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Changes in Renal Function Following Nephroureterectomy May Affect the Use of Perioperative Chemotherapy

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Abstract

Background—Nephroureterectomy alone fails to adequately treat many patients with advanced upper tract urothelial carcinoma (UTUC). Perioperative platinum-based chemotherapy has been proposed but requires adequate renal function.

Objective—Our aim was to determine whether the ability to deliver platinum-based chemotherapy following nephroureterectomy is affected by postoperative changes in renal function.

Design, settings, and participants—We retrospectively reviewed data on 388 patients undergoing nephroureterectomy for UTUC between 1991 and 2009. Four institutions were included.

Intervention—All patients underwent nephroureterectomy.

Measurements—All patients had serum creatinine measured before and after surgery. The value closest to 3 mo after surgery was taken as the postoperative value (range: 2[en]52 wk).

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Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease study equation. EGFR values before and after surgery were compared using the paired *t* test. We chose an eGFR of 45 and 60 ml/min per 1.73 m² as possible cut-offs for chemotherapy eligibility and compared eligibility before and after surgery using the chi-square test.

Results and limitations—Our cohort of 388 patients included 233 men (60%) with a median age of 70 yr. Mean eGFR decreased by 24% after surgery. Using a cut-off of 60 ml/min per 1.73 m², 49% of patients were eligible for chemotherapy before surgery, but only 19% of patients remained eligible postoperatively. Using a cut-off of 45 ml/min per 1.73 m², 80% of patients were eligible preoperatively, but only 55% remained eligible after surgery. This distribution persisted when we limited the analysis to patients with advanced pathologic stage (T3 or higher). Patients older than the median age of 70 yr were more likely to be ineligible for chemotherapy both pre- and postoperatively by either definition, and they were significantly more likely to have an eGFR <45 ml/min per 1.73 m² postoperatively, regardless of their starting eGFR. This study is limited by its retrospective nature, and there was some variability in the timing of postoperative serum creatinine measurements.

Conclusions—EGFR is significantly diminished after nephroureterectomy, particularly in elderly patients. These changes in renal function likely affect eligibility for adjuvant cisplatin-based therapy. Accordingly, we suggest strong consideration of neoadjuvant regimens.

Keywords

Urothelial carcinoma; Transitional cell carcinoma; Kidney; Nephroureterectomy; Chronic kidney disease; Chemotherapy

1. Introduction

Upper tract urothelial carcinoma (UTUC) accounts for 10% of renal malignancies and 5% of urothelial carcinoma (UC) [1,2]. Although the gold standard therapy for UTUC is nephroureterectomy, the 5-yr disease-specific survival after surgery ranges from 61% to 76% in large contemporary series [3,6]. Survival outcomes are lower for locally advanced cancers (pT3[4]) and node-positive disease. Collectively, these patients have a 5-yr disease-specific survival rate near 35%, indicating a need for effective systemic therapy in this cohort. However, whereas cisplatin-based multidrug regimens are known to be effective in bladder UC, evidence regarding efficacy and timing of perioperative systemic therapy in UTUC is lacking.

Neoadjuvant and adjuvant chemotherapy regimens have been extensively studied in UC of the bladder. Cisplatin-based neoadjuvant regimens, in particular, have shown a long-term survival advantage. Grossman et al reported an increase in 5-yr disease-free survival of 14% in those receiving neoadjuvant methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin in combination with radical cystectomy [7]. Careful review of the currently available data supports the efficacy of cisplatin-based neoadjuvant therapy in lower tract UC [7,8]. Extrapolating data from UC of the lower tract suggests that cisplatin-based regimens should be efficacious in upper tract disease as well. However, the timing of chemotherapy in UTUC may be crucial because surgical management of the disease often requires nephrectomy. It is well documented that in the setting of renal cortical tumors, radical nephrectomy has a deleterious effect on kidney function and estimated glomerular filtration rate (eGFR) [9]. A creatinine clearance (CrCl) ≥ 60 ml/min per 1.73 m² has defined eligibility in past and present studies of perioperative cisplatin-based chemotherapy for UC of the bladder [7,10] and in an ongoing phase 2 study of neoadjuvant gemcitabine and

cisplatin for UTUC [11]. Hussain et al described the use of a fractionated dosing scheme for gemcitabine/cisplatin therapy in UC patients with a CrCl as low as 40 ml/min [12].

We speculate that nephroureterectomy diminishes eGFR significantly, rendering many patients ineligible for effective systemic therapy following surgery for UTUC. Using the abbreviated Modification in Diet and Renal Disease (MDRD) study equation, we assessed the proportion of patients eligible for cisplatin-based chemotherapy based on cut-offs of eGFR ≥ 60 ml/min per 1.73 m^2 or eGFR ≥ 45 ml/min per 1.73 m^2 before and after nephroureterectomy.

2. Methods

Internal review board approval and the required data-sharing agreements were obtained from all institutions involved. Each institution undertook a retrospective review of patients undergoing nephroureterectomy for UTUC. Data of interest included patient age at surgery, race, pathologic stage, and pre- and postoperative creatinine. Patients with available data who were operated on between 1991 and 2009 were included. eGFR was calculated using the abbreviated MDRD equation: $\text{eGFR} = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$, multiplied by 0.742 for female patients and by 1.212 for black patients [13]. Comparison of eGFR before and after surgery was performed using the serum creatinine drawn closest to 3 mo after surgery (range: 2 wk to 1 yr after surgery). This timing was selected to best approximate the measured serum creatinine that would affect the delivery of adjuvant chemotherapy. The pre- and postoperative mean eGFR for all patients were compared using the paired *t* test. We also evaluated for the pre- and postoperative incidence of eGFR ≥ 60 ml/min per 1.73 m^2 and eGFR ≥ 45 ml/min per 1.73 m^2 . The percentage of patients falling below each cut-off was calculated before and after surgery. Statistical significance was calculated using the chi-square test. We then assessed the impact of age on the decrement in renal function following nephroureterectomy. We separated our population into age-based cohorts using the median age as a cut point. We compared the number of patients in each age group that remained eligible for chemotherapy after surgery using our predetermined eligibility cut-offs (eGFR of 60 and 45 ml/min per 1.73 m^2). The chi-square test was used to evaluate the differences between age group categories. All statistical calculations were two tailed, and $p < 0.05$ was deemed significant. Stata v.8.0 was used for all statistical analysis (StataCorp, College Station, TX, USA).

3. Results

Four institutions contributed patients: Memorial Sloan-Kettering Cancer Center, New York University Langone Medical Center, Penn State Milton S. Hershey Medical Center, and the University of Pittsburgh Medical Center. A total of 388 patients were available for analysis. The median age at surgery was 70 yr (interquartile range [IQR]: 62[en]76), and 233 (60%) were men. Table 1 lists the demographic, pathologic staging, and surgical data.

Comparison of pre- and postoperative serum creatinine levels for each patient revealed a mean difference of -0.32 mg/dl (95% confidence interval [CI] -0.28 to -0.36 ; $p < 0.001$; Table 2). A similar analysis performed for eGFR before and after nephroureterectomy demonstrated a mean difference between pre- and postoperative eGFR of -13.9 ml/min per 1.73 m^2 (95% CI, -12.4 to -15.4); $p < 0.001$ and a median percentage loss of 24% (IQR: 8[en]34%) of the starting eGFR (Table 2 and Fig. 1).

Using 60 ml/min per 1.73 m^2 as the eligibility cut-off for cisplatin-based chemotherapy, 49% of the population was eligible prior to nephroureterectomy, whereas following surgery only 19% remained eligible. Using a cut-off of 45 ml/min per 1.73 m^2 , 80% of the cohort

was eligible for fractionated cisplatin dosing, whereas only 55% remained above the cut-off postoperatively.

Outcomes were stratified by pathologic stage (Table 2). Of 130 patients with pT3, 40% had an eGFR >60 ml/min per 1.73 m² preoperatively, a proportion that fell to 26% after surgery. Patients with pT3 were significantly less likely to have a preoperative eGFR >60 ml/min per 1.73 m² when compared to patients with pathologic stage pT2 (40% vs 53%; $p = 0.01$). Similarly, among patients with pT3, 75% had eGFR >45 ml/min per 1.73 m² before nephroureterectomy, falling to 59% after surgery. Although patients with more advanced disease (>pT3) tended to be less likely to have preoperative eGFR >45 ml/min per 1.73 m², this trend did not reach statistical significance (75% vs 83%; $p = 0.09$).

We then stratified our study population by age at surgery, using the median age of the cohort (70 yr) as a cut-off. We used these age categories and our predetermined cut-offs for chemotherapy eligibility to further evaluate pre- and postoperative eGFR as shown in Table 3 and Figure 2. Patients ≥70 yr were more likely to have a preoperative eGFR <60 ml/min per 1.73 m² (64% vs 37%; $p < 0.001$) and twice as likely to have eGFR <45 ml/min per 1.73 m² (27% vs 12%; $p < 0.001$) compared with younger patients. The mean eGFR decreased significantly after surgery in both age groups. Patients <70 yr of age were more likely to maintain eligibility for chemotherapy by both cut-offs, but the difference between age groups was not statistically significant using the higher cut-off (eGFR >60 ml/min per 1.73 m²). However, older patients were significantly more likely to fall below an eGFR of 45 ml/min per 1.73 m², regardless of whether they started with an eGFR >60 ml/min per 1.73 m² ($p = 0.004$) or an eGFR >45 ml/min per 1.73 m² ($p < 0.001$).

4. Discussion

Recently, a large collaborative effort published the outcomes of radical nephroureterectomy in 1363 patients pooled from 12 institutions [6]. More than half of the evaluated patients were pathologic stage T2 or higher, 23% of the 590 patients who had lymph nodes removed (median of two nodes resected among this group) had lymph node involvement, and 28% of patients experienced disease recurrence at a median follow-up of 10.4 mo. During the follow-up period there were 313 disease-specific deaths. As previously stated, 5-yr disease-specific survival has been shown to range from 61% to 76% [3,6]. Patients with invasive disease or positive lymph nodes have higher mortality rates. The University of Texas Southwestern group evaluated 74 patients with stage III (pT3N0M0) or IV (pT4 or any N+ or M+) disease and found a 30% 5-yr disease-specific survival rate for this group [14]. Margulis reported 5-yr survival rates of 35.3% for patients with positive lymph nodes, and 74.7%, 54%, and 12.2% for stages pT2, pT3, and pT4, respectively [6].

Thus, although nephroureterectomy provides disease control in patients with localized UTUC, patients with metastatic or locally advanced disease likely require multimodal therapy. At this time, there are no level 1 data supporting the use of perioperative chemotherapy for UTUC. Several small retrospective series have examined the use of chemotherapy in both neoadjuvant and adjuvant settings. Igawa et al reported a correlation between pathologic response to neoadjuvant chemotherapy and outcome in a retrospective review of 15 patients with UTUC, but statistical significance was not reached [15]. In 2006, Kwak et al published a study on 43 patients with pathologic stage T2 UTUC, 32 of whom received adjuvant cisplatin-based chemotherapy. They found an association between adjuvant chemotherapy and overall survival in their multivariate model [16]. Michael et al [17] and Bamias et al [18] reported 5-yr overall survival of 47% and 52%, respectively, after adjuvant chemotherapy, survival rates that are higher than expected for the advanced stage patients included in those trials, further supporting a possible survival impact for adjuvant

therapy. However, in 2009 an international collaboration showed no survival benefit associated with chemotherapy in 121 adjuvantly treated patients in a high-risk group of 542 patients. These findings are not easily interpreted due to multiple confounding factors including heterogeneity of chemotherapy regimens (10% did not receive cisplatin), short follow-up of 26 mo, and a chemotherapy cohort weighted toward higher stage and grade disease [19].

Despite insufficient direct evidence, data extrapolated from lower tract UC suggest that perioperative chemotherapy should be effective in UTUC. Given the currently available data regarding chemotherapy in UC and the known shortcomings of surgery in treating advanced UTUC, we conclude that carefully planned prospective randomized trials of perioperative chemotherapy are needed in UTUC. Cisplatin is a known nephrotoxin, and eligibility for cisplatin-based therapy is heavily based on kidney function. In this study, we evaluated the impact of nephroureterectomy on eligibility for cisplatin-based chemotherapy using two predetermined eGFR cut-offs. We chose an eGFR of 60 ml/min per 1.73 m², which has traditionally defined eligibility for full-dose cisplatin therapy and also represents the transition into stage III chronic kidney disease. We also chose an eGFR of 45 ml/min per 1.73 m², which has been previously cited as a more strict definition of chronic kidney disease (CKD) and has been shown to be associated with a higher risk of comorbidities related to CKD [20,21]. The eGFR cut-off of 45 ml/min per 1.73 m² is also an attractive compromise between the eGFR of 40 ml/min per 1.73 m² used as the lower limit qualifying patients for reduced-dose cisplatin by Hussain et al and the eGFR of 50[en]55 ml/min per 1.73 m² that has been used to qualify patients as ineligible for cisplatin in several European studies [18,22].

In 2006 a group from the United Kingdom published a retrospective review of 131 patients with UTUC, demonstrating an 18% decrement in eGFR (by MDRD) at a median follow-up of 5 yr after nephroureterectomy. They showed that patients >70 yr, as well as those with risk factors for renal disease, had a greater deterioration in eGFR [23]. We calculated the eGFR for 388 patients pre- and postnephroureterectomy at a median 3 mo from surgery (all within 1 yr). Our data confirm that eGFR is likely to decrease in a clinically significant fashion as a result of nephroureterectomy in patients with UTUC, but over a time period that will affect eligibility for adjuvant chemotherapy. The median decrement in eGFR was 24% of the presurgery value, which exceeds that reported by the United Kingdom group, possibly due to the earlier timing of our postoperative serum creatinine measurement. Older patients (>70 yr) were more likely to be ineligible for cisplatin-based therapy preoperatively by either definition. After surgery, older patients starting with a eGFR <60 ml/min per 1.73 m² tended to be more likely than younger patients to fall to below this cut-off after nephroureterectomy, but this did not reach statistical significance. A more concerning finding, however, is that regardless of their starting eGFR, older patients were significantly more likely than younger patients to manifest a eGFR <45 ml/min per 1.73 m² after surgery. Nearly a third of patients >70 yr who entered surgery with a eGFR <60 ml/min per 1.73 m² were left with a postoperative eGFR <45 ml/min per 1.73 m².

Patients with advanced disease (>pT3) showed a deterioration of eGFR similar to that of the overall group, but they were significantly more likely to manifest a preoperative eGFR <60 ml/min per 1.73 m². This may reflect the comorbidity profile of patients with advanced disease but could also result from a higher incidence of obstructing lesions in this group. In the future, if these patients are to be considered for neoadjuvant chemotherapy, it will be important to maximize preoperative renal function via ureteral stents or percutaneous drainage when indicated.

Clearly, cisplatin-based chemotherapy is a viable option for a significantly higher percentage of patients if it is delivered prior to rather than following nephroureterectomy. More work is needed to demonstrate the effectiveness of cisplatin-based chemotherapy for UTUC and to develop adequate clinical tools that will allow clinicians to identify at-risk patients preoperatively for neoadjuvant chemotherapy trials. Our findings support the development of neoadjuvant chemotherapy protocols in patients considering nephroureterectomy for UTUC. However, selection of patients for such trials will require careful consideration because our ability to stage the upper tract clinically is limited with currently available technologies [24[en]26]. Further development of imaging technologies with resolution capable of better assessing the regional lymph nodes and the depth of invasion of UTUC will be important.

Trials of less nephrotoxic systemic chemotherapeutics also seem warranted based on the current data. Two small phase 2 studies on metastatic UC indicate that carboplatin-based regimens may have less toxicity than cisplatin-based therapies, but median survival times were shorter than those observed with cisplatin-based therapy [27,28]. Split-dose regimens have allowed the use of cisplatin in patients with reduced eGFR [12]. Further research in this area seems appropriate.

Our study is limited by its retrospective nature and by the data available in our multi-institutional data set. Most of our patients did not undergo radionuclide imaging to determine differential renal function, so the potential impact of removing nonfunctioning kidneys on our data is unclear. Our data are also subject to the limitations of GFR estimation by the MDRD equation. The MDRD equation has been shown to outperform the Cockcroft-Gault equation and measured urinary clearance, although it is less accurate in patients with a higher GFR [13]. The use of the MDRD equation in the construction of oncology trials and in the dosing of chemotherapeutics has been recommended [29].

5. Conclusions

The efficacy of perioperative cisplatin-based chemotherapy for UTUC remains unknown. Surgery alone is frequently inadequate in patients with advanced disease. There remains a significant need for the development of prospective trials using perioperative chemotherapy in UTUC. Our study demonstrates that a large proportion of patients, particularly >70 yr of age, are rendered ineligible for cisplatin therapy following surgery. Neoadjuvant protocols should be strongly considered when developing UTUC trials.

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Fig. 1. Comparative scatterplot of estimated glomerular filtration rate (eGFR) before and after surgery. Gray lines represent the mean eGFR for each group. Dashed lines denote 45 ml/min per 1.73 m² and 60 ml/min per 1.73 m² cut-offs.

Fig. 2. Percentage of patients with pre- and postoperative estimated glomerular filtration rate (eGFR) in selected ranges (>65 ml/min per 1.73 m², between 45 and 65 ml/min per 1.73 m², and <45 ml/min per 1.73 m²) stratified by age.

Table 1

Patient characteristics

Patients, <i>n</i>	388	[en]
Gender, No. (%)		
Male	233	(60)
Female	155	(40)
Age at surgery, yr		
Median (IQR)	70	(62[en]76)
Race, No. (%)		
Black	23	(6)
Nonblack	365	(94)
Procedure, No. (%)		
Laparoscopic	164	(42)
Open	224	(58)
Pathologic stage (<i>n</i> = 387), No. (%)		
T0 [*]	10	(5)
Ta	87	(22)
Tis	23	(6)
T1	79	(20)
T2	58	(15)
T3	115	(30)
T4	15	(4)

IQR = interquartile range.

* pT0 represents either patients who were completely resected endoscopically prior to nephroureterectomy or unsampled malignancy at the time of pathology.

Table 2
Effect of nephroureterectomy on renal function: data for entire cohort and stratified by pathologic stage

eGFR = estimated glomerular filtration rate; IQR = interquartile range; SD = standard deviation.

Patients, <i>n</i>	388		
Surgery to postoperative creatinine, d			
Median (IQR)	91	(47.5[en]118)	
Mean (SD)	91	(55.9)	
	Preoperative	Postoperative	<i>p</i>
Creatinine (mg/dl)			
Mean (SD)	1.25 (0.43)	1.57 (0.62)	<0.001
Median (IQR)	1.2 (1[en]1.4)	1.4 (1.2[en]1.7)	
eGFR, ml/min per 1.73 m ²			
Mean (SD)	61.7 (21.1)	47.9 (16.26)	<0.001
Median (IQR)	59.3 (46.8[en]75.5)	46.5 (38.3[en]57.3)	
eGFR ≥ 60 ml/min per 1.73 m ² , No. (%)	191 (49)	73 (19)	[en]
eGFR ≥ 60 ml/min per 1.73 m ² (<i>n</i> = 387), No. (%)			[en]
Ta	51 (57)	15 (17)	
Tis	16 (70)	4 (17)	
T1	40 (51)	9 (11)	
T2	26 (45)	9 (16)	
T3	49 (43)	31 (27)	
T4	3 (20)	3 (20)	
eGFR >45 ml/min per 1.73 m ² , No. (%)	312 (80)	213 (55)	[en]
eGFR ≥ 45 ml/min/1.73 m ² (<i>n</i> = 387), No. (%)			[en]
Ta	71 (82)	45 (52)	
Tis	22 (96)	12 (52)	
T1	62 (78)	36 (46)	
T2	48 (83)	36 (63)	
T3	88 (77)	69 (60)	
T4	10 (67)	8 (53)	

Table 3

Effect of nephroureterectomy on renal function *

	Preoperative	Postoperative	<i>p</i>
<70 yr of age (<i>n</i> = 185)			
eGFR, ml/min per 1.73 m ²			
Mean (SD)	67.8 (21.7)	53.1 (17.6)	<0.001
Median (IQR)	65.7 (53.7[en]80)	51.5 (43.3[en]60.6)	
eGFR ≥ 60 ml/min per 1.73 m ² , No. (%)	117 (63)	47 (25)	
eGFR < 45 ml/min per 1.73 m ² , No. (%)	163 (88)	130 (70)	
70 yr of age (<i>n</i> = 203)			
eGFR, ml/min per 1.73 m ²			
Mean (SD)	56.3 (19)	43.0 (13.2)	<0.001
Median (IQR)	52.7 (42.3[en]65.9)	42.3 (34.5[en]51.7)	
eGFR ≥ 60 ml/min per 1.73 m ² , No. (%)	73 (36)	25 (12)	
eGFR < 45 ml/min per 1.73 m ² , No. (%)	148 (73)	83 (41)	
	<70 yr of age	70 yr of age	<i>p</i>
Preop eGFR ≥ 60 ml/min per 1.73 m ²			
Postop eGFR ≥ 60 ml/min per 1.73 m ² , No. (%)	41 (35)	19 (26)	0.2
Postop eGFR < 60 ml/min per 1.73 m ² , No. (%)	76 (65)	54 (74)	
Postop eGFR ≥ 45 ml/min per 1.73 m ² , No. (%)	103 (88)	52 (71)	0.004
Postop eGFR < 45 ml/min per 1.73 m ² , No. (%)	14 (12)	21 (29)	
Preop eGFR < 45 ml/min per 1.73 m ²			
Postop eGFR < 45 ml/min per 1.73 m ² , No. (%)	126 (77)	79 (53)	<0.001
Postop eGFR ≥ 45 ml/min per 1.73 m ² , No. (%)	37 (23)	69 (47)	

eGFR = estimated glomerular filtration rate; IQR = interquartile range; SD = standard deviation.

* Cohort stratified by age.