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REVIEW

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# Accurate measurement of individual glomerular filtration rate in cancer patients: an ongoing challenge

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**Abstract** A narrow therapeutic index is a characteristic feature of cytotoxic agents. Some of these agents are almost entirely eliminated renally in unchanged active form. As a consequence, assessment of the individual glomerular filtration rate (GFR) may help to predict the pharmacokinetic behaviour of cytotoxic agents in plasma more precisely. In addition, GFR-adapted individualization of cancer chemotherapy may have an enormous impact on the severity of side effects. Several methods are available to determine GFR or creatinine clearance (CrCl). GFR-measurement based on experimental methods with radiolabelled isotopes, contrast media or inulin helps to reflect the real situation very closely. In addition, 24-h urine collection is a convenient and feasible method to measure creatinine clearance. Finally, several mathematical equations exist to estimate GFR or CrCl based on serum creatinine and other parameters. Only a few of these equations have been developed in oncologic patients. However, some of these equations are routinely used in clinical practice, because they allow a rapid estimation of GFR. Based on the fact that clinically relevant differences have been assessed between calculated values and the real situation, mathematical calculation of GFR or CrCl does not seem to be appropriate to assess individual renal function precisely enough over a broad range of individual GFR or CrCl. Whether the measurement of low-molecular-weight proteins, such as cystatin C and ß-trace protein, may help to reflect the real situation more precisely is a matter of controversial debate.

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## Introduction

An accurate assessment of renal function is important when cancer patients receive cytotoxic chemotherapy, particulary for those agents which are primarily eliminated in unchanged form through the kidney. Well-known examples of such agents are carboplatin (Calvert et al. 1982; Egorin et al. 1984), topotecan (Furman et al. 1996; Stewart et al. 1994), the adenosine deaminase inhibitors (Breithaupt and Kuenzlen 1982; Hersh et al. 1986; Smyth et al. 1980; Wan et al. 1974) and bleomycin (Alberts et al. 1978). Based on the narrow therapeutic index of most cytotoxic agents, dosing solely based on body surface area (BSA) may result in severe side effects or lower response rates than expected. This phenomenon has been thoroughly demonstrated with carboplatin in patients with ovarian carcinoma (Jodrell et al. 1992). In general, the glomerular filtration rate (GFR) is accepted as the best marker to determine renal function in patients most precisely.

## Methods determing GFR or creatinine clearance

Currently, there are several methods available to determine GFR or creatinine clearance (CrCl) in individual patients.

### Radioisotopic markers

A very accurate determination of individual GFR can be obtained by measuring the clearance of the radiolabelled isotopes, such as $^{51}$Cr-EDTA (chromium 51-ethylene diamine tetra-acetic acid) (Chantler et al. 1969) and $^{99}$Tc-DTPA (technetium-99m diethyl triamine penta-acetic

acid) (Fawdry et al. 1985; Rehling et al. 1984). However, $^{51}$Cr-EDTA is not approved in the US and many other countries for human use and due to its radiation exposure, the method is not feasible in children and pregnant women. Furthermore, the method is invasive, expensive and not available in many hospitals.

## Inulin clearance

For many years, inulin has been used as a gold standard to determine GFR, because the diagnostic agent is neither reabsorbed nor tubularly secreted or metabolized by the kidneys. Inulin is a physiologically inert substance which does not alter kidney function. This marker is administered intravenously as an infusion or as a bolus. Plasma and urine sampling at defined time points is necessary, in order to determine inulin clearance precisely, which is one of the major limitations of this method (Gutman et al. 1965). In addition, inulin is poorly soluble in aqueous solutions which makes administration somewhat difficult.

Alternatively, the inulin-like marker sinistrin has been described to be useful (Buclin et al. 1997, 1998). Sinistrin, a polyfructose, is more soluble than inulin which makes administration much more easier. However, one study reported that volunteers receiving sinistrin developed anaphylactic reactions (Chandra and Barron 2002).

## Contrast medium as a marker

A further useful marker for individual GFR assessment is the iodinated contrast agent iohexol (Lewis et al. 1989). There are some disadvantages related to the use of this agent such as the risks of iodine allergies and anaphylaxis which limit the use of iohexol. Finally, iohexol levels in blood and urine have to be determined by high-performance liquid chromatography (HPLC; Frennby and Sterner 2002).

## Serum creatinine as a marker

The use of creatinine as a marker to estimate GFR is based on the assumption that creatinine is primarily eliminated by glomerular filtration and creatinine production and excretion are constant. As a consequence, serum creatinine levels are inversely correlated with GFR. However, creatinine production is influenced by age, gender, muscle mass, physical condition and nutrition. In addition, creatinine excretion depends on active tubular secretion (Perrone et al. 1992). A further disadvantage is the sensitivity of the creatinine assays with substances in the plasma, especially using the Jaffé method. Moreover, serum creatinine may suggest an underlying normal renal function (e.g. 0.6–1.2 mg/dl) in spite of decreasesd GFR levels, in the so-called "creatinine blind range". Therefore, there is no linear relationship between serum creatinine and GFR.

## Creatinine clearance through 24-h urine collection or mathematical equations

In clinical practice, urine collection over 24-h is an established tool to estimate individual CrCl via determination of creatinine. This method requires an accurate collection of urine over 24 h which is however, often accompanied with collection failures. Consequently, it is difficult to get accurate and complete urine collection under very standardized conditions (Millward et al. 1996; Robinson et al. 1990; Tsubaki et al. 1993). Moreover, creatinine clearance overestimates GFR because creatinine is tubularly secreted. Recently, the MDRD formula has been recommended in adults by the DOQI guidelines of the American National Kidney foundation (American National Kidney Foundation 2002). The formula estimates GFR standardized for BSA (up to 90 ml/min/1.73 $m^2$) from three blood parameters and variables as sex, race and age. It has been published by Levey et al. 1999 during their MDRD Study in 1999 based on a non-oncologic population group. Among several formulas equation Nr. 7 (Table 1) was the most accurate. To our knowledge, there is no study which compares the MDRD formula with other formulas in cancer patients.

In additon, there are various published equations estimating CrCl based on serum creatinine levels and other variables. The different formulas are summarized in Table 1. Most equations predict CrCl. To our knowledge, there are four equations estimating GFR from serum creatinine concentrations (Edwards and Whyte 1959; Levey et al. 1999; Martin et al. 1998; Wright et al. 2001). Undoubtedly, the use of such mathematical equations is easily feasible in everyday clinical practice.

The first mathematical equation was described by Edwards and Whyte (1959) to calculate GFR. Further formulas were published in the 1970 s. In 1971, Jelliffe published the first equation, which estimates CrCl (Jelliffe 1971). Both formulas, Edwards and Whyte and Jelliffe, included the parameters sex and serum creatinine. Jelliffe revised the equation in 1973 (Jelliffe-2) by considering age as an additonal parameter (Jelliffe 1973) because of the significant age-related decline in muscle mass. Moreover, in the same period Mawer et al. (1972), Cockcroft and Gault (1976) and Bjornsson (1979) published their equations. They used sex, weight, age and serum creatinine for the prediction of CrCl. In contrast to the Jelliffe-2 formula, the Cockcroft and Gault formula does not consider patient's BSA (Du and Du Bois 1989). In 1981, Hull et al. (1981) and 4 years later, Gates (1985) published equations including only sex, age and serum creatinine, however, their formulas did not appear to be superior to the Jelliffe-2 or Cockcroft and Gault formulas. In 1988, Salazar and Corcoran were

**Table 1** Survey of the mathematical equations

| Author | Original Equation | Units | Reference |
|---|---|---|---|
| Edwards–Whyte | Male: $\mathrm{GFR} = \left(\frac{94.3}{\mathrm{SCr}}\right) - 1.8$<br>Female: $\mathrm{GFR} = \left(\frac{69.9}{\mathrm{SCr}}\right) + 2.2$ | GFR = ml/min<br>SCr = serum creatinine = mg/100 ml = mg/dl | Edwards and Whyte (1959) |
| Jelliffe-1 | Male: $\mathrm{CrCl} = \left(\frac{100}{\mathrm{SCr}}\right) - (12)$<br>Female: $\mathrm{CrCl} = \left(\frac{80}{\mathrm{SCr}}\right) - (7)$ | CrCl = ml/min/1.73 $m^2$<br>SCr = mg/100 ml = mg/dl | Jelliffe (1971) |
| Mawer | Male: $\mathrm{CrCl} = \frac{\{\mathrm{weight} \times [29.3 - (0.203 \times \mathrm{age})] \times [1 - (0.03 \times \mathrm{SCr})]\}}{14.4 \times \mathrm{SCr}}$<br>Female: $\mathrm{CrCl} = \frac{\{\mathrm{weight} \times [25.3 - (0.175 \times \mathrm{age})] \times [1 - (0.03 \times \mathrm{SCr})]\}}{14.4 \times \mathrm{SCr}}$ | CrCl = ml/min<br>Weight = kgAge = years<br>SCr = mg/100 ml = mg/dl | Mawer et al. (1972) |
| Jelliffe-2 | Male: $\mathrm{CrCl} = \frac{\{98 - 0.8 \times (\mathrm{age} - 20)\}}{\mathrm{SCr}}$<br>Female: $\mathrm{CrCl} = \left\{\frac{\{98 - 0.8 \times (\mathrm{age} - 20)\}}{\mathrm{SCr}}\right\} \times 0.90$ | CrCl = ml/min/1.73 $m^2$<br>Age = rounded to the nearest 10 years<br>SCr = mg/100 ml = mg/dl | Jelliffe (1973) |
| Cockcroft–Gault | Male: $\mathrm{CrCl} = \frac{[(140 - \mathrm{age}) \times (\mathrm{weight})]}{72 \times \mathrm{SCr}}$<br>Female: $\mathrm{CrCl} = \frac{[(140 - \mathrm{age}) \times (\mathrm{weight})]}{72 \times \mathrm{SCr}} \times 0.85$ | CrCl = ml/minAge = years<br>Weight = kg<br>SCr = mg/100 ml = mg/dl | Cockcroft and Gault (1976) |
| Bjornsson | Male: $\mathrm{CrCl} = \frac{\{[27 - (0.173 \times \mathrm{age})] \times \mathrm{weight} \times 0.07\}}{\mathrm{SCr}}$<br>Female: $\mathrm{CrCl} = \frac{\{[25 - (0.175 \times \mathrm{age})] \times \mathrm{weight} \times 0.07\}}{\mathrm{SCr}}$ | CrCl = ml/minAge = years<br>Weight = kg<br>SCr = mg/100 ml = mg/dl | Bjornsson (1979) |
| Hull | Male: $\mathrm{CrCl} = \left[\frac{(145 - \mathrm{age})}{\mathrm{SCr}}\right] - (3)$<br>Female: $\mathrm{CrCl} = \left(\frac{(145 - \mathrm{age})}{\mathrm{SCr}} - 3\right) \times 0.85$ | CrCl = ml/min/70 kg<br>Age = years<br>SCr = mg/dl | Hull et al. (1981) |
| Gates | Male: $\mathrm{CrCl} = [\ 89.4 \times (\mathrm{SCr}^{-1.2})\ ] + \{\ (55 - \mathrm{age}) \times [\ 0.447 \times (\mathrm{SCr}^{-1.1})\ ]\ \}$<br>Female: $\mathrm{CrCl} = [\ 60 \times (\mathrm{SCr}^{-1.1})\ ] + \{\ (56 - \mathrm{age}) \times [\ 0.3 \times (\mathrm{SCr}^{-1.1})\ ]\ \}$ | CrCl = ml/min/1.73 $m^2$<br>Age = years<br>SCr = mg/dl | Gates (1985) |
| Salazar-Corcoran | Male: $\mathrm{CrCl} = \frac{(137 - \mathrm{age}) \times \{(0.285 \times \mathrm{weight}) + [12.1 \times (\mathrm{height} \times \mathrm{height})]\}}{(51 \times \mathrm{SCr})}$<br>Female: $\mathrm{CrCl} = \frac{(146 - \mathrm{age}) \times \{(0.287 \times \mathrm{weight}) + [9.74 \times (\mathrm{height} \times \mathrm{height})]\}}{(60 \times \mathrm{SCr})}$ | CrCl = ml/min<br>Age = years<br>Weight = kg<br>Height = meters (m)<br>SCr = mg/100 ml = mg/dl | Salazar and Corcoran (1988) |
| Robinson | Male: $\mathrm{CrCl} = [\ 2.11 - 0.007 \times (\mathrm{age}) - 14.638 \times (\mathrm{SCr}) + 0.0166 \times (\mathrm{weight})\ ]$<br>Female: $\mathrm{CrCl} = [\ 2.11 - 0.007 \times (\mathrm{age}) - 14.638 \times (\mathrm{SCr}) + 0.0166 \times (\mathrm{weight})\ ] - 0.329$ | CrCl = ml/s<br>Age = years<br>Weight = kg<br>SCr = mmol/l | Robinson et al. (1990) |
| Tsubaki | Male: $\mathrm{CrCl} = 0.75 \times \mathrm{CrCl}$ Cockcroft and Gault<br>Female: $\mathrm{CrCl} = 0.75 \times \mathrm{CrCl}$ Cockcroft and Gault | CrCl = ml/min<br>Age = years<br>Weight = kg<br>SCr = mg/100 ml = mg/dl | Tsubaki et al. (1993) |
| Davis-Chandler | Male: $\mathrm{CrCl} = \frac{(140 - \mathrm{age})}{\mathrm{SCr}}$<br>Female: $CrCl = \left[\frac{(140 - \mathrm{age})}{\mathrm{SCr}}\right] \times 0.85$ | CrCl = ml/min<br>Age = years<br>SCr = mg/100 ml = mg/dl | Davis and Chandler (1996) |

**Table 1** (Contd.)

| Author | Original Equation | Units | Reference |
|---|---|---|---|
| Martin | Male: $GFR = \frac{\{163 \times \text{weight} \times [1-(0.00496 \times \text{age})] \times [1]\}}{SCr}$<br>Female: $GFR = \frac{\{163 \times \text{weight} \times [1-(0.00496 \times \text{age})] \times [1-(0.252 \times 1)]\}}{SCr}$ | GFR = ml/min<br>Weight (actual body weight) = kg<br>Age = years<br>SCr = μmol/l | Martin et al. (1998) |
| MDRD | $GFR = 0.69 \times \left[\frac{100}{SCr}\right]$ (1)<br>GFR = 0.84 × [ CrCl Cockcroft and Gault ]* (2)<br>GFR = 0.81 × [ CrCl ]* (3)<br>$GFR = 1.11 \times \left[\frac{CrCl+UreaCl}{2}\right] *$ (4)<br>$GFR = 1.04 \times [CrCl]^{+0.751} \times [UreaCl]^{+0.226} \times [race] *$ (5)<br>Male: $GFR = 198 \times [SCr]^{-0.858} \times [age]^{-0.167} \times [1.0] \times [race] \times [Surea]^{-0.293} \times [Urineurea]^{+0.249}$<br>Female: $GFR = 198 \times [SCr]^{-0.858} \times [age]^{-0.167} \times [0.822] \times [race] \times [Surea]^{-0.293} \times [Urineurea]^{+0.249}$ (6)<br>Male : $GFR = 170 \times [SCr]^{-0.999} \times [age]^{-0.176} \times [1.0] \times [race] \times [Surea]^{-0.170} \times [Salbu]^{+0.318}$<br>Female : $GFR = 170 \times [SCr]^{-0.999} \times [age]^{-0.176} \times [0.762] \times [race] \times [Surea]^{-0.170} \times [Salbu]^{+0.318}$ (7)<br>Race: White 1.0 Black: Equation 5: 1.109 Equation 6: 1.178 Equation 7: 1.180 | GFR = ml/min/1.73 $m^2$<br>SCr = mg/dlCrCl = ml/min/1.73 $m^2$<br>Weight = kg<br>BSA = $m^2$<br>UreaCl = urea clearance = ml/min/1.73 $m^2$<br>Age = years<br>Surea = serum urea nitrogen concentration = mg/dl<br>Urineurea = urine urea nitrogen concentration = g/dl<br>Salbu = serum albumin concentration = g/dl | Levey et al. (1999) |
| Wright | Using enzymatic serum creatinine:Equation 1 with CK:<br>Male: $GFR = \frac{(4520-34 \times \text{age}+522 \times \ln(CK) \times BSA \times (1))}{SCr}$<br>Female: $GFR = \frac{(4520-34 \times \text{age}+522 \times \ln(CK) \times BSA \times (1-0.217 \times 1))}{SCr}$<br>Equation 2 without CK:<br>Male: $GFR = \frac{(4520-32.8 \times \text{age}) \times BSA \times (1)}{SCr}$<br>Female: $GFR = \frac{(6230-32.8 \times \text{age}) \times BSA \times (1-0.23 \times 1)}{SCr}$<br>Using Jaffé serum creatinine:Equation 3 with CK:<br>Male: $GFR = \frac{(4520-40 \times \text{age}+570 \times \ln(CK)) \times BSA \times (1)}{SCr}$<br>Female: $GFR = \frac{(4520-40 \times \text{age}+570 \times \ln(CK)) \times BSA \times (1-0.15 \times 1)}{SCr}$<br>Equation 4 without CK:<br>Male: $GFR = \frac{(6580-38.8 \times \text{age}) \times BSA \times (1)}{SCr}$<br>Female: $GFR = \frac{(6580-38.8 \times \text{age}) \times BSA \times (1-0.168 \times 1)}{SCr}$ | GFR = ml/min<br>Age = years<br>Ln(CK) = natural logarithm of creatine kinase = U/l<br>BSA = $m^2$<br>SCr = μmol/l | Wright et al. (2001) |

*Cockcroft-Gault formula and creatinine clearance are adjusted for body surface area, *BSA* Dubois body surface area = $0.007184 \times \text{weight(kg)}^{0.425} \times \text{height(cm)}^{0.725}$ (Du and Du Bois 1989), *cm* centimetres, Creatinine clearance (ml/min) = (UCr × *V*/ SCr × *t*). Ucr urine creatinine (mg/dl), *t* time of urine collection 24 h = min, Creatinine clearance corrected for BSA (ml× $\text{min}^{-1}$ × 1.73 $\text{m}^{-2}$) = CrCl × (1.73/*BSA*), Cockcroft and Gault corrected for BSA (ml×$\text{min}^{-1}$ ×1.73 $\text{m}^{-2}$) = CrCl *Cockcroft and Gault* × (1.73/*BSA*)

**Table 2** Chronological review of mathematical equations predicting CrCl or GFR: non-oncological patient group equation

| Author | Publication year | Original Result | Cohort of patients used for deriving equation | Blood values in equation | Method for creatinine assay | Demographic values in equation | Reference |
|---|---|---|---|---|---|---|---|
| Edwards–Whyte | 1959 | GFR = ml/min | 168 patients (80 women, 88 men) | Serum creatinine | Jaffé (Alkaline picrate) | Sex | Edwards and Whyte (1959) |
| Jelliffe-1 | 1971 | CrCl = ml/min/1.73 $m^2$ | 41 patients (16 women, 25 men) | Serum creatinine | Jaffé (Alkaline picrate) | Sex | Jelliffe (1971) |
| Mawer | 1972 | CrCl = ml/min | 16 patients (6 women, 10 men) with normal renal function till anuric determing renal clearance of kanamycin | Serum creatinine | No information | Sex, weight, age | Mawer et al. (1972) |
| Jelliffe-2 | 1973 | CrCl = ml/min/1.73 $m^2$ | No information | Serum creatinine | No information | Sex, age (next 10 years) | Jelliffe (1973) |
| Cockcroft–Gault | 1976 | CrCl = ml/min | 249 patients (only men) | Serum creatinine | Jaffé (Alkaline picrate) | Sex, weight, age | Cockcroft and Gault (1976) |
| Bjornsson | 1979 | CrCl = ml/min | No information | Serum creatinine | No information | Sex, weight, age | Bjornsson (1979) |
| Hull | 1981 | CrCl = ml/min/70 kg | 103 patients (69 women, 75 men) | Serum creatinine | Jaffé (Alkaline picrate) | Sex, age | Hull et al. (1981) |
| Gates | 1985 | CrCl = ml/min/1.73 $m^2$ | 179 patients (84 women, 95 men) training sample 90 patients validation sample 89 patients | Serum creatinine | No information | Sex, age | Gates (1985) |
| Salazar–Corcoran | 1988 | CrCl = ml/min | Animal model: obese overfed rat; Human: 368 patients (219 women, 149 men), obesity > 29.9 kg/$m^2$ | Serum creatinine | Jaffé (Alkaline picrate) | Sex, weight height, age | Salazar and Corcoran (1988) |
| Davis–Chandler | 1996 | CrCl = ml/min | 50 trauma patients (14 women, 36 men) | Serum creatinine | Jaffé (Alkaline picrate) | Sex, age | Davis and Chandler (1996) |
| MDRD Study (Eq. 7) | 1999 | GFR = ml/min/1.73 $m^2$ | 1628 patients (645 women, 983 men; 1304 white, 197 black) training sample: 1070validation sample: 558 | Serum creatinine Serum albumin (bromcresol green method) Serum urea nitrogen (urease method) | Jaffé (Alkaline picrate) | Sex, ethnicity, age | Levey et al. (1999) |

**Table 3** Chronological review of mathematical equations predicting CrCl or GFR: oncologic patient group equation

| Author | Publication year | Original Result | Cohort of patients used for deriving equation | Blood values in equation | Method for creatinine assay | Demographic values in equation | Reference |
|---|---|---|---|---|---|---|---|
| Robinson | 1990 | CrCl = ml/s | 106 patients (germ cell tumour (53), lymphoma (22), overian (17) and cervical cancer (6), osteosarcoma (4), other (4)) receiving cisplatin, carboplatin or methotrexate | Serum creatinine | Jaffé (Alkaline picrate) | Sex, weight, age | Robinson et al. (1990) |
| Tsubaki | 1993 | CrCl = ml/min | 80 women (40 with cervical, ovarian, endometrial, or vulvar cancer, 40 without cancer) | Serum creatinine | Jaffé (Alkaline picrate) | Sex, weight, age | Tsubaki et al. (1993) |
| Martin | 1998 | GFR = ml/min | 123 patients (45 women, 78 men) with various tumour typestraining sample: 80 (26 women, 54 men) validation sample: 43 (19 women, 24 men) | Serum creatinine | Enzymatic | Sex, weight, age | Martin et al. (1998) |
| Wright | 2001 | GFR = ml/min | 98 patients with various tumour types training sample: 62 validation sample: 38 | Serum creatinine Creatin kinase | Enzymatic (equation 1 and 2)/ Jaffé (Alkaline picrate) (equation 3 and 4) | Sex, weight, height, age | Wright et al. (2001) |

among the first to describe an equation especially for the prediction of CrCl in obese patients (Salazar and Corcoran 1988). This equation predicts CrCl based on fat-free body mass. In 1990, the first equation which primarily included oncology patients was presented by Robinson et al. (1990). A further equation derived by Tsubaki et al. (1993) three years later was based on patients with gynecological cancers. In this equation the calculated CrCl from the Cockcroft and Gault formula is multiplied by 0.75. In 1996, Davis and Chandler published a further equation including only sex, age and serum creatinine (Davis and Chandler 1996). This equation is derived from a non-oncological patient group. Furthermore, in 1998 Martin et al. presented another equation predicting GFR (Martin et al. 1998) which is based on oncologic patients with various tumor types. Moreover, their equation used an enzymatic creatinine assay estimating serum creatinine concentration.

Cancer patients may suffer from cachexia and malnutrition. As a consequence, serum creatinine may reach values below 0.6 mg/dl which makes the use of the above mentioned formulas very difficult. Therefore, more appropriate mathematical calculations appear to be needed to assess the individual renal function in a broad spectrum of patients more precisely. Wright et al. published four formulas in 2001 to predict GFR (Wright et al. 2001) in cancer patients based on two different methods of determing serum creatinine called the enzymatic method and the Jaffé method and including or excluding the value of creatine kinase. Moreover, these equations include sex, weight, height and age as parameters. In conclusion, the various mathematical equations mostly calculate GFR or CrCl on parameters like sex, weight and age. However, a significant over- and underestimation of real values by mathematical calculation may occur.

In general, most equations underestimate GFR values, if real conditions exceed 80 ml/min, whereas overestimation of the GFR has been observed when values are lower than 40 ml/min measured by radioisotopic markers. Moreover, the Martin equation, developed to predict GFR in cancer patients, underestimates GFR in females and overestimates GFR in males (Poole et al. 2002). It was suggested that in elderly cancer patients the Wright equation may be the most accurate, precise and least biased equation for the calculation of GFR higher than 50 ml/min (Marx et al. 2004). Indeed, one comparative trial indicated that the average deviation from measured to calculated values was low. However, significant over- and underestimation of GFR has been observed by mathematical calculation using the Martin or Wright formula when measured GFR by radioisotopes were in low or high range, respectively. In conclusion, the use of these specific equations derived from cancer patients does not appear to improve the accuracy or precision of these estimates compared to other formulas, but this needs further investigation (Montgomery et al. 2000).

So far, the most widely used of these mathematical equations in adult cancer patients are those published by Cockcroft and Gault (1976) and Jelliffe (1973). Mathematically calculated GFR or CrCl values offer a less accurate prediction of renal function, however, they allow a rapid calculation on a very low-cost level. Tables 2 and 3 summarize the described equations.

### Low-molecular-weight proteins

Several low-molecular-weight proteins have been proposed to be useful for the assessment of individual renal elimination capacity. These proteins are easily eliminated by glomerular filtration based on their shape and their molecular weight followed by reabsorption and catabolism in the proximal tubule. Such small proteins have even been suggested to replace serum creatinine as reference for estimating renal function in the near future. Until now, these methods have never been tested in larger prospective clinical studies.

Cystatin C, a low-molecular-weight protein (13 kDa) and a potent inhibitor of cysteine proteases, is produced by nucleated cells at a constant rate. It is mainly recovered in extracellular fluids, like blood. Its serum level depends on GFR, because cystatin C is neither secreted via renal tubules nor it is taken up into the blood along the nephron (Jacobsson et al. 1995). In patients with known reduced renal function, cystatin C has been proposed to provide better results to detect mild or moderately impaired GFR than serum creatinine (Kyhse–Andersen et al. 1994; Newman et al. 1995; Price and Finney 2000). Compared to serum creatinine, cystatin C excretion is independent of gender and age (Bokenkamp et al. 1998; Dharnidharka et al. 2002). Studies have shown that serum cystatin C concentrations are an accurate method determing GFR over a broad range of constitutive values (Kyhse–Andersen et al. 1994; Price and Finney 2000; Tian et al. 1997). However, in cancer patients, the use of cystatin C as a parameter for renal function is still limited. There is some evidence that cystatin C concentrations are not affected by the presence of malignancies or inflammation (Newman et al. 1995). However, one study observed a significant correlation between increased serum cystatin C and malignant progression in melanoma and colorectal cancer (Kos et al. 1998). In summary, cystatin C appears to be superior to serum creatinine as a marker, but the costs of measuring cystatin C compared to serum creatinine may limit its broad and regular use. Further evaluation of serum cystatin C as a marker for accurate GFR determination will be necessary, especially in cancer patients.

ß-trace protein (BTP) shares a lot of characteristics with cystatin C. It is also a low-molecular-weight glycoprotein (23–29 kDa) containing 168 amino acids. The molecular weight depends on the degree of glycosylation (Priem et al. 1999). BTP has been identified as prostaglandin D synthase primarily isolated from the cerebrospinal fluid (CSF) (Hoffmann et al. 1997). It is synthesized mainly in the cells of the choroid plexus and is recovered in CSF in concentrations approximately 35-fold higher than in plasma (Melegos et al. 1999). Preliminarily studies indicated that serum BTP concentrations are increased in patients with renal impairment (Hoffmann et al. 1997; Melegos et al. 1999). Measurement of BTP appears to be a better method to determine a reduced GFR than serum creatinine in the so-called "creatinine blind range" (Priem et al. 1999). However, it has not been superior to cystatin C for GFR assessment (Priem et al. 2001). Serum BTP has been suggested to be a potentially useful marker in the detection of mild renal impairment.

To our knowlegde, there are no reports about the usefulness of BTP assessment in cancer patients as a new marker to predict GFR accurately.

## Conclusions

New strategies appear to be needed to assess individual CrCl more easily before cancer chemotherapy is started. Based on the fact that the treatment of elderly cancer patients is of increasing importance in clinical oncology, the need for accurate assessment of decreased renal function is obvious. Various methods exist estimating individual GFR or CrCl. However, mathematical calculations do not predict values accurately enough, whereas the use of 24-h urine collection is dependent on patient compliance and the use of radioisotopes is not feasible in routine clinical practice. Accurate drug dosing based on renal function is important when renal elimination reflects the predominant pathway of drug excretion (Lipp and Bokemeyer 1999). For example, about 75% of administered carboplatin dose is eliminated via glomerular filtration. Dosing of carboplatin based on GFR has become the standard practice in patients with ovarian cancer in order to reach a defined therapeutic index (Bokemeyer and Lipp 1997). A clear correlation has been demonstrated between the rate of drug excretion (clearance) and total systemic drug exposure quantified by the area under the plasma concentration versus time curve (AUC) according to the Calvert equation (Calvert et al. 1989):

$$\mathrm{Dose(mg)} = \mathrm{AUC(mg\,ml^{-1}min)} \times \left(\mathrm{GFR\left(ml\ min^{-1}\right)} + 25\right).$$

The use of the Calvert equation helps to avoid severe toxicity which has been demonstrated to be closely related to AUC values exceeding 7.5 mg/ml/min (Egorin et al. 1984; Jodrell et al. 1992). The aim of using GFR is to achieve a target AUC which ensures ideal dosing for patients with a broad range of individual GFR. Otherwise oncologic patients may either develop more myelotoxicity than expected or therapeutic drug levels will be subtherapeutic (Jodrell et al. 1992). A further example is the clearance of bleomycin, a polypeptide antineoplastic agent, which is used in the treatment of germ-cell tumors and lymphoma. Its pulmonary toxicity is increased in patients with reduced GFR when dosage modifications are neglected. Patients with a GFR lower than 80 ml/min are at higher risk for bleomycin pulmonary toxicity, particulary if they are aged over 40 years, and have received a cumulative dose of bleomycin exceeding 300 units (O'Sullivan et al. 2003). Capecitabine, an oral fluoropyrimidine used in the treatment of different solid

tumors, has recently been compared to i.v. 5-fluorouracil/leucovorin in patients with metastatic colorectal cancer. In this study, the incidence of grade 3 or 4 side effects from capecitabine was higher in patients with moderately reduced renal function when dosage modification was of no concern compared to those with normal renal function, whereas the objective response rate to capecitabine in patients with moderately impaired renal function was comparable to that in patients with normal or mildly impaired renal function (Cassidy et al. 2002). These data indicate that an impaired excretion of capecitabine and its metabolites (e.g. 5′ deoxyfluorouridine) may have a significant impact on all over drug toxicity.

In addition, accurate measurement of CrCl or GFR is needed when patients receive nephrotoxic agents like cisplatin (Reece et al. 1987). The use of this drug requires repeated assessment of kidney function during repeated cycles to avoid severe forms of chronic renal impairment.

Despite the importance of measuring GFR or CrCl in individual patients, the ideal method for assessment is not yet available which would include features like rapid estimation with high accuracy at low costs. Although, several mathematical equations exist to predict GFR or CrCl, they do not appear to be accurate enough. Low-molecular-weight proteins, like cystatin C and BTP, may be useful alternatives for rapid and accurate determination of GFR, however, their place in clinical oncology has to be studied in more detail.

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