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Original Research Article

The prognostic factors of bladder urothelial carcinoma after radical nephroureterectomy

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ABSTRACT

Background: We aimed to determine the factors for prediction of bladder transitional cell carcinoma (TCC) development secondary to upper urinary system TCC.
Methods: Fifty-six patients that underwent radical nephroureterectomy and concomitant partial cystectomy at a single site. All patents were diagnosed with cystoscopy, cytological study and CT-urography. International prostate symptom score and post-void residual urine >50 ml were taken as basis to identify lower urinary tract symptoms (LUTS). The relationship between age, gender, tumor localization, tumor grade, tumor size, disease stage, carcinoma *in situ* (CIS) positivity, LUTS positivity and development of TCC were analyzed. The SPSS 25.0 software package was used in the statistical analysis of the data. The survival curve was plotted using the standard Kaplan-Meier methodology. P<0.05 was considered statistically significant in all tests.
Results: Thirty patients developed bladder TCC (53.6%). Mean age for patients with and without bladder TCC were 71.40±7.6 and 65.73±7.1, respectively. None of the patients enrolled had concomitant TCC. Single variable analysis revealed advanced age (p<0.006), tumor stage (p<0.0001), LUTS (p<0.0001) to TCC development was statistically significant. Risk of developing TCC was 9-fold in LUTS (+) patients. Multivariate analysis results showed LUTS to TCC development was statistically significant (OR=34.52, 95% CI=3.8-52.3; p<0.002).
Conclusions: As a result, tumor stage, LUTS and age increases the risk of developing blader TCC after nephroureterectomy. LUTS should also be investigated, and if positive, we postulate that its early treatment is important for preventing development of bladder TCC.

Keywords: Upper urinary tract urothelial carcinoma, Bladder cancer, Nephroureterectomy

INTRODUCTION

Urothelial carcinomas are the 4th most common type of cancer after prostate, lung and colorectal cancers.[1,2] Urothelial carcinomas consist 90-95% of bladder cancers. 90-95% of upper urinary tract tumor are urothelial carcinomas.[1-5] Upper urinary tract urothelial carcinoma (UTUC) consists 5-10% of all urinary system carcinomas.[1-6] 60% and 15-25% of UTUC and bladder urothelial carcinomas are invasive at time of diagnosis, respectively.[1,3,4] UTUC peak at 70 and 80 years of age. Male/female ratio is 3/1.[7,8]

UTUC has a 22-47% and 17% ratios of developing bladder urothelial cancers and concomitant bladder cancer, respectively. Ratio of developing cancer at the opposite site is 2-6%.[9-13]

UTUCs are more progressive and have higher mortality ratio with respect to urothelial carcinomas of bladder. Five-year survival rates are <50% for stages pT2/pT3 and <10% for pT4.[14-16] UTUC cause development of urothelial cancers in bladder and opposite kidney, severely decreasing survival rates and quality of life for the patients. The factors contributing to development of

bladder urothelial cancers secondary to UTUC are demonstrated by many studies.[17-19]

A search in the electronic literature database (PubMed) revealed that no study has so far been conducted on relationship between bladder urothelial carcinoma secondary to UTUC and LUTS. In this study, we aimed to determine the factors (age, gender, tumor stage, tumor grade, tumor size, tumor localization, time period for nephroureterectomy, LUTS for prediction of bladder TCC development secondary to UTUC.

METHODS

Fifty-six patients that underwent radical nephroureterectomy and concomitant partial cystectomy at İbni Sina hospital, Ankara university school of medicine between November 2011 and 2014 due to upper urinary system TCC were enrolled in the study. The ethics committee approval was received from the medical ethics committee of the Ankara university school of medicine (No:09-381-14). The 47 patients were men, 9 were women.

Inclusion criteria

Patients who underwent radical nephroureterectomy due to upper urinary tract TCC and concurrent partial cystectomy were included.

Exclusion criteria

Patients with bladder TCC concurrently with upper urinary tract TCC, patients who were on follow-up with the diagnosis of bladder TCC previously to radical nephroureterectomy and patients with a pathology result of non-TCC tumor in radical nephroureterectomy specimen were excluded.

Preoperative CT-urography and intraoperative cystoscopy (previously to radical nephroureterectomy) were taken and cytology was performed in all patients for diagnosis. CT-urography for the evaluation of tumor location and size, 2017 TNM staging system for staging and 1973/2004 WHO/international society of urologic pathology grading system for the grading of tumor histology were used.[20,21] International prostate symptom score (IPSS) and post-void residual urine >50 mL were taken as basis to identify LUTS. In patients with findings consonant to upper urinary tract TCC in CT urography, nephroureterectomy and concurrent partial cystectomy were performed. The patients were followed up at 3 and 6 months, then every 6 months for 3 years, and annually thereafter. Cystoscopy and cytology were performed to identify bladder tumor in the follow-up. Moreover, contralateral upper urinary tract was annually evaluated through BT urography. The date when bladder tumor developed was noted in the follow-up (1st, 2nd, and etc. year following radical nephroureterectomy). Furthermore, cases of mortality, local recurrence, and metastasis were noted down. The data of the patients were retrospectively evaluated.

The patients were evaluated in two groups: Group-1: Patients developing bladder TCC and group-2: Patients who did not develop bladder TCC.

In patients with bladder TCC due to upper urinary tract TCC, the relation between age, type, location of tumor, stage, grade, size, CIS existence, LUTUC existence and developing bladder TCC was evaluated.

Surgical technique

All patients underwent intraoperative cystoscopy just before nephoureterectomy. Our patients were with local stage cancer (only one patient in stage pT3, there no patients with stage pT4 cancer) in preoperative imaging (CT-Urografi).We performed nephroureterectomy extravesical cuff excision through Gibson incision using open method. Kidney +ureter +bladder cuff was excised massively. The defect in the bladder was closed in two-layer, being mucosa and muscle/serosa (mucosa with 3/0 Caprosyn and muscle/serosa with 2/0 Vycril). Then, the bladder was filled with steril liquid and was checked for hermeticity. All patients received single-dose intravesical chemotherapy (Mitomycin 40 mg or Epirubicin 50 mg) at the postoperative sixth hour. Intravesical catheter was removed on the postoperative sixth day.

Statistical tests and analyses

The SPSS 25.0 software package was used in the statistical analysis of the data. Categorical measurements were expressed in numbers and percentages and continuous measurements were expressed in mean and standard deviation (median and minimum-maximum, where necessary) values. The Chi-square test or Fisher's test was used in the comparison of categorical variables. Distributions were analyzed for a comparison of continuous measurements between the groups, wherein the Student's t test was used for variables with a parametric distribution and the Mann-Whitney U test for variables with a non-parametric distribution. A multiple logistic regression analysis step-wise model was used to know associations between measurements with groups as dependent variable(mortality was dependent variables). Overall survival was analyzed using the Wald test, and the log-rank test was used to examine their relationship when different parameters were applied. The survival curve was plotted using the standard Kaplan-Meier methodology. $P<0.05$ was considered statistically significant in all tests.

Ethics committee approval

The ethics committee approval was received from the medical ethics committee of the Ankara university school of medicine (No: 09-381-14).

Informed consent

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

RESULTS

Thirty out of 56 patients developed bladder TCC (53.6%), 26 patients did not develop bladder TCC (46.4%) (Table 1). Association between bladder TCC development secondary to upper urinary system TCC was investigated for age, gender, tumor localization, tumor grade, tumor stage, tumor size, CIS positivity and LUTS positivity.

Age

Mean age for patients with and without bladder TCC were 71.40±7.6 and 65.73±7.1, respectively. Single variate analysis indicated that increasing age was a statistically significant factor for development of bladder TCC (p<0.006) (Table 1).

Gender

Single variate analysis for gender showed bladder TCC development in 57.4% of men (27/47) and 33.3% of women (3/9). Contribution of gender to TCC development was not statistically significant (p<0.277) (Table 1).

Tumor localization

Bladder TCC developed in 41.1% of patients with tumors in renal pelvis (23/56), 1.8% of patients with tumor in proximal ureter (1/56), 5.4% of patients with tumors in mid-ureter localization (3/56), 51.8% of patients with tumors in distal-ureter localization (29/56). The contribution of tumor localization to the TCC development was not statistically significant (p=0.580) (Table 1).

Tumor size

The following results were obtained regarding association of tumor size with TCC development: Tumor > 1 cm: 26.8% (15/56). Tumor <1 cm: 73.2% (41/56). The contribution of tumor size to TCC development was borderline insignificant according to the Chi-square test (p<0.079) (Table 1).

Tumor stage

No bladder TCC developed in patients with tumor staged at Ta% 30.4 (17/56). Stage T1, T2, T3 tumors developed bladder TCC with ratios of 41.1% (23/56), 26.8% (15/56), 1.8% (1/56), respectively. No T4 tumor was detected in patients enrolled in the study. The contribution of tumor stage to TCC development was statistically significant according to Chi-square test (p<0.0001) (Table 1).

Tumor grade

The following data are obtained from the study regarding the relationship between tumor grade and the bladder TCC. Ratio of the bladder TCC development is 55.4% for the low-grade upper urinary system tumors (31/56).

This ratio is 44.6% (25/56) for high-grade tumors. The contribution of tumor grade to TCC development was not statistically significant (p<0.430) (Table 1).

LUTS

We investigated ratio of bladder TCC development in patients with LUTS. The following data are obtained: ratio of bladder TCC development in patients with LUTS was 41.1% (23/56). This ratio was 58.9% in patients without LUTS (33/56). The contribution of LUTS to TCC development was statistically significant (p<0.0001) (Table 1).

CIS

Ratios of bladder TCC development in the CIS (+) and CIS (-) patients were 10.7% (6/56) and 89,3% (50/56), respectively. The contribution of CIS to TCC development was not statistically significant according to the Chi-square test (p<0.675) (Table 1).

Multivariate analysis was used for determination of independent risk factors. Variables of tumor stage, LUTS and age were investigated. The contribution of LUTS to TCC development was statistically significant (OR=34.52, 95% CI=3.8-52.3; p<0.002). The tumor stage and the age were not statistically significant (shown in Table 2).

The overall survivals of the patients were 38.8±1.8 months; One-year surveillance was 98.1% and five-year surveillance was 84.9%.

There was no statistically significant difference in survival between patients with and without bladder TCC (Table 3).

One patient (63-year-old male) died due to miocardial infarction and one patient died due to pneumonia during the follow-up. In one patient, local recurrence occure in bladder cuff excision stump and gemcitabine with cisplatine (GC) chemotherapy was administered by consulting medical oncology and open method local recurrence mass excision was performed.

Pulmonary metastasis developed in his follow-up and therefore died. İn other one development of metastasis during the follow-up.

Table 1: Patient characteristics of 2 groups and univariate analysis for prediction of bladder TCC development after nephroureterectomy.

Parameters	Total		Group 1 (Patients that developed bladder TCC), (n=30)		Group 2 (Patients that did not develop bladder TCC), (n=26)		P value
	N	%	N	%	N	%	
Gender							
Men	47	83.9	27	90.0	20	76.9	0.277
Women	9	16.1	3	10.0	6	23.1	
Tumor localization							
Renal pelvis	23	41.1	12	40.0	11	42.3	0.580
Proximal ureter	1	1.8	0	0.0	1	3.8	
Mid-ureter	3	5.4	1	3.3	2	7.7	
Distal ureter	29	51.8	17	56.7	12	46.2	
Tumor size							
<1 cm	15	26.8	5	16.7	10	38.5	0.079
>1 cm	41	73.2	25	83.3	16	61.5	
Tumor stage							
Ta	17	30.4	1	3.3	16	61.5	0.0001
T1	23	41.1	13	43.3	10	38.5	
T2	15	26.8	15	50.0	0	0.0	
T3	1	1.8	1	3.3	0	0.0	
T4	-	-	-	-	-	-	
Tumor grade							
Low grade	31	55.4	15	50.0	16	61.5	0.430
High grade	25	44.6	15	50.0	10	38.5	
Overall survival in follow-up period							
Live	53	94.6	28	93.3	25	96.2	1.000
died	3	5.4	2	6.7	1	3.8	
Cancer specific survival in follow-up period							
Live	55	98.2	29	96.7	26	100.0	1.000
Died	1	1.8	1	3.3	0	0.0	
LUTS							
Yes	23	41.1	21	70.0	2	7.7	0.0001
No	33	58.9	9	30.0	24	92.3	
CİS							
CİS+	6	10.7	4	13.3	2	7.7	0.675
CİS-	50	89.3	26	86.7	24	92.3	

Table 2: Results of multivariate analysis of risk factors for intravesical recurrence after nephroureterectomy.

Variables	B	SE	Wald	Df	P	Odds ratio	95% CI for odds ratio	
							Lower	Upper
Age (in years)	-0.034	0.074	0.210	1	0.647	0.97	0.8	1.1
LUTS	3.796	1.254	9.160	1	0.002	34.52	3.8	52.3
Constant	-6.663	6.044	1.216	1	0.270	0.001		

Table 3: Overall and cancer specific survival rates of patients with or without bladder TCC.

Variables	Estimate mean	Std. error	95% CI mean		One year survival rates (%)	2 years survival rates (%)	5 years survival rates (%)	P
			Lower bound	Upper bound				
Overall survival	38.819	1.79	35.30	42.33	98.1	95.6	84.9	-
Cancer specific survival	59.2	0.77	57.71	60.73	98.1	98.1	98.1	-
TCC								
Patients developed bladder TCC	46.10	1.29	43.56	48.64	96.4	89.5	89.5	0.109
Patients that did not developed bladder TCC	59.56	0.42	58.73	60.38	100	100	88.9	

DISCUSSION

We found in our study the contribution of LUTS to TCC development was statistically significant (OR=34.52, 95% CI=3.8-52.3; p<0.002). Tumor stage and age were not statistically significant. LUTS causing bladder cancer may be associated with CIS and intravesical obstruction. The number of patient with CIS+ was very low (6/56). We think tahat carcinogens or flying tumor cells affect bladder mucosa for long time in infravesical obstruction.

Cosentino et al investigated the factors predicting the concomitant development of UTUC and bladder urothelial cancers.[22] They studied variables of age, gender, localization, stage, multifocality, grade and clinical symptoms; 76 of the 450 patients (17%) had concomitant bladder urothelial carcinoma. Tumor sites were renal pelvis in 25 (31%), upper ureter in 8 (14%) and distal ureter in 37 (49%) patients. Ratios of concomitant development with bladder urothelial carcinomas for renal pelvis, upper ureter, distal ureter were 10%, 18%, and 33%, respectively (Mean=1.7; 95% Cl=1007-2906; p=0.047). Other factors were not found statistically significant (age, gender, stage, tumor grade, clinical symptoms). In our study, we had no phenomenon with UTUC and concomitant bladder urothelial carcinoma. Single variate analysis in our study revealed age (p<0.006), tumor stage (p<0.0001) and LUTS (p<0.0001) as statistically variables in predicting development of bladder urothelial carcinomas. Multivariate analysis of the data in our study indicated LUTS (OR=34.52, 95% CI=3.8-52.3; p<0.002) to be statistically significant variables for prediction of concomitant bladder urothelial carcinoma development. Xylinas et al published a collection in 2012 regarding development of bladder urothelial cancers in patients with multifocal CIS in upper urinary system, reviewing 2681 phenomena nephrectomized due to UTUC between the years 1987 and 2007; 68 of these were diagnosed with upper urinary system CIS.[9] Multivariate COX analysis showed multifocal CIS in upper urothelial system to be risky in terms of urothelial cancer of bladder (p<0.032). In our study, CIS (+) in upper urinary system was not a statistically significant variable for development of urothelial carcinoma of bladder (p<0.675). This may be due to low number of patients enrolled in our study.

Zigeuner et al enrolled 191 phenomena in 2006 and 51 of them (27%) developed bladder urothelial carcinoma. The study investigated effects of age, gender, tumor stage, localization, grade, positivity of surgical margins on development of urothelial cancers.[10] Multivariate analysis indicated that urothelial localization of the tumor and tumor grade are statistically significant; p<0.03 and p<0.04 (RR=2.1, 95% CI=1.1-4.2) and (RR=2.2, 95% CI=1.03-4.7)) respectively. Our study did not show any statistical significance for tumor localization and grade (p<0.560 and p<0.430). A study by Novara et al reviewed data of 231 patients from 3 sites retrospectively, who underwent nephroureterectomy between the years 1989 and 2005 with diagnosis of UTUC, 109 of the 231 patients (47.2%) developed bladder urothelial carcinoma.[23] The multivariate analysis in this study indicated that UTUC in urethra significantly increases development of metachronous bladder urothelial cancers (p<0.02). Our study results were not significant for association between urothelial localization of tumor and development of bladder urothelial carcinoma. Li et al studied the excision methods of bladder cuff (extravesical, intravesical, transurethral) in 301 UTUC patients on development of bladder urothelial cancer development.[12] There was no statistically significant difference among excision methods on development of bladder urothelial carcinoma (p<0.62). We generally prefer extravesical method. In this respect, we did not compare it with other surgical approaches.

Novara et al reported that 6% of 234 patients with UTUC also developed contralateral UTUC.[23] There was no contralateral UTUC phenomenon in our study. There was no study data in electronic literature database (PubMed) regarding the relationship of LUTS positivity in UTUC patients with bladder urothelial carcinoma development. In our study, we investigated the effect of LUTS positivity with bladder urothelial carcinoma development. Bladder TCC ratio in LUTS (+) and LUTS (-) patients in our study were 70% (21/30) and 7.7% (2/26), respectively. The contribution of LUTS to TCC development was statistically significant according to multivariate analysis (OR=34.52, 95% CI=3.8-52.3; p<0.002). Moreover, risk for developing bladder TCC was increased 9-fold in LUSS (+). In this respect, UTUC patients should be investigated for LUTS, and if positive, it should be treated. Recurrences were more common during the first 2 years. This patient group should undergo cystoscopy control for the first 2-year period.

There was no patient with development of metastasis during the follow-up. This possibly results from the fact that our patients were at local stage (number of patients at stage pT4, 0; that of patients at stage pT3, 1), most of the patients were at lower grade (31/56), and the number of patient with CIS+ was very low (6/56).

The shortcomings of our study are the small number of patients and its retrospective nature.Prospective randomized studies are needed.

CONCLUSION

This patient group should also be monitored closely for the first 2 years; LUTS should also be investigated, and if positive, we postulate that its early treatment is important for preventing development of bladder TCC.

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