



# An Update on Kidney Diseases and Cancer

Zahra Taheri<sup>1\*</sup> 

<sup>1</sup>Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran.

\*Corresponding author: Zahra Taheri, Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran Email: Zahra\_Taheri\_2005@yahoo.com.

DOI: [10.22034/pmj.2024.2030994.1038](https://doi.org/10.22034/pmj.2024.2030994.1038)

Submitted: 2024-04-27

Accepted: 2024-08-13

#### Keywords:

Kidney diseases  
Cancer  
Chemotherapy  
CKD  
AKI

#### How to Cite this Article:

Z. Taheri, "An Update on Kidney Diseases and Cancer" *Personalized Medicine Journal*, Vol. 9, no. 34, pp. 35- 44.

#### Abstract:

Numerous individuals worldwide are grappling with kidney disease or malignancy. Renal cell carcinoma (RCC) and chronic kidney disease (CKD) are directionally associated and share risk factors. The investigation of the correlation between cancer chemotherapy and renal disorders is of importance due to the kidneys' involvement in detoxification. The current disparity between the occurrence of cancer and kidney problems is addressed by this investigation. CKD can induce RCC via a cystic disorder or oxidative stress. RCC promotes CKD in terms of tumor interactions, physical removal of a kidney mass, and perioperative acute renal disease. Kidney failure leads to renal cancer-specific pathways. For example, renal progenitors are converted to tumor-initiating cells via HIF, Notch, mTOR, and Hippo pathways. Furthermore, progress in cancer treatment during recent years increased the overall survival of patients with advanced malignancies faced with early and late adverse effects from therapeutics. There are conflicting findings about the dosing of typical chemotherapeutics because of loss of kidney function. Recommended doses are usually based on expert opinion, not scientific evidence. This investigation evaluated the issues in cancer patients with kidney problems that can help patients by informing physicians about GFR loss and its effect on chemotherapy.

## INTRODUCTION

Worldwide, a large number of individuals are afflicted with cancer or kidney illness. Renal tumors and kidney disease are associated with similar risk factors. Renal cancer may result from risk factors for kidney illnesses such as obesity, diabetes, age, hypertension, smoking, nephrotoxic medications, and heavy metals, according to epidemiologic study (1-4). On the other hand, smoking, diabetes, and obesity are linked to nephron loss as a result of glomerular hyperfiltration and CKD linked to glomerulosclerosis (4). After all, renal damage ultimately results in hypertension and, less often, hypertension causes kidney injury. Another sensitive indicator of early CKD is hypertension (2). Nephrotoxic medicines and heavy metals stimulate necroinflammation and oxidative stress associated with toxic acute kidney injury (AKI) (3). Site-specific kidney diseases lead to determined kinds of kidney cancer. Moreover, different kidney cancer types are associated with specific kidney diseases (5). Because of the role of kidneys in detoxification, studying the relationship between cancer chemotherapy, and kidney disorders is significant. This study fills the current gap between

cancer occurrence and the treatment of kidney problems.

### From Renal Failure to Renal Tumor: Pathways and Mechanisms

The proliferation of long-lived renal progenitor cells during kidney repair is the cause of cancerogenesis (6). These cells are the source of epithelial cells in the glomerulus, the nephron, and the collecting duct (7). Kidney progenitors frequently exhibit delayed, spontaneous proliferation to compensate for the loss of ductal epithelial cells and podocytes (7, 8). The majority of ductal epithelial cells are proliferative and dedifferentiated in response to injury (9). However, the population of putative renal progenitors compensates for epithelial cell loss by the detachment of podocytes and necrosis of tubular epithelial cells through clonal proliferation (8, 10). Based on Lindgren et al. reports, transcriptomics and protein profiles of renal progenitors are similar to Papillary renal cell carcinomas (pRCCs), and papillary adenomas (11). The upregulation of the Notch1 pathway increases renal progenitor proliferation in AKI, papillary adenomas, and pRCC in transgenic animals (12). Renal progenitors of collecting

ducts can lead to oncocytoma, and carcinoma renal cell carcinoma (RCC) in this site (13).

According to estimation, 22%-36% of RCC patients who underwent partial or complete nephrectomy had an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m<sup>2</sup> before surgery. Up to 45% of CKD patients with proteinuria may have background CKD (14, 15). Kidney failure leads to renal cancer-specific pathways. Through pathways like HIF, Notch, mTOR, and Hippo, renal progenitors transformed into tumor-initiating cells (12). HIF pathway plays a role in the hypoxic condition of AKI, CKD (16), and clear cell renal cell carcinoma (ccRCC) (17).

### HIF pathway

In hypertensive individuals and those with the HIF pathway, the renin-angiotensin system, prostaglandins, and endothelin can induce vessel constriction, which may lead to kidney cancer and CKD (17).

### mTOR pathway

The protein kinase B/mTOR pathway, in conjunction with hyperglycemia and hyperinsulinemia, is responsible for the development of RCC and diabetic renal disease in diabetes mellitus (17, 18). RCC was frequently associated with alterations in the phosphoinositide 3-kinase–protein kinase B–mTOR pathway, including PTEN, MTOR, and PIK3CA (19).

### Notch pathway

The orientation and polarity of the mitotic spindle are regulated by Notch (20). In renal progenitor cells, aberrant notch expression results in atypical mitoses via the disruption of cell cycle checkpoints and/or mitotic spindle adjustment (12). Renal progenitor cells, papillary adenomas, and RCC are more likely to become malignant when the notch pathway is active, which is linked to renal failure (21).

### Hippo pathway

The Hippo pathway, which is influenced by the yes-associated protein 1/transcriptional coactivator with PDZ-binding motif [YAP/TAZ] protein, is disrupted in cystic renal disease, acute kidney injury (AKI), and certain sporadic cancers. Thus, there is a potential correlation between RCC and cell growth in cysts (24). Salvador homolog-1 (SAV1) is a constituent of the Hippo pathway. The Hippo-YAP1 signaling pathway causes a loss of copy number and leads to the development of high-grade ccRCC (25). Furthermore, spontaneous pRCC is caused by the loss of chromosome 22. The tumor suppressor genes for Neurofibromatosis type 2 (NF2) are located on this chromosome. NF2 produces SAV1, a regulator of the Hippo pathway, and SMARCB1, a matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1 (SWI/

SNF related, actin-dependent regulator of chromatin) that codes for a part of the lactate nonfermentable complex/chromatin-altering switch (26).

### c-Met–hepatocyte growth factor pathway

Human oncogenesis is associated with iron overload (27). RCC is ultimately brought on by the generation of reactive oxygen species (a Fenton reaction) in the renal proximal tubules of mice after repeated iron treatment. Numerous genomic alterations were seen in these mice. The most often altered locus were a CDKN2a/2b deletion and a MET amplification. Tumor diameters are also correlated with met amplification and/or expression (28).

### Chromatin remodeling pathways

Aberrant chromosomal arm 3p genes polybromo 1 (PBRM1), SET domain-containing protein 2 (SETD2), BRCA-associated protein-1 (BAP1), or SMARCB1 are among the chromatin remodelling pathways linked to ccRCC. Moreover, ccRCC is often linked to TP53 alterations and loss of CDKN2A as a result of deletions, mutations, or promoter hypermethylation (5).

### Chronic Kidney Disease and Tumor Associations

CKD and tumors correlated via inter-relationships, such as chronic inflammation, collection of carcinogenic compounds, oxidative stress, and excessive parathyroid hormone.

### Chronic Inflammation

In CKD, inflammation is complicated. Dialysis, oxidative stress, acidosis, metabolic abnormalities in adipose tissue, and intestinal problems are all risk factors for infection (29). Reduced renal excretion activity leads to increased plasma half-lives of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (30). The research found that infections afflicted 23.6% (95% CI: 22.8-24.6) of CKD patients, and hospitalization rates were greater for both groups (31).

### Accumulation of Carcinogenic Compounds

Patients with end-stage kidney disease (ESKD) develop uremic as a result of high circulating nitrogen levels, which are impacted by carcinogens and agents. For example, uremic patients on dialysis have higher levels of circulating carcinogens such as 2-amino-6-methyldipyrido [1,2-a:3',2'-d]imidazole (Glu-P-1) and 2-aminodipyrido [1,2-a:3',2'-d]imidazole (Glu-P-2) than healthy people. These two substances' concentrations may stay increased in uremic individuals for a lengthy period, as they did after 30 days of dialysis (32).

### Oxidative Stress

When the equilibrium between oxidation and

antioxidant activity in the body is disrupted, oxidative stress ensues. In CKD, oxidative activity increases while the antioxidant system decreases. For example, in early CKD, neutrophils, monocytes, and macrophages may be produced. This resulted in the synergistic production of reactive oxygen species (ROS) (33). In a study of 87 CKD patients, the plasma oxidative stress indicator 8-epiPGF2a demonstrated a substantial direct connection with CKD development (34). Simultaneously, increasing ROS impeded pro-oxidant clearance in CKD patients, creating a prooxidant environment. The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) responded to antioxidant reagents through the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) pathway (35). During oxidative stress, the cytoplasmic covalent bond between Nrf2-keap1 and Nrf2 was disrupted, enabling Nrf2 to enter the nucleus. The Nrf2/Maf complex is subsequently formed by heterodimerization with Maf (musculoaponeurotic fibrosarcoma oncogene homolog) proteins. This complex transcribes the ARE-dependent gene of antioxidant and cytoprotective factors (36). In mononuclear cells of peripheral blood from uremic and hemodialysis patients, Nrf2-dependent antioxidant genes including heme oxygenase-1 (HO-1), glutamate-cysteine ligase modifier subunit (GCLM), and catalase were downregulated. Oxidant genes were overexpressed and NF- $\kappa$ B was increased at the same time (37). NF- $\kappa$ B may be stimulated by certain T cell types (38). DNA fixation of lymphocytes in chronic renal failure (CRF) individuals on dialysis was similar to that of healthy people. Still, it significantly decreased following UV or gamma exposure in the CRF people. So, CRF patients might have less ability to repair DNA and obtain this ability via dialysis. Unrepaired or improperly fixed DNA would cause mutations, aberrations in the chromosome, and even cancer (39). The lymphocytes of dialysis patients displayed indications of permanent genomic damage, such as aberrant dispersion of whole chromosomes, chromosomal breakage, and sister chromatid swaps. These anomalies raised the risk of uterine tumors, lymphoma, and cancers of the kidney, prostate, and liver (40). Variations in the DNA fixation enzyme genes of Xeroderma pigmentosum complementation group D (XPD) and X-ray cross-complementing group 1 (XRCC1) were reported to have significant relationships with ESKD (41).

### Excessive Parathyroid Hormone

Lower phosphorus excretion from the slow renal failure results in higher circulating phosphorous and a mix of phosphorous and calcium phosphate lowered circulation calcium. Reduced active vitamin D, low

blood calcium, and high serum phosphorous were the main causes of secondary hyperparathyroidism (SHPT) (42). Renal carcinoma (32) is caused by parathyroid hormone (PTH) and its receptors. In late CKD, PTH also overexpressed Fibroblast growth factor-23 (FGF23) to balance the increased phosphate outflow from additional bone turnover (43). FGF23 is a hormone that originates from bone and inhibits the production of vitamin D hormone and phosphate reabsorption in the kidneys (44). The upregulation of FGF-23 in individuals with CKD may be associated with the adjustment of FGF-23 through bone remodelling, which is facilitated by the diffusion of low molecular weight FGFs. Prostate cancer, paraneoplastic malfunctions, and hypophosphatemia are the results of FGF23 overactivation through FGF/FGFR signal transduction. Consequently, FGF-23 may be linked to the development of cancer (45).

### Chronic Kidney Disease in Tumor Survivors

The overall survival rate for those with advanced cancers has risen recently due to advancements in cancer therapy. Adverse consequences from therapies, including cardiac difficulties, neuropathy, bone loss, recurring malignancies, and renal failure, were seen by tumor survivors both early and late. One of the most prevalent kidney failures in these people is CDK, which manifests in a variety of ways in different survivors (46, 47).

### CKD in Childhood Tumor Survivors

Childhood tumor survivors are at high risk for both acute and chronic renal failure. Nephrotoxic chemotherapy therapies such as ifosfamide, cisplatin, methotrexate, and high-dose cyclophosphamide may cause CKD and nephron loss. Furthermore, progressive chronic kidney disease (CKD) may develop in adolescence or adulthood in these children who have a higher risk of AKI because to volume depletion, sepsis-related acute tubular necrosis, tumor lysis syndrome, and loss of juvenile nephrons (48).

### CKD in Patients Who Have Survived Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplant patients often have chronic kidney disease (CKD) (HSCT). Due to various types of autologous vs. allogenic and transplant times, as well as the absence of a consensus definition, the prevalence of CKD in these individuals ranges from 0 to 60% (49). Three kinds of chronic kidney disease (CKD) may be distinguished based on the specific causes of the condition: thrombotic microangiopathy, nephrotic syndrome, and chronic calcineurin inhibitor toxicity. On the other hand, the etiology of CKD in some individuals remains unknown (48).

### **CKD in Cancer Survivors Exposed to Immunotherapy**

To enhance the anticancer capabilities of the host, tumor immune-therapeutics orchestrate the immune response. Cytotoxic T lymphocyte-associated protein 4, programmed death protein 1, and programmed-death ligand 1 are the targets of monoclonal antibodies known as immune checkpoint inhibitors (ICIs). ICIs have the potential to eradicate critical negative regulators of T-cells. Despite the promising activity of ICIs, they are unsuccessful in 60%-80% of cases as a result of autoimmune adverse effects that affect nearly every human organ system. Allergic interstitial nephritis (AIN) is the most frequent kidney immune-linked adverse event. An ICI-related AIN affects 3%-5% of the individuals treated with ICIs (50, 51). Glomerular disorders are significantly less usual than AIN (52).

### **Chronic Kidney Disease and Cancer-Associated Mortality**

CKD is linked with cancer mortality. In retrospective observational research on 961 stage IV tumor people having an average age of 69 years and 48.2% women, 15.6% had CKD. During the mean of 9.8 months, 66.4% of people died, of whom 82.44% died due to tumors. Whole death and cancer-associated mortality were significantly more prevalent in CKD individuals than in non-CKD individuals after adjusting for prognostic variables, including ECOG PS and tumor therapy (HR 1.41, 95% CI 1.13–1.77 vs. HR 1.43, 95% CI 1.12–1.83, respectively). A substantially increased mortality risk was associated with CKD in individuals with breast, kidney, and urinary tract malignancies. Additionally, for kidney and urinary tract cancer (HR 3.33, 95% CI 1.42–7.78) as well as breast cancers (HR 7.01, 95% CI 1.47–33.4), the association between CKD and cancer-associated mortality was site-dependent (53). Compared to those without CKD, the CKD patients were older, had more advanced ECOG PS, and had less anticancer therapy. Inadequate performance is linked to a worse survival rate in individuals with advanced cancer (54). Canadian research found that patients with ECOG PS 4 with advanced malignancies had an average life of 25 days, whereas those with ECOG PS 3 had an average survival of 50 days (55). Additionally, ECOG PS was lower in CKD patients than in healthy persons, and frailty is more frequent in CKD patients than in healthy individuals (56). For patients with stage IV malignancies, palliative chemotherapy is the recommended course of action to prolong survival, lessen symptoms, and enhance quality of life (57). However, because of more frequent side effects in cancer people with CKD, it is less common to prescribe antitumor medication than those without CKD (58). Therefore, the correlation between CKD, and tumor mortality could be a result of the lack

of cancer treatment in CKD patients (53).

### **Cancer Drug Dosing in CKD**

Kidneys eliminated a lot of anti-tumor drugs. To determine an appropriate equilibrium between drug impression and toxicity, medicine doses should be regulated based on renal activity. As most anti-tumor therapeutics cannot be monitored, adjustment is performed based on the evaluation of renal activity (59).

According to a study by Launay-Vacher et al., 50–60% of patients with tumors had a renal activity that is below normal or an eGFR of less than 90 mL/minute per 1.73 m<sup>2</sup> (60). Furthermore, during anti-tumor treatment, patients with tumors often have a steady deterioration in renal function. A median decrease in GFR of 7 ml/min per 1.73 m<sup>2</sup> was seen 24 months after diagnosis in a retrospective study of French cancer patients (59). The overestimation of renal activity causes overdosing or improper drug choice and likely elevated toxicity. However, its undervalue leads to underdosing or unsuitable element elimination and likely suboptimal tumor resultants (61). During drug development, most of the time, merely individuals with normal or mild renal failure are considered in clinical trials (62). As a result, data from persons with severe kidney failure and ESKD necessary kidney renewal are few, and only a few innovative therapy submissions to the FDA include data from them (63). The frequent exclusion of CKD patients from cancer clinical trials is a problem and a barrier to adequate dosing of cancer patients with CKD. As a result, it promotes a lack of adequate clinical treatment for this group (64).

### **CHANGES OF PHARMACOKINETICS AND PHARMACODYNAMICS IN CKD PATIENTS**

The efficacy of a medication is contingent upon its pharmacokinetic and pharmacodynamic properties. The pharmacodynamic properties of a medication are determined by its receptor/cellular targets, downstream signal transduction pathways, and interactions. The absorption, distribution, metabolism, and excretion of a medication are all examples of its pharmacokinetic properties. In individuals with kidney failure, a drug's pharmacokinetic and pharmacodynamic characteristics can be altered. Some therapeutics are not omitted by the renal activity, but their metabolites are detoxified by the kidneys (65).

### **CHEMOTHERAPEUTICS AND KIDNEY INJURIES**

Since there have been some contradictory reports regarding the dosage of common chemotherapeutics, we have examined some of the most often used drugs to treat cancer in this section, including methotrexate/pemetrexed, 5-fluorouracil/capecitabine, cyclophosphamide, ifosfamide, and cisplatin. Cisplatin

Cisplatin is a common drug against a wide range

of cancers. Cisplatin therapy as platinum-based chemotherapy leads to AKI in 6% to 30% of people who have testicular cancer depending on the population (66). Cisplatin induces AKI and urinary magnesium wasting by disrupting the S3 sector of the proximal tubule and distal nephron. Carboplatin and oxaliplatin do not cause severe renal damage, however, there have been cases of AKI and acute interstitial nephritis (AIN) after carboplatin treatment (67). The most common cisplatin-related side effects were nausea/vomiting, nephrotoxicity, and bone marrow suppression. Cisplatin is not an acceptable choice for persons with severe renal failure due to its nephrotoxicity influence on CKD progression and non-kidney side effects. The second constraint is more severe in ESKD patients who have decreased renal function (68). On non-dialysis days, they may get lesser dosages of cisplatin since it is strongly and permanently bound. The unbound cisplatin is dialyzed, and the bound moiety does not replace it (69).

**Carboplatin**

Carboplatin is usually administered therapeutically against different cancers. Carboplatin dose calculated with the Calvert Formula. Carboplatin-based multichemotherapy was efficacious in individuals undergoing hemodialysis and peritoneal dialysis, without enhancing toxicity or diminishing efficacy (70, 71). In hemodialysis patients, the Calvert formula

is considered to have a GFR of zero, as are other formulae that are used for peritoneal dialysis (Table 1) (72). Carboplatin is frequently dialyzable, as it does not bind to protein rapidly after injection, in contrast to cisplatin. However, dialysis becomes ineffective as a result of its binding to plasma components after 24 hours. Therefore, hemodialysis should be performed within 24 hours of carboplatin administration, but not right following administration (69).

**Cyclophosphamide**

Cyclophosphamide is employed to manage a variety of solid and liquid malignancies. Hemodialysis is required for 12 hours following treatment, as cyclophosphamide and its metabolites are eliminated through this process. The dosage of cyclophosphamide was decreased to one-fourth in patients undergoing peritoneal dialysis (69).

**Ifosfamide**

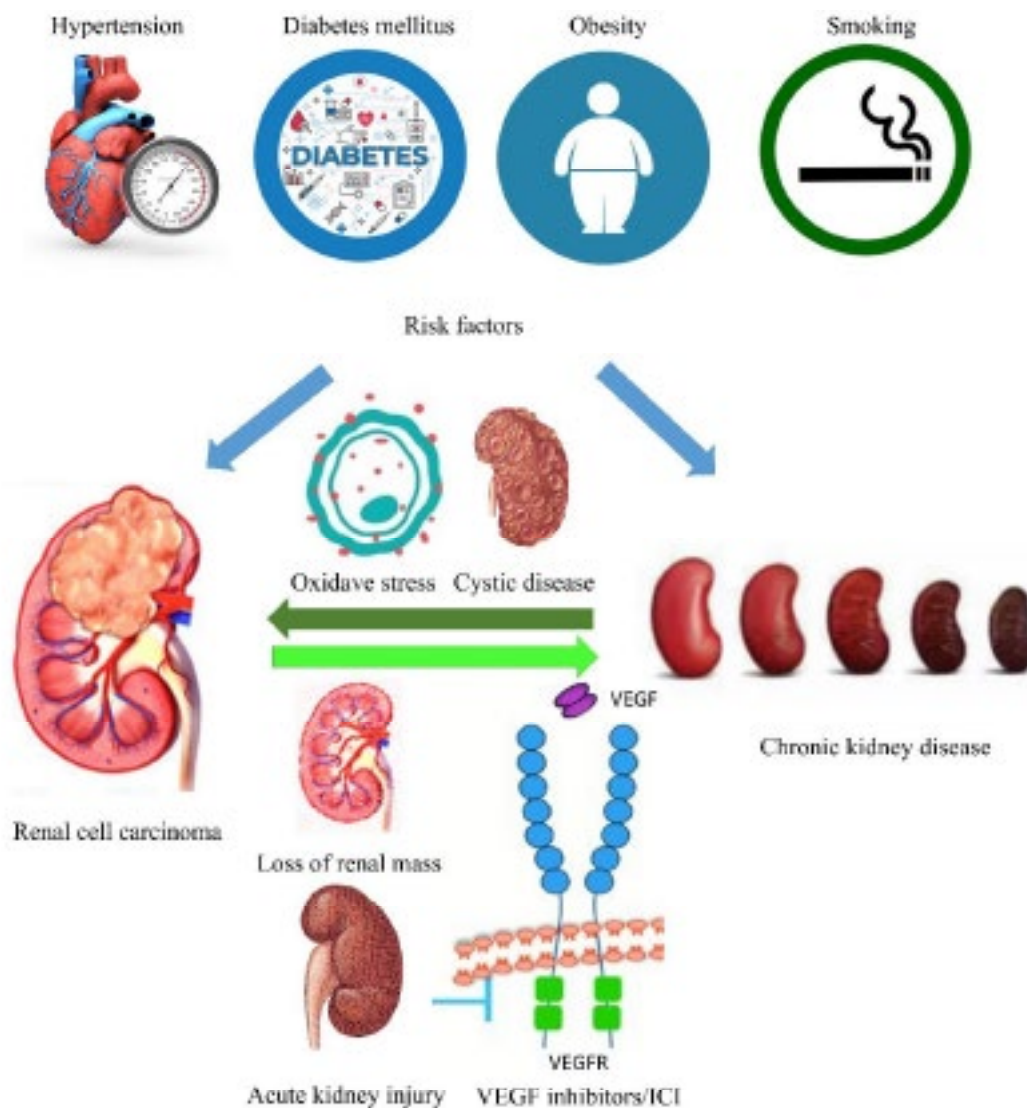
Cyclophosphamide-associated agents like ifosfamide, as well as chloroacetaldehyde metabolites, are their accumulation cause AKI and progressive CKD nephrotoxic via myelosuppressive, neurotoxicity, and tubular injury (73, 74).

A mitochondrial toxicity, chloroacetaldehyde is a metabolite of ifosfamide, another treatment for testicular sarcomas (48). Ifosfamide toxicity was comparable to that of other Fanconi-like

**Table 1.** Usual formulas to estimate GFR based on serum creatinine

Equation	Advantage	Disadvantage	Reference
<b>Calvert Formula (81):</b> dose (mg) = AUC (mg/mL x min) x [GFR (mL/min) + 25 (mL/min)].	Accurate	The GFR must be measured, containing invasive and inconvenient methods	(82, 83)
<b>Cockcroft-Gault (84)</b>  (((140-age) x weight)/(72xScr))x0.85 (only for women)	Accurate  Widely apply in cancer sufferers	Imprecise in the elderly  Biased in BMI ≥30 and BMI <18.5	(85)
<b>MDRD (86)</b>  186 × (SCr) <sup>-1.154</sup> × (age) <sup>-0.203</sup> × 1.212 (only for blacks) × 0.742 (only for women)	More precise  Accurate in elderly  Accurate BMI ≥30	Biased in BMI <18.5  Not widely used in cancer sufferers	(87, 88)
<b>CKD-EPI</b>  Women with SCr ≤ 0.7: 144 × (0.993) <sup>age</sup> × (SCr/0.7) <sup>-0.329</sup> Women with SCr > 0.7: 144 × (0.993) <sup>age</sup> × (SCr/0.7) <sup>-1.209</sup> Men with SCr ≤ 0.9: 141 × (0.993) <sup>age</sup> × (SCr/0.9) <sup>-0.411</sup> Men with SCr > 0.9: 141 × (0.993) <sup>age</sup> × (SCr/0.9) <sup>-1.209</sup>	More precise  Accurate in elderly  Accurate BMI ≥30	Biased in BMI <18.5  Not widely applied in cancer sufferers	(89)

Abbreviations: SCr, serum creatinine; BMI, body mass index



**Fig 1.** Inter-relationships between various host risk factors, chronic kidney disease, and renal cell carcinoma

syndromes, such as hypophosphatemia, metabolic acidosis, hypokalemia, and tubular proteinuria. It has the potential to result in lower eGFR and progressive tubular failure (75). Additionally, Ifosfamide may induce frequent episodes of nephrogenic diabetes insipidus. The following are risk factors for ifosfamide nephrotoxicity: stored cumulative dose, previous nephrectomy, basis CKD, and previous or simultaneous cisplatin subjection. Mesna coadministration can mitigate the risk of hemorrhagic cystitis caused by the other ifosfamide metabolite, acrolein; however, its impact on nephrotoxicity remains uncertain (76). Children who received an average stored ifosfamide dosage of 54 g/m<sup>2</sup> showed encouraging long-term renal function after 10 years; 90% of the children had regular tubular activity and 79% showed eGFR. 90 milliliters per minute for 77 square meters. There is little information available on individuals using

ifosfamide and long-term renal follow-up. Over the course of five years, the average eGFR dropped from 82 to 67 mL/min/1.73 m<sup>2</sup> in a retrospective cohort of 259 people, and none of them had ESKD (78).

#### **Methotrexate/Pemetrexed**

Both methotrexate (MTX) and its derivative pemetrexed inhibit the cellular division pathways linked to folate. It first experiences renal excretion, precipitation of MTX high dosage in renal tubules, and temporary acute kidney injury. AKI causes an increase in serum MTX, which is quickly decreased by hemodialysis to avoid extra-renal damage. Since it usually reverses, more dialysis or the recombinant enzyme glucarpidase (GPDG2) of metabolites for hydrolysis is strongly advised (79).

#### **Fluorouracil/Capecitabine**

5-Fluorouracil and the oral pro-drug form of it,

capecitabine, do not have nephrotoxicity. However, as 5-FU metabolites accumulate in CKD people, they are not administered to individuals suffering from advanced CKD (69). Despite this, in some studies, capecitabine was successfully administered to CKD V patients or those on hemodialysis (69, 80).

## CONCLUSION

There is a bidirectional relationship and shared risk factors between renal cell carcinoma and chronic kidney disorders. Cystic abnormalities or oxidative stress in people with chronic kidney disease may cause RCC. RCC may also make chronic kidney disease (CKD) worse due to tumor interactions, nephrectomy or partial kidneyectomy, and post-operative acute renal sickness. Furthermore, renal damage with vascular endothelial growth factor blockers and immune checkpoint inhibitors may result in chronic kidney disease. On the other hand, according to the once-nephrology reports, cancer morbidity in CKD patients and paraneoplastic renal diseases is high. Elevated tumor risk in CKD might be a result of chronic inflammation, carcinogen accumulation, oxidative stress, failure of DNA repair, as well as increased parathyroid hormone. The paraneoplastic renal failure was associated with hematologic malignancies, carcinoma, and anti-tumor treatments. Regarding the high risk of tumor in CKD, regular tumor screening, such as marker assessment monitoring, imaging evaluation, and endoscopy is highly recommended for early diagnosis and a more successful prognosis.

It is essential to investigate the long-term renal consequences of recently synthesized anticancer targets. By understanding the risks of chronic kidney disease (CKD) and its causes, we may prevent renal side effects by limiting the prescription or dosage of anticancer medications and the eligibility for clinical trial participation in cancer patients. Tumor death is associated with chronic kidney disease (CKD). Consequently, strategies to prevent AKI and the shift from AKI to CKD are needed to improve outcomes for tumor survivors. Since renin-angiotensin-aldosterone blockade, sodium-glucose cotransporter 2 suppressors, and selective mineralocorticoid receptor antagonists are renal therapies, their effectiveness in treating chronic kidney disease (CKD) or lowering eGFR elimination in tumor survivors will be highlighted. The interaction of renal disorders with tumors influences anti-cancer therapy. Control of this situation is tough. The pitfalls of circulating creatinine as a GFR biomarker are problematic. However, physicians should know about GFR loss and its effect on chemotherapy.

## Consent for publication

Not applicable.

## Funding

Not applicable.

## Conflict of interest

No conflict of interest.

## Acknowledgements

Declared none.

## REFERENCES

1. Lee M, Wang Q, Wanchoo R, Eswarappa M, Deshpande P, Sise ME. Chronic Kidney Disease in Cancer Survivors. *Advances in Chronic Kidney Disease*. 2021;28(5):469-76. e1.
2. Carriazo S, Vanessa Perez-Gomez M, Ortiz A. Hypertensive nephropathy: a major roadblock hindering the advance of precision nephrology. Oxford University Press; 2020. p. 504-9.
3. Mulay SR, Linkermann A, Anders H-J. Necroinflammation in kidney disease. *Journal of the American Society of Nephrology: JASN*. 2016;27(1):27.
4. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *The Lancet*. 2017;389(10075):1238-52.
5. Peired AJ, Lazzeri E, Guzzi F, Anders H-J, Romagnani P. From kidney injury to kidney cancer. *Kidney International*. 2021;100(1):55-66.
6. Young MD, Mitchell TJ, Vieira Braga FA, Tran MG, Stewart BJ, Ferdinand JR, et al. Single-cell transcriptomes from human kidneys reveal the cellular identity of renal tumors. *Science*. 2018;361(6402):594-9.
7. Lazzeri E, Angelotti ML, Peired A, Conte C, Marschner JA, Maggi L, et al. Endocycle-related tubular cell hypertrophy and progenitor proliferation recover renal function after acute kidney injury. *Nature communications*. 2018;9(1):1344.
8. Lasagni L, Angelotti ML, Ronconi E, Lombardi D, Nardi S, Peired A, et al. Podocyte regeneration driven by renal progenitors determines glomerular disease remission and can be pharmacologically enhanced. *Stem cell reports*. 2015;5(2):248-63.
9. Kusaba T, Lalli M, Kramann R, Kobayashi A, Humphreys BD. Differentiated kidney epithelial cells repair injured proximal tubule. *Proceedings of the National Academy of Sciences*. 2014;111(4):1527-32.
10. Kang HM, Huang S, Reidy K, Han SH, Chinga F, Susztak K. Sox9-positive progenitor cells play a key role in renal tubule epithelial regeneration in mice. *Cell reports*. 2016;14(4):861-71.
11. Lindgren D, Boström A-K, Nilsson K, Hansson J, Sjölund J, Möller C, et al. Isolation and characterization of progenitor-like cells from human renal proximal tubules. *The American journal of pathology*. 2011;178(2):828-37.
12. Peired AJ, Antonelli G, Angelotti ML, Allinovi M, Guzzi F, Sisti A, et al. Acute kidney injury promotes development of papillary renal cell adenoma and carcinoma from renal progenitor cells. *Science translational medicine*. 2020;12(536):eaaw6003.
13. Christensen BM, Kim Y-H, Kwon T-H, Nielsen S. Lithium treatment induces a marked proliferation of primarily principal cells in rat kidney inner medullary collecting duct. *American Journal of Physiology-Renal Physiology*. 2006;291(1):F39-F48.
14. Dey S, Hamilton Z, Noyes SL, Tobert CM, Keeley J, Derweesh IH, et al. Chronic kidney disease is more common in locally advanced renal cell carcinoma.

- Urology.2017;105:101-7.
- 15.O'Donnell K, Tourojman M, Tobert CM, Kirmiz SW, Riedinger CB, Demirjian S, et al. Proteinuria is a predictor of renal functional decline in patients with kidney cancer. *The Journal of Urology*. 2016;196(3):658-63.
  - 16.Shu S, Wang Y, Zheng M, Liu Z, Cai J, Tang C, et al. Hypoxia and hypoxia-inducible factors in kidney injury and repair. *Cells*. 2019;8(3):207.
  - 17.Chappell JC, Payne LB, Rathmell WK. Hypoxia, angiogenesis, and metabolism in the hereditary kidney cancers. *The Journal of clinical investigation*. 2019;129(2):442-51.
  - 18.Anders H-J, Huber TB, Isermann B, Schiffer M. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nature Reviews Nephrology*. 2018;14(6):361-77.
  - 19.Guo H, German P, Bai S, Barnes S, Guo W, Qi X, et al. The PI3K/AKT pathway and renal cell carcinoma. *Journal of genetics and genomics*. 2015;42(7):343-53.
  - 20.Charnley M, Ludford-Menting M, Pham K, Russell SM. A new role for Notch in the control of polarity and asymmetric cell division of developing T cells. *Journal of Cell Science*. 2020;133(5):jcs235358.
  - 21.Lasagni L, Ballerini L, Angelotti ML, Parente E, Sagrinati C, Mazzinghi B, et al. Notch activation differentially regulates renal progenitors proliferation and differentiation toward the podocyte lineage in glomerular disorders. *Stem cells*. 2010;28(9):1674-85.
  - 22.Seeger-Nukpezah T, Geynisman DM, Nikonova AS, Benzing T, Golemis EA. The hallmarks of cancer: relevance to the pathogenesis of polycystic kidney disease. *Nature Reviews Nephrology*. 2015;11(9):515-34.
  - 23.Anorga S, Overstreet JM, Falke LL, Tang J, Goldschmeding RG, Higgins PJ, et al. Deregulation of Hippo-TAZ pathway during renal injury confers a fibrotic maladaptive phenotype. *The FASEB Journal*. 2018;32(5):2644.
  - 24.Xie J, Wang X, Proud CG. mTOR inhibitors in cancer therapy. *F1000Research*. 2016;5.
  - 25.Matsuura K, Nakada C, Mashio M, Narimatsu T, Yoshimoto T, Tanigawa M, et al. Downregulation of SAV1 plays a role in pathogenesis of high-grade clear cell renal cell carcinoma. *BMC cancer*. 2011;11(1):1-10.
  - 26.Lee S, Karas PJ, Hadley CC, Bayley V JC, Khan AB, Jalali A, et al. The role of merlin/NF2 loss in meningioma biology. *Cancers*. 2019;11(11):1633.
  - 27.Boffetta P, Fontana L, Stewart P, Zaridze D, Szeszenia-Dabrowska N, Janout V, et al. Occupational exposure to arsenic, cadmium, chromium, lead and nickel, and renal cell carcinoma: a case-control study from Central and Eastern Europe. *Occupational and environmental medicine*. 2011;68(10):723-8.
  - 28.Akatsuka S, Yamashita Y, Ohara H, Liu Y-T, Izumiya M, Abe K, et al. Fenton reaction induced cancer in wild type rats recapitulates genomic alterations observed in human cancer. 2012.
  - 29.Ebert T, Pawelzik S-C, Witasz A, Arefin S, Hobson S, Kublickiene K, et al. Inflammation and premature ageing in chronic kidney disease. *Toxins*. 2020;12(4):227.
  30. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. *Clinical journal of the American Society of Nephrology: CJASN*. 2012;7(12):1938.
  - 31.Ishigami J, Grams ME, Chang AR, Carrero JJ, Coresh J, Matsushita K. CKD and risk for hospitalization with infection: the atherosclerosis risk in communities (ARIC) study. *American Journal of Kidney Diseases*. 2017;69(6):752-61.
  - 32.Hu M, Wang Q, Liu B, Ma Q, Zhang T, Huang T, et al. Chronic Kidney Disease and Cancer: Inter-Relationships and Mechanisms. *Frontiers in Cell and Developmental Biology*. 2022;10:868715-.
  - 33.Putri AY, Thaha M. Role of oxidative stress on chronic kidney disease progression. *Acta Medica Indonesiana*. 2014;46(3):244-52.
  - 34.Dounousi E, Papavasiliou E, Makedou A, Ioannou K, Katopodis KP, Tselepis A, et al. Oxidative stress is progressively enhanced with advancing stages of CKD. *American Journal of Kidney Diseases*. 2006;48(5):752-60.
  - 35.Shaw P, Chattopadhyay A. Nrf2-ARE signaling in cellular protection: Mechanism of action and the regulatory mechanisms. *Journal of Cellular Physiology*. 2020;235(4):3119-30.
  - 36.Tu W, Wang H, Li S, Liu Q, Sha H. The anti-inflammatory and anti-oxidant mechanisms of the Keap1/Nrf2/ARE signaling pathway in chronic diseases. *Aging and disease*. 2019;10(3):637.
  - 37.Feng Y-L, Chen H, Chen D-Q, Vaziri ND, Su W, Ma S-X, et al. Activated NF-κB/Nrf2 and Wnt/β-catenin pathways are associated with lipid metabolism in CKD patients with microalbuminuria and macroalbuminuria. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*. 2019;1865(9):2317-32.
  - 38.Giri DK, Aggarwal BB. Constitutive activation of NF-κB causes resistance to apoptosis in human cutaneous T cell lymphoma HuT-78 cells: autocrine role of tumor necrosis factor and reactive oxygen intermediates. *Journal of Biological Chemistry*. 1998;273(22):14008-14.
  - 39.Helena JM, Joubert AM, Grobbelaar S, Nolte EM, Nel M, Pepper MS, et al. Deoxyribonucleic acid damage and repair: Capitalizing on our understanding of the mechanisms of maintaining genomic integrity for therapeutic purposes. *International Journal of Molecular Sciences*. 2018;19(4):1148.
  - 40.Buemi M, Floccari F, Cošta C, Caccamo C, Belghity N, Campo S, et al. Dialysis-Related Genotoxicity: Sister Chromatid Exchanges and DNA Lesions in T and B Lymphocytes of Uremic Patients. *Genomic Damage in Patients on Hemodiafiltration: Genomic Damage in Patients on Hemodiafiltration. Blood purification*. 2006;24(5-6):569-74.
  - 41.Trabulus S, Guven GS, Altiparmak MR, Batar B, Tun O, Yalin AS, et al. DNA repair XRCC1 Arg399Gln polymorphism is associated with the risk of development of end-stage renal disease. *Molecular biology reports*. 2012;39:6995-7001.
  - 42.Lau WL, Obi Y, Kalantar-Zadeh K. Parathyroidectomy in the management of secondary hyperparathyroidism. *Clinical journal of the American Society of Nephrology: CJASN*. 2018;13(6):952.
  - 43.Quarles LD. Role of FGF23 in vitamin D and phosphate metabolism: implications in chronic kidney disease. *Experimental cell research*. 2012;318(9):1040-8.
  - 44.Erben RG. Physiological actions of fibroblast growth factor-23. *Frontiers in endocrinology*. 2018:267.
  - 45.Lee EK, Martinez MCR, Blakely K, Santos KD, Hoang VC, Chow A, et al. FGF23: mediator of poor prognosis in a sizeable subgroup of patients with castration-resistant prostate cancer presenting with severe hypophosphatemia? *Medical hypotheses*. 2014;83(4):482-7.
  - 46.Clemens E, van den Heuvel-Eibrink MM, Mulder RL, Kremer LC, Hudson MM, Skinner R, et al. Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood

- Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. *The Lancet Oncology*. 2019;20(1):e29-e41.
47. Schaapveld M, Aleman BM, van Eggermond AM, Janus CP, Krol AD, van der Maazen RW, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. *New England Journal of Medicine*. 2015;373(26):2499-511.
48. Lee M, Wang Q, Wanchoo R, Eswarappa M, Deshpande P, Sise ME. Chronic kidney disease in cancer survivors. *Advances in Chronic Kidney Disease*. 2021;28(5):469-76. e1.
49. Ellis MJ, Parikh CR, Inrig JK, Kambay M, Patel UD. Chronic kidney disease after hematopoietic cell transplantation: a systematic review. *American Journal of Transplantation*. 2008;8(11):2378-90.
50. Seethapathy H, Zhao S, Chute DF, Zubiri L, Oppong Y, Strohbehm I, et al. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. *Clinical Journal of the American Society of Nephrology: CJASN*. 2019;14(12):1692.
51. Seethapathy H, Zhao S, Strohbehm IA, Lee M, Chute DF, Bates H, et al. Incidence and clinical features of immune-related acute kidney injury in patients receiving programmed cell death ligand-1 inhibitors. *Kidney international reports*. 2020;5(10):1700-5.
52. Mamlouk O, Selamet U, Machado S, Abdelrahim M, Glass WF, Tchakarov A, et al. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. *Journal for immunotherapy of cancer*. 2019;7(1):1-13.
53. Ishii T, Fujimaru T, Nakano E, Takahashi O, Nakayama M, Yamauchi T, et al. Association between chronic kidney disease and mortality in stage IV cancer. *International Journal of Clinical Oncology*. 2020;25(9):1587-95. [DOI: 10.1007/s10147-020-01715-9].
54. Maltoni M, Scarpi E, Pittureri C, Martini F, Montanari L, Amaducci E, et al. Prospective comparison of prognostic scores in palliative care cancer populations. *The oncologist*. 2012;17(3):446-54.
55. Jang RW, Caraiscos VB, Swami N, Banerjee S, Mak E, Kaya E, et al. Simple prognostic model for patients with advanced cancer based on performance status. *Journal of oncology practice*. 2014;10(5):e335-e41.
56. Shlipak MG, Stehman-Breen C, Fried LF, Song X, Siscovick D, Fried LP, et al. The presence of frailty in elderly persons with chronic renal insufficiency. *American journal of kidney diseases*. 2004;43(5):861-7.
57. Caires-Lima R, Cayres K, Protásio B, Caires I, Andrade J, Rocha L, et al. Palliative chemotherapy outcomes in patients with ECOG-PS higher than 1. *Ecancermedicalscience*. 2018;12.
58. Wei Y-F, Chen J-Y, Lee H-S, Wu J-T, Hsu C-K, Hsu Y-C. Association of chronic kidney disease with mortality risk in patients with lung cancer: a nationwide Taiwan population-based cohort study. *BMJ open*. 2018;8(1):e019661.
59. Launay-Vacher V, Spano J-P, Janus N, Gligorov J, Ray-Coquard I, Oudard S, et al. Renal insufficiency and anticancer drugs in elderly cancer patients: a subgroup analysis of the IRMA study. *Critical reviews in oncology/hematology*. 2009;70(2):124-33.
60. Launay-Vacher V, Oudard S, Janus N, Gligorov J, Pourrat X, Rixe O, et al. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer*. 2007;110(6):1376-84.
61. Launay-Vacher V, Aapro M, De Castro Jr G, Cohen E, Deray G, Dooley M, et al. Renal effects of molecular targeted therapies in oncology: a review by the Cancer and the Kidney International Network (C-KIN). *Annals of Oncology*. 2015;26(8):1677-84.
62. Kitchlu A, Shapiro J, Amir E, Garg AX, Kim SJ, Wald R, et al. Representation of patients with chronic kidney disease in trials of cancer therapy. *Jama*. 2018;319(23):2437-9.
63. Zhang Y, Zhang L, Abraham S, Apparaju S, Wu TC, Strong J, et al. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. *Clinical Pharmacology & Therapeutics*. 2009;85(3):305-11.
64. Sprangers B, Jhaveri KD, Perazella MA. Improving cancer care for patients with chronic kidney disease. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2020;38(3):188-92.
65. Latcha S. Pharmacokinetics of chemotherapeutic agents in kidney disease. *Onco-nephrology curriculum*. 2016:1-9.
66. Motwani SS, McMahon GM, Humphreys BD, Partridge AH, Waikar SS, Curhan GC. Development and validation of a risk prediction model for acute kidney injury after the first course of cisplatin. *Journal of Clinical Oncology*. 2018;36(7):682.
67. Asai A, Katsuno T, Yamaguchi M, Iwagaito S, Nobata H, Kinashi H, et al. Carboplatin-related acute interstitial nephritis in a patient with pancreatic neuroendocrine tumor. *CEN case reports*. 2020;9:114-21.
68. Watanabe R, Takiguchi Y, Moriya T, Oda S, Kurosu K, Tanabe N, et al. Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. *British journal of cancer*. 2003;88(1):25-30.
69. Janus N, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. *Annals of Oncology*. 2010;21(7):1395-403.
70. Inoue A, Saijo Y, Kikuchi T, Gomi K, Suzuki T, Maemondo M, et al. Pharmacokinetic analysis of combination chemotherapy with carboplatin and etoposide in small-cell lung cancer patients undergoing hemodialysis. *Annals of oncology*. 2004;15(1):51-4.
71. Veal GJ, English MW, Grundy RG, Shakespeare C, Glaser A, Waters F, et al. Pharmacokinetically guided dosing of carboplatin in paediatric cancer patients with bilateral nephrectomy. *Cancer chemotherapy and pharmacology*. 2004;54:295-300.
72. Guddati AK, Joy PS, Marak CP. Dose adjustment of carboplatin in patients on peritoneal dialysis. *Medical oncology (Northwood, London, England)*. 2014;31(5):946. [DOI: 10.1007/s12032-014-0946-z].
73. Ensergueix G, Pallet N, Joly D, Levi C, Chauvet S, Trivin C, et al. Ifosfamide nephrotoxicity in adult patients. *Clinical kidney journal*. 2020;13(4):660-5.
74. Kaijser G, Beijnen J, Bult A, Underberg W. Ifosfamide metabolism and pharmacokinetics. *Anticancer research*. 1994;14(2A):517-31.
75. Stöhr W, Paulides M, Bielack S, Jürgens H, Treuner J, Rossi R, et al. Ifosfamide-induced nephrotoxicity in 593 sarcoma patients: a report from the Late Effects Surveillance System. *Pediatric blood & cancer*. 2007;48(4):447-52.
76. Skinner R, Cotterill S, Stevens M. Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. *British journal of cancer*. 2000;82(10):1636-45.
77. Oberlin O, Fawaz O, Rey A, Niaudet P, Ridola V, Orbach D, et al. Long-term evaluation of Ifosfamide-related nephrotoxicity in children. *Journal of clinical oncology*.

- 2009;27(32):5350-5.
78. Farry JK, Flombaum CD, Latcha S. Long term renal toxicity of ifosfamide in adult patients—5 year data. *European Journal of Cancer*. 2012;48(9):1326-31.
79. Kumar N, Shirali AC, editors. What is the best therapy for toxicity in the setting of methotrexate-associated acute kidney injury: high-flux hemodialysis or carboxypeptidase G2? *Seminars in dialysis*; 2014.
80. Jhaveri KD, Flombaum C, Shah M, Latcha S. A retrospective observational study on the use of capecitabine in patients with severe renal impairment (GFR < 30 mL/min) and end stage renal disease on hemodialysis. *Journal of Oncology Pharmacy Practice*. 2012;18(1):140-7.
81. Van Warmerdam L, Rodenhuis S, ten Bokkel Huinink W, Maes Rt, Beijnen J. The use of the Calvert formula to determine the optimal carboplatin dosage. *Journal of cancer research and clinical oncology*. 1995;121:478-86.
82. Shepherd ST, Gillen G, Morrison P, Forte C, Macpherson IR, White JD, et al. Performance of formulae based estimates of glomerular filtration rate for carboplatin dosing in stage 1 seminoma. *European Journal of Cancer*. 2014;50(5):944-52.
83. Mazloom AL. Tolerability of Carboplatin When Using Rounded Serum Creatinine Values. 2012.
84. Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
85. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clinical journal of the American Society of Nephrology: CJASN*. 2010;5(6):1003.
86. Levey AS, Coresh J, Greene T, Stevens LA, Zhang Y, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Annals of internal medicine*. 2006;145(4):247-54.
87. Rhee J, Kwon JM, Han SH, Kim SH, Park CH, Jeon JH, et al. Cockcroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration equations for estimating glomerular filtration rates in cancer patients receiving cisplatin-based chemotherapy. *Kidney Research and Clinical Practice*. 2017;36(4):342.
88. Séronie-Vivien S, Toullec S, Malard L, Thomas F, Durrand V, Chatelut E. Contribution of the MDRD equation and of cystatin C for renal function estimates in cancer patients. *Medical Oncology*. 2006;23:63-73.
89. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Annals of internal medicine*. 2009;150(9):604-12.