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ORIGINAL ARTICLE

Is the eGFR formula adequate for evaluating renal function before chemotherapy in patients with urogenital cancer? A suggestion for clinical application of eGFR formula

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Abstract
Background Accurate evaluation of renal function is required before cancer chemotherapy. Various kinds of formula have been developed for estimating creatinine clearance (Ccr) or glomerular filtration rate (GFR) conveniently. We retrospectively examined the reliability of the GFR estimating formula using the renal function data in cancer chemotherapy.
Methods Clinical data of 12 patients with urogenital cancer from 1998 to 2013 in Saga University Hospital were reviewed. Patients were treated with 6–21 (median 10.5) courses of chemotherapy and those patients underwent 9–29 (median 14.5) times of 24hrCcr tests before and during chemotherapy. We compared estimated GFR (eGFR) with 24hrCcr. In addition, we developed a novel method to estimate the Ccr using the patient-inherent 24hrCcr/eGFR ratio, which is calculated from initial 3 or 4 determinations of 24hrCcr and the corresponding eGFR. Those estimated Ccrs were also compared with 24hrCcr.
Results The dissociation between 24hrCcr and eGFR was not constant, and a large dissociation was observed in some cases. The newly devised estimated Ccr demonstrated less dissociation from 24hrCcr compared with eGFR.
Conclusions The eGFR formula is not adequate for the clinical use in cancer chemotherapy. The absolute value of eGFR is not reliable, but clinical use of eGFR as relative value seems to be acceptable. To avoid troublesome 24hrCcr measurement in long-term cancer chemotherapy, eGFR formula can be used for estimating Ccr in combination with the specific inherent 24hrCcr/eGFR ratio, which is obtained from 3 or 4 times of actual 24hrCcr measurements.

Keywords Creatinine clearance · eGFR formula · Renal function · Cancer chemotherapy

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Introduction

Recently, cancer chemotherapy for elderly patients or patients with impaired renal function is not uncommon. Especially, in the field of urologic oncology, there are many cases with solitary kidney or impaired renal function due to the obstructive lesions in their urinary tract. In such situations, accurate evaluation of renal function is required before chemotherapy with nephrotoxic anticancer agents [1, 2]. In the dose setting of chemotherapeutic agents, glomerular filtration rate (GFR) is the most significant factor among the several renal function tests. Inulin clearance test is the gold standard for GFR measurement, but it is not practical when considering the cost performance and technical complexity. Endogenous creatinine clearance (Ccr) test is, in general, applied for estimating GFR, but it has some disadvantages, such as troublesome procedures in urine collection for 24 h and measured values of Ccr often fluctuate with wide range.

Since Cockcroft and Gault [3] previously proposed the formula to estimate the Ccr from serum creatinine, age, body weight and gender in 1976, a lot of attempts have been made for the purpose of estimating GFR conveniently. Based on the renal function data in Modification of Diet in Renal Disease (MDRD) study, Levey et al. [4] devised the original MDRD eGFR formula in 1999, in

Table 1 Background of 12 patients who underwent multiple creatinine clearance tests during cancer chemotherapy

Case	Age	Sex	Diagnosis	Body weight (kg)	Body surface area (m^2)	Chemotherapy regimen	No of chemo. courses	No of Ccr tests
1	33	Male	T	69.4	1.81	BEP 3x + EP 1x + VIP 4x	8	13
2	31	Male	T	60.2	1.71	BEP 1x + EP 3x + VIP 2x	6	13
3	24	Male	T	57.4	1.73	PEP 3x + VIP 1x + cisRTx 2x + VIP 3x	8	29
4	47	Male	T	55.0	1.56	BEP 4x + VIP 3x	7	10
5	22	Male	T	51.0	1.58	MVAC 4x + GC 2x	11	14
6	69	Male	U	45.9	1.43	MVAC 4x + GC 6x	6	15
7	65	Male	U	44.1	1.40	GC 10x + MVAC 2x	10	9
8	57	Female	U	48.1	1.42	GC 11x + MVAC 4x + PIN 6x	12	13
9	68	Male	U	80.1	1.89	MVAC 2x + GCa 6x + MVACa 8x	21	21
10	71	Female	U	46.1	1.33	GC 5x + GCa 14x + MVACa 2x	16	18
11	76	Male	U	59.7	1.63	GC 5x + GCa 14x + MVACa 2x	21	21
12	67	Female	U	57.7	1.53	GC 3x + GCa 8x	11	18

T testicular cancer, *U* urothelial cancer, *BEP* bleomycin + etoposide + cisplatin, *EP* etoposide + cisplatin, VIP etoposide + ifosfamide + cisplatin, *CisRT*× cisplatin with radiation, *TIP* paclitaxel + ifosfamide + cisplatin, *MVAC* methotrexate + vinblastine + adriamycin + cisplatin, *GC* gemcitabine + cisplatin, *PIN* paclitaxel + ifosfamide + nedaplatin, *GCa* gemcitabine + carboplatin, *MVACa* methotrexate + vinblastine + adriamycin + carboplatin

which eGFR was calculated from serum creatinine, serum albumin, blood urea nitrogen, age, gender, and ethnicity. One year later, they proposed a simplified version of the original MDRD equation utilizing serum creatinine, age, gender, and ethnicity [5]. Also in Japan, Japanese Society of Nephrology proposed the modified version of MDRD eGFR formula for Japanese patients [6]. The eGFR formula has been widely recognized as a convenient tool to assess the renal function in clinical fields. However, the MDRD eGFR formula is originally devised for the use of epidemiological studies as a tool to estimate the renal function of the targeted group consisting from large numbers of patients. The MDRD eGFR formula is not the equation for evaluating the renal function of the individual patient with different background in his/her kidney.

To assess the reliability of the eGFR formula for estimating renal function, we retrospectively examined the renal function data in the patients treated with cancer chemotherapy for urogenital malignancies.

Patients and methods

Clinical data of 12 cases with testicular cancer or urothelial cancer between August 1998 and March 2013 in Urology Department, Saga University Hospital were reviewed in the present retrospective study. Patients were treated with platinum-based cancer chemotherapy and those patients underwent multiple 24 h creatinine clearance (24hrCcr) tests before and after each chemotherapy course. Table 1 showed the characteristics of 12 patients. Five males received chemotherapy for their testicular cancer. Four males and 3 females underwent chemotherapy for their urothelial cancer. Various kinds of combination chemotherapy containing cisplatin or its derivatives were carried out for those patients. They were treated with 6–21 (median 10.5) courses of chemotherapy and they received 9–29 (median 14.5) times of 24hrCcr tests during chemotherapy.

In 24hrCcr test, urine samples were collected for 24 h, thereafter 24hrCcr was calculated from serum creatinine, urinary creatinine and urine volume for 24 h. The eGFR was calculated from serum creatinine, age and gender by the Japanese version MDRD eGFR formula ("Appendix" 1). For the data presentation and analysis, reversely corrected eGFR values by body surface area of each patient were utilized, because eGFR formula gives the corrected eGFR to 1.73 m^2 body surface area.

In the present study, we devised a novel method to estimate Ccr using the patient-inherent 24hrCcr/eGFR ratio, which was calculated from the initial 3 or 4 sets of measured 24hrCcr and the corresponding eGFR. The estimated Ccr (eCcr) was calculated from eGFR and the inherent 24hrCcr/eGFR ratio of each case ("Appendix" 2). Measured 24hrCcr, estimated GFR by Japanese version MDRD eGFR equation and the newly introduced eCcr were compared.

Our present study has been approved by IRB/Ethics Committee, Saga University Hospital (approval number 2014-05-10).

Results

Figure 1 demonstrates the changes in measured 24hrCcr and eGFR of 12 cases. Generally, young male patients with

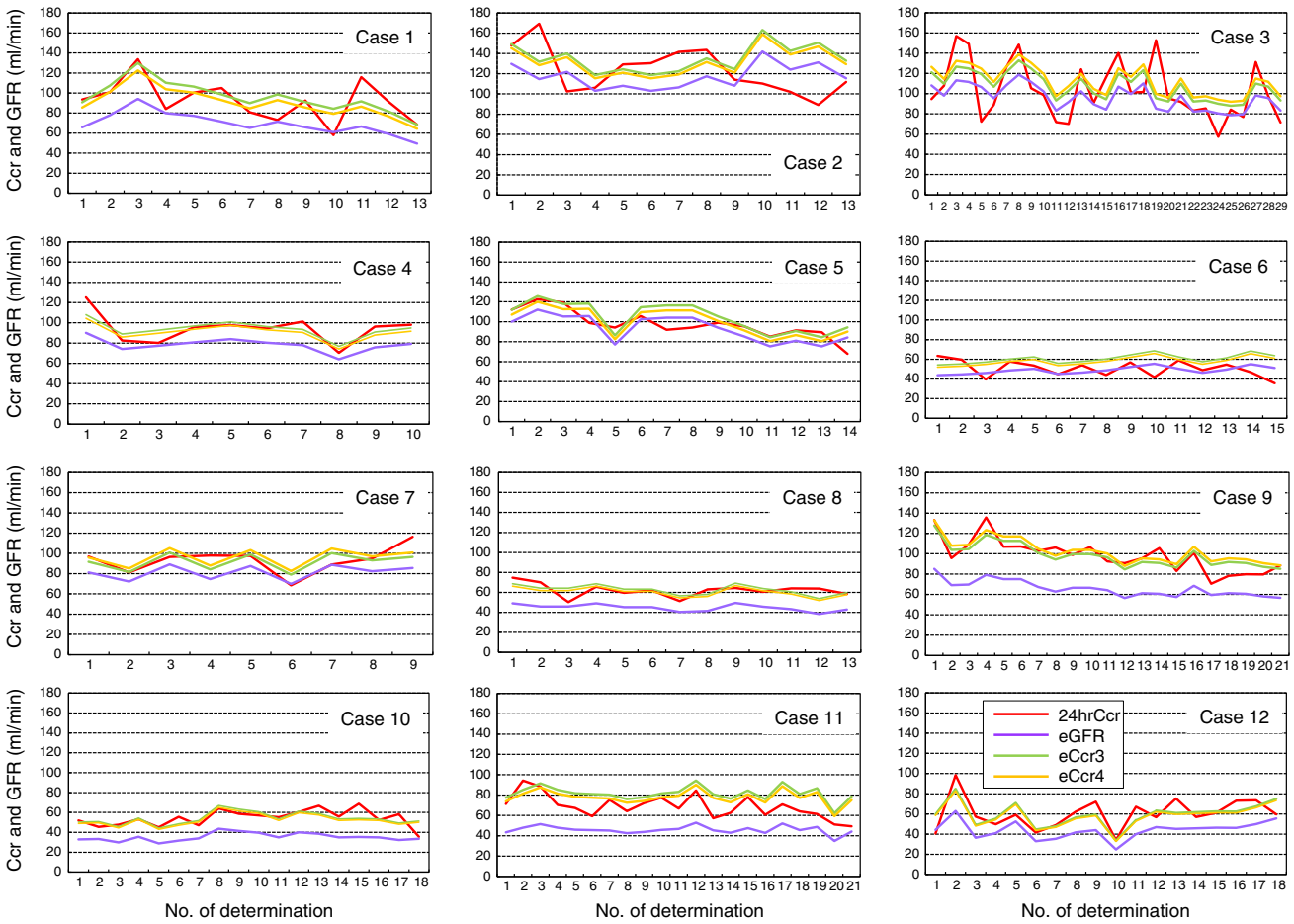


Fig. 1 Changes in Ccr and eGFR of 12 cases. *24hrCcr* measured Ccr using urine samples collected for 24 h. *eGFR* estimated GFR calculated by the Japanese version MDRD eGFR formula. *eCcr3* estimated Ccr calculated from eGFR and 24hrCcr/eGFR ratio obtained from the initial 3 determinations. *eCcr4* estimated Ccr calculated from eGFR and 24hrCcr/eGFR ratio obtained from the initial 4 determinations

well-functioning kidneys showed wide range fluctuation in their 24hrCcr (case 1, 2 and 3). On the other hand, 24hrCcr was low but stable in elderly patients with relatively small physical constitution and impaired renal function (case 6, 8 and 10). Measured 24hrCcr was greater than eGFR at each determination in all cases except cases 3, 5, and 6, in which eGFR was well associated with measured 24hrCcr.

Table 2 indicates the mean values of serum creatinine, 24hrCcr, eGFR and 24hrCcr/eGFR ratio of 12 cases. The 24hrCcr/eGFR ratio was calculated from the data of 9 (case 7) to 29 (case 3) times of 24hrCcr tests and the corresponding eGFR. The minimum value of 24hrCcr/eGFR ratio was 1.05 ± 0.03 (case 5) and 1.05 ± 0.05 (case 6). The maximum value was 1.54 ± 0.05 (case 10). The 24hrCcr/eGFR ratio was distributed between approximately 1.0 and 1.5 with relatively narrow range.

Mean 24hrCcr/eGFR ratio calculated from the initial 3 pairs or 4 pairs of 24hrCcr tests and the corresponding eGFR are also indicated in Table 2. The dissociation in the 24hrCcr/eGFR ratio between total determinations and the initial 3 or 4 determinations was greater than 10 % in cases 6 and 11. In case 6, mean 24hrCcr/eGFR ratio calculated from 15 determinations, the initial 3 determinations, and the initial 4 determinations were, respectively, 1.05, 1.22 (116.2 %), and 1.21 (115.2 %). Similarly in case 11, mean 24hrCcr/eGFR ratio calculated from 21 determinations, the initial 3 determinations, and the initial 4 determinations were, respectively, 1.50, 1.78 (118.7 %), and 1.70 (113.3 %). Large difference in mean 24hrCcr/eGFR ratio was not observed between mean value obtained from all determinations and mean value from the initial 3 or 4 determinations in each case.

Figure 2 indicates the correlation of 24hrCcr/eGFR ratio with serum creatinine. The 24hrCcr/eGFR ratio increased higher according to an increase of serum creatinine level with significant correlation ($P = 0.038$).

Our data presented in Table 2 and Fig. 2 suggest that the individual fluctuation of 24hrCcr/eGFR ratio itself was not

Table 2 Serum creatinine, 24hrCcr, eGFR and 24hrCcr/eGFR ratio of 12 cases

Case	*n*	sCr (mg/dl)	24hrCcr (ml/min)	eGFR (ml/min)	24hrCcr/eGFR ratio		
					Total tests	Initial 3 tests (%)	Initial 4 tests (%)
1	13	1.08 ± 0.04	92.1 ± 5.6	69.6 ± 3.1	1.33 ± 0.06	1.38 ± 0.04 (103.8)	1.30 ± 0.09 (97.7)
2	13	0.64 ± 0.02	122.9 ± 6.3	117.3 ± 3.3	1.06 ± 0.07	1.15 ± 0.18 (108.5)	1.12 ± 0.13 (105.7)
3	29	0.81 ± 0.02	103.1 ± 5.1	96.1 ± 2.2	1.07 ± 0.04	1.12 ± 0.15 (104.7)	1.17 ± 0.12 (109.3)
4	10	0.76 ± 0.02	94.2 ± 4.6	78.4 ± 2.1	1.20 ± 0.03	1.18 ± 0.11 (98.3)	1.18 ± 0.08 (98.3)
5	14	0.79 ± 0.03	97.7 ± 3.8	93.3 ± 3.5	1.05 ± 0.03	1.12 ± 0.01 (106.7)	1.07 ± 0.05 (101.9)
6	15	0.98 ± 0.02	50.7 ± 2.1	48.9 ± 0.9	1.05 ± 0.05	1.22 ± 0.18 (116.2)	1.21 ± 0.13 (115.2)
7	9	0.61 ± 0.02	93.2 ± 4.4	81.2 ± 2.5	1.15 ± 0.04	1.13 ± 0.03 (98.3)	1.18 ± 0.05 (102.6)
8	13	0.84 ± 0.02	62.1 ± 1.8	44.7 ± 1.0	1.39 ± 0.04	1.38 ± 0.14 (99.3)	1.37 ± 0.10 (98.6)
9	21	0.97 ± 0.02	98.5 ± 3.6	65.8 ± 1.7	1.49 ± 0.03	1.50 ± 0.06 (100.7)	1.56 ± 0.07 (104.7)
10	18	0.93 ± 0.02	54.3 ± 2.0	35.3 ± 0.9	1.54 ± 0.05	1.51 ± 0.07 (98.1)	1.51 ± 0.05 (98.1)
11	21	1.14 ± 0.02	68.9 ± 2.5	45.9 ± 0.9	1.50 ± 0.04	1.78 ± 0.10 (118.7)	1.70 ± 0.10 (113.3)
12	18	0.90 ± 0.04	60.5 ± 3.6	44.0 ± 2.0	1.38 ± 0.05	1.35 ± 0.22 (97.8)	1.32 ± 0.16 (95.7)

Data were presented as mean ± SE

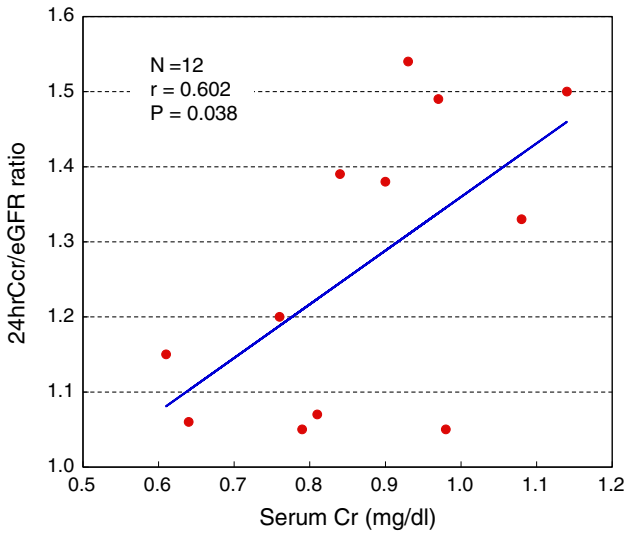


Fig. 2 Correlation of 24hrCcr/eGFR ratio with serum creatinine

so large and each patient has his/her inherent 24hrCcr/eGFR ratio correlating with their renal function. In addition, those case-inherent 24hrCcr/eGFR ratios can be estimated from 3 or 4 actual measurements of 24hrCcr and the corresponding eGFR.

As described in patients and methods, we devised a novel method to estimate Ccr using the patient-inherent 24hrCcr/eGFR ratio ("Appendix" 2). The estimated Ccr value calculated from eGFR and case-inherent 24hrCcr/eGFR ratio is also plotted in Fig. 1. In this figure, eCcr3 and eCcr4 represent estimated Ccr calculated from eGFR and 24hrCcr/eGFR ratio obtained from the initial 3 and 4 sets of determinations, respectively. The curves of eCcr3 and eCcr4 fitted well with 24hrCcr curve in each case, although 24hrCcr curve itself fluctuated.

Association of the estimated values of eGFR, eCcr3 and eCcr4 with measured 24hrCcr value was statistically evaluated. Figure 3 shows the differences in Ccr or GFR values between 24hrCcr test and various estimation tools. D-eGFR, D-eCcr3 and D-eCcr4 represent the average differences in Ccr or GFR values from 24hrCcr to eGFR, eCcr3 and eCcr4, respectively. There was no statistical difference among D-eGFR, D-eCcr3, and D-eCcr4 in cases 1, 2, 3, 5, 6 and 7. However, D-eGFR was statistically greater than D-eCcr3 and D-eCcr4 in other 6 cases. There was no statistical difference between D-eCcr3 and D-eCcr4 in all cases.

Discussion

The eGFR formula was devised as a simple and convenient tool for evaluating the renal function in the field of epidemiologic study dealing with large population. In the clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012 [7], the following description is accomplished as the instructions for using eGFR. (1) The eGFR is not a tool for evaluating the renal function of the individual patient. Inulin clearance test is recommended for the accurate evaluation of GFR. However, in general, endogenous 24hrCcr test is often used for estimating GFR because inulin clearance test is cumbersome and complicated in the ordinary clinical setting. (2) The eGFR formula is a simple equation with accuracy to the extent that the estimated value is within the range of measured GFR ±30 % in 75 % of cases. (3) The eGFR equation gives the

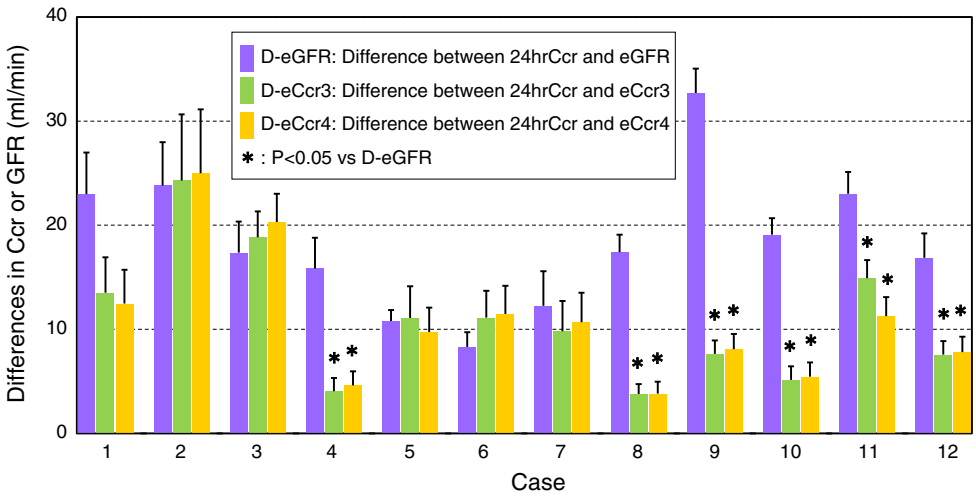


Fig. 3 Differences in Ccr and GFR between 24hrCcr test and various estimation tools in each case. D-eGFR, D-eCcr3 and D-eCcr4 represent the average differences in Ccr and GFR from 24hrCcr to GFR, eCcr3 and eCcr4, respectively. Statistical difference was analyzed by Student's *t* test

corrected GFR (ml/min/1.73 m^2) by assuming that the patient has standard body surface area with 1.73 m^2 (63 kg body weight and 170 cm height). For the setting of the drug dose, reverse correction of eGFR by the body surface area is necessary because drug dose is defined by individual body size of each patient. In addition to the above instructions, we should pay attention to the following drawbacks of the eGFR formula. The eGFR is calculated based on the assumption that the damage of each individual kidney is in the average aging state, which was estimated from large population. The eGFR formula is not intended to be made to estimate the renal function of the individual patient with different background in his/her kidney.

Considering the several drawbacks of eGFR formula, evaluating the individual renal function by the eGFR formula is not recommended in routine clinical works. The eGFR formula may be useful for renal function screening, but the eGFR formula is not an accurate equation for evaluating renal function of the individual patient, especially for the elderly patients with various comorbidity and sometimes critical problems in their urinary tract. It is unconceivable that accurate GFR can be automatically obtained only by applying serum creatinine, age and gender into one simple formula.

There are several reports [8–11] evaluating the accuracy of various estimating formulas to assess the renal function in cancer patients. It is the common conclusion in these reports that there is no adequate equation to estimate renal function accurately and the measurement by 24hrCcr method may be necessary to evaluate renal function properly. Raj RV et al. [12] retrospectively assessed the efficacy of 12 formulas, which calculate Ccr or GFR, utilizing the database of 208 patients who underwent cisplatin-based chemotherapy. They demonstrated that current formulas estimating Ccr or GFR by mathematic calculations tend to underestimate measured Ccr, especially in elderly patients over 65 years. They also described that Ccr calculating formula is not adequate and it would be reasonable to return 12- or 24-hrCcr measurement as a methodology for determining renal eligibility before cancer chemotherapy.

Recently, GFR estimating formula using cystatin C has been introduced [7, "Appendix" 3]. Cystatin C is a low molecule serum protein which is produced steadily by all types of nucleated cells in the body and cleared from the blood by the glomerular filtration. Cystatin C is considered to be a better marker for determining GFR than creatinine, because serum levels of cystatin C are independent of body weight, muscle volume, age and sex. However, the accuracy of eGFR formula using serum creatinine and eGFR formula using serum cystatin C is reported to be comparable [7].

GFR can be estimated from the clearance of creatinine or inulin. Inulin is freely filtered into urine through glomerulus without reabsorption or secretion by renal tubules. Therefore, inulin clearance is GFR itself. On the other hand, creatinine is partly secreted into urine through renal tubules in addition to the glomerular filtration. That is why Ccr shows greater value than true GFR. Tubular secretion of creatinine relatively increases in accordance with the decrease of GFR; therefore, the dissociation of Ccr and GFR becomes larger with the decrease of renal function. It was reported that endogenous 24hrCcr test showed 30 % lager value than actual GFR value in the clinical study to develop the Japanese version eGFR formula [7]. However, in that clinical study, renal function tests including 24hrCcr tests and inulin clearance tests were mainly conducted in the patients with relatively poor renal function.

The dissociation of true GFR value and Ccr is not still evaluated enough in the patient with well-functioning kidney.

Usually, 24hrCcr is higher than eGFR since creatinine is secreted from renal tubules. However, 24hrCcr is occasionally lower than eGFR (in cases 2, 3, 5, 6). It is difficult to show clear reasons to explain these events. In cases 2, 3 and 5, the inadequate setting of the age factor in eGFR equation ($Age^{-0.287}$) could be related to an overestimation of GFR for young adult when considering that these phenomena were observed in young adult with the age 31, 24, and 22 years old, respectively.

In our present study, we devised a novel method to estimate Ccr using the patient-inherent 24hrCcr/eGFR ratio. To find patient-inherent 24hrCcr/eGFR ratio, we proposed to utilize the initial 3 or 4 sets of measured 24hrCcr and the corresponding eGFR. We supposed that one pair or two pairs of 24hrCcr and the corresponding eGFR were not enough to estimate inherent 24hrCcr/eGFR ratio because of the physiological fluctuation of 24hrCcr values. However, 5 or more times of 24hrCcr tests are not practical in routine clinical works. Therefore, we chose 3 or 4 sets of determinations. Fortunately, large dissociation in mean 24hrCcr/eGFR ratio was not observed between mean value from all determinations and mean value from the initial 3 to 4 determinations (Table 2). If the 24hrCcr tests show stable values in the initial 3 determinations, inherent 24hrCcr/eGFR ratio can be obtained from these 3 determinations. In case of fluctuated 24hrCcr, 4 determinations are recommended.

As to the dissociation in the 24hrCcr/eGFR ratio between total determinations and the initial 3 or 4 determinations, greater than 10 % dissociation was observed in cases 6 and 11 (Table 2). It is difficult to speculate the reason why the dissociation was great in these two cases. These two cases were elderly patients (69 and 76 years old) with relatively high serum creatinine levels (0.98 ± 0.02 and 1.14 ± 0.02 mg/dl) among 12 cases in the present study. In the elderly patients with impaired renal function, careful judgment might be required in the calculation of the 24hrCcr/eGFR ratio.

A 24hrCcr test is a basic method for evaluating individual renal function. A 24hrCcr test shows widely fluctuating value, because renal handling of creatinine is physiologically affected by several pre-renal and renal factors, such as intake of meat, muscular exercise, changes in blood pressure, administration of drugs affecting tubular secretion of creatinine. However, the fluctuation of 24hrCcr does not necessarily mean that 24hrCcr is less reliable measurement. As described before, 24hrCcr often shows greater value than true GFR value because of tubular secretion of creatinine. It is well recognized that cisplatin [13] and its derivatives [14, 15] are excreted into urine not only by glomerular filtration but also by tubular secretion in the same manner as creatinine [16]. We believe that estimating the renal function by 24hrCcr test is reasonable in dose setting of platinum-containing anticancer agents in cancer chemotherapy. In the dose setting of anticancer agents, there is no accurate and adequate formula to estimate GFR or Ccr by simple calculation using limited biological factors. At present it would be better to measure 24hrCcr actually, although obtained Ccr value often fluctuates.

In conclusion, the eGFR formula is not adequate for the clinical use in cancer chemotherapy. The absolute value obtained from eGFR formula is not reliable, but clinical use of eGFR as relative value seems to be acceptable. To avoid troublesome 24hrCcr measurement in long-term cancer chemotherapy, eGFR formula can be used for estimating Ccr in combination with the specific inherent 24hrCcr/eGFR ratio which is obtained from 3 or 4 times of actual 24hrCcr measurements.

Conflict of interest The authors have no conflict of interest.

Appendix 1

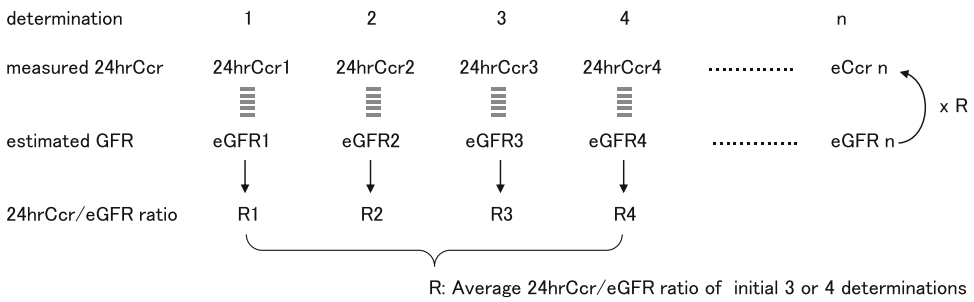
Japanese version MDRD eGFR formula

$$eGFR\ (ml/min/1.73m^2) = 194 \times sCr\ (mg/dl)^{-1.094} \times Age\ (year)^{-0.287} \quad (\text{if Female} \times 0.739)$$

Appendix 2

eCcr formula to calculate Ccr from eGFR and 24hrCcr/eGFR ratio

$$eCcr = eGFR \times R\ (24hrCcr/eGFR\ ratio)$$



Appendix 3

eGFR formula using cystatin C (Cys)

$$eGFRcys\ (ml/min/1.73m^2) = (104 \times sCys\ (mg/dl)^{-1.019} \times 0.996^{Age\ (year)}) - 8 \quad \text{for Male}$$

$$eGFRcys\ (ml/min/1.73m^2) = (104 \times sCys\ (mg/dl)^{-1.019} \times 0.996^{Age\ (year)} \times 0.929) - 8 \quad \text{for Female}$$

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