Original Study

# Survival Outcomes Associated With Female Primary Urethral Carcinoma: Review of a Single Institutional Experience

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## Abstract

**Female primary urethral carcinoma is rare, and treatment standards are nonexistent, particularly for the use of multimodal therapy in locally advanced disease. We reviewed 39 patients with primary urethral carcinoma in regard to presentation, treatment, and outcomes. Multimodal therapy shows a nonsignificant interval increase in overall and recurrence-free survival, but the sequence, type, and delivery of multimodal therapy is poorly defined.**

**Background:** Primary urethral carcinoma (PUC) is rare, and standard treatment recommendations are lacking. We examined the variation in treatments and survival outcomes of female PUC at a single, tertiary referral cancer center. **Methods:** Records of women with PUC referred to our multidisciplinary genitourinary oncology service between 2003 and 2017 were reviewed. Clinical, demographic, pathologic, primary and salvage therapy details, and overall (OS) and recurrence-free survival (RFS) were recorded. Survival outcomes were analyzed for the entire cohort, and cases of locally-advanced ($\geq$ T2 tumor), non-metastatic PUC were evaluated according to treatment intensity. Multimodal treatment (cystourethrectomy + concomitant therapy) was compared with non-multimodal therapy. Contingency analyses and Kaplan-Meier estimates were performed. **Results:** Thirty-nine women with PUC were identified. In total, median OS was 36 months (95% confidence interval, 10.6-61.4 months). Twenty-four had T3 to T4 disease, 12 were node-positive, and 3 had distant metastases. Histology included 22 adenocarcinomas, 11 urothelial, 5 squamous, and 1 neuroendocrine. Patients with locally advanced, non-metastatic disease (n = 25) had significantly reduced OS (36 vs. 99 months; $P = .016$) and RFS (46 months vs. unmet; $P = .011$) compared with patients with locally confined tumors. Approximately one-half of locally advanced cases were managed with multimodal therapy (4 with neoadjuvant therapy + cystourethrectomy, 8 with cystourethrectomy + adjuvant therapy, and 1 with chemoradiation + consolidative cystourethrectomy). Multimodal therapy had nonsignificant longer OS (36 vs. 16 months) and RFS (58 vs. 16 months), $P > .05$. **Conclusions:** Locally advanced female PUC has relatively poor survival outcomes. Although we observed a nonsignificant interval improvement in survival with multimodality therapy, the treatment paradigm is inconsistent. Because it is a rare disease, collaborative multi-institutional studies are needed.

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## Introduction

Female urethral carcinoma is a rare tumor with incidence rates of 1.5 per million in the United States, accounting for < 1% of female malignancies.[1,2] Consequently, treatment standards are lacking, and management decisions are often made on a case-to-case basis with limited supporting evidence.[1-7] Primary urethral carcinoma (PUC) is an aggressive disease with 5-year survival ranging between 40% and 60%.[1,2,6,8] Patients usually present in a delayed fashion in the seventh decade of life and are often misdiagnosed initially.[4,9,10] Though National Comprehensive Cancer Network guidelines recommend neoadjuvant chemotherapy followed by surgery for locally advanced disease (T3 and T4 urethral tumors),[11,12] there is a lack of consistency in integrating and delivering effective therapies for female PUC in part owing to the absence of an evidence base.

The infrequency of PUC greatly influences the dearth of supporting evidence for effective management strategies, and therefore, guidance in treating these patients is difficult, particularly for advanced disease. Large-scale database studies using the National Cancer Registry have demonstrated the late-stage presentation and the aggressive nature of PUC, but data regarding comparative effectiveness of multimodal treatment strategies is limited owing to the absence of clinical granularity in these studies.[3,5] Although National Comprehensive Cancer Network recommendations and large database studies recommend multimodal treatment approaches to PUC, few patients actually received multiple coordinated treatments. For example, one recent National Cancer Database (NCDB) study of 1749 patients with PUC (men and women) found that only 15.6% of patients received definitive multimodal therapy, and an overall survival (OS) benefit was noted only for PUC of urothelial orgin.[5] Women composed only 37% of this patient cohort and, consistent with the natural history of female PUC, adenocarcinoma was the most common histologic subtype (48%) among women. Despite this large dataset, disease characteristics specific to female PUC are poorly evaluated, and the sequence, regimen, and timing of multimodal therapy remain unclear.

PUC guidelines based on clinical trial evidence are unlikely to be established. Therefore, institutional reports continue to be useful in expanding the current literature to better understand this rare tumor. Our objective was to provide a detailed examination of the presentations, various treatment regimens specifically evaluating multimodal therapy, and survival outcomes for women with PUC presenting to our tertiary referral cancer center.

## Patients and Methods

### *Patient Cohort*

After Institutional Review Board approval, we performed a chart review of female patients diagnosed with PUC managed through our multidisciplinary genitourinary oncology service from 2003 to 2017. All patients with a primary diagnosis of urethral cancer were included. Patients with urothelial carcinoma of the bladder invading into the urethra and non-carcinoma malignancies were excluded.

### *Data Collected*

Demographic and clinical characteristics were recorded, including clinical symptoms and time from symptoms to diagnosis. Tumor size was recorded at its largest diameter according to imaging or pathologic diagnosis if imaging was unavailable. Tumor location was qualified as distal (visible at meatus), proximal, or encompassing the entire length of the urethra (noted as mid). Because operative and nonoperative patients were included, 2010 American Joint Committee on Cancer TNM staging was recorded for pathologic diagnosis following surgery or the most definitive clinical staging with biopsy confirmation.[13] Histopathology was reviewed by board-certified, dedicated genitourinary pathologists. Treatment details, including surgical interventions, radiation therapy (RT), chemotherapy, treatment sequence, and intent were documented.

### *Outcomes and Survival*

To assess the utility of multimodality treatment, only patients with locally advanced (≥ clinical or pathologic T2), non-metastatic disease who received treatment with curative intent were analyzed. Patients were categorized into 2 groups (multimodal and non-multimodal). Multimodal therapy included patients treated with primary, definitive extirpative surgery defined as radical cystourethrectomy (RCU) and lymph node dissection with at least 1 additional therapy (chemotherapy and/or RT) irrespective of neoadjuvant or adjuvant delivery. Non-multimodal was defined as any other primary treatment regimen (RCU alone, local excision ± additional therapy, primary chemotherapy ± RT). A contemporary NCDB evaluation of urethral cancer has suggested a similar definition for multimodal management.[5] The flow diagram in Figure 1 illustrates included/excluded patient and treatment courses.

Posttreatment surveillance was tailored to individual risk factors for recurrence. At a minimum, surveillance included a clinical visit, laboratory tests, and cross-sectional body imaging at 3 to 6 months following treatment and every 6 months thereafter for at least 2 years. Survival status was determined via clinical notes and hospital-based administrative data systems. Recurrence was recorded as evidence of new disease confirmed on imaging (local or metastatic) following evidence of response to primary treatment. Data for surviving patients were censored at the time of their last visit. OS was calculated from the date of primary treatment to the date of death or last follow-up. Recurrence-free survival (RFS) was calculated from the date of primary treatment to the date of recurrence (detected clinically or on imaging).

### *Statistical Analysis*

Demographic and clinical factors were stratified by treatment group and compared using $\chi^2$ or Fischer exact tests as appropriate. Kaplan-Meier analyses with log-rank testing were used to report OS and RFS stratified by T stage and multimodal therapy. Multivariable analysis was not performed owing to the limited number of patients. All analyses were performed using SPSS Statistics, version 24 software (IBM, Armonk, NY), and $P < .05$ was considered significant.

## Results

### *Total Cohort Patient Characteristics*

A total of 39 women with primary urethral cancer were identified from January 2003 to June 2017. Patient characteristics are shown in Table 1. Median age at diagnosis was 65 years (interquartile range, 57-71 years). Patients commonly presented with lower