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Review

A brief review on the diagnostic and therapeutic principles of primary urethral cancer

Hengchuan Su ^{a,b}, Yao Zhu ^{a,b,*}, Dingwei Ye ^{a,b,*}

^a Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, China

^b Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

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Abstract *Objective:* Primary urethral carcinoma (PUC) is a rare malignant carcinoma but with limited therapeutic options. This review aims to provide an overview of the current strategies on this patient settings.

Methods: Recent literature ranging from January 1987 and December 2021 was assessed through PubMed search to assess the diagnostic and therapeutic principles of PUC.

Results: A complete of examination including cystoscopy, imaging, and biopsy should be conducted for these patients. Once diagnosed, the clinical decision of PUC should be made according to the tumor location, pathological pattern, and extent of the tumor. For patients with superficial and distal urethral lesions, organ sparing approaches or radical reconstructive procedures can be utilized. While for more advanced disease or nodal involvement, an optimal multimodal treatment strategy consisted of surgery and radiochemotherapy should be adopted. For patients with urothelial carcinoma of the prostate, the management including transurethral resection of the prostate followed by bacille Calmette-Guerin or radical cystoprostatectomy should depend on the infiltration depth of PUC.

Conclusion: A complete of examination is important for the diagnosis of PUC. The management of PUC should be determined by the location, pathological pattern, and extent of the tumor. More multi-institutional collaborations should be held to investigate better treatment modalities for PUC.

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* Corresponding author. Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, China.

E-mail address: mailzhuyao@163.com (Y. Zhu), dwyeli@163.com (D. Ye).

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1. Introduction

Primary urethral carcinoma (PUC) is a rare malignant tumor and accounts for under 1% of all malignancies. The Surveillance, Epidemiology, and End Results (SEER) registry showed in Europe the annual incidence of PUC is estimated to be 1.6 per million in men and 0.6 per million in women with an age-standardized ratio, while in the USA, the annual incidence is 4.3 per million in men and 1.5 per million in women [1,2]. African Americans exhibited highest incidence rate (3.33/1 000 000) followed by Caucasians (1.72/1 000 000), Hispanics (1.57/1 000 000), and other race groups (1.57/1 000 000), in that order [3]. According to an analysis by the SEER program, the peak incidence of PUC was in the more than 75 years of age group (7.6 per million) and almost negligible in ages less than 55 years [4].

Due to the rarity of PUC, the data regarding the diagnostic and therapeutic principles were limited. The purpose of this article is to review the current literature about PUC and help to improve the diagnosis and treatment planning of PUC patients.

2. Diagnostic assessment

2.1. Clinical history

PUC patients would show no specific symptoms in early stages and can be mistakenly diagnosed with more common urethral strictures, especially for female patients, with greater than 70% of women reporting recurrent urinary tract infections, irritative voiding symptoms, or dyspareunia. Once diagnosed, most female patients would harbor T3-4N0M0 (29%) stage disease while most male patients would harbor T1N0M0 (32%) stage disease [5]. Most PUC patients would initially present with visible hematuria or bloody urethral discharge symptoms. Locally advanced PUC patients (T3/T4) (45%–57%) may present with further symptoms, such as an extra-urethral mass, bladder outlet obstruction, pelvic pain, urethrocutaneous fistula, abscess formation, or dyspareunia [6].

2.2. Clinical examination

Clinical evaluation of patients included a rectal exam for men and pelvic examination with palpation of the urethra in women. In men, the suspicious external genitalia indurations may be palpated or digital rectal examination by physical examination. In women, bilateral inguinal palpation should be performed for local clinical staging to assess the presence of enlarged lymph nodes (LNs), describing location, size, and mobility [7]. Bimanual examination should also be performed for local clinical staging and to exclude the presence of colorectal or gynecological malignancies [8].

2.3. Urinary cytology

Cytological assessment of urine specimens could be used to detect the PUC with sensitivity of 50%–80% [9]. Detection rates of urinary cytology depended on the pathological

type. For male patients, the sensitivity values for urothelial carcinoma (UC) and squamous cell carcinoma (SCC) were reported to be 80% and 50%, respectively. While for female patients, the sensitivity values for UC and SCC were found to be 50% and 77%, respectively [10].

2.4. Cytological assessment of urine specimens

Urethrocystoscopy and biopsy could be used to assess the urethral tumor extent, location, and underlying histology [10]. Biopsy sites (proximal or distal end) should be marked and sent together with clinical information to the pathologist. Urethrocystoscopy could also be used to exclude the presence of concomitant bladder tumors, since urethral cancer could also originate from the bladder through micrometastasis [11]. Transurethral resection of larger lesions could be performed for histological diagnosis. In patients with suspected UC of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra could help the diagnosis of UC of the prostate, which would be detailed below.

2.5. Diagnosis of UC of the prostate

Prostatic UC may involve the mucosa of the prostatic transitional urothelium, the prostatic ducts, acini, and/or prostatic stroma. Urethrocystoscopy and biopsy of the urethral lesion are fundamental for the diagnosis of UC of the prostate. Cystoscopy is considered the “gold standard” for monitoring PUC of the prostate urethra, with diagnostic sensitivity of 83.3% and specificity of 95.1% [12,13]. Donat et al. [14] observed the sensitivity of transurethral biopsy for prostatic stromal invasion was 56% and specificity was 92% in a study of 246 male patients who underwent a radical cystectomy. von Rundstedt et al. [15] found transurethral resection biopsy could detect carcinoma *in situ* (CIS) and invasive UC arising from the prostatic urethra in 72 cases with 71.3% sensitivity and 100% specificity. Resectoscope loop biopsy of the prostatic urethra (between the 5 and 7 o’ clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate. Further prospective studies about better approach for evaluative prostatic urethral biopsies are needed.

2.6. Diagnostic imaging

Radiological imaging could help to assess local tumor extent and detect lymphatic and distant metastatic spread in urethral carcinoma patients. A combination of tumor biopsy, magnetic resonance imaging (MRI), and computed tomography (CT) could help the diagnosis and stage of urethral cancer [16].

The accuracy values of CT for clinical tumor and nodal staging were found to be 72.9% and 70.6%, respectively. If imaging of the remainder of the urothelium is required, CT urography should be performed [17]. The CT scan should include pre- and post-contrast images along with delayed series to allow for evaluation of the entire urinary tract.

MRI could provide superior soft tissue contrast compared with CT and evaluate local tumor extent and presence of

regional LN metastases, especially for inguinal and pelvic LNs. In addition, MRI could monitor tumor response to neoadjuvant chemoradiotherapy [18]. The previous study has observed MRI could have a very high accuracy of approximately 93% for clinical nodal staging to predict pathological LN involvement [19].

3. Treatment of PUC

The histological type of PUC is associated with gender and location of tumor. The male urethra is subdivided into anterior (fossa navicularis, penile urethra, and bulbar urethra) and posterior (membranous urethra and prostatic urethra) segments. Carcinomas in the prostatic urethra are primarily urothelial or transitional cell in origin, while carcinomas in the penile and bulbomembranous urethra are more likely to be squamous cell. In a study which included 2065 PUC patients, UC (53.6%–78%), SCC (12%–34.8%), and adenocarcinoma (AC) (5%–11.6%) were the most common histological types of male PUC [20].

While in women, it is divided into an anterior segment and a posterior segment. The proximal third of the female urethra is lined by transitional urothelium while the distal two thirds are lined by stratified squamous urothelium. Two recent studies which respectively included 2137 and 419 PUC patients showed AC is the predominant histological type (38%–46.7%) in female followed by SCC (25.4%–28%), UC (24.9%–28%), and other histological entities (6%) [21,22].

According to the RARECARE project, the 1- and 5-year overall survival (OS) rates of PUC patients are 71% and 54% in Europe, respectively [23]. Prognostic factors of PUC patients include age, race, tumor-node-metastasis-stage, tumor location, treatment modality, presence of concomitant bladder cancer, location of recurrence, and underlying histology [24,25]. In the study by Derksen et al. [26], AC had shorter median survival than other histological types, and the 5-year OS rates of SCC, UC, and AC were 64%, 61%, and 31%, respectively. Meis et al. [27] also reported advanced stage and metastasis were respectively found in 64% and 18% of AC patients, and within 2 years 64% died of the disease. Since advanced stage was present in 65% and LN involvement was present in 19% of AC patients, AC type has stronger invasion and metastasis potential. In addition, LN metastasis is more likely to happen in SCC and AC compared to UC. As a result, tumor histology may exert an important influence on the prognosis and management of PUC. No matter which type of pathology, surgery for the primary tumor was essential and conferred a survival advantage for non-metastatic PUC patients [28].

3.1. Localized PUC in males

Currently, there are no treatment guidelines that specifically address urethral CIS. However, urethral CIS has a potentially lethal behavior and may have some biological similarity with bladder CIS rather than penile CIS. If the urethral CIS is untreated, half of the cases will progress to be nodal involvement [29]. Surgical excision of the urethra to achieve negative margins could be conducted as an appropriate management strategy when feasible [30].

LN dissection in the presence of detectable lymphadenopathy and other features of high-grade disease such as lymphovascular invasion are advised and could result in survival benefits [31].

Distal urethral tumors exhibit significantly improved survival rates compared with proximal tumors. In the previous study, penile-preserving surgery was not associated with local recurrence for those patients with pT1-3N0-2 distal urethral carcinoma, even with less than 5 mm resection margins [32]. In a retrospective study of 18 patients with tumors limited to the meatus, fossa navicularis, and penile urethra, they received penile preserving surgery and no local recurrences were observed at a median follow-up of 26 months [33]. However, some study found penis-preserving surgery may be associated with a higher risk of progression in patients with positive proximal margins, especially for patients with lymphovascular and perineural invasion of the primary tumor [34]. As a result, organ-sparing treatment should only be offered to highly selected individuals based on histopathological analysis of proximal urethral specimen [35].

If the tumor was located in bulbous urethra, urethrectomy in men with or without cystoprostatectomy should be conducted. For low stage lesions, transurethral resection can be appropriate. For T2 stage lesions, total penectomy and urethrectomy with possible cystoprostatectomy, and pelvic lymphadenectomy were needed and could allow local disease to be controlled [36]. However, despite these treatments, proximal PUC was associated with poor survival outcomes and progression to distant metastatic disease within 6 months and needed adjuvant and neoadjuvant radiochemotherapy, especially for SCC [37].

3.2. Localized urethral carcinoma in females

Complete surgical excision of the primary lesion is important for localized urethral carcinoma in women. Ablative surgical techniques, *i.e.*, partial urethrectomy or laser in women can be performed for small anterior urethral tumors. Dimarco et al. [38] found partial urethrectomy could result in a high urethral recurrence rate (22%) and a 5-year disease-specific survival of 66%. For bigger urethral tumors, radical urethrectomy should be conducted for better survival benefit. Radical urethrectomy should remove urethra with a wide margin of periurethral tissue and the bulbocavernous muscle up to the bladder neck and pelvic bone. Complete extirpative surgery could lead to a 5-year disease-specific survival of 52% [38]. A suprapubic urostomy for urinary diversion in these cases should be needed.

In contrast to the anterior urethra, patients with the posterior urethral tumor has a lower 5-year OS (54% vs. 25%) and disease-specific survival (69% vs. 46%) [39]. For these patients, surgical management should include anterior pelvic exenteration, cystectomy, urethrectomy, hysterectomy, oophorectomy, and extended pelvic lymphadenectomy. The addition of vulvar or vaginal resections may also be needed in order to achieve a negative margin [40]. Radiation therapy using brachytherapy, external beam radiation therapy, or both is an acceptable organ-sparing alternative to surgery and could help to maintain integrity and function of the lower urinary tract in women with PUC.

In one study, the addition of brachytherapy to external beam radiation therapy reduced the risk of local recurrence by a factor of 4.2 [41]. However, Son et al. [42] revealed no benefits in OS for patients treated with surgery combined with radiation therapy for Stage T1-T2, limiting recommendation for a combined therapeutic approach.

3.3. Preoperative cisplatin-based chemotherapy or radiotherapy

For those PUC patients with locally advanced T3 or T4 stage but no clinical nodes, NCCN guidelines have recommended cisplatin-based combination chemotherapy followed by surgical consolidation, which could avoid treatment delays due to postoperative complications that may exist in the setting of adjuvant chemotherapy [43,44]. Dayyani et al. [45] found histology specific neoadjuvant chemotherapy followed by radical surgery resulted in an overall response rate of 72% and longer OS (25.6 months). In a series of 124 patients, 39 (31%) were treated with perioperative platinum-based chemotherapy for advanced PUC and had improved OS compared with those who underwent upfront surgery with or without adjuvant chemotherapy [46,47].

As for preoperative radiotherapy, some study found that neoadjuvant radiotherapy could improve local control but had no impact on survival [48]. The potential risk for complications and worse healing caused by preoperative RT may also decrease the use of preoperative radiotherapy. The role of perioperative RT needs to be explored for PUC.

3.4. Multimodal treatment in advanced PUC

For advanced SCC of the urethra, the low survival rates for surgical monotherapy (0–40%) and primary radiation monotherapy (5-year survival of 0–25%) have prompted investigation of multimodal treatment approaches [49,50]. NCCN guidelines have recommended chemoradiation as the preferred treatment for SCC node-positive patients [43]. In a cohort of 2614 patients with non-metastatic PUC patients, multimodal therapy including surgery and radiation was associated with better OS compared to surgery alone in patients of transitional cell carcinoma ($p < 0.01$) (surgery + RT vs. surgery: hazard ratio 0.45, 95% confidence interval 0.26–0.77) [42]. Different pathological types of PUC may have different benefits from multimodal therapy. UC and AC may benefit more from the combined surgery and radiation than patients with SCC.

For locally advanced SCC, coordinated chemoradiation therapy may offer a potential for genital preservation [51]. Cohen et al. [52] have observed local RT with concurrent chemotherapy (5-fluorouracil and mitomycin C) could replace surgery in locally advanced SCC and 83% of the patients had a complete response to the primary chemoradiation therapy protocol, and the 5-year OS and disease-specific survival rates were 60% and 83%, respectively. For recurrent PUC, multimodal therapy including surgery or radiation may also bring benefit. Gakis et al. [53] found salvage surgery or RT-based salvage therapy

could significantly improve 3-year OS (38.0%) compared to patients who received no salvage therapy after recurrence ($p < 0.05$).

3.5. Management of regional LNs

Distinct from penile cancer, clinically enlarged LNs in PUC patients are more likely to be associated with metastatic disease and biopsy or inguinal lymphadenectomy should be proposed. For PUC patients who are clinically N0, there is no clear role for prophylactic inguinal lymphadenectomy. Wertz et al. [54] analyzed 725 men with urethral SCC and found the node positivity rate in patients with T1 to T4 and N0 is 9%, and did not recommend routine prophylactic inguinal lymphadenectomy for patients with urethral SCC who are clinically N0.

Many advanced PUC patients would present with nodal metastasis and have a poor prognosis with a lower overall and cancer-specific survival [55]. For PUC patients with clinically enlarged LNs, multimodal treatment including regional LN dissection, RT, or chemotherapy could be used to control nodal metastasis. Regional lymphadenectomy could be used as initial treatment since cure might be achievable by surgery followed by RT or chemotherapy.

3.6. Treatment of UC of the prostate

The management of UC of the prostate is similar to urothelial cell carcinoma of the bladder. For patients with Ta or Tis prostatic urethral carcinoma, local treatment with extensive transurethral resection of the prostate (TURP) and subsequent bacille Calmette-Guerin (BCG) instillation is effective. BCG could reach a better complete remission for patients compared with other intravesical therapy (63% vs. 47%) [56]. Compared with BCG alone, patients who had TURP and BCG had better improvement in complete response (66% vs. 95%) [57]. TURP could open the bladder neck and help BCG to penetrate into the prostate. If patients were recurrent or not responded to BCG, radical cystoprostatectomy should be conducted. After TURP and BCG, 18%–28% of PUC patients would present with disease recurrence and ultimately needed cystoprostatectomy and the OS ranged from 66% to 91% at a median follow-up of 27–90 months [58].

In patients with extensive ductal or stromal involvement, radical cystoprostatectomy with extended pelvic lymphadenectomy should be pursued. Patients with prostatic stromal invasion had a higher nodal metastasis rate than those without and positive LNs in 50% of patients were found above the bifurcation of the iliac vessels [59]. No specific evidence recommended chemotherapy and radiotherapy in treatment for prostatic stromal invasion.

Orthotopic neobladder diversion was previously thought to be contraindicated in UC patients and may lead to recurrence. However, some studies have found the feasibility of this treatment and PUC patients with a neobladder had a lower probability of urethral recurrence compared with those with cutaneous diversion [60]. More studies are

still needed to clarify the value of orthotopic neobladder diversion for PUC patients of prostatic stromal invasion.

3.7. Metastatic disease

The literature which focuses on the management of metastatic PUC patients is limited. Systemic chemotherapy has been recognized as cornerstone of therapy for metastatic PUC. PUC with chemotherapy had longer survival than those without (14 months vs. 7 months) and chemotherapy use could act as an independent predictor of lower overall mortality, including AC and other variant histology subtypes, except metastatic SCC [61]. The chemotherapy in metastatic disease should be based on the histology of the tumor. If UC is the predominant pathological type, the treatment could refer to metastatic bladder cancer, such as gemcitabine plus cisplatin or high dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin plus granulocyte-colony-stimulating factor scheme. Immunotherapy has been attempted in PUC patients in large clinical trial. However, in terms of response rates, no subgroup analyses are available [62].

4. Follow-up

The follow-up is important for the management of PUC patients and it should be based on the patients' individual risk factors. However, no clear guidelines have systematically explored the surveillance regimens. European Association of Urology guidelines have only recommended a more extensive follow-up for those receiving urethra-sparing surgery [25]. In one study, surveillance for PUC included an out-patient visit, urinary cytology, urethroscopy, uroflow, and cross-sectional imaging 3–6 months after surgery and subsequently every 6 months for at least 2 years [48]. In another study, PUC patients firstly received short-term follow-up with an outpatient clinic visit every 3–4 weeks and then semiannually. For those underwent extensive urethral reconstruction, long-term follow-up was performed including laboratory tests, uroflow, retrograde urethrography, and annual urine cytology [63].

5. Conclusion

The management of PUC should be determined by the location, pathological pattern, and extent of the tumor. For patients with superficial and distal urethral lesions, organ sparing approaches can be utilized whereas more advanced disease should be managed with an optimal multimodal treatment strategy. More multi-institutional collaborations in future should be held to investigate better treatment modalities for PUC.

Author contributions

Study concept and design: Yao Zhu, Dingwei Ye.

Data acquisition: Hengchuan Su.

Data analysis: Hengchuan Su.

Drafting of manuscript: Hengchuan Su.

Critical revision of the manuscript: Yao Zhu, Dingwei Ye.

Conflicts of interest

The authors declare no conflict of interest.

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