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.

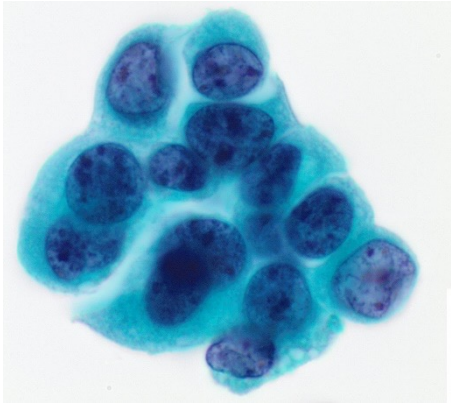
Donovan et al., Journal Medical Radiation Sciences 2020

Urinalysis w/ Cytology

Test	Ref Range & Units	Value
Color	Yellow	Yellow
Clarity	Clear	Turbid
pH	5.0 – 8.0	7.5
Protein	Negative	1+
Blood	Negative	2+
Glucose	Negative	Negative
Leukocyte Esterase	Negative	3+
RBCs	<3 / HPF	21-50
WBCs	<3 / HPF	>50
Bacteria	Negative, Few/ HPF	Few

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

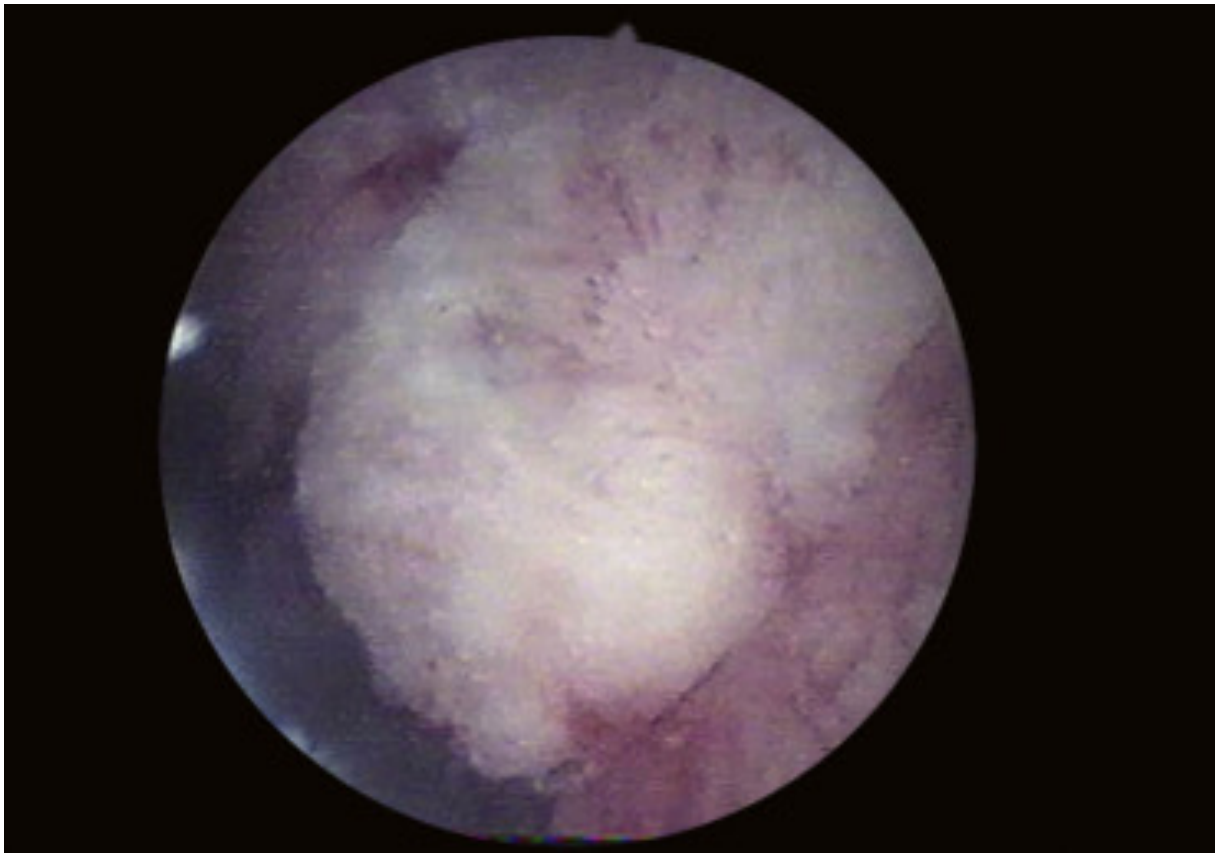
IMPRESSION:

- 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 statis, recurrent infections, trauma, smoking, HPV 16, prior urothelial ca, prior RT
- Histology
  - Urothelial (54-65%) > Squamous (16-22%) > Adeno (10-16%)

Swartz et al. *Urology* 2006.

Visser et al. *European Journal of Cancer.* 2012.

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

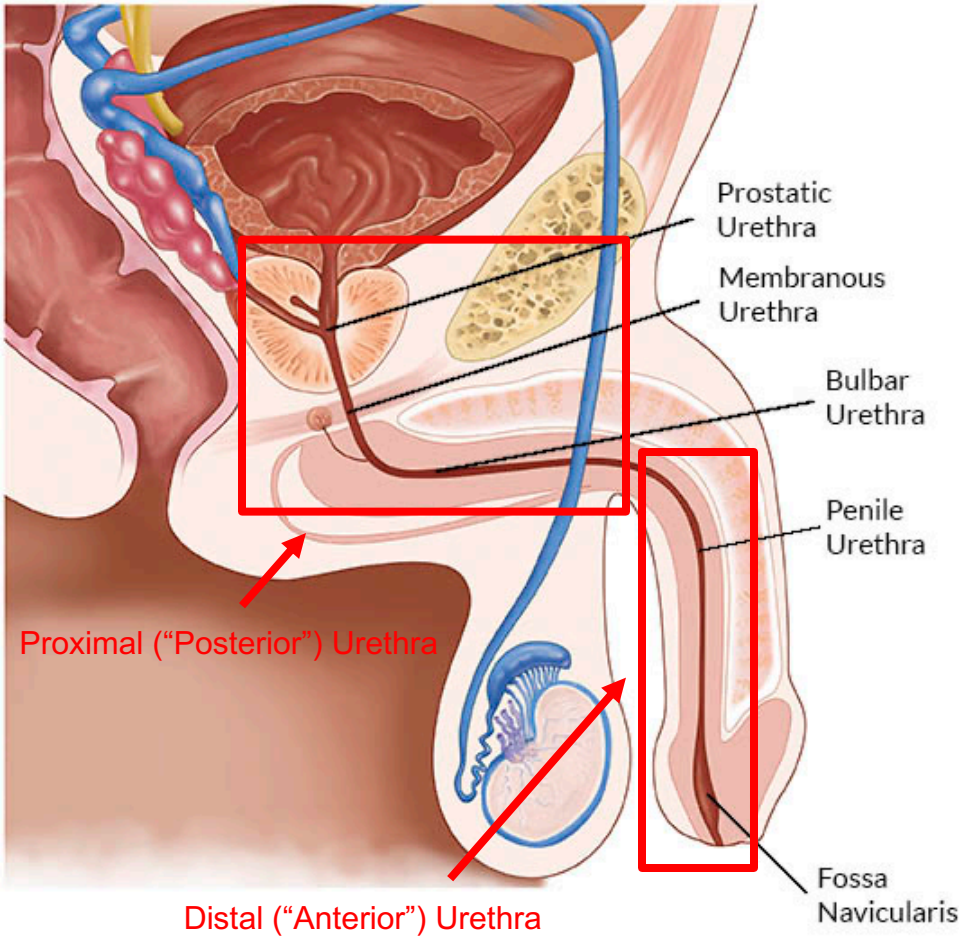
Prognosis

- 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.
Swartz et al. *Urology* 2006.
Visser et al. *European Journal of Cancer.* 2012.

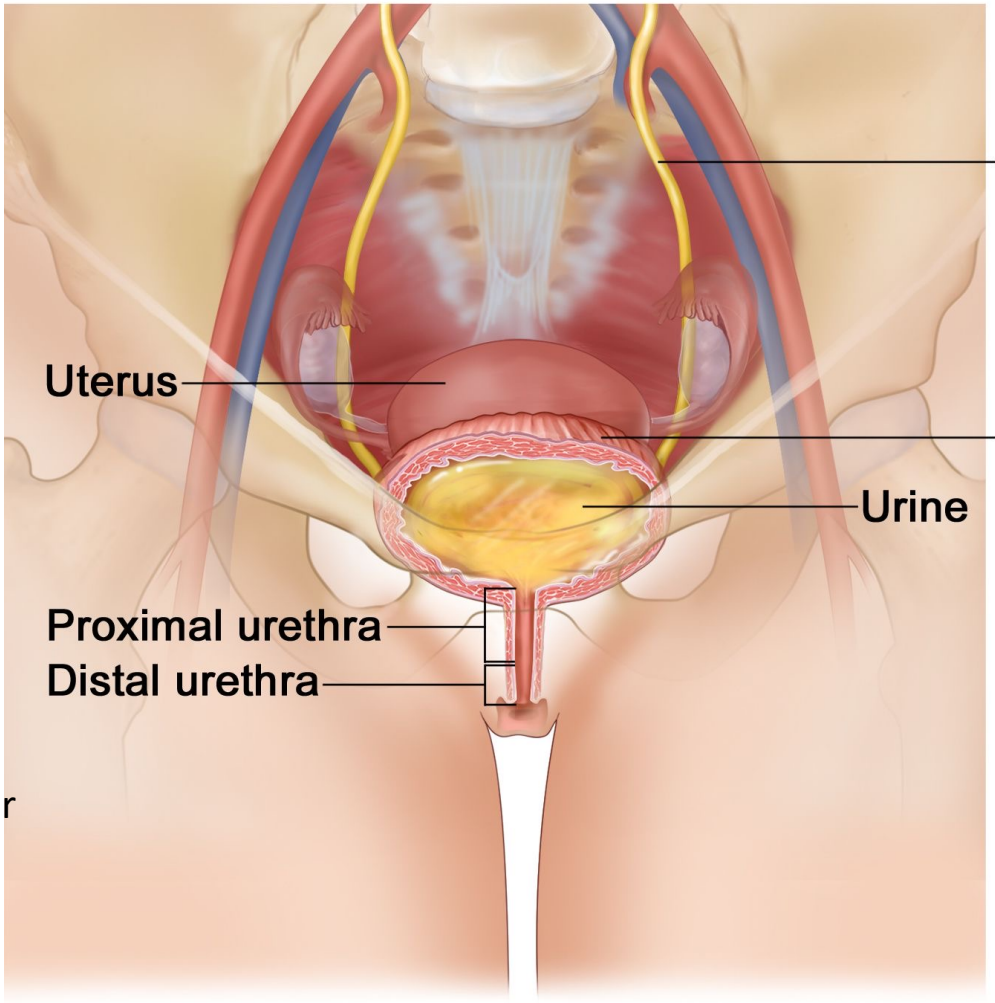
Male Urethral Anatomy

- 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)



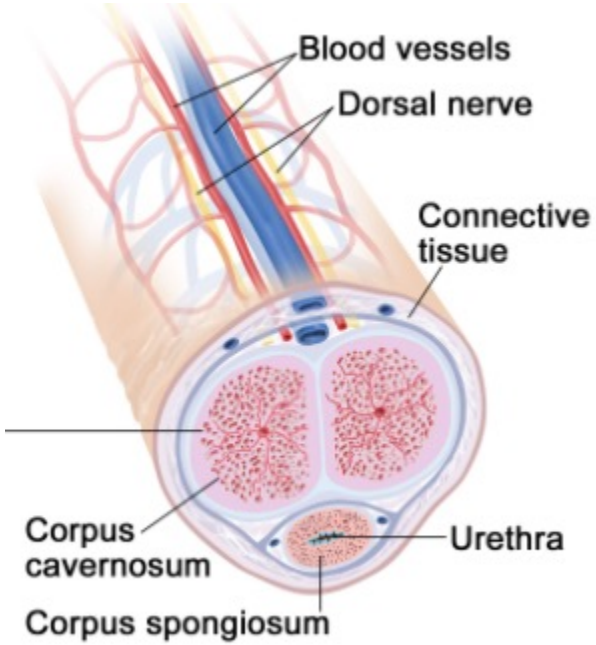
Work-Up

- 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)

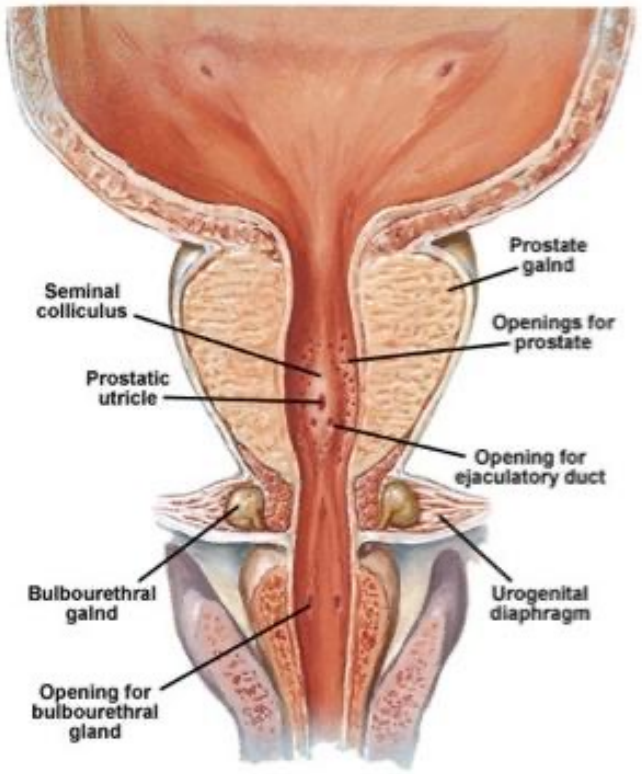
T Stage (Male/Female Urethra)	
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Invades subepithelial connective tissue
T2	Invades corpus spongiosum or periurethral muscle
T3	Invades corpus cavernosum or anterior vagina
T4	Invades other adjacent organs (e.g.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



AJCC/UICC 8th Edition Staging

Prostatic Urethra

T Stage (Prostatic Urethra)	
Tis pu	Carcinoma *in situ,* involvement of prostatic urethra
Tis pd	Carcinoma *in situ,* involvement of prostatic ducts
T1	Invades subepithelial connective tissue
T2	Invades prostatic stroma, corpus spongiosum or periurethral muscle
T3	Invades corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Invades other adjacent organs (e.g. bladder or rectum)



AJCC/UICC 8th Edition Staging

N/M & Stage Group (Applies to all)

N/M Stage	
N – Regional Lymph Nodes	
N0	0 regional lymph node metastases
N1	1 regional lymph node metastases
N2	2+ regional lymph node metastases
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

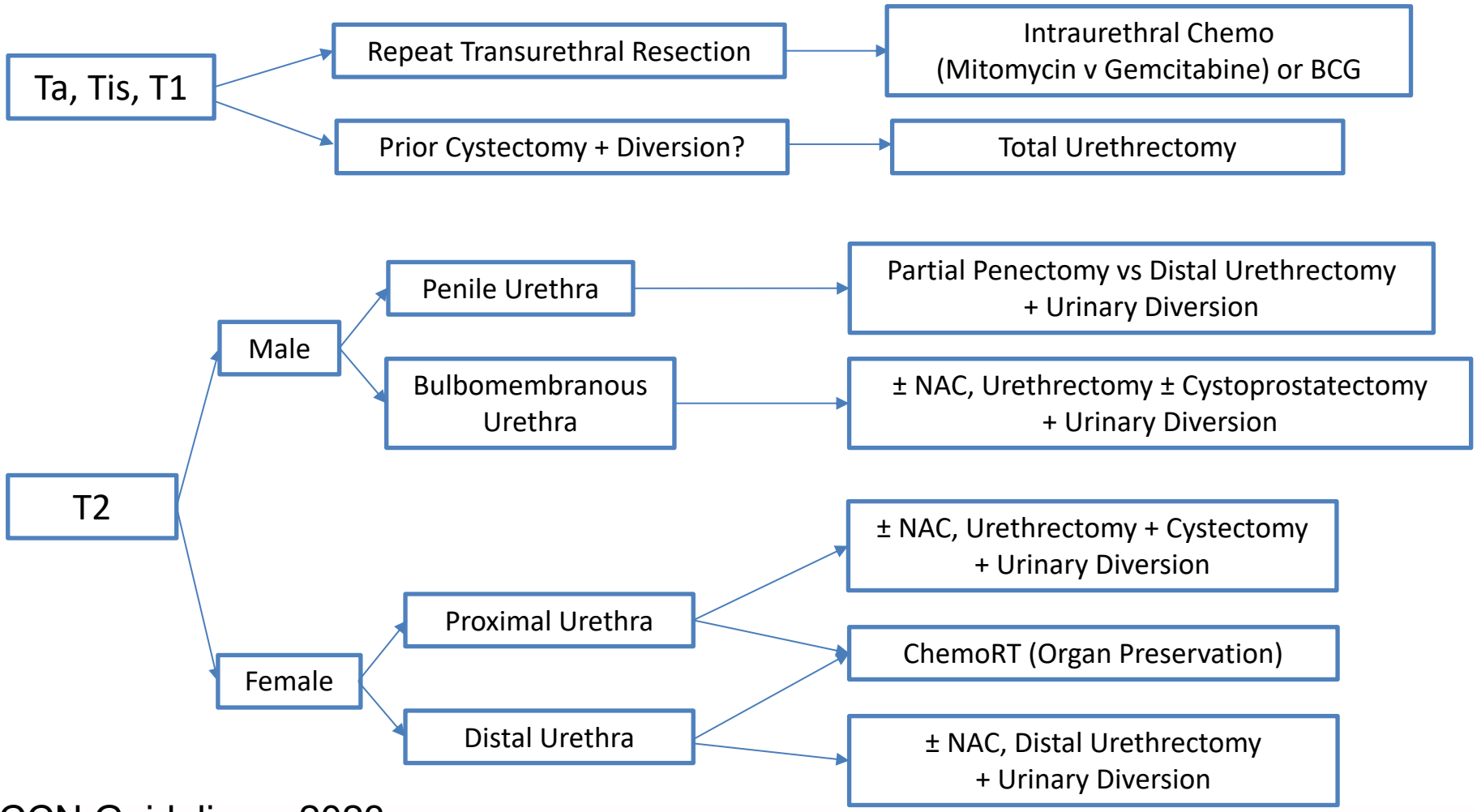
Stage Group			
	N Stage		
T Stage	N0	N1	N2
T1	I	III	IV
T2	II	III	IV
T3	III	III	IV
T4	IV	IV	IV
M Stage			
M1	IV	IV	IV

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

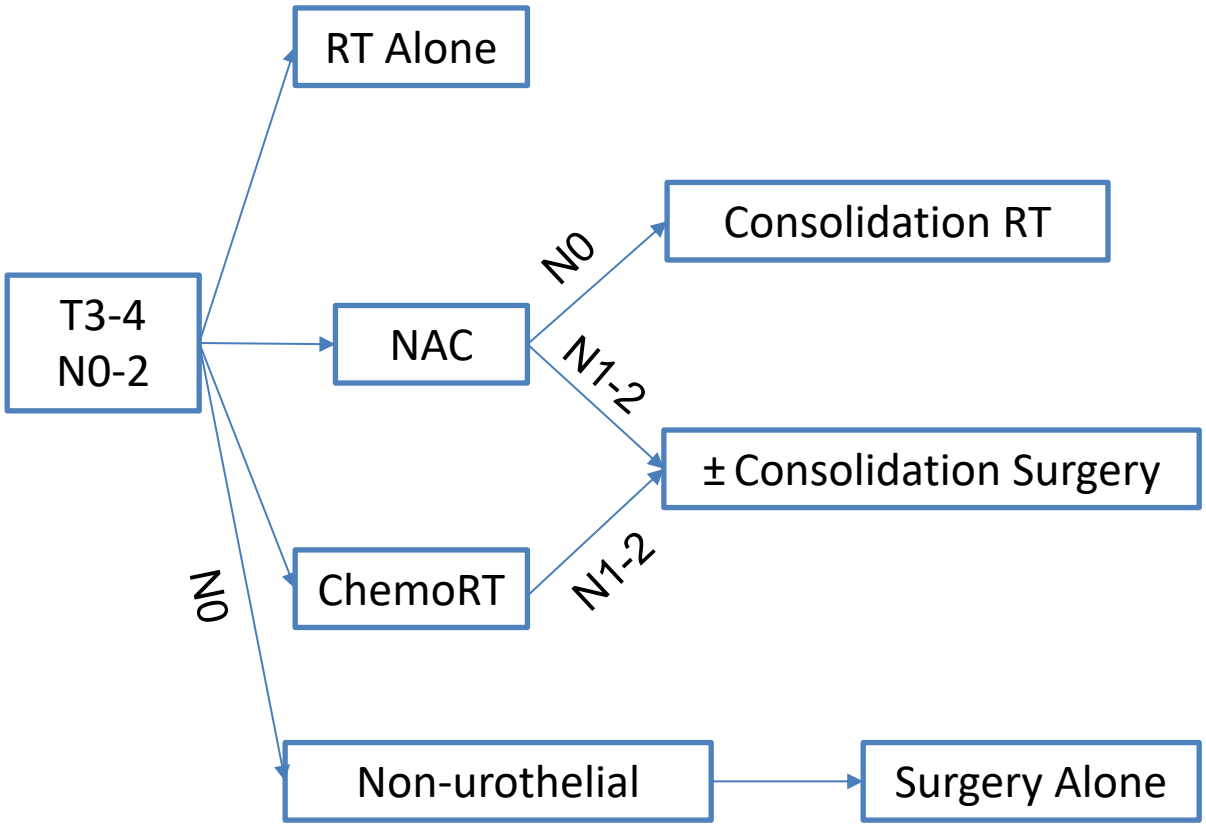
Male/Female Urethra (Excludes Prostatic)



NCCN Guidelines. 2023

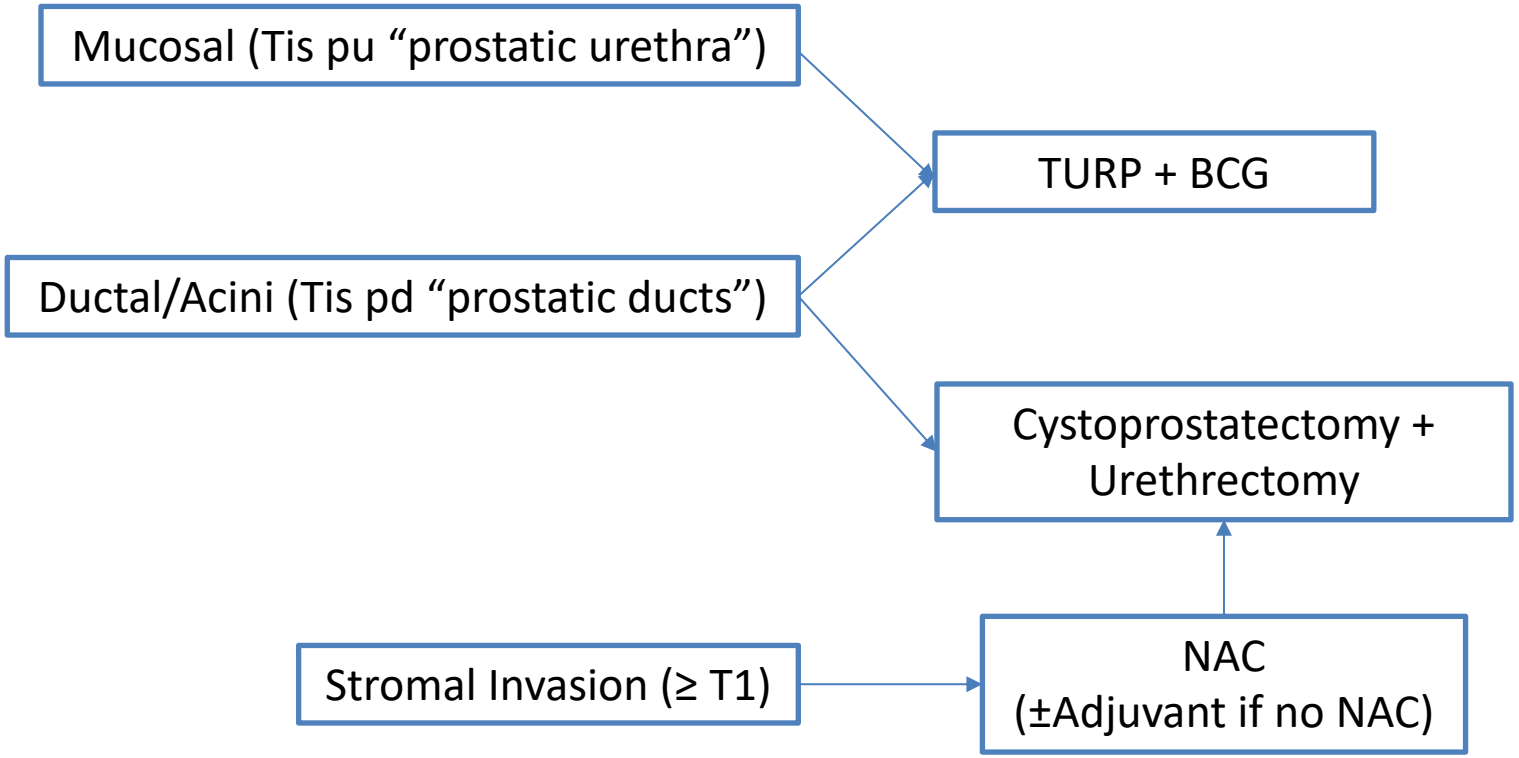
Late Stage Management

Male/Female Urethra (Excludes Prostatic)



NCCN Guidelines. 2023

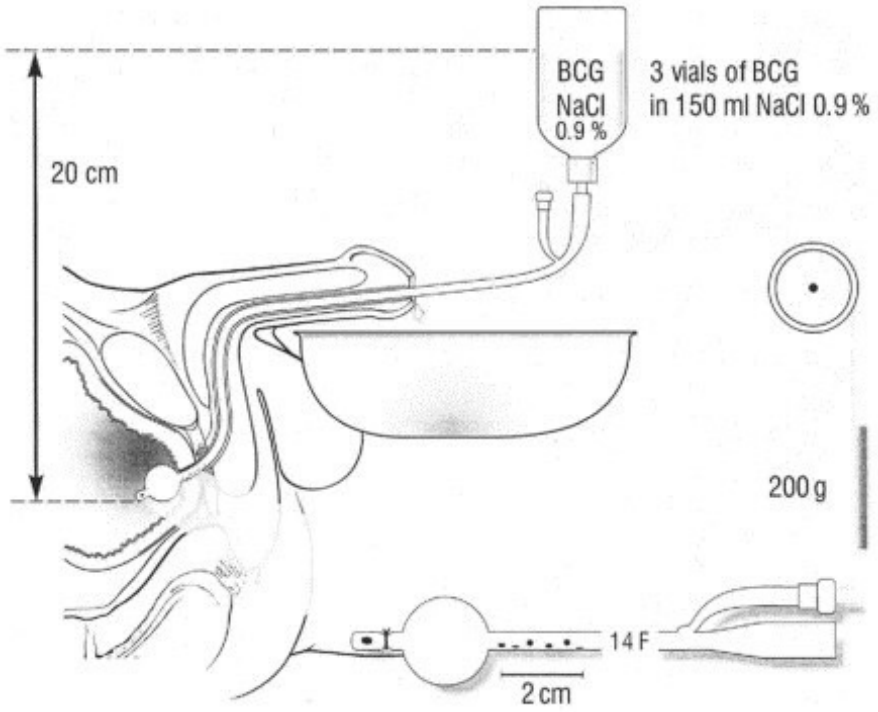
Prostatic Urethra Management



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



Varol et al. *J Urol*. 2004.
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

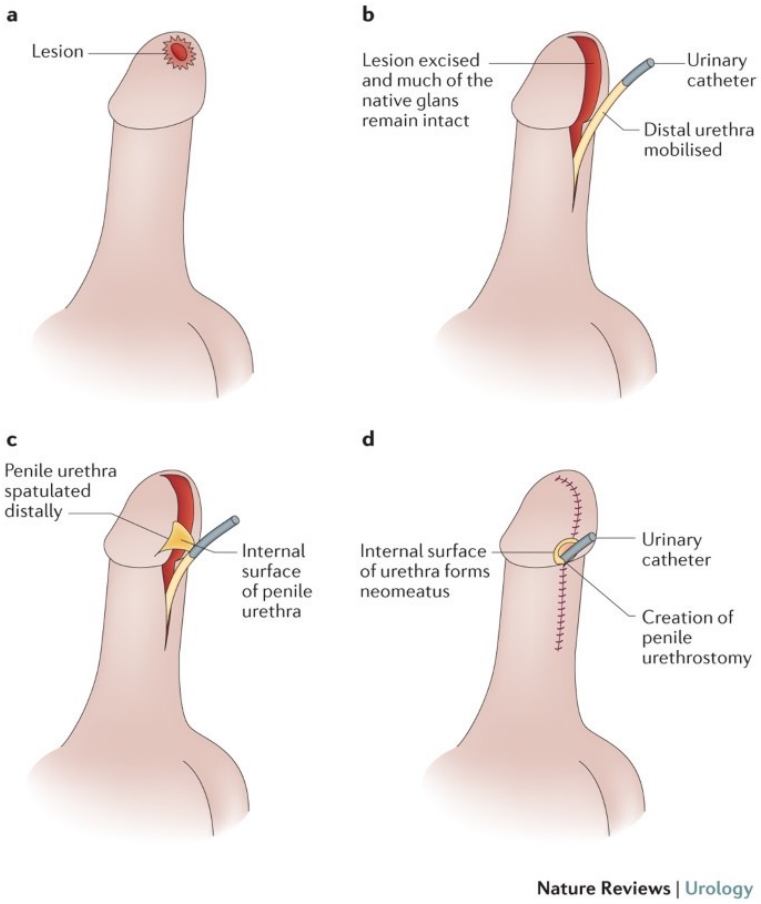
Dayyani et al. *Urologic Oncology: Seminars and Original Investigations*. 2013.

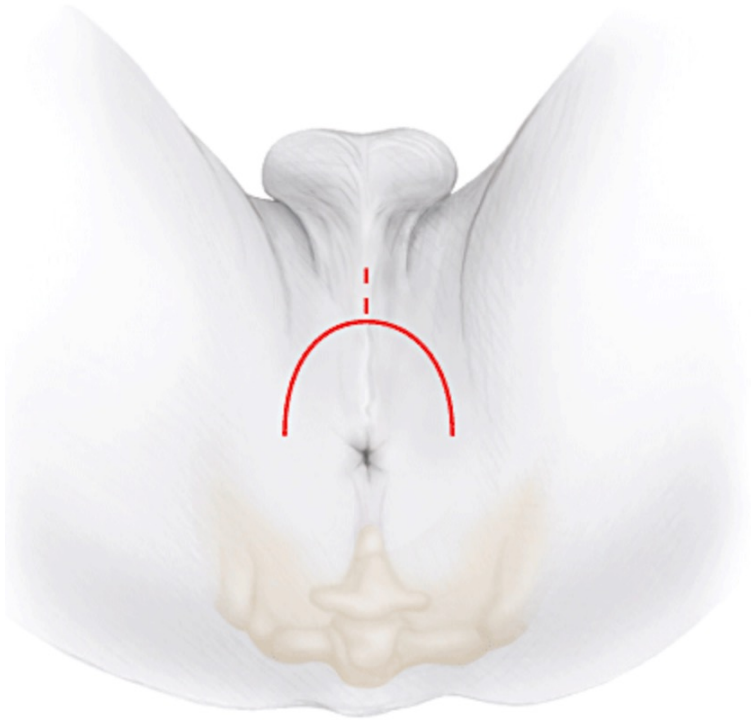
Surgery For Men

- 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

Janisch et al. *European Urology Focus*. 2019.

Distal Urethrectomy Diversion

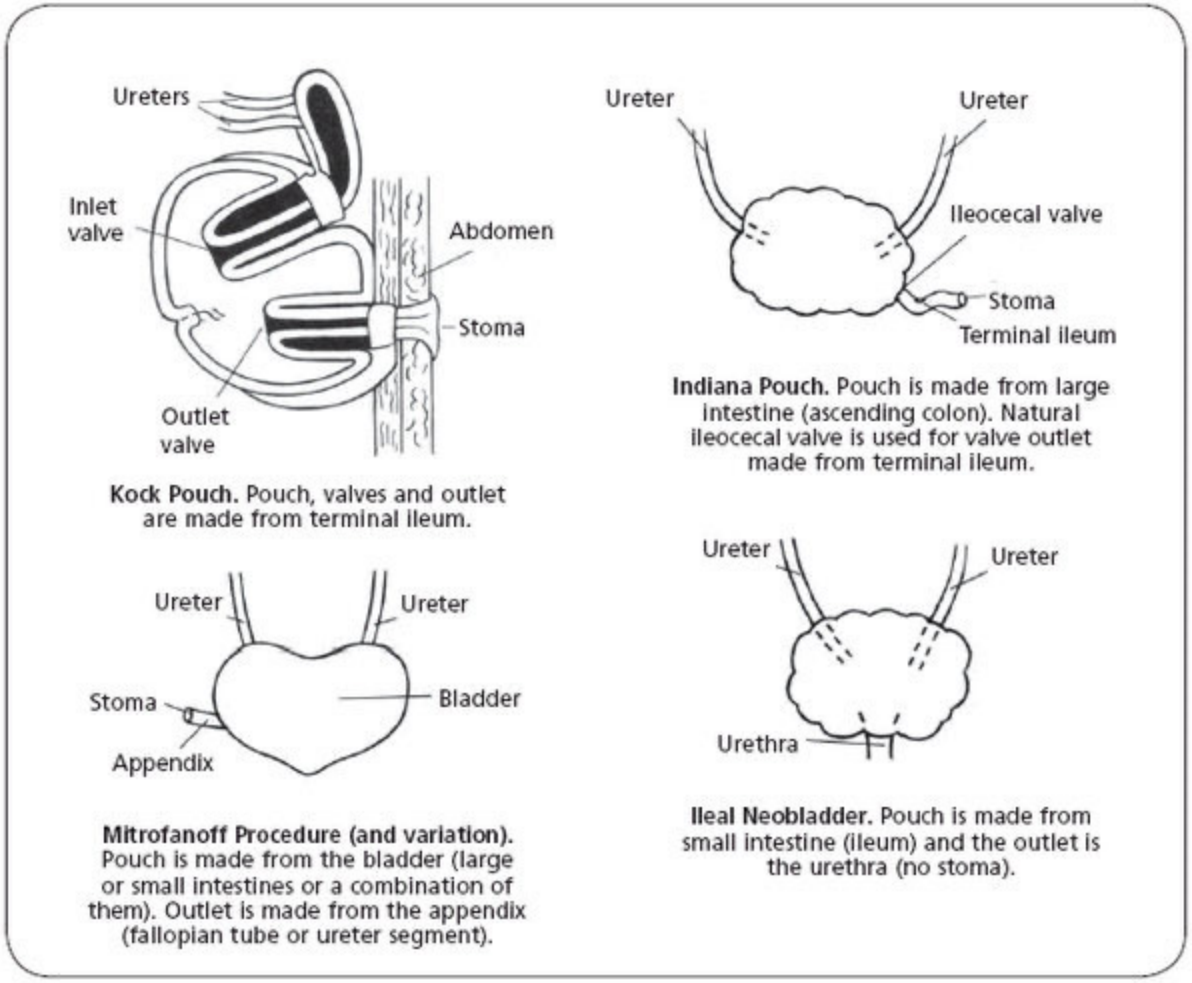




Burnett AL. *Nature Reviews Urology*. 2016.

Myers JB & McAninch JW. *BJUI*. 2016.

Proximal (Cysto)urethrectomy Diversion



American Cancer Society. 2023

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

Janisch et al. *European Urology Focus*. 2019.

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

NCCN Guidelines. Jan 2023.

Adjuvant Therapy

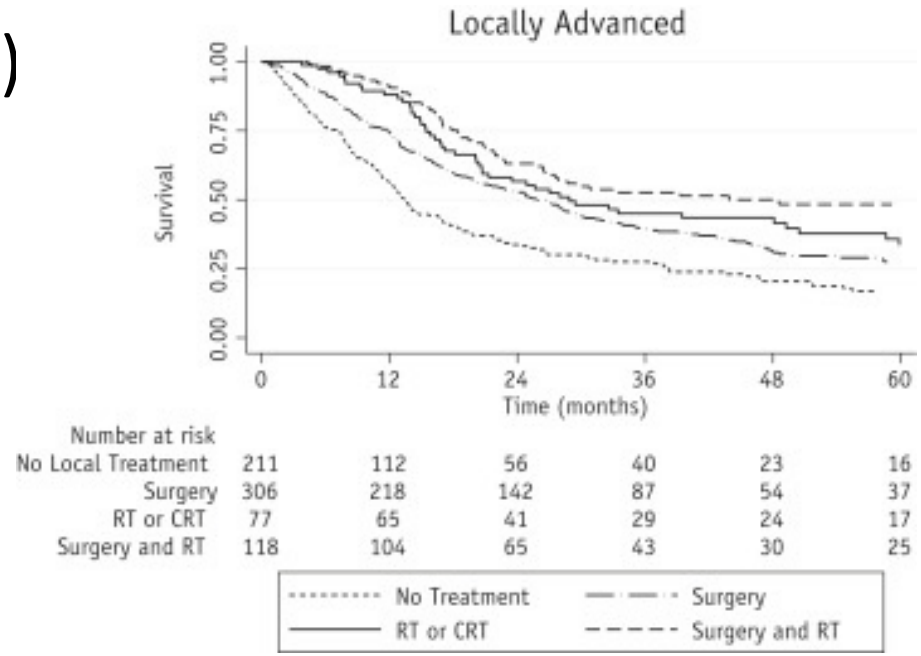
- Risk adapted w/ chemo and/or RT
  - +Margins w/ re-resection unfeasible
  - pT3-4, N+
  - Prostatic urethra stromal invasion (give chemo if not given NAC)
- Chemo regimens similar to NAC setting
  - Possible worse survival if adjuvant vs NAC
- Adjuvant RT associated with improved OS for later stage 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.

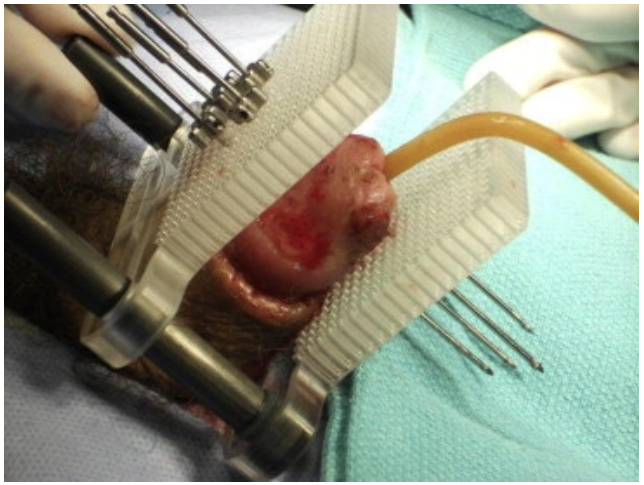
Organ Preservation - ChemoRT

- 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%)

Kent et al. *Journal of Urology.* 2015.
Cohen et al. *Journal of Urology.* 2008.
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 α/β = 10)
  - Brachy alone: 60-70 Gy
  - EBRT (45 Gy) + Brachy boost: 20-30 Gy (65-75 Gy EQD2)
  - No consensus dose/fx



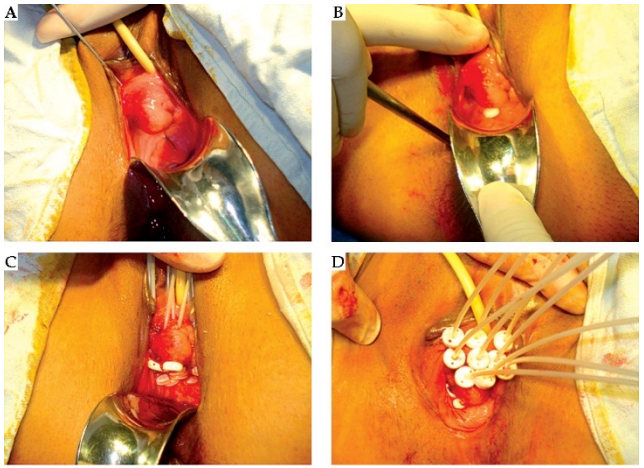


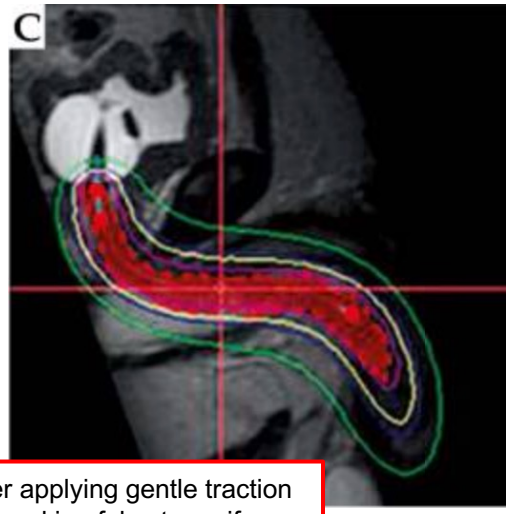
Fig. 2. Clinical photographs demonstrating the implant procedure. A) shows free hand insertion of the implant needle:

Crook et al. *Brachytherapy.* 2013.

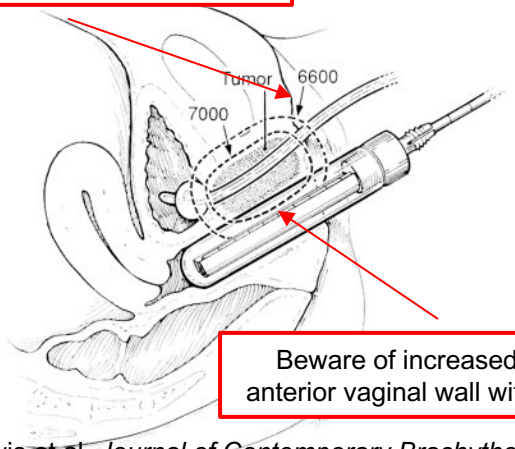
Sharma et al. *Journal of Contemporary Brachytherapy.* 2016.

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!

Lewis et al. *Journal of Contemporary Brachytherapy. 2015.*

Kuettel et al. *The Journal of Urology. 1997.*

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

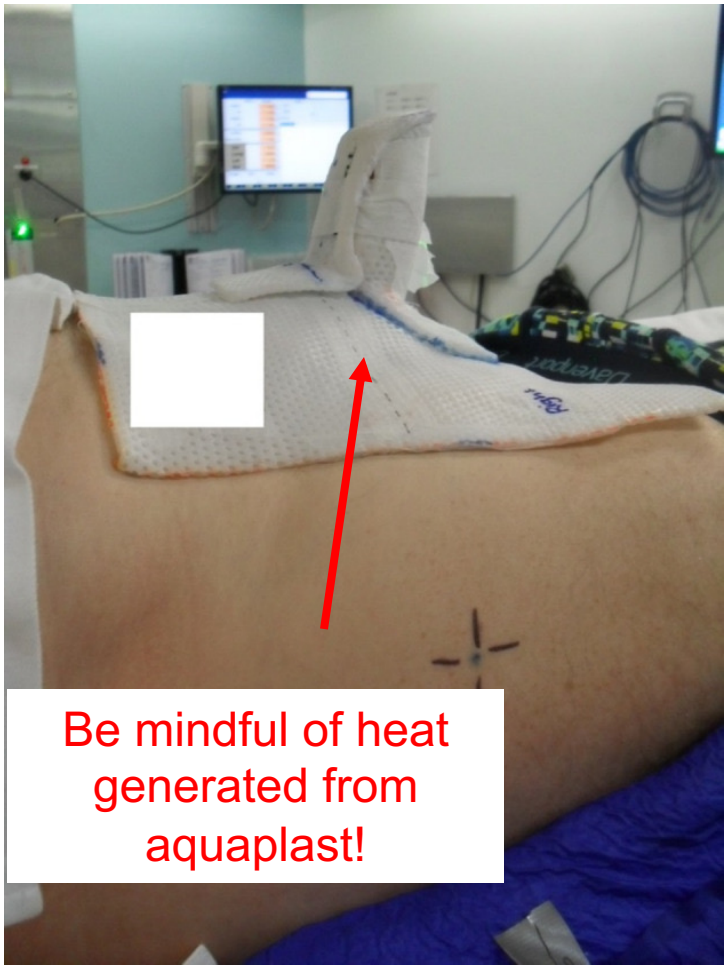
Case Continued

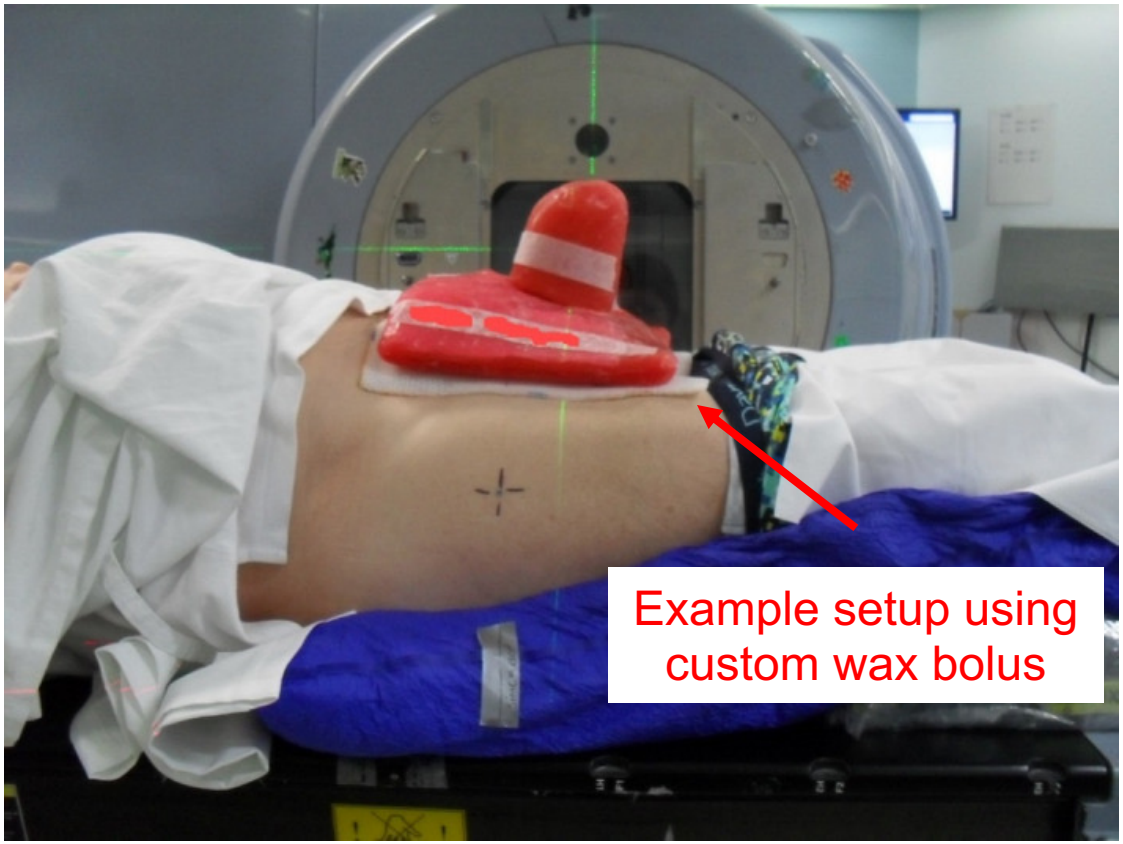
- Discussed at multidisciplinary tumor board
- Identified as T2-3N0 urothelial carcinoma of the distal penile urethra
- Consensus for chemoradiation with single agent gemcitabine

CT simulation

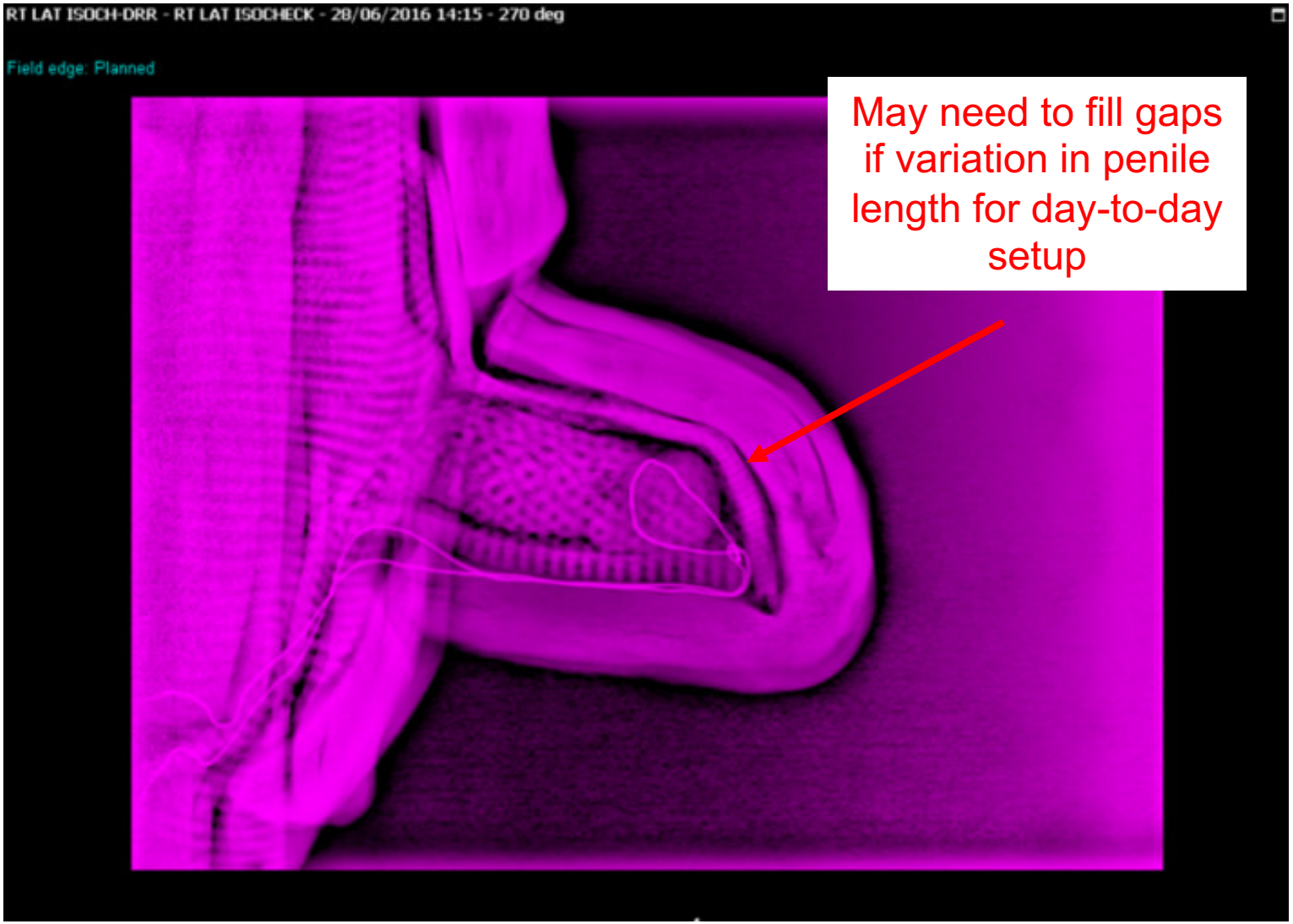
- CT simulation with 2 mm slice thickness
- IV contrast
- Supine vs frogleg (to cover inguinals) vs prone (submerge penis in water container)
- Retract pannus in obese patients to prevent skin blousing effect
- Arms on chest vs overhead
- Bladder comfortably full, rectum empty
- Immobilization with pelvic 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 Immobilizaiton





Donovan et al., Journal Medical Radiation Sciences 2020



Donovan et al., Journal Medical Radiation Sciences 2020

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)

Contuoring Pearls

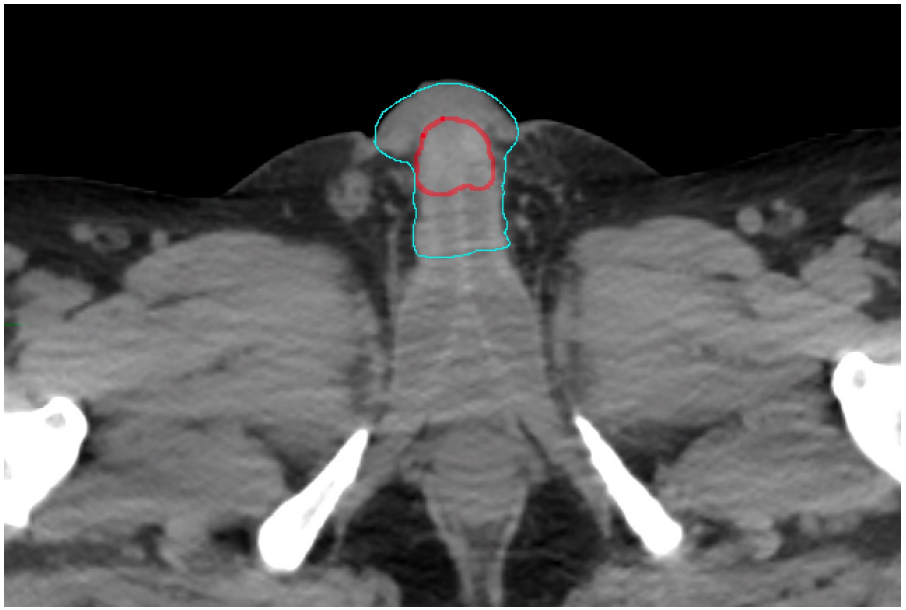
- **CTV 54-60**:
  - Areas of prior ENE+, margins+, operative bed if adjuvant
- **CTV 50.4:**
  - Areas at risk for microscopic disease (e.g. penile shaft, perineum, pre-chemo extent of disease)
- **CTV 45 (+7 mm)**:
  - Elective pelvic/inguinal nodal coverage
    - Superior: Bifurcation of common iliacs (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)

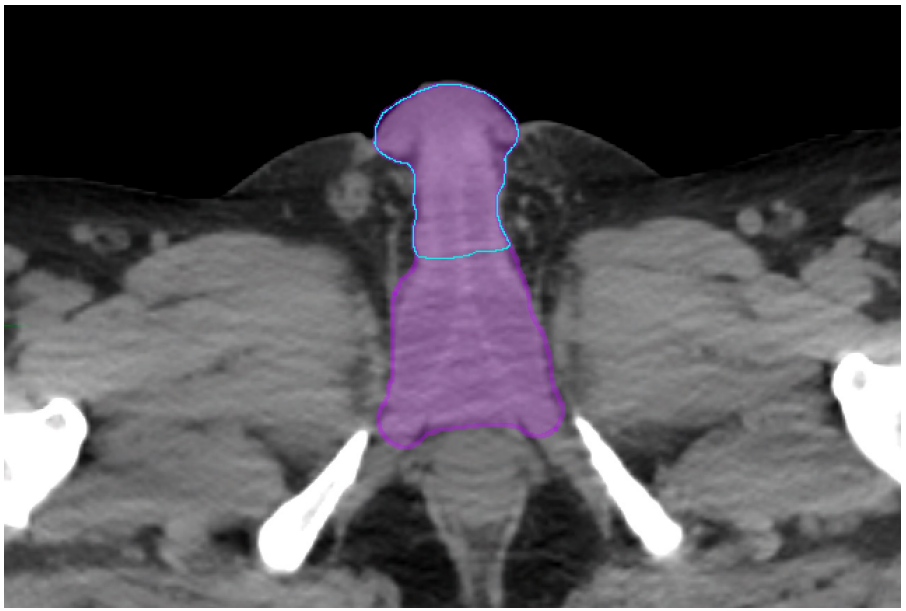
GTVp

CTV 66 = GTVp + 2 cm



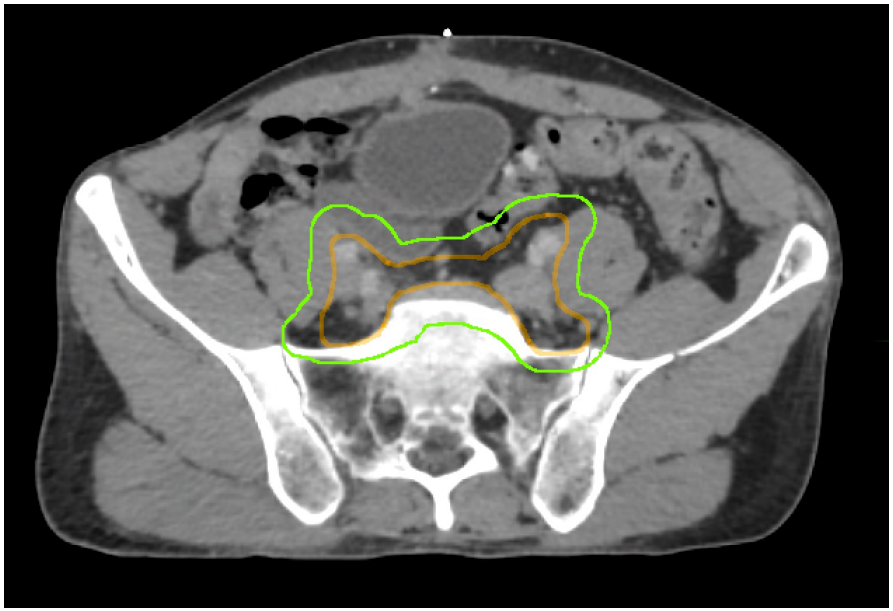
CTV 66

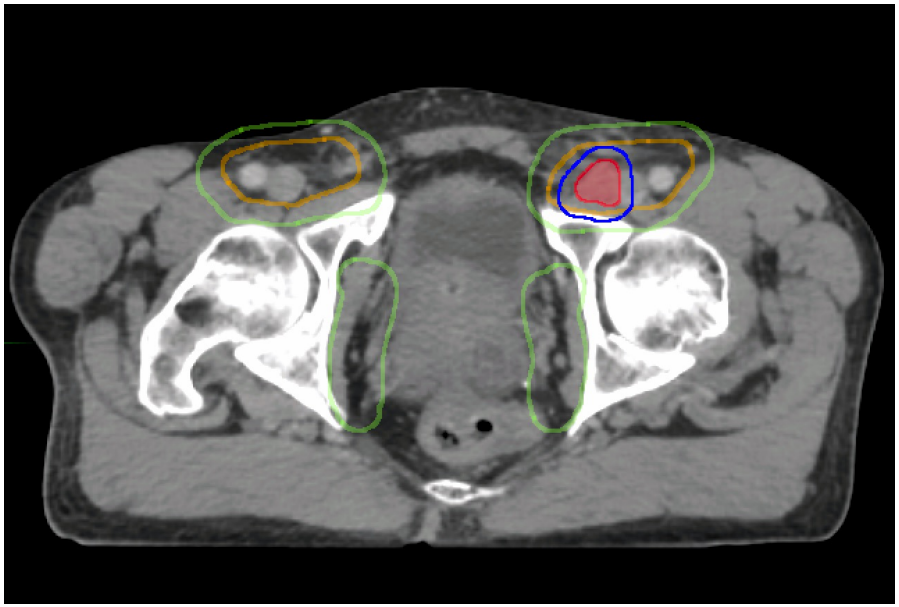
CTV 50.4 = GTVp + 2 cm +
extend to cover perineum/penis



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

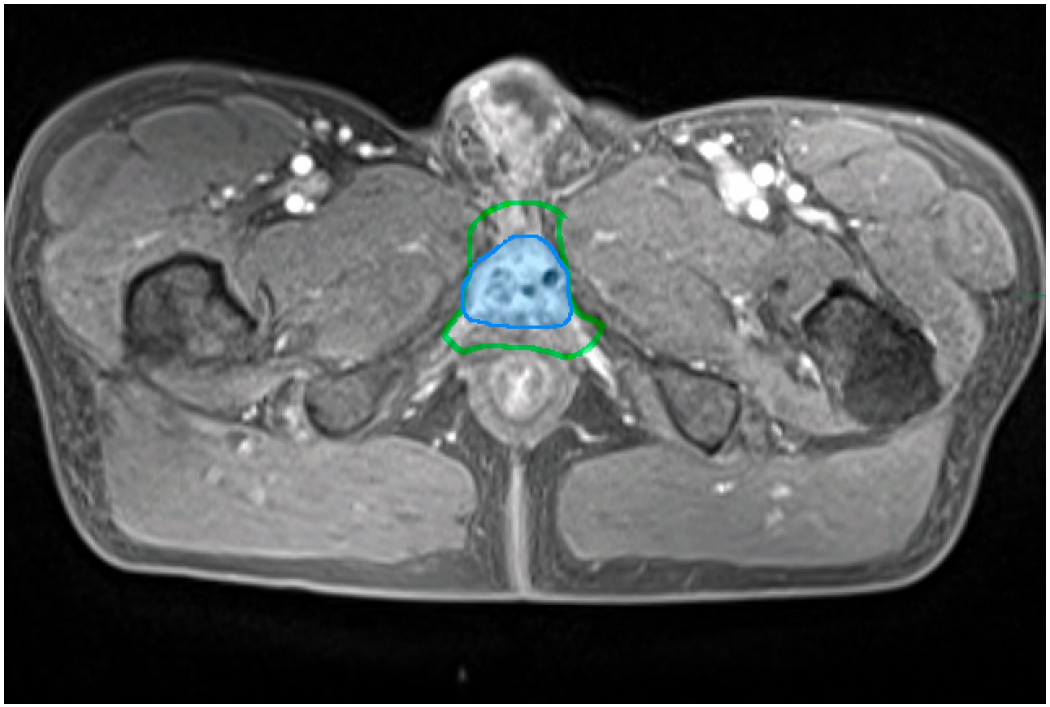
PTV 60-66 = GTVn + 5 mm

Fuse MRI to assist with target delineation

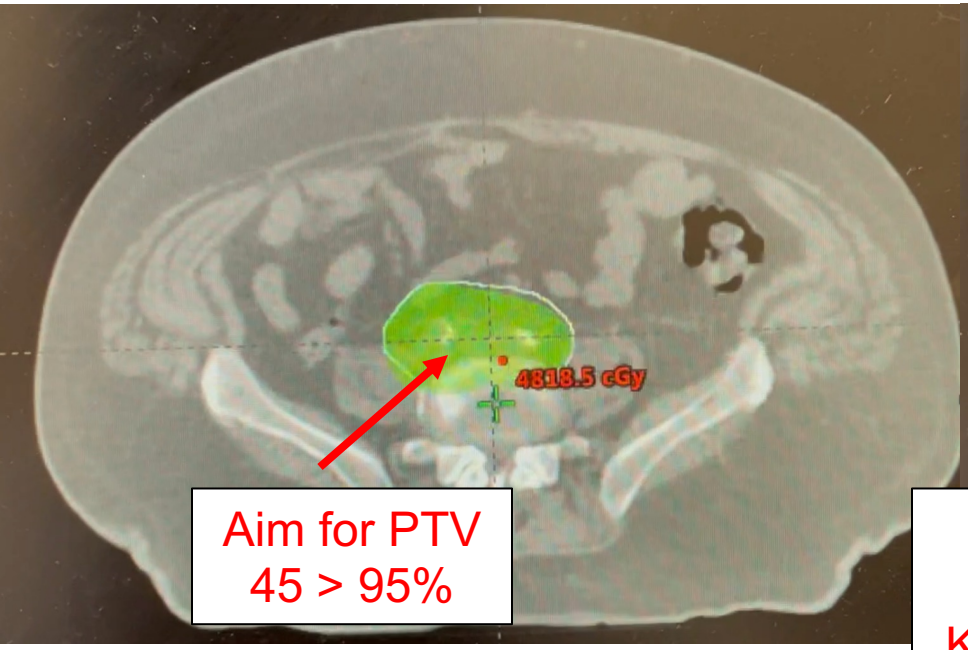
Example for post-op disease recurrence:

GTVp

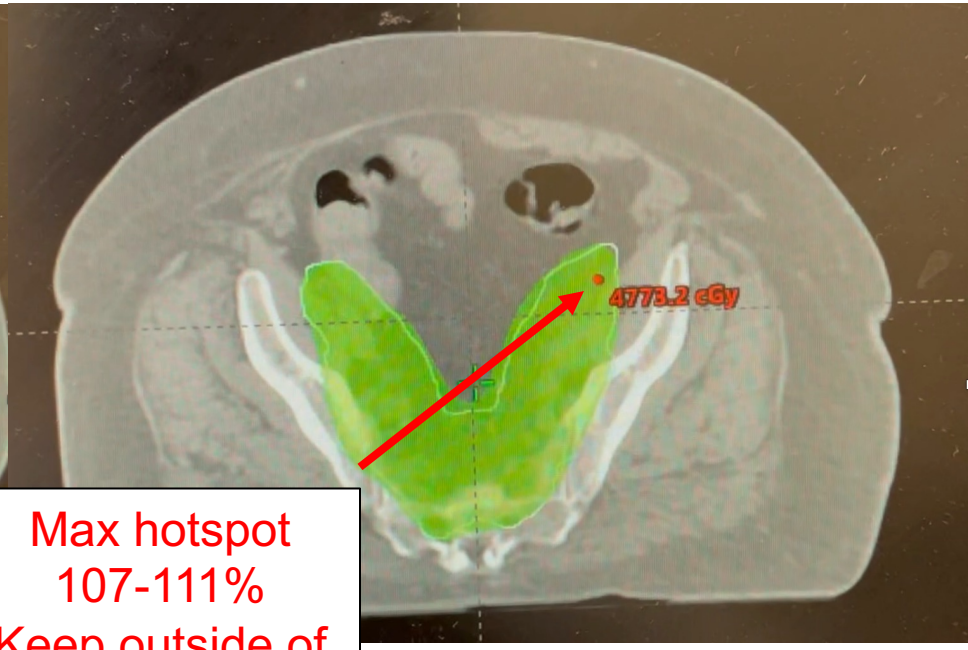
CTV 54-60 = operative bed with inclusion of CTV 66-70 (GTVp + 1-2 cm)



Plan Evaluation

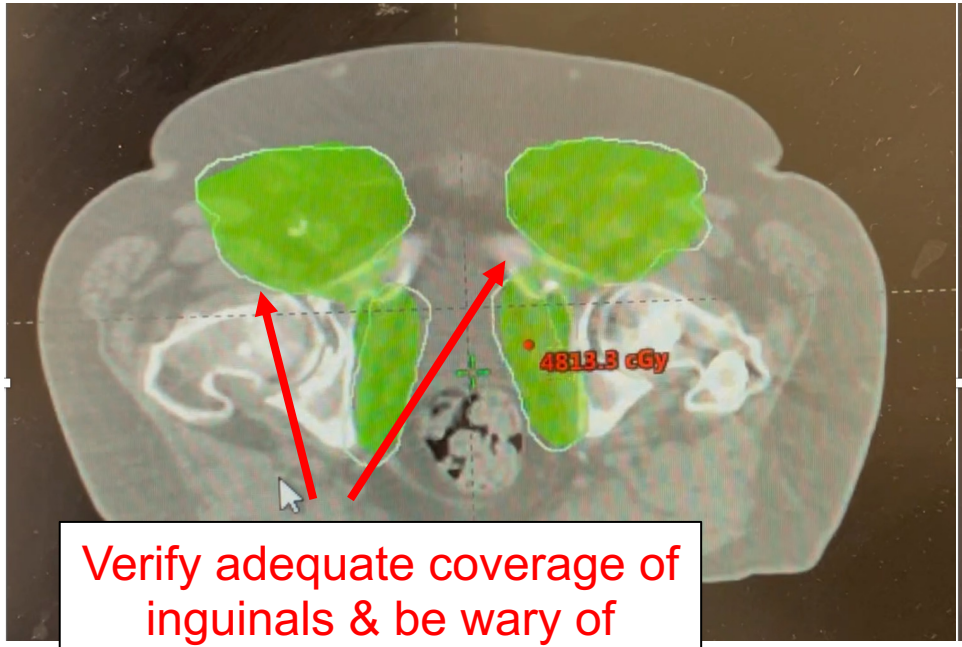


Aim for PTV
45 > 95%

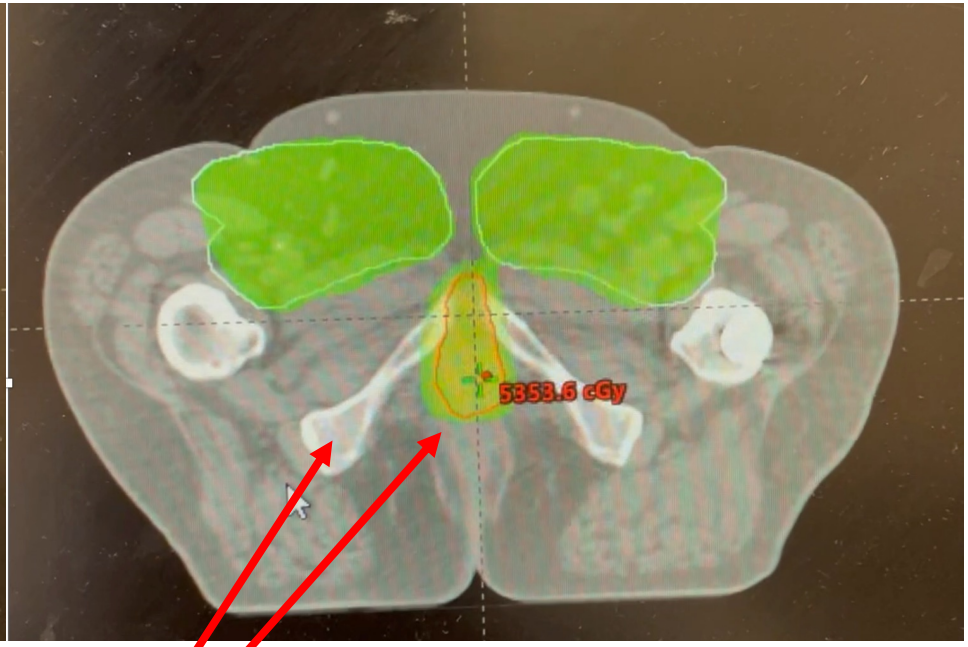


Max hotspot
107-111%
Keep outside of bowel, LS plexus, etc

Plan Evaluation

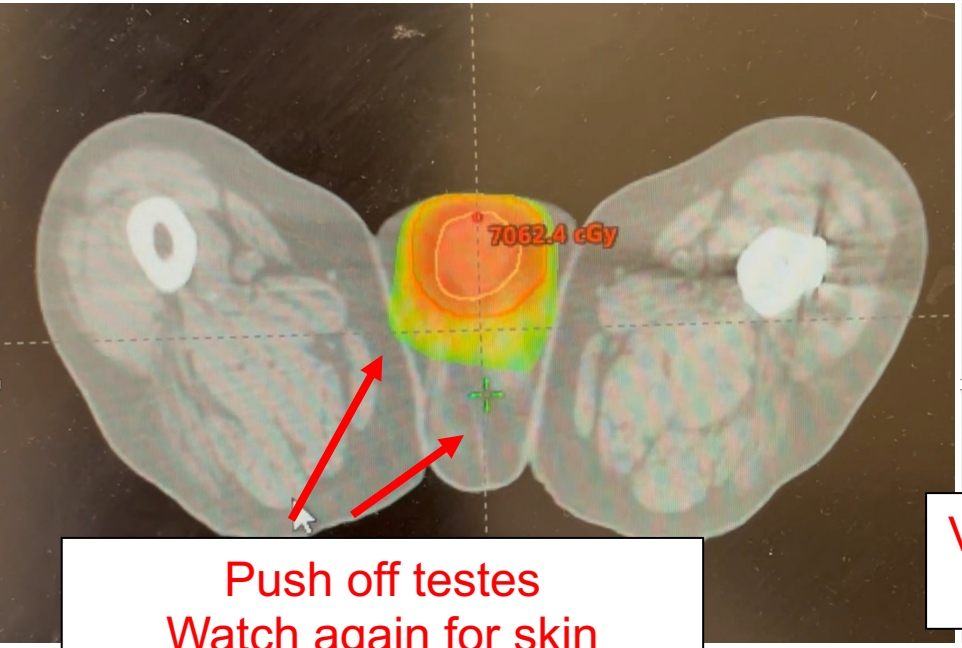


Verify adequate coverage of inguinals & be wary of bolusing at skin creases

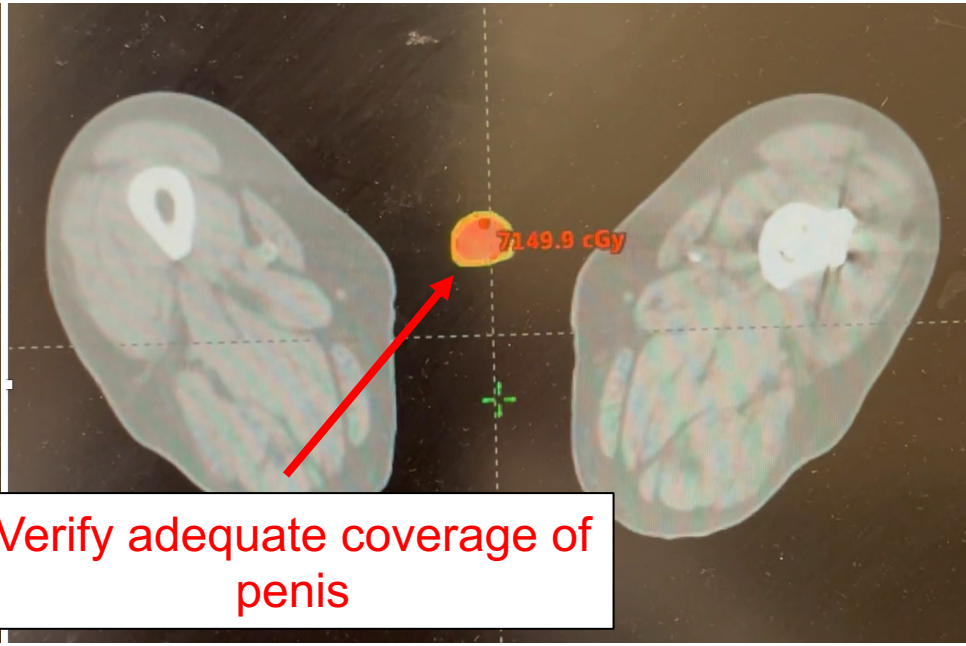


Push off rectum and bone

Plan Evaluation



Push off testes
Watch again for skin bolusing



Verify adequate coverage of penis

EBRT Institutional Constraints

PTV	D99 ≥ 100
Dmax	107-111%
Bladder	V35 < 60%; V45 < 50%
Bone	Max < 50 Gy
Bowel (Small)	Max < 54 Gy
Bowel (Large)	Max < 58 Gy
Cauda	Max < 60 Gy
Femoral Heads	V30 < 50%; V40 < 35%; V44 < 5%
Kidneys	Mean < 15 Gy
LS Plexus	Max < 60 Gy
Penile Bulb (if not in CTV)	ALARA
Rectum	V45 < 50%; V65 < 15%; V65 < 10cc
Spinal Cord	Max < 45 Gy
Testes (± lead shielding)	ALARA
Vagina (if not in CTV)	ALARA

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

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