**CEUS of the Prostate**

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**Prostate Cancer**

**2017 Data**

- Incidence: 161,360  
- Deaths: 26,730

- Third leading cause of cancer death in men (after lung & colon Ca)

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**The Prostate Cancer Screening Dilemma**

- Screening tests - not specific  
  - Digital Rectal Examination (DRE)  
  - Serum Prostate Specific Antigen (PSA)  
  - Transrectal ultrasound (TRUS)

- Positive biopsy rate is 1/3 to 1/4  
- Repeat biopsies with multiple cores

- ~ 1,000,000 men annually subjected to prostate biopsy, many with saturation biopsy - how many insignificant cancers do we find?

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**Normal Prostatic Echotexture:**

- Outer gland: usually iso- to hyper-echoic  
- Inner gland: less echogenic

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**Abnormal Prostatic Echotexture:**

- Prostatitis  
- Infiltrating Cancer

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**The Biopsy Dilemma**

- Sextant misses 30% of cancers

- Newer biopsy strategies  
  - 10-12 cores or “saturation” biopsy  
  - Increased pathology costs & morbidity  
  - 2/3 of prostate biopsies are “negative”

- “If you drill more wells, you will find more oil” - JB Hunt

- How many wells should we dig?

- Are we finding non-significant cancers?
The Ideal Diagnostic Study

- High sensitivity / specificity for cancer
- Most importantly, accurate diagnosis of clinically significant disease
  - Lesion stage (size)
  - Gleason score
  - Microvascular Density

Gleason sum 9

Microvessel Density

Normal Prostate
Gleason 6 Cancer

Conventional Gray Scale Features of Prostate Cancer

- Usually isoechoic - hypoechoic
- Rarely echogenic
- Focal contour bulge
  - size
  - cellular differentiation
  - fibrotic reaction

Gleason 9 & 10

Normal Blood Flow to Prostate

- Radial, evenly distributed
- Symmetric within PZ
- BPH:
  - Increased inner gland flow
  - Large BPH nodules can distort/compress PZ
  - High flow of BPH nodules can overwhelm subtle PZ foci
- confounders: prostatitis, recent ejaculation, patient position

Color vs Power Doppler

40 y.o. with Gleason 8 PCa

Color
Power

Doppler Detection of Prostate Cancer

Gleason 7 midline PCa
Jefferson Experience: Sonographic Accuracy

- Sonographic Accuracy:
  - Sensitivity 44.1%
  - Specificity 73.6%
  - Kappa of 0.12

- Targeted biopsy:
  - Gray scale: Sensitivity 27.0%
  - Doppler: Odds Ratio = 3.7
  - Color & Power Doppler are approximately equal in accuracy, but fail to detect over 50% of PCa

Ultrasound Contrast Agents

- Color/Power Doppler can detect vessel diameter ≥1mm
  - Larger, feeder vessels to malignant foci
- Microvessels within CaP 10-50 μm
  - Not visible with standard Color/Power Doppler
- Microvessels can be visualized with contrast-enhanced US

Imavist™ - Gleason 6 - Left Base
Contrast-enhanced Doppler

Left Mid: Gleason 6
Harmonic Gray Scale Enhancement

- Gray scale resolution is superior to Doppler
- Better estimate of true tumor boundaries

Continuous vs. Intermittent Harmonic Imaging

- Intermittent → Increased overall enhancement
- Intermittent → Contrast passes into distal circulation
- Size selective vascular enhancement
  - longer delay → smaller vessels

Continuous
Gleason 7, Left mid-gland
Contrast-enhanced Harmonic Imaging vs color/power Doppler
Benign Nodule at Prostate Base
No contrast enhancement

Conventional vs. Contrast-Enhanced TRUS

Definity trial: 60 pts
Improved detection with CE-TRUS
\( p = 0.027 \)
Halpern et al. Radiology

Results confirmed in
DOD trial of 301 pts
Halpern et al. Cancer

Flash Replenishment Imaging

- Microflow technique
  - High power flash pulses destroy bubbles
  - Low power pulses demonstrate replenishment
- Composite image
  - Vascular architecture is constructed through maximum intensity capture of temporal data in consecutive low power images

Gleason 10 Pca
Continuous & Flash Replenishment Imaging

Gleason 9 Pca
Flash Replenishment Imaging
Gleason 6: Right Base

Gleason 7: Right Mid-Gland

Gleason 8: Left Mid-Gland

MFI Directed Biopsies

<table>
<thead>
<tr>
<th>Cancer detected by core</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic Cores</td>
<td>50 (8.3 %)</td>
<td>550 (91.7 %)</td>
</tr>
<tr>
<td>Directed Cores</td>
<td>29 (12.9 %)</td>
<td>196 (87.1 %)</td>
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<tr>
<td>Odds Ratio = 2.01; p = 0.034</td>
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</tbody>
</table>

Linden, Trabulsi, Halpern, J Urol, 2007

5-α-reductase inhibitors

- Commonly used for symptomatic BPH
- Long duration:
  - Shrinks prostate
  - Atrophy
  - Apoptosis
- Short Duration:
  - Decreased vascularity
  - Treatment for BPH related bleeding prior to TURP
  - Reduce BPH-related vascularity prior to biopsy

Dutasteride/Contrast US Protocol

- NCI Funded (R01-CA118003)
- To quantify prostate cancer detection with CEUS ± short-term pretreatment with dutasteride
- Randomized, double blinded placebo controlled trial of oral dutasteride pretreatment followed by CEUS in all study participants
- Max of 6 targeted biopsies
  - Grayscale, non-contrast Doppler
  - CE-TRUS with Definity (Doppler, Harmonic, MFI)

Results

- 272 study subjects
  - 134 randomized to dutasteride
  - 138 randomized to placebo
- No difference in the proportion of positive cores among subjects who received dutasteride pretreatment vs placebo
  - Targeted: (88/574 = 15.3%) vs (114/659 = 17.3%; p = 0.35)
  - Systematic: (126/1608 = 7.8%) vs (150/1656 = 9.1%; p = 0.21)
- Positive biopsy rate was higher with
  - targeted approach 203/1237 (16.4%) vs
  - systematic approach 276/3264 (8.5%)
    (odds ratio = 2.1; 95% CI: 1.7-2.6, p<0.001)

Targeted vs Systematic Biopsy

**Comparison of Cancers Detected**

- Among 105 subjects with Pca detected by systematic biopsy:
  - Those detected by CEUS targeted bx
    - Mean of 3.5 positive systematic cores / patient
    - Mean percent core involvement was 32%
  - Those detected only by systematic bx
    - Mean of 1.5 positive systematic cores / patient
    - Mean percent core involvement was 15%

ROC for Detection of All Cancers

When grayscale imaging is combined with contrast enhanced harmonic imaging in a single predictive model, the $A_z$ of 0.64 is increased relative to conventional grayscale imaging alone or harmonic imaging alone (p<0.005)

ROC for Detection of High Volume (>50% core involvement) Gleason ≥ 7

When grayscale imaging is combined with contrast enhanced imaging in a single predictive model, the $A_z$ of 0.88 is increased relative to conventional grayscale or Doppler imaging (p<0.005)

Grayscale + MFI yielded the highest $A_z$ of 0.90

Discussion

- Frequency of positive cores among CEUS targeted biopsy relative to systematic biopsy is increased by a factor of two (16.4 versus 8.5%)
- CEUS is a good test for detection of high grade prostate cancer (with an ROC $A_z$ of 0.80), but it is an excellent test for the discrimination of high grade/high volume cancers ($A_z=0.90$)
- Pretreatment with dutasteride does not improve the detection of prostate cancer with CEUS
Subharmonic Imaging

- Conventional second harmonic imaging
  - Limited by reduced blood-to-tissue contrast resulting from second harmonic generation and accumulation in tissue
- Subharmonic imaging
  - Transmit at a fundamental frequency ($f_0$) and receive at the subharmonic ($f_0/2$)
  - Less interference from tissue generated subharmonic signal

Subharmonic Imaging vs Conventional Doppler

<table>
<thead>
<tr>
<th></th>
<th>Spatial Resolution</th>
<th>Temporal Resolution</th>
<th>Sensitivity to Flow</th>
<th>Imaging Neovessels</th>
<th>Artifact</th>
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</thead>
<tbody>
<tr>
<td>Conventional Gray Scale</td>
<td>+++</td>
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<tr>
<td>Color Doppler</td>
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<tr>
<td>Power Doppler</td>
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<tr>
<td>Contrast: Color Doppler</td>
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<tr>
<td>Power Doppler</td>
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Conclusion

Focal Prostate Cancer Treatment

- Prostate cancer is difficult to define
- Ablation of the prostate may injure adjacent structures
  - Urethra
  - Neurovascular bundles
  - Rectum
- Incomplete ablation - residual cancer

Contrast US Guidance for Ablation: Canine

- Devitalized tissue shows no contrast

Contrast US Guidance for Ablation: Canine
- Cold saline infusion to protect urethra & NVB’s


Contrast US Guidance for Ablation: Humans

Pre-HIFU

Post-HIFU


The Present

- Half of prostate cancers are invisible with conventional ultrasound
- Conventional ultrasound detection is minimally better than chance

The Future

- Better Doppler techniques for cancer detection
- Selective enhancement of neovessels with contrast & microflow imaging of cancers
- Improved technique will select patients for biopsy, and limit the number of biopsy sites