Influence of preoperative hydronephrosis and ureteral orifice involvement in the survival of patients undergoing radical cystectomy: A retrospective comparative study

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ABSTRACT

Objective: The aim of the present study was to evaluate the influence of preoperative hydronephrosis and ureteral orifice involvement (UOI) on survival of patients undergoing radical cystectomy (RC) for bladder cancer (BC).

Material and methods: A total of 162 patients with BC underwent RC between January 2006 and March 2017. Patients were divided into two groups for both presences of preoperative hydronephrosis and orifice involvement at final pathology. Additionally, tumors with orifice involvement were subgrouped histopathologically after RC as those with only UOI and those with invasive to the ureter with an additional concurrent site at final pathology.

Results: Preoperative hydronephrosis was detected in 57 patients. Preoperative and postoperative creatinine on month 3 were higher in the preoperative hydronephrosis (+) group ($p<0.001$). In addition, postoperative T stage, surgical margin positivity, invasion of urethra, and pathological upstaging were higher in this group. Cancer-specific survival (CSS) and overall survival (OS) were better in the hydronephrosis (–) group than in the hydronephrosis (+) group ($p=0.001$ and $p=0.001$, respectively). Preoperative hydronephrosis was found to be an independent factor in pathological upstaging. Patients were divided into two groups according to the presence of UOI. Group 1 consisted of patients without UOI, and group 2 with UOI. Preoperative hydronephrosis, hydronephrosis grade, and T stage were statistically higher in tumors with UOI. Moreover, CSS and OS were lower in group 2 than in group 1.

Conclusion: Preoperative hydronephrosis and UOI are predicting factors on survival of patients undergoing RC for BC. Preoperative hydronephrosis was found to be an independent factor in pathological upstaging.

Keywords: Orifice involvement; preoperative hydronephrosis; radical cystectomy; survival.

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Introduction

Bladder cancer (BC) comprises a heterogeneous group of tumors. Selecting an ideal treatment method is a dilemma many times. Moreover, the clinical course and prognosis of the disease is quite difficult to predict. Radical cystectomy (RC) is considered as the standard treatment for patients with muscle-invasive bladder cancer (MIBC). By the aid of neoadjuvant chemotherapy, local and distant control of disease can be achieved with 5-year survival rates up to 80% in most favorable cases.[1] Predicting outcomes and assessing the value of RC in this population depend on accurate staging.[2] In the study by Ficarra et al.[3], 50% of patients clinically staged with organ-confined disease were found to have extravesical disease after RC. Many factors are effective in predicting the course of the disease. These factors include gender, clinical and pathological stages, nodal involvement, hydroureteronephrosis (HUN), and lymphovascular invasion.[4-7]

Urologists search for easy-to-assess and highly reproducible prognostic markers for selecting the appropriate therapy in patients with BC.[8] HUN is a common finding in patients with BC.

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The initial study investigating the effect of HUN on survival of patients after RC was reported by Leibovitch et al.[9] in 1993. In their study, they showed that ureteral obstruction is significantly associated with lower overall and stage-specific survival rates. The significance of preoperative HUN on oncologic outcome has been evaluated by multiple studies with conflicting results.[2,4,8-11] Some of these studies support the value of HUN as an indicator of survival, whereas other studies indicate opposing views on the role of HUN as an independent prognostic variable in patients with urothelial carcinoma of the bladder (UCB) treated with RC.

Hydroureteronephrosis may be associated with orifice involvement. Jancke et al.[11] evaluated tumor growth located around the ureteric orifice at the primary diagnosis of Ta/T1 BC in relation to effects on recurrence and progression. They stated that although tumor growth located around the ureteric orifice in primary Ta/T1 BC is associated with recurrence but not progression, it could be taken into consideration in the management and follow-up of patients with this disease. In contrast to other tumor localizations, urologists tend to approach BCs with orifice involvement with caution and suspicion. This is especially true for muscle-invasive tumors.

In this comparative study, we both discussed the influence of preoperative HUN and ureteral orifice involvement (UOI) on survival of patients undergoing RC for BC.

Material and methods

Patients with UCB who underwent open RC and extended lymph node dissection at our tertiary referral center between January 2006 and March 2017 were evaluated. Operative pathological and follow-up clinical data were reviewed. The indications for RC were tumor invasion into the muscularis propria, prostatic stroma, or non-muscle-invasive disease (Ta, T1, or carcinoma in situ) refractory to transurethral resection with intravesical therapy. Patients were excluded if their cystectomy was not performed for UCB, if they also had a diagnosis of upper tract UC, if they had obstructing stones, or if their medical records were not complete enough to determine the preoperative status of the upper tracts or postoperative pathological stage.

All patients had a complete preoperative work-up, such as physical examination, blood count, blood urea nitrogen, creatinine, electrolyte analysis, chest X-ray, abdominal ultrasound, intravenous pyelogram (IVP) in early cases, computed tomography (CT) scan of the abdomen, and bone scan when necessary. In patients with reduced renal function, magnetic resonance imaging instead of an IVP/CT scan was performed.

Patients were divided into two groups according to the presence of preoperative HUN as HUN (–) and HUN (+). HUN was defined as dilatation of the renal pelvis and calyces with or without secondary changes of the renal parenchyma or renal function. HUN, which was defined by an anteroposterior diameter of the renal pelvis >10 mm, was diagnosed by renal ultrasound, CT scan, or IVP. Additionally, tumors with orifice involvement were also grouped histopathologically after RC as those with only UOI and those with invasive to the ureter with an additional concurrent site at final pathology. Patients were divided into two groups according to UOI at final pathology as group 1 consisted of patients without UOI and group 2 with UOI. Furthermore, patients with UOI (group 2) was subdivided into two subgroups as histological ureteral invasion positive (group 2a) and negative (group 2b). In addition, patients were divided into four groups as HUN (+)/UOI (+), HUN (+)/UOI (–), HUN (–)/UOI (+), and HUN (–)/UOI (–) according to the presence of HUN and UOI.

All procedures were performed in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Data were analyzed using the IBM Statistical Package for the Social Sciences, version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) software program. Mann–Whitney U test and Pearson chi-square test analyses for univariate analysis and binary logistic regression analysis for multivariate analysis were used between the groups for both presences of preoperative HUN and orifice involvement at final pathology. Moreover, propensity score matching was performed for preoperative HUN. After the propensity score matching, binary logistic regression analysis was used for prediction of HUN. In addition, Kaplan–Meier survival analysis and log-rank test were used for overall survival (OS) and cancer-specific survival (CSS) times between the groups. Mann–Whitney U test, Kruskal–Wallis test, and Pearson chi-square test analyses were used between the subgroups. In addition, Pearson correlation test was used between UOI and ureteral invasion. Data are expressed as mean±SD. However, results of analysis are presented as median. A p value <0.05 was considered as statistically significant.

Results

There were 170 patients who underwent RC between January 2006 and March 2017 at our tertiary referral center. Eight patients were excluded from the study according to the exclusion criteria mentioned above. A total of 162 patients with UCB pathology were included in the study. Patients' characteristics without preoperative HUN and with concomitant preoperative HUN are shown in Table 1. The mean age of the patients was 64.2±9.1 (range: 32-83) years, and the mean follow-up time was 32.6±31.6 months. There were a limited number of female pa-

Table 1. Patient characteristics without preoperative hydronephrosis and with concomitant preoperative hydronephrosis

		Preoperative hydronephrosis (−) (n=105)	Preoperative hydronephrosis (+) (n=57)	p*
Age (years)	64.5±9	63.6±9.5	0.617	
Gender	Female	7	7	0.225
	Male	98	50	
Time to radical cystectomy (days)		44.6±14.9	52.5±27.4	0.380
Preoperative T stage	Ta	1	1	0.177
	T1	8	5	
	T2	95	47	
	T3	1	4	
Preoperative tumor grade	Grade 1	2	1	0.909
	Grade 2	4	3	
	Grade 3	99	53	
CIS	Positive	34	13	0.234
	Negative	70	42	
Preoperative creatinine (mg/dL)		1.07±0.36	1.44±0.59	<0.001
Postoperative 3-month creatinine (mg/dL)		1.26±0.63	1.57±0.64	<0.001
Δ Creatinine		0.22±0.57	0.11±0.63	0.585
Postoperative T stage	T1	23	7	0.014
	T2	53	20	
	T3	15	13	
	T4	14	17	
Postoperative tumor grade	1	6	5	0.439
	2	7	2	
	3	87	55	
Surgical margin positivity	Positive	12	18	0.002
	Negative	93	39	
Lymph node metastasis	Positive	18	15	0.167
	Negative	90	39	
Percentage of positive lymph node		3.7±10	8.4±17.4	0.056
Invasıon of prostate	Positive	2	7	0.679
	Negative	91	43	
Invasion of urethra	Positive	4	7	0.024
	Negative	100	44	
Involvement of ureteral orifice	Positive	14	19	0.003
	Negative	91	38	OR: 3.2
Lymphovascular invasion	Positive	18	9	0.959
	Negative	86	44	
Perineural invasion	Positive	17	5	0.238
	Negative	87	48	
Upstaging	Positive	33	33	0.001
	Negative	72	24	
Overall survival (month)		62.5±5.2	35.1±5.6	0.001
Cancer-specific survival (month)		76±5.4	44.2±7.2	0.001

*Mann-Whitney U test, Pearson Chi-square test, Kaplan–Meier survival analysis and log-rank test. CIS: carcinoma in situ

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Table 2 Patient characteristics, preoperative and postoperative data, and statistical analysis according to the presence of ureteral orifice involvement

		Involvement of ureteral orifice (–) (n=129)	Involvement of ureteral orifice (+) (n=33)	p*	p**
Age (years)		63.7±9.5	66±6.7	0.188	–
Gender	Female	9	5	0.136	–
	Male	120	28		
Preoperative hydronephrosis	Positive	38	19	0.003	0.013
	Negative	91	14		HR: 0.35
					(CI: 0.153–0.799)
Preoperative hydronephrosis grade	Grade 1	3	1	0.008	–
	Grade 2	11	3		
	Grade 3	20	8		
	Grade 4	3	7		
Preoperative T stage	Ta	2	0	0.005	0.032
	T1	9	4		HR: 0.082
	T2	117	25		(CI: 0.008–0.807)
	T3	1	4		
Preoperative tumor grade	Grade 1	3	0	0.256	–
	Grade 2	7	0		
	Grade 3	129	33		
CIS	Positive	36	11	0.594	–
	Negative	90	22		
Preoperative creatinine (mg/dL)		1.21±0.51	1.38±0.47	0.267	–
Postoperative 3-month creatinine (mg/dL)		1.4±0.7	1.38±0.63	0.813	–
Δ creatinine		0.2±0.6	0.1±0.7	0.484	–
Postoperative T stage	T1	28	2	<0.001	–
	T2	65	8		
	T3	20	8		
	T4	16	15		
Postoperative tumor grade	1	5	3	0.558	–
	2	5	1		
	3	103	29		
Surgical margin positivity	Positive	14	16	<0.001	0.028
	Negative	115	17		HR: 0.118
					(CI: 0.018–0.798)
Lymph node metastasis	Positive	22	9	0.160	–
	Negative	102	22		
Percentage of positive lymph node		4.2±11.4	9.4±17.7	0.069	–
Invasıon of prostate	Positive	11	8	0.006	–
	Negative	113	21		
Invasion of urethra	Positive	4	7	0.001	–
	Negative	121	23		
Lymphovascular invasion	Positive	14	13	<0.001	0.016
	Negative	111	19		HR: 0.23
					(CI: 0.069–0.763)
Perineural invasion	Positive	13	9	0.01	–
	Negative	112	23		
Upstaging	Positive	43	23	<0.001	–
	Negative	86	10		
Overall survival (month)		58.6±4.7	26.7±4.3	0.006	–
Cancer-specific survival (month)		74±5	28.4±4.4	<0.001	–

*Mann-Whitney U test, Pearson Chi-square test, Kaplan–Meier survival analysis and log-rank test. **Binary logistic regression analysis. CIS: carcinoma in situ

tients (14 of 162). Preoperative HUN is detected in 57 patients. Preoperative and postoperative findings of patients with HUN (–) and (+) groups are shown in Table 1. Preoperative and postoperative creatinine on month 3 were higher in the preoperative HUN (+) group (p<0.001). In addition, postoperative T stage, surgical margin positivity, invasion of urethra, and upstaging were higher in this group. There were 33 patients who had UOI. UOI was significantly higher in the HUN (+) group (p=0.003, odds ratio (OR): 3.2). CSS and OS were better in the HUN (–) group than in the HUN (+) group (p=0.001 and p=0.001, respectively). Preoperative HUN was found to be an independent factor in upstaging. Seven of 14 T1 patients, 54 of 141 T2 patients, and 4 of 5 T3 patients were upstaged.

We performed propensity score matching among patients with preoperative HUN (–) and (+). A total of 22 patients were excluded after matching. In the logistic regression analysis of 140 patients after propensity score matching, preoperative HUN was found to be a statistically significant predictor (p<0.001, OR: 0.295, confidence interval: 0.164–0.530).

Patients were divided into two groups according to the presence of UOI. Group 1 consisted of patients without UOI, and group 2 with UOI. Patients' characteristics, preoperative and postoperative data, and statistical analysis between these groups are presented in Table 2. Preoperative HUN, hydronephrosis grade, and T stage were statistically higher in group 2 than in group 1. Postoperative T stage, surgical margin positivity, inva-

Table 3. Evaluation of HUN (+)/UOI (+), HUN (+)/UOI (–), HUN (–)/UOI (+), and HUN (–)/UOI (–) groups according to HUN and UOI presences

		HUN (+)/UOI (+) (n=19)	HUN (+)/UOI (–) (n=38)	HUN (–)/UOI (+) (n=14)	HUN (–)/UOI (–) (n=91)	p
Postoperative T stage	T1	2	5	0	23	<0.001
	T2	3	17	5	48	
	T3	5	8	3	12	
	T4	9	8	6	8	
Surgical margin positivity, n (%)		9 (47.4)	9 (23.7)	7 (50)	4 (4.4)	<0.001
Upstaging, n (%)		14 (73.7)	19 (50)	9 (64.3)	23 (25.3)	<0.001
Overall survival		24.6±4.8	39.8±7.6	30.1±7.9	65.5±5.6	0.002
Cancer-specific survival		24.6±4.9	56.3±9.7	35±8.4	79.9±5.7	<0.001

**Pearson Chi-square test, Kaplan–Meier survival analysis and log-rank test. HUN: hydroureteronephrosis; UOI: ureteral orifice involvement

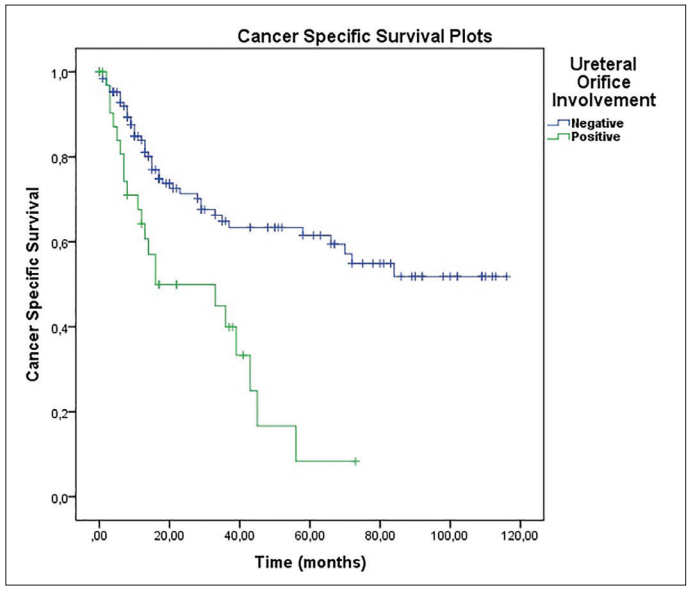

Figure 1. Cancer-specific survival plots of the groups according to ureteral orifice involvement presence

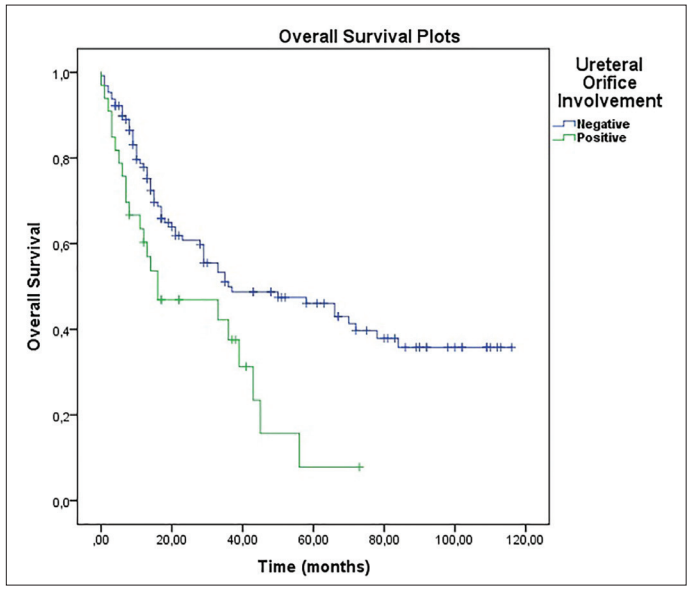

Figure 2. Overall survival plots of the groups according to ureteral orifice involvement presence

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sion of prostate, invasion of urethra, lymphovascular invasion, perineural invasion, and upstaging rates were also found to be significantly higher in group 2. CSS (74±5 months for group 1 and 28.4±4.4 months for group 2, p<0.001) and OS (58.6±4.7 months for group 1 and 26.7±4.3 months for group 2, p=0.006) were significantly lower in group 2 than in group 1. Kaplan–Meier survival plots are shown in Figures 1 and 2. In addition, in the evaluation of HUN (+)/UOI (+), HUN (+)/UOI (–), HUN (–)/UOI (+), and HUN (–)/UOI (–) groups according to HUN and UOI presences, postoperative T stage, surgical margin positivity, upstaging, OS, and CSS were statistically different between the groups (Table 3).

Among 33 tumors with UOI, histological ureteral invasion occurred in 15 patients. Histological ureteral invasion was positively correlated with UOI (R=0.632, p<0.001). In subgroup analysis, there was no difference according to preoperative HUN, HUN grade, and preoperative and postoperative T stages in patients with histological ureteral invasion positive or negative.

Discussion

Whatever the reason leading to HUN, HUN at the time of diagnosis of BC is a valid marker for advanced disease. As a predictor of advanced bladder carcinoma, HUN could improve clinical staging accuracy and patient selection for neoadjuvant chemotherapy.[2] Chapman et al.[11] have shown that preoperative HUN is an independent predictor of decreased survival in patients undergoing RC for UCB and found that preoperative HUN predicts advanced pT stage, as well as positive surgical margins. Identifying HUN preoperatively may help predict upstaging and node positive disease, which in turn could improve prognostication and at least improve risk stratification.[2] Despite the generally accepted views about the impact of HUN on the prognosis of the disease, the most important question to be answered is the role of HUN at the time of diagnosis as an independent prognostic factor for recurrence-free survival of patients with UC. In many studies, it was shown that HUN at the time of diagnosis of BC is associated with a high probability of advanced tumors and found as an independent prognostic factor for recurrence-free survival.[2,8,11] In contrast to these studies, preoperative HUN was found to be significant on univariate analysis, but lost its significance on multivariate analysis.[12-14]

In this comparative study, we discussed the impact of preoperative HUN on postoperative pathological findings, CSS, and OS. Our results revealed that preoperative and postoperative creatinine on month 3, postoperative T stage, surgical margin positivity, invasion of urethra, and upstaging were significantly higher in the HUN (+) group. BC with concomitant HUN had poorer CSS and OS than BC without HUN. Tumors accompanied with that HUN should always be approached with caution.

Although tumors involving the bladder and ureter have been well described, there are only few studies in the pathology literature specifically analyzing tumors involving the ureteral orifice.[15] HUN may be due to intramural or extravesical tumor extension leading to ureteral compression or infiltration, tumor involving the ureteral orifice, and presence of simultaneous ureteral tumor.[9] Svatek et al.[16] evaluated the influence of intravesical tumor location on nodal metastasis and mortality after cystectomy and concluded that patients with bladder tumor in the trigone have a greater risk of lymph node metastasis at cystectomy and decreased CSS. They also stated that tumor location may be a useful prognostic factor in risk stratification of patients with MIBC. Different studies investigating the role of tumor location within the urinary bladder showed that tumor location gave important knowledge about the prognostic significance of disease.[17-21] In a clinicopathologic analysis of 93 cases with UC involving the ureteral orifice, Annan et al.[15] performed a search for biopsy and resection specimens (transurethral resection, RC/cystoprostatectomy, nephroureterectomy, and bladder cuff resection) of UC involving the ureteral orifice. Although they focused primarily on the index tumor involving the ureteral orifice (those with only UOI), they found that at least one other tumor is located at another site within the bladder in 70/93 (75%) cases. They concluded that careful examination of the ureteral orifice needs to be performed by both urologists and pathologists when examining cases of UCB. In another study, Leibovitch et al.[9] found that the tumor extends to the external layer of the detrusor muscle (>T2a) in all hydronephrotic cases without UOI, and they found low-stage disease in most cases with intravesical involvement of the ureteral orifices. Annan et al.[15] found invasive UC (including aggressive variants) in 45% of cases in their series although the ureteral orifice is not a site typically biopsied. Furthermore, they stated that 75% have tumors located at other sites of the bladder. In their series of 788 patients who were treated with RC with curative intent for transitional cell carcinoma of the bladder without neoadjuvant/adjuvant radiotherapy/chemotherapy, Bartsch et al.[8] investigated the prognostic impact of HUN in BC. They concluded that HUN is a significant marker for advanced disease as long as the tumor does not involve the ureteral orifice and is an independent prognostic marker for recurrence-free survival and tumor-specific survival. They stated that the presence of HUN without involvement of the ureteral orifices may be a helpful marker for the decision-making process. In the current study, involvement of the ureteral orifice was correlated with postoperative advanced stage, higher surgical margin positivity, and upstaging poorer CSS and OS. Whether or not pathologic ureter invasion was present, orifice involvement is an important finding alone and is directly related to the organ non-confined disease.

The present study had several limitations. These limitations included its retrospective design and the lack of information about different localization of concurrent bladder tumors with UOI.

This could lead to misclassification of intravesical tumor location. We are limited somewhat by the unknown selection criteria and small numbers of patients. In addition, neoadjuvant and adjuvant treatments were not recorded due to the lack of information in the medical records. Thus, the study group may not have been treated in a homogenous manner. Another shortcoming in our analysis was the inability to capture potential independent prognostic factors, such as tumor volume and additional RC pathological variables. There are a limited number of patients with UOI. Moreover, a propensity score matching was not performed.

In conclusion, preoperative HUN and UOI are predicting factors on survival of patients undergoing RC for MIBC. Preoperative hydronephrosis was found to be an independent factor in upstaging. UOI with or without ureteral invasion is an important finding alone, and this is directly related to the organ non-confined disease.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

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