Common Problems in Urology... and new solutions!

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Common Problems, new approaches

• Genomic tests for prostate cancer
• Erectile dysfunction
• Peyronie’s disease
• 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
  – Oncotype 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 Oncotype 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, 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

<table>
<thead>
<tr>
<th>Androgen Signaling</th>
<th>Cellular Organization</th>
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<td>AZGP1, FAM13C, KLK2, SBD52</td>
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<th>Stromal Response</th>
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<tr>
<th>Proliferation</th>
<th>GPS = 0.735<em>Stromal Response group -0.352</em>Androgen Signaling group +0.095<em>Proliferation group -0.368</em>Cellular Organization group</th>
</tr>
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Scaled between 0 and 100

**GPS Test Development:**
- 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**

**Quick facts about Prolaris and Oncotype Dx**
- Both tests are based on multiple genetic alterations
- Oncotype 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

*Cooperberg et al, AUA 2013*
Quick facts about Prolaris and Oncotype Dx

- Require at least 1mm of tissue in biopsy specimen
- No specimen 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
  - Available now
- Udenafil (Zydena)
  - Daily dose
  - Long half life 12-13 hours
  - Not yet approved in US
Peyronie's disease

new medical treatment

Penile curvature caused by plaque formation

Normal Tunical Anatomy

Recent onset

With calcification

Stable > 3 months

Dorsal or dorsal lateral curvatures

Others

Pentoxifylline or colchicine for 3 months

Xiaflex

Surgery
What is Xiaflex and why does it work?

*Xiaflex* : Collagenase
*Clostridium Histolyticum (CCH)*

Animal Collagenase vs. Bacteria Collagenase

- Collagenases digest native collagen in the triple helix region.
- Bacterial collagenase is unique because it can degrade both water-insoluble native collagens and water-soluble denatured ones.
- It can attack almost all collagen types, and is able to make multiple cleavages within triple helical regions (Mookhtiar and Van Wart 1992).
Results

- Curvature change:
  - CCH: 34% (-17.0 ± 14.8 degrees)
  - Placebo: 18.2% (-9.3 ± 13.6 degree)

- Bother score changes:
  - CCH: -2.8 ± 3.8
  - Placebo: -1.8 ± 3.5

Complications in 551 men

Penile ecchymosis, pain and edema: 45%
Corporeal rupture: 3 men
Hematoma: 3

Xiaflex is not recommended in:

- Ventral curvature
- Septal fibrosis
- True lateral curvature
- Large calcification
Asymptomatic microhematuria
- >3RBC on urinalysis
- Not just hemoglobin on urine dip
- New AUA recommendation is to evaluate any patient with >3 RBC and not to repeat the test for confirmation of RBC
- Evaluate for benign source
- All patients over age 35 with risk factors should undergo cystoscopy
- All patients without obvious benign cause need upper tract imaging

Persistent microhematuria
- Annual UA recommended
- After complete evaluation, if UA negative for two years then ok to stop testing
- If microhematuria persists, consider re-evaluating within 3-5 years

HEMATURIA EVALUATION

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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
- Bladder/ureteral/urethral mass
- Benign etiology (stones, infection, BPH)

Hematuria evaluation

1. Upper tract imaging
   - CTabd/pelvis noncontrast, IV contrast, delayed
   - MRI with and without contrast (will miss stones)
   - Ultrasound (may miss ureteral or renal pelvis tumors)

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)

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

Sessile tumors. Exophytic and endophytic components.
Risk factors

• Familial (Lynch Syndrome II)
• Aristolochia poisoning (Chinese herbal nephropathy)
• Analgesic abuse

Treatment of non-muscle invasive disease

• TURBT alone
• TURBT + intravesical therapy
  – BCG
  – Will convert to PPD+
• Surveillance
  – Cystoscopy every three months for 2yrs
  – Cystoscopy every six months for 2 years
  – Cystoscopy annually for life

Treatment of muscle invasive disease or recurrent 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

Benign mass on CT/US/MRI
- Renal cyst
- Renal abscess/pyelonephritis/focal lobar nephronia
- Benign solid tumors
  - Angiomyolipoma
  - Oncocytoma

Malignant mass on CT/US/MRI
- Renal cell carcinoma
- Urothelial carcinoma
- Metastatic
Renal abscess

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


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

Yang G et al, BJU Int, Feb 2012
Case #1

54yo man, HTN cr 1.1
Complex due to proximity to hilum

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
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 will show no growth

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Needle</th>
<th>Time</th>
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<tbody>
<tr>
<td>Gibbons et al</td>
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<td>Auvert et al</td>
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<td>Oncocytoma</td>
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<td>Kiser et al</td>
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<td>24d</td>
<td>Papillary RCC</td>
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<td>Shenoy et al</td>
<td>23</td>
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<tr>
<td>Abe et al</td>
<td>14</td>
<td>18mo</td>
<td>liposarcoma</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
Central, indistinct, close to collecting system and hilum
Pathology: fat necrosis and multinucleated giant cell reaction

70yo woman, regional adenopathy, possible renal vein involvement
Open radical nephrectomy with node dissection

**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

Ablative therapies

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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<tr>
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<td>1.3</td>
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<td>Local progression %</td>
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<td>Metastasis</td>
<td>1.8</td>
<td>1</td>
<td>2.5</td>
<td>.06</td>
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</table>

Duffey et al J Endour 2012
Kunkle and Uzzo Cancer 2008

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.
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

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

OAB Treatments
- Behavioral
- Pharmacological
- Surgical

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

Nocturia
- 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

Summary of OAB

- OAB is THIRD most common chronic condition in the United States!
- Lifestyle modifications and medications best first step
- Temporary and permanent surgical therapies are available as well

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Thank you!!