

CASE REPORTS

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Combined surgical and chemotherapy treatment for invasive primary urethral cancer: a case presentation

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Abstract

Background The European Association of Urology (EAU) defines primary urethral carcinoma (PUC) as a carcinoma that arises in the urethra without a previous diagnosis of carcinoma elsewhere in the urinary system. It is considered as a rare cancer, accounting for less than 1% of all malignant tumors and 5% of malignant tumors of the urinary system. The difficulty in diagnosis and its rarity can lead to delayed diagnosis and decreased survival. We think that a case report to be made in the literature for this rare disease with no consensus on treatment will contribute to disease management.

Case presentation In this article, we describe the diagnosis and treatment process of a 75-year-old patient who was diagnosed with primary urethral cancer and had urethral discharge and difficulty in urination. The biopsy result from the suspected hyperemic area in the urethra in cystourethroscopy was primary urethral cancer. Urethrectomy followed by urethroplasty was performed on the patient's 2-cm primary urethral cancerous tissue. In the postoperative first month, an F-18 FDG whole-body PET scan for oncological evaluation showed increased pathological F-18 FDG uptake in the periphery of the mass in the penile urethra and indistinguishable boundaries from the prostatic urethra. After this, adjuvant gemcitabine and carboplatin therapy was planned by the oncology team.

Conclusions Based on our outcome in this case, we believe that chemotherapy combined with surgery increases the chance of successful treatment in locally advanced urethral cancer.

Keywords Primary urethral tumor, Urethroplasty, Urethra, Case report, Case presentation

1 Background

The European Association of Urology (EAU) defines primary urethral carcinoma (PUC) as a carcinoma that arises in the urethra without a previous diagnosis of carcinoma elsewhere in the urinary system [1]. It is considered as a rare cancer, accounting for less than 1% of all

malignant tumors and 5% of malignant tumors of the urinary system [2]. In the USA, the annual incidence rate has been reported as 4.3 million in males and 1.5 million in females [3].

It has been reported that morbidity increases with age in both genders in this disease, which exhibits an aggressive course [4]. Predisposing factors for men include long-term irritations such as recurrent catheterization, urethral strictures, urethroplasty, radiotherapy, and urethral infection/urethritis following sexually transmitted diseases. For women, etiology has been associated with recurrent urinary tract infections, urethral diverticulum, and human papillomavirus infection [5].

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The most common histological type in men with primary urethral carcinoma is reported to be urothelial carcinoma (54–65%), followed by squamous cell carcinoma (SCC) (16–22%) and adenocarcinoma (AC) (10–16%) [3, 6]. In women, urothelial carcinoma (45%) is also the most common histological type, followed by AC (29%) and SCC (19%) [7]. Among these histological types, adenocarcinoma is considered as the most aggressive malignancy due to its high lymph node metastasis rate and contribution to disease progression, followed by squamous cell carcinoma and urothelial carcinoma [7].

Primary urethral carcinoma is a challenging disease for early diagnosis due to the absence of prominent symptoms and specific screening indicators [8]. The difficulty in diagnosis and its rarity can lead to delayed diagnosis and decreased survival. In the intermediate and advanced stages, it can present with symptoms such as voiding dysfunction, sexual difficulties, irritation symptoms, and hematuria. A detailed medical history, physical examination, along with imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT), as well as cystoscopy and confirmatory tissue biopsy, are necessary to detect the disease [9, 10]. Cystoscopy is considered the gold standard diagnostic method due to its ability to visualize tumor size, shape, degree of invasion, and enable tissue sampling [10].

Most studies on PUC consist of small sample sizes and retrospective studies with inconsistent patient demographics. Therefore, there is no consensus on the treatment of PUC [11]. The purpose of this case report is to present a patient who underwent urethrectomy and subsequent urethroplasty due to this rare disease. It is believed that this presentation can contribute to optimizing the treatment of PUC.

2 Case presentation

A 75-year-old male patient presented to our clinic with a complaint of urethral discharge and difficulty urinating, for approximately 4 months. No pathological findings were detected during the physical examination. He had no additional medical history except hypertension. Complete blood count and biochemical tests showed no abnormal findings. A complete urine analysis revealed the presence of leukocytes and erythrocytes. Due to the patient's symptoms and laboratory results, the patient underwent urethrocystoscopy.

During urethrocystoscopy, a biopsy was taken from a suspicious hyperemic area located 2 cm distal to the verumontanum, causing a 2-cm stricture. There were no pathological findings in the bladder. The pathology report indicated HIGH-GRADE INVASIVE UROTHELIAL CARCINOMA (pT1, without subepithelial connective tissue invasion or invasion into the muscle layer). Based

on this result, one month later, the patient underwent repeat cystourethroscopy and endoscopic tumor resection. The pathology report confirmed HIGH-GRADE INVASIVE UROTHELIAL CARCINOMA pT2 (with subepithelial connective tissue invasion and invasion into the muscle layer).

Based on the patient's subsequent clinical findings, a decision was made to perform urethrectomy. The patient was taken to surgery by a competent surgeon specialized in urethral surgeries. After the urethra was dissected, a urethrectomy was performed on the 2 cm area containing the tumor. The surgical margin, as determined by frozen section examination, was reported as benign. The proximal and distal part of the urethra was then anastomosed to perform urethroplasty. The pathology report of the urethrectomy indicated HIGH-GRADE INVASIVE UROTHELIAL CARCINOMA pT2 (with subepithelial connective tissue invasion and invasion into the muscle layer), and the surgical margins were reported as intact. No complications were observed after the surgery. Three weeks later, the patient's catheter was removed, and no stricture pattern was observed in the uroflowmetry.

In the postoperative first month, an F-18 FDG whole-body PET scan for oncological evaluation showed increased pathological F-18 FDG uptake in the periphery of the mass in the penile urethra and indistinguishable boundaries from the prostatic urethra (Fig. 1). Moreover, a moderately hypermetabolic lymph node (metastasis) was observed in the mediastinum.

In the postoperative first month, adjuvant gemcitabine and carboplatin therapy was planned by the oncology team. The treatment consisted of 6 cycles and

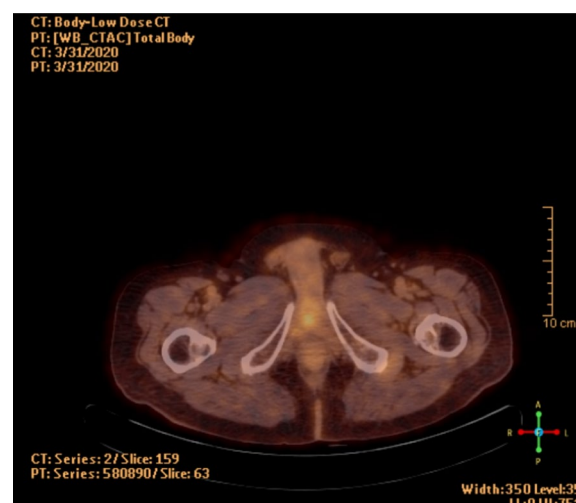


Fig. 1 Postoperative first month, increased pathological F-18 FDG uptake in the periphery of the mass in the penile urethra and indistinguishable boundaries from the prostatic urethra

administered every 21 days. Meanwhile, in the postoperative fourth month, a follow-up F-18 FDG whole-body PET scan was performed. When compared to the previous PET scan, there was a 24% increase in F-18 FDG uptake in the mediastinal lymph node and a 4% decrease in F-18 FDG uptake in the proximal urethral lesion. Furthermore, no hypermetabolic lesions were observed in

the prostatic urethral region in this imaging. Although there was an increase in FDG uptake in the mediastinal lymph node, the response to treatment was considered favorable due to regression observed in the primary lesion area.

After completing the final cycle of chemotherapy in the postoperative sixth month, the patient was reevaluated using F-18 FDG whole-body PET scan. It was observed that the hypermetabolic lesion in the proximal urethra and the FDG metabolism in the mediastinal lymph node had decreased to moderate levels (Fig. 2). This response was considered as a positive treatment outcome.

In the postoperative sixth month, penile MRI revealed fibronodular intensity changes in the surgical area (Fig. 3).

During the 2-year follow-up, abdominal and pelvic MRI showed no evidence of disease recurrence, and significant improvement in the patient's urinary symptoms was observed.

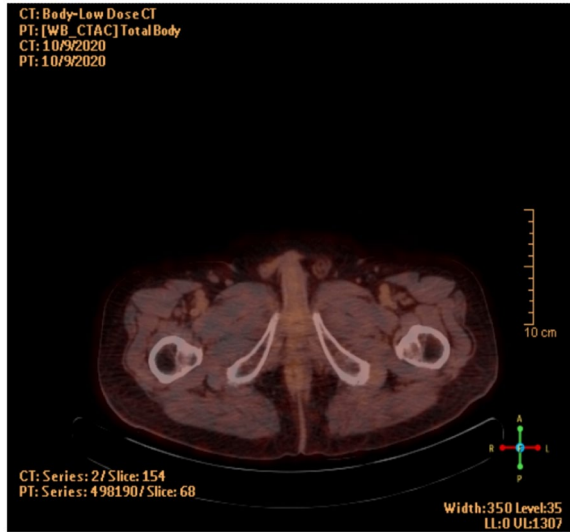
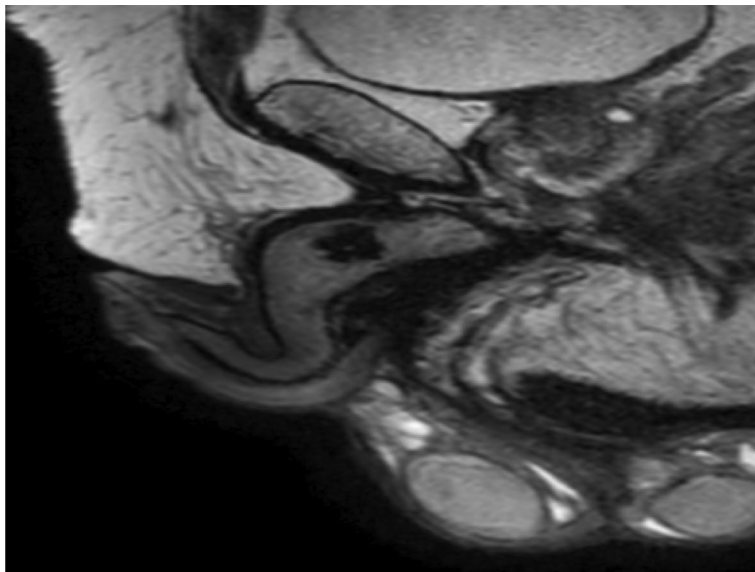


Fig. 2 Postoperative sixth month, decreased FDG metabolism was observed in the hypermetabolic lesion in the proximal urethra

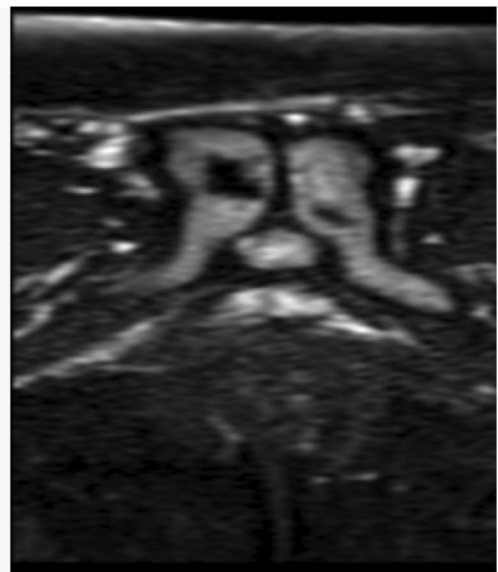
3 Discussion

Primary urethral carcinoma is a rare disease. Therefore, even the smallest developments related to PUC will shed some light on the treatment. The application of urethroplasty in the treatment of this disease arouses interest.

The survival rates in PUC are known to be associated with the clinical stage at presentation [12]. Generally, distal tumors have been found to be associated with lower



a. Sagittal Section MRI



b. Transverse Section MRI

Fig. 3 **a** Sagittal section MRI (postoperative sixth month, penile MRI revealed fibronodular intensity changes in the surgical area), **b** transverse section MRI (postoperative sixth month, penile MRI revealed fibronodular intensity changes in the surgical area)

stages compared to proximal tumors, which may be attributed to delayed diagnosis in patients with proximal tumors [12]. Additionally, advanced age, nodal involvement, and metastasis have been identified as poor prognostic factors [4, 13].

In a study conducted in the USA involving patients with PUC, the 5-year and 10-year survival rates were reported as 46% and 29%, respectively, while the overall cancer 5-year and 10-year survival rates were reported as 68% and 60% [3]. Another study conducted in Europe reported 1-year and 5-year survival rates of 71% and 54%, respectively [6]. Tumor staging is of significant importance due to its impact on survival, and the TNM staging system is used as in other cancers. Treatment approaches, including surgery, radiotherapy, chemotherapy, and neoadjuvant chemotherapy, vary depending on the localization of the disease, local advancement, and presence of metastasis [10].

Bacillus Calmette–Guérin (BCG), hydroxycamptothecin, and platinum treatments can be given as intravesical perfusion chemotherapy in patients with superficial (Stage Ta-Tcis) prostatic urethral carcinoma after transurethral resection (TUR) [10].

In cases of local disease outside the prostatic urethra in men, options such as urethrectomy and partial urethrectomy are considered based on the location of the disease. Particularly in cases of distal localization, partial urethrectomy has been favored due to higher survival rates after urethrectomy, aiming to achieve positive oncological outcomes and improved quality of life for the patient [14].

Radiation monotherapy may be recommended for early-stage patients seeking an organ-sparing treatment. However, the patient should be informed that there are few data on treatment results and that skin necrosis, fistula, and urethral stricture may develop [15]. The chemoradiotherapy option, on the other hand, can be recommended for early stage patients who are suitable for organ-preserving therapy and for those with advanced disease who are not suitable for surgery [16]. There is no proven benefit of prophylactic inguinal or pelvic lymphadenectomy in PUC. Neoadjuvant chemotherapy and regional lymph node dissection can be applied to clinically enlarged inguinal and pelvic lymph nodes. As an alternative approach to reduce morbidity due to surgery, a surgical approach can be considered in those who do not respond to chemoradiotherapy first [14, 17].

The low survival rates observed in monotherapy approaches such as urethrectomy and radiation therapy have led to the investigation of multimodal treatment methods. In a single-center study by Dalbagni et al., which included 40 operated patients and 6 patients who

underwent salvage surgery after radiotherapy, the 5-year overall survival and disease-specific survival rates were reported as 42% and 50%, respectively. The overall survival rate was found to be more favorable in superficial disease compared to invasive disease (83% vs. 36%) and in anterior urethral tumors compared to bulbar urethral tumors (69% vs. 26%). The 5-year recurrence-free survival and metastasis-free survival rates were reported as 51% and 56%, respectively. In this study, it was emphasized that multimodal treatment to be given in combination with surgery, chemotherapy, and radiation in locally advanced disease would be appropriate. In a cohort of 44 patients diagnosed with advanced-stage PUC, it was reported that 43% of patients had positive lymph nodes and 16% had distant metastatic disease. Surgical treatment combined with adjuvant/neoadjuvant therapy was reported to have better overall survival rates compared to chemotherapy monotherapy (46.9 months vs. 21.7 months, $p=0.02$) [18].

Eng et al. conducted a study involving 14 patients with early-stage and 17 patients with advanced-stage urethral cancer. Thirteen patients in the early-stage group underwent surgical treatment, while one patient received chemoradiotherapy. In the advanced-stage group, radiation therapy ± chemotherapy was administered to 17 patients (16 patients received combined treatment and 1 patient received radiotherapy). During a 7-year follow-up, an overall survival rate of 45% was recorded. Among the 14 patients in the early-stage group, 8 were reported disease-free at their last follow-up, while in the advanced-stage group, 5 out of 17 patients were disease-free. The study suggests that monotherapy may be applicable for early-stage cases, but multimodal treatment appears to be more beneficial for advanced-stage urethral cancer patients [19].

This case presentation is consistent with current literature, where chemotherapy was administered after urethrectomy for locally advanced disease, and there has been no recurrence detected during the 2-year follow-up period.

4 Conclusions

There is no standard treatment protocol for urethral carcinoma. Particularly in advanced-stage disease, treatment regimens consisting of monotherapy can yield unsuccessful results. Even if surgical treatment yields negative surgical margins, micrometastatic disease can reduce treatment success. Therefore, in locally advanced urethral cancer, the administration of chemotherapy in combination with surgery is believed to increase the chances of successful treatment.

Abbreviations

EAU	European Association of Urology
PUC	Primary urethral carcinoma
SCC	Squamous cell carcinoma
AC	Adenocarcinoma
MRI	Magnetic resonance imaging
CT	Computed tomography
F-18 FDG PET	18-Fluoro-deoxyglucose positron emission tomography
BCG	Bacillus Calmette–Guérin
TUR	Transurethral resection

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Author contributions

AS involved in protocol development and research design, data collection and management, data analysis, manuscript writing/ editing. SB took part in data collection, research design. MBD involved in manuscript writing/ editing, supervision. KK took part in protocol development, data collection. SC involved in protocol development, research design. YO took part in protocol development, research design. OLT took part in manuscript writing/ editing, supervision. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Patient consent was obtained for case presentation.

Consent for publication

The patient consents to the publication of the case report.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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