



## Review Article

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# Review on Organ Preserving Techniques in Patients with Urethral Carcinoma

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## Abstract

Tumors of the urethra are rare and often require radical surgery when dealing with locally advanced tumors to achieve adequate local control of the disease. In males, these procedures include partial or total penectomy for distal urethral carcinoma or total penectomy with cystoprostatectomy for proximal urethral carcinoma. In females with locally advanced urethral carcinoma, anterior exenteration may be required for better oncological outcomes. Patients diagnosed with urethral carcinoma at earlier stage may be amenable for genital sparing surgery which offers preservation of body image and better quality of life. We sought to review the current available literature describing different techniques of surgical management in patients with primary urethral carcinoma and subsequent survival and oncological outcomes.

**Keywords:** Organ preserving; Penile preserving; Urethral carcinoma

**Abbreviations:** AC: Adenocarcinoma; CRT: Chemoradiation Therapy; PUC: Primary Urethral Carcinoma; SCC: Squamous Cell Carcinoma; SEER: Surveillance Epidemiology and End Results; TUR: Transurethral Resection

## Introduction

Primary Urethral carcinomas (PUC) constitute a small percentage of all Urothelial tumors arising from the urinary tract and accounting for <1% of all malignancies in Europe [1]. In a review of PUC in the Surveillance, Epidemiology and End Results (SEER) database, the age adjusted incidence rate was 4.3 per million in men and 1.5 per million in women. The peaked incidence is at age group  $\geq 75$  year (7.6 per million) [2]. The predominant histologic type of PUC is Urothelial carcinoma (55%), followed by Squamous cell carcinoma (SCC; 21.5%) and Adenocarcinoma (AC; 16.4%) [2]. Various predisposing factors for male PUC have been reported including urethral strictures, chronic irritation subsequent to intermittent catheterization/urethroplasty, sexually transmitted diseases and external beam irradiation [3]. Urethral diverticula and recurrent urinary tract infections are associated with PUC in female [4]. In a SEER analysis over a period of 29 years, 1075 men and 540 women patients with PUC were identified, with annual age adjusted incidence rate of 4.3 per million and 1.5 per million for males and females respectively [5]. In the same analysis, the median 5 and 10-year overall survival rates was 46% and 29%

respectively. The cancer specific survival at 5 and 10 years was 68% and 60% respectively [5].

Clinical staging, size and location of the urethral lesion are the important determinants in the management options and prognosis of patients with PUC [6]. In the proximal urethra, tumors tend to be more advanced and have a poor outcomes with 5 year disease-free survival of 20-30% with radical surgery alone [7]. By contrast, distal tumors (penile and glanular) tend to be of low stage and have better outcomes with cure rates of 70%-90% after treatment [8]. The prior goal for the urologist is to achieve local control for patients with PUC by surgical excision. Subsequently, the standard approach for an invasive disease in males has been partial or total penectomy for distal urethral tumors, and total penectomy with cystoprostatectomy for proximal tumors [9]. While in females, total urethrectomy up to anterior exenteration has been traditionally performed in invasive tumors [10]. Recently, urethra-preserving surgery is starting to be applicable in selected patients primarily for the distal urethral tumors [11].

## Methods

A search strategy was performed to identify all published articles in peer-reviewed journals which describe different urethral preserving surgical techniques for patients with PUC from 1985 to November 2016. The search was conducted through PubMed, Web of Science and Cochrane Library Central Search. The search strategy included the following terms: “genital preservation”, “penile preserving surgery”, “organ sparing surgery”, “urethral carcinoma” and “invasive carcinoma of the urethra”. We considered English language publications not classified as case report, editorial, comment, letter or news. All pertinent studies collected were examined to extract relevant data pertained to conservative surgical therapy for PUC patients.

### Treatment of localized distal urethral carcinoma in male patients

Smith et al. [12] described different operative techniques in his 18-Patient series of urethral cancer. Patients included in the study were reported to have anterior PUC with varying stage (T1-3) and grade (G1-3). Six out of the 18 patients had lymph node positive disease. In urethral lesions visible at the urethral meatus, slitting of the ventral surface with biopsy of the lesion and application of topical chemotherapy (5% 5-fluorouracil) was done. The glandular urethra remained hypospadiac for at least 6 months to ensure local control. For confirmed T1 lesions, distal urethrectomy via bivalving and excision with 5-mm clear margin was done and then covered by buccal mucosal graft. The graft was quilted to the glanular spongiosum by 5/0 absorbable sutures with urethral catheter for 5 days. A second stage urethral closure over a urethral catheter performed at least 3 months later.

In the same study, Tumors extended into the glans was managed by glansectomy and hypospadias formation after excision of the urethra 5mm proximal to the tumor. The corporal head is then covered with partial thickness skin graft harvested from the thigh. Distal corpectomy was done in patients who had tumors invading the distal corpora. In this study, no local recurrences reported over a mean follow up period of 26 months (12).

### Treatment of localized urethral carcinoma in female patients

In female, local control is crucial to hinder local and systemic progression. In a long-term series of 27 female patients who had partial urethrectomy for PUC pT1-3, local recurrence with no bladder recurrence was reported in 6 (22%) patients [13]. In those who recurred, the 5 years post-recurrence mortality rate was 71%. More conservative management such as transurethral resection and laser ablation of small distal tumors demonstrate local failure rate of 16%, with a cancer specific survival rate of 50% [13]. Radiotherapy might be an alternative to conserving surgery for PUC female patients. Garden's et al reported on 97 women with PUC treated by radiation. The reported 5-year local control rate was 64% with 7-year cancer specific survival of 49%. Patients with locally advanced tumors, tumors involved the entire urethra or fixed primary lesion were associated with poorer survival ( $p<0.05$ ) [14]. Patients in this study received either external beam irradiation, brachytherapy or both (median, 65 Gy). Reported complications

after radiotherapy includes urethral stenosis, fistula, cystitis and/or hemorrhage.

### Treatment of advanced urethral carcinoma

Local tumor control can be achieved by cisplatin-based chemotherapy in advanced urethral carcinomas. Multidisciplinary approach comprising of chemotherapy and surgery is essential in managing locally advanced PUC for better oncological and survival outcomes. In the retrospective study of Dayyani et al. [15], 44 patients with advanced PUC received neoadjuvant cisplatin-based chemotherapeutic regimens according to the underlying histology. The most prevalent histological types were squamous cell carcinoma and adenocarcinoma. The local response rate to various regimens was 72% with median overall survival of 32 months for the entire group of patients. Better survival data reported in patients who received salvage surgery ( $n=27$ ) compared with those treated with chemotherapy alone (46.9 months vs. 21.7 months). Urethrectomy and radical cystectomy were the most performed procedures in this cohort. For locally advanced SCC of the urethra, local radiotherapy with concurrent radio sensitizing chemotherapeutic agents with curative intent had been described in various case serious and case reports [16-19]. Cohen et al. [20] reported survival outcomes of 18 patients who had invasive urethral carcinoma and received chemoradiation therapy (CRT) protocol. Tumor histology was SCC in 17 of them. Patients were subjected to External beam radiation therapy concurrently with chemotherapy (Mitomycin-C and 5-fluorouracil). Complete response was achieved in 83% of the cohort. The 5-year overall survival and disease-specific survival rates were 60% and 83% respectively. In all patients with no recurrence after CRT protocol ( $n=10$ ) had subsequent urethral stricture disease and required endoscopic and surgical management. The 5-year disease free survival rate was higher in patients received salvage surgery than patients received CRT only (72% vs 54%).

### Treatment of urothelial carcinoma of the prostate

Majority of patients diagnosed with noninvasive urothelial carcinoma of the prostate (Ta, Tis) have associated bladder urothelial tumors. Urethra-sparing approach with transurethral resection (TUR) and subsequent intravesical BCG instillation has been proven to be effective [21,22]. Follow up prostatic urethral biopsies is warranted to detect early tumor recurrence which is usually an indication for cystectomy. However, in patients with prostatic ductal involvement, better oncological results reported in patients underwent radical cystoprostatectomy rather than urethral/bladder conserving protocol. Local disease control rate of 57%- 75% was reported in patients with ductal involvement received BCG instillation [22-24]. Prostatic stromal invasion is an indication for more aggressive treatment rather organ preservation, since the reported survival outcomes were dismal. In one report, the 5-year survival outcomes for patients with prostatic stromal invasion was 16% despite receiving radical treatment in 88%. In other study of 24 patients with prostatic stromal invasion underwent radical cystoprostatectomy, 12 (50%) were found to have positive lymph node positive disease with tendency to be above the iliac bifurcation [25].

## Conclusion

Urethral conserving surgery in localized PUC is an alternative treatment option in both genders. In male patients, organ preserving approaches are hypospadias formation with topical chemotherapy, distal urethrectomy, glansctomy and distal corpectomy. In female patients, radiotherapy might be considered as alternative to surgery. In advanced urethral carcinoma, management should be based on multidisciplinary approach of urologists and oncologists. For noninvasive prostatic urethral carcinoma, local control is feasible by conservative treatment in the form of TUR and subsequent BCG instillation. However, radical treatment should be proposed in cases of local recurrence and extensive ductal or stromal involvement.

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