URETHRAL CANCER

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Objectives

- Urethral cancer (male, female)
  - Epidemiology
  - Etiology
  - Anatomy and Histology
  - Spread
  - Presentation
  - Diagnosis
  - Staging
  - Management
- Urethral recurrence after cystectomy
- Urethral cancer within urethral diverticulum
Epidemiology

Rare <1% of all male and all female GU ca

Male
- >50s

Female
- 50-60s
- 4x more common than males
- The only GU ca more common in females
- 85% white

Rare and very aggressive → much controversy about optimal management

Etiology

Male
- Chronic inflammation (STDs 25%, strictures 50%, urethritis)
- HPV 16 in SCC

Female
- Chronic inflammation (STDs, urethritis, diverticula)
- Caruncles
- Parturition
- Polyps
- Leukoplakia
- HPV 16
- Other viruses
Classification

- Primary vs Metastatic
- Location (Anterior vs Posterior)
- Histology
- Staging (TNM, Superficial vs Invasive)

Anatomy & Histology

Pelvic nodes (iliac/obturator)

Inguinal nodes (superficial/deep)
“Dual” blood supply of urethra

- Antegrade flow
  - Bulbourethral - spong
  - Cavernosal
  - Dorsal – spong to glans

- “Retrograde” flow
  - To spong via glans
**Pelvic nodes (iliac/obturator)**

**Inguinal nodes (superficial/deep)**

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**Histology**

**MALE**
- 80% SCC
- 15% TCC
- 5% adeno, melanoma, lymphoma, paraganglioma, sarcoma, undifferentiated

By location:
- 60% bulbomembranous
  - SCC 80%, TCC 10%, adeno or undifferentiated 10%
- 30% penile
  - SCC 90%, TCC 10%
- 10% prostatic
  - TCC 90%, SCC 10%

**FEMALE**
- 50-70% SCC
- 25% adeno
  - *Most common in diverticula*
- 10% TCC
- Rare - lymphoma, neuroendocrine carcinoma, sarcomas, paragangliomas, melanoma, and metastasis
**Spread**

**MALE**
- Local extension
  - Vascular spaces of corpus spongiosum, periurethral tissues
- Lymphatic
  - Anterior → inguinal, occ ext iliac
  - Posterior → pelvic
- Hematogenous
  - Uncommon, advanced dis

**FEMALE**
- Local extension
  - Distal → skin/vulva ulcers
  - Proximal → vagina or bladder
- Lymphatic
  - Uncommon early
  - Anterior → inguinal
  - Posterior → pelvic
- Hematogenous
  - Uncommon
  - Lung, liver, bone, brain

**Presentation**
- 96-98% symptomatic
- Urethral bleeding
- Obstructive voiding symptoms
- Palpable or bulging mass
- Frequency
- Dysuria
Diagnosis

- Hx
- PE – inguinal nodes?
- Urine cytology - ?*
- Cystourethroscopy + bx (TUR or needle)
  - If urethral adenoca → need GI consult, colonoscopy to r/o colon primary
- EUA
  - Bimanual of rectum, perineum, urethra, external genitalia
  - +/- flexible sigmoidoscopy
- CT abdo/pelvis
  - soft tissue, LNs, bone
- CXR
- MRI
  - invasion of corpora cavernosum

Urine Cytology

Cytology not reliable to diagnose primary urethral carcinoma (Touijer and Dalbagni, 2004)

41 female, 29 male pts with primary urethral ca

Female
- 59% positive cytology; SN highest in SCC 77%

Male
- 55% positive cytology; SN highest in TCC 80%
- 73% SN in men with tumors of pendulous urethra
History of obstructive voiding symptoms in male

Retrograde urethrogram – irregular stricture of bulbous urethra

Kawashima A et al. Radiographics 2004;24:S195-S216

Squamous cell carcinoma of the male urethra

T2 weighted MR
focal mass (M) in corpus spongiosum (cs) at penoscrotal junction

Mass (large arrow) not invading the corpus cavernosa (small arrows)
History of incomplete emptying in female

Voiding cystourethrogram – irregular narrowing in urethra with sinus tracts

Kawashima A et al. Radiographics 2004;24:S195-S216

Large urethral carcinoma in 40 yo female

T1 weighted fat suppressed MR post gadolinium

Large urethral carcinoma in 40 yo female

T2 weighted MR with vaginal gel (white) – no invasion through vaginal wall


Staging

- TNM female = male
- TCC prostate staged separately

At diagnosis:
- 1/3 pts have palpable nodes
  - 90% malignant
- 1/2 pts with proximal or advanced local diz have palpable nodes
- 20% have pelvic nodal mets
  - another 15% will develop during follow-up
- Mets outside pelvis rare
No significant differences in survival based on histologic subtype

Treatment based on location and clinical stage

Superficial disease better survival than invasive disease

Anterior lesions assoc with improved survival vs posterior lesions in both males and females (Zeidman et al 1992, Dalbagni et al 1998)
General Management

**MALES**
- Surgery!!!
- Anterior control better than posterior
  - Local invasion/distant mets
- Penile urethra
  - Partial penectomy
  - Radiation (if refuse sx)
- Bulbomembranous
  - Radical excision
- Advanced/mets
  - Sx + Chemo/radiation

**FEMALES**
- Distal 1/3 urethra
  - Circumferential excision
  - Laser coagulation
- Proximal 2/3 urethra
  - Anterior exenteration + radiation/chemo

Outcomes - Male urethral ca

- Overall survival rate low
- Dalbagni et al 1999
  - 46 men with primary urethral ca
  - Median follow-up 125mos
  - Overall survival rate at 5 years
    - All comers: 42%; disease specific 50%
    - 83% superficial
    - 36% invasive
    - 69% anterior tumors
    - 26% posterior tumors
- New treatment strategies needed
General Management

- Multimodal therapy for high stage?

- Gheiler et al, 1998
  - 21 patients with primary urethral ca
  - Mean follow-up 42.1mos
  - Overall survival 62%
  - Ta-2 N0M0 - 8/9 (89%) disease free
  - T3-4N0-2M0 - 5/12 (42%) disease free
    - 10pts had chemo+radn+sx→50% disease free
    - 2pts surgery alone →0% disease free
  - Advanced disease has better outcome with multimodal therapy

Management in Males

- Penile urethra
  - Superficial, papillary, low grade, SC-CIS
    - TUR or local excision (not SC-CIS)
    - distal urethrectomy + penile urethrostomy
  - Infiltration of spongiosum
    - Distal half penile urethra
      - Partial penectomy with 2cm negative margin
  - Proximal half penile urethra
    - Total penectomy
      - 13% local recurrence rate
  - Iliinguinal lymphadenectomy if palpable LNs and no pelvic or distant mets
    - No role for prophylactic LND
Distal urethrectomy with partial glansectomy – residual penile urethrostomy

**Management in Males**

- **Bulbomembranous urethra**
  - Poor survival for all forms of treatment
  - Radical excision best long term control and lowest recurrence

  - Radical cystectomy, PLND, total penectomy
  - +/- resection of pubic rami, adjacent urogenital diaphragm (increased resection margin/control)
Ischiopubic rami resected

Cystoprostatectomy
Urethrectomy
Penectomy
Inferior pubectomy

Radiation
- Few reports for early stage lesions who refuse surgery
- Unknown long term results
- Preserves penis, does not prevent recurrence
- Skin ulceration/necrosis, stricture, chronic edema

Chemotherapy (small studies)
- Neo/adjuvant chemo for advanced/met
- Neoadjuvant MVAC – active against TCC only
- Neoadjuvant BMP – active against SCC

- Multimodal therapy also used for advanced/mets

Management in Males
Management in Females

Most significant prognostic factors for local control and survival
- anatomic location
- extent of primary tumor
- Anterior>>posterior
- Superficial>>invasive

Distal 1/3 urethra
- Cure rate 70-90% local excision alone
- Small, exophytic, superficial
  ◦ Circumferential excision of distal urethra + portion of anterior vaginal wall
  ◦ Laser coagulation described
- T2 or T3
  ◦ Radical urethrectomy up to level of bladder with diversion
  ◦ Partial urethrectomy +/- radiation
    - recurrence rate of 0-50%

Complications
- Meatal stenosis – spatulate urethra
- Incontinence – approx ant vag wall and labia, sling
Management in Females

- **Radiation**
  - Brachy, external beam, combined
  - Effective for low stage, distal ca
    - 5 yr survival in 84 pt series (Garden et al 1993)
      - 74% if part urethra involved
      - 55% if whole urethra involved
  - Complex 20-40%: stricture, necrosis, fistula, incontinence, vulvar abscess, cellulitis, cystitis
  - Neoadjuvant irradiation has some survival advantage

- **Groin dissection if**
  - palpable nodes without distant mets or
  - regional adenopathy during surveillance

Management in Females

- **Proximal 2/3 urethra**
  - More likely to be high stage, involve vagina, bladder
  - Anterior extent alone
    - 5 yr survival 10-17%, local recurrence 67% (Klein et al 1983)
    - Combination therapy recommended
      - Mean 5 yr survival radiation+sx – 54% (Terry et al 1997)

- **Advanced female urethral ca**
  - Proximal location
  - Encompass entire urethra
  - Involves external genitalia, vagina, bladder
    - Cystourethrectomy, PLND, wide or complete vaginal excision
    - +/- partial vulvectomy, labial excision
    - +/- pubic symphysis and inferior pubic rami if lesion anterior at pubis
Management in Females

- Chemo/rad + sx recommended in advanced ca
  - SCC – 5 –fluorouracil + mitomycin C
  - TCC – MVAC or GC

- Chemo acts as radiosensitizer
- Ant exent + high dose intraop brachy + EB rad may improve survival (Dalbagni et al 2001)

Urethral Recurrence after Cystectomy

- ~40% of urethral recurrence diagnosed within 1 year after cystectomy
  - Median time to diagnosis = 18 months (Clark et al, 2004)
  - Late recurrence reported (Freeman et al, 1996)

- ~60% will have symptoms
  - urethral bleeding (cutaneous), hematuria (orthotopic), discharge, mass
  - cysto + biopsy
  - CT/MRI
Urethral Recurrence after Cystectomy

- Can be due to
  - Unrecognized urethral involvement at time of cystec
  - Tumor spillage or implantation
  - Growth from positive margin
  - De novo TCC from field change (most likely)

Males

- After cutaneous diversion
  - 2.1-11% recurrence rate (Freeman et al, 1996)
  - Prostatic stromal invasion increases risk of urethral recurrence
  - Post cystectomy monitoring: urethral wash cytology

- Treatment: total urethrectomy including urethral meatus
Urethral Recurrence after Cystectomy

Stein et al 2005 – predictors for urethral recurrence

- 768 men post rad cystectomy for bladder ca
- 13 yr median followup
- 45 anterior urethra recurrences @ median 2yrs
- Probability of urethral recurrence
  - 7% @ 5 yrs, 10% @ 10 yrs
- 129 pts with TCC involving prostate
  - 11% urethral recurrence
  - 5yr recurrence risk if
    - superficial prostate (ductal, mucosal) = 12%
    - Stroma-invasive = 18%
    - No prostatic involvement = 6%

- **Prostatic involvement esp stromal most significant predictor of urethral recurrence**

Urethral Recurrence after Cystectomy

How should the urethra be sampled to identify prostatic involvement?

- Lebret et al 1998
- 118 pts; prospective study, min 10yr f/up
- All underwent endoscopic latero-montanal biopsy
  2 weeks prior + intraop frozen section urethra
  - 106 negative x 2
  - 12 had TCC x 2 → en bloc urethrec at time of cystec
  - 9 had -ve frozens but +ve biopsy → urethra preserved
  - None of the 9 developed urethral recurrence

- Intraop frozen section of apical prostatic urethra sufficient
Urethral Recurrence after Cystectomy

- After orthotopic diversion
  - 0.5-4% recurrence rate (Freeman et al, 1996)
  - Low incidence if negative frozen section of distal prostatic urethral margin at time of cystectomy
  - Post cystectomy monitoring: Voided urine cytology

- Treatment:
  - CIS: can try urethral BCG perfusion
  - Papillary or invasive disease: total urethrectomy with excision of cuff of pouch adjacent to anastomosis and cutaneous diversion often using portion of existing neobladder

Urethral recurrence after cystectomy

- Clark et al 2004 – predictors of survival
  - 1094 patients post cystectomy for invasive bladder ca
  - Retrospective; 47 men diagnosed with urethral TCC
  - Median time to diagnosis - 18.5 mos after cystectomy
    - 40% diagnosed within 1 year
    - 57% symptomatic
    - 31% asymptomatic with abnormal cytology – cytology done yearly
  - 41 pts underwent urethrectomy
    - 38 - total
    - 3 - perineal urethrostomy

- Overall survival at 26 mos after diagnosis of urethral TCC
  - 23% (36/47 dead – 25 of metastatic disease)
  - 21% disease free
- Stage (superficial vs invasive) at dx most important predictor of survival
Females
Few reported cases - no consensus
- After cutaneous diversion
  - total urethrectomy
- After orthotopic diversion
  - urethrectomy + resection of area of urethra-pouch anastomosis
  - Conversion to cutaneous diversion (continent or conduit) if absence of mets

Stein et al 1998 – predictors for urethral ca in females
- 71 female cystectomy specimen for bladder ca
- 19% bladder neck involvement
  - 60% had normal proximal urethras
- 7% urethral involvement
  - All pts had BN involvement
- **BN tumor most sig risk factor for tumor involving urethra**
- 47 had intraop frozen sections of proximal urethra
  - 45 had no urethral involvement
  - 2 had urethral tumor
  - All correlated with final specimen
- **Can reliably evaluate distal urethral margin with intraop frozens**
Urethral Carcinoma within Diverticulum

- 5% of all female urethral carcinoma
- Adenocarcinoma most common
  - TCC second most common

Diverticula
- 30-50’s
- Thought to arise from obstructed periurethral glands (adenoca)
- Most are benign (Thomas et al, 2008)
  - 90 patients with diverticulectomy
    - 6% adenocarcinoma
    - 66% chronic inflammation

Hx, PE, cysto+biopsy, MRI

Treatment
- Invasive disease: anterior exenteration and urethrectomy
- High rate of local recurrence with subsequent need for anterior exent if diverticulectomy alone (Rajan et al, 1993)
- Multimodal therapy may be advantageous (Gheiler et al, 1998)
Urethral Carcinoma within a Diverticulum

21 patients with urethral carcinoma (Gheiler et al, 1998)
- 4 patients within a diverticulum T2-3
- Multimodal therapy beneficial

<table>
<thead>
<tr>
<th>Location</th>
<th>Histology</th>
<th>Stage</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>Adenocarcinoma</td>
<td>pT3N1</td>
<td>Pelvic exenteration</td>
<td>24 mo, recurrence</td>
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<tr>
<td>Proximal</td>
<td>Adenocarcinoma</td>
<td>pT3N2</td>
<td>Neoadjuvant Ch/R; pelvic exenteration</td>
<td>48 mo, DF</td>
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<tr>
<td>Proximal</td>
<td>Adenocarcinoma</td>
<td>cT2N2</td>
<td>Ch/R; pelvic exenteration</td>
<td>50 mo, recurrence</td>
</tr>
<tr>
<td>Distal</td>
<td>Adenocarcinoma</td>
<td>cT2N0</td>
<td>Distal urethrectomy</td>
<td>70 mo, recurrence</td>
</tr>
</tbody>
</table>

69 yo female with frequency and dysuria x months. Palpable mass on anterior vaginal wall.

XR shows several radioopaque calculi in pelvis

69 yo female with frequency and dysuria x months. Palpable mass on anterior vaginal wall.

CT shows periurethral tumour (*) with arrows showing dependent calculi in diverticulum

T2 weighted MR with hypointense urethral tumor in diverticulum
T1 weighted fat suppressed image post gadolinium with tumor enhancing.


69 yo female with dysuria, frequency x months

Anterior exenteration and total urethrectomy specimen. Tumor and stones within diverticulum.
Primary urethral cancer is rare but aggressive
- Poor survival
- Predictors of survival
  - Stage at diagnosis (superficial>>>deep)
  - Location of tumor (anterior>>>posterior)
- Multimodal therapy seems to increase survival in advanced disease
- Recurrence post cystectomy requires aggressive treatment
- Cancer within diverticulae usually present at high stage also requiring aggressive management
- Optimal multimodality treatments controversial

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