Over the past several years, much attention has been paid to the overdiagnosis and overtreatment of low-risk prostate cancer. At the heart of the matter is whether a significant fraction of tumors detected by screening might not have adversely affected patients’ lifespan or quality of life if they remained undetected. Learn where you stand during this discussion on the current prostate screening guidelines and treatment options available to men. You’ll examine the emotional and financial burdens of various options available as the incidence of prostate cancer grows.

Content Area: Clinical Practice

Content Level: Intermediate

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Nothing to Disclose

Objectives:
At the end of this session, participants will be able to:
1. Describe the natural course of prostate cancer.
2. Understand the prostate cancer screening guidelines.
3. Identify the risks and benefits of treating low-risk prostate cancer.

Content Outline:
I. Introduction
II. Prostate cancer screening guidelines
   A. PSA/DRE
III. Treatment modalities
   A. Surgery

B. Radiation therapy
   1. Conventional
   2. Brachytherapy
   3. Radiosurgery
   4. Hormonal therapy
   5. Wait and see

IV. Side effects/complications
A. Urinary
B. Rectal
C. Sexual

V. Risks versus benefits of treatment
A. Physical
B. Psychosocial
C. Financial

Bibliography:
American Cancer Society. www.cancer.org


Myriad Laboratories. www.myriad.com


**Prostate Cancer Incidence**

- Most common cancer in men
  - Median age @ diagnosis: 67
  - 80% confined to prostate gland
  - Estimated new cases in 2014: 233,000
- Second leading cause of cancer related deaths
  - Estimated deaths in 2014: 29,480

Siegel, R. et al, 2014

**Prostate Cancer: Risk Factors**

- Advancing age
- Race/Ethnicity
- Family History/Genetic Susceptibility
- Benign prostatic hyperplasia
- Histologic precursors
  - Prostatic intraepithelial neoplasia (PIN)
- Dietary Factors
- Occupational Exposures
- Sexual practices
- Sexually transmitted diseases
- Tobacco use
- Vasectomy

Gunderson & Tepper, 2012

**Prostate Cancer: Common Presentation**

- Asymptomatic
- Urinary symptoms
- Erectile dysfunction

**Prostate Cancer: Screening Tests**

- Prostate Specific Antigen (PSA):
  - Substance made by cells in prostate gland.
  - Mostly found in semen but small amount found in blood
  - Normal Value: Less than 4 ng/mL.
- Free PSA:
  - Ratio of how much PSA circulates compared to total PSA level
  - Percentage of free PSA is lower in men who have prostate cancer
  - Biopsy recommended for men who have a free PSA of 10% or less

**PSA & Its Indexes**

- Used to improve sensitivity & specificity of PSA testing:
  - PSA Density:
    - PSA may vary depending on volume of prostate gland
  - PSA Velocity/PSA Slope
    - Rate at which PSA increases
    - Correlated with age

**Age Specific Reference Ranges for Serum PSA**

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Asian Americans</th>
<th>African Americans</th>
<th>Caucasians</th>
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<tbody>
<tr>
<td>40 to 49</td>
<td>0 to 2.0 ng/mL</td>
<td>0 to 2.0 ng/mL</td>
<td>0 to 2.5 ng/mL</td>
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<tr>
<td>50 to 59</td>
<td>0 to 3.0 ng/mL</td>
<td>0 to 4.0 ng/mL</td>
<td>0 to 3.5 ng/mL</td>
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<tr>
<td>60 to 69</td>
<td>0 to 4.0 ng/mL</td>
<td>0 to 4.5 ng/mL</td>
<td>0 to 4.5 ng/mL</td>
</tr>
<tr>
<td>70 to 79</td>
<td>0 to 5.0 ng/mL</td>
<td>0 to 5.5 ng/mL</td>
<td>0 to 6.5 ng/mL</td>
</tr>
</tbody>
</table>

Partin et al, 1996
Other Prostate Cancer Tests

- PCA 3 Gene:
  - Urine test
  - Non-coding segment of mRNA located on chromosome 9 which is overexpressed by prostate cancer cells
  - Work in progress
  - Higher specificity than PSA

Diagnostic Work-up

- Digital rectal exam (DRE):
  - Positive predictive value has increased with PSA
- Transrectal ultrasound & biopsy (TRUS):
  - Targeted prostate biopsies utilizing MRI technology to visualize prostate cancer, and fusion of the MR images with real-time ultrasound
- CAT abdomen/pelvis
- Bone scan
- Pelvic MRI

Prostate Cancer: Histology

- Adenocarcinoma
- Other:
  - Sarcoma
  - Transitional cell carcinoma

Prostate Cancer: Staging

- T1: Clinically in-apparent tumor neither palpable nor visible on imaging
  - T1a: Tumor incidental histologic finding in 5% or less of tissue resected
  - T1b: tumor incidental histologic finding in more than 5% of tissue resected
  - T1c: tumor identified by needle biopsy
- T2: Confined within prostate
  - T2a: ≤1/2 of one lobe
  - T2b: >1/2 of one lobe
  - T2c: Tumor involving both lobes

Prostate Cancer: Grading

Gleason Grade

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>10 yr DSS</th>
<th>15 yr DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>86%</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>63%</td>
<td>50%</td>
</tr>
<tr>
<td>7</td>
<td>54%</td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td>29%</td>
<td>16%</td>
</tr>
<tr>
<td>9</td>
<td>29%</td>
<td>16%</td>
</tr>
<tr>
<td>10</td>
<td>8%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Gleason & Mellinger, 1974

Prostate Cancer: Staging

- T3 : Tumor extending beyond prostate
  - T3a: Extracapsular extension (ECE) [pT3a includes bladder neck invasion*]
  - T3b: Seminal vesicle involvement (SVI)
- T4: Spread to contiguous organs; tumor is fixed or invades adjacent structures other than seminal vesicles (bladder neck, external sphincter, rectum, levator muscles, pelvic wall)
**Prostate Cancer: Staging**

- **Regional Lymph Node**
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node
    - (External iliac, internal iliac, obturator, or presacral nodes)
- **Distant Metastasis**
  - M0: No distant metastasis
  - M1: Distant metastasis
    - M1a: Non-regional lymph nodes
    - M1b: Bone(s)
    - M1c: Other site(s) with or without bone disease

Retrieved from AJCC, 7th edition

**Common Metastatic Sites**

- Bone
- Spine
- Lymph nodes
- Lungs
- Liver

**NCCN Risk Stratification (2011):**

- **Very low risk:**
  - T1a, G1-G3, PSA < 10,
  - Fewer than 5 prostate biopsy cores positive, <50% cancer in each core,
  - PSA density < 0.15 ng/mL/g

- **Low risk:**
  - T1a-T2a and G1-G3, or PSA 10-20

- **Intermediate risk:**
  - T2b-T2c, or G1-G3, or PSA 10-20

- **High risk:**
  - T3a or T4 or G4-G5, or PSA >20

- **Locally advanced (Very high):** T3b-T4

- **Metastatic:** N1 and M1

Retrieved from www.nccn.org

**National Comprehensive Cancer Network (NCCN) Guidelines on Active Surveillance**

<table>
<thead>
<tr>
<th>Recurrence Risk</th>
<th>Expected Survival</th>
<th>Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt; 20 years</td>
<td>Active surveillance preferred</td>
</tr>
</tbody>
</table>
| ≥ 20 years      | Active surveillance | Radiotherapy
|                 | Radical prostatectomy |

**Treatment Options: Low Risk Prostate Cancer**

- Active Surveillance or Watchful Waiting
- External Beam Radiotherapy (EBRT):
  - Standard Fractionation
  - Hypofractionation
  - SBRT
  - Protons
- Brachytherapy:
  - LDR
  - HDR
- Radical Prostatectomy (RP):
  - Robotic Assisted
  - Open Retropubic


Retrieved from www.nccn.org
**Active Surveillance**

- Men seeking second opinion
  - Can lead to more difficulty with decision making
  - Professional opinions may differ
- Psychosocial distress
- May miss opportunity to treat

**Surgery: Acute Effects**

- Bleeding
- Infection
- Urinary incontinence

**Surgery: Complications/Late Effects**

- Urinary incontinence
- Erectile dysfunction

**Radiation Therapy: Acute Side Effects**

- Fatigue
- Urinary symptoms:
  - 50% of patients have frequency, urgency, or dysuria during treatment
- Rectal symptoms:
  - Acute radiation proctitis occurs in 20% of patients
  - Depends on dose and treatment volume
  - Radiation enteritis if whole pelvis
- Sexual dysfunction

**Radiation Therapy: Late Effects**

- Urinary:
  - Hemorrhagic cystitis
  - Bladder contracture/Urinary stricture
- Rectal:
  - Persistent diarrhea
  - Tenesmus
  - Rectal urgency
  - Hematochezia
  - Rectal stricture/ulcer/perforation/fistula formation
- Erectile dysfunction:
  - Ejaculatory volume may be decreased
  - Frequency of ED increases over time
  - By 2 yrs post EBRT: 60-70% have moderate to severe ED
  - Also affected by concomitant ADT and comorbidities (HTN, DM)

**Psychosocial Impact of Early Stage Prostate Cancer**

- Psychosocial reaction to diagnosis, treatment selection & treatment related side effects
- Treatment decision maybe based on quality of life and longevity

Zehl et al., 2001; Galbraith et al., 2005; Albaugh & Hacker, 2005; Galbraith et al., 2012
Quality of Life Concerns: Fatigue

- Disturbing to men who have led active lives
- Management interventions:
  - Exercise
  - Counseling/Psychotherapy
  - Psychostimulants

Quality of Life Concerns: Urinary

- Fear of urine leakage/incontinence
- Fear of urine smell

Quality of Life Concerns: Rectal

- Fear of bowel incontinence
- Use of incontinence pads/diapers

Quality of Life Concerns: Sexuality

- Feared complication of erectile dysfunction
- More than mechanical
- Intimacy with partner
- Relationships with women in social situations

Anxiety & PSA Hypervigilance

- Changes in PSA post treatment
- Sense of feeling like a “dead man”

Cost of Treating Low Risk Prostate Cancer: Active Surveillance

- PSA
- Free PSA
- TRUS
Cost of Treating Low Risk Prostate Cancer: Surgery

- Radical prostatectomy
- Robotic prostatectomy

Cost of Treating Low Risk Prostate Cancer: Radiation Therapy

- External beam
- IMRT
- IMRT/IGRT
- Brachytherapy
- Radiosurgery
- Active surveillance/"Watchful Watching"

PIVOT Study (1994-2002)

- 731 men diagnosed with prostate cancer (PSA/biopsy)
- Median age: 67
- Randomized to radical prostatectomy versus observation
- Results: Not Statistically Significant
  - Risk of dying of any cause: Surgery 47% versus Observation 49.9%
  - Risk of dying from prostate cancer: Surgery 5.8% versus Observation 8.9%

ProtecT Trial

- Being performed in United Kingdom
- Active surveillance versus radiation therapy versus prostatectomy for localized prostate cancer
- First reports of study expected in 2015

National Comprehensive Cancer Network (NCCN) Screening Guidelines

- NCCN panelists note the variability in prostate tumor behavior
  - Key point is discussion between patient and provider about the risks and benefits of early detection of and treatments for prostate cancer
  - Goal is to evaluate aggressiveness of the cancer
- Once a patient age 40 starts having risk and benefit discussion about baseline digital rectal exam (DRE) and absolute PSA values
  - May annually follow up with DRE and repeat PSA in patients with elevated PSA (≥1.0 ng/mL), African Americans, men taking 5-alpha-reductase inhibitors
  - Testing and biopsy decisions should be individualized for men > age 75 years
- Further timing of follow-ups and DRE and PSA testing dependent on age, and life expectancy
  - Trying to determine need for TRUS-guided biopsy, and may also use PSA density, percent-free PSA, and PSA velocity to determine need for biopsy or if cancer is present

ASTRO: Choosing Wisely Campaign

- Treatment for low risk prostate cancer should not be initiated without discussion of active surveillance
- Proton beam therapy not recommended outside of clinical trials
American Cancer Society (ACS) Screening Guidelines

- ACS supports informed discussion between healthcare provider and asymptomatic men about screening for prostate cancer
  - Average risk: annually beginning age 50 years with 10+ year life expectancy
  - Age 45 if high risk: High risk includes African-American men or those with first-degree relative with prostate cancer <65 years of age
  - Age 40 if very high risk: Very high risk includes multiple family members with prostate cancer at early age
  - Include information about uncertainties, risks, and potential benefits
- If testing performed, PSA with or without DRE
- 2009 guidelines reaffirmed in 2013

Retrieved from www.cancer.org

US Preventive Services Task Force (USPSTF) Screening Recommendations

- Per the 2012 USPSTF, no healthy man should undergo PSA screening unless symptoms of prostate cancer present
  - Full implications have yet to be realized

Retrieved from www.uspreventativetaskforce.org

American Urological Association (AUA) Screening Guidelines

- Recommendations based on age and risk
  - Average risk:
    - < Age 40, not recommended
    - Age 40-54: do not recommend routine screening
    - Age 55-69: informed shared decision making about screening risk and potential benefits
    - Age 70+ or patients with <10-15 years life expectancy: do not recommend routine screening
  - Alternatively, can individualize based on baseline PSA
  - High risk: <55 with positive family history or African-American race; decisions should be individualized
  - If decision to screen, frequency should be 2+ years instead of annual
  - Panel believes this will reduce overdiagnoses and false-positives while maintaining the majority of the benefits

Retrieved from www.auanet.org

United States Preventative Services Task Force (USPSTF) Guidelines

- The USPSTF recommends against PSA-based screening for prostate cancer.
  - “Prostate cancer is a serious health problem that affects thousands of men and their families. But before getting a PSA test, all men deserve to know what the science tells us about PSA screening: there is a very small potential benefit and significant potential harms. We encourage clinicians to consider this evidence and not screen their patients with a PSA test unless the individual being screened understands what is known about PSA screening and makes the personal decision that even a small possibility of benefit outweighs the known risk of harms.”

—USPSTF Co-Chair Michael LeFevre, M.D., M.S.P.H. May 22, 2012

Retrieved from www.uspreventativetaskforce.org

So to Treat or Not to Treat…

- Indolent nature of some prostate cancers
  - Can these patients be identified with reasonable accuracy?
- Competing comorbidities
- Does delaying treatment put these patients at an increased risk?
  - When does the “switch” get turned on?

Retrieved from www.ons.org

On the Horizon…

- Prolaris®:
  - Novel prognostic test directly measuring tumor cell growth characteristics
  - Stratifies risk of disease progressing
- Diet
  - Healthier fats may fight early stage prostate cancer

Retrieved from www.ons.org
Future Research Needs…

- Prospective, randomized trial of molecular/genetic markers of potential prostate cancer lethality
- Randomized trial: Active surveillance versus Active treatment
- Advanced technical testing

Retrieved from www.myriad.com