Management of Proximal Primary Urethral Cancer

Should Multidisciplinary Therapy Be the Gold Standard?

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KEYWORDS

• Urethral carcinoma • Primary • Urethral cancer • Multimodal therapy • Surgery • Chemotherapy • Radiotherapy

KEY POINTS

- Primary urethral cancer is rare, with proximal lesions accounting for 66% of diagnosed urethral tumors.
- Risk factors for survival include age, black race, tumor size, stage and grade, nodal involvement and metastasis, proximal location, histology, and the presence of concomitant bladder cancer.
- Patients with proximal urethral cancer who receive neoadjuvant multimodal therapy demonstrate improved survival compared with surgery with or without adjuvant chemotherapy.

INTRODUCTION

Primary urethral cancer (PUC) of the proximal urethra is an exceeding rare tumor, whose natural history is particularly aggressive. These tumors occur more commonly in men, and differ by location and histologic subtype. Patient symptoms often include urinary obstruction, irritative voiding symptoms, or hematuria. Risk factors include urethral strictures, chronic irritation, radiation treatment, human papilloma virus, and urethral diverticula (females). Most PUC are localized; however, 30% to 40% of patients present with regional lymph node metastasis. Although surgery and radiation treatment are options for early stage or distal urethral disease, advanced-stage and proximal PUC require multimodal treatment to optimize survival. However, controversy exists regarding the optimal multidisciplinary treatment strategy for male squamous cell carcinoma (SCC) of the urethra. Multi-institutional studies are critical to delineate the optimal treatment strategy in the future. This article examines this difficult disease, with a critical evaluation of the literature and an emphasis on the optimal treatment strategies for proximal PUC.

Epidemiology

PUC is exceeding rare, accounting for less than 1% of all malignancies.[1–3] The incidence of PUC increases with age, peaking in the greater than 75 year age group, and is more common in African Americans.[3] According to the Surveillance, Epidemiology, and End Results database, 4.3 per million and 1.5 per million men and women, respectively, in the United States develop PUC yearly.[3] This is slightly higher than the reported rates of PUC in Europe, where 1.6 per million men and 0.6 per million women develop PUC yearly.[2]

Etiology

The risk factors for developing PUC differ between men and women.[4–13] Risk factors for men include

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urethral stricture, chronic irritation from intermittent catheterization, prior radiation therapy, and sexually transmitted disease (human papillomavirus serotype 16). This is in contrast to women, whose risk factors for developing PUC include the following[14–17]: urethral diverticulum, chronic irritation and infection with human papillomavirus, and recurrent urinary tract infections.

Histology

The histologic subtypes of PUC reflect the gender and location of the primary tumor. In men, urothelial cancer is the most frequently seen histologic type, accounting for 47% to 73% of tumors, whereas SCC (12%–30%) and adenocarcinoma (5%–16%) account for the remaining cases.[2,3,18,19] Females have a slightly different incidence of tumor type. Although urothelial cancers are the most common, occurring in 45% of cases, adenocarcinoma is more prevalent than SCC, occurring in 29% and 19% of cases, respectively.[20]

Staging and Classification Systems

PUC is staged according to the TNM classification system, and is different depending on whether the tumor occurs in the prostatic urethra, or more distally[21] (**Table 1**). Although not directly measured by the TNM classification system, tumor location is an important factor that plays an integral role in PUC outcomes. PUC tumor locations are often referred to as occurring either proximally or distally. Although this is nonspecific nomenclature, its use has been propagated in the literature. Proximal PUC refer to tumors of the prostatic, membranous, and bulbar urethra, whereas distal tumors involve the penile and fossa navicularis urethra.

These anatomic considerations have treatment implications because of the varied lymphatic drainage of the urethra. The lymphatic drainage of the anterior urethra (bulbar, penile, and fossa navicularis urethra) is to the inguinal lymph nodes and subsequently pelvic lymph nodes, whereas the posterior urethra (prostatic and membranous urethra) drain into the pelvic lymph nodes. In women, the distal two-thirds drain into the superficial and deep inguinal lymph nodes, whereas the proximal third of the urethra drains into the pelvic lymph nodes.[22]

DIAGNOSIS

Presentation

Men may present with obstructive (41%–48%) or irritative urinary symptoms (20%), hematuria or

Table 1
TNM classification for urethral carcinoma

T: Primary Tumor	
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T0	No evidence of primary tumor
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following structures: corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following structures: corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck
T4	Tumor invades other adjacent organs
Primary Tumor in Prostatic Urethra	
Tx	Primary tumor cannot be assessed
Tis pu	Carcinoma in situ in the prostatic urethra
Tis pd	Carcinoma in situ in the prostatic ducts
T0	No evidence of primary tumor
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following structures: corpus spongiosum, prostatic stroma, periurethral muscle
T3	Tumor invades any of the following structures: corpus cavernosum, beyond prostatic capsule, bladder neck
T4	Tumor invades other adjacent organs
N: Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single lymph node $\leq$2 cm in greatest dimension
N2	Metastasis in a single lymph node $\geq$3 cm in greatest dimension
M: Distant Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Abbreviations: M, metastasis; N, lymph nodes; Pd, prostatic ducts; Pu, prostatic urethra; T, tumor.

From Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumors. UICC International Union Against Cancer. 7th edition. Wiley-Blackwell; 2009.