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Patterns, risks and outcomes of urethral recurrence after radical cystectomy for urothelial cancer; over 20 year single center experience



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HIGHLIGHTS

- Today, radical cystectomy is the golden standard in muscle invasive form.
- Urethral recurrence was observed in 11 (3.8%) patients in our 20 years experience.
- The most important factor that affects urethral recurrence was pathological T stage.
- Urethral recurrence was observed in ileal conduit group more than in orthotopic ones.

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ABSTRACT

Purpose: To evaluate the factors affecting urethral recurrence after radical cystectomy for bladder cancer and relationship between urinary diversion type and urethral recurrence rates. **Patients and methods:** In our 504 radical cystectomy series, 287 male patients whose final pathological were urothelial carcinoma were included in the study. The relationship between urethral recurrence and pathological stage, grade, lymph node involvement and diversion type was researched in addition to risk factors for urethral recurrence. **Results:** A Total of 287 patients. Orthotopic continent urinary diversion (OCD) and ileal conduit (IC) was performed after radical cystectomy in 141 (49.1%) and 146 (50.9%) patients respectively. Urethral recurrence was observed in 11 (3.8%) patients and urethral recurrence rates in OCD and IC groups were 1.4% and 6.2% ($p = 0.034$). Pathological stages of recurrent patients were 2 pT1, 1 pT2 and 8 pT4 respectively ($p < 0.001$). Urethral recurrence was significantly lower in OCD group when compared to IC group ($p = 0.036$). When all parameters were analyzed using Cox multivariate regression analysis, the most important factor that affects urethral recurrence was pathological T stage ($p < 0.001$). Risk factors for urethral recurrence were present in 92 patients. Urethral recurrence rates in patients with and without risk factors were 8.69% and 1.53% ($p < 0.01$). **Conclusions:** In this study, pathological stage was found to be the most important factor affecting urethral recurrence and prostatic stromal invasion was an important prognostic factor in these cases. Although risk factors for urethral recurrence were similar in both groups, urethral recurrence rates were significantly lower in OCD group when compared to IC group.

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1. Introduction

Bladder cancer is the 4th most frequent type of cancer in males after prostate, lung and colon cancer [1]. Bladder tumors are the

2nd most common malignancy of genitourinary system, males being four times more susceptible than females [2,3]. In about 20–40 % newly diagnosed bladder cancer patients, the disease already invaded the muscle tissue and perivesical fat [4].

Today, radical cystectomy (RC) is the golden standard in muscle invasive bladder cancer treatment. RC with extended lymph node dissection operation is related with high survival rates and effective

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local control. However, one in three patients has recurrences in the post-operative period and patients eventually die from cancer [5]. Distant metastases and local recurrences are related with very low survival rates.

In patients who underwent RC, recurrence rates are around 30% and usually recurrences are seen within 3 years following surgery [6,7]. Recurrences can be systemic, local, urethral or in the upper tract. Urethral recurrence rate is 10% after RC [8]. Presence of carcinoma in situ, multifocal tumors, prostatic stromal invasion and diversion types are all reported as risk factors for urethral recurrence [8–13].

In this study, our main objective was to evaluate the urethral recurrence rates and risk factors after radical cystectomy for urothelial bladder cancer, and also to evaluate its relationship with urinary diversion types.

2. Materials and methods

The records of 504 bladder cancer patients who received radical cystectomy, bilateral pelvic lymph node dissection and urinary diversion between 1991 and 2013 were retrospectively reviewed. Of these 504 cases, 287 male patients whose final pathology was urothelial carcinoma and on follow-up list for urethral recurrence, were included in the study. Radical cystectomy indications were defined as either muscle invasive bladder cancer or non-muscle invasive bladder cancer that could not be controlled with intravesical treatments or transurethral resection. Exclusion criteria were as follows: non-urothelial bladder tumors, female patients, out of follow up patients. Prophylactic urethrectomy was performed in 4 patients whose urethral surgical margins were positive at the frozen section analysis performed during the operation. Also

these patients were excluded from the study. Fig. 1 shows the schema of the study design. All patients were treated with limited or extended lymph node dissection and urinary diversion. Patients were followed in postoperative period in accordance with our clinical follow-up protocol (3-month periods in first 2 years, 6-month periods in the third year and annual check-ups after that). Follow-up examinations included physical examination, chest x-rays, biochemical markers, USG, CT, urethral washing cytology in ileal conduit and urine cytology in orthotopic continent diversion cases. The relationship between urinary recurrence and pathological stage, grade, lymph node involvement and urinary diversion was researched. In addition, the relation between urethral recurrence rates and urethral risk factors such as prostatic stromal invasion, multicentricity and tumors at bladder neck were also inquired. Statistical analysis was performed with SPSS 15.0 using chi-square and Cox regression multivariate tests.

3. Results

Orthotopic co genitourinary system continent urinary diversion (OCD) and ileal conduit (IC) was performed after radical cystectomy in 141 (49.1%) and 146 (50.9%) patients respectively. Urethral recurrence was observed in 11 (3.8%) patients and urethral recurrence rates in OCD and IC groups were 1.4% and 6.2% ($p = 0.034$). Mean ages of patients with and without urethral recurrence were 54.90 ± 10.14 (range 40–69) and 61.01 ± 9.19 (range, 34–85) ($p = 0.658$). Average follow-up period was 28.60 ± 20.88 (range, 8–122) months in patients with recurrence and 34.09 ± 26.61 (range, 9–144) months in cases without recurrence. Three (27.2%) patients had symptomatic urethral recurrence while the rest of cases were diagnosed by urethral washing cytology. Urethrectomy was performed in 2 patients with recurrence who were operated previously with ileal conduit technique. Four patients in IC group who did not accept the urethrectomy were treated with local radiotherapy meanwhile 3 cases with accompanying systemic disease were treated with systemic chemotherapy. In OCD group, 2 cases that developed urethral recurrence were diagnosed with TUR-BT and 1 case with superficial recurrence was treated with intraurethral BCG. The other case with invasive recurrence was treated with systemic chemotherapy because of accompanying systemic recurrences. Two patients diagnosed with urethral recurrence had a stage of pT1, one case had pT2 and 8 cases had pT4 disease ($p < 0.001$). Demographic values of the recurrent patients are shown on Table 1. There was no significant relationship between lymph node involvement and urethral recurrence ($p = 0.304$). Also, there was no significant relationship between pathological grade and urethral recurrence ($p = 0.794$). When disease-specific survival rates in patients with and without recurrence were analyzed, no statistically significant relation was found ($p = 0.268$). OCD group had significantly lower recurrence rates than IC group ($p = 0.036$). When all parameters were included in Cox regression multivariate test, the most important factor was the

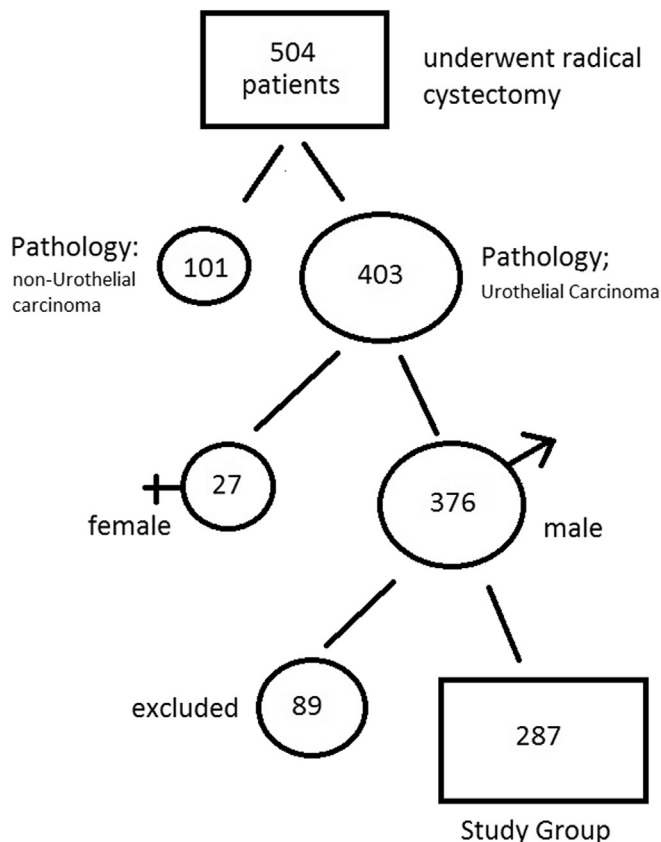


Fig. 1. The schema of the study design.

Table 1
Demographics of the urethral recurrence patients.

Age	54.90 ± 10.14 (40–69)	
Sex	Male	11
	Female	0
Diversion type	OCD	2 (%1.4)
	IC	9 (%6.2)
Stage	pT1	2
	pT2	1
	pT4	8
Follow-up period (months)	28.60 ± 20.88 (8–122)	

OCD: Orthotopic urinary diversion, IC: Ileal Conduit.

pathological T stage ($p < 0.001$) but diversion type had no effect ($p = 0.063$). Of the 287 cases, 92 patients had urethral recurrence risk factors such as prostatic stromal invasion, multicentric tumors and bladder neck tumors. In this group, 4 of 12 cases (33.3%) in prostatic stromal invasion group, 2 of 32 (6.25%) cases in multicentric tumor group and 2 in 48 (4.16%) cases in bladder neck tumor group had urethral recurrence. Urethral recurrence rates in patients with and without risk factors were 8.69% and 1.53% respectively ($p < 0.01$). Urethral recurrence rates and risk factor groups are shown on Table 2.

4. Discussion

Today, radical cystectomy (RC) is the golden standard in muscle invasive bladder cancer treatment. However, one in three patients has recurrences in the post-operative period [5]. Recurrences usually happen during the first three years postoperatively and unfortunately survival rates drop dramatically after systemic metastases and local recurrences [6,7]. Mitra et al.'s study reported median survival periods as 7.95 months in local recurrences, 5.95 in systemic recurrences and 3.98 months in both local and systemic recurrences [8].

Recurrences diagnosed in operated invasive bladder cancer patients can be seen as systemic, local, urethral or in upper urinary system urothelium. Although different recurrence rates in remaining urethra after RC were reported in various studies, wide series report this rate around 10% [9]. In addition, various studies reported prostatic stromal invasion, carcinoma in situ (CIS), multifocal tumors and diversion type as risk factors for urethral recurrence [9,14].

In previous studies, prostatic stromal invasion presence was defined as an important risk factor in urethral recurrences following cystectomy [9,12,14]. Some researchers reported recurrence rates in patients with prostate involvement as high as 30–37% [12,13]. Stein et al.'s research on 768 cases reported 5-year urethral recurrence rate as 5% if no prostatic involvement is present, 12% if there's superficial involvement and 18% in invasive prostate involvement [15]. We also diagnosed 12 cases with prostatic stromal invasion and 30% of those cases developed urethral recurrence. This result, in accordance with the literature, once again suggests that prostatic involvement is the most important risk factor for recurrence in the remaining urethra.

In general, pathological stage and lymph node involvement during the initial diagnosis are the most important factors of prognosis and these two factors are closely related with local and systemic recurrences [16,17]. Again, pathological stage is shown to be an important factor in urethral recurrence rates [18,19]. In our study, 8 of 11 urethral recurrences were initially diagnosed with pT4 stage tumors. This result is also statistically significant, showing that advanced local stage is an important parameter in urethral recurrence.

Urinary diversion and neobladder construction are essential in RC operations. For this reason, bowel segments are used in IC and various OCD procedures. OCD is the preferred treatment today due to the fact that it has physiologically the closest resemblance to an actual bladder in terms of storage and emptying and its positive

factors on the patient's social and daily life [20–22].

The increasing interest in OCD also increased the effort of preserving the urethra for anastomosis and continence as well [15]. Today, it is commonly accepted that unless patient has urethral recurrence risk factors, every patient deserves a chance of OCD [23]. Since the most important risk factor for urethral recurrence is prostatic stromal involvement, transurethral resection biopsies obtained before RC and perioperative biopsies should be studied before OCD in order to define any prostatic involvement.

When literature was reviewed, it can be seen that urothelial cancer risk in the remaining urethra is significantly lower in OCD patients compared with IC patients [10,15,23,24]. Stein et al.'s study on 397 OCD and 371 cutaneous diversion case series found 16 urethral recurrences in OCD group and 29 in cutaneous diversion group. Again in the same study, urethral recurrence rates for first 5 years after operation was found to be approximately 5% in OCD group and 9% in cutaneous diversion group [15]. In another study, Hassan et al. diagnosed only one case of recurrence in the remaining urethra in a series of 196 RC with OCD cases [23]. There are a few explanations why orthotopic patients have lower recurrence rates when compared to cutaneous diversion with remaining urethra. One of them is the washing and protective properties of urine as well as some protective fluids secreted from ileum [25]. In our study, we detected 2 (1.4%) recurrences in OCD group and 9 (6.2%) recurrences in IC group. Apart from the hypotheses mentioned above, pT4 cases who are in the risk group for urethral recurrence received IC treatments more commonly, which might be a factor for more frequent recurrence.

Urethral recurrences seen after RC can be both symptomatic and asymptomatic. Unfortunately, once the recurrence becomes symptomatic, metastases are also frequent and those cases have a worse prognosis compared to asymptomatic patients. Symptoms include hematuria, bloody urethral discharge, pain, palpable masses and differences in voiding habits [19]. Almost in half of the cases, recurrence can be diagnosed with cytologic review of urethral washing, so it is very important to obtain urethral washing samples in follow-up visits [10,15]. Nevertheless, Lin et al. claimed that there was no significant survival difference in patients followed and not followed with urethral washing after RC [26]. They concluded this outcome after evaluating results of patients who underwent urethrectomy after cystectomy followed by routine urethral wash cytology versus those not followed by urethral wash cytology who presented with bleeding or urethral discharge.

The treatment of choice in urethral recurrence after RC is delayed total urethrectomy which can be diagnosed by the urethral cytology washing, or when a patient develops bloody discharge or when a local recurrence is clinically obvious in the perineum or penis [27]. Classically this urethrectomy can be done through a perineal incision, however in select patients, endoscopic treatment or urethral instillation can be performed. Giannarini et al.'s series of 495 patients reported 24 urethral recurrences in which 21 (88%) was diagnosed in routine urethral washing sample cytology. They reported that 90% of pathological diagnosis of recurrences were CIS and patients can be spared from urethrectomy by treating them with BCG [28]. However, when the urothelial cancer diagnosed in remaining urethra has an invasive nature and symptomatic urethrectomy as well as adjuvant chemotherapy should be considered. In urethral recurrent cases with systemic metastasis chemotherapy should be the treatment of choice.

On the other hand, in the high-risk category, with bladder neck or prostatic stromal invasion by TCC, prophylactic urethrectomy is mandatory [18]. Classically this urethrectomy can be done through a perineal incision or a prepubic urethrectomy through a caudally extended midline abdominal incision. Van Poppel et al. developed the prophylactic prepubic urethrectomy in 1998, and they

Table 2
Urethral recurrence numbers and rates of risk-factor patients.

Risk factor	Patients (n)	Urethral recurrence cases (n)	%
Prostatic stromal invasion	12	4	33.3
Multicentric tumor	32	2	6.25
Bladder neck tumor	48	2	4.16
No risk factor	195	3	1.53

recommended that all patients who were not considered for bladder replacement should undergo this procedure [29,30].

5. Conclusions

Urethral recurrence rates were found 3.8% in our RC series which is compatible with the literature. Also, pathological stage was found to be the most important factor affecting urethral recurrence and prostatic stromal invasion was an important prognostic factor in these cases. Although risk factors for urethral recurrence were similar in both groups, urethral recurrence rates were significantly lower in OCD group when compared to IC group.

Ethical approval

Ethic Committee of Izmir Katip Çelebi University, Ataturk Training and Research Hospital.

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None.

Author contribution

Uğur Balci: Study design, writing.

Engin Dogantekin: writing.

Kutan Özer: data collections.

Sacit Nuri Görgel: data collections and analysis.

Cengiz Girgin: data analysis and study design.

Çetin Dinçel: supervision of the manuscript.

Conflicts of interest

None.

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