

Urethral Recurrence After Cystectomy and Orthotopic Bladder Reconstruction: A Rare Case of Recurrent Bladder Cancer After 12 Years and Review of the Literature

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ABSTRACT

INTRODUCTION: Radical cystectomy combined with orthotopic urinary diversion is a chosen approach for treating invasive bladder cancer. However, urothelial cell carcinoma is characterized by its potential for recurrence and the development of multiple tumors in the urinary tracts. In the natural progression of transitional cell carcinoma, the remaining ureteral stump is considered a predicted site for possible recurrence after radical cystectomy. Currently, there is no specific recommendation for the diagnosis and management of this condition.

OBJECTIVE: We report a rare case in a 74-year-old male patient who was diagnosed with anterior urethral carcinoma following a history of radical cystectomy and Hautmann ileal neobladder reconstruction. Additionally, we summarize some novel findings regarding risk factors, diagnosis, treatment, and prognosis in patients with recurrent bladder cancer in the urethra after radical cystectomy.

METHODS: A case report and mini review.

RESULTS: The patient was diagnosed with recurrent bladder cancer in the urethral after radical cystectomy using magnetic resonance imaging of the pelvis, cystoscopy, and biopsy. Complete urethrectomy and creation of a permanent percutaneous urinary diversion were performed. No intraoperative or postoperative complications were recorded. The patient was discharged 3 days after the surgery.

CONCLUSION: Urethral cancer following radical cystectomy for bladder cancer treatment is a rare condition. Risk factors for this occurrence include male gender, non-use of orthotopic neobladder reconstruction technique, invasive tumors in the prostatic urethra, and multifocal tumors. The treatment of these tumors can be determined based on the extent of invasion and histological characteristics, leading to the choice between radical urethrectomy or alternative conservative treatments.

KEYWORDS: Bladder cancer, radical cystectomy, urethral recurrence, urothelial cell carcinoma

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Introduction

Bladder cancer ranks sixth among all cancers in the United States and over 81 000 new diagnosed cases were reported each year.¹ Radical cystectomy with urinary diversion remains the standard treatment for muscle invasive bladder cancer. Furthermore, radical cystectomy is also an option for non-muscle invasive recurrent bladder cancer or high-risk cases.^{2,3} As it originates from the urothelial tissue of the urinary tract, there is a potential for cancer recurrence in the remaining urethral after bladder removal. The recurrent rate in the urethra after radical cystectomy ranges from 1% to 8% and often detected within the first 2 years after surgery.⁴ Therefore, monitoring and early detection of recurrent tumors in the urethra have become crucial aspects to address in clinical practice. However, there was a lack of clinical guidelines for diagnosing and managing bladder cancer recurrence in the urethra following radical cystectomy and urinary diversion.

In this context, we presented a rare clinical case about a 74-year-old man who was diagnosed with recurrent bladder cancer in the urethra after 12 years of radical cystectomy and orthotopic neobladder reconstruction. Moreover, a literature review of the current evidence and proposed approaches for bladder cancer recurrence early detection, diagnosis, and treatment was also provided, contributing to a comprehensive overview of clinical practice for this condition.

Clinical Case Report

A 74-year-old male patient presented for consultation with complaints of dysuria, straining during urination, and a gradually weakening urinary stream over the past month.

Twelve years ago, the patient was diagnosed with muscle invasive bladder cancer and underwent a radical cystectomy with orthotopic neobladder reconstruction using the Hautmann technique. At that time, postoperative pathological results



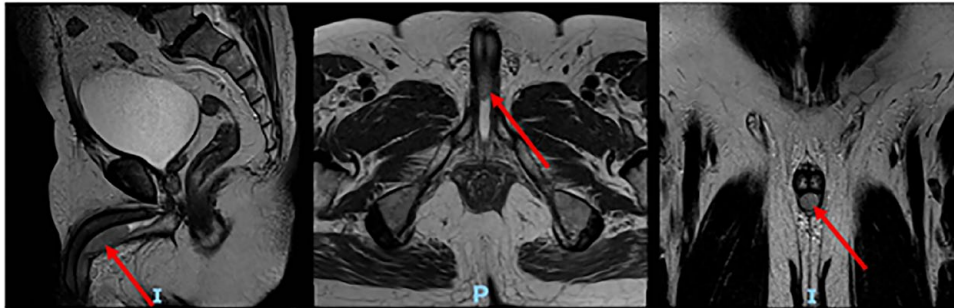


Figure 1. Pelvic magnetic resonance imaging showing the anterior-urethra mass (red arrows) before treatment.

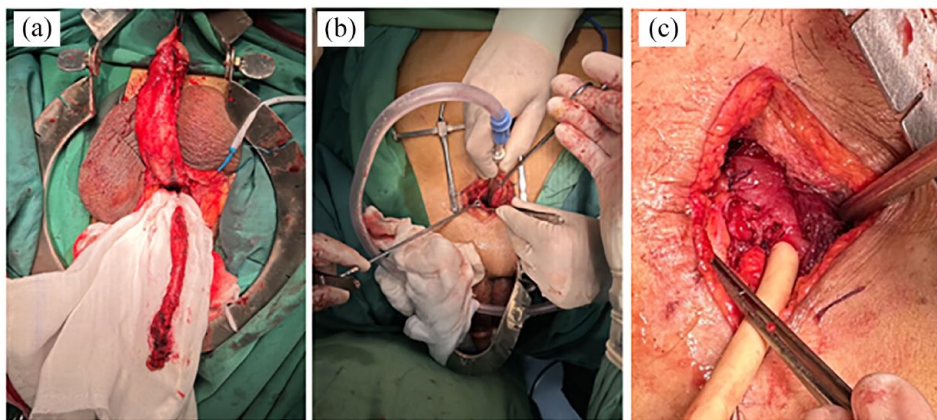


Figure 2. Surgical procedure of complete urethrectomy (A) and creation of percutaneous urinary diversion (B and C).

revealed multiple sites of high-grade invasive transitional cell carcinoma, with muscle invasion and right pelvic lymph nodes metastasis; however, no tumor in the prostatic urethra, bladder neck or carcinoma in situ (CIS) was found. After the previous surgery, the patient received 6 cycles of chemotherapy with the Gen-Cis regimen and had regular follow-ups every 6 months. Six months before the current admission, the patient was diagnosed with a left ureteral stone and underwent retrograde endoscopic lithotripsy; no evidence of recurrent tumors was observed.

In this admission, together with the main complaints of dysuria, straining during urination, and a weakening urinary stream, a physical examination revealed a mass with a dimension of about 3-centimeter (cm) in the penile urethra. On digital rectal examination, we observed that the patient's pelvic structures were mobile and there was no evidence of invasive tumor. The pelvis magnetic resonance imaging (MRI) scan showed a 12 × 65-millimeter (mm) mass in the penile urethra with low T1 signal, high T2 signal, restricted diffusion on DWI, and strong enhancement after contrast administration (Figure 1). No pelvic lymphadenopathy had been observed. Besides, the patient was without any symptoms suggesting cancer metastasis, including findings on chest X-ray. Cystoscopy revealed a protruding urethral mass in the penile urethra, 7 cm from the urethral meatus, measuring 3 × 1.5 cm, with no mass in the neobladder, and with a well-formed urothelialization of

intestine lining. Biopsy results of the urethral mass confirmed high-grade urothelial carcinoma.

The patient underwent complete urethrectomy including the urethral meatus. Urethrectomy surgery was performed smoothly without evidence of gross tumor extending into the corpus spongiosum (Figure 2). The intraoperative frozen section was taken, and the result showed no cancer cells. During the surgery, we meticulously examined the neobladder, which appeared smooth and free of tumors. Therefore, we decided to close the bladder neck and create a permanent percutaneous urinary diversion by cystostomy. Neither intraoperative nor postoperative complications were noted, and the patient was discharged 3 days after the surgery. The gross examination after complete urethrectomy showed a predominantly intraurethral mass with some localize in the corpus spongiosum, without invasion into the corpus cavernosum (Figure 3). The final pathological diagnosis was high-grade invasive papillary urothelial carcinoma, infiltrating beyond the transitional epithelium layer, with no cancer cells at the surgical margins.

The patient underwent monthly follow-up examinations in the first 3 months after surgery, and the surgical incision healed well. The patient had no complaint about the continuous catheter placed to divert urine. After 3 months, the patient was able to self-change the percutaneous cystostomy catheter and use a urinary stoma bag for social convenience. We also performed a cystoscopy examination of the neobladder at the three-month

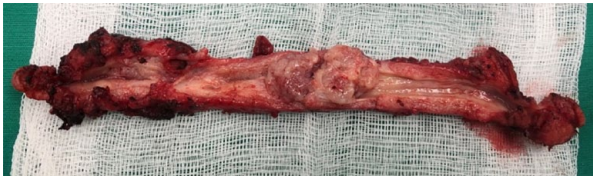


Figure 3. Gross specimen of the urethral mass and corpus spongiosum containing urethra after surgery.

postoperative mark through the cystostomy channel and observed normal bladder mucosa. The neobladder neck was securely closed and had healed well.

Discussion and Literature Review

Bladder cancer is the most common urothelial carcinoma, accounting for 90% to 95% of cases.³ Approximately 25% of diagnosed patients have muscle invasive bladder cancer, and radical cystectomy with urinary diversion is current the standard treatment.^{3,5} Since the 1950s, radical cystectomy has often been accompanied by urethrectomy to prevent recurrence in males with multiple tumors, extensive carcinoma in situ, or concurrence of urothelial tumor of the urinary tract. In women, urethrectomy was routinely performed until the 1990s, as it was believed that preserving the urethra had limited significance and negatively impacted survival rate in case of recurrence at that site. As orthotopic neobladder reconstruction became more common, routine urethrectomy became less frequent.⁴

As of now, there was still no clinical guideline for monitoring and treating urethral recurrence of bladder cancer.^{4,6} Current viewpoints have yet to support routine urethrectomy due to the need to preserve the urethra as the outlet for the neobladder, and removing it does not improve survival time but may even increase morbidity and negatively impact quality of life.³

Risk factors of cancer recurrence

Recent studies have identified several risk factors that suggest a higher likelihood of recurrent bladder cancer in the urethra. A systematic review and meta-analysis by Laukhtina in 2021, based on 51 studies, indicated that the rate of urethral recurrence ranges from 0.8% to 13.7%. Male gender was found to be a significant risk factor (pOR: 3.16, 95% CI 1.83-5.47, $P < .001$), whereas orthotopic neobladder reconstruction was identified as a protective factor (pOR: 0.44, 95% CI 0.31-0.61, $P < .001$). The presence of carcinoma in the prostatic urethra (pHR: 5.44, 95% CI 3.58-8.26, $P < .001$), invasive prostatic urethral carcinoma (pHR: 5.90, 95% CI 1.82-19.17, $P = .003$), and multifocal tumors (pHR: 2.97, 95% CI 2.05-4.29, $P < .001$) were also identified as risk factors.⁷ Laukhtina et al et al. also suggested that when there were factors such as invasion of the prostate, multifocal tumors, or tumors at the bladder neck, patients should be classified as having a high risk of urethral

recurrence. Based on the existing limited evidence, the authors of the study proposed an algorithm for the surveillance, diagnosis, and treatment of urethral recurrence after radical cystectomy and orthotopic neobladder reconstruction (Supplemental Figure S1).⁸

While urethral recurrence in bladder cancer was reported with several risk factors suggesting the condition, there is the possibility of primary cancer deriving at the urethra. Primary urethral cancer is defined as cancer that is initially happening in the urethra, not as a result of cancer cells spreading from other locations within the urinary tract.⁹ In this case report, it was quite challenging to determine whether the patient had primary urethral cancer or a recurrence of urethral tumor following bladder cancer. Nevertheless, primary urethral cancer is an extremely rare type of cancer with a prevalence of less than 1% of all urinary tract cancers and an incidence rate of under 4 per 100 000 cases.^{9,10} Therefore, with literature supporting evidence, this male patient with a history of bladder tumors in multiple locations was considered to have risk factors of recurrence as well as was preferred to have the diagnosis of urethral recurrence.

Preventing urethral recurrence has also been mentioned in some clinical guidelines. For patients undergoing radical cystectomy with urinary diversion, the American Urological Association (AUA) guidelines in 2020 emphasized the need to determine negative surgical margins in the urethra with cancer cells.⁵ According to the European Association of Urology (EAU) guidelines, evaluating the urethral surgical margins with intraoperative frozen section biopsy was recommended, and if the results were negative, routine urethrectomy might not be necessary.³ This could be the reason why in cases with orthotopic neobladder reconstruction, the incidence of urethral recurrence was often lower compared to those who underwent diversion without using urethra.^{3,6,7,11} Additionally, experts' opinions supported the importance of monitoring for the presence of urethral recurrence after radical cystectomy.⁵ Moreover, Laukhtina et al proposed that if frozen section analysis shows tumor cells in patients at high-risk of urethral recurrence, immediate urethrectomy was necessary.⁸

In most cases, urethral cancer recurrence is observed within the first 2 years. In this clinical case, the patient's cancer recurrence in the urethra after 12 years following bladder removal is a rare occurrence. Despite having risk factors like being male and having tumors in multiple locations, orthotopic neobladder reconstruction surgery performed with clear margins and post-operative systemic chemotherapy may have contributed to delaying the recurrence of the tumor.

Monitoring and early recurrent diagnosis

Experts' opinions support the importance of monitoring for the presence of urethral recurrence after radical cystectomy.⁵ The approach to monitoring and early detection of urethral

recurrence is still a matter of debate. Recurrence, if any, typically occurs within 8 to 33 months after surgery, while some reports documented cases of recurrence even after 20 years.⁴

Generally, patients with recurrent bladder cancer in the urethra may experience symptoms such as abnormal urethral bleeding or discharge (80%), urethral pain (32%), and rarely, the palpable presence of an abnormal mass within the urethra or the changes in urinary habits that the patient could perceive may also occur.^{4,11} Due to the lack of specific recommendations, some authors propose monitoring and diagnosing only when patients present with symptoms,⁶ while other perspectives suggest the need for surveillance through urethral endoscopy, urinary cytology, or urethral discharge analysis.⁷ Laukhtina et al proposed a surveillance protocol involving regular evaluation of clinical symptoms, urethral wash cytology, or urethroscopy every 6 months during the initial 2 years post-surgery, followed by annual assessments for a minimum of 5 years in orthotopic neobladder patients.⁸

In the clinical case presented, the patient's recurrence was detected 12 years after the initial treatment, and this finding was relatively early, considering that 6 months before the diagnosis of recurrence, cystoscopy did not reveal any urethral mass. Thanks to the presence of lower urinary tract symptoms and the clinical sensitivity of the physician, the patient was promptly diagnosed at an early, localized stage of the disease.

Diagnosis tests

When diagnosing urethral tumors, imaging studies are necessary to assess the stage of the tumor. For primary urethral tumors, the recommendations of the EAU in 2023 suggest using MRI to evaluate the size, extent of invasion of the tumor, and regional lymph nodes.¹⁰ Compared to computed tomography (CT) scans, MRI has advantages in detecting smaller lesions in the urethra, providing clearer and more detailed images for anatomical identification. A study by Park and Park on 12 patients with recurrent urethral cancer recorded a detection rate of 41.67% (5/12) on CT scan images, while in the group that used MRI, the detection rate was 100% ($P = .0147$).¹² This indicates that MRI could be a reliable method in diagnosing recurrent urethral tumors.

Treatment methods and prognosis

Regarding treatment, there is currently no standard approach for managing recurrent urethral cancer after radical cystectomy. For patients with percutaneous urinary diversion, complete urethrectomy, including the urethral meatus, is considered a reasonable treatment option. However, for patients with orthotopic neobladder reconstruction, some authors argue that complete urethrectomy and urinary diversion through the skin may be overly aggressive. Instead, conservative treatments such as endoscopic resection of the tumor, urethral instillation of 5-fluorouracil (5-FU) or BCG (Bacillus Calmette-Guérin)

therapy, can be considered for low-grade and non-invasive tumors.^{4,13} Apparently, due to the limited number of reported and followed cases of urethral recurrence after treatment, there is still insufficient evidence to establish treatment recommendations.⁸ Overall, most authors generally agree that for non-invasive and low-grade tumors, conservative treatment options can be considered in selected cases, while complete urethrectomy may be necessary for invasive or high-grade tumors.^{4,8}

In the clinical case we presented, the MRI images and gross examination of the tumor suggested that it invaded the corpus spongiosum but had not infiltrated the corpus cavernosum, and there were no signs of lymph node involvement or distant metastasis. The biopsy sample from cystoscopy revealed high-grade tumors in the bladder. Therefore, the decision to perform a total urethrectomy was justified. The postoperative pathological findings supported the initial assessment. Therefore, surgery can be considered as a definitive treatment without the need for any additional therapeutic options.

The impact of urethral recurrence on overall survival has been assessed in several studies. In a retrospective study by Boorjian et al involving 1506 patients who underwent radical cystectomy and were followed up for the long term, 85 patients (5.6%) experienced urethral recurrence.¹¹ Accordingly, the 3-year and 5-year overall survival rates for patients with urethral recurrence were 74% and 63%, respectively. Interestingly, the prognosis for urethral recurrence was found to be more favorable compared to recurrence in other locations such as the abdominal cavity, pelvic region, or distant metastasis.¹¹ Additionally, when comparing with patients who did not experience urethral recurrence, the authors did not find statistically significant differences in the 5-year and 10-year survival rates.¹¹ Moreover, a systematic review and meta-analysis conducted by Laukhtina et al reported that urethral recurrence did not significantly impact overall survival.⁷ A recent retrospective study conducted by Khanna et al involving 2930 patients who underwent radical cystectomy revealed that cases of urethral recurrence with apparent clinical symptoms were associated with adverse cancer-specific survival (HR 7.3, 95% CI 5.46-9.76) and overall survival rates (HR 1.86, 95% CI 1.54-2.24).¹⁴ Further meta-analyses and studies are needed to provide a more objective assessment of the prognosis for these patients.

Conclusion

Bladder cancer recurrence in the urethra after radical cystectomy is a rare condition. Male gender, non-use of orthotopic bladder reconstruction technique, involvement of the prostatic urethra, and multiple tumor nodules have been suggested as risk factors increasing the likelihood of recurrence in the urethra and requiring special monitoring for these patient groups. To diagnose this condition, a combination of monitoring patient symptoms, urinary cytology, and performing diagnostic endoscopy is essential. Treatment options for urethral recurrence depend on the extent of invasion and histological characteristics, with the choice of radical urethrectomy or alternative

conservative treatments. However, overall survival rates for patients with urethral recurrence after radical cystectomy are generally comparable to those without recurrence except for symptomatic patients.

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Ethical Statement

The consent form was obtained before the study, and signed by the involved patient who was informed about the study and voluntarily disclosed information.

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Supplemental Material

Supplemental material for this article is available online.

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