

Treatment and outcomes of urethral recurrence after orthotopic neobladder replacement in patients with bladder cancer — practice in a single centre

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Abstract

Objectives: To report on the treatment of urethral recurrence after orthotopic urinary diversion at our institution.

Methods: We retrospectively reviewed clinical information of urethral recurrence in patients who underwent radical cystectomy and orthotopic urinary diversion between January 1998 and January 2013.

Results: Of 341 patients, 282 presented for follow-up (median follow-up: 56 months; range: 1–174 months). Eight patients developed local recurrence of urothelial cancer after radical cystectomy. The rate of urethral recurrence (1.4%) in female patients who underwent orthotopic urinary diversion was lower than in male patients (3.3%). The median (range) time to recurrence was 33 (6–120) months after radical cystectomy and orthotopic urinary diversion. Recurrences were treated by transurethral resection of tumour, urethrectomy, neobladder resection, revision of urinary diversion, adjuvant chemotherapy, or radiation therapy, based on individual circumstances. Survival analysis showed that 5-year cancer-specific survival was significantly higher in patients with urethral recurrence alone (83.3%), compared with patients with other recurrences, including pelvic/abdomen recurrence and distant metastasis (26.8%).

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Conclusions: En bloc urethrectomy and revision of urinary diversion remain the principle surgical choices. Selection of transurethral tumour resection was based on tumour stage and was used in carefully chosen patients. Cancer-specific survival might depend on multidisciplinary therapy.

Keywords

Orthotopic neobladder, urethral recurrence, bladder cancer, cystectomy, urinary diversion, urethra, urothelial cancer, survival analysis

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Introduction

Radical cystectomy with pelvic lymphadenectomy and urinary diversion remains the gold standard for treatment of patients with invasive bladder cancer.¹ Because urethrectomy does not confer a significant independent survival benefit, it is infrequently performed at the time of the radical cystectomy.² This procedure provides the possibility of establishing an orthotopic urinary diversion, which has become the most popular and superior option in the last 20 years.³ Previous reports have indicated that 0.5% to 18% of patients with muscle-invasive bladder cancer may develop a urethral recurrence after undergoing radical cystectomy.^{4–9} Published evidence suggests that tumour multifocality, prostate involvement with urothelial carcinoma (UC), and the type of urinary diversion (conduit vs. orthotopic neobladder) are significantly associated with urethral recurrence following radical cystectomy. Notably, the rate of urethral recurrences was significantly lower in patients with orthotopic division than in patients with other urinary divisions, after radical cystectomy.^{9,10} Depending on the pathology of the transitional cell carcinoma (TCC), treatment of these recurrences includes surgical en bloc urethral resection, radiotherapy, and chemotherapy. In the

present analysis of patients from our institution, we report the outcomes and complications of treatment of urethral recurrences after radical cystectomy and orthotopic urinary diversion.

Patients and methods

Patients

Patients in this study underwent radical cystectomy with orthotopic urinary diversion to treat bladder UC at our institution, between 1998 and 2013. All patients were subjected to radical en bloc cystectomy for bladder cancer and the creation of both orthotopic ileocolonic and ileal neobladders. The selection criteria for orthotopic urinary diversion depended on urethral section frozen pathology and patient wishes in addition to general indications. The operative techniques have been described by other clinicians.^{11,12} These orthotopic neobladder operations were performed by a single surgical group. The Institutional Review Board of Southwest Hospital, The Third Military Medical University approved this retrospective investigation. All patients provided verbal informed consent, as required by the Institutional Review Board. This investigation was approved by our Institutional Review Board (No.KY201403).

Diagnosis

All patients had postoperative follow-up examinations every 3 months during the first year and every 6 months thereafter. Routine follow-up examinations included routine urinalyses, renal function tests, serum electrolyte level determinations, and kidney ultrasounds. Urodynamic examinations were performed at 3, 6, and 12 months after radical cystectomy and orthotopic urinary diversion. In patients with suspected urethral recurrences, urethral wash cytology (catheterization with a Foley catheter (8F) and closure of neobladder neck with a 5 mL urethral balloon, followed by insertion of a second Foley catheter (8F) into the urethra and subsequent washing with normal saline infusion), urethroscopy, or magnetic resonance imaging of the pelvis was performed. A urethral recurrence was diagnosed by using both cystoscopy and biopsy. All patients were evaluated before the surgical treatment of urethral recurrence with a complete medical history, physical examination, laboratory investigation, radiologic imaging (chest X-ray, CT (computed tomography) scan of the abdomen and pelvis), and an examination under anaesthesia. Additional imaging (CT of the chest, bone scan, and magnetic resonance imaging) was performed at the discretion of the treating physician. All pathological specimens were reviewed by a pathologist who used the 2009 TNM classification of the International Union Against Cancer and the WHO 2004 grading system.^{13,14}

Treatment

The treatment of urethral recurrence was personalized for each individual, on the basis of clinical and pathological findings. Treatment options included urethrectomy, neobladder resection, transurethral resection (TUR) of the tumour, and adjuvant chemotherapy or radiation therapy.

Chemotherapy comprised four cycles of MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or GC (gemcitabine and cisplatin). Complications of the surgical operation were evaluated by the Clavien system,¹⁵ and disease outcomes were evaluated by cancer-specific survival (CSS).

Statistical methods

The rate of urethral recurrence was compared between female and male patients by Fisher's exact probability test. Probability of survival was calculated by the Kaplan-Meier method, with significant differences evaluated by the log-rank test. Statistical analyses were performed with SPSS 19.0 (IBM Corp., Armonk, NY, USA). A P value <0.05 was considered to be statistically significant.

Results

Between 1998 and 2013, radical cystectomy with orthotopic urinary diversion was performed in 341 patients (279 males, 82 females) with bladder UC at our institution. Patients underwent radical en bloc cystectomy for bladder cancer, as well as the creation of orthotopic ileocolonic (75 Le Bag pouches) and ileal neobladders (266 Studer pouches). Procedures were performed by open surgery (281 patients) or by laparoscopic methods (40 patients). Patients who received orthotopic neobladders were between 26 and 80 years old. The median time of follow-up was 56 months (1–174 months).

Of the 341 patients who underwent orthotopic neobladder reconstruction, 59 were lost to follow-up. General data and pathological characteristics of the patients followed up are summarized in Table 1. There were no differences regarding pathological grade or stage between male and female patients. Of the 282 patients who were followed up, recurrences occurred as distant metastasis in 49 patients (17.3%)

Table 1. Baseline characteristics of patients (male vs. female) who received radical cystectomy and orthotopic urinary diversion.

Variable	Male (n=210)	Female(n=72)
Age, years (range)	61.5 (26–80)	63 (37–78)
Follow-up, months (range)	62 (1–174)	48 (2–96)
Pathological stage of bladder cancer		
pTis	1 (0.5%)	1 (1.3%)
pTa	2 (1.0%)	0 (0%)
pT1	35 (16.7%)	9 (12.5%)
pT2	115 (54.8%)	48 (66.7%)
pT3	46 (21.9%)	12 (16.7%)
pT4	11 (5.2%)	2 (2.7%)
Pathological nodal status		
N0	138 (65.7%)	53(73.6%)
N1	41 (19.5%)	14 (19.4%)
N2	26 (12.4%)	4 (5.6%)
N3	2 (1.0%)	0 (0%)
Nx	3 (1.4%)	1 (1.4%)
Distant metastasis recurrence	41 (19.5%)	8 (11.1%)
Pelvic/abdomen recurrence	72 (34.3%)	21 (29.2%)
Urethral recurrence	7 (3.3%)	1 (1.4%)

and as pelvic/abdomen recurrences in 93 patients (34.0%). Of the 282 patients who were followed up, eight (2.8%) were diagnosed with urethral recurrences. The incidence of recurrence was 3.3% (7/210) in male patients and 1.4% (1/72) in female patients. The rate of recurrence was lower in female patients than in male patients, but the difference was not statistically significant.

The clinical features of patients with urethral recurrences are summarized in Table 2. Eight patients exhibited recurrence within the urethra (median age 66.5 years, range 46–75). The median time from radical cystectomy to urethral recurrence was 33 (6–120) months. One patient received adjuvant chemotherapy for prostatic stromal invasion. The baseline pathological stages of bladder cancer in patients with urethral recurrences were T1 in one patient, T2 in five patients, T3 in one patient, and T4 in one patient. The pathological stages of recurrences were Ta in one patient, T1 in three patients, T2 in two patients, and T3

in two patients. The grades were papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade, and high grade in one, four, and three patients, respectively. Of the eight patients with recurrence, six had negative urethral margins, one had a hyperplastic margin, and one had no available information regarding margin at the time of radical cystectomy. Recurrent tumour developed at the urethro-neobladder anastomosis in one patient and distal to the anastomosis in seven patients. Urethral wash cytology showed four positives among eight patients; three were high grade on final pathology.

One female patient presented at 6 months with voiding habit changes and bladder emptying failure after a radical cystectomy. She was diagnosed with a urethral recurrent tumour and underwent TUR of the tumour; she remained alive and tumour-free for 2 years. Among seven male patients, one presented with voiding habit changes and six presented with gross

Table 2. Treatment and outcome of urethral recurrence in patients after radical cystectomy and orthotopic urinary diversion.

Variable	P1	P2	P3	P4	P5	P6	P7	P8
Sex	Male	Male	Male	Male	Male	Male	Male	Female
Pathology of bladder cancer	pT1N0 (HG), multiple	pT2aN0 (LG)	pT2bN0 (LG)	pT2aN0 (LG), multiple hyperplasia	pT4aN0 (LG)	pT2aN0 (LG)	pT3aN0 (HG)	pT2aN0 (LG)
Margin of urethra	No	No	unknown	hyperplasia	No	No	No	No
Adjuvant chemotherapy	No	No	No	No	Chemotherapy (GC)	No	Chemotherapy (GC)	No
Time from RC to UR (months)	30	24	120	18	12	18	60	6
Site of UR	Bulbar	Membranous	Membranous	Penile	Urethral	Membranous	Bulbar	Urethral
Pathology of UR	pT1 (LG)	pT1 (LG)	pT2 (LG)	pT1 (HG)	pT2 (LG)	pT3 (HG)	pT3 (HG)	pT2a (PUNLMP)
Treatment for UR	TUR	TUR (1 time)	TUR (2 times)	Urethrectomy, NR, Bricker conduit	Urethrectomy, NR, Bricker conduit	Urethrectomy, NR, Bricker conduit	Urethrectomy, NR, Bricker conduit	TUR
Complications (Clavien grade)	No	No	No	No	Prolonged nausea (II)	Prolonged nausea (II), deep leg vein thrombosis (IIIa)	Minor ileal fistula (II), wound infectious (IIIa)	No
Adjuvant therapy	No	No	Salvage Chemotherapy (GC)	No	Chemotherapy (MVAC)	Chemotherapy (GC) and radiation	Radiation	No
CSS from time of UR (months)	48	36	30	60	20	18	13	24
Cancer status	No evidence of cancer	No evidence of cancer	Dead from cancer (liver metastasis)	No evidence of cancer	No evidence of cancer	Dead from cancer (lung metastasis)	Dead from cancer (lung metastasis)	No evidence of cancer

RC: radical cystectomy, UR: urethral recurrence, PUNLMP: papillary neoplasm of low malignant potential, LG: low grade, HG: high grade, NR: transurethral resection of tumour, NR: neobladder resection, CSS: cancer-specific survival.

haematuria at 12 to 120 months after radical cystectomy. Three patients underwent TURs of their tumours; two patients who failed TUR eventually underwent urethrectomy, resection of the neobladder, and ileal conduit diversion (P2 and P3). Four patients underwent urethral and neobladder resection, of which three underwent ileal conduit diversion and one underwent continent cutaneous urinary diversion. Of the six patients who underwent urethrectomy, resection of the neobladder, and revision of the urinary diversion, the complications were ileus (40%, 2/6), minor ileal fistula (20%, 1/6), wound infection (20%, 1/6), and deep vein thrombosis (20%, 1/6). Three patients had no complications. The incidence of complications was 50% (3/6) in patients who underwent urethrectomy; the incidence of gastrointestinal complications was 60% (3/5) among all adverse events. Three patients with complications presented with hypoproteinaemia. All complications eventually resolved with conservative treatment.

Of all patients with invasive recurrences, two received adjuvant chemotherapy (GC),

one received adjuvant radiation therapy, and one received both adjuvant chemotherapy and radiation therapy after urethrectomy. One received adjuvant chemotherapy until presenting with liver metastasis, and responded well to chemotherapy. At the final follow-up, five patients had no evidence of disease, whereas three had died due to metastases to the liver, lung, or bone.

Five-year CSS was 61.9% among all patients who were followed up (Figure 1a). When all patients with recurrence were stratified into non-urethral recurrence and urethral recurrence, Kaplan-Meier curves showed that 5-year CSS was significantly higher in patients with urethral recurrence alone (83.3%) than in patients with pelvic/abdomen recurrence and distant metastasis (26.8%) ($P=0.001$) (Figure 1b).

Discussion

Our series showed that the overall rate of urethral recurrence was 2.9% after radical cystectomy and orthotopic diversion. The incidence of urethral recurrence was lower

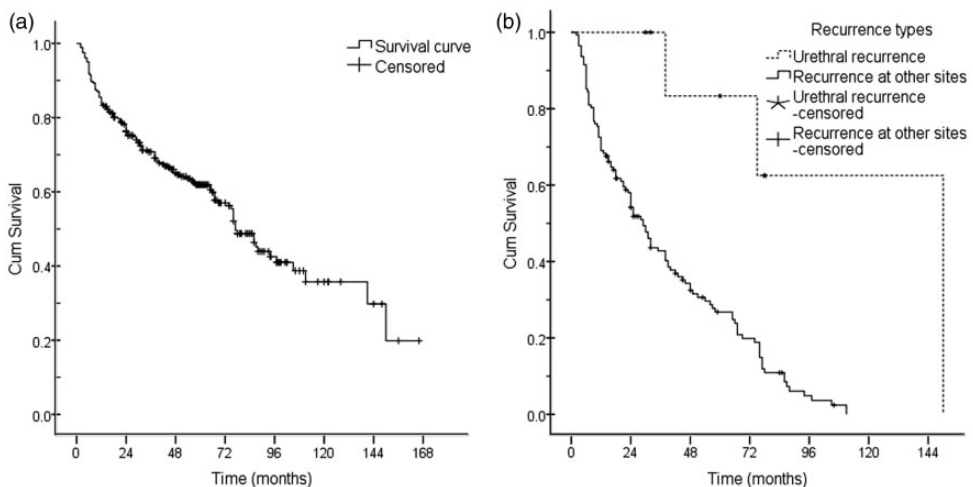


Figure 1. Kaplan-Meier analysis of survival rate for radical cystectomy. (a) Five-year cancer-specific survival was 61.9% in all patients who were followed up. (b) Cancer-specific survival was significantly higher in patients with urethral recurrence alone than in patients with pelvic/abdomen recurrence and distant metastasis.

in women (1.4%) than in men (3.3%); these incidences were consistent with previous reports. No significant difference was found in a comparison of urethral recurrence between male and female patients in our cohort. We believe that these statistical results might be partly a result of the limited number of case samples. Prior studies showed that prostate involvement with UC, tumour multifocality, and type of urinary diversion were significantly associated with the urethra following radical cystectomy in men.^{9,10} There are few reported cases of urethral TCC in women after radical cystectomy and orthotopic urinary diversion.¹⁶⁻²¹ The risk of urethral recurrence for women remains controversial. The most consistent association with a risk of urethral recurrence is with TCC of the bladder neck in some reports.¹⁶ A prospective pathological evaluation of 71 women undergoing radical cystectomy suggested that more than 60% of women with bladder neck involvement had no evidence of urethral TCC. Intraoperative frozen section analysis in 47 cases accurately predicted involvement of the urethra by TCC in every case (two with and 45 without urethral TCC).²² A recent multi-institutional study with long-term follow-up indicated that a positive final urethral margin was associated with urethral recurrence, while women with involvement of the bladder trigone and positive nodes were not at increased risk of urethral recurrence.²³ In our series, compared to that of bladder cancer, the pathological grade of UC was different in urethral recurrences after radical cystectomy. This result of heterogeneous neoplasms indicated that the recurrence mechanism was due to the field effect and multifocality. Although urethral recurrence was an infrequent event after orthotopic urinary diversion, treatment of urethral recurrence remains challenging.

The complications of surgical treatment of urethral recurrence after orthotopic

urinary diversion are not well documented. The fundamental surgical role is to perform en bloc urethrectomy, neobladder resection, and re-cutaneous urinary diversion.^{24,25}

This surgical procedure is technically complicated, and surgical success depends on the patient's general health, the extent of adhesions, and the surgeon's skill/experience. In our series, half of the patients presented with gastrointestinal complications; the proportion of gastrointestinal complications, relative to overall incidence of adverse events, was 60% (3/5). The rate of gastrointestinal complications was significantly higher for the surgical treatment of urethral recurrence than for previous primary radical cystectomy and orthotopic urinary diversion.²⁶ In the en bloc urethrectomy, neobladder resection and secondary urinary diversion to manage adhesions were important for the operation. Adhesions were a primary cause of gastrointestinal complications. Most patients with post-surgical complications presented with hypoproteinaemia. Postoperative hypoproteinaemia can lead to organ oedema, decreased immunity, and dynamic changes in circulation. In addition to careful skill in performing the operation, correcting hypoproteinaemia in a timely fashion reduces complications related to the gastrointestinal system and wounds. All complications were cured by conservative treatment, despite the seriousness of the complications, including ileal fistula and deep vein thrombosis.

Several papers have reported transurethral treatment of noninvasive urethral recurrence, avoiding urethrectomy and revision of the urinary diversion.^{4,27} Identifying recurrent noninvasive urethral tumour is an important pre-surgical task. Though the sample of recurrences is small, the outcomes in our series suggested that en bloc urethrectomy was the primary surgical choice in cases of urethral recurrence after radical cystectomy and orthotopic diversion. The decision to use transurethral

treatment should be prudent and used in carefully selected cases where the pathological stage has been determined. In these cases, active salvage en bloc urethrectomy remains effective. Patients with urethral recurrence alone should be distinguished from those with other pelvic/abdomen recurrences or distant metastases. Some patients with urethral recurrences who undergo surgical treatment might obtain long-term CSS, while patients with pelvic/abdomen recurrences or distant metastases might not. Kaplan-Meier analysis indicated that the CSS was significantly longer in patients with urethral recurrence than in patients with pelvic/abdomen recurrence and distant metastasis.

The Mayo Clinic reviewed 1506 patients who underwent radical cystectomy to identify patients with urethral recurrences and found that detection of asymptomatic urethral recurrence was associated with significantly lower disease stage and improved patient survival.⁹ Because most patients (1243) underwent cutaneous urinary diversions, it remains to be determined whether the conclusions of the Mayo Clinic were consistent with findings in patients who underwent orthotopic diversions. Considering the early findings of urethral recurrences, active surveillance for patients with a high risk of urethral recurrence is important. In our series, only one patient who had involvement of the prostate after radical cystectomy underwent surveillance by cystoscopy every 6 months. One patient ignored his symptoms and delayed the diagnosis. Other patients underwent cystoscopy after the appearance of minor symptoms, such as haematuria or voiding dysfunction. However, cytology was specific only in high-grade urethral recurrences. Many patients experienced significant delays in diagnosis due to many factors, including poor public awareness, patient fear, administrative delay, and medical resource limitation.²⁸ Early detection of

urethral recurrence would be a new approach in this field.²⁹

In conclusion, the rate of urethral recurrence in female patients who underwent orthotopic urinary diversion was lower than in male patients. En bloc urethrectomy and revision of urinary diversion remain the principle surgical options. Selection of transurethral tumour resection is based on the tumour stage and should only be used in carefully selected patients. If treatment fails, salvage en bloc urethrectomy cannot be avoided. Long-term outcomes depend on tumour stage and complete surgical resection of the tumour; thus, tumour control may benefit from multidisciplinary therapy.

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