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Original Research / Özgün Araştırma

Risk factors for intravesical recurrence after radical nephrourethrectomy in upper urinary tract urothelial tumors: retrospective single-center study

Üst üriner trakt ürotelyal tümörlerinde radikal nefroüretrektomi sonrası intravezikal nüks için risk faktörleri: retrospektif tek merkezli çalışma

Taner Kargı, Mithat Ekşi

University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, İstanbul, Turkey

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Yazışma / Correspondence
Mithat Ekşi
Dr.Sadi Konuk Hospital, Department of Urology, Zuhuratbaba, Dr. Tevfik Sağlam Cd No:11, 34147, Bakırköy,
İstanbul / Türkiye
E-mail: mithat_eksi@hotmail.com
Tel: +90 506 252 82 83

ORCID
T.K. 0000-0001-5874-3489
M.E. 0000-0003-1490-3756

Özet

Amaç: Üst üriner sistem karsinomu (UTUC) nedeniyle radikal nefroüreterektomi (RNU) uygulanan hasta serimizde mesane kanserinin metakron nüksünü öngören faktörleri inceledik.

Gereç ve Yöntemler: Merkezimizde Eylül 2009 ile Mart 2020 tarihleri arasında UTUC kaynaklı RNU olan hastalar çalışmaya dahil edildi. Hastalar intravezikal nüks (IVR) olan ve olmayan olarak sınıflandırıldı ve nüksü öngören faktörler değerlendirildi.

Bulgular: Çalışmaya toplam 50 hasta dahil edildi. Toplam 50 hastanın 19›unda (%38) IVR gelişmiştir ve ortalama takip süresi 39,5 ± 25,3 aydır. Demografik özellikler, başvuru hemoglobini, glomerüler filtrasyon hızı ve hidronefroz derecesi, preoperatif üreterorenoskopi ve sitoloji pozitiflik öyküsü açısından iki grup arasında anlamlı fark yoktu (p>0.05). IVR (+) grubunda anlamlı olarak daha fazla mesane kanseri öyküsü vardı (sırasıyla %35,5'e karşı %52,6, p=0.019). Üreter tümörü olan hasta sayısı IVR (-) grubunda 10 (%32,3) iken IVR (+) grubunda 9 (%47,4) idi ve anlamlı olarak daha yüksekti (p=0,04). Tüm hasta grubunda 28 (%56) T2-T4 patolojisi olan hasta vardı ve oran IVR (+) grubunda anlamlı olarak daha fazlaydı (sırasıyla %63,2 ve %51,6, p=0.038).

Sonuç: Daha önce mesane kanseri öyküsü olan hastalarda, özellikle üreteral ve yüksek patolojik T evreli UTUC'larda mesane kanserinin metakron nüksü için dikkatli olunmalıdır.

Anahtar Kelimeler: üst üriner sistem ürotelyal karsinomu, intravezikal nüks, risk faktörü, nefroüreterektomi

Abstract

Objective: We examined factors predicting metachronous recurrence of bladder cancer in our series of patients who underwent radical nephroureterectomy (RNU) for upper system urothelial carcinoma (UTUC).

Material and Methods: Patients with UTUC-induced RNU in our center from September 2009 to March 2020 were included in the study. Patients were classified as having and not having an intravesical recurrence (IVR), and the factors predicting recurrence were evaluated.

Results: A total of 50 patients were included in the study. IVR was developed in 19 (38%) of 50 patients, with a mean follow-up of 39.5 ± 25.3 months. There was no significant difference between the two groups in demographic characteristics, admission hemoglobin, glomerular filtration rate, and degree of hydronephrosis in preoperative ureterorenoscopy and cytology positivity history (p>0.05). The IVR (+) group had significantly more previous history of bladder cancer (35.5% vs. 52.6%, p=0.019, respectively). While the number of patients with ureteral tumors was 10 (32.3%) in the IVR (-) group, it was 9 (47.4%) in the IVR (+) group, and it was significantly higher. There are 28 (56%) patients with T2-T4 pathology in the entire patient group, and the rate is significantly greater in the IVR (+) group (63.2% vs. 51.6%, p=0.038, respectively).

Conclusion: Caution should be exercised for metachronous bladder cancer recurrence in patients with a previous history of bladder cancer, especially in ureteral and high pathological T-stage UTUCs.

Keywords: upper urinary tract urothelial carcinoma, intravesical recurrence, risk factor, nephroureterectomy

The study was approved by University of Health Sciences, Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinic Investigations Ethic Committee (Approval No: 2022-08-04, Date: 2022/04/18). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) constitutes 5% of all urothelial carcinomas and 5-15% of renal tumors. (1, 2) UTUC is more progressive and prone to recurrence than bladder carcinomas. In addition, almost half of the tumors in these patients are invasive, and 19% of patients have metastases at the time of diagnosis. (3)

Due to multifocality, recurrence, and prognosis, the gold standard therapy at UTUC is radical nephroureterectomy (RNU) with bladder cuff excision. (4) The risk of bladder cancer after RNU is reported as 35-40% in the literature, which is quite high. (5, 6) In 82-89% of the patients, intravesical recurrence (IVR) is observed within 2 years. (6, 7)

It is important to know the factors predicting metachronous bladder recurrence due to progression, recurrence, and poor prognosis tendency. However, the development of IVR after RNU may depend on many variables, such as patient and tumor characteristics and the treatment modality. Male gender, preoperative chronic renal failure, positive urinary cytology, ureteral location, multifocality, pathological T stage, surgical margin positivity, and laparoscopic approach were identified as risk variables that increased IVR in a meta-analysis (8). In our study, we examined factors predicting metachronous recurrence of bladder cancer in our series of patients who underwent RNU for UTUC.

MATERIAL AND METHODS

The Ethics Committee approved our study of our institute. (Approval Number: 2022/126) Patients who underwent RNU due to UTUC in our center from 2009 to March 2020 were included in the study. Patients with pathology other than urothelial carcinoma, bilateral renal tumors at the time of diagnosis, nephrectomy of the contralateral kidney for UTUC, patients with metastatic disease at the time of diagnosis, receiving neoadjuvant chemotherapy or radiotherapy, patients with a history of cystectomy or undergoing simultaneous cystectomy were excluded from the study.

Patients were examined with preoperative routine blood and urine tests, contrast-enhanced + non-contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI) urography. Evaluation of the lungs was made with thorax CT. All patients underwent preoperative cystoscopy for the presence of synchronized bladder tumors. Diagnostic ureterorenoscopy (URS) and/or biopsy were performed to confirm previous radiological findings in suspicious cases and when the surgical team prefers.

Patient characteristics such as age, gender, body mass index (BMI), Charlson Comorbidity Index (CCI), and tobacco use were recorded. Hemoglobin levels at the time of admission, degree of hydroureteronephrosis, history of preoperative URS, presence of previous bladder tumor and histopathological features, and, if available, history of intravesical therapy were scanned from the patient files. Tumor size, localization, RNU technique, lymph node (LN) dissection, perioperative complications, and postoperative histopathological results were recorded. Patients were classified as having and not having an IVR, and the factors predicting recurrence were evaluated.

In the postoperative period, the patients were followed up with physical examination, urinalysis, cytology, thorax radiography or CT, and axial abdominal imaging with and without contrast according to the renal failure status. They were followed up with cystoscopy every 3 months in the first year, then every 6 months for 2 years, and annually for the next 2 years, depending on the recurrence.

Surgical Technique

The open or laparoscopic decision was made based on the team's experience and patient-tumor characteristics. The main aim of applying the RNU procedure was to remove the gerota fascia, kidney, whole ureter, and bladder cuff. When LN involvement was detected on perioperative imaging or intraoperative palpable nodules, local LN dissection was undertaken. Laparoscopic RNU was performed with the four-trocar technique, open RNU with lumbotomy incision, and cuff excision with Gibson incision with extravesical technique.

Expert genitourinary pathologists evaluated specimens according to American Joint Committee on Cancer Classification 2010 and World Health Organization 2004 standards. Patients who had undergone surgery before the current guidelines were re-examined for

compliance with the histopathological standard. In renal pelvic cancers, the maximum tumor diameter was measured, and in ureter cancers, the entire length of the lesion along the long axis was measured. When there were multiple tumors in the ureter, the total lengths of the lesions along the long axis were calculated. When a tumor was found in both the renal pelvis and the ureter at the same time, it was classified as a renal pelvic or a ureteral tumor based on the location of the dominant tumor. The presence of two or more histologically confirmed tumors anywhere from the renal pelvis to the ureter was described as tumor multifocality.

Adjuvant platinum-based CT (two cycles of gemcitabine and cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin) was given to advanced-stage patients (muscle-invasive pathology or positive LN).

Patients were divided into two groups: with (+) and without (-) IVR, and patient, tumor, and surgical characteristics were compared. The categorical data were presented as numbers and percentages. Mean and Standard Deviation values were calculated for numerical data. Kolmogorov-Smirnov test was used to test the normal distribution of numerical data. The student's t-test was used to compare numerical data with normal distribution. Mann-Whitney U test was used to compare the mean of the non-normally distributed data. Frequencies of categorical variables were compared using Pearson Chi-square and Fisher's exact test. A p-value below 0.05 was considered statistically significant. Statistical analysis was performed using Statistical Package of Social Sciences version 21 (IBM SPSS Statistics; IBM Corp., Armonk, NY).

RESULTS

A total of 50 patients were included in the study. The mean age of the patients was 62.2 ± 12.2 years. Nine (18%) patients were female, and 41 (82%) were male. The mean BMI was calculated as 26.5 ± 4.1 kg/m2. IVR was developed in 19 (38%) of 50 patients, with a mean follow-up of 39.5 ± 25.3 months. The mean time to IVR was 13.8 ± 13.1 months. There was no significant difference between the two groups in terms of age, gender, BMI, tobacco use, CCI, hemoglobin level and glomerular filtration rate (GFR) at admission, and degree of hydronephrosis (p>0.05, Table 1).

Table 2 shows the patients› preoperative evaluations, perioperative characteristics, and postoperative histopathologic data. A total of 7 (14%) patients underwent diagnostic URS, 8 (16%) patients underwent URS with biopsy, and 7 (14%) patients had preoperative cytology positivity. When the two groups were compared, no significant difference was found regarding the history of preoperative URS and cytology positivity (p>0.05). The IVR (+) group had significantly more previous history of bladder cancer (35.5% vs. 52.6%, p=0.019, respectively). There was no significant difference between the two groups in terms of carcinoma in situ (CIS) and intravesical therapy before RNU (p>0.05).

When the location of the dominant tumor was examined, the renal pelvic tumor was detected in 21 (67.7%) patients in the IVR (-) group and 10 (52.6%) patients in the IVR (+) group. While the number of patients with ureteral tumors was 10 (32.3%) in the IVR (-) group, it was 9 (47.4%) in the IVR (+) group and was significantly higher than the other group. (p=0,04) In the entire patient group, the mean number of tumors was 1.06 ± 0.2, and the tumor size was 36.2 ± 15 mm, and there was no significant difference between the two groups (p>0.05).

35 (70%) patients underwent RNU with an open approach, and 15 (30%) patients with the laparoscopic technique. A total of 47 (94%) patients underwent cuff excision. Three patients could not undergo cuff excision for intraoperative reasons. Concerning surgical technique, there was no significant difference between the two groups. (p>0.05) When examining postoperative pathology, there were 15 (48.4%) patients with Ta-T1 pathology in the IVR (-) group and 7 (36.8%) in the IVR (+) group. There are 28 (56%) T2-T4 pathology patients in the entire patient group, and the rate is significantly greater in the IVR (+) group (63.2% vs. 51.6%, p=0.038, respectively). The high-grade tumor rate was 67.7% in the IVR (-) group, while it was 57.9% in the IVR (+) group, and there was no statistical difference between the groups (p>0.05). There was no statistically significant difference between the two groups in terms of intravesical treatment and adjuvant chemotherapy following RNU. (p>0.05)

Table 1: Demographic and preoperative datas

Parameters (mean ± SD)	***Total n=50***	***IVR (-) n= 31 (62)***	***IVR(+) n= 19 (38)***	***p***
Age (years)	62,2 ± 12,2	63 ± 12,7	61,1 ± 11,5	0,600
Gender (n ; %)				0,231
F	9 (18)	4 (12,9)	5 (26,3)	
M	41 (82)	27 (87,1)	14 (73,7)	
BMI (kg/m²)	26,5 ± 4,1	26 ± 3,7	27,2 ± 4,7	0,342
Smoking⁺	15 (30)	10 (32,2)	5 (26,3)	0,276[&]
Charlson Comorbidity Index				0,582
2	7 (14)	5 (16,1)	2 (10,5)	
3	7 (14)	2 (6,5)	5 (26,3)	
4	10 (20)	7 (22,6)	3 (15,8)	
5	11 (22)	6 (19,4)	5 (26,3)	
6	10 (22)	7 (22,6)	3 (15,8)	
7	1 (2)	1 (3,2)	0 (0)	
8	3 (6)	2 (6,5)	1 (5,3)	
9	1 (2)	1 (3,2)	0 (0)	
Hemoglobin levels at admission	12,8 ± 2,2	12,5 ± 2,4	13,2 ± 1,9	0,291
GFR levels at admission	76,2 ± 22,8	72,9 ± 19,7	81,5 ± 26,9	0,205
Hydronephrosis Grade				0,405
0	9 (18)	7 (22,6)	2 (10,5)	
1	9 (18)	6 (19,4)	3 (15,8)	
2	17 (34)	9 (29)	8 (42,1)	
3	14 (28)	8 (25,8)	6 (31,6)	
4	1 (2)	1 (3,2)	0 (0)	

[&] Mann-Whitney U Test +Presented as median (**IQR**)
IVR: Intravesical Recurrence, **GFR:** Glomerulation Filtration Rate, **BMI:** Body Mass Index

Table 2. The preoperative evaluations, perioperative characteristics, and postoperative histopathologic data of the patients

Parameters (mean ± SD)	***Total n=50***	***IVR (-) n= 31 (62)***	***IVR(+) n= 19 (38)***	***p***
Preoperative URS				0,850[!]
None	35 (70)	21 (67,8)	14 (73,7)	
Diagnostic	7 (14)	5 (16,1)	2 (10,5)	
URS + Biopsy	8 (16)	5 (16,1)	3 (15,8)	
Preoperative Cytology Positivity	7 (14)	5 (16,1)	2 (10,5)	0,142[!]
Previous History of Bladder Cancer	21 (42)	11 (35,5)	10 (52,6)	**0,019**
Presence of Concurrent Bladder Tumor	2 (4)	2 (6,5)	0 (0)	0,519[!]
History of preoperative intravesical CIS	2 (4)	0 (0)	2 (10,5)	0,140[!]
Preoperative Intravesical Treatment History	15 (30)	8 (25,8)	7 (36,8)	0,409

Tumor location				**0,04**
Pelvis	31 (62)	21 (67,7)	10 (52,6)	
Ureter	19 (38)	10 (32,3)	9 (47,4)	
Number of tumors in the Upper System	1,06 ± 0,2	1,06 ± 0,2	1,05 ± 0,2	0,867
Tumor Size	36,2 ± 15	37,2 ± 15,6	34,4 ± 14,3	0,532
Surgical Technique				0,372
Open RNU	35 (70)	23 (74,2)	12 (63,2)	
Laparoscopic RNU	15 (30)	8 (25,8)	7 (36,8)	
Cuff Excision	47 (94)	30 (96,8)	17 (89,5)	0,320
RNU specimen stage				**0,038**
Ta – T1	22 (44)	15 (48,4)	7 (36,8)	
T2 - T4	28 (56)	16 (51,6)	12 (63,2)	
CIS in RNU specimen	2 (4)	2 (6,5)	0 (0)	0,519[!]
Grade				0,349
Low Grade	18 (36)	10 (32,3)	8 (42,1)	
High Grade	32 (64)	21 (67,7)	11 (57,9)	
Adjuvant Intravesical Treatment History	2 (4)	0 (0)	2 (10,5)	0,140[!]
Adjuvant Chemotherapy	10 (20)	6 (19,4)	4 (21,1)	0,579[!]
Recurrence Time[+]	13,8 ± 13,1	N/U	13,8 ± 13,1	
Follow-up Time	39,5 ± 25,3	45 ± 27,9	30,6 ± 17,7	0,03

[!] Fisher Exact Test +Presented as median (**IQR**)
URS: ureterorenoscopy, **CIS**: carcinoma in situ, **RNU**: radical nephroureterectomy

DISCUSSION

In UTUC, the pathogenesis of tumor recurrence in the bladder after surgery remains a controversial issue. One of the main theories is that developing bladder tumors are implanted by a single transformed cell inseminated into the lumen (9), and another theory argues that pathology originates from a panureteral defect (10). However, data supporting a monoclonal and oligoclonal origin of metachronal multifocal urothelial carcinoma show that both mechanisms may be true (8).

Studies on intravesical treatments support implantation theory. (8) In a randomized controlled study, a single dose of mitomycin-C after RNU was found to cause an 11% reduction in the risk of IVR in the postoperative 12-month period (11). It has been reported that installing a single dose of pirarubicin reduces IVR (12). European Guidelines also support intravesical CT after RNU. (13) However, considering the potential side effects, including the risk of extravasation, it should be considered that such treatments are not innocent, and patient selection should be made meticulously. Therefore, it is critical to understand the IVR predictors to choose patients at high risk of IVR for local adjuvant therapies or to determine the frequency of protocols such as postoperative cystoscopic follow-up.

The risk of bladder cancer after RNU is 35-40% in the literature and is quite high. (5, 6) In our study, this rate was 38% in the mean follow-up period of 39.5 months. A higher rate of bladder cancer history was found in the group that developed IVR, and these patients were found to have a higher T-stage and a higher rate of ureteral localization with UTUC. In a meta-analysis by Seisen et al., it was shown that urothelial tumors were predictors of IVR compared to pelvic tumors (8). According to the same meta-analysis, other risk variables that increase IVR include male gender, positive preoperative urinary cytology, multifocality, pathological T stage, and laparoscopic approach.

Ureter tumors are thought to tend to spread to the

bladder because of their close anatomical location; this may be due to high urine flow and mechanical stress caused by intraluminal pressure (14). In the study by Yamashita et al., 83% of the patients had IVR within the first two years, and it was found that having a high-grade tumor was a significant risk factor (7). The authors argue that a rigorous surveillance protocol should be followed, especially in the first 2 years with a high-grade UTUC. They also reported that in the presence of a ureteral tumor, the length of the tumor is more important than the tumor's location in IVR. When they categorize ureter cancers based on the overall length, the total lesion length is 5 mm, and the IVR rate is 33%; when the total length is greater than 10 mm, the IVR rate increases to 55%. (7) However, meta-analysis supporting that ureteral tumors are predictors of IVR also showed that size was unrelated to IVR. (8) This suggests that the dominant mechanism for intraluminal transplantation in UTUC depends on the fragility of intercellular adhesions in invasive tumors. However, such differences may be due to inaccuracies in the length calculation, especially in ureter cancers (e.g., taking the longest tumor as the basis or taking the total tumor length when there are multiple tumors). When multiple tumors were detected in our study, we took the total tumor length as the basis and found no significant difference in tumor size between the two groups.

IVR may be detected more frequently in invasive tumors, according to studies demonstrating that the T stage of the RNU specimen may impact IVR (8, 15). In our study, T2-4 diseases were statistically significantly more frequently detected in the IVR (+) group. This situation forces us to plan more rigorous follow-up protocols and evaluate in favor of adjuvant intravesical treatment, especially in high-stage ureteric tumors.

In a study by Alothman et al., biopsy with preoperative URS, tumor multifocality, and a history of prior bladder cancer were risk factors in the patient series, with 40% intravesical recurrence over the median 18-month follow-up period. (5) Although our preoperative URS and tumor multifocality data did not support it, we determined that the history of previous bladder cancer was significantly higher in the group with IVR. The meta-analysis of Seisen et al. also supports that the previous bladder cancer history is an IVR predictor (8). The authors noted that this supported the theory that the lower and upper urothelial system's metachronous malignancies were created by transformed cells with distinct genetic alterations. Data suggesting that preoperative URS increases IVR (16, 17) support implantation theory due to transplantation after the ureteroscopic examination. A recent meta-analysis found that preoperative URS did not affect oncological outcomes in RNU patients but posed a risk for intravesical recurrence. (18) It has been suggested that URS should not be routinely used in diagnosis if the diagnosis made by imaging is relatively clear. (17) The data of our study do not support that history of preoperative URS is an important risk factor for IVR.

There was little difference in oncological outcomes between open and laparoscopic RNU for UTUC in two major multicenter studies of patients who received RNU for UTUC. (19, 20) However, there are also data showing that laparoscopic RNU is associated with worse oncologic outcomes than open (21). In the same study, no significant difference was found in IVR. In the literature, findings show that laparoscopic RNU is related to IVR, in addition to studies (5, 22) that show no difference in intravesical cancer recurrence between open and laparoscopic RNU (8, 23). In addition, the excision of the bladder cuff is important in UTUC surgery. (24) Even though the meta-analysis findings reveal inconsistent outcomes for endoscopic distal ureter excision, it demonstrates that the extravesical method is a predictor of IVR. (8) In our patients, we performed an open bladder cuff excision with Gibson incision with an extravesical technique in distal ureter treatment management. In our study, 47 (94%) of 50 patients received extravesical cuff excision, and cuff excision could not be completed in three patients due to intraoperative complications. Although there was no significant difference in IVR recurrence, we can assume this is due to the small number of patients without cuff excision.

The main limitation of our study is its retrospective design and the low number of patients. The inability to undertake multivariate analysis due to the small number of patients reduces the statistical power of our study. In addition, our case series consists of surgeries

that different surgical teams have performed for many years. Consequently, differences in surgeon experience, especially in laparoscopic technique, can disrupt the homogeneity of patient management between groups.

CONCLUSION

Caution should be exercised for metachronous recurrence of bladder cancer in patients with a previous history of bladder cancer, especially in ureteral and high pathological T-stage UTUCs. The increased risk of IVR requires rigorous follow-up of these patients and a compelling rationale for postoperative adjuvant therapy.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by University of Health Sciences Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinic Investigations Ethic Committee (Approval No: 2022-08-04, Date 2022/04/18) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; TK, Data acquisition; ME, Data analysis and interpretation; TK, ME, Drafting the manuscript; TK, ME, Critical revision of the manuscript for scientific and factual content; TK, ME, Statistical analysis; ME, Supervision; TK, ME.

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