Coincidental Bladder Cuff Transitional Cell Carcinoma in Nephroureterectomy Specimens: Risk Factors, Prognosis and Clinical Implementation

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Purpose: There is a lack of reporting of the bladder cuff pathology in the literature and ongoing debate regarding the role of bladder cuff excision (BCE) in the prognosis in patients with upper tract urothelial carcinoma (UTUC). We aimed to know the risk factors, the survival, and the clinical course of such pathology.

Materials and Methods: The study was retrospective, from 1983-2013 on 305 patients who had diagnosed with UTUC. Patients were managed by radical open/ laparoscopic nephroureterectomy with bladder cuff excision. The tumor was staged using 1997 TNM classification and the 3-tiered WHO grading system was used for grading. Patients who found to have a malignant bladder cuff on the final pathology were further analyzed for the risk factors for such disease and its effect on survivaltheir outcomes.

Results: 13/ 281 (4.6%) cases were found to have malignant bladder cuff. Regarding tumor stage; one case was diagnosed with Tis, eight had T1 and four cases had T2 malignant bladder cuff. All cases were with pure ureteric or multifocalcentric tumors, and none had pure pelvicalyceal tumors (p = .001).
Local recurrence at the surgical site and distant metastasis were significantly higher among patients with malignant bladder cuff (p = .001 and .002 respectively), and the last sustained its significance in multivariate analysis. Those patients had a poor prognosis when compared to non-malignant bladder cuff cases (Log Rank test, p = .001)

Conclusion: Ureteric tumor is the only independent risk factor for malignant bladder cuff at the final pathology and is associated with increased risks for invasive bladder tumor, distant metastasis and poor survival in comparison with non-malignant bladder cuff. In a clinical implementation, BCE is considered as a mandatory step in management of ureteric tumors, while it could be omitted in pure and low grade renal pelvis tumors.

Keywords: urologic neoplasms; kidney pelvis neoplasms; ureteral neoplasms; nephroureterectomy; bladder cuff; bladder cuff excision .

INTRODUCTION

Upper Tact Urothelial Carcinoma (UTUC) arises from the urothelial lining of the urinary tract from the renal calyces to the ureteral orifice. They comprise 10 % of all renal tumors and 5% of all urothelial malignancies[(1)].
While pathological criteria of UTUC were mentioned in detail in some series[(2,3)], there is a lack of reporting on bladder cuff pathology.
Although Krogh et al. reported a 19 % ureteric stump recurrence after conservative resection[(4)], a recent multi-institutional retrospective analysis of 4,210 patients with renal pelvic UTUC, comparing the oncologic outcome between patients who underwent nephroureterectomy (NU) with or without bladder cuff excision (BCE), concluded that NU without BCE can be considered for patients with renal pelvic UTUC with pT1and pT2[(5)].
The lack of reporting of bladder cuff pathology, and the ongoing debate in the literature, compelled us to review the final pathology in our series with 305 patients. We aimed to determine the risk factors and how malignant bladder cuff in the final pathology might affect the clinical course and the survival.

MATERIALS AND METHODS

After institutional review board approval, from 1983 to 2013, a retrospective analysis was conducted on 305 patients registered in an electronic database with UTUC at the final pathology. All the pathological reports were carefully reviewed for bladder cuff pathology. Those who were found to have a malignant bladder cuff in the final pathology were further analyzed for risk factors and their outcomes.
Preoperative radiologic workup / operative procedures: The pre-operative evaluation included a complete history, physical examination, and standard routine laboratory, as well as radiological investigations (CT and/ or MRI). In the majority of patients, cystoscopy & retrograde uretropyelography and/or diagnostic ureteros-

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Table 1. Bivariate analysis of risk factors for coincidental malignant bladder cuff post surgical management of UTUC

Variable	Malignant bladder cuff, N (%), total number (281)				*P* - Value
	No		Yes		
Gender					
Male	238	(96)	10	(4)	0.1
Female	30	(90)	3	(10)	
Hx of bladder tumor (pre-operative)					
No					
Yes	230	(95)	11	(5)	0.9
	38	(95)	2	(5)	
Concomitant bladder tumor					
No					
Yes	199	(96)	7	(4)	0.15
	69	(92)	6	(8)	
Side of the tumor					
Right					
Left	120	(96)	5	(4)	0.6
	148	(95)	8	(5)	
Surgical approach					
Open NU					
Lap. NU	244	(95)	13	(5)	0.2
	24	(100)	-		
Site of the tumor					
Kidney (pelvi-calyceal)	120	(100)	-	-	
Ureter	102	(96)	4	(4)	0.001
Kidney and ureter	46	(84)	9	(16)	
Ureteric tumor					
No	120	(100)	-	-	0.001
Yes	148	(92)	13	(8)	
Tumor site within the ureter					
No	120	(100)	-	-	
Proximal	38	(97)	1	(3)	0.001
Distal	88	(90)	8	(10)	
Multifocal	22	(85)	4	(15)	
Presence of CIS					
No	256	(96)	11	(4)	0.07
Yes	12	(86)	2	(14)	
Tumor grade					
Grade I TCC	11	(100)	-	--	
Grade II TCC	168	(96)	6	(4)	0.2
Grade III TCC	89	(92)	7	(8)	
Tumor stage					
Non muscle invasive	172	(96)	7	(4)	0.4
Muscle invasive	96	(94)	6	(6)	

*Decimals were removed & percentage was given for rows & a statistically significant ($P < .05$) with

copy were done in separate sessions; any concomitant bladder tumors were resected, and when feasible, upper tract tumors were biopsied.

Most of the patients were treated by one stage standard radical open NU +BCE, but 24 cases were done laparoscopically. Renal sparing surgeries (ureterectomy and Boari flap / ureteroureterostomy) were done for 15 cases, mostly for solitary functioning renal units.

Tumor characteristics and pathologic evaluation:

Surgical specimens were processed according to the standard pathological procedure. The tumor was staged according to the 1997 TNM classification, and the most traditional 3-tiered WHO grading system was used for pathological grading by different pathologists.

Postoperative follow-up:

In our study, the follow-up was calculated on the analysis from the time of surgery till the time of last follow-up. The postoperative regimen in the first two years included a cystoscopy every three months and contrast-enhanced CT every 6 months. From the third to fifth year, a cystoscopy every 6 months and a CT annually; thereafter, clinical examination, urine analysis and cytology were ordered annually. Patients with incidentally discovered malignant bladder cuff were put under strict surveillance and follow up.

Patients who developed bladder tumors were treated with trans-urethral resection and intra-vesical chemo-immunotherapy. In our protocol, alternating schedule of BCG and Epirubicin is given for 6 weeks, and then followed by check cystoscopy. Patients with no recurrence were given the same protocol, monthly for nine months. Those who were found to have recurrence, were given the 6 weeks protocol again. Radical cystectomy was offered to invasive bladder tumor or any recurrence beyond the scope of endoscopic resection.

Statistical methods

Data was collected using a SPSS® version 21, spreadsheet. For continuous data with normal distribution,

Table 2. Bivariate analysis of recurrence after surgical management of UTUC with bladder cuff pathology*

Characteristics	Coincidental malignant bldder cuff, N (%)				*p*- Value
Recurrent bladder tumor	**No**		**Yes**		
No	143	(95)	7	(5)	0.9
Yes	125	(95)	6	(5)	
Recurrent invasive bladder tumor					
No	260	(96)	11	(4)	0.01
Yes	8	(80)	2	(20)	
Contra-lateral recurrence					
No	266	(95)	13	5	0.7
Yes	2	(100)	--	--	
Uretheral recurrence					
No	261	(95)	12	(5)	0.2
Yes	7	(88)	1	(12)	
Local recurrence					
No	257	(96)	9	(4)	0.001
Yes	11	(73)	4	(27)	
Distant metastasis					
No	251	(97)	8	(3)	0.001
Yes	17	(77)	5	(23)	

mean + SD were used for expression and median, and range for abnormally-distributed data. For categorical and nominal variables, frequency and percentage were used for expression, and Chi-square test was used for analysis. Cancer specific survival was estimated using Kaplan-Meier methods and the event was identified as death from the tumor or diagnosed with metastasis or local recurrence at the time of the last follow-up. Log-rank test was used to study the effect URS on survival. Cox proportional hazards regression was used for multivariate analysis in a forward-selection strategy. In all tests, the *P* value was 2-sided, and significance was set at $P < .05$.

RESULTS

Among the 305 patients with UTUC, 8 cases had non-TCC on the final histopathology, 15 cases were treated with renal-sparing surgeries, and 1 case with non-inclusive pathology report. Those were eliminated from the study leaving 281 patients for review.

The mean age of our patient population was 59+11 years, and 88 % were male with a median follow-up period of 34 months (range, 6-300 months).

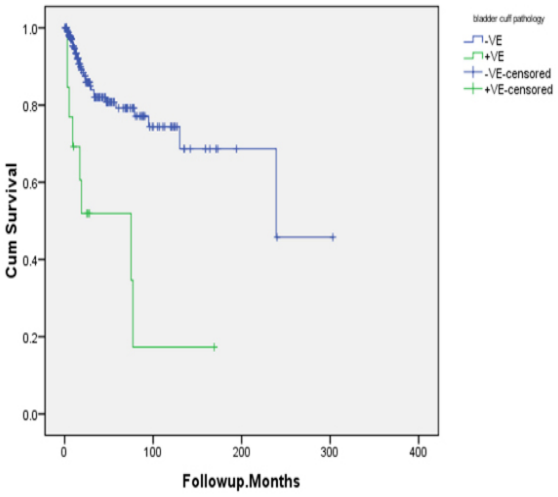

Figure 1. Kaplan-Meier curve of cancer-specific survival stratified by bladder cuff pathology

Thirteen among 281 total cases (4.6%) were found to have malignant bladder cuff, comprising 8% among the total ureteric tumor cases (13/152). Regarding tumor stage, one case had Tis, eight had T1 and four cases had T2 malignant bladder cuff. All cases were with pure ureteric or multifocal tumors, and none had pure pelvicalyceal tumors ($P = .001$). There was a high incidence of malignant bladder cuff in distal ureteric compared to proximal ureteric tumors ($P = .001$). **Table 1**

Coincidental malignant bladder cuff was not a significant risk factor for bladder recurrence post-surgical management of UTUC; however, it was associated with high incidence of invasive bladder tumor ($P = .01$). Local recurrence at the surgical site and distant metastasis were significantly higher among patients with malignant bladder cuff ($P = .001$, **Table 2**). Distant metastasis sustained its significance in multivariate analysis and Cox Regression Models ($P = .01$, **Table 3**). Those patients had a poor survival when compared to non-malignant bladder cuff cases on short, intermediate, and long-term follow up (Breslow, Tarone-Ware, and Log Rank tests, $P = .001$, **Figure 1**)

Regarding the 4 patients with T2 pathological staging in the bladder cuff specimen, 2 patients were advised to receive cystectomy and urinary diversion as a radical treatment. Both refused but accepted to receive adjuvant intravesical therapy. Both patients presented with treatment failure. The remaining 9 patients with noninvasive pathology of the bladder cuff received full course of adjuvant therapy. Three patients showed local pelvic recurrence within 6 months of the surgery and died of the disease.

DISCUSSION

To the best of our knowledge, our review is the first to study the risk factors and the survival that may be associated with malignant bladder cuff. Also, we aimed to determine its influence on the potential outcome. RNU with BCE is known as the standard method of treat-

Table 3. Multivariate analysis and Cox Regression Models

	95% CI	Exp(B)	*P*-value
Recurrent invasive bladder tumor	---	--	0.6
Local recurrence	---	--	0.07
Distant metastasis	6.9 - 24.1	12	0.01

ment for UTUC[6]. Different methods were described for BCE; tansvesical, extravesical and endoscopic with no difference in terms of recurrence free survival, cancer specific survival, and overall survival among these methods. Whatever technique is used, BCE is an additional procedure that requires extra time, and another incision or patient's repositioning − all of which add to the complexity of the surgery and the overall morbidity[7].

Tumor location is the only significant risk factor for malignant bladder cuff in our series. When tumor location was grouped as ureteric and non-ureteric, all cases were with pure ureteric or multifocal tumors and none had pure pelvicalyceal tumors ($P = .001$). Moreover, the more distal the ureteric tumors, the higher the chance of malignant bladder cuff. The majority (9/13, 70%) were with distal ureteric tumors ($P = .001$). Ureteral tumor location 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. Also, ureteric tumors are associated with a high incidence of bladder tumor recurrence[4,8].

In our review, female gender was more liable to have coincidental malignant bladder cuff with marginal significance ($P = .05$). Similarly, Chou et al who reported a more aggressive course of UTUC in female than male[9].

There is an ongoing debate regarding the role of BCE and its influence on survival. It was reported that there is a high incidence of recurrence with inadequate bladder cuff excision[4,10]. However, BCE omission increased cancer specific mortality (CSM) only in patients with pT3N0/x, pT4N0/x and pT (N1-3) with no compromise in patients with renal pelvic UTUC with pT1 and pT2[11]. In editorial comment, Zlotta[12] stated that such a finding in the patients with the advanced UTUC may be a confounder as one would expect patients with more advanced disease and more aggressive tumors to die from metastatic disease rather than from recurrence at the bladder level[12]. The findings from our series support this opinion. All UTUC cases of grade I had no malignant bladder cuff. Conservative management of UTUC either by endoscopic maneuvers[13] or segmental ureterectomy[14] has been established for low grade, low stage disease. Conservative management does not involve BCE and is done with preservation of the entire urinary unit. The main drawback for omitting bladder cuff excision is inability to accurately survey the ureteral stump during follow-up period□ this should be put into consideration.

On deciding to do distal ureterectomy as a conservative treatment for urothelial cancer in the distal ureter, our results support complete bladder cuff excision because there is a high incidence of coincidental TCC in the bladder cuff in such cases.

From the results, no coincidental malignant bladder cuff cases were noticed in the laparoscopy arm. When the surgical approach was correlated with tumor location, we found that the majority of laparoscopic cases were pure renal-pelvic (17 cases) and only 7 were only pure ureteric tumors.

In our series, while coincidental malignant bladder cuff was not a significant risk factor for the development of overall bladder recurrence, however, it was a risk factor for development of invasive bladder tumor, local recurrence at the surgical site as well as distant metastasis. In this investigation, patients with T2 bladder tumor staging of the bladder cuff had a dismal outcome with disease dissemination in 3 out of 4 patients whilst the remaining patient died within 8 months of an unrelated cause. Interestingly, patients with noninvasive pathology of the bladder cuff but with positive margin showed the same poor prognosis. On the other hand, patients with noninvasive pathology and negative margin were well-controlled under adjuvant therapy and surveillance. Even those who developed later muscle invasive disease were non-metastatic at time of diagnosis and we could proceed to radical cystectomy with intent to cure.

Coincidental malignant bladder cuff was associated with high local recurrence at the surgical site and distant metastasis ($P = .001$), and the last sustained its significance in Multivariate analysis and Cox Regression Models (**Table 3**). Although the bladder cuff was excised, this finding may suggest a more aggressive nature of the disease in those patients or urothelial instability in the rest of bladder mucosa[12]. There are many risk factors for local recurrence which were reported by Mellouli et al. and Kim et al[15,16].

In a clinical implementation of our study, pure renal pelvis tumors, especially those with low grade, can be managed without BCE with low chance of recurrence on the bladder cuff level. However, BCE is indicated for ureteric tumors and it could be considered as a mandatory step for distal ureteric tumors. Regardless their pathologic staging, patients with coincidental malignant bladder cuff have very poor survival when compared with those who have free bladder cuff.

Although our research was a retrospective; however, this could be accepted in rare diseases like UTUC, and very rare findings like coincidental malignant bladder cuff. Moreover, this topic is seldom mentioned in the literature− that adds to the power of our report.

CONCLUSIONS

Ureteric tumor is the only independent risk factor for malignant bladder cuff at the final pathology which associated with increased risks for invasive bladder tumor, distant metastasis and poor survival in comparison to non-malignant bladder cuff. In a clinical implementation, BCE is considered as a mandatory step in management of ureteric tumors, while it could be omitted in pure and low grade renal pelvis tumors. Patients with positive bladder cuff staged as T2 need immediate, aggressive surgical approach and adjuvant treatment.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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