BLADDER CANCER AND URINARY DIVERSION

The Essentials 2013

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Disclosures

- None
Bladder Cancer

- 61,420 new cases
- 13,060 cancer related deaths
- Second most common GU malignancy
- Male female ratio slightly less than 3:1
- Men 4th most common (7th death)
- Women 8th most common (10th death)
- One half as common in African-Americans
- 2/3 over the age of 65, rare under age 30
Bladder Cancer

- Overwhelmingly a sporadic disease
- Environment and Occupational exposure have a role
- Analinedyes
- Cyclophosphomide(acrolein) 9X
- Ionizing Radiation
- Chronic Infection [stone, indwelling catheter]
- Phenacetin ingestion, dietary fat
- Tobacco exposure
Bladder Pathology

Normal Urothelium → Atypia → dysplasia → CIS

- P53
- pRb
- p14ARF
- p21
- p21

- Papillary tumors
- 9q
- 17p

Muscle invasive
Bladder Cancer-Pathology

Over 90% of lesions are **transitional cell carcinoma**

- 5-7% of lesions are **pure squamous cell**. Associated with chronic irritation [stones, foley catheter, Schistosomiasis]
- 1-2% **Adenocarcinoma** [urachal carcinoma, cystitis glandularis]. Rule out **metastatic source**.

**Metaplastic elements** of squamous or Adenocarcinoma in TCC is different than pure tumor devoid of TCC
# Classification of Papillary Urothelial Neoplasms

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Papilloma</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Grade 1</td>
<td>PULMP  low grade</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Low and high grade</td>
</tr>
<tr>
<td>Grade 3</td>
<td>High grade</td>
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## Bladder Cancer-Staging

<table>
<thead>
<tr>
<th>Tumor depth</th>
<th>Strong-Jewett</th>
<th>UICC/AJCC</th>
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<tbody>
<tr>
<td>urothelium</td>
<td>0</td>
<td>pTa</td>
</tr>
<tr>
<td>Cis</td>
<td>cis</td>
<td>pTis</td>
</tr>
<tr>
<td>Lamina propria</td>
<td>A</td>
<td>pT1</td>
</tr>
<tr>
<td>Superficial muscle</td>
<td>B1</td>
<td>pT2</td>
</tr>
<tr>
<td>Deep muscle</td>
<td>B2</td>
<td>pT3a</td>
</tr>
<tr>
<td>Perivesical fat</td>
<td>C</td>
<td>pT3b</td>
</tr>
<tr>
<td>Adjacent organs</td>
<td>D</td>
<td>pT4a</td>
</tr>
<tr>
<td>Pelvic wall</td>
<td>D</td>
<td>pT4b</td>
</tr>
</tbody>
</table>
Bladder Cancer-Staging

BLADDER CANCER STAGING (TNM)

- Ureters
- Muscularis Propria
- Perivesical Fat
- Adjacent organs

Layers:
- Lamina Propria
- Urothelial layer (mucosa)

Stages:
- Tis
- Ta
- T1
- T2
- T3a
- T3b
- T4
Superficial TCC

- Most tumors are transitional cell carcinomas
- 70% are superficial
- 10-20% progress to muscle invasion
Bladder Cancer-Diagnosis

Urine Cytology-
A high specificity for true cancer diagnosis.
20% false negative
1-12% false positive (inflammation, prior chemotherapy or XRT)
Urine Cytology
Urinary Marker Characteristics

Ideal marker displays 100% sensitivity, specificity and accuracy

SENSITIVITY - the ability to detect disease
SPECIFICITY - the ability to exclude healthy individuals

Low Specificity - false positives
diagnosis anxiety (elevated PSA)
unnecessary diagnostic evaluations

Low Sensitivity - False negatives
missed diagnosis
delay in therapy
disease progression
Urinary Markers-Detection and Surveillance

BTA, BTA stat, BTA trak
NMP22
Telomerase
HA-Haase
Microsatellite Analysis
Urovysion [FISH]
BCLA
Fluorescence in situ hybridization

- Fish assay to detect loss of 9p21 and aneuploidy of 3,7,17

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>FISH</td>
<td>71%</td>
<td>95% CI (58-82)</td>
</tr>
<tr>
<td>BTA stat</td>
<td>50%</td>
<td>95% CI (37-63)</td>
</tr>
<tr>
<td>Cytology</td>
<td>26%</td>
<td>95% CI (16-39)</td>
</tr>
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</table>

**Sensitivity** - 176 Patients with history of TCC

**Specificity** - 94.5%

55% of TaG1 and 100% of Tis detected
FISH

Normal urothelial cell

Malignant cell
Bladder Cancer-Diagnosis

- Newer markers may have impact on length of cystoscopic interval
  - marker level high
  - greater hazard of recurrence
  - shorten cystoscopy interval
- Many “false positive” marker values demonstrate a diagnostic lead time of 6-12 months
TURBT

• Classic treatment is transurethral resection

• Important to obtain muscle in the specimen for accurate staging

• Surveillance every 3 months for 1 yr then every 6 months for 2 yrs and then yearly thereafter
# Bladder Cancer-Natural History

<table>
<thead>
<tr>
<th>pathology</th>
<th>%recurrence</th>
<th>%progression</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>63</td>
<td>2-10</td>
</tr>
<tr>
<td>Grade 2</td>
<td>67</td>
<td>11-19</td>
</tr>
<tr>
<td>Grade 3</td>
<td>71</td>
<td>33-45</td>
</tr>
<tr>
<td>Stage Ta</td>
<td>52</td>
<td>4</td>
</tr>
<tr>
<td>Stage T1</td>
<td>77</td>
<td>30</td>
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Bladder Cancer

Treatment of Superficial Bladder Cancer with Intravesical Chemotherapy
INTRAVESICAL AGENTS

- MITOMYCIN C
- DOXORUBICIN
- VALRUBICIN
- EPIRUBICIN
- THIOTEPA

GEMCITABINE
TAXANES
The goal of intravesical therapy with chemotherapeutic agents is to decrease recurrence, prevent progression and eradicate residual disease after TUR resection.
CONCLUSIONS

- An ideal intravesical agent does not exist
- Prophylactic benefit is real
- Benefit demonstrated in first 3 years of therapy
- Little effect on tumor progression
- Single instillation may confer recurrence protection 35%
BCG

- BCG-Bacillus Calmette-Guerin
- Attenuated strain of mycobacterium
- Anticancer activity noted in some tumor systems (melanoma)
- Factors for success: limited tumor burden
  - Immune status
  - Proximity of tumor cells
BCG

- Exact mechanism of action is unknown
- Tumor contact with BCG is required. This is mediated by novel fibronectin receptors and classic integrin receptors
- Appears that T-helper cell response is significant in BCG activity
- IL 12 and INF gamma up regulated
- NOS induction by BCG may also play a role
- PMN response may also be important
BCG-Contraindications

- Persistent UTI
- Immunocompromised
- Immunosuppressed
- Poor functional reserve
- Hepatic insufficiency
BCG-Clinical Effectiveness

- Principle therapy for carcinoma in situ with a 60-80% CR (average 76%)
- Eradication of residual papillary disease in 45 to 60% of cases
- Effective prophylactic agent in decreasing recurrence 20-65% (average 40%)
- Durability of response is an issue: 50-60% at 4 years and 30% at 10 years
BCG-SWOG 6 plus 3 Trial

- Immunostimulation of prolonged period to decrease recurrence and progression
- 6 wk induction plus 3 weekly instillations at 3 and 6 months and 6 months for 3 years
- Median recurrence free survival 76 months in maintenance arm and 35 months in non maintenance arm
BCG- Complications

- LUT Symptoms  80-90%
- Low grade fever  60-80%
- Arthralgia  0.6%
- Pneumonia/Hepatitis  0.7%
- Prostatitis  0.9%
- BCG Sepsis  rare
BCG-Treatment Failure

Treatment failure after one course
- what is the clinical cost/benefit of retreatment?
  7% progression rate
  77% complete response

Treatment failure after two courses
  30% progression rate over 3-5 yrs
  50% metastatic disease over 3-5 yrs

Role for Cystectomy
BCG Alternatives

- BCG and interferon can be administered simultaneously
- 1/3 dose of BCG with 50 million units of INFα2B
- Boosters of 1/10, 1/30, or 1/100 BCG can be used with interferon-trials in progress to determine true clinical effectiveness
Role of Vitamins

**Megadoses of vitamins** (40,000 units vit A, 100mg vit B6, 2000mg vit C, 400 units vit E, 90mg zinc)

Randomized trial of Ta and T1 patients that underwent TUR

recurrence rate-40% in megadose group and 80% in RDA group
TCC-Follow Up

- Presently tumor markers do not direct follow up interval - regular screening cystoscopy is the gold standard
- Upper tract recurrence classically 2-3%
- Cumulative risk of upper tract disease can be higher and continual follow up of upper tracts required
Muscle Invasive Disease-Preoperative Staging

- CT or MR scan - serious understaging and overstaging with respect to T stage and nodal status
- Useful in evaluating hydronephrosis
- Potential value in organ sparing techniques
- Bone scans - useful in pts with clinical signs of advanced disease
- PET scanning limited value in bladder cancer
Muscle Invasive - Treatment Options

- TUR only
- Radical Cystectomy
- Chemo-radiation
Muscle Invasive - Timing of Cystectomy

Cystectomy beyond 12 weeks
- 62% v 35% overall 3 yr survival
- 42% v 84% extravesical or N+ disease

Increase in pT3 status with treatment beyond 90 days - 81% v 52%

Overall and disease specific survival improved if treated within 3 months
Preoperative Assessment - Patient Age

- Multiple series demonstrate low mortality and excellent outcomes in elderly (>75 yrs) patients, approx 2%
- Excellent results in ASA 3-4 patients
- Less long term followup in octogenarians
  - one series of 96 patients - 3.1% perioperative mortality
General Outcomes - Cystectomy

Five year Survival

- P2, P3a cancers - 50-86%
- P3b, P4 cancers - 11-55%
- N+ cancers - 9-40% depending on p stage and # of pos. nodes
General Outcomes - Cystectomy

- Surgical mortality 1-3%
- Minor complications 25-35%
- Major complications 4-6%
- Blood loss 200-1800 cc
Urinary Diversion

- Principle form of therapy is radical cystectomy and urinary diversion
- Classic diversion is the ileal conduit
- More intricate “neobladders” are available
Continent Cutaneous - Urinary Diversion

- Continent cutaneous diversion can be accomplished with a right colon pouch or ileum.
- Continence is provided by plicating or intusscepting the distal ileum and the effect of the ileocecal valve.
Continent Urinary Diversion

- Orthotopic diversions bring the neobladder to the urethra and allow for more natural voiding
- Use of distal ileum most common
- Daytime continence excellent
- 12% hypercontinence especially in women
- Continent diversions require longer surgery and are well suited for younger and active patients
Bladder Sparing - Chemoradiation

- Feasible therapy for appropriate patients
- Smaller lesion with no hydronephrosis
- Better results with repeat TUR -> T0
- Disease specific survival approx 45%
- On average 25-30% require cystectomy
Asymptomatic Microscopic Hematuria

**Definition** - 3 or more red blood cells per high power field from 2 of 3 properly collected urinalysis specimens

Prevalence varies from 0.19% - 21%

-range varies based on age, sex, amount of followup, and number of screenings per patient
Risk Factors for Significant Disease in Patients with Microscopic Hematuria

- Smoking history
- Benzenes or aromatic amines
- Gross hematuria
- Age > 40 yrs
- History of irritative voiding symptoms
- History of urinary tract infection
- Analgesic abuse
- History of pelvic irradiation
Microscopic Hematuria

- Dipstick Method
  limited specificity (65%) for 2-5 red cells per high power field
  should be confirmed by microscopic evaluation of urinary sediment
Microscopic Hematuria

Renal parenchymal disease
- significant proteinuria
- red cell casts or dysmorphic red cells
- renal insufficiency

Urinary Tract Infection
- treat appropriately, repeat UA 6 wks post treatment. If hematuria resolves -> no evaluation
Patient with newly diagnosed asymptomatic microscopic hematuria

Examine benign causes, including menstruation, vigorous exercise, sexual activity, viral illness, trauma and infection.

If one or more of the following are present:
- Microscopic hematuria accompanied by significant proteinuria**
- Dysmorphic red blood cells or red cell casts
- Elevated serum creatinine level (based on normal reference ranges for men and women)

Evaluation for primary renal disease

If conditions suggestive of primary renal disease are not present (i.e., normal creatinine level, absence of proteinuria, absence of dysmorphic red blood cells or red cells casts), or if any of the following are present:
- Smoking history
- Occupational exposure to chemicals or dyes (benzenes or aromatic amines)
- History of gross hematuria
- Age > 40 years
- Previous urologic disorder or disease
- History of irritative voiding symptoms
- History of recurrent urinary tract infection despite appropriate use of antibiotics

Urologic evaluation (see Figure 2)
Patient without conditions suggestive of primary renal disease

Low-risk patient:
- Age < 40 years
- No smoking history
- No history of chemical exposure
- No history of irritative voiding symptoms
- No history of gross hematuria
- No history of urologic disorder or disease

Upper tract imaging

Cytology
- Negative
- Positive
- Treat

Cystoscopy
- Negative
- Consider
- Urinalysis, blood pressure and cytology at 6, 12, 24 and 36 months
- Positive
- Negative
- Positive
- Persistent hematuria, hypertension, proteinuria, glomerular bleeding
- Negative for 3 years
- No further urologic monitoring
- Evaluate for primary renal disease.
- Gross hematuria, abnormal cytology, irritative voiding symptoms without infection
- Repeat complete evaluation.

Cystoscopy
- Negative
- Positive
- Treat

Positive, atypical or suspicious

High-risk patients

Complete evaluation (upper tract imaging, cytology, cystoscopy)

Positive
- Treat

Negative
- Urinalysis, blood pressure and cytology at 6, 12, 24 and 36 months

Glomerular bleeding or proteinuria
- Renal biopsy

Isolated hematuria
- Biopsy controversial
Microscopic Hematuria

- Imaging Modalities
  - IVU
  - Renal Ultrasound
  - CT Urogram
Imaging Modalities - Advantages & Disadvantages

- **Intravenous Urography**
  - widely available and cost efficient
  - limited sensitivity for small renal masses
  - cannot distinguish solid from cystic mass
  - further lesion characterization with CT or US necessary
Imaging Modalities - Advantages & Disadvantages

- Ultrasonography
  excellent for characterization of renal cyst
  limited in detection of small lesions (<3cm)
Imaging Modalities - Advantages & Disadvantages

- Computed tomography
  preferred modality for detection solid mass
  detection rate for renal mass = MR
  best modality for stones, renal infection
  sensitivity 94% for stones compared to
  52% for IVU and 19% for US
  more expensive than IVU, but higher efficacy for the range of pathology
Microscopic Hematuria

- Followup of negative initial evaluation
  - UA, cytology, blood pressure @ 6, 12, 24, 36 months
  - urologic reevaluation
    1) gross hematuria
    2) abnormal cytology
    3) irritative symptoms with no infection