFRcys underestimated Cin among patients with cancer, and cancer was the only significant factor to affect eGFRcys/Cin in multivariate analysis, suggesting elevation of sCys-C value due to cancer. A similar result was reported in the paper by Nakai K et al [18], which concluded that sCys-C was not a reliable marker of GFR in patients with cancer, probably in relation to its nature as a cystein protease inhibitor. In that study, 82 patients with cancer were evaluated for renal function by 24 h-Ccr and reciprocal sCys-C, namely 1/sCys-C. The correlation coefficient between 24 h-Ccr and 1/sCys-C was significantly lower in patients with cancer than in 206 patients with various degree of renal function, which suggested elevation of sCys-C value in patients with cancer. Several lines of evidences demonstrated that sCys-C level was elevated in patients with cancer [9, 10, 19, 20], however, the mechanism and degree of sCys-C elevation in association with cancer were not evident. Further study is required on sCys-C and cancer. On the contrary, Chew-Harris JS and colleagues reported better accuracy in sCr and sCys-C-based CKD-EPI equation among non-cancer patients [11]. In their paper, between estimated Ccr by CGF and CKD-EPI equation based on sCr and sCys-C significant difference was observed; however, superiority among CKD-EPI equations based on sCr, sCys-C, or combination of sCr and sCys-C was not evident. Ccr theoretically is higher than GFR, which was reconfirmed in our study. Although adjustment formula for Ccr to GFR was reported [15], bias between Ccr and GFR varied in each patient. More accurate evaluation of GFR like Cin should be considered in patients for drug dosing of carboplatin [8].

Overestimation in eGFRcreat due to decreased body muscle mass volume in patients with cancer was not shown in this study. There were significant differences in age, body weight, BMI, sCr, and albumin among the patients, but Cin and urinary creatinine excretion were similar between cancer patients and non-cancer patients, suggesting preserved body muscle mass volume even in patients with cancer. Since study subjects were patients with cancer who were scheduled to receive carboplatin or S-1 chemotherapy, patients with malnutrition might not be included in this study. The accuracy of eGFRcreat in extremely low body muscle mass volume should be analyzed in another study, but clinical significance of Cin measurement in such cases with poor prognosis is doubtful. In the present study, all patients with cancer whose GFR values were measured for drug dosing studies of carboplatin or S-1 were included; therefore, our result would be more practical in clinical practice.

Study subjects in our study did not include seminoma or ovarian cancer. Carboplatin is effective in the adjuvant treatment of Stage I seminoma. Cathomas R and colleagues reported that all MDRD, CGF and sCr-based CKD-EPI

underestimated measured GFR with a radioisotope [(51)Cr EDTA or (99 m)Tc DTPA] in patients with seminoma [21]. Since patients with seminoma are relatively young and have better GFR compared to patients with other types of cancer, so the accuracy of GFR equations may be different from the present study. However, patients with seminoma requiring Cin measurement for carboplatin dosing are rare in Nagoya University Hospital and none was included in this study. And since Cin has been measured by a simple method [22] at our hospital since 2010. It is impossible to study further cases using the same protocol using standard Cin method. Renal function evaluation among Japanese patients with seminoma will be analyzed in another multicenter study.

There were several limitations in this study. First, the number of subjects was not large. But the study sample size was similar to previous Japanese report [16] and our objective was mainly in sCys-C and eGFRcys. Second, sampling bias cannot be denied. However, patients with and without cancer had Cin measured by the same protocol except 8 patients with GFR <15 mL/min/1.73 m^2 in patients without cancer. Third, drug clearance was not analyzed. Our group had already reported on drug dosing and eGFRcreat or Ccr in carboplatin [13] and in S-1 [14]. Many other factors influencing drug clearance in addition to GFR. The accuracy of GFR equations and methods to adjust drug dosing should be separately analyzed.

In conclusion, eGFRcys underestimated Cin among patients with cancer who were scheduled for carboplatin or S-1 administration, and cancer was a significant factor to influence eGFRcys/Cin, suggesting sCys-C elevation due to cancer. For renal function evaluation among patients with cancer, eGFRcys should not be used, because it underestimates GFR.

Acknowledgments This study was supported in part by JSPS KAKENHI, Research Grant form Aichi Jinzou Zaidan and Research Grant-in-Aid for Intractable Renal Diseases Research, Research on rare and intractable diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest AY received speaker honoraria from TAIHO Phamaceutical Co., Ltd., Japan.

References

1. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol. 1989;7:1748–56.
2. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, Goodlow JL, Tan S, Wiltshaw E. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol. 1992;10:520–8.
3. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol. 2009;20:2305–13.
4. Itoh Y, Hosogaya S, Ichihara K, et al. Standardization of serum cystatin C immunoassay using calibrator of each assay system, in which assigned values are transerred from ERM-DA471/IFCC. Rinshokagaku. 2012;41:62–71.
5. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20–9.
6. Horio M, Imai E, Yasuda Y, Watanabe T. Matsuo S; Collaborators Developing the Japanese Equation for Estimated GFR. GFR estimation using standardized serum cystatin C in Japan. Am J Kidney Dis. 2013;61:197–203.
7. Grubb A, Horio M, Hansson LO, Björk J, Nyman U, Flodin M, Larsson A, Bökenkamp A, Yasuda Y, Blufpand H, Lindström V, Zegers I, Althaus H, Blirup-Jensen S, Itoh Y, Sjöström P, Nordin G, Christensson A, Klima H, Sunde K, Hjort-Christensen P, Armbruster D, Ferrero C. Generation of a new cystatin C-based estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. Clin Chem. 2014;60:974–86.
8. Matzke GR, Aronoff GR, Atkinson AJ Jr, Bennett WM, Decker BS, Eckardt KU, Golper T, Grabe DW, Kasiske B, Keller F, Kielstein JT, Mehta R, Mueller BA, Pasko DA, Schaefer F, Sica DA, Inker LA, Umans JG, Murray P. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2011;80:1122–37.
9. Kos J, Stabuc B, Schweiger A, Krasovec M, Cimerman N, Kopitar-Jerala N, Vrhovec I. Cathepsins B, H, and L and their inhibitors stefin A and cystatin C in sera of melanoma patients. Clin Cancer Res. 1997;3:1815–22.
10. Kos J, Nielsen HJ, Krašovec M, Christensen IJ, Cimerman N, Stephens RW, Brunner N. Prognostic values of cathepsin B and carcinoembryonic antigen in sera of patients with colorectal cancer. Clin Cancer Res. 1998;4:1511–6.
11. Chew-Harris JS, Florkowski CM, George PM, Endre ZH. Comparative performances of the new chronic kidney disease epidemiology equations incorporating cystatin C for use in cancer patients. Asia Pac J Clin Oncol. 2014. doi:10.1111/ajco.12312.
12. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Performance of GFR equations in Japanese subjects. Clin Exp Nephrol. 2013;17:352–8.
13. Shimokata T, Ando Y, Yasuda Y, Hamada A, Kawada K, Saito H, Matsuo S, Kondo M, Imaizumi K, Hasegawa Y. Prospective evaluation of pharmacokinetically guided dosing of carboplatin in Japanese patients with cancer. Cancer Sci. 2010;101:2601–5.
14. Ando Y, Kawada K, Inada M, Morita S, Mitsuma A, Yasuda Y, Hiramatsu M, Fujimoto Y, Fujita K. Pharmacokinetic study of S-1 in patients in whom inulin clearance was measured. Oncology. 2012;83:38–44.
15. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
16. Funakoshi Y, Fujiwara Y, Kiyota N, Mukohara T, Shimada T, Toyoda M, Imamura Y, Chayahara N, Umezu M, Otsuki N, Nibu K, Minami H. Prediction of glomerular filtration rate in cancer patients by an equation for Japanese estimated glomerular filtration rate. Jpn J Clin Oncol. 2013;43:271–7.
17. Horio M, Imai E, Yasuda Y, Watanabe T, Yokoyama H, Makino H, Matsuo S. Serum albumin, but not glycated albumin was a

potent factor affecting the performance of GFR equation based on serum creatinine. Clin Exp Nephrol. 2015;19:284–92.
18. Nakai K, Kikuchi M, Fujimoto K, Kaneko Y, Omori S, Nakai K, Suwabe A. Serum levels of cystatin C in patients with malignancy. Clin Exp Nephrol. 2008;12:132–9.
19. Demirtaş S, Akan O, Can M, Elmali E, Akan H. Cystatin C can be affected by nonrenal factors: a preliminary study on leukemia. Clin Biochem. 2006;39:115–8.
20. Yano M, Hirai K, Naito Z, Yokoyama M, Ishiwata T, Shiraki Y, Inokuchi M, Asano G. Expression of cathepsin B and cystatin C in human breast cancer. Surg Today. 2001;31:385–9.
21. Cathomas R, Klingbiel D, Geldart TR, Mead GM, Ellis S, Wheater M, Simmonds P, Nagaraj N, von Moos R, Fehr M. Relevant risk of carboplatin underdosing in cancer patients with normal renal function using estimated GFR: lessons from a stage I seminoma cohort. Ann Oncol. 2014;25:1591–7.
22. Horio M, Imai E, Yasuda Y, Hishida A. Matsuo S; Japanese equation for estimating GFR. Simple sampling strategy for measuring inulin renal clearance. Clin Exp Nephrol. 2009;13:50–4.