Common Problems in Urology

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Common Problems, new approaches

- Genomic tests for prostate cancer
- Erectile dysfunction
- Hematuria evaluation
- Management of incidental renal masses
- Incontinence and overactive bladder

PSA screening

- IF you and your patient decide to screen
  - Clearly a controversial issue
- What are the new genetic/genomic tests
  - Prolaris
  - Genome DX
- What do they tell you (and what don’t they)

Case

- 55yo man in excellent health, no lower urinary tract symptoms, anxious about diagnosis. PSA 4, cT1c, Gleason 3+3 in 4/12 cores. Normal erectile function, no lower urinary tract symptoms.
- Trying to decide whether to undergo robotic prostatectomy, brachytherapy seed implantation, or active surveillance.
- Asks you about Prolaris or Genome Dx after reading about them in the New York Times
What are these tests?

- They tell you the likelihood of cancer progression by grade or stage
- Helpful for patients deciding on active surveillance vs. treatment
- They DO NOT TELL YOU IF THE PATIENT HAS PROSTATE CANCER
- They require tissue obtained from biopsy
- This is NOT a substitute for PSA screening
- This is NOT a noninvasive way of diagnosing prostate cancer

Many candidate assays

- Tissue: DNA CNV, RNA expression, methylation, IHC/FISH
- Blood: miRNA, metabolic analytes, proteins
- Urine/EPS: RNA transcripts (post-DRE), metabolic analytes
- Imaging: PET, MRSI

The Myriad Prolaris Assay

Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study

- 31 cell cycle progression (CCP) genes, normalized to 15 housekeeper genes
- Score is expressed as average centered expression of CCP genes relative to housekeeper genes; negative scores = less active CCP, positive scores = more active CCP

CCP score stratifies outcomes


Cooperberg et al, JCO 31:1428, 2013
Onco
type DX® Genomic Prostate Score (GPS)

- Quantitative 17-gene RT-PCR assay on manually microdissected tumor tissue from needle biopsy
- Genes and biological pathways predictive of multiple endpoints, with emphasis on clinical recurrence
- Optimized for very small tissue input: six 5 micron sections of single needle biopsy block with as little as 1 mm tumor length

GPS = 0.735*Stromal Response group -0.352*Androgen Signaling group -0.095*Proliferation group -0.368*Cellular Organization group
Scaled between 0 and 100

GPS Test Development: Two Major Challenges Addressed

- Biopsy under-sampling and tumor heterogeneity: Identified genes that predict clinical outcome in both dominant and highest grade regions
- Very small biopsy tumor volumes: Developed standardized quantitative methods for reliable gene expression measurement in prostate needle biopsies

A Wide Distribution of GPS at Each Level of Clinical Risk by CAPRA Score

Pre-Specified Primary Analysis

GPS From Biopsy Predicts RP Pathology Independent of Gleason Score
- Multinomial multivariable logistic regression
- 5 degree

<table>
<thead>
<tr>
<th>Variable</th>
<th>LR Chi-Square</th>
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<tr>
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<tr>
<td>Central Biopsy Gleason Score</td>
<td>32.86</td>
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Cooperberg et al, AUA 2013
Quick facts about Prolaris and Genome Dx

• Both tests are based on multiple genetic alterations
• Genome Dx can predict grade and stage independent of biopsy Gleason grade
• Expensive ~$4000 and not often covered by insurance
• Difficult to interpret
• Good for patients trying to decide whether to pursue active surveillance or treatment for cure with Gleason 3+3 or low volume Gleason 3+4 prostate cancer

Quick facts about Prolaris and Genome Dx

• Require at least 1mm of tissue in biopsy specimen
• No older than 6 months
• The company may help offset costs/payment plan

ERECTILE DYSFUNCTION

What’s new?
PDE5 inhibitors

• Viagra, Levitra
• Cialis daily or prn
• Avanafil (Stendra)
  – Rapid onset of action ~15-30mins
  – FDA Approved Apr 27, 2012
  – Should be available Dec 2013
• Udenafil (Zydena)
  – Daily dose
  – Long half life 12-13 hours
  – Not yet approved in US

HEMATUREA EVALUATION

Case

• 55yo man with painless gross hematuria. He has been treated with Cipro for a presumed urinary tract infection for 7 days but the bleeding continues intermittently. He is trying to quit smoking but is otherwise well.

• 65yo woman with dysuria, microscopic hematuria, frequency, urgency. Cultures intermittently positive and negative. Several courses of antibiotics given as well as anticholinergics.

Hematuria differential dx

Kidney mass

Benign etiology (stones, infection, BPH)

Bladder/ureteral/urethral mass
Hematuria evaluation

1. Upper tract imaging
   - CTabd/pelvis noncontrast, IV contrast, delayed
   - MRI with and without contrast
   - ultrasound

2. Lower tract imaging
   - Cystoscopy (scope into the bladder)

3. Urine cytology

Diagnosis: bladder cancer

carcinoma in situ
Flat, diffuse malignant cells confined to the epithelium (Tis)

Sessile tumors. Exophytic and endophytic components.
Epidemiology

- Transitional cell carcinoma now called urothelial carcinoma
- Fifth most common malignancy
- Peak incidence 60 - 70 years
- Male:female 3:1
- 75-80% are superficial with recurrence 50-80%
- 10-20% of superficial tumors progress to muscle-invasion

Risk factors

- Cigarette smoking (50% of cases)
- Schistosomiasis (squamous cell cancer)
- Chronic UTI or catheter (Squamous cell ca)
- Arylamine exposure (20-25% of cases) – rubber, dye workers
- Pelvic radiation
- Cyclophosphamide chemotherapy

Risk factors

- Familial (Lynch Syndrome II)
- Aristolochia poisoning (chinese herbal nephropathy)
- Analgesic abuse

Staging: depth of invasion

- Peritoneum
- Subserosa and perivesical fat
- Muscles
- Lamina propria
- Submucosa
- Mucosa
- Epithelium
- Region affected
  - Ta (a)
  - T1 (a)
  - T2a (b)
  - T2b (b)
  - T3a (c)

- Infiltration of detrusor, nerves, perivesical fat
- Invasion of pelvic musculature
### Treatment of non-muscle invasive disease
- TURBT alone
- TURBT + intravesical therapy
  - BCG
- Surveillance
  - Cystoscopy every three months for 2 yrs
  - Cystoscopy every six months for 2 years
  - Cystoscopy annually for life

### Treatment of muscle invasive disease or recurrent invasive disease
- Neoadjuvant chemotherapy
  - gemcitabine/cisplatin
- Radical cystoprostatectomy (men) or cystectomy/hysterectomy (women) with urinary diversion
  - Ileal conduit
  - Neobladder
  - Catheterizable pouch
- Bladder salvage with chemoradiation

### Hematuria differential dx
- Kidney mass
- Bladder/ureteral/urethral mass
- Benign etiology (stones, infection, LUTS)

### Renal mass on CT/US/MRI
- Cyst
  - Benign
  - Infection
  - Abscess
  - Pyelonephritis
- Solid
  - AML oncocytoma
- Metastatic
  - Renal cell carcinoma
  - Urothelial carcinoma
  - Metastatic
Renal mass: Benign

- Renal cyst
- Renal abscess/pyelonephritis/focal lobar nephronia
- Benign solid tumors
  - Angiomyolipoma
  - Oncocytoma

Renal cyst

AML – with fat, smooth muscle (M) and blood vessels
Oncocytoma
  • Benign
  • Eosinophilic cells due to increased mitochondria
Usually indistinguishable from malignant solid tumor on imaging

Renal mass: Malignant
  • Renal cell carcinoma
    – 70-80% of renal masses
  • Urothelial carcinoma (used to be called transitional cell carcinoma)
  • Metastatic disease

Renal cell carcinoma

Renal cell carcinoma: where are we now?
  • 64,770 new cases annually
  • 13,570 deaths
  • Increasing incidence of renal cell carcinoma
  • Identification of small, incidental masses
  • Growing interest in surveillance of small renal masses
Stage distribution


Significant Recent Changes

Impacting all Aspects of Disease

- Minimally invasive nephron-sparing
  - Laparoscopic partial
  - Robotic-assisted partial
  - Ablative technologies
- Systemic therapy
  - mTOR and VEGF targeting

Significant Changes

All Aspects of Disease

- Understanding biological basis
  - Inactivation of VHL in >50% of sporadic cases
  - Elucidation of HIF-VEGF pathway
  - Hereditary forms
- Laparoscopic radical nephrectomy
  - First performed in 1990
  - Largely replaced open nephrectomy
  - For cancers as well as living donor harvest

Progress?

Impact of these Changes on Disease

Chow WH et al, JNCI, Apr 2007
Small renal masses...

- Options
- Surgery: nephron sparing or radical?
- Surveillance: is it safe?
- Ablation: which patients, which lesions?

What is the Role of Surgery?

Critical for Localized Disease

- Refined techniques of nephron-sparing surgery
  - Indicated and feasible in nearly all cases
  - Optimize cancer outcomes
  - Reduce morbidity
  - Minimize long-term impact on health

Current Management

Treatment Trends in SEER (cT1)

- Under-utilization of nephron-sparing options

Case #1

54yo man, HTN cr 1.1
Nephron-Sparing Surgery

Open vs. Robotic
- Essentially the same approach
- Adequate renal mobilization
- Complete visualization of tumor margins
  - We have to be able to see the tumor to resect it
- Vascular control
- Meticulous tumor excision
- Renorrhaphy
- Use of intra-operative ultrasound

Nephron-Sparing Surgery

Robotic Tricks for warm ischemia
- Patience in exposure of tumor—see all edges
- Mass always seems more cranial than on imaging
- Artery alone vs. artery + vein occlusion
- Identify all accessory renal arteries
- ...

Nephron-Sparing Surgery

When is Open Surgery Preferable?
- Posterior, upper pole location
- Adjacent to the hilum
- Entirely endophytic—can’t see it
- Solitary kidney for cold ischemia
- Anticipation of complex repair
  - Vascular
  - Collecting system
To nephron spare or not to spare…

- Many if not most lesions are amenable to partial nephrectomy
- Open or laparoscopic/robotic
- Impact of renal insufficiency on overall health more appreciated
- Equivalent oncologic outcomes
- >95% RFS
- Slow adoption of nephron sparing techniques looking at SEER trends
  - Longer surgery, longer stay
  - More complications, more risk
  - Learning curve

Surveillance

- Historically for ill patient with limited life expectancy
- VHL data extrapolated to use a 3cm size limit
- Meta-analyses and observational studies have shown 1-2% metastasis in lesions <3cm

Surveillance-growth rates

- Mean growth 0.2-0.8cm/yr
- Faster growing tumors more likely to metastasize
- Many benign tumors grow at same rate as malignant
- 1/3 of tumors do not grow

Best patients for surveillance

- Stable tumors
  - Tumors with NO GROWTH have NOT METASTASIZED in any study
- Smaller tumors
  - Fewer tumors <3cm metastasize compared to >3cm and none <2cm
- Patients with limited life expectancy
  - Metastasis usually is a late event, after 3 years on surveillance
- Complete evaluation
  - Patient must have no evidence of mets when surveillance starts (so check)
Case #2

- 76yo man with slowly growing left renal mass

- **PMH**
  - COPD on oxygen
  - PVD, stasis ulcers
  - PE/DVT
  - GI bleed
  - HTN
  - Lung mass
  - Recent pneumonia and placed on hospice
  - Renal insufficiency

Role of renal biopsy
Renal biopsy

- Accuracy: ranges from 60%-90% in the literature
- Concern for tumor seeding, bleeding, false negative
- Best results with 2-3 cores using 18 gauge needle
- Difficulty of diagnosing oncocytoma
- Tumor heterogeneity

Tumor seeding

- Tumor seeding: <0.01% incidence. 6 cases in world literature. No cases reported since 1994. Volpe et al J Urol 2009

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<tr>
<th>Reference</th>
<th>Needle</th>
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<td>Auvert et al</td>
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<td>Kiser et al</td>
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<td>24d</td>
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<td>Shenoy et al</td>
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<td>Abe et al</td>
<td>14</td>
<td>18mo</td>
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Case #3

- 59yo woman with history of tetralogy of Fallot repair, GFR>60
- PMH: HTN, arrhythmia
- Incidental renal mass seen during evaluation for GI symptoms

Reference: 
- Volpe et al J Urol 2009
Pathology: fat necrosis and multinucleated giant cell reaction

70yo woman, regional adenopathy, possible renal vein involvement

Path: Renal lymphoma with positive nodes

Best patients to biopsy

- Suspicion of abscess, metastasis, lymphoma
- Guide targeted therapy or surveillance
  - Subtype determines treatment, clear cell, papillary, sarcomatoid
- NO suspicion for urothelial carcinoma, negative cytology
Ablative therapies

• Percutaneous or laparoscopic
• Cryoablation or radiofrequency ablation

Cryoablation seems to have lower rates of recurrence, progression, and retreatment than RFA.

Ablation and recurrence

• Limited follow up, 5 years is longest in literature
• 2 and 5 year RFS 83% and 74%
• When incomplete ablations are excluded this rises to 91% and 85%
• Complication rate <20% most are minor

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Duffey et al J Endour 2012
Kunkle and Uzzo Cancer 2008

Case #4: peripheral lesion
Central lesions
Upper pole, anterior, or adjacent organs

Ideal patients for cryoablation
- Peripheral posterior/lateral lesions <4cm
- Away from spleen, liver, bowel
- Not central
- Not close to vessels
- Older patients, comorbidities which make them poor surgical candidates
- Performed by UCSF Interventional Radiology (and they do a great job!)

Renal mass summary
- Nephron sparing is feasible for many patients with small renal masses, either via surgery or ablation
- Partial nephrectomy can be performed open or laparoscopically/robotically on most masses.
- Recurrence free survival rates with cryoablation are similar to surgical resection (>95% vs 85%).
- Renal biopsy is safe and increasingly accurate.
- Surveillance is appropriate for older patients with small masses. Metastasis occurs in 2-5% of patient with masses <3cm

Incontinence and Overactive bladder
Stress Incontinence vs. Urge Incontinence

- **Symptom**: leak with activities that increase abdominal pressure (cough)
- **Sign**: leak of urine via urethra which coincides with cough
- **Condition**: leak of urine when abdominal pressure increases and bladder not contracting (urodynamics)

- **Symptom**: leak before able to get to the toilet with urge
- **Sign**: spontaneous leak without cough
- **Condition**: involuntary bladder contraction associated with leak

Overactive Bladder

Stress Incontinence Treatments (Women)

- Surgical
  - Urethral injection (synthetic materials)
  - Suspension/Sling (a few examples)
    - Burch suspension (sutures only)
    - Pubovaginal sling
    - Mid-urethral sling
      - The slings can be done with different materials, but synthetic mesh is still the predominant

Male Stress Incontinence Treatments

- Mild Injectable Therapy
- Mild - Moderate Male Slings
- Severe Artificial Sphincter
Overactive Bladder

Definition

- Urinary urgency
- With or without urge incontinence
- Usually with frequency & nocturia

International Continence Society 2003

Epidemiology

- OAB affects 16% of population
- 33 million adults
- Prevalence: women = men


How widespread are the symptoms of an overactive bladder and how are they managed? *Br J Urol Int* 2001;87:760-766.

Prevalence of Chronic Conditions in the US

- Behavioral
- Pharmacological
- Surgical


OAB Treatments
Behavior Modification

- Lifestyle modification
  - limit fluid (4-6 glasses)
  - avoid caffeine, alcohol
  - dosing of diuretic
  - elevate legs
  - compression stockings
  - afternoon nap

Nocturia

Behavior Modification

- Timed voiding
  - assisted toileting
- Bladder retraining
  - Kegel exercises (can suppress urge)
  - restore cortical control
  - support & encouragement important
  - more effective in frequency or urgency of non-neurologic origin

Medications

- Anticholinergic
  - Ditropan
  - Detrol
  - Vesicare
  - Enablex
  - Sanctura
  - Oxytrol (patch) – recent FDA approved OTC for women
  - Gelnique (gel)
  - Toviaz – similar to Detrol

Beta 3 Agonist – New class
- Myrbetrique (Mirabegron)
  - new kid on the block
- Side effect profile very different

Medication Side Effects

- Anticholinergic
  - Dry mouth
  - Constipation
  - Blurry vision
  - Confusion
  - And others...

- Mirabegron
  - Hypertension
  - Urinary retention
  - Nasopharyngitis
  - UTI
  - Headache
Surgical Therapies

- Nerve Stimulation
  - Posterior tibial nerve (SANS, TENS)
  - Sacral nerve (InterStim®)
- Botulinum toxin injection into the bladder – FDA approved!
- Bladder augmentation

Botulinum A

- Easy outpatient procedure
- Efficacy 50-70% (some nearly 100% improvement)
- Lasts 6 months
- Main side effect: retention, UTI
- No serious complications
- FDA approved

Benefits of Sacral Stimulation Therapy

- Effective treatment in properly screened patients
- Safe
- Reversible
- Does not preclude use of other treatments

Contributors:
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Thank you!!