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Original Article

Muscle-invasive bladder and urethral cancer recurrence after surgical management of upper tract urothelial carcinoma: A review of 305 patients

Üst üriner sistem (ÜÜS) ürotelyal karsinomun cerrahi tedavisi sonrası kasa invaziv mesane ve üretra kanser rekürensi: Üç yüz beş hastanın gözden geçirilmesi

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ABSTRACT

Objective: Bladder cancer recurrence after management of upper tract urothelial carcinoma (UTUC) is a common disease. Although the incidence and risk factors for the development of noninvasive bladder tumor have been reported in many series, rare studies have reported on muscle invasive bladder cancer (MIBC) and its urethral recurrence. We aimed to report the incidence, risk factors and survival rate for the development of MIBC and urethral tumors after surgical management of UTUC.

Material and methods: We retrospectively reviewed patients who were surgically treated for UTUC from 1983 to 2013. The tumor was categorized according to the 1997 TNM staging and the 3-tiered WHO grading systems. The primary endpoint of this study was the occurrence of any post-treatment MIBC and its urethral recurrences. We studied the possible risk factors that may contribute to the development of such pathology as well as the prognosis of this pathology.

Results: A total of 297 patients were eligible for analysis. Intravesical tumor recurrence was observed in 139 (46.8%) patients and radical cystectomy was warranted for 36 patients (MIBC or multicentric bladder recurrence). Twenty-seven patients were fit for surgery with ileal loop conduit was the urinary diversion for the majority, and others received radiotherapy. Ureteral tumor was the only statistically significant risk factor (p=0.001) and the incidence increased as the ureteral tumors became more distal (p=0.01). Occurrence of invasive or multicenteric bladder recurrence was a predictor for local, urethral recurrence and distant metastasis (p=0.016, 0.0001 and 0.01 respectively). Seven patients had urethral urothelial carcinoma; 5 were diagnosed at the time of cystectomy and 2 were discovered later (1 and 3 years after cystectomy).

Conclusion: MIBC is a relatively uncommon (6%) post UTUC, and ureteral tumors, especially distal in location, are the independent risk factor. Extended surveillance for those patients is needed. Urethral cancer recurrence is rare (2%); most cases are localized in the posterior urethra, they are noninvasive, and may develop even after cystectomy.

Keywords: Intravesical recurrence; invasive bladder tumor; radical cystectomy; urothelial carcinoma; urethrectomy; urinary bladder neoplasms; urologic neoplasms.

ÖZ

Amaç: Üst üriner sistem (ÜÜS) ürotelyal karsinomu tedavisinden sonra mesane kanser rekürensi sık görülür. Birçok seride noninvaziv mesane kanseri gelişme insidansı ve risk faktörleri bildirilmiş olmasına rağmen kasa invaziv mesane kanseri (KİMK) ve üretra rekürensi nadiren rapor edilmiştir.

Gereç ve yöntemler: Bu çalışmada 1983 ile 2013 yılları arası cerrahi tedavi uygulanmış hastaları geriye dönük olarak gözden geçirdik. Tümör 1997 TNM sınıflandırması ve 3 dereceli WHO derecelendirme sistemine kategorize edilmiştir. Bu çalışmanın birincil sonlanım noktası tedavi sonrası herhangi bir kasa invaziv mesane tümörü ve üretra rekürensinin oluşmasıydı. Bu patolojinin gelişmesine katkıda bulunabilen olası risk faktörleri ve bu patolojinin prognozunu inceledik.

Bulgular: Analiz için toplam 297 hasta uygundu. Yüz otuz dokuz (%46,8) hastada intravezikal tümör rekürensi gözlenmiş, 36 hastaya (KİMK veya çok odaklı mesane kanser rekürensi) radikal sisitektomi gerekmiştir. Cerrahiye uygun 27 hastaya üriner diversiyon olarak ileal lup kondüiti yapılmış, geri kalan hastalar radyoterapi almıştır. Üreter tümörü tek başına istatistiksel açıdan anlamlı risk faktörü (p=0,001) olup distale doğru lokalize oldukça insidansı artmıştı (p=0,01). İnvaziv veya çok odaklı mesane kanseri rekürensi lokal, üretral rekürens ve uzak metastazın belirleyicisiydi (sırasıyla, p=0,016, 0,0001 ve 0,01).

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Yedi hastada üretranın değişici epitel hücreli karsinomu vardı. Beş hastaya sistektomi anında tanı konmuştu. İki hasta ise sistektomiden 1 ve 3 yıl sonra ortaya çıkmıştı.

Sonuç: KİMK, ÜÜS ürotelyal karsinomundan sonra göreceli olarak sık görülmemektedir (%6). Özellikle distal üreter tümörleri bağımsız bir risk faktörüdür. Bu hastaların uzun süre izlenmesi gerekir. Üretra nüksü nadiren görülür (%2). Olguların çoğu posterior üretraya lokalize, noninvaziv tümörler olup sistektomiden sonra bile gelişebilirler.

Anahtar Kelimeler: İntravezikal rekürens; invaziv mesane tümörü; radikal sistektomi; değişici epitel hücreli karsinom; üretrektomi; mesane neoplazileri; ürolojik neoplaziler.

Introduction

Upper tact urothelial carcinoma (UTUC) arises from the urothelial lining of the urinary tract, extending from renal calyces to ureteral orifice. It comprises 10% of all renal tumors and 5% of all urothelial malignancies. Multiple anatomic synchronous or metachronous locations in the urinary tract is a common feature of UTUC.[1]

Although the incidence and risk factors for the development of noninvasive bladder tumors were reported in many series[2,3], rare studies reported invasive bladder cancer, radical cystectomy, and urethral recurrences after surgical management of UTUC.[4] Those patients should have a special attention, with a strict and prolonged follow-up regimen.

Urologists aimed to report the incidence, risk factors and survival rate for the development of muscle-invasive bladder and urethral tumors after surgical management of UTUC. Moreover, we aimed to report the pathological characteristics seen after radical cystectomy and urethrectomy. Our series comprised a large series of UTUC patients treated in a tertiary urology institute.

Material and methods

After institutional review board approval, we retrospectively reviewed our ongoing database for patients who were surgically treated for UTUC from 1983 to 2013.

Preoperative work up/operative procedures

The preoperative evaluation included complete history, physical examination and standard routine laboratory, as well as radiological investigations including computed tomography (CT) and/or magnetic resonance imaging (MRI). In the majority of patients, cystoscopy and retrograde uretropyelography and/or diagnostic ureteroscopy were done in a separate session, and any concomitant bladder tumors were resected, and when feasible, upper tract tumors were biopsied. Standard radical nephroureterectomy (RNU) procedure was accomplished through an open approach in the majority of the patients, while 24 cases were done laparoscopically and 13 were managed by open renal-sparing surgeries for solitary functioning renal units.

Tumor characteristics and pathologic evaluation

Tumors were staged according to the 1997 TNM classification. The most conventional 3-tiered World Health Organization grading system was used by different pathologists to determine the pathologic grade.[5] The tumors were localized in pelvicalyceal, ureteral, or both pelvicalyceal and ureteral regions. Multifocality was defined as the presence of 2 tumor foci in noncontiguous locations within the ipsilateral renal unit.

Follow-up regimen

In the first 2 years, cystoscopy was performed once every 3 months and contrast-enhanced CT every 6 months. From the third to fifth year, cystoscopy was performed every 6 months and CT annually. Thereafter, urinalysis and cytological examination were completed annually during the clinical examination.

Study outcome

The primary endpoint of this study was the occurrence of invasive/multicentric bladder cancer warranting radical cystectomy in addition to urethral tumor necessitating urethrectomy. We studied the possible risk factors that may contribute to the development of such pathology in terms of sex, past history, concomitant bladder tumor, surgical approach, tumor location, stage, grade and more. Moreover; we also studied the cancer survival rates for those patients.

Statistical analysis

Frequency and percentage were used for nominal and categorical variables. Mean (±SD) was used for normally distributed data; otherwise, median and range were used. *Chi*-square test was used for analysis of nominal data. Cancer specific survival was estimated using Kaplan-Meier methods, with differences assessed using the log-rank test; survival time was calculated from the date of RNU. In all tests P-value was two-sided and significance was set at $p<0.05$. Statistical analysis was performed using the commercial computer software Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) version 16.

Results

Of 322 patients, 17 with incomplete files, eight patients with non- urothelial carcinoma at the final pathology were eliminated

leaving 297 patients eligible for review. The mean age of the patients was 59±11 years (range, 26-85 years) and the study included 262 men (88.2%). The median follow-up period was 34 months (range, 6-300 months). The tumor was right-sided in 135 cases (45.4%). Forty-nine patients (16.4%) had a history of bladder tumors, and concomitant bladder tumors were found and resected in 78 (26.2%) cases.

Table 1. Pathological criteria after radical cystectomy/ uretherectomy, and surgical management of upper tract urothelial carcinoma (n=27)

Characteristics	
Time to radical cystectomy in months, median (range)	20 (7-70)
Type of surgery	
Radical cystectomy alone	20
Radical cystourethrectomy	5
Radical cystectomy followed by late uretherectomy	2
Pathological grade	
Free of tumor	1
Grade I	2
Grade II	12
Grade III	12
Pathological stage	
T0	1
T1	15
T2	6
T3	4
T4	1
Type of urinary diversion	
Ileal loop conduit	22
Orthotopic bladder diversion	4
Continent urinary diversion	1
Post urethrecotomy	
Urethra site	
Anterior	1
Posterior	6
Pathological grade	
Grade I	1
Grade II	3
Grade III	3
Pathological stage	
Tis	2
Ta	1
T1	2
T2	2

Intravesical tumor recurrence after RNU was observed in 139 (46.8%) patients after a median follow-up of 33 months (6-300). All were treated with transuretheral resection ± intravesical chemoimmunotherapy, except 36 patients (18 with invasive and 18 with mulicentric bladder tumors). Twenty-seven of them were fit for radical cystectomy and others received radiotherapy. Seven had urethral urothelial carcinoma; 5 were diagnosed at the time of cystectomy and 2 were discovered later (1 and 3 years after cystectomy). The pathological criteria for postradical cystectomy and urethrectomy are shown in Table 1. Regarding urinary diversion, ileal loop conduit was done for 22, while orthotopic bladder diversion for 4, and continent urinary reservoir was done for 1 patient.

We analyzed possible risk factors for the development of bladder tumors after management of UTUC as shown in Table 2. It can be observed that none of the following were significant predictors: sex, past history of bladder tumor, concomitant bladder tumor, surgical approach, laterality of the tumor, UTUC stage, grade or multicentricity at the time of diagnosis of UTUC. Ureteral tumors (p=0.04) and presence of carcinoma in situ (CIS) (p=0.04) were the only significant predictors for the development of bladder tumors after surgical management of UTUC. After eliminating 106 patients with previous and/or concomitant bladder tumors, the presence of a ureteral tumor became strongly statistically significant (p=0.001) and the incidence increased as the ureteral tumors become more distal (p=0.01) as shown in Table 3.

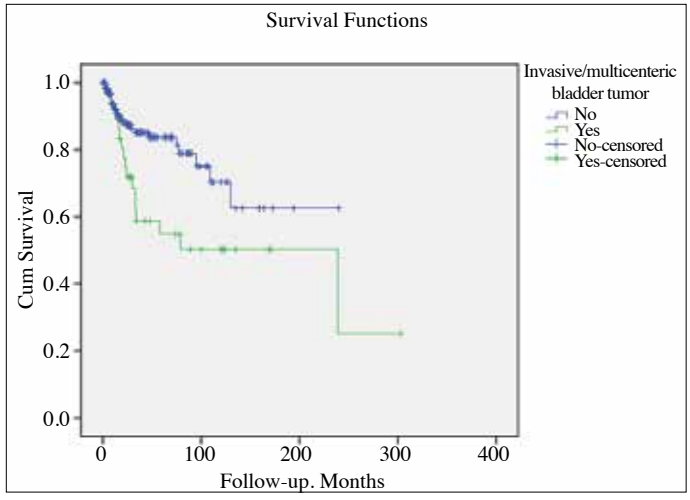

Figure 1. Kaplan-Meier curve of cancer-specific survival rates stratified based on recurrent invasive/multicenteric bladder cancer (p=0.01)

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Table 2. Bivariate analysis of risk factors for development of invasive or multicenteric bladder tumor after surgical management of upper tract urothelial carcinoma

	Invasive or multicenteric bladder tumor, n=297				
Variable	**No, n (%)**		**Yes, n (%)**		**p**
Gender					
Male	230	(88)	32	(12)	0.8
Female	31	(89)	4	(11)	
Hx of bladder tumor (preoperative)					
No	220	(89)	28	(11)	0.3
Yes	41	(84)	8	(16)	
Concomitant bladder tumor					
No	190	(87)	29	(13)	
Yes	71	(91)	7	(9)	0.3
Laterality of the tumor					
Right	118	(88)	16	(12)	0.9
Left	143	(88)	20	(12)	
Surgical approach					
Open NU	228	(88)	32	(12)	
Lap. NU	22	(92)	2	(8)	0.7
Renal-sparing	11	(85)	2	(15)	
Location of the tumor					
Kidney (pelvi-calyceal)	113	(93)	8	(7)	
Ureter	100	(93)	20	(7)	0.04
Kidney and ureter	48	(86)	8	(14)	
Ureteral tumor					
No	113	(93)	8	(7)	0.01
Yes	148	(84)	28	(16)	
Positive bladder cuff for tumor					
No	250	(89)	33	(11)	
Yes	11	(78)	3	(22)	0.2
Multifocality					
No	170	(88)	23	(12)	
Yes	91	(88)	13	(12)	0.8
Presence of CIS					
No	250	(89)	32	(11)	0.04
Yes	11	(73)	4	(27)	
Tumor grade					
Grade I	12	(92)	1	(8)	
Grade II	163	(84)	21	(16)	0.7
Grade III	86	(86)	14	(14)	
Tumor stage					
Non- muscle invasive	171	(88)	23	(12)	0.8
Muscle invasive	90	(87)	13	(13)	

*Decimals were deleted for simplification and percentage was given for rows. NU: nephroureterectomy; CIS: carcinoma in situ

Table 3. Bivariate analysis of risk factors for invasive or multicentric bladder tumor after elimination of patients who had previous and/or concomitant bladder tumors*

	Invasive or multicentric of bladder tumor, n (%), total number (191)				
Variable	**No**		**Yes**		**p**
Gender					
Male	147	(88)	21	(12)	0.5
Female	19	(83)	4	(17)	
Laterality of the tumor					
Right	76	(88)	10	(12)	0.5
Left	90	(86)	15	(14)	
Surgical approach					
Open NU	148	(87)	23	(13)	
Lap. NU	13	(87)	2	(13)	0.6
Conservative	5	(100)	0	-	
Location of the tumor					
Kidney	90	(94)	6	(6)	
Ureter	53	(79)	14	(21)	0.01
Kidney and ureter	23	(82)	5	(18)	
Ureteral tumor					
No	91	(94)	6	(6)	0.004
Yes	75	(80)	19	(20)	
Location of Ureteral tumors					
No	90	(94)	6	(6)	
Proximal	28	(88)	4	(12)	0.01
Distal	24	(74)	12	(26)	
Multicenteric	14	(83)	3	(17)	
Positive bladder cuff for tumor					
No	161	(88)	23	(12)	0.2
Yes	5	(75)	2	(25)	
Multifocality					
No	105	(86)	15	(14)	0.7
Yes	61	(86)	10	(14)	
Presence of CIS					
No	160	(88)	22	(12)	0.06
Yes	6	(67)	3	(33)	
Tumor grade					
Grade I	4	(80)	1	(20)	
Grade II	108	(86)	14	(14)	0.6
Grade III	54	(84)	10	(16)	
Tumor stage					
Non muscle invasive	112	(88)	15	(12)	0.4
Muscle invasive	54	(84)	10	(16)	

*Decimals were deleted for simplification and percentage was given for rows. NU: nephroureterectomy; CIS: carcinoma in situ

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Table 4. Recurrence for patients with invasive or multicentric bladder tumors

	Invasive or multicentric bladder tumor recurrence, n (%), total number = 297				
Characteristics	**No**		**Yes**		**p**
Contralateral recurrence					
No	259	(88)	35	(12)	0.2
Yes	2	(65)	1	(35)	
Urethral recurrence					
No	260	(90)	29	(10)	0.001
Yes	1	(12)	7	(88)	
Local recurrence					
No	250	(89)	31	(11)	0.016
Yes	11	(69)	5	(31)	
Distant metastasis					
No	243	(89)	29	(11)	0.01
Yes	18	(72)	7	(28)	

Percentage was given for rows. Decimals were deleted for simplification

Occurrence of invasive/multicentric recurrent bladder tumors was a predictor for local recurrence at the surgical site (p=0.016), distant metastasis (p=0.01), and urethral recurrence (p=0.0001), as shown in Table 4. Such pathology adversely affected short, intermediate and long-term cancer- specific survival after surgical management of UTUC (Breslow, Tarone-Ware and Log Rank tests, p=0.04 and 0.01 and 0.009 respectively), as shown in Figure 1.

Discussion

The incidence of metachronous bladder tumor after surgical management of UTUC still reaches 50% in some series.[3,6] In our study, 46.8% of our patients developed recurrent bladder tumors after a median follow-up period of 35 months (range 6-300). More than half these patients (56%) developed one recurrence. Reported risk factors that might contribute to the development of such pathology are; primary tumor location in the ureter[7], multifocality[8], stage, surgical procedures[3], as well as sex and systemic chemotherapy.[9]

Gender has not been identified as a risk factor for tumor recurrence in our study or other investigations.[7,10] Also, it has been suggested that low pathological grade[11] and stage[12] are inversely correlated with the risk of tumor recurrence. On the other hand, high pathological grade[7] and stage[10] have been considered to be risk factors. Our study denied the impact of either factor on future bladder recurrence.

Recurrences of MIBC, urethral cancer and radical cystectomy performed after surgical management of UTUC are rarely reported in the literature. In our study, MIBC developed in 18 patients (6%), which is similar to what was reported by Kim et al.[4] In addition, 18 patients were found to have recurrent multicentric bladder tumors beyond the scope of resection leaving a total of 36 patients who needed definite management. Twenty-seven were surgically treated by radical cystectomy, and ileal loop was done for the majority of them as a urinary diversion, while the others were treated by radiotherapy. Seven patients had urethral recurrences; most of them were diagnosed at the time of the invasive bladder tumor, and most were localized in the posterior urethra.

Urothelial instability is one the theories for the development of recurrent bladder and urethral cancers following surgical management of UTUC. We found that presence of CIS is a risk factor for the development of invasive/multicenteric bladder cancers in bivariate analysis. This is in agreement to what was reported by Pieras et al.[13] and Wheat et al.[14].

Location of UTUC is the main risk factor for radical cystectomy with bivariate analysis in all patients who had UTUC. Ureteral tumor is a risk factor for the development of MIBC and radical cystectomy. Because post-UTUC invasive bladder tumor may be an extension of prior bladder tumor or concomitant bladder tumors, to consolidate our results, we did a second analysis. We eliminated from our study the patients with post-UTUC invasive bladder tumor, leaving only those who had developed *de novo* bladder tumor after the management of UTUC. This analysis included 191 patients, and ureteral tumor became strongly statistically significant. When the ureteral tumor was found as the only significant independent factor in the final analysis, multivariate analysis was omitted.

Renal pelvis and ureteral tumors are not the same disease in terms of invasion and prognosis. Park et al.[15] reported higher local and distant disease failure in ureteral tumors than in renal pelvis tumors. Moreover, location of ureteral tumor was proved to be significantly associated with an increased risk of disease recurrence and cancer-specific death after surgery for UTUC compared with renal pelvis tumors.[11]

Migration of tumor cells is one of the theories that explains high incidence of tumor recurrence from the upper to the lower urinary tract cancers (30-50%) as compared with recurrence from the lower to upper urinary tract cancers (3-5%).[16] The ureter is a narrow tunnel, with continuous peristalsis, that makes a pathway for detached tumor cells, which may settle in the

bladder, particularly at an increasing rate with the proximity of the ureteral tumor to the bladder.[8] This seeding theory was supported through the identical p53 gene mutation in both UTUC and synchronous lower urothelial cancers.[17] We even found a trend of increased incidence of bladder tumors in patients with distal rather than proximal ureteral tumors.

In accordance with our results, location of the ureteral tumor also was the only risk factor for the development of MIBC, as was reported by Kim et al.[4] In contrast, a few research studies denied such impact, not only on intravesical recurrence[11], but also on cancer- specific survival following management of UTUC.[18] Development of invasive/multicentric bladder tumor is a strong indicator for the development of uretheral cancer, and other disease failure. Urethral cancer may even develop later, ie. one or three years after cystectomy.

Our study was a retrospective investigation, like the majority of the research studies on UTUCs due to the rarity of the disease. Also, we had incomplete data about smoking for all patients. However, we included a considerable number of patients presented to a single tertiary urology institute in the region.

In conclusion, although recurrent bladder tumor is common after surgical management of UTUC, MIBC is relatively uncommon (6%) and ureteral tumor, especially distal ureteral in location, is the independent risk factor. Those patients are in need of more close and extended surveillance because MIBC may develop 7 years post-operatively. Urethral cancer is rare (2%); most cases are in the posterior urethra, noninvasive, and may develop even after cystectomy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Urology and Nephrology Center, Mansoura University (83/2014).

Informed Consent: The study was a retrospective study with no ethical issues, so no patient consent was taken.

Peer-review: Externally peer-reviewed.

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Hasta Onamı: Çalışma etik bir konuyla ilgili olmayan retrospektif bir çalışmadır ve bu nedenle herhangi bir hasta izni alınmamıştır.

Hakem Değerlendirmesi: Dış bağımsız.

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