**THE PROSTATE CANCER SCREENING DILEMMA**

- Traditional screening tests - not specific
  - Digital Rectal Examination (DRE)
  - Serum Prostate Specific Antigen (PSA)
  - Transrectal ultrasound (TRUS)
- Free PSA / 4K Score / Multiparametric MRI - expensive
- Positive biopsy rate is 1/3 to 1/4
- Repeat biopsies with multiple cores
- Over 1,000,000 men annually subjected to prostate biopsy - how many insignificant cancers do we find?

**THE IDEAL DIAGNOSTIC STUDY**

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

**"CLINICALLY SIGNIFICANT DISEASE"**

- Criteria for Treatment versus Active Surveillance
  - Treat intermediate to high grade prostate cancer: ≥Gleason 7, or
  - Elevated volume: ≥ 25% positive biopsy cores or ≥50% core involvement on any one core
- Criteria for Greater Therapeutic Intervention in Intermediate Risk Disease
  - Gleason grade group 2 or higher (Gleason 4+3)
  - Gleason grade group 2 with
    - >15% of biopsy cores positive, or
    - Multiple intermediate risk features (Gleason grade group 2, PSA>10 or clinical stage of cT2b or worse)

**MICROVESSEL DENSITY**

- Normal Prostate
- Gleason 6 Cancer
Conventional Ultrasound Diagnostic Criteria

- Contour
- Echo-Texture
- Doppler Flow

Gleason 6 with rectal wall invasion on right

NORMAL BLOOD FLOW TO PROSTATE

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

Color vs. Power Doppler

40 y.o. with Gleason 8 PCa

Color
Power

DOPPLER DETECTION OF PROSTATE CANCER

- Hypervascularity in a Gleason 7 cancer

JEFFERSON EXPERIENCE – TRADITIONAL US

500 subjects 1998 - 1999

Gray scale

- Sensitivity 44.1%
- Specificity 73.6%
- Kappa of 0.12

Doppler

- Sensitivity 27.0%
- Specificity 77.1%
- Kappa of 0.03

- Targeted biopsy of patients with prostate cancer
  - Gray scale: Odds Ratio = 1.9
  - 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 vis. with standard Color/Power Doppler
- Microvessels can be visualized with contrast-enhanced US
DOPPLER ENHANCEMENT - GLEASON 6 - LEFT BASE

VISUALIZATION OF NEOVASCULARITY
INTERMITTENT IMAGING - LOW MI

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

AJR 2000; 174:1575-1580

CONTINUOUS VS. INTERMITTENT IMAGING

Continuous vs. IntermitteGleason 9 lesion left base

CONTINUOUS VS. INTERMITTENT IMAGING

Gleason 6 lesion left base

GLEASON 7, LEFT MID-GLAND

BASELINE VS. CONTRAST-ENHANCED TRUS

Definity trial: 60 pts
Improved detection with CE-TRUS
p = 0.027
Results confirmed in DOD trial of 301 pts
**MICROFLOW IMAGING**

- Flash-replenishment 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 9 PCA FLASH REPLENISHMENT IMAGING**

**GLEASON 8: LEFT MID-GLAND**

**GLEASON 7: RIGHT 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>90 (8.3%)</td>
<td>550 (91.7%)</td>
</tr>
<tr>
<td>Directed Cores</td>
<td>29 (12.9%)</td>
<td>196 (87.1%)</td>
</tr>
</tbody>
</table>

Odds Ratio = 2.01, p = 0.034

Linden, Trabulsi, Halpern, J Urol, 2007

**JEFFERSON NCI CLINICAL TRIAL (R01-CA118003)**

- 272 study subjects
- Max of 6 targeted biopsies
  - Grayscale, non-contrast Doppler
  - CE-TRUS with Definity (Doppler, Harmonic, MFI)
- Blinded standard systematic 12 core bx
- Positive biopsy rate was higher with
  - CEUS 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)
- Higher proportion of Gleason score ≥7 with CEUS
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%

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 is increased relative to conventional grayscale or Doppler imaging (p<0.02)

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)

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 (f₀) and receive at the subharmonic (f₀/2)
  • Less interference from tissue generated subharmonic signal

BPH: SUBHARMONIC IMAGING VS CONVENTIONAL DOPPLER

BPH: SUBHARMONIC IMAGING – REAL TIME SWEEP
PCA: SUBHARMONIC IMAGING VS CONVENTIONAL DOPPLER

PCA: SUBHARMONIC IMAGING – REAL TIME SWEEP

Negative MRI. Gleason 6 core obtained from Left base on targeted bx

SUBHARMONIC RESULTS
• Pilot study of 55 patients; NIH R21CA202214-01
• Prostate cancer was identified in 24/55 patients, including 9/31 patients with a negative prior prostate MRI.
• Among 31 negative MRI studies
  • 9 patients with PCa
  • 6 with Gleason 6 on sextant (1 also on targeted)
  • 2 with a Gleason 7 on sextant
  • 1 with Gleason 7/9 on targeted/sextant

SUBHARMONIC RESULTS
• Multivariate Conditional Logistic Regression
  • Dependent variable: PCa within sextant
  • Independent variables: grayscale, color, & power
  • SHI remains as a significant CE mode (p=0.03)
• SHI is an independent predictor of the presence of PCa, beyond baseline grayscale and Doppler imaging

CONCLUSION
THE GOAL OF CE PROSTATE SONOGRAPHY

- Selective enhancement of neovessels with contrast & microflow imaging of cancers
- Improved technique will select patients for biopsy, and limit the number of biopsy sites
- Improved targeted focal ablation may obviate the need for more radical therapy