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The association of preoperative reduced glomerular filtration rate with higher staging and histology grades in patients with urinary tract cancers

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Abstract

Purpose Studies have shown the increased incidence of urinary tract cancers which are associated with a decrease in glomerular filtration rate (GFR). We hypothesized that patients with GFR < 60 ml/min/1.73 m^2 have an increased risk for higher staging and histology grades of cancers and, therefore, the increased risk for cancer recurrence and cancer-related death.

Methods Retrospective clinical data and pathology reports were completed for 2116 patients. Patients were divided into two subgroups regarding GFR; the first group with GFR < 60 ml/min/1.73 m^2 and the second group with GFR > 60 ml/min/1.73 m^2 and regarding cancer recurrence. Cancers were also divided by stages (1–4) according to TNM classification. Patients were followed-up during 3 years.

Results We have found significantly higher number of cancers with higher histology grades and higher staging in group of patients with GFR < 60 ml/min/1.73 m^2 in all urinary tract localizations. GFR was the strongest predictor for higher cancer histology grade and only significant predictor for higher cancer staging. Patients with GFR < 60 ml/min/1.73 m^2 had OR for higher histology grade, higher staging, and cancer recurrence of 10.7, 5.3, and 11.3 compared to patients with GFR > 60 ml/min.

Conclusions Higher staging and histology grades in patients with urinary tract cancers are associated with reduced GFR. Reduced GFR in these patients is a risk factor for cancer recurrence and cancer-related survival. Possible involvement of uremic toxins must be taken into account especially when cancers are predominantly located in estrogen sensitive organs. These patients should be intensively monitored and probably be more aggressively treated.

Keywords Glomerular filtration rate · Histology · Recurrence · Staging · Urinary tract cancers

Introduction

Studies have shown the increased incidence of cancers, especially those located in the urinary tract, not only in patients on hemodialysis or transplant recipients but even in patients with mild or moderate chronic kidney disease (CKD) [1, 2]. Increased incidence is associated with a decrease in glomerular filtration rate (GFR) which is in men at least 40% for men [3, 4]. Studies on large cohort of patients showed the association between increased risk of death from urinary tract cancers and GFR < 60 ml/min/1.73 m^2 [5]. The exact reason for this occurence is not yet fully understood, but GFR decline is associated with high-grade tumor activity [6]. Bladder cancer recurrence and progression is strongly associated with impaired GFR especially below the cut-off of < 60 ml/min/1.73 m^2 [7, 8]. The formation of more

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aggressive cancers through cell differentiation is accelerated with uremic toxins and impaired immunity [9]. Furthermore, chronic inflammation and oxidative stress, which are manifestations of CKD, lead to cancer proliferation, angiogenesis, and transformation to higher histology grades and, therefore, more aggressive forms of cancers [10]. Similar findings were reported for renal cell cancer with the association of increased cancer diameter and decreased GFR [11]. Anemia, common in CKD, is associated with poorer survival of patients with urothelial cancers due to its impact on cancer sample size, tumor T stage, and histology grade [12].

Urinary tract cancers' incidence and recurrence is increased with the decrease of GFR, so we hypothesized that patients with GFR < 60 ml/min/1.73 m^2 have an increased risk for higher staging and histology grades of cancers and, therefore, the increased risk for cancer recurrence and cancer-related death. To test this hypothesis, we analyzed all urinary tract cancers depending on site-specific distribution of different types, staging and histology grades and divided them by a GFR cutoff of 60 ml/min.

Methods

Retrospective clinical data and pathology reports were completed for 2116 patients between January 2011 and December 2015. Inclusion criteria were: age older than 18 years and the presence of urinary tract cancer. Renal function was defined as an estimated GFR (ml/min/1.73 m^2) using the CKD-EPI equation [13]. Serum creatinine was taken serial, with GFR estimation, at least three times—at cancer diagnosis, at preoperative anesthesiological exam, and at hospital admission taking the mean value of these three values. Patients were excluded from the study if they had a previous chronic kidney disease or if the cause for decrease in GFR was obstructive nephropathy. All cancers were diagnosed by one pathologist who was blind of other patients' data. For evaluation of the tumor stage, we used 2009 TNM classification [14] for histology grade of urothelial cancers that we used 2004 WHO classification [15], and for kidney cancers, we used 2016 WHO classification [16]. Bladder, urethral, and renal cancers were diagnosed using the standard diagnostic algorithms which consisted of abdominal ultrasonography, computed tomography scan, and urine cytology and cystoscopy for urothelial cancer. Surgery was performed in all patients diagnosed with urinary tract cancers, and in the most cases, it was open surgery. Additional systemic therapy was applied when indicated. All these patients were constantly reevaluated through computed tomography (CT) without contrast media, abdominal ultrasound, skeletal scintigraphy, and positron emission tomography (PET)-CT according to European Urological Association Guidelines and cancer type [17].

Data on medical history, laboratory results, and medication were collected from patients' charts. Patients were divided into two subgroups regarding GFR: the first group with GFR < 60 ml/min/1.73 m^2 and the second group with GFR > 60 ml/min/1.73 m^2 and regarding cancer recurrence. Cancers were also divided by stages (1–4) according to TNM classification and European Urological Association Guidelines for different site-specific cancers (stage 1: T1N0M0; stage 2: T2N0M0; stage 3: T3N0M0; stage 4: T4AnyNM0 or AnyTAnyNM1). Patients were followed-up during 3 years through regular controls in the outpatient clinic, and during that time, cancer recurrence and development of non-urinary tract cancers were recorded. The data regarding site specificity and different types of these non-urinary tract cancers were collected. Bladder cancer recurrence was defined as recurrent urothelial cancer in bladder proven by second transurethral resection no matter with or without upstaging or upgrading. Urethral and kidney cancer recurrence was defined as urothelial carcinoma in the renal pelvis or ureter areas or kidney cancer in the kidney proven by surgical pathology.

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., USA). Categorical data were expressed as numbers and frequencies. Correlations were obtained using Pearson's test for normally distributed variables and Spearman rank correlation for non-normally distributed variables. Normally distributed variables were presented, as means + standard deviations and Student's t test for independent samples were used for comparison of the two groups. Non-normally distributed data were presented as median and interquartile range and Mann–Whitney U test was used in comparison of the two groups. Categorical variables were compared using χ^2 test. Multiple linear regression was used to explore the influence of different variables on cancer histology grade and recurrence, while logistic regression was used for categorical dependent variables. We have used available data on cancer rates specific for age and sex from the Croatian National Cancer Registry [18] for 2014. The standardized incidence ratio (SIR), the ratio of observed to expected cancers, was used to estimate the relative risk, 95% CI for these ratios were calculated with the assumption that the observed number of cancer cases followed a Poisson's distribution. The survival analysis was done with Kaplan–Meier curves which were tested with log-rank test, while hazard ratios were estimated with Cox proportional hazards regression. A p value < 0.05 (two-sided tests) was considered significant.

Results

We have enrolled 2116 patients with urinary tract cancers (Table 1). Those patients consisted of 1457 men (68.8%) and 659 women (31.2%) with a mean age of 65.8 ± 9.5 years.

There were no significant differences in number of cancers between gender, smokers, and different comorbidities (all $p > 0.05$). Diabetes, arterial hypertension, and positive family history of urinary tract cancers were present in 173 (8.2%), 342 (16.2%), and 83 (3.9%) patients, respectively. In the study group, 413 patients (19.5%) died from various causes; 272 (65.8%) patients died from disseminated cancers, and 141 (34.2%) died from fatal stroke, myocardial infarction, or heart failure. There were 1372 cancers of the bladder, 137 ureter, and 607 kidney cancers. Ureter and bladder cancers were only transitional cell type, while kidney cancers were clear cell and papillary type. All renal and ureteral cancers were only unilateral. All cancers localized in the urinary tract were analyzed by one pathologist. We have not found an increased incidence of bladder, ureter, and kidney cancers (SIR 0.9; CI 0.8–1.0; SIR 0.8; CI 0.7–0.9; SIR 1.0; CI 0.9–1.1) when compared to the general population, analyzed from the Croatian National Cancer Registry [18].

When patients were divided into two groups based on GFR < 60 and > 60 ml/min/1.73 m^2, we have found that patients with GFR < 60 ml/min/1.73 m^2 were significantly older than patients with GFR > 60 ml/min/1.73 m^2 ($p < 0.05$). We have not found any differences in sex, smokers, diabetics, hypertonics, hemoglobin, and positive family history of urinary tract cancer (all $p > 0.05$) (Table 2). Patients with GFR < 60 ml/min/1.73 m^2 had significantly higher number of ureter cancers and kidney clear cell cancers and significantly lower number of bladder cancers when compared to patients with GFR > 60 ml/min/1.73 m^2 (all $p < 0.05$). We have found significantly higher number of bladder and ureter cancers with high histology grade, higher number of kidney clear cell type of cancer with higher histology grades (II–IV) and kidney papillary type of cancer with histology grade type 2 in group of patients with GFR < 60 ml/min/1.73 m^2 (all $p < 0.01$). Patients with GFR < 60 ml/min/1.73 m^2 had significantly higher number of cancers with higher staging (S2–S4 for bladder, S2–S3 for ureter and S2–S4 for kidney) in all urinary tract localizations ($p < 0.05$). Furthermore, in this group of patients, we have found significantly higher number of cancer recurrence and other non-urinary tract cancers (all $p < 0.001$). Patients with GFR < 60 ml/min/1.73 m^2 survived significantly shorter ($p < 0.001$).

When patients were divided into two groups based on cancer recurrence, we have found that patients with cancer recurrence were significantly older than patients without cancer recurrence ($p < 0.05$). We have not found any differences in sex, smokers, diabetics, hypertonics, systemic therapy, hemoglobin, and positive family history of urinary tract cancer (all $p > 0.05$) (Table 3). Patients with cancer recurrence had significantly lower GFR than patients without cancer recurrence. Significantly, higher number of bladder and ureteral cancers recurred when compared to kidney cancers. Mostly, bladder cancer recurred (76.3%). On average, every

Table 1 Demographic, clinical, and laboratory data with site-specific distribution of different types and histology grades of cancers in all group of patients

Age (years)	65.8 ± 9.5
Males [*N* (%)]	1457 (68.8)
Smoker [*N* (%)]	588 (27.8)
Diabetes	173 (8.2)
Hypertension	342 (16.2)
Positive family history of urinary tract cancer [*N* (%)]	83 (3.9)
Creatinine (μmol/l)	121 (60–366)
GFR (ml/min/1.73 $m^{2)}$	65.2 ± 4.7
Hemoglobin (g/l)	130.5 + 12.3
Cancer localization and different types [*N* (%)]	
Bladder	1372 (64.8)
Transitional cell	1372 (100)
Ureter	137 (6.5)
Transitional cell	137 (100)
Kidney	607 (28.7)
Clear cell	462 (76.1)
Papillary	145 (23.8)
Cancer localization and different staging [*N* (%)]	
Bladder	
S1	805 (58.7)
S2	344 (25.1)
S3	211 (15.4)
S4	12 (0.8)
Ureter	
S1	44 (32.2)
S2	43 (31.4)
S3	26 (18.9)
S4	24 (17.5)
Kidney	
S1	178 (29.3)
S2	171 (28.2)
S3	209 (34.4)
S4	49 (8.1)
Cancer localization and different histology grades [*N* (%)]	
Bladder	
Low grade	1149 (83.7)
High grade	223 (16.3)
Ureter	
Low grade	87 (63.5)
High grade	50 (36.5)
Kidney	
Clear cell	
Grade I	128 (27.7)
Grade II	121 (26.2)
Grade III	174 (37.7)
Grade IV	39 (8.4)
Papillary	
Type 1	97 (66.9)
Type 2	48 (33.1)

Table 1 (continued)

Cancer recurrence (yes) *N* (%)	1179 (55.7)

GFR glomerular filtration rate, *S* stage

third bladder cancer recurred more than once, while only 20% of ureter and 3.5% of kidney cancers recurred more than once. Patients with cancer recurrence had significantly higher number of bladder and ureteral transitional cell type of cancer when compared to patients without cancer recurrence, while kidney clear cell and papillary types of cancer were in significantly lower number in this group of patients. We have found significantly higher number of bladder and ureter cancers with high histology grade, higher number of kidney clear cell type of cancer with higher histology grades (II–IV), and kidney papillary type of cancer with histology grade type 2 in group of patients with cancer recurrence (all $p < 0.01$). Patients with cancer recurrence had significantly higher number of bladder, ureter, and kidney cancers with higher staging (S2–S3; S2–S3; S3–S4) ($p < 0.01$).

Patients with urinary tract cancers had an other non-urinary tract cancer in 100 (4.7%) cases. Three quarters of them (80%) had GFR < 60 ml/min/1.73 m^2. Site-specific distribution of different types of non-urinary tract cancers in patients divided by GFR < 60 and GFR > 60 ml/min/1.73 m^2 is shown in Table 4. Site and type-specific non-urinary tract cancers in our population of patients were mostly localized in estrogen positive receptor organs and in 72% of cases were adenocarcinoma.

On univariate analysis cancer higher histology grades, higher staging, cancer recurrence, and the presence of non-urinary tract cancer were in all patients positively correlated with age ($r = 0.043$; $p = 0.04$; $r = 0.068$; $p = 0.03$; $r = 0.136$; $p < 0.001$; $r = 0.075$; $p = 0.001$), while negatively correlated with GFR ($r = -0.444$; $p < 0.001$; $r = -0.527$; $p < 0.001$; $r = -0.138$; $p < 0.001$; $r = -0.114$; $p < 0.001$). The same associations were found for different cancer localizations (all $p < 0.05$). Lower GFR was positively associated with age ($r = -0.247$; $p < 0.001$). In the linear regression model, GFR was the strongest predictor for higher cancer histology grade ($\beta = -0.407$, $p < 0.001$) and only significant predictor for higher cancer staging ($\beta = -0.372$, $p < 0.001$). Other predictor for higher cancer histology grade was hemoglobin ($\beta = -0.123$, $p = 0.001$), while, interestingly, age was not associated with higher cancer histology grade and higher staging. Reduced GFR was a predictor for higher cancer histology grade and higher staging in all group of patients and in different cancer localizations (all $p < 0.01$). We have found similar association for GFR with cancer recurrence ($\beta = -0.423$, $p < 0.001$) in all group of patients and for different cancer localizations (all $p < 0.01$). On logistic regression, patients with GFR < 60 ml/min/1.73 m^2 had OR for higher histology grade, higher staging, and cancer recurrence of 10.7 [CI 8.41, 12.32], 5.3 [CI 3.83, 6.97], and 11.3 [CI 9.17, 13.22] compared to patients with GFR > 60 ml/min/1.73 m^2. Patients with GFR < 60 ml/min/1.73 m^2 had OR for development of non-urinary tract cancers of 4.08 [CI 3.56, 5.10] compared to patients with GFR > 60 ml/min/1.73 m^2. Significantly, a higher number of patients with GFR < 60 ml/min/1.73 m^2 (187 (69%); $p < 0.001$) have died from disseminated cancers when compared to patients with GFR > 60 ml/min/1.73 m^2. Survival was negatively correlated with age and GFR ($r = -0.323$; $p = 0.02$; $r = -0.531$; $p < 0.001$). Patients with GFR < 60 ml/min/1.73 m^2 have survived significantly shorter when compared to patients with GFR > 60 ml/min/1.73 m^2 (31.0 (95% CI 30.4, 31.7) vs. 34.3 (95% CI 34.0, 34.7) months, log-rank $p < 0.001$).

Lower GFR (HR 0.98 [0.97, 0.99]) was associated with higher cancer-related mortality but, interestingly, age (HR 0.99 [0.98, 1.01]) was not.

Discussion

In this study, we have found that in the group of urinary tract cancer patients, those with GFR < 60 ml/min/1.73 m^2 have significantly higher number of transitional cell bladder and ureter cancers and kidney clear cell and papillary type of cancers with higher histology grade than in patients with GFR > 60 ml/min/1.73 m^2. Furthermore, these patients had significantly higher number of cancers with higher staging in all urinary tract localizations. Cancers recurred more often when GFR was below 60 ml/min/1.73 m^2.

CKD is a risk factor for cancer development and cancer mortality especially cancers of the kidney, urinary tract, digestive tract, and lung [1, 2, 19]. Reduced GFR below 60 ml/min/1.73 m^2 has been associated with higher cancer incidence, higher cancer recurrence, and higher cancer-related mortality, especially in older people [1, 3–5]. These findings are also similar for urinary tract cancers [5, 7, 8, 20], but studies were limited to site-specific cancers of urinary tract, while this is the first study which analyzed association of reduced GFR with bladder, ureter, and kidney cancers.

Reasons for this increasing risk of urinary tract cancers incidence, recurrence, and mortality in patients with reduced GFR remain still unexplained. It is reported that GFR decline results with higher histology grades and stages and, therefore, more aggressive cancers with higher recurrence rates and higher mortality [6, 10, 21]. The results from our study showed that GFR decline is the strongest predictor for higher histology grades and only predictor for higher stages for all and site-specific urinary tract cancers. Interestingly, OR was higher for higher histology grades than higher cancer stages. These results could explain why patients with

Table 2 Demographic, clinical and laboratory data with site-specific distribution of different types, staging, and histology grades of cancers between patients with GFR < 60 ml/min/1.73 m^2 and GFR > 60 ml/min/1.73 m^2

	GFR < 60 ml/min/1.73 m^2, $N = 916$	GFR > 60 ml/min/1.73 m^2, $N = 1200$	p
Age (years)	68.3 ± 9.9	63.8 ± 8.7	< 0.001
Males [*N* (%)]	693 (47.6)	764 (52.4)	0.51
Smoker [*N* (%)]	312 (34.1)	276 (23.0)	0.48
Diabetes	83 (9.1)	90 (7.5)	0.59
Hypertension	173 (18.9)	169 (14.1)	0.52
Positive family history of urinary tract cancer [*N* (%)]	37 (4.1)	46 (3.8)	0.68
Hemoglobin (g/l)	128.3 + 11.2	132.7 + 12.9	0.27
Cancer localization and different types [*N* (%)]			
Bladder	521 (57.0)	851 (70.9)	< 0.001
Transitional cell	521 (100.0)	851 (100)	
Ureter	81 (8.9)	56 (4.7)	< 0.001
Transitional cell	81 (100)	56 (100)	
Kidney	314 (34.1)	293 (24.4)	< 0.001
Clear cell	245 (78.0)	217 (74.1)	< 0.001
Papillary	69 (22.0)	76 (25.9)	0.28
Cancer localization and different staging [*N* (%)]			
Bladder			
S1	137 (26.3)	688 (78.5)	0.001
S2	219 (42.0)	125 (14.7)	< 0.001
S3	153 (29.4)	58 (6.8)	< 0.001
S4	12 (2.3)	0 (0)	< 0.001
Ureter			
S1	8 (9.9)	36 (64.2)	< 0.001
S2	33 (40.7)	10 (17.9)	< 0.01
S3	34 (42.0)	10 (17.9)	< 0.01
S4	6 (7.4)	0 (0)	0.04
Kidney			
S1	23 (7.3)	155 (52.9)	< 0.001
S2	117 (37.3)	54 (18.4)	< 0.001
S3	133 (42.4)	76 (26.0)	< 0.001
S4	41 (13.0)	8 (2.7)	< 0.001
Cancer localization and different histology grades [*N* (%)]			
Bladder			
Low grade	356 (68.3)	793 (93.2)	< 0.001
High grade	165 (31.7)	58 (6.8)	< 0.001
Ureter			
Low grade	41 (50.6)	46 (82.1)	< 0.001
High grade	40 (49.4)	10 (17.9)	< 0.001
Kidney			
Clear cell			
Grade I	10 (4.1)	118 (54.4)	< 0.001
Grade II	77 (31.4)	44 (20.3)	< 0.01
Grade III	123 (50.2)	51 (23.5)	< 0.001
Grade IV	35 (14.3)	4 (1.8)	< 0.001
Papillary			
Type 1	31 (44.9)	66 (86.9)	< 0.001
Type 2	38 (55.1)	10 (13.1)	< 0.001
Cancer recurrence (yes) *N* (%)	571 (62.3)	609 (50.8)	< 0.001
Secondary/other cancer (yes) *N* (%)	80 (8.7)	20 (1.6)	< 0.001
Survival (months)	31.0 + 1.2	34.3 + 1.4	< 0.001

Results are shown as mean ± SD or median (interquartile range), categorical variables were compared using χ^2 test

GFR glomerular filtration rate, *S* stage

Table 3 Demographic, clinical and laboratory data with site-specific distribution of different types, staging and histology grades of cancers between patients with and without cancer recurrence

	Cancer recurrence	Without cancer recurrence	*p*
	N = 1179	*N* = 937	
Age (years)	68.1 ± 9.7	62.8 ± 8.1	< 0.001
Males [*N* (%)]	773 (65.6)	684 (73.1)	0.34
Smoker [*N* (%)]	331 (28.1)	257 (27.5)	0.84
Diabetes	98 (8.3)	75 (8.1)	0.86
Hypertension	198 (16.8)	144 (15.4)	0.76
Positive family history of urinary tract cancer [*N* (%)]	48 (4.7)	35 (3.7)	0.51
Creatinine (μmol/l)	128 (68–387)	106 (56–341)	0.01
GFR (ml/min/1.73 m^2)	62.5 ± 4.1	68.7 ± 5.3	< 0.001
Hemoglobin (g/l)	130.2 + 12.1	131.0 + 12.7	0.83
Cancer localization and different types [*N* (%)]			
Bladder	899 (76.3)	473 (50.5)	< 0.001
Transitional cell	899 (100)	473 (100)	
Ureter	100 (8.5)	37 (3.9)	< 0.001
Transitional cell	100 (100)	37 (100)	
Kidney	180 (15.2)	427 (45.6)	< 0.001
Clear cell	172 (95.5)	290 (67.9)	< 0.001
Papillary	8 (4.5)	137 (32.1)	< 0.001
Cancer localization and different staging [*N* (%)]			
Bladder			
S1	457 (50.9)	348 (73.6)	< 0.001
S2	261 (29.0)	83 (17.6)	< 0.001
S3	172 (19.1)	39 (8.2)	< 0.001
S4	9 (1.0)	3 (0.6)	0.49
Ureter			
S1	14 (14.0)	30 (81.1)	< 0.001
S2	39 (39.0)	4 (10.8)	< 0.01
S3	41 (41.0)	3 (8.1)	< 0.01
S4	6 (6.0)	0 (0)	0.13
Kidney			
S1	15 (5.4)	163 (33.1)	< 0.001
S2	56 (21.7)	115 (11.2)	0.29
S3	84 (42.4)	125 (26.0)	< 0.001
S4	25 (13.0)	24 (2.7)	< 0.001
Cancer localization and different histology grades [*N* (%)]			
Bladder			
Low grade	718 (79.9)	431 (91.1)	< 0.001
High grade	181 (20.1)	42 (8.9)	< 0.001
Ureter			
Low grade	53 (53.0)	34 (91.9)	< 0.001
High grade	47 (47.0)	3 (8.1)	< 0.001
Kidney			
Clear cell			
Grade I	7 (4.1)	121 (41.7)	< 0.001
Grade II	57 (33.1)	64 (22.1)	< 0.01
Grade III	82 (47.7)	92 (31.7)	< 0.01
Grade IV	26 (15.1)	13 (4.5)	< 0.001
Papillary			
Type 1	1 (12.5)	96 (70.1)	< 0.001
Type 2	7 (87.5)	41 (29.9)	< 0.001

Results are shown as mean ± SD or median (interquartile range), categorical variables were compared using χ^2 test

GFR glomerular filtration rate, *S* stage

Table 4 Site-specific distribution of different types of non-urinary cancers in patients with GFR < 60 ml/min/1.73 m^2 and patients with GFR > 60 ml/min/1.73 m^2

	GFR < 60 ml/min/1.73 m^2	GFR > 60 ml/min/1.73 m^2	*p*
Cancer localization	*N* = 80	*N* = 20	< 0.001
Testicle (teratoma)	3	0	0.39
Prostate (adenocarcinoma)	30	2	0.02
Thyroid gland (papillary)	8	3	0.52
Lung	5	5	0.01
Adenocarcinoma	4	0	0.31
Squamous	1	5	< 0.001
Breast (papillary)	4	1	0.74
Digestive tract	20	6	0.65
Gastric (adenocarcinoma)	4	2	0.39
Pancreas (adenocarcinoma)	1	2	0.04
Colon (adenocarcinoma)	15	2	0.35
Female reproductive system Endometrium (adenocarcinoma)	9	1	0.40
Melanoma	1	3	< 0.01

Categorical variables were compared using χ^2 test

cancer recurrence had significantly higher number of cancers with higher histology grades and higher stages when compared to patients without cancer recurrence for all and for site-specific urinary tract cancers. Nevertheless, reduced GFR remained a significant predictor for cancer recurrence independently of different histology grades and cancer stages.

CKD manifestations such as uremic toxins, impaired immunity, anemia, chronic inflammation, and oxidative stress are associated with the development of more aggressive urinary tract cancers [9–11, 22, 23]. Our results showed a negative association of anemia with higher cancer histology grades, but the association of anemia with cancer recurrence was not present as in the previous studies [12,

24]. Although patients with GFR < 60 ml/min/1.73 m^2 and patients with cancer recurrence were significantly older when compared to patients with GFR > 60 ml/min/1.73 m^2, and without cancer recurrence in the linear regression model, we have not found the association of age with higher cancer histology grades, higher cancer stages, or cancer recurrence.

It was reported that reduced GFR was associated with poorer survival of patients with urothelial cancers due to its impact on cancer size, stage and cell differentiation [7, 8]. Our results are in accordance with those reports, where significantly higher number of patients with GFR < 60 ml/min/1.73 m^2 died from cancer-related deaths. Although survival was associated with both age and reduced GFR, when the survival analysis was adjusted for age, patients with reduced GFR have survived significantly shorter, while cancer-related mortality was associated only with reduced GFR and not age.

Additional contribution to the importance of reduced GFR in cancer incidence was our results on significantly higher number of patients with reduced GFR and other non-urinary tract cancers which were predominantly adenocarcinomas and localized mostly in digestive tract, lung, and thyroid gland which is in accordance with the previous reports [1, 2, 19]. The exact reason for this incidence could not be explained by our results, but obviously, even mild-to-moderate CKD stages have an impaired hormone metabolism which could partially be responsible for this non-urinary tract cancer incidence [25]. Considering site and type-specific non-urinary tract cancers in our population of patients with reduced GFR which were mostly localized in estrogen positive receptor organs and in 72% of cases were adenocarcinomas, we can assume that reduced GFR might be associated with exposure to some cancerogenic substance the concentrations of which could be determined from the blood and from the urine.

This is the first study which analyzed the impact of reduced GFR on cancer staging, histology grades, recurrence, and cancer-related survival in all urinary tract cancers and in different site-specific distribution. In this retrospective study, we found that patients with reduced GFR have significantly higher number of urinary tract cancers with higher staging and higher histology grades and worse prognosis with higher cancer recurrence rates than patients with GFR > 60 ml/min/1.73 m^2. Our results confirmed our hypothesis that reduced GFR could be considered as an additional prognostic marker for poorer outcome in patients with urinary tract cancers. Decrease in GFR affects future treatment regarding imaging modalities and usage of contrast, which can additionally decrease GFR, need for hemodialysis, higher intra- and perioperative mortality and anticancer treatment. Chemotherapeutic agents are often altered in these patients through changes in pharmacokinetics by uremia which can result with the accumulation of toxic components and over-dosage [26]. This requires dosing according to the calculated GFR formulas, which will allow the safe use of chemotherapy in patients with underlying kidney disease. This is especially challenging when taking into account the fact that patients with decrease of GFR had more aggressive cancers and, therefore, needs a more aggressive treatment modality. Treatment should be individualized especially in patients dependent on dialysis treatment when the early involvement of palliative care service is the preferred option.

Our work has several limitations. First, it is a retrospective study and various risk factors such as diuresis were not recorded. Second, we have enrolled patients from only one centre. Third, although we have excluded all patients with prior known CKD, the duration of reduced GFR until it was diagnosed was not known. This is a limitation which weakens the argument that reduced GFR is associated with the poorer prognosis of urinary tract cancers. Fourth, the numbers of some different types of non-urinary cancers are small. Therefore, the interpretation of statistical analysis significance should be considered carefully. Fifth, we have not collected BMI for all patients, and therefore, we could not calculate CKD-EPI adjusted for BSA formula which is the most precise formula for cancer patients.

Conclusions

Higher staging and histology grades in patients with urinary tract cancers are associated with reduced GFR. This association is the same for bladder, ureter, and kidney cancers. Reduced GFR in these patients is a risk factor for cancer recurrence and cancer-related survival.

Possible involvement of uremic toxins as a direct consequence of CKD must be taken into account especially when cancers are predominantly located in estrogen sensitive organs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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