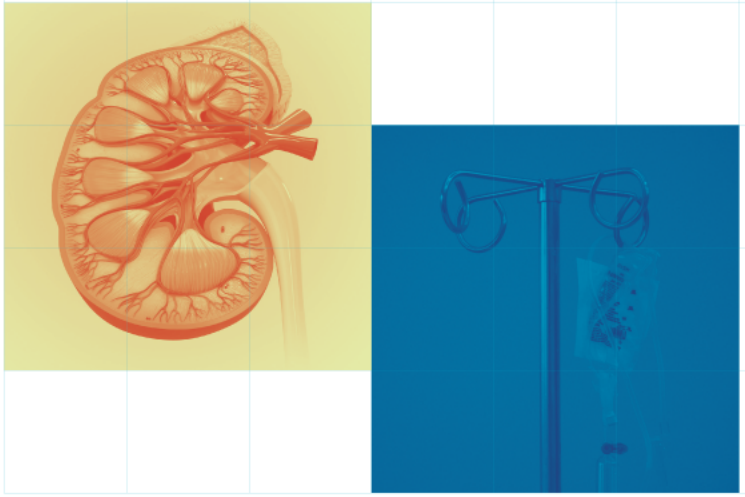
Kako pravilno izračunati dozu kemoterapije i odrediti renalnu funkciju?

Zajednički simpozij Hrvatskog društva za internističku onkologiju i Hrvatskog društva za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

Marija Miletić, dr. med.[1]

Tamara Knežević, dr. med.[2]

[1] KBC Sestre milosrdnice, Klinika za onkologiju i nuklearnu medicinu
[2] KBC Zagreb, Klinika za unutarnje bolesti



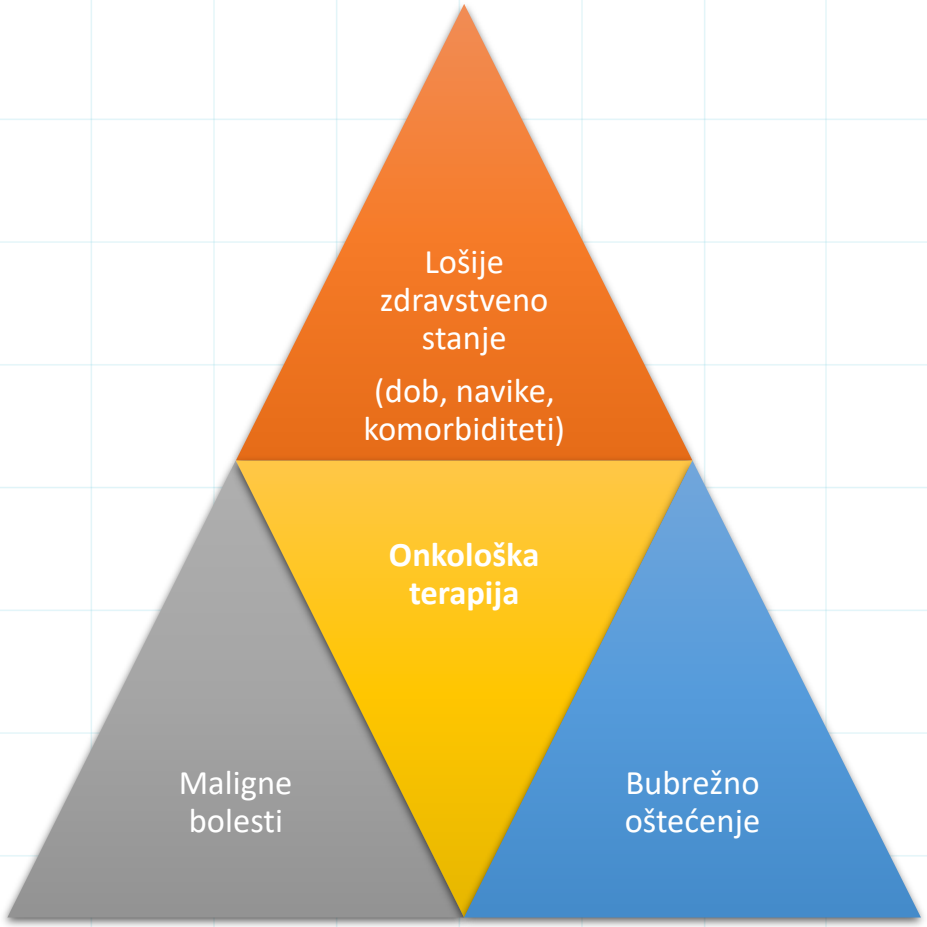
8.2.2020.

Hrvatski liječnički zbor, Zagreb

HDIO

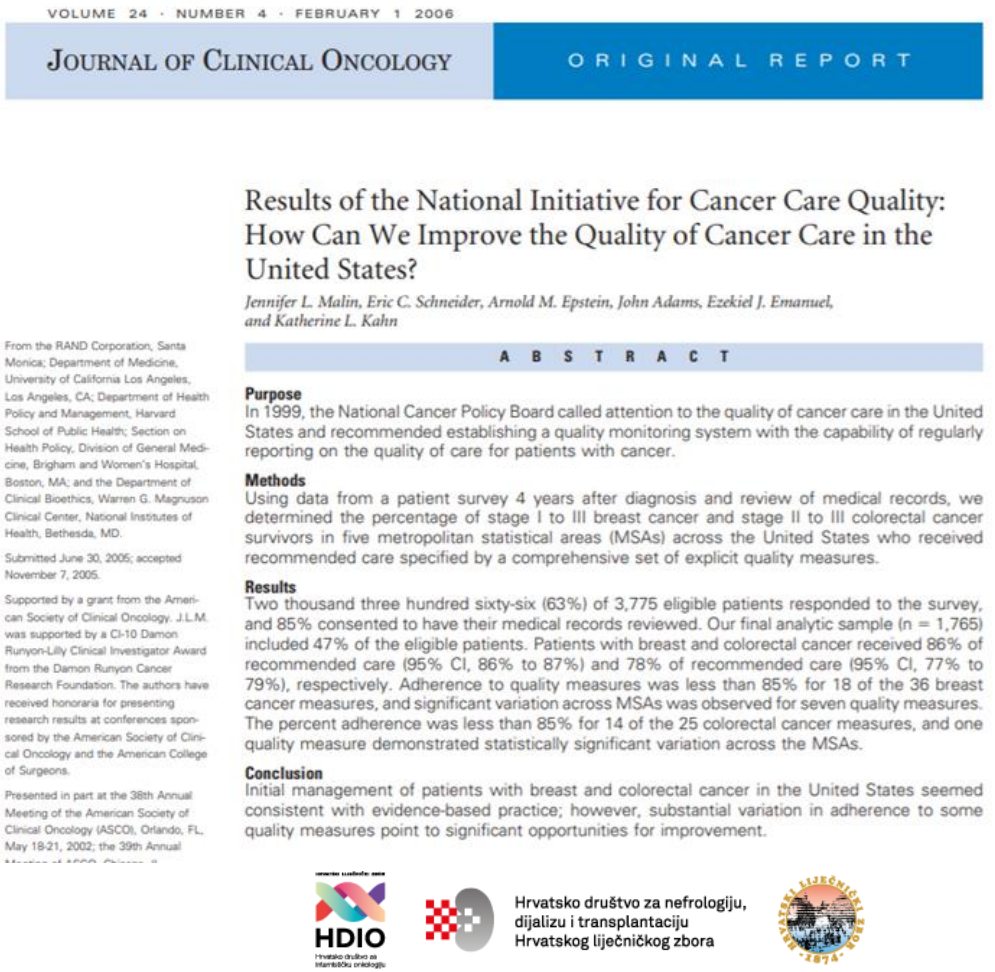
Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

I. Uvod


Lošije zdravstveno stanje
(dob, navike, komorbiditeti)
Onkološka terapija
Maligne bolesti
Bubrežno oštećenje

I. Uvod

How Can We Improve the Quality of Cancer Care?



VOLUME 24 · NUMBER 4 · FEBRUARY 1 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Results of the National Initiative for Cancer Care Quality: How Can We Improve the Quality of Cancer Care in the United States?

Jennifer L. Malin, Eric C. Schneider, Arnold M. Epstein, John Adams, Ezekiel J. Emanuel, and Katherine L. Kahn

From the RAND Corporation, Santa Monica; Department of Medicine, University of California Los Angeles, Los Angeles, CA; Department of Health Policy and Management, Harvard School of Public Health; Section on Health Policy, Division of General Medicine, Brigham and Women's Hospital, Boston, MA; and the Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD.

Submitted June 30, 2005; accepted November 7, 2005.

Supported by a grant from the American Society of Clinical Oncology. J.L.M. was supported by a CI-10 Damon Runyon-Lilly Clinical Investigator Award from the Damon Runyon Cancer Research Foundation. The authors have received honoraria for presenting research results at conferences sponsored by the American Society of Clinical Oncology and the American College of Surgeons.

Presented in part at the 38th Annual Meeting of the American Society of Clinical Oncology (ASCO), Orlando, FL, May 18-21, 2002; the 39th Annual

A B S T R A C T

Purpose
In 1999, the National Cancer Policy Board called attention to the quality of cancer care in the United States and recommended establishing a quality monitoring system with the capability of regularly reporting on the quality of care for patients with cancer.

Methods
Using data from a patient survey 4 years after diagnosis and review of medical records, we determined the percentage of stage I to III breast cancer and stage II to III colorectal cancer survivors in five metropolitan statistical areas (MSAs) across the United States who received recommended care specified by a comprehensive set of explicit quality measures.

Results
Two thousand three hundred sixty-six (63%) of 3,775 eligible patients responded to the survey, and 85% consented to have their medical records reviewed. Our final analytic sample (n = 1,765) included 47% of the eligible patients. Patients with breast and colorectal cancer received 86% of recommended care (95% CI, 86% to 87%) and 78% of recommended care (95% CI, 77% to 79%), respectively. Adherence to quality measures was less than 85% for 18 of the 36 breast cancer measures, and significant variation across MSAs was observed for seven quality measures. The percent adherence was less than 85% for 14 of the 25 colorectal cancer measures, and one quality measure demonstrated statistically significant variation across the MSAs.

Conclusion
Initial management of patients with breast and colorectal cancer in the United States seemed consistent with evidence-based practice; however, substantial variation in adherence to some quality measures point to significant opportunities for improvement.

HDIO

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

I. Uvod


ANTROPOMETRIJSKE KARAKTERISTIKE BOLESNIKA
POLIFARMACIJA
Klinički odgovor na primijenjeni lijek
OKOLIŠNI ČIMBENICI
FARMAKOGENOMIKA
KOMORBIDITETI
(bubrežno & jetreno oštećenje)
PROTOKOLI

I. Uvod

- farmakokinetika kemoterapeutika (tzv. *ADME*)
- Optimalna doza=maksimalno podnošljiva, uz prihvatljivi profil toksičnosti, a kojom postižemo najbolju stopu tumorskog odgovora
- Doziranje onkološke terapije:
  - BSA (engl. *body surface area*)
    - **kemoterapeutici** & neka monoklonska Pt
  - tjelesna težina
  - eGRF, AUC
  - fiksne doze

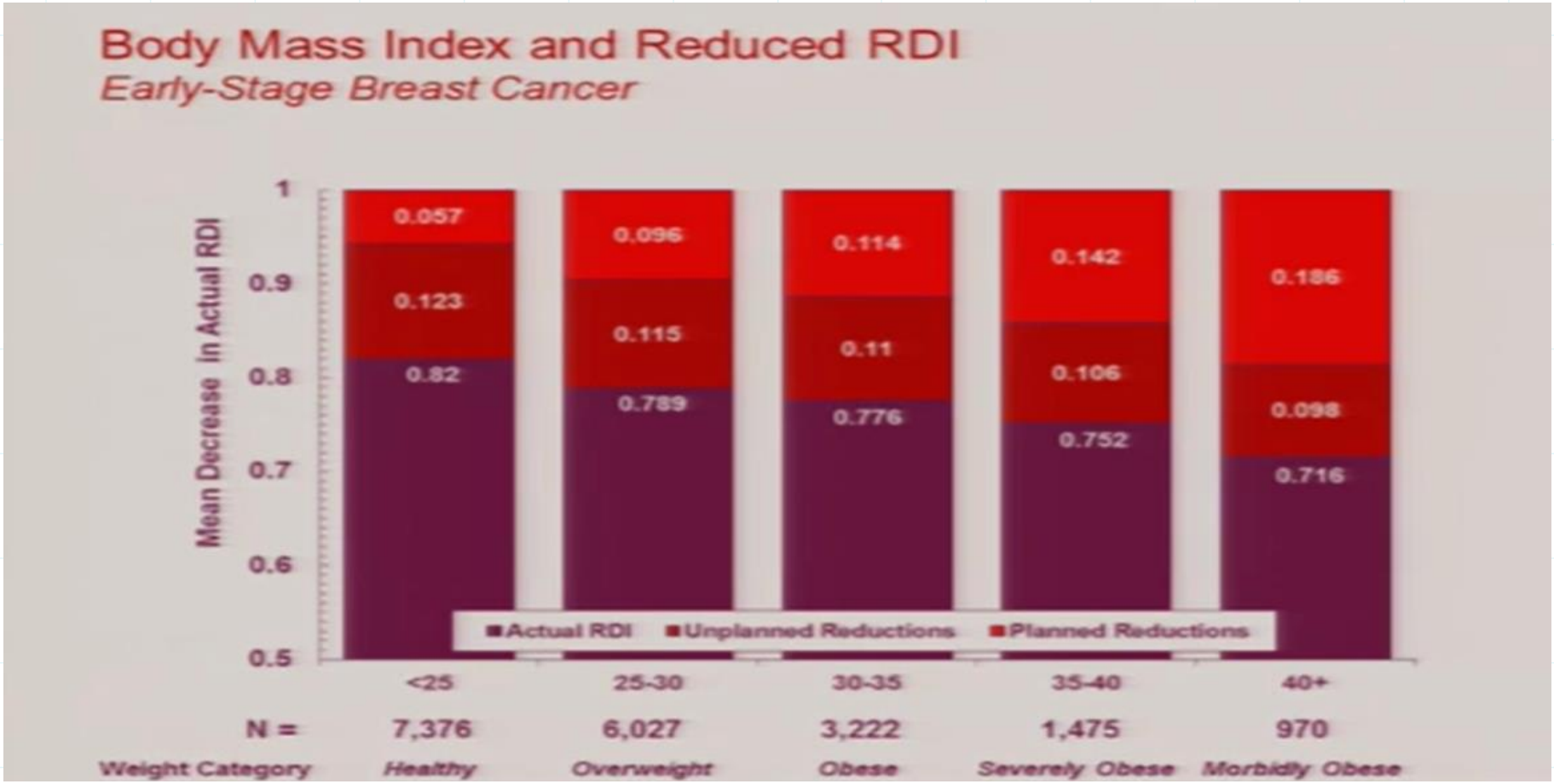
II.I. Doziranje temeljem BSA

Zašto baš BSA?

- Druge biometrijske mjere – npr. *lean body mass*, *ideal body mass*, *body mass indeks*
- odnos intra- i ekstracelularne tekućine (edemi, ascites), sarkopenija
- tjelesni ekstremi (pretilost, kaheksija)

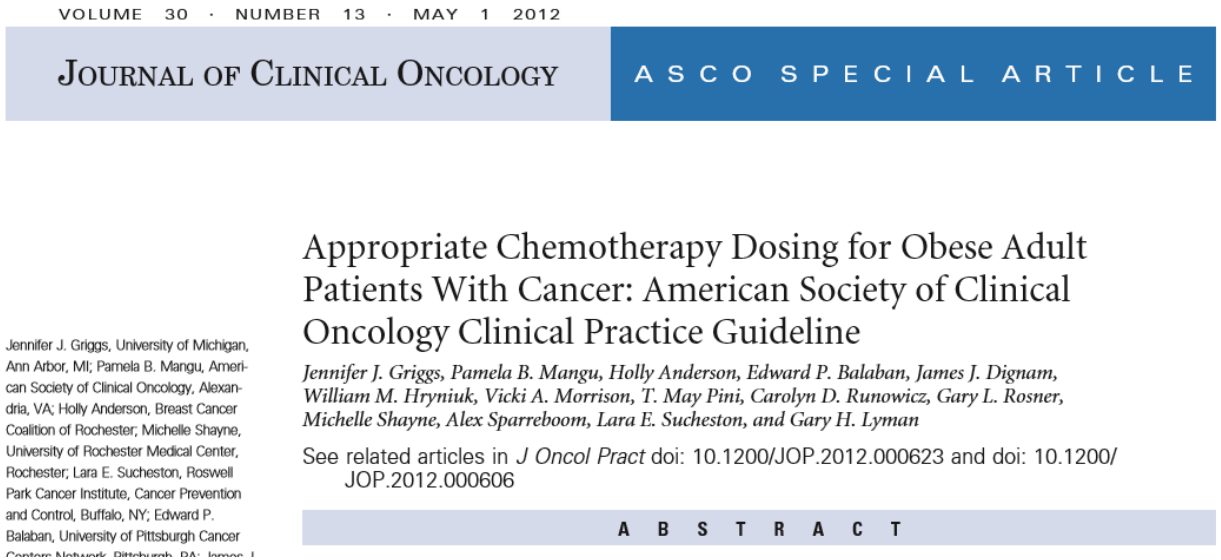
PODACI		Simboli u formulama
Spol :	muški ženski	
Tjelesna masa (težina) (m):	100 kg	m = masa u kg
Visina tijela (v):	173 cm	v = visina u m
Dob (neobavezno):	56 godine	d = dob u godinama
(ostavite prazno, ako ne želite korekciju za dob)	Izračunaj	Izbriši
REZULTATI		Formule za izračunavanje
Tjelesna površina =	2.13 m^2	= 0.20247 x $v^{0.725}$ x $m^{0.425}$
Masa nemasnog dijela tijela =	67 kg	= (1.10 x m) - 128 (m^2 / (100 x v^2)) = (1.07 x m) - 148 (m^2 / (100 x v^2))
Idealna tjelesna masa =	69 kg	= 50 + 92 (v - 1.52) = 45.5 + 92 (v - 1.52)
Indeks tjelesne mase (BMI) =	33.4 kg/m^2	= m/v^2
BMI s korekcijom za dob =	30.799999 kg/m^2	= (m/v^2) - (d - 30) / 10 ; 30<d<75

II.I. Doziranje temeljem BSA (debljina)



Lyman et al., J Clin Oncol. 2003.

II.I. Doziranje temeljem BSA (debljina)



VOLUME 30 · NUMBER 13 · MAY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Jennifer J. Griggs, Pamela B. Mangu, Holly Anderson, Edward P. Balaban, James J. Dignam, William M. Hryniuk, Vicki A. Morrison, T. May Pini, Carolyn D. Runowicz, Gary L. Rosner, Michelle Shayne, Alex Sparreboom, Lara E. Sucheston, and Gary H. Lyman

Jennifer J. Griggs, University of Michigan, Ann Arbor, MI; Pamela B. Mangu, American Society of Clinical Oncology, Alexandria, VA; Holly Anderson, Breast Cancer Coalition of Rochester; Michelle Shayne, University of Rochester Medical Center, Rochester; Lara E. Sucheston, Roswell Park Cancer Institute, Cancer Prevention and Control, Buffalo, NY; Edward P. Balaban, University of Pittsburgh Cancer

See related articles in *J Oncol Pract* doi: 10.1200/JOP.2012.000623 and doi: 10.1200/JOP.2012.000606

ABSTRACT

ASCO preporuke (2012.)

1. Koristiti stvarnu tj. težinu za izračun doze kemoterapije, posebno kada je terapijski cilj **IZLJEČENJE**.
2. Nuspojave kemoterapije zbrinjavati jednako kao kod bolesnika normalne tj. težine.

KOMORBIDITETI, sarkopenija, kumulativne doze

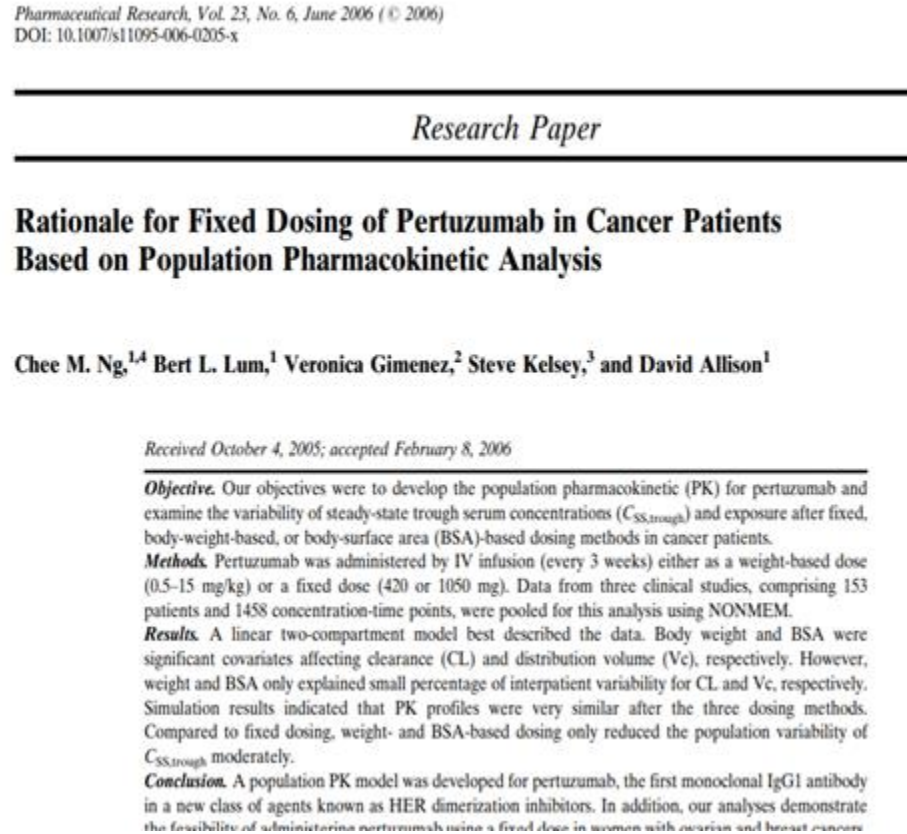
II.II. Doziranje temeljem tjelesne težine

- kemoterapeutici
  - kladribin (*CLL, leukemija vlasastih stanica*), melfalan (*multipli mijelom*)

- monoklonska Pt
  - ipilimumab, bevacizumab, trastuzumab, panitumumab, brentuximab, ramucirumab

II.III. Fiksne doze (engl. „*flat-dose*”)

- **kemoterapeutici**
  - *bleomicin* (karcinom testisa *vrs*. Hodgkin limfom)
  - *vinkristin* (2mg *vrs.* 1.4 mg/m^2)
- **monoklonska Pt**
  - rekombinantna humana hijaluronidaza
    - *trastuzumab, rituximab*
  - *pertuzumab*



Pharmaceutical Research, Vol. 23, No. 6, June 2006 (© 2006)
DOI: 10.1007/s11095-006-0205-x

Research Paper

Rationale for Fixed Dosing of Pertuzumab in Cancer Patients Based on Population Pharmacokinetic Analysis

Chee M. Ng,[1,4] Bert L. Lum,[1] Veronica Gimenez,[2] Steve Kelsey,[3] and David Allison[1]

Received October 4, 2005; accepted February 8, 2006

Objective. Our objectives were to develop the population pharmacokinetic (PK) for pertuzumab and examine the variability of steady-state trough serum concentrations ($C_{SS,trough}$) and exposure after fixed, body-weight-based, or body-surface area (BSA)-based dosing methods in cancer patients.
Methods. Pertuzumab was administered by IV infusion (every 3 weeks) either as a weight-based dose (0.5–15 mg/kg) or a fixed dose (420 or 1050 mg). Data from three clinical studies, comprising 153 patients and 1458 concentration-time points, were pooled for this analysis using NONMEM.
Results. A linear two-compartment model best described the data. Body weight and BSA were significant covariates affecting clearance (CL) and distribution volume (Vc), respectively. However, weight and BSA only explained small percentage of interpatient variability for CL and Vc, respectively. Simulation results indicated that PK profiles were very similar after the three dosing methods. Compared to fixed dosing, weight- and BSA-based dosing only reduced the population variability of $C_{SS,trough}$ moderately.
Conclusion. A population PK model was developed for pertuzumab, the first monoclonal IgG1 antibody in a new class of agents known as HER dimerization inhibitors. In addition, our analyses demonstrate

HDIO

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

II.III. Fiksne doze (engl. „*flat-dose*”)

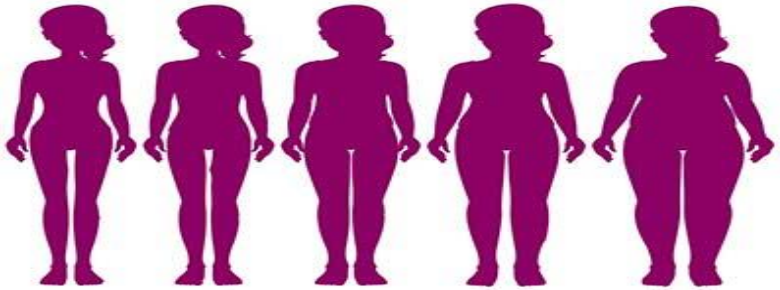
- **kemoterapeutici**
  - *bleomicin* (karcinom testisa *vrs*. Hodgkin limfom)
  - *vinkristin* (2mg *vrs.* 1.4 mg/m^2)
- **monoklonska Pt**
  - rekombinantna humana hijaluronidaza
    - *trastuzumab, rituximab*
  - *pertuzumab*
- **inhibitori kontrolnih točaka** (*nivolumab & pembrolizumab*)
- **inhibitori kinaza** (*TKI, BRAFi, mTOR*)

II.IV. Računanje doze prema AUC-u

- kemoterapeutici koji se izlučuju bubregom
- doza (mg)=AUC 4-6mL/min x eGFR + 25
  - AUC 6=900 mg
  - AUC 5=750 mg
  - AUC 4=600 mg

III. Praktične preporuke

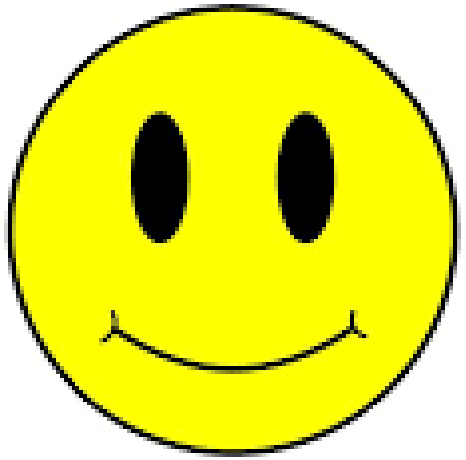
- formula za izračun BSA ?
- vaganje bolesnika prije svakog ciklusa ?
- „*capping*” BSA – 2.01m^2 & BSA=2.51m^2
- maksimalna kumulativna doza !
  - bleomicin (400 U)
  - antraciklini (npr. doxorubicin 450 mg/m^2)
- zaokruživanje doza ?
  - bevacizumab 800mg *vrs.* 810mg *vrs.* 790mg



IV. Zaključak (I)

Obvezni smo poznavati farmakokinetiku i farmakodinamiku lijekova koje primjenjujemo, moguće interakcije s drugim lijekovima, prilagoditi doze ovisno o podnošenju liječenja i na taj način pridonijeti što boljem učinku liječenja, u smislu optimalnog terapijskog odgovora, uz izbjegavanje i ublažavanje ev. pojave nuspojava.

- **Many current doses and schedules in clinical use have probably not been developed based on what might be therapeutically optimal, but may have been dependent on extraneous or practical issues such as the 5 day working week.**

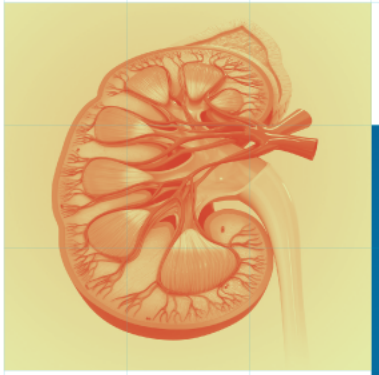


Zajednički simpozij Hrvatskog društva za internističku onkologiju i Hrvatskog društva za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

Kako pravilno odrediti bubrežnu funkciju u onkoloških bolesnika?

Tamara Knežević, dr. med.

Zavod za nefrologiju, arterijsku hipertenziju, dijalizu i transplantaciju, KBC Zagreb



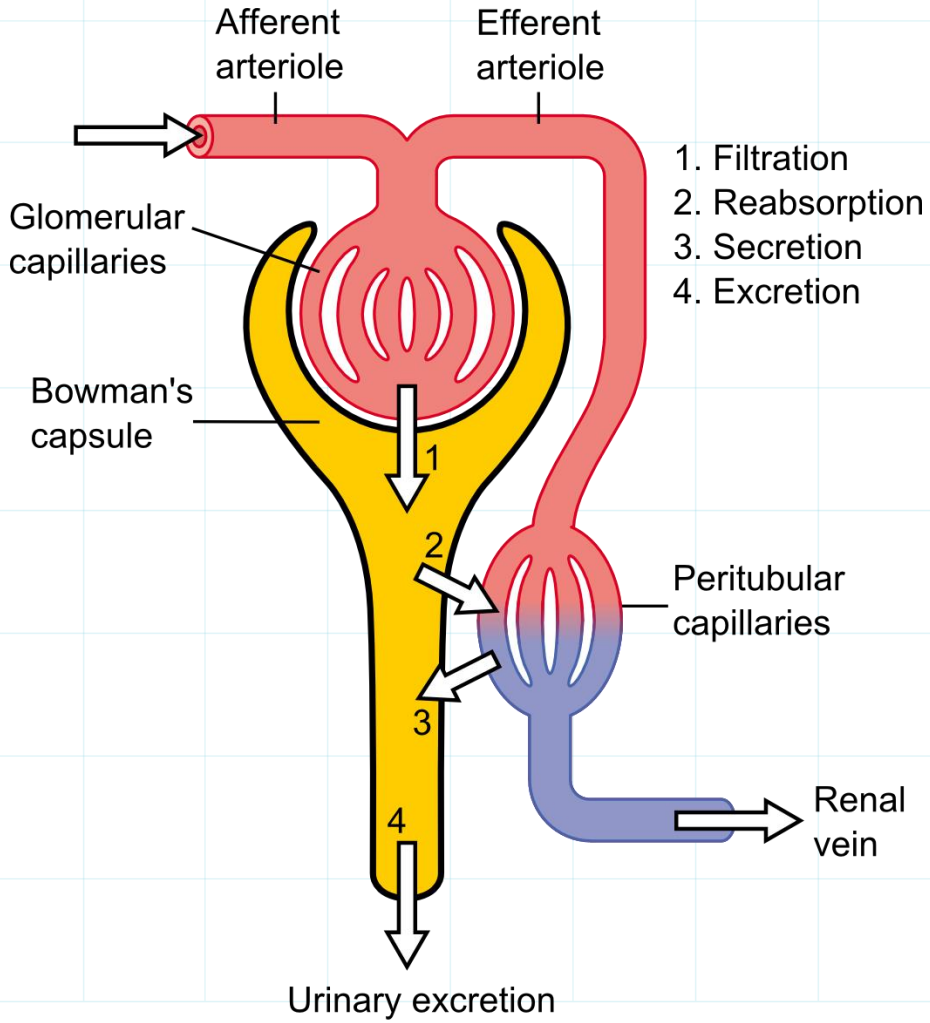
8.2.2020.

Hrvatski liječnički zbor, Zagreb

HDIO

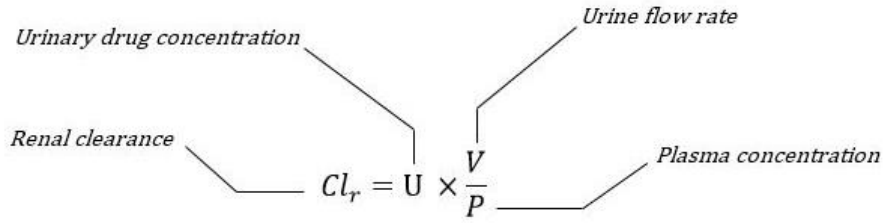
Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

Mechanisms of renal (drug) excretion; clearance



Excretion = Filtration – Reabsorption + Secretion

Clearance is a pharmacokinetic measurement of the **volume of plasma from which a substance is completely removed per unit time.** Usually, clearance is measured in L/h or mL/min.



CrCl vs. true GFR

Creatinine clearance co-indicentally matches eGFR down to 60 mL/min

- 10% of UCr is from tubular secretion
- 10% of SCr is from non-creatinine chromogens
- These values cancel out eachother

Clearance vs. GFR

- GFR does not account for tubular secretion → NOT appropriate for drugs with PK profiles different than Cr
- Most drug doses were determined prior to CKD-EPI and MDRD equations and so they were determined using CG equation

CKD and cancer – emerging evidence for a connection

- **Over 50%** of solid tumor patients have eCrCl or eGFR <90 mL/min and **up to 20%** have <60 mL/min (situation is even more dire in **hematologic** patients)
- Vice versa, after **dialysis**, cancer risk **increases 10 to 80%** according to studies, with relative risks significantly higher than the general population for about ten cancer sites.
- There is emerging evidence for an **excess risk of cancer in patients at early CKD stages**.

Br J Cancer. 2010 Dec 7;103(12):1815-21.
Cancer. 2007 Sep 15;110(6):1376-84.
J Nephrol. 2010; 23(3): 253–262.

Why it is important to **accurately** estimate KF?

- Approximately **50%** of all anticancer drugs are excreted **predominantly in the urine** as unchanged drug or active metabolite(s)
- Risk of most types of cancer **increases with age**
- Prevalence of **cachexia** in cancer patients is between **50 to 90%**
- Results of French Renal Insufficiency and Anticancer Medications (IRMA) study showed that while **only 7.2% patients had SCr>110** umol/L, **57.4%** (using MDRD) and **52.9%** (using CG) of all study patients **had renal insufficiency**
- Over 53% of anticancer drug prescriptions required dose adjustments

J Cachexia Sarcopenia Muscle. 2018 Dec; 9(7): 1189–1191.

Cancer. 2007 Sep 15;110(6):1376-84.

Table 2. Selected drugs with kidney function cutoffs for eligibility and dose modifications

Drug	Kidney Function Cutoff Below Which Not to Treat, ml/min	Kidney Function Ranges with Dose Modifications, ml/min	Reference
Bendamustine	30	—	42
Bleomycin	—	5%–10% to 40% 10%–20% to 45% 20%–30% to 55% 30%–40% to 60% 40%–50% to 70%	41
Capecitabine	30	30%–50% to 75%	43
Cisplatin	60	—	37
Etoposide	15	15%–50% to 75%	44
Fludarabine	30	30%–49% to 60% 50%–79% to 80%	45
Methotrexate	60	—	46
Mitomycin	30[a]	—	47
Oxaliplatin	—	<30%–75%	48
Pemetrexed	45	—	49
Pentostatin	—	50%–60% to 50%	50
Topotecan	10	20%–39% to 50%	51

—, not applicable.
[a]Related to hydroxypropyl-β-cyclodextrin excipient.

What are the dosing problems in cancer patients?

- Appropriate way to estimate kidney function is important within the general medical population, but it is particularly crucial in patients with cancer due to the **highly toxic adverse event profiles** and often **steep dose-therapeutic response relationships** that characterize anticancer agents as a class.
- Anticancer drug dosing is typically done on the basis of **maximum tolerated dose** (highest dose that may be administered without unacceptable toxicity).
- **Dose reductions or alternative agent selection** due to decreased eGFR may lead to reduced effectiveness, failure of therapy, use of less effective or more toxic second- or third-line agents, and ultimately, decreased survival.

Clin J Am Soc Nephrol. 2019 Apr 5;14(4):587-595.

HDIO

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

Different methods to estimate GFR

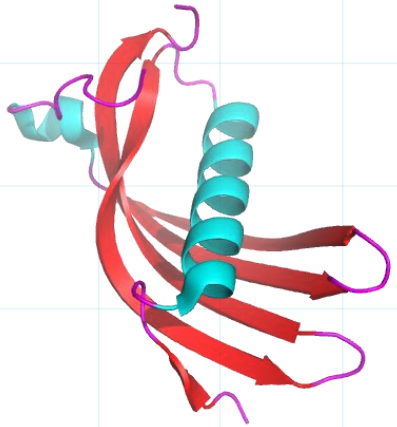
Table 1. Comparison of bedside equations used to estimate kidney function

Variables	Measures	Study Population Demographics	Study Population Kidney Function	Advantages	Limitations
CG (1976) Age, SCr, sex, weight	eCrCl, ml/min	*n*=236 (subpopulation	Average CrCl	Convenient to use	Estimates creatinine clearance
Age, SCr, sex, race	eGFR, ml/min per 1.73 m^2	*n*=5253 Mean age 43 yr, 13% >65 yr 58% men 63% white, 32% black, 1% Asian Patients with CKD	Mean GFR 68 ml/min per 1.73 m^2	P30=91.5% with cystatin C Uses iothalamate clearance as standard Uses standardized SCr laboratory values Improves on MDRD estimation at GFR>60 ml/min per 1.73 m^2	Not used for determining most kidney drug-dosing recommendations

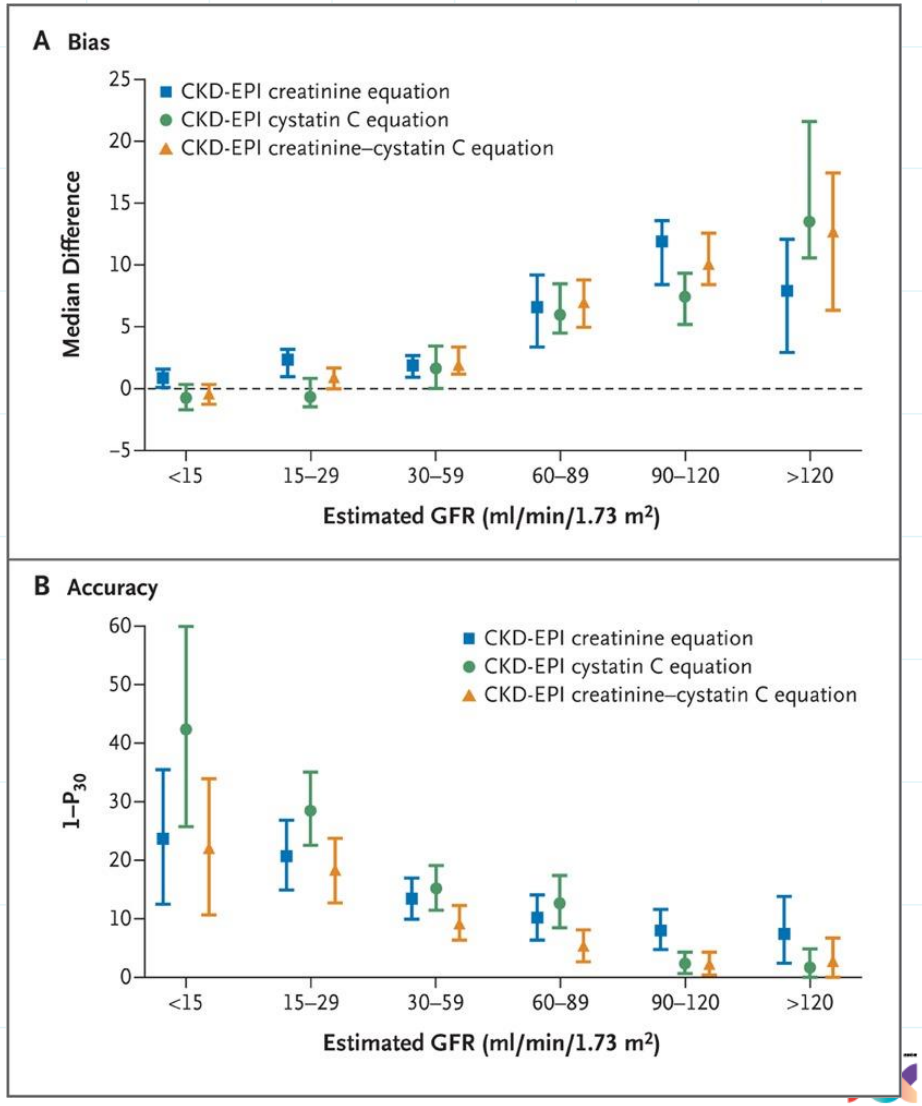
CG, Cockcroft–Gault; eCrCl, estimated creatinine clearance; mCrCl, measured creatinine clearance; CrCl, creatinine clearance; SCr, serum creatinine; MDRD, Modification of Diet in Renal Disease; P30, percentage of estimates that were within 30% of the reference value; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

None of the widely-used equations has been derived for use in cancer patients!

Does cystatin C improve the accuracy of creatinine-based eGFR formulas?



Cystatin C, a 122 amino acid with molecular weight (13-kDa) cysteine protease inhibitor, produced by all nucleated cells, **freely filtered** by the renal glomerulus, **no tubular secretion**, reabsorbed and completely catabolized by tubular cells, **not excreted**



The combined creatinine–cystatin C equation **performed better** than equations based on either of these markers alone and **may be useful** as a confirmatory test for chronic kidney disease.

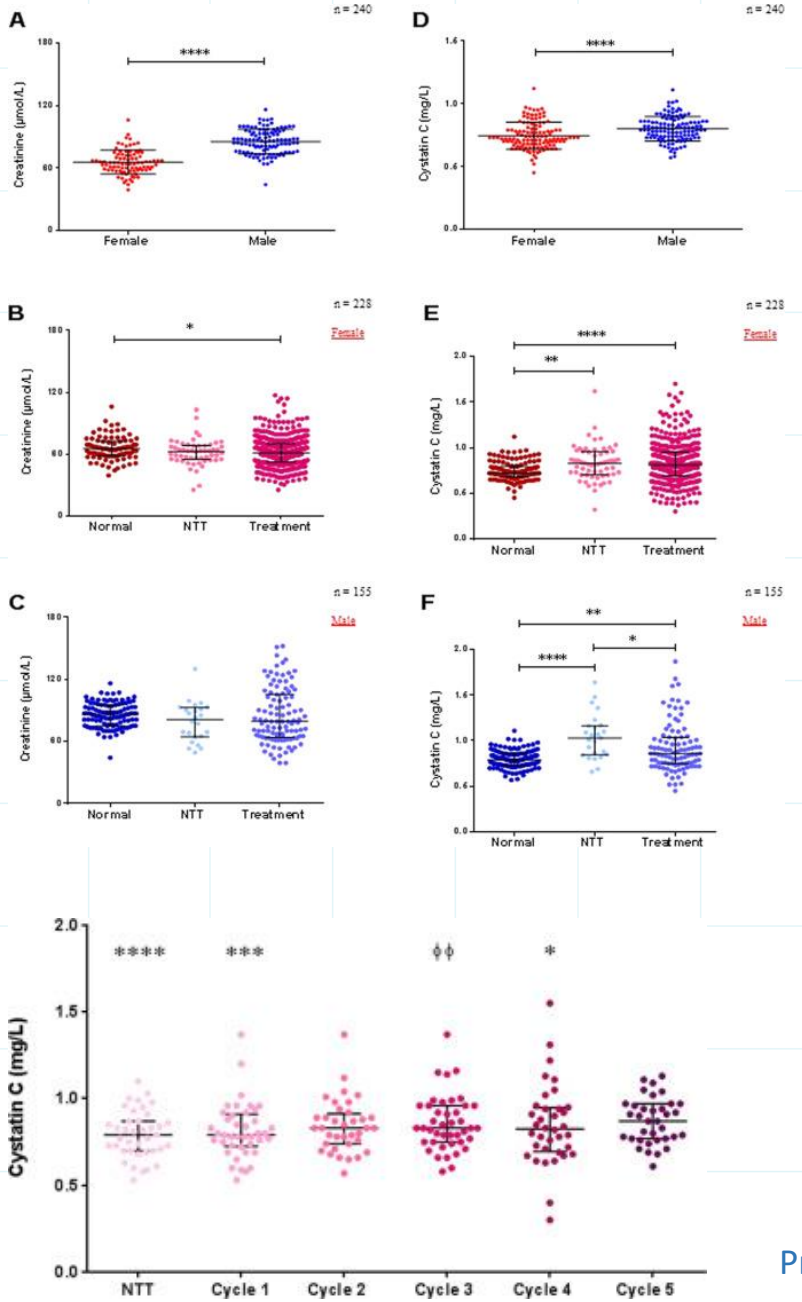
Proved to be a good biomarker in general population, diabetics, cardiovascular disease, across different CKD stages and ethnicities.....

...but is it a good biomarker in cancer patients?

N Engl J Med 2012; 367:20-29

HDIO

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora



Cystatin C concentrations were **significantly higher in oncology patients both prior to commencing chemotherapy and during cycles of treatment** when compared with a reference population. Cystatin C concentrations also **increased significantly during chemotherapy** in a subset of female patients evaluated. **Poor agreement** was demonstrated between CKD-EPI CysC and creatinine-based GFR estimates within the investigated GFR ranges, with improved agreement when using the combined CKD-EPI SCr/CysC formula.

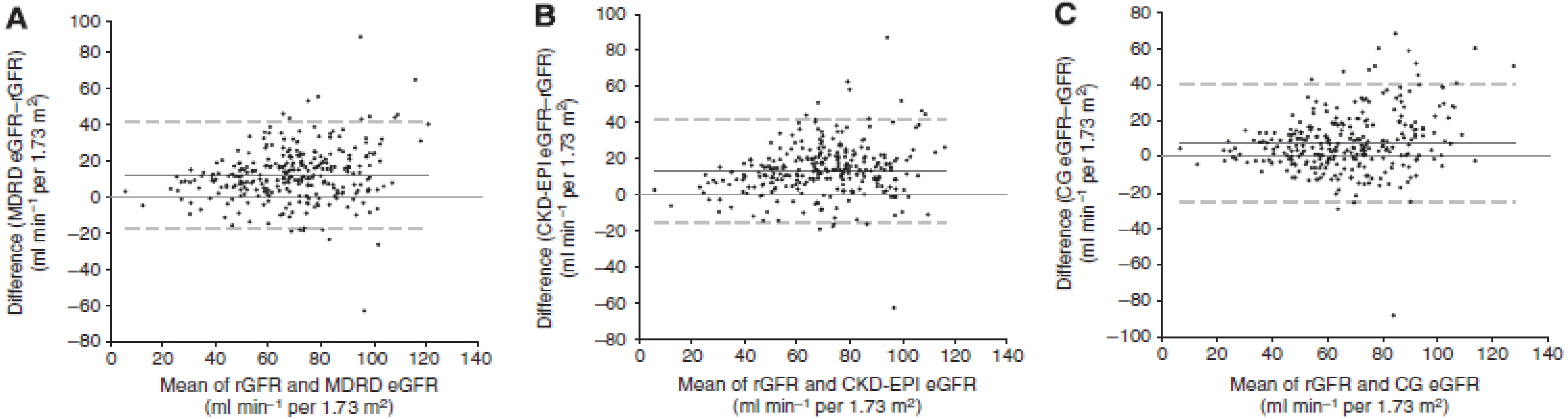
This study demonstrated a **malignancy and treatment-mediated effect** on cystatin C measures, which may **confound its clinical utility** in estimating GFR in oncology patients.

Pract Lab Med. 2017 Aug; 8: 95–104.

British Journal of Cancer (2012) 107, 1310–1316

www.bjcancer.com

Overestimation of carboplatin doses is avoided by radionuclide GFR measurement



Difference in eGFR.....

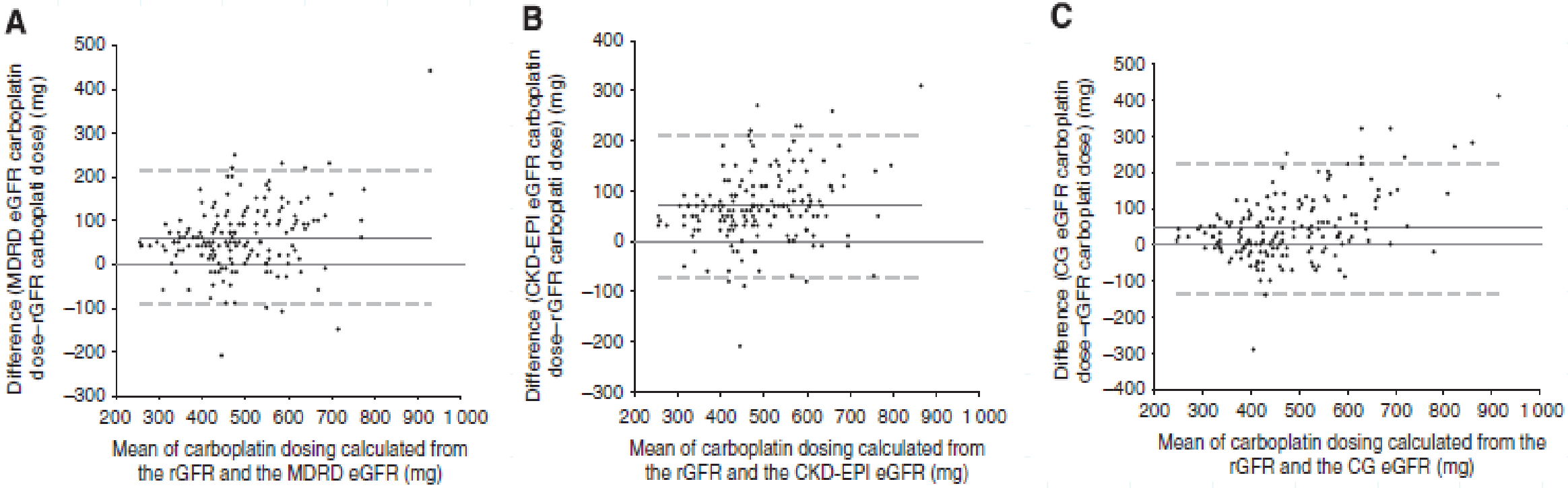
HDIO

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

British Journal of Cancer (2012) 107, 1310–1316

www.bjcancer.com

Overestimation of carboplatin doses is avoided by radionuclide GFR measurement



.....translates to difference in carboplatin dose.....

HDIO

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

British Journal of Cancer (2012) 107, 1310–1316

www.bjcancer.com

Overestimation of carboplatin doses is avoided by radionuclide GFR measurement

Table 7 Percentage of carboplatin doses, calculated using the eGFR, within 5, 10, 20, 30 and 50% of the carboplatin dose calculated using the rGFR

	% Within certain percentage of rGFR carboplatin dose				
eGFR	**5**	**10**	**20**	**30**	**50**
MDRD	18	32	69	86	96
CKD-EPI	13	25	64	82	95
CG	26	43	72	86	97

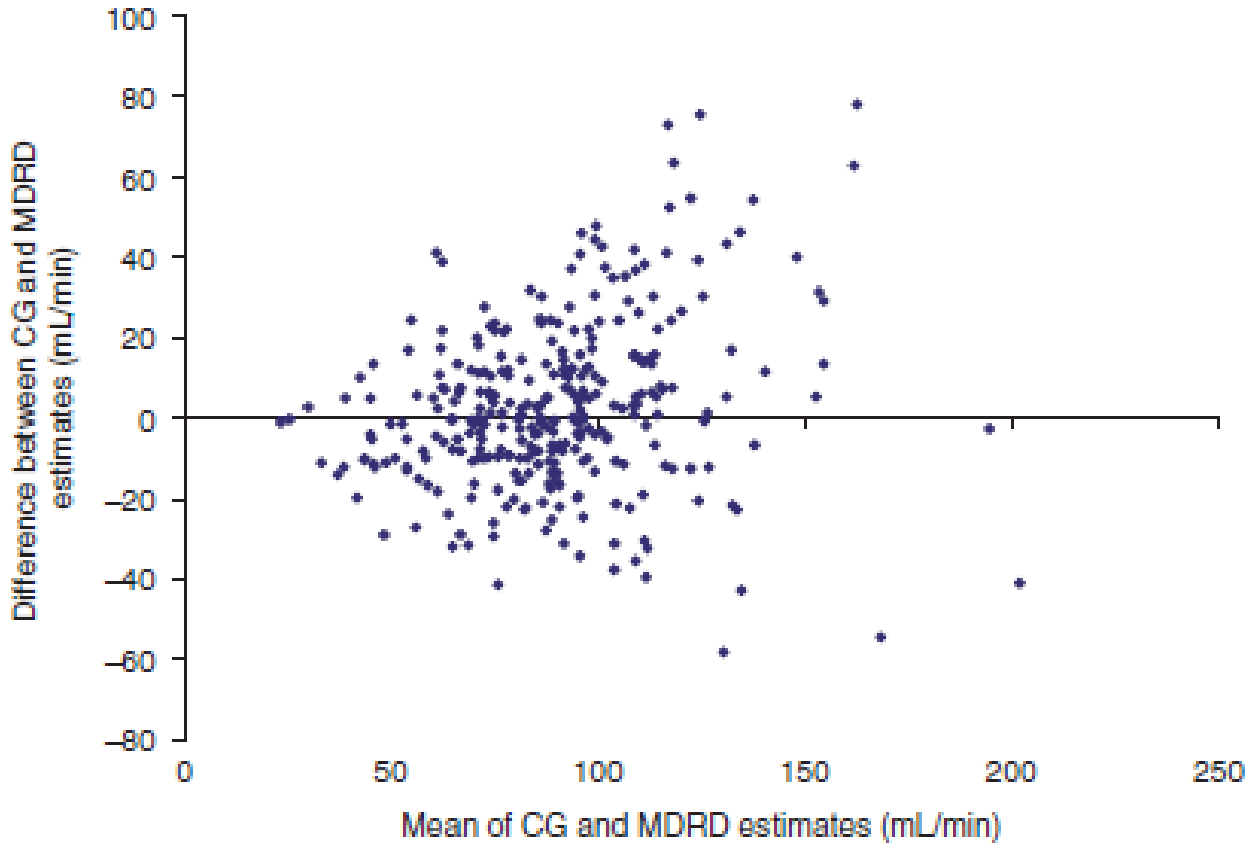
Abbreviations: CG = Cockcroft-Gault; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; rGFR = radionuclide glomerular filtration rate.

In conclusion, we have shown that **both the MDRD and the CKD-EPI estimation equations performed poorly** compared with the reference standard rGFR using 51Cr-EDTA in a heterogeneous oncology patient population that is also ethnically diverse. We have also shown that **both equations are poor across the range of common cancer types and less common cancer types treated with carboplatin-based or non-carboplatin-based chemotherapy regimens. The large inaccuracies** seen in carboplatin dosing by the use of eGFR values lead us to **recommend that an exogenous filtration marker, such as rGFR, should be used** for accurate carboplatin chemotherapy dose calculation, however, if no rGFR is available then the use of the **CG equation is preferred**.

HDIO

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

What about non-carboplatin cth?



There is good concordance of the GFR derived from the CG and MDRD formulas for most cancer patients, with less than 10% of patients expected to receive a different initial dose of chemotherapy. The MDRD formula may be a reasonable alternative to the CG formula for dosing of cancer drugs which are renally excreted or nephrotoxic.

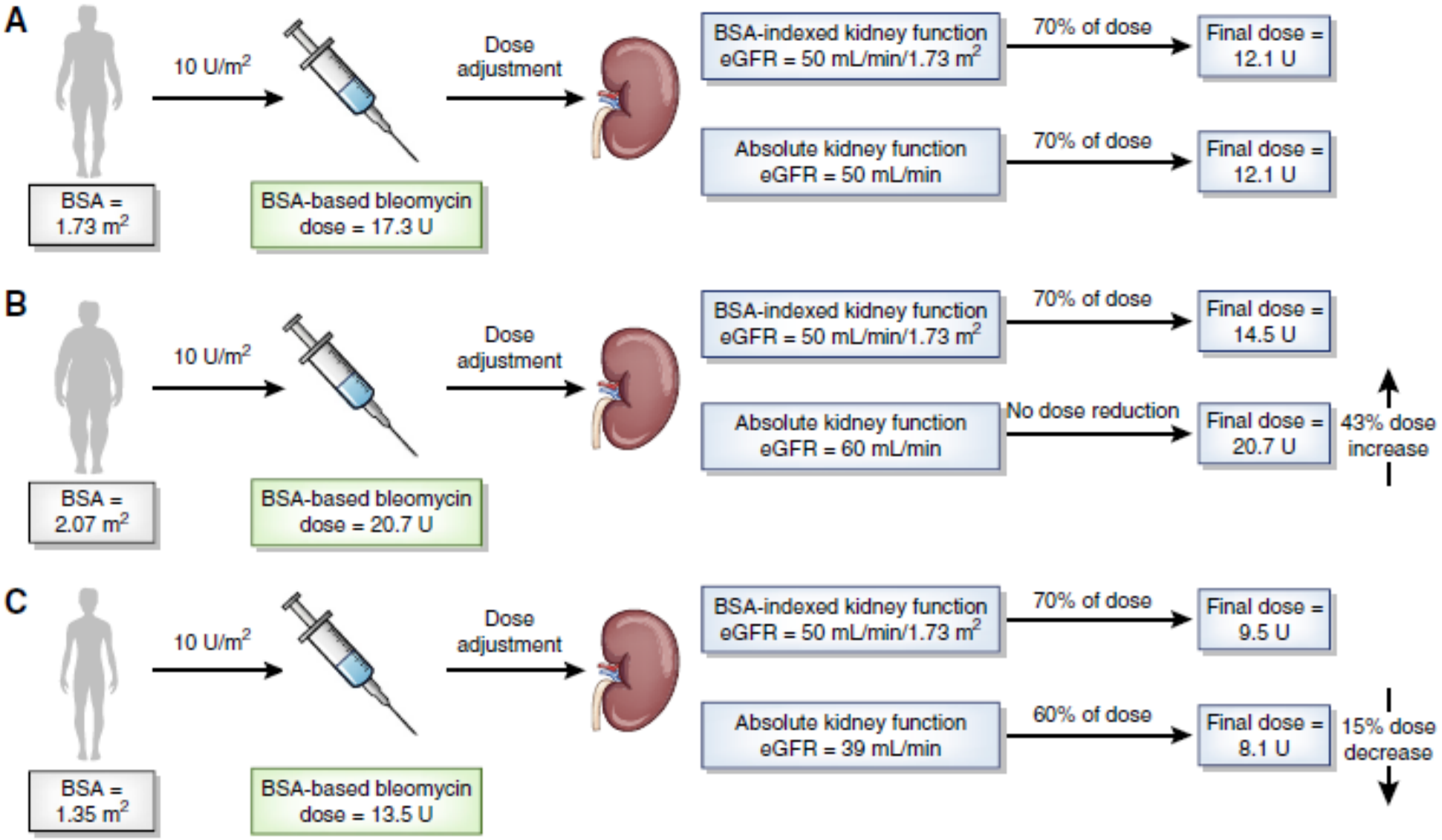
J Oncol Pharm Pract. 2010 Jun;16(2):113-9.

So… which formula should we use?

- As mentioned, most formulas currently in use are derived in non-cancer patients (or in general population)
- NCCN vaguely recommends **use of CrCl** in their guidelines pertaining to elderly adults and **“GFR calculations”** in their guidelines related to adolescent and young adults, whereas the SIOG **does not state a preferred estimation method**
- Even though CG formula is known to be **markedly less accurate** in the elderly and patients with extremes of body composition and decreased muscle mass, **it is the most widely used formula in KF evaluation today**

National Comprehensive Cancer Network (NCCN), International Society of Geriatric Oncology (SIOG)

Mililiters or mililiters per 1.73 m^2... That is the question...



Area under the curve...

- The dose administered should be adjusted in proportion to the reduction of creatinine clearance for patients with renal impairment since they require lower doses to achieve AUCs comparable with those seen with patients with normal renal function.

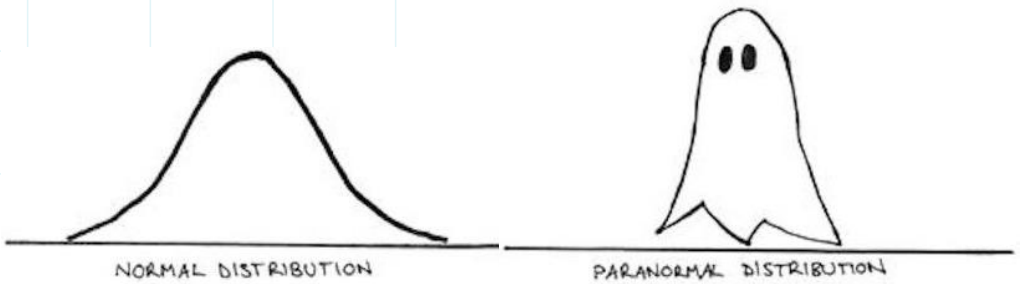
- Calvert et al. have proposed the following formula for calculation of dose:

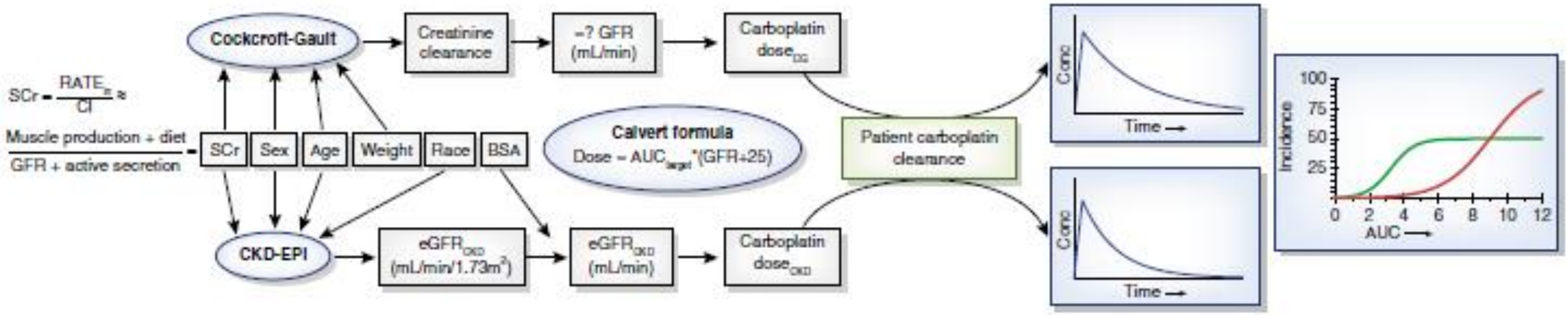
Carboplatin Dose (mg) = Target area under the curve (AUC mg·min/mL) x (GFR* + 25)

- Where the target AUC [area under the plasma concentration x time curve] is in the target range of 5 to 7 mg/ml per min for acceptable toxicity in patients receiving single agent carboplatin.

* Cockcroft-Gault Equation

Area under the curve...



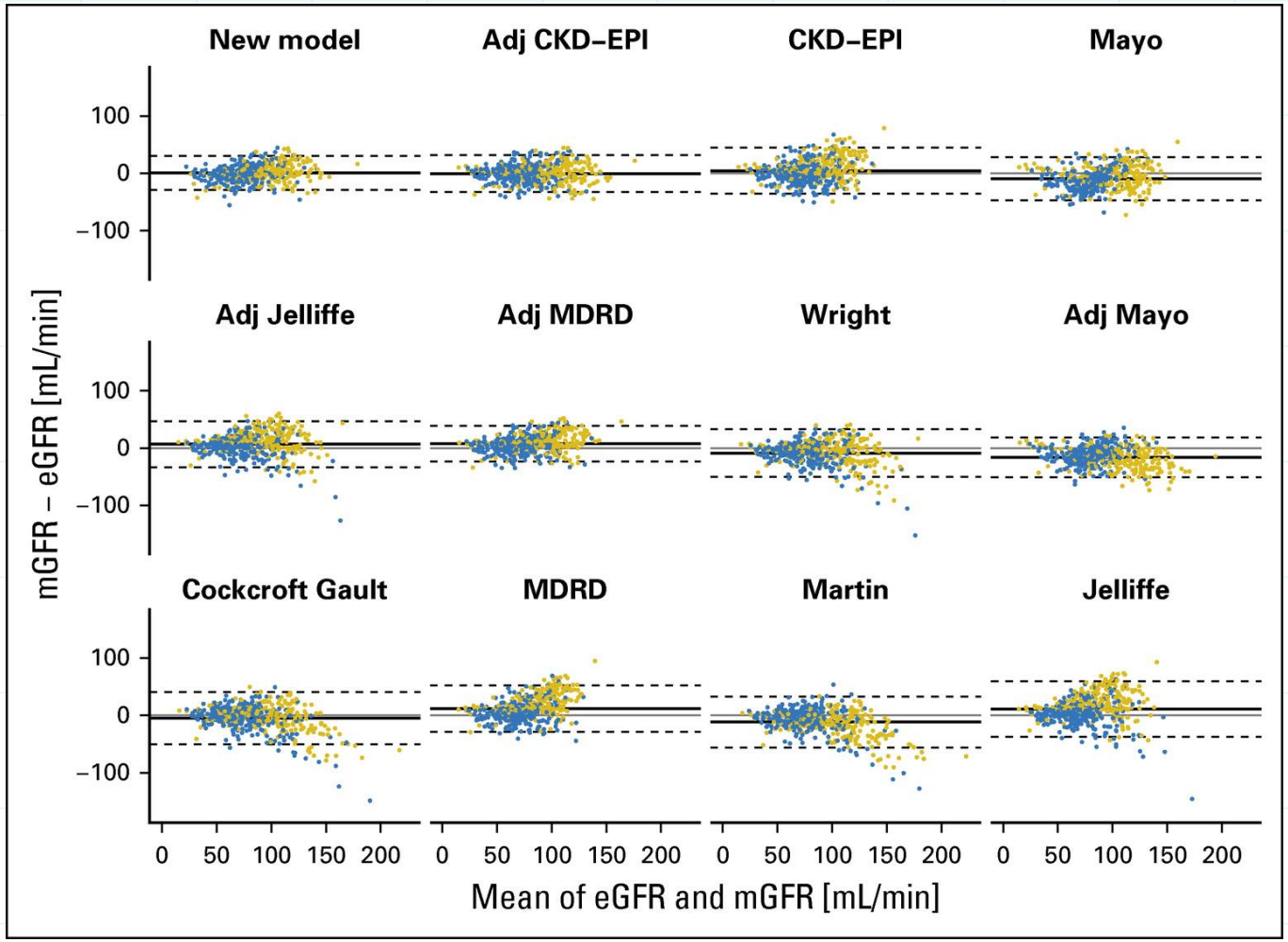


Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

Think about the future…

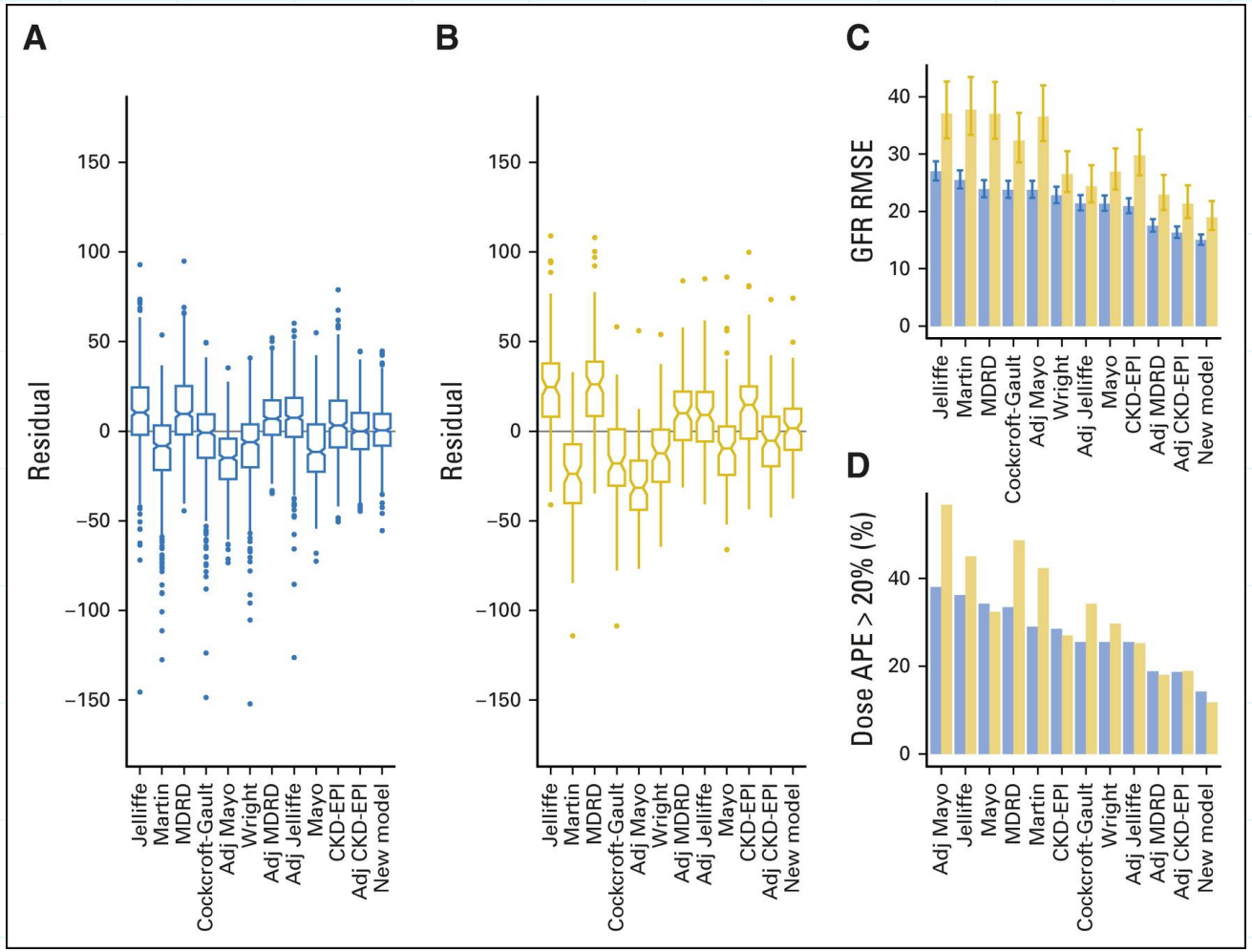
- Onconephrology…
- The available formulae have documented limitations in small data sets of cancer patients who are commonly sarcopenic and cachectic.
- As such, the adjustment of CKD-EPI, lacking weight and height measurements, to **body surface area (BSA)** seemed the most accurate model to estimate GFR in cancer patients.
- This led to the new model by Janowitz et al…

Janowitz and Williams' (JW) equation



Sleilalty et al. Intern Med J. 2018 Nov; 48(11)1382-1388

Janowitz and Williams' (JW) equation



Sleilalty et al. Intern Med J. 2018 Nov; 48(11)1382-1388

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

Conclusions

- No ideal way to measure GFR (or clearance)
- No ideal way to accurately dose Cth
- Appropriate formula depends on type of Cth used
- Despite the recent physiopathological advances in understanding the mechanism of anticancer drug nephrotoxicity, **prevention still relies on drug dosage decrease**, and active screening for renal abnormalities as part of the usual biological work up in patients treated with anticancer drugs
- „Precision medicine”