Urethral Cancer

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Case Presentation

• HPI:
  – 75 year old male presents with intermittent hematuria for 2 years.

• ROS:
  – Reports good urinary function. No urinary retention or dysuria.

• PMHx:
  – MDS, T2DM, cirrhosis, OA, prior UTIs, epididymitis, kidney stones

• Social Hx:
  – Current smoker with >40 pack years
  – Heavy EtOH use, quit in 2012.

• Fam Hx:
  – Negative for history of malignancy
Case Physical Exam

• Moderate erythema of the penile shaft and scrotum.
• Meatus patent without visible lesions. No masses of the external genitalia including the penile glans, shaft, and testes.
• No palpable groin lymphadenopathy bilaterally.

Donovan et al., Journal Medical Radiation Sciences 2020
# Urinalysis w/ Cytology

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref Range &amp; Units</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Clarity</td>
<td>Clear</td>
<td>Turbid</td>
</tr>
<tr>
<td>pH</td>
<td>5.0 – 8.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Protein</td>
<td>Negative</td>
<td>1+</td>
</tr>
<tr>
<td>Blood</td>
<td>Negative</td>
<td>2+</td>
</tr>
<tr>
<td>Glucose</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Leukocyte Esterase</td>
<td>Negative</td>
<td>3+</td>
</tr>
<tr>
<td>RBCs</td>
<td>&lt;3 / HPF</td>
<td>21-50</td>
</tr>
<tr>
<td>WBCs</td>
<td>&lt;3 / HPF</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Negative, Few/HPF</td>
<td>Few</td>
</tr>
</tbody>
</table>

**Findings:**
- Mixed inflammatory and red blood cells present
- Cells with high nuclear to cytoplasm ratio suggestive of high-grade urothelial carcinoma with squamous features
CT Urogram

• No pathologically enlarged lymph nodes in the abdomen or pelvis.
• Likely contrast pooling in the proximal left ureter limiting evaluation of the bladder and distal ureter.
• Recommended cystoscopy/ureteroscopy for further evaluation.
FDG PET/CT

IMPRESSSION:

- No distant hypermetabolic disease suggestive of nodal or distant metastasis
- Nonspecific hypermetabolic focus centered in the distal corpus spongiosum
- May suggest infectious/inflammatory process, malignancy, or urine pooling in distal penile urethra. Please correlate clinically.
Cystourethroscopy

FINDINGS:

• 4 cm circumferential tumor 5-10 mm from the meatus. Normal bladder.

Geavlete et al. Handbook of Endourology 2016
Case Continued

• Biopsy showed HG papillary urothelial cell carcinoma with squamous features of the distal penile urethra.
• CT chest was negative for distant metastatic disease
• Patient refused penectomy with subtotal urethrectomy and perineal urethrostomy. Agreed to non-surgical management.
Background

• Rare, accounts for <1% of all malignancies
• 1.69 per 1 million, incidence increases with age
• 2:1 African American to Caucasian
• 5:1 Male to Female Sex
• Risk factors = chronic inflammation
  – STDs, urethritis, urethral strictures, urethral diverticula, urinary stasis, recurrent infections, trauma, smoking, HPV 16, prior urothelial ca, prior RT
• Histology
  – Urothelial (54-65%) > Squamous (16-22%) > Adeno (10-16%)

Presentation

• In males
  – Hematuria (initial terminal urine flow), difficulty voiding, dysuria, urethral discharge, urinary retention if advanced
  – Misdiagnosed as benign stricture (much more common)
  – Consider bx for recurrent stricture
  – Dx often delayed (most often stage III)

• In females
  – Irritative voiding sx or hematuria
  – Often mistaken for UTI
  – Recurrent or persistent pelvic sx like dyspareunia should raise concern

• 20-50% LN involvement at presentation, <1/2 palpable
• 10% distant mets – lungs, liver, brain, bone
Prognosis

• Overall poor prognosis
  – 3-yr OS = 54% (T1-2 N0 = 62%; T3-4 N1-2 = 28%)
  – 5-yr OS = 43 – 54%
  – 10-yr OS = 29 - 32%

• Unfavorable risk factors:
  – Age > 65, black race, T3-4, N+, high grade, proximal ("posterior") lesions, adenocarcinoma, urothelial

• Favorable risk factors:
  – Young age, T1-2, N0, distal ("anterior") lesions, squamous

Champ et al. Urology 2012.
Son et al. IJROBP. 2018.
Male Urethral Anatomy

- 21 cm in length
  - Prostatic/bulbomembranous urethra
    - Transitional epithelium like bladder and upper urinary tract
  - Penile urethra
    - Pseudostratified columnar epithelium
  - Meatus
    - Stratified squamous epithelium
- Most common site of urethral cancers: bulbomembranous > penile > prostatic
- Lymphatic drainage
  - Proximal urethra: external iliac, obturator, internal iliac LNs
  - Distal urethra: superficial and deep inguinal LNs
  - If direct extension to penis: lymphatics to inguinal and pelvic nodes
Female Urethral Anatomy

- 3 to 4 cm in length
  - Anterior segment: distal 1/3rd
    - Transitional epithelium
  - Posterior segment: proximal 2/3rd
    - Stratified squamous epithelium
    - Columnar epithelium entire length

- Lymphatic drainage
  - Similar to males
  - Proximal 2/3: pelvic LNs
  - Distal 1/3: superficial or deep inguinal LNs

- Male equivalent of Skene’s gland?
  - Prostate, some with PSA positivity (glandular metaplasia leading to columnar/mucinous adenocarcinoma)
Work-Up

- **H&P:**
  - Examine palpable urethra, inguinal LNs, bimanual exam (women), DRE (men), EUA

- **Imaging:**
  - CXR vs CT Chest
  - CT Abd/Pelvis
  - CT/MR Urogram
  - MRI pelvis
  - No data on PET

- **Labs/Studies:**
  - Urine cytology
  - Cystourethroscopy
  - Retrograde urethrography (men)
  - PSA (men)

- **Biopsy:**
  - TUR(P)
  - Transvaginal if feasible

- **Prostatic Urethra:**
  - PNB (abn DRE)
  - Bladder biopsies
### AJCC/UICC 8th Edition Staging

**Male/Female Urethra (Excludes Prostatic)**

<table>
<thead>
<tr>
<th>T Stage (Male/Female Urethra)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Ta</td>
<td>Non-invasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Invades corpus spongiosum or periurethral muscle</td>
</tr>
<tr>
<td>T3</td>
<td>Invades corpus cavernosum or anterior vagina</td>
</tr>
<tr>
<td>T4</td>
<td>Invades other adjacent organs (e.g. bladder wall)</td>
</tr>
</tbody>
</table>

**Diagram:**
- Blood vessels
- Dorsal nerve
- Connective tissue
- Corpus cavernosum
- Corpus spongiosum
- Urethra

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## AJCC/UICC 8th Edition Staging

**Prostatic Urethra**

<table>
<thead>
<tr>
<th>T Stage (Prostatic Urethra)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis pu</td>
<td>Carcinoma <em>in situ</em>, involvement of prostatic urethra</td>
</tr>
<tr>
<td>Tis pd</td>
<td>Carcinoma <em>in situ</em>, involvement of prostatic ducts</td>
</tr>
<tr>
<td>T1</td>
<td>Invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Invades prostatic stroma, corpus spongiosum or periurethral muscle</td>
</tr>
<tr>
<td>T3</td>
<td>Invades corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)</td>
</tr>
<tr>
<td>T4</td>
<td>Invades other adjacent organs (e.g. bladder or rectum)</td>
</tr>
</tbody>
</table>
## AJCC/UICC 8th Edition Staging

### N/M & Stage Group (Applies to all)

<table>
<thead>
<tr>
<th>N/M Stage</th>
<th>Stage Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N – Regional Lymph Nodes</strong></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>T Stage</td>
</tr>
<tr>
<td>N1</td>
<td>T1</td>
</tr>
<tr>
<td>N2</td>
<td>T2</td>
</tr>
<tr>
<td><strong>M – Distant Metastasis</strong></td>
<td>T3</td>
</tr>
<tr>
<td>M0</td>
<td>T4</td>
</tr>
<tr>
<td>M1</td>
<td></td>
</tr>
</tbody>
</table>

### N/M Stage

- **N0**: 0 regional lymph node metastases
- **N1**: 1 regional lymph node metastases
- **N2**: 2+ regional lymph node metastases

### Stage Group

- **T0**: N0
- **T1**: I
- **T2**: II
- **T3**: III
- **T4**: IV

- **M0**: No distant metastasis
- **M1**: Distant metastasis

- **M1**: IV

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Management

• No prospective trials
  – Treatment from small case series + extrapolated from other urinary tract/pelvic malignancies
• Differs by stage, histology, and location
• Tis, Ta, T1-2 = Typically surgery
• T3-4, N0-2 = Typically multimodal therapy
• M1 = Systemic + palliative therapy
Early Stage Management

*Male/Female Urethra (Excludes Prostatic)*

- **Ta, Tis, T1**
  - Repeat Transurethral Resection
  - Prior Cystectomy + Diversion?
  - Intraurethral Chemo (Mitomycin vs Gemcitabine) or BCG

- **T2**
  - Male
    - Penile Urethra
      - Partial Penectomy vs Distal Urethrectomy + Urinary Diversion
    - Bulbomembranous Urethra
      - ± NAC, Urethrectomy ± Cystoprostatectomy + Urinary Diversion
  - Female
    - Proximal Urethra
      - ± NAC, Urethrectomy + Cystectomy + Urinary Diversion
    - Distal Urethra
      - ChemoRT (Organ Preservation)
      - ± NAC, Distal Urethrectomy + Urinary Diversion

NCCN Guidelines. 2023

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Late Stage Management

Male/Female Urethra (Excludes Prostatic)

- T3-4 N0-2
  - RT Alone
  - NAC
    - N0
    - N1-2
      - ± Consolidation Surgery
  - ChemoRT
    - N0
      - Non-urothelial
      - Surgery Alone

NCCN Guidelines. 2023
Prostatic Urethra Management

Mucosal (Tis pu “prostatic urethra”)
- TURP + BCG

Ductal/Acini (Tis pd “prostatic ducts”)
- Cystoprostatectomy + Urethrectomy

Stromal Invasion (≥ T1)
- NAC
  (±Adjuvant if no NAC)

NCCN Guidelines. 2023
TUR/TURP + Intraurethral BCG/Chemo

- For Tis, Ta, T1
- Extrapolated from bladder cancer
- Maximal safe TUR/TURP → BCG 6-12 weekly cycles
- Data mostly only for prostatic urethra:
  - BCG alone: CR ~65%
  - TURP/BCG: CR ~90-95%
  - 5yr RFS: ~30% if bladder involved

Gofrit et al. BJUI. 2009.
Neoadjuvant Chemo

- Multiagent cisplatin-based regimens
  - SCC: cis + gem + ifos (CGI) vs ifos + taxol + cis (ITP)
  - Adeno: Gem-FLP
  - Urothelial: MVAC vs CGI vs ITP
- Locally-advanced benefit?
  - Response rate: 14% CR, 58% PR
  - Median OS (± surgery): 46.9 vs 21.7 months
  - Potential to downstage for less extensive surgery
- Neoadjuvant chemoradiation is also feasible

Gakis et al. Ann Oncol. 2015
Surgery For Men

• Proximal = urethrectomy ± cystoprostatectomy
  – Resect bladder and/or prostate if necessary for clear margins
  – Bladder often involved for prostatic urethra cases
• Distal = (partial) penectomy vs subtotal urethrectomy
• Urinary diversion options differ by extent of resection

Distal Urethrectomy Diversion

Lesion

Lesion excised and much of the native glans remain intact

Urinary catheter

Distal urethra mobilised

Penile urethra spatulated distally

Internal surface of penile urethra

Internal surface of urethra forms neomeatus

Creation of penile urethrostomy


Proximal (Cysto)urethrectomy Diversion

**Kock Pouch.** Pouch, valves and outlet are made from terminal ileum.

**Indiana Pouch.** Pouch is made from large intestine (ascending colon). Natural ileocecal valve is used for valve outlet made from terminal ileum.

**Mitrofanoff Procedure (and variation).** Pouch is made from the bladder (large or small intestines or a combination of them). Outlet is made from the appendix (fallopian tube or ureter segment).

**Ileal Neobladder.** Pouch is made from small intestine (ileum) and the outlet is the urethra (no stoma).
Surgery for Women

• Complicated by short length of urethra
  – Often managed with complete urethrectomy + (partial) cystectomy
  – TUR technically difficult given anatomy

• Distal urethrectomy feasible if neg. margins
  – May have greater risk of LRF
  – Reports of >50% urinary incontinence or retention

• More extensive disease may require exenteration

DiMarco et al. Urologic Oncology. 2003
Lymphadenectomy?

- Controversial w/ no consensus
  - Always for cN+
  - Consider inguinals if distal, pelvic ± inguinal if proximal
  - Consider for salvage in late stage recurrence

Adjuvant Therapy

• Risk adapted w/ chemo and/or RT
  – +Margins w/ re-resection unfeasible
  – pT3-4, N+
  – Prostatic urethra stromal invasion (give chemo if not given NAC)

• Chemo regimens similar to NAC setting
  – Possible worse survival if adjuvant vs NAC

• Adjuvant RT associated with improved OS for later stage disease

Gakis et al. Ann Oncol. 2015
Son et al. IJROBP. 2018.
Adjuvant Radiation Therapy

• NCDB Analysis (2004 – 2013)
  – N = 2614, 28m follow-up
  – T0-4 N0-2 M0
  – Examined OS by treatment received
  – OS: S+RT >> S alone (HR = 0.58)
    • For T3-4 N+ adeno or urothelial
    • No survival benefit in SqCC
    • 93% adjuvant RT (EBRT or EBRT + brachy)
  – No OS benefit with chemo

Median dose (IQR)
EBRT + S = 59.4 (50.4 – 66)
EBRT + brachy = 45 (45 – 50.4)
EBRT alone = 66 (63 – 70.2)

Son et al. IJROBP. 2018.
Organ Preservation - ChemoRT

- Consider for patients declining surgery, poor surgical candidacy, advanced disease, neoadj.
  - T1-2 N0 = RT +/- chemo
  - T3-4 N+ = Seq or concurrent chemoRT
    - SqCC: anal ca regimens (5FU + MMC; cis + 5FU)
    - Urothelial: bladder regimens (gem; cis; 5FU + MMC)
    - Adeno: no consensus (consider above regimens)
  - 5yr OS = 60%; DSS = 83%
  - Consolidation surgery may still improve DFS after (72 vs 54%)

Gakis et al. Ann Oncol. 2015
Interstitial Brachytherapy

• Can be considered for boost after EBRT for gross residual disease

• Male: Similar approach as primary carcinoma of the penis
  – Consider for lesions < 4 cm and T1, some early T2.
  – Interstitial: Six needles placed 1 cm apart with 1 cm radius around urethra.

• Female: 8-12 needles around urethral orifice to tumor + 1-2 cm.

• Dose (EQD2 for $\alpha/\beta = 10$)
  – Brachy alone: 60-70 Gy
  – EBRT (45 Gy) + Brachy boost: 20-30 Gy (65-75 Gy EQD2)
  – No consensus dose/fix

Intracavitary Brachytherapy

- Transurethral debulking may facilitate intracavitary BT (to avoid interstitial needles)
- Typically foley-based approach to serve as channel for source
- Treat to 60-70 Gy
  - Ex: HDR 36 Gy/9 fx + 24 Gy/6 fx boost (EQD2 = 70 Gy)
- Contour entire urethra on MRI to define a HR-CTV
- Vaginal cylinder can be used to displace posterior rectum for female anatomy

Consider applying gentle traction and marking foley to verify consistent foley positioning

Beware of increased dose to anterior vaginal wall with cylinder!

Recurrence

• Directed by pattern of recurrence, histology, feasible salvage options
  – Systemic therapy in most cases
  – Consider more extensive surgery if possible
    • Complete penectomy, exenteration, lymphadenectomy
  – RT monotherapy or chemoradiation if no prior radiation

• Palliation if no safe local therapies or treatment is unacceptably morbid
Case Continued

• Discussed at multidisciplinary tumor board
• Identified as T2-3N0 urothelial carcinoma of the distal penile urethra
• Consensus for chemoradiation with single agent gemcitabine
CT simulation

- CT simulation with 2 mm slice thickness
- IV contrast
- Supine vs frogleg (to cover inguinals) vs prone (submerge penis in water container)
- Retract pannus in obese patients to prevent skin blousing effect
- Arms on chest vs overhead
- Bladder comfortably full, rectum empty
- Immobilization with pelvic vaclock, knee roll
- Penile shaft placed on foam block for reproducibility and to spare scrotal skin (can consider testes lead shield as well)
- Consider additional immobilization if concerns for penis position reproducibility (e.g. aquaplast mold)
- Customize bolus for penis
Aquaplast Mold Immobilization

Be mindful of heat generated from aquaplast!

Example setup using custom wax bolus

Donovan et al., Journal Medical Radiation Sciences 2020
May need to fill gaps if variation in penile length for day-to-day setup
Contouring Pearls

- **Dose:** 66-70Gy/60-66 Gy/54-60 Gy/45-50.4 Gy in 25-33 fx
  - Sequential boost given no data on SIB
  - IMRT though technically feasible with 3DCRT

- **GTVp:**
  - Primary disease based on available imaging (e.g. MRI, PET)

- **GTVn:**
  - Gross nodal disease

- **CTV 66-70:**
  - GTVp + 1-2 cm

- **GTVn 60-66:**
  - Gross nodal disease
  - May reduce to 54 Gy for OARs (typically for bowel, rectum, bladder or LS plexus)
Contouring Pearls

- **CTV 54-60:**
  - Areas of prior ENE+, margins+, operative bed if adjuvant

- **CTV 50.4:**
  - Areas at risk for microscopic disease (e.g. penile shaft, perineum, pre-chemo extent of disease)

- **CTV 45 (+7 mm):**
  - Elective pelvic/inguinal nodal coverage
    - Superior: Bifurcation of common iliacs (extend to bifurcation of aorta if prostatic)
    - Include pre-sacral to inferior border of S3, internal iliac, external iliac, obturator
    - Inferior: Inguinal LN to lesser trochanter
Case: Contours

• **Dose**: 66 Gy/50.4 Gy/45 Gy sequential boost in 25-33 fx

• **CTV 66**: GTVp + 2 cm

• **CTV 50.4**:  
  – GTVp + 2 cm  
  – Included entire penile shaft, perineum

• **CTV 45**:  
  – Encompasses CTV 50.4  
  – Elective pelvic and inguinal nodal coverage

• **CTVs cropped at natural uninvolved anatomic boundaries** (e.g. bone, bowel, bladder, muscle)

• **PTV**: + 0.5 cm (per institution standard)
GTVp

CTV 66 = GTVp + 2 cm

CTV 50.4 = GTVp + 2 cm + extend to cover perineum/penis
CTV 45 = From bifurcation of common iliacs (vessels + 7 mm)

PTV 45 = CTV 45 + 5 mm

CTV 45 = Extend to obturators, inguinals at lesser trochanter

PTV 45 = CTV 45 + 5 mm

For N+:

GTVn 60-66

PTV 60-66 = GTVn + 5 mm
Fuse MRI to assist with target delineation

Example for post-op disease recurrence:

**GTVp**

**CTV 54-60** = operative bed with inclusion of CTV 66-70 (GTVp + 1-2 cm)
Plan Evaluation

Aim for PTV 45 > 95%

Max hotspot 107-111%
Keep outside of bowel, LS plexus, etc
Plan Evaluation

Verify adequate coverage of inguinals & be wary of bolusing at skin creases

Push off rectum and bone
Plan Evaluation

Push off testes
Watch again for skin bolusing

Verify adequate coverage of penis
# EBRT Institutional Constraints

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTV</strong></td>
<td>D99 ≥ 100</td>
</tr>
<tr>
<td>Dmax</td>
<td>107-111%</td>
</tr>
<tr>
<td>Bladder</td>
<td>V35 &lt; 60%; V45 &lt; 50%</td>
</tr>
<tr>
<td>Bone</td>
<td>Max &lt; 50 Gy</td>
</tr>
<tr>
<td>Bowel (Small)</td>
<td>Max &lt; 54 Gy</td>
</tr>
<tr>
<td>Bowel (Large)</td>
<td>Max &lt; 58 Gy</td>
</tr>
<tr>
<td>Cauda</td>
<td>Max &lt; 60 Gy</td>
</tr>
<tr>
<td>Femoral Heads</td>
<td>V30 &lt; 50%; V40 &lt; 35%; V44 &lt; 5%</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Mean &lt; 15 Gy</td>
</tr>
<tr>
<td>LS Plexus</td>
<td>Max &lt; 60 Gy</td>
</tr>
<tr>
<td>Penile Bulb (if not in CTV)</td>
<td>ALARA</td>
</tr>
<tr>
<td>Rectum</td>
<td>V45 &lt; 50%; V65 &lt; 15%; V65 &lt; 10cc</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Max &lt; 45 Gy</td>
</tr>
<tr>
<td>Testes (± lead shielding)</td>
<td>ALARA</td>
</tr>
<tr>
<td>Vagina (if not in CTV)</td>
<td>ALARA</td>
</tr>
</tbody>
</table>
Follow-up

• No evidence for optimal surveillance, consider routine oncologic principles

• H&P with complete GU/Gyn and lymph node evaluation
  – Year 1-2: every 3-4 mo
  – Year 3-5: every 5-6 mo
  – >5 yrs: every 12 mo

• Consider interval CT, MRI, PET/CT, cystourethroscopy, urine cytology

• Recurrences more common in proximal as opposed to distal locations

• As indicated: Smoking cessation, pelvic rehabilitation (e.g. vaginal dilator), referral for sexual dysfunction, infertility counseling
Conclusions

• Primary urethral cancer is a rare malignancy with poor prognosis
• Management is extrapolated from other malignancies due to rarity and no randomized trials
• Best approached following a multidisciplinary discussion
• Early stage can be treated like NMIBC (TURBT + intraurethral BCG)
• Late stage is conditionally multimodal therapy with NAC ± surgery ± RT vs CRT ± surgery
• Organ preserving management is feasible with CRT
• Brachytherapy has been described though no consensus exists
References


References


References

