Journal of MedVerse Research & Practice

nurexus.com

Key Components in the Evaluation and Management of Primary Urethral Carcinoma

Dr. Deshmuk[1], Dr. Varma[2], Dr. Yuvi[3]

Assistant Professor, Department of Urology

Saveetha Medical College & Research Institute, Thandalam, Kanchipuram

Email ID: deshmukdr@gmail.com

Submission Date: 20.11.2023	Accepted Date: 16.12.2023	Published Date: 31.12.2023

Abstract

Primary urethral carcinoma (PUC) is an uncommon cancer with few therapeutic alternatives. This overview aims to summarize current approaches for managing this condition. The majority of existing research consists of retrospective analyses with limited sample sizes and unclear treatment guidelines. Diagnosing this ailment presents significant challenges. Tumors located in the proximal (posterior) region may go undetected until the disease has progressed, as they are challenging to detect through physical examination. Additionally, early-stage tumors in distant areas might be mistaken for infections, leading to delayed treatment and potentially worse outcomes. In our case, the patient received a diagnosis of primary urethral cancer at the First Clinical Hospital of Yichang, confirmed through cystoscopy and biopsy procedures. Given her elderly status, compromised health, and financial constraints, she opted against undergoing extensive surgical intervention. The absence of a standardized protocol for treating primary urethral cancer in clinical settings has led to variations in surgical approaches and post-operative adjuvant therapies across different medical institutions, resulting in diverse prognostic outcomes. Further research, ideally in the form of randomized prospective controlled trials, is necessary to establish uniform treatment strategies for patients.

Keywords: Primary, cystoscopy, urethral carcinoma

Introduction

Primary urethral carcinoma represents a neoplastic entity, constituting less than 1% of all malignancies (1,2). PUC can be categorized histologically into three principal types: urothelial carcinoma (UC), squamous cell carcinoma (SCC), and adenocarcinoma (AC) (3). The optimal therapeutic strategies for PUC remain inadequately delineated, necessitating consensus regarding the most efficacious treatment modalities (4). In male patients, Squamous cell carcinoma constitutes 12-30% of cases, while adenocarcinoma represents 5-16% [5,6,7].

Among female patients with primary urethral carcinomas (PUCs), urothelial carcinoma (UC) similarly predominates, comprising approximately 45% of cases. However, adenocarcinoma is diagnosed more frequently than squamous cell carcinoma, with incidence rates of 29% and 19%, respectively [8]. Dirksen et al. also identified adenocarcinoma as the most aggressive variant of malignancy, followed by carcinoma in terms of severity [8]. The emergence of adenocarcinoma as a lymph node metastasis likely

elucidates this observation, further contributing to disease progression [8]. Early detection of PUC is imperative for effective intervention, as this malignancy often manifests without overt symptoms and lacks specific screening biomarkers. During intermediate and advanced stages, patients may report significant symptoms, including urinary obstruction, dyspareunia, irritation, and hematuria. Although various diagnostic modalities, including MRI scan and CT scan, are utilized for PUC detection, cystoscopy and biopsy are regarded as the most definitive diagnostic techniques. Primary urethral carcinomas (PUC) are infrequent malignancies, representing less than 1% of all cancer diagnoses.

The rarity of this cancer type has culminated in the absence of standardized management protocols. Various medical institutions implement diverse strategies predicated on the specific histological subtypes of PUC. The limited case numbers have resulted in a lack of consensus on optimal therapeutic approaches for this rare urological malignancy. Among different racial demographics, African Americans demonstrate the highest incidence rate (3.33/1,000,000), followed by Caucasians (1.72/1,000,000), while Hispanics and other racial groups reflect an equivalent rate (1.57/1,000,000) [11]. An analysis conducted by the SEER program indicated that the incidence of PUC peaked in individuals aged over 75. The study from the SEER program established that the highest rate of PUC was observed in the cohort exceeding 75 years (7.6 per million),

Diagnostic assessment

Clinical history

Initially, PUC may not display any specific symptoms, leading to potential misdiagnosis as common urethral strictures, especially in females. More than 70% of women experience recurrent urinary tract infections, symptoms of irritable voiding, or discomfort during sexual intercourse. When diagnosed, the majority of female patients are identified as having T3-4N0M0 stage disease (29%), whereas most male patients are found to have T1N0M0 stage disease (32%) [13]. Of greater significance, patients with penile urethral cancer (PUC) typically present with symptoms such as visible blood in the urine or bloody discharge from the urethra. In cases of locally advanced PUC (T3 / T4)(45 %e57 %), patients may experience additional symptoms, including an extra-urethral mass, obstruction of the bladder outlet, pain in the pelvic region, formation of a urethrocutaneous fistula, development of an abscess, or pain during sexual intercourse[14].

Clinical examination

For male patients, evaluation included a digital rectal examination, while female patients underwent a pelvic exam that involved palpation of the urethra.. In male patients, potential induration of the external genitalia can be detected through manual examination, using a finger inserted into the rectum. For female patients, a thorough examination of both inguinal regions should be conducted through palpation to evaluate the local clinical stage and detect any enlarged lymph nodes (LN). This assessment should include noting the position, dimensions, and movability of the nodes [20]. Additionally, a two-handed examination is necessary to determine the local clinical stage and rule out the possibility cancers [21].

Urinary cytology

Urine specimen evaluation can be employed to identify PUC with a sensitivity range of 50% to 80% [22]. The effectiveness of urinary cytology in detecting cancer varies based on the pathological type. Studies revealed that male patients showed sensitivity rates of 80% for urothelial carcinoma (UC) and 50% for squamous cell carcinoma (SCC). Conversely, female patients demonstrated sensitivity rates of 50% for UC and 77% for SCC [23].

Cytological assessment of urine specimens

To evaluate, Physicians can employ cystoscopy and urethral biopsy techniques [23]. When obtaining biopsy samples, it is important to mark the sites (proximal or distal) and provide this information, along with clinical details, to the pathologist. Additionally, urethral cystoscopy serves as a method to exclude the presence of associated bladder tumors, as urethral cancer may originate in the bladder through micro metastases [24]. For histological diagnosis, larger lesions can be removed through transurethral resection. When ulcerative urethritis or prostatic ducts are suspected, a resectoscope biopsy of the prostatic urethra may be beneficial in identifying ulcerative prostatitis. This procedure is elaborated on in subsequent sections.

Diagnosis of UC of the prostate

Table 1: Reproduced with authorization from the American Joint Committee on Cancer TNM staging system for urethral carcinoma (15). The T category indicates the degree of tumor penetration, the N category denotes the extent of lymph node involvement, and the M category signifies the presence of distant metastases.

Stages	Details
T stage	
Tx	The tumor cannot be assessed
Tis	Carcinoma in situ
Ta	Non-invasive carcinoma
T1	Lamina propria invasion
T2	Spongiosum, prostate, or periurethral muscle invasion
T3	Cavernosum, vagina, or bladder neck invasion
T4	All regional nodes are negative
N stage	
N0	All regional nodes are negative
N1	Single positive node <2 cm
N2	Single positive node >2 cm or multiple nodes
M stage	
M0	No metastasis
M1	Distant metastasis

Grading of urothelial urethral carcinoma	
PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated
Grading of nonurothelial urethral carcinoma	
Gx	Tumor grade not assessable

G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

TNM = tumor-node-metastasis; WHO = World Health Organization.

Primary urethral cancer (PUC) is characterized by its irregular nature and difficulty in detection, often leading to late-stage diagnosis [18]. The primary methods for identifying PUC include physical examination, cystoscopy followed by tissue biopsy for confirmation, and imaging techniques. Due to its scarcity and elusive nature, this malignancy may go unnoticed until advanced stages, resulting in delayed treatment initiation. This postponement in intervention allows the disease to progress to a more complex state, ultimately reducing overall patient survival rates. Considering that better outcomes are linked to early identification and asymptomatic PUC [18,19], it is essential to detect these tumors before symptoms appear. To evaluate local clinical staging and exclude the possibility of colorectal or gynecological cancers, a bimanual physical examination should be performed [21].

Diagnostic imaging

In patients with urethral carcinoma, radiography can be employed to evaluate the extent of local tumor growth, identify lymphatic spread, and detect distant metastases. Identifying and categorizing urethral cancer can be accomplished through the use of several diagnostic methods, including a biopsy of the tumor, as well as imaging techniques such as MRI scan and CT scan. [25]. For imaging studies, it is strongly advised to conduct CT scans of the thorax, abdominal region, and pelvic area. These imaging techniques are essential for evaluating soft tissue and lymph node involvement, as well as detecting any remote metastases. A thorough CT examination should include both pre-contrast and post-contrast imaging and delayed-phase scans to enable a thorough evaluation of the entire urinary system. Recent studies have demonstrated that MRI surpasses other imaging techniques in detecting disease onset, owing to its exceptional sensitivity in evaluating local tumor involvement and monitoring responses to chemoradiotherapy [26,27].

Treatment of PUC

The male urethra has anterior and posterior sections, with lymphatic drainage differing between the two. Anterior lymph flows to the inguinal nodes before reaching the pelvic nodes, while posterior lymph drains directly to the pelvic nodes. Urethral tumours with cell type, with the bubo membranous urethra most commonly affected (60%), followed by the penile urethra and prostate. Urothelial carcinoma is the predominant type (77.6%), with histological variations based on location. Symptoms include dysuria, urinary retention, and perineal pain.

The female urethra, shorter at 3-4 cm, is divided into anterior and posterior sections with distinct lymphatic pathways. Urothelial cancer is highly prevalent, with adenocarcinoma more frequent in younger women. Adenocarcinoma from paraurethral glands has clear cell and columnar/mucinous variants, with distinct immunohistochemical markers. Most women with PUC present with urinary symptoms or recurrent infections.

Treatment of PUC in males

No specific treatment guidelines exist for urethral CIS, which resembles bladder CIS more than penile CIS. Without treatment, urethral CIS leads to lymph node involvement in 50% of cases. Surgical

urethral removal to achieve clear margins is a key approach, and lymph node dissection is recommended for lymphadenopathy or high-grade disease to improve survival outcomes.

Distal urethral tumours have better survival rates than proximal ones. Penis-preserving surgery for distal urethral carcinoma has shown no local recurrence with margins under 5 mm in select cases, though risks increase with positive proximal margins or lymphatic invasion. Organ-sparing treatments should be reserved for carefully selected patients.

For men with urethral tumours, treatment includes urethral resection, with or without cystoprostatectomy. Low-grade lesions may undergo transurethral resection, while T2 lesions often require penectomy and pelvic lymphadenectomy. Proximal tumours generally result in poor outcomes and may necessitate chemoradiotherapy.

Treatment of PUC in females & Anterior Urethra

Treatment strategies for anterior female PUC are determined by the extent of the tumor. For small tumors located in the distal urethra, laser therapy or endoscopic resection may be employed. Exophytic tumors can be addressed through partial urethrectomy. Nevertheless, there is limited research supporting the effectiveness of urethral-sparing approaches for local control. A study conducted by DiMarco et al. revealed five-year survival rates ranging from 64% to 66%. Common post-treatment complications included urinary incontinence (42%) and retention (8%).

For advanced cases, bladder-preserving surgeries, such as transvaginal radical urethrectomy, offer local cure potential. Radical urethrectomy provides the best outcomes for brachytherapy and alternative, achieving a five-year survival rate of 71-74%. However, complications like radiation cystitis and urethral strictures occur in 16-49% of cases.

Posterior Urethra

When comparing primary urethral carcinoma (PUC) of the anterior and posterior female urethra, patients receiving surgical, radiotherapy, or combinatory treatments exhibited significantly inferior outcomes for posterior PUC. Specifically, the five-year 25% versus 54%, and disease-specific survival rates were 46% against 69%. The surgical protocol for anterior pelvic exenteration necessitates extensive pelvic lymph node dissection and resection of multiple organs; however, evaluating aggressive surgical outcomes is complicated by concurrent therapies. A study by Dalbagni et al. indicated a median post-cystectomy survival of 36 months, with another investigation revealing five-year survival rates of 39% and 52% respectively. Alternatively, Milosevic et al. examined radiation therapy alone, reporting a 37% relapse-free rate and a 20% cause-specific survival rate over 7.6 years, with brachytherapy not enhancing outcomes in advanced cases. Complications from radiation therapy were prevalent, with a significant percentage of patients experiencing adverse effects, highlighting the necessity for multimodal treatment strategies to optimize outcomes in advanced PUC.

Follow-up

Managing PUC patients necessitates individualized follow-up based on each patient's specific risk factors. Nevertheless, comprehensive guidelines for surveillance protocols are currently lacking. The European Association of Urology recommendations only indicate that patients who undergo urethra-preserving procedures should receive more intensive follow-up care [38].In one research, the PUC monitoring protocol encompassed outpatient consultations, urine cytology examinations, urethrocystoscopy procedures, uroflowmetry, and cross-sectional imaging. These were conducted 3-6 months after surgery and

subsequently every 6 months for a minimum of 2 years [39]. A separate investigation monitored PUC patients initially every 2-4 weeks in an outpatient setting, followed by biannual check-ups. For patients who underwent extensive urethral reconstruction, a comprehensive follow-up regimen was implemented. This included laboratory assessments, uroflowmetry, regressive urethrography, and annual urine cytology tests [40].

Summary

Primary urethral carcinoma (PUC) is an exceptionally rare malignancy, representing less than 1% of all cancers. It encompasses three major histological subtypes: urothelial carcinoma (UC), squamous cell carcinoma (SCC), and adenocarcinoma (AC). In males, SCC accounts for 12–30% of cases and AC for 5–16%, whereas in females, UC predominates (45%), followed by AC (29%) and SCC (19%). Adenocarcinoma is identified as the most aggressive subtype, often linked to lymph node metastasis and poorer outcomes. The disease typically presents in individuals above 60 years of age, with a slightly higher incidence among African Americans.

Early-stage PUC is often asymptomatic, leading to delayed diagnosis and advanced-stage presentation. Common symptoms include haematuria, urinary obstruction, pain during intercourse, and recurrent urinary tract infections. Clinical evaluation involves physical examination (digital rectal or pelvic exam), cystoscopy, and biopsy. Urinary cytology demonstrates variable sensitivity depending on tumor histology, being more effective for UC than SCC. Imaging modalities such as CT and MRI are crucial for assessing local invasion, lymph node involvement, and distant metastasis. MRI is particularly advantageous for evaluating tumour extent and treatment response.

PUC staging follows the TNM system, with grading based on histological differentiation. Management depends on tumour location, stage, and patient sex. In men, distal urethral tumours may be managed with organ-sparing surgery if margins are clear, while proximal tumours often necessitate penectomy or chemoradiotherapy. In women, treatment varies according to tumour site: anterior urethral tumours may be treated with laser ablation or partial urethrectomy, whereas advanced or posterior tumours often require radical urethrectomy or exenteration. Radiation therapy may serve as a primary or adjunctive treatment but carries risks of complications such as cystitis and strictures.

Prognosis is influenced by tumour stage, location, and histological type. Generally, anterior urethral tumours have better outcomes than posterior ones. Five-year survival rates range between 25% and 70%, depending on the treatment modality and stage. Post-treatment follow-up is essential due to the risk of recurrence. Although no standardized surveillance protocol exists, periodic cystoscopy, urine cytology, uroflowmetry, and imaging every 3–6 months are commonly recommended.

Overall, the rarity of PUC has limited large-scale research, resulting in non-uniform treatment strategies. Early detection through vigilant clinical evaluation and multimodal management involving surgery, radiotherapy, and chemotherapy can improve survival outcomes. Multicentric collaborative studies are needed to establish standardized diagnostic and therapeutic guidelines for this uncommon urological malignancy.

Conclusion

When addressing PUC, it is essential to consider the tumour's gravity, clinical characteristics, and site. In contrast, those with more advanced conditions should receive an optimal combination of treatments. To explore more effective PUC management strategies, increased collaboration among multiple institutions is necessary in the future.

References

1. Zinman LN, Vanni AJ. Management of proximal primary urethral cancer: should multidisciplinary therapy be the gold standard? Urol Clin North Am 2016;43:505-13.
2. Swartz MA, Porter MP, Lin DW, et al. Incidence of primary urethral carcinoma in the United States. Urology 2006;68:1164-8.
3. Gakis G, Witjes JA, Comperat E, et al. EAU guidelines on primary urethral carcinoma. Eur Urol 2013;64:823-30.
4. Dalbagni G, Zhang ZF, Lacombe L, et al. Female urethral carcinoma: an analysis of treatment outcome and a plea for a standardized management strategy. Br J Urol 1998;82:835-41.
5. Visser O, Adolfsson J, Rossi S, et al. Incidence and survival of rare urogenital cancers in Europe. Eur J Cancer (Oxford, England : 1990). 2012;48(4):456–64.
6. Swartz MA, Porter MP, Lin DW, et al. Incidence of primary urethral carcinoma in the United States. Urology. 2006;68(6):1164–8.
7. Rabbani F. Prognostic factors in male urethral cancer. Cancer. 2011;117(11):2426–34.
8. Derksen JW, Visser O, de la Riviere GB, et al. Primary urethral carcinoma in females: an epidemiologic study on demographical factors, histological types, tumour stage and survival. World J Urol. 2013;31(1):147–53.
9. O. Visser, J. Adolfsson, S. Rossi, J. Verne, G. Gatta, M. Maffezzini, et al. the RARECARE working group. Incidence and survival of rare urogenital cancers in Europe Eur J Cancer, 48 (2012), pp. 456- 464
10. M. Aron, S. Park, B.M. Lowenthal, S. Gupta, D. Sahoo, J.C. Cheville, et al. Primary female urethral carcinoma: proposed staging modifications based on assessment of female urethral histology and analysis of a large series of female urethral carcinomas Am J Surg Pathol, 44 (2020), pp. 1591-1601M.
11. Wenzel, L. Nocera, C. Collà Ruvolo, C. Würnschimmel, Z. Tian, S.F. Shariat, et al. Incidence rates and contemporary trends in primary urethral cancer. Cancer Causes Control, 32 (2021), pp. 627-634
12. Cassell 3rd Ayun, Burgess Manobah, Soeghen Willie Diagnostic and therapeutic challenges of rare urogenital cancers: urothelial carcinoma of the renal pelvis, ureters and urethra World J Oncol, 12 (2021),pp. 20-27
13. J. Krukowski, M. Czajkowski, J. Kłącz, O. Wawrzaszek, M. Gołębiewska, M. MatuszewskiPrimary urethral carcinoma— unexpected cause of urethral stricture. Case report and review of the literature Med Ultrason, 21 (2019),pp. 494-496
14. Janisch F, Abufaraj M, Fajkovic H, Kimura S, Iwata T, Nyirady P, et al. Current diseasemanagement of primary urethral carcinoma. Eur Urol Focus 2019;5:722e34.
15. Amin MB, Edge SB. AJCC cancer staging manual. Springer, 2017.
16. Edge SB. AJCC cancer staging manual. Springer 2010;7:97-100.
17. Stewart SB, Leder RA, Inman BA. Imaging tumors of the penis and urethra. Urol Clin North Am 2010;37:353-67.
18. Dalbagni G, Zhang ZF, Lacombe L, et al. Male urethral carcinoma: analysis of treatment outcome. Urology 1999;53:1126-32.
19. Boorjian SA, Kim SP, Weight CJ, et al. Risk factors and outcomes of urethral recurrence following radical cystectomy. Eur Urol 2011;60:1266-72.
20. Karnes RJ, Breau RH, Lightner DJ. Surgery for urethral cancer. Urol Clin 2010;37:445e57.
21. Barkan GA, Wojcik EM, Nayar R, Savic-Prince S, Quek ML, Kurtycz DF, et al. The Paris System for reporting urinary cytology: the quest to develop a standardized terminology. Acta Cytol 2016;60:185e97.

22. Wang N, Min J, Wei Q, Tan W, Dang Q. Primary urothelium carcinoma of the distal urethra in a male: case report and literature review. Onco Targets Ther 2020;13:6011e5.
23. Gakis G, Efstathiou JA, Daneshmand S, Keegan KA, Clayman RH, Hrbacek J, et al. Oncological outcomes of patients with concomitant bladder and urethral carcinoma. Urol Int 2016;97:134e41.
24. Walsh E, Kelly N, Daly P, Shah N, Cullen I. Urethral cancer managed with phallus preserving surgery: a case report. J Med Case Rep 2021;15:91.
25. Stewart SB, Leder RA, Inman BA. Imaging tumors of the penis and urethra. Urol Clin North Am. 2010;37(3):353–367. doi:10.1016/j. ucl.2010.04.014
26. Gourtsoyianni S, Hudolin T, Sala E, Goldman D, Bochner BH, Hricak H. MRI at the completion of chemoradiotherapy can accurately evaluate the extent of disease in women with advanced urethral carcinoma undergoing anterior pelvic exenteration. ClinRadiol. 2011;66(11):1072–1078. doi:10.1016/j.crad.2011.07.039
27. Ray B, Canto AR, Whitmore WF. Experience with primary carcinoma of the male urethra. J Urol. 1977. doi:10.1016/S0022-5347(17) 58546-8
28. Rabbani F. Prognostic factors in male urethral cancer.Cancer.2011;117(11):2426–2434.doi:10.1002/cncr.25787
29. Karnes RJ, Breau RH, Lightner DJ. Surgery for urethral cancer. Urol Clin North Am. 2010;37(3):445–457. doi:10.1016/j.ucl.2010.04.011
30. Kent M, Zinman L, Girshovich L, Sands J, Vanni A. Combined chemoradiation as primary treatment for invasive male urethral cancer. J Urol. 2015;193(2):532–537. doi:10.1016/j.juro.2014.07.105
31. Dalbagni G, Zhang ZF, Lacombe L, Herr HW. Male urethral carcinoma: analysis of treatment outcome. Urology. 1999;53 (6):1126–113doi:10.1016/S0090-4295(98)00659-1
32. Carroll PR, Dixon CM. Surgical anatomy of the male and female urethra. Urol Clin North Am. Weghaupt K, Gerstner GJ, Kucera H. Radiation therapy for primary carcinoma of the female urethra: a survey over 25 years. Gynecol Oncol. 1984. doi:10.1016/0090-8258(84)90060-X
33. Milosevic MF, Warde PR, Banerjee D, et al. Urethral carcinoma in women: results of treatment with primary radiotherapy. RadiotherOncol.2000;56(1):29–35. doi:10.1016/S0167-8140(00)00208-5
34. Dalbagni C, Zhang ZF, Lacombi- L, Hi-Rr HW. Female urethral carcinoma: an analysis of treatment outcome and a plea for a standardized management strategy. Br J Urol. 1998;82(6):835–841. doi:10.1046/j.1464-410X.1998.00878.x
35. Dayyani F, Pettaway CA, Kamat AM, Munsell MF, Sircar K, Pagliaro LC. Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. Urol Oncol Semin OrigInvestig. 2013.doi:10.1016/j.urolonc.2012.01.011