PROSTATE CANCER

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OUTLINE

• PSA screening controversy
• How to use PSA more effectively
• Treatment of localized prostate cancer
• Treatment related adverse effects
## 2013 Estimated Cancer Incidence

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>238,590</td>
<td>232,340</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>118,080</td>
<td>110,110</td>
</tr>
<tr>
<td>Colorectum</td>
<td>73,680</td>
<td>69,140</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>54,610</td>
<td>49,560</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>45,060</td>
<td>45,310</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,430</td>
<td>32,140</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>37,600</td>
<td>31,630</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>29,620</td>
<td>24,720</td>
</tr>
<tr>
<td>Leukemia</td>
<td>27,880</td>
<td>22,480</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,740</td>
<td>22,240</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>854,790</strong></td>
<td><strong>805,500</strong></td>
</tr>
</tbody>
</table>

*Excluding basal and squamous cell skin cancers*
2013 Estimated Cancer Deaths

*Excluding basal and squamous cell skin cancers*
Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, PhD, on behalf of the U.S. Preventive Services Task Force*

Annals of Internal Medicine 2012;157:120-134

American Urological Association (AUA) Guideline

EARLY DETECTION OF PROSTATE CANCER: AUA GUIDELINE

H. Ballentine Carter, Peter C. Albertsen, Michael J. Barry, Ruth Etzioni, Stephen J. Freedland, Kirsten Lynn Greene, Lars Holmberg, Philip Kantoff, Badrinath R. Konety, Mohammad Hassan Murad, David F. Penson and Anthony L. Zietman
## Screening for Prostate Cancer

**Clinical Summary of U.S. Preventive Services Task Force Recommendation**

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult Males</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td><strong>Do not use prostate-specific antigen (PSA)-based screening for prostate cancer.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Grade: D</strong></td>
</tr>
</tbody>
</table>

### Screening Tests

Contemporary recommendations for prostate cancer screening all incorporate the measurement of serum PSA levels; other methods of detection, such as digital rectal examination or ultrasonography, may be included.

There is convincing evidence that PSA-based screening programs result in the detection of many cases of asymptomatic prostate cancer, and that a substantial percentage of men who have asymptomatic cancer detected by PSA screening have a tumor that either will not progress or will progress so slowly that it would have remained asymptomatic for the man's lifetime (i.e., PSA-based screening results in considerable overdiagnosis).

### Interventions

Management strategies for localized prostate cancer include watchful waiting, active surveillance, surgery, and radiation therapy. There is no consensus regarding optimal treatment.

### Balance of Harms and Benefits

The reduction in prostate cancer mortality 10 to 14 years after PSA-based screening is, at most, very small, even for men in the optimal age range of 55 to 69 years.

The harms of screening include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harm of false-positive test results, and overdiagnosis.

Harms of treatment include erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for premature death. Because of the current inability to reliably distinguish tumors that will remain indolent from those destined to be lethal, many men are being subjected to the harms of treatment for prostate cancer that will never become symptomatic.

The benefits of PSA-based screening for prostate cancer do not outweigh the harms.
# Table 3. PSA-Based Screening for Prostate Cancer*

## Why not screen for prostate cancer?
Screening may benefit a small number of men but will result in harm to many others. A person choosing to be screened should believe that the possibility of benefit is more important than the risk for harm. The USPSTF assessment of the balance of benefits and harms in a screened population is that the benefits do not outweigh the harms.

## What are the benefits and harms of screening 1000 men aged 55–69 y† with a PSA test every 1–4 y for 10 y?

### Possible benefit of screening

<table>
<thead>
<tr>
<th>Reduced 10 y risk for dying of prostate cancer</th>
<th>Men, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Die of prostate cancer with no screening</td>
<td>5 in 1000</td>
</tr>
<tr>
<td>Die of prostate cancer with screening</td>
<td>4–5 in 1000</td>
</tr>
<tr>
<td>Do not die of prostate cancer because of screening</td>
<td>0–1 in 1000</td>
</tr>
</tbody>
</table>

## Harms of screening

### At least 1 false-positive screening PSA test result
Most positive test results lead to biopsy. Of men having biopsy, up to 33% will have moderate or major bothersome symptoms, including pain, fever, bleeding, infection, and temporary urinary difficulties; 1% will be hospitalized.

### Prostate cancer diagnosis
Although a diagnosis of prostate cancer may not be considered a harm, currently 90% of diagnosed men are treated and, thus, are at risk for the harms of treatment. A large majority of the men who are being treated would do well without treatment. A substantial percentage of these men would have remained asymptomatic for life.

### Complications of treatment (among persons who are screened)‡

| Develop serious cardiovascular events due to treatment | 2 in 1000 |
| Develop deep venous thrombosis or pulmonary embolus due to treatment | 1 in 1000 |
| Develop erectile dysfunction due to treatment | 29 in 1000 |
| Develop urinary incontinence due to treatment | 18 in 1000 |
| Die due to treatment | <1 in 1000 |
AUA Guidelines

- **< 40 years**: do not screen
- **40-54 years**: do not routinely screen unless high risk (family history or race)
- **55-69 years**: shared decision making
  - Screening interval of ≥ 2 years instead of annual
- **≥70 years or <10-15 year life expectancy**: do not routinely screen
Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D.,

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,
PLCO

- ~76,700 men, f/u: 13 yrs
- No difference in mortality
- 44% had undergone prior screening
- 52% contamination in control arm
- ~40% compliance with biopsy recommendation
**PLCO**
- ~76,700 men, f/u: 13 yrs
- No difference in mortality
- 44% had undergone prior screening
- 52% contamination in control arm
- ~40% compliance with biopsy recommendation

**ERSPC**
- 182,160 men, f/u: 11 yrs
- 21% mortality reduction
- 29% after adjustment for non-compliance
- Number needed to be invited to screen: **1055**
- Number of cancers that need to be detected: **37**
What should you do?

Do not screen at all
What should you do?

Do not screen at all
or
Screen, but maximize benefit and minimize harm
How to use PSA more effectively

- Screen the right patients
- Re-check PSA in several weeks
- Risk stratify by checking PSA early
- Reduce the fear of ‘cancer’
- Talk to and partner with your Urologist/s
Screen the right patients

• Screen patients with life expectancy >10-15 years
• Do not screen elderly patients or those with co-morbidities that limit life expectancy
• Older men are being inappropriately screened
OUTLINE

• PSA screening controversy
• **How to use PSA more effectively**
• Treatment of localized prostate cancer
• Treatment related adverse effects
How to use PSA more effectively

• Screen the right patients
• **Re-check PSA in several weeks**
• Risk stratify by checking PSA early
• Reduce the fear of ‘cancer’
• Talk to and partner with you Urologist/s
Recheck PSA in several weeks

Variation of Serum Prostate-Specific Antigen Levels
An Evaluation of Year-to-Year Fluctuations

<table>
<thead>
<tr>
<th>PSA level, ng/ml</th>
<th>No. of Participants</th>
<th>Returned for Next Visit</th>
<th>No. (%) of Participants With Normal Next Time After Abnormal PSA Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4.0</td>
<td>172</td>
<td>154</td>
<td>46 (30)</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>319</td>
<td>291</td>
<td>76 (26)</td>
</tr>
<tr>
<td>Age-specific PSA level</td>
<td>139</td>
<td>117</td>
<td>43 (37)</td>
</tr>
<tr>
<td>Free PSA ratio</td>
<td>156</td>
<td>143</td>
<td>50 (35)</td>
</tr>
</tbody>
</table>

Abbreviation: PSA, prostate-specific antigen.
*Excludes 37 men diagnosed as having prostate cancer and 3 men with a marked drop in PSA level, which suggested they were receiving treatment.
How to use PSA more effectively

• Screen the right patients
• Re-check PSA in several weeks
• Risk stratify by checking PSA early
• Reduce the fear of ‘cancer’
• Talk to and partner with your Urologist/s
Risk stratify by checking PSA early

• PSA at an early age predicts the risk of having, and the risk of developing metastases or mortality
• 75\textsuperscript{th} centile:
  – Age 45-50: 1.0 ng/ml
  – Age 60: 2.0 ng/ml
Long term prostate cancer prediction

- PSA measured at age 44-50 predicts long term risk of prostate cancer and of advanced cancer
- 75th centile ~1 ng/ml
90% of deaths occurred in men with PSA > 2ng/ml
90% of deaths occurred in men with PSA > 2ng/ml

75th centile:
- Age 45-50: 1.0 ng/ml
- Age 60: 2.0 ng/ml
Personalized screening schedule

- If PSA less than population median for age then consider not re-screening at all or re-screen after 5 years
- If PSA between 50\textsuperscript{th} - 75\textsuperscript{th} centile then screen q2-4 years
- If PSA > 75\textsuperscript{th} centile then annual screening and consider biopsy at lower thresholds

- PSA distribution in the US population:
How to use PSA more effectively

• Screen the right patients
• Re-check PSA in several weeks
• Risk stratify by checking PSA early
• Reduce the fear of ‘cancer’
• Talk to and partner with your Urologist/s
Reduce the fear of ‘cancer’

- Most men with prostate cancer do not die from the cancer but die with the cancer.
- Some experts suggest that the word ‘cancer’ for Gleason 6 (low grade) prostate cancer should not be used.
- Introduce ‘Active surveillance’ early-on.
Partner with your urologist/s

- Talk to your urologist about their beliefs and practices about PSA screening
- Partner with them to reduce over-diagnosis and over-treatment of your patients
- Help them promote active surveillance
OUTLINE

- PSA screening controversy
- How to use PSA more effectively
- Treatment of localized prostate cancer
- Treatment related adverse effects
Treatment of localized prostate cancer

• Active surveillance

• Surgery
  – Robotic assisted laparoscopic surgery
  – Open prosatectomy

• Radiation
  – Brachytherapy
  – External beam
Active Surveillance

• Excellent option for low risk cancer, for elderly patients and those with limited life expectancy
• Involves periodic disease monitoring with PSA, DRE, repeat biopsy etc.
Outcomes of Localized Prostate Cancer Following Conservative Management

Figure. Competing Risk of Death by Age at Diagnosis, Cancer Stage, and Grade

- Probability of being alive
- Nonprostate cancer mortality
- Prostate cancer mortality

<table>
<thead>
<tr>
<th>Age at Diagnosis, y</th>
<th>Stage T1a or b</th>
<th>Stage T1c</th>
<th>Stage T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 to 69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 to 74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 to 79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• 450 patients
• 10 yr overall survival: 68%
• 10 yr cancer specific survival: 97.2%
Challenges

• ‘Cancer’ is a scary word
• Patient anxiety: want to be treated
• Pressure from family and friends
• Medico-legal concerns
SURGERY

SPCG-4 Trial: Scandinavian trial

Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

N Engl J Med 370;10  NEJM.org  March 6, 2014
Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D.,

PIVOT Trial: United States

Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D.,
SPCG-4 Trial

- Started in the Pre-PSA era
- Patient’s had higher risk cancer than in the PIVOT trial
- 695 men, ~23 years follow-up
- Surgery superior to watchful waiting, HR: 0.56
- Number needed to treat to prevent one death: 8
SPCG-4

• Greater benefit in younger men (<65)
  – HR: 0.45, NNT ~4

• Greater benefit in intermediate-risk cancer
  – HR: 0.38
PIVOT trial

- PSA era: so lower risk men
- 731 men, 10 year median follow-up
- No benefit of surgery: HR: 0.88
- But
  - Improved survival with surgery if PSA > 10 or men have intermediate risk cancer
### Death from Any Cause

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observation</th>
<th>Radical Prostatectomy</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>183/367</td>
<td>171/364</td>
<td>0.88 (0.71–1.08)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>50/131</td>
<td>43/122</td>
<td>0.89 (0.59–1.34)</td>
<td>0.85</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>133/236</td>
<td>128/242</td>
<td>0.84 (0.63–1.08)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>119/220</td>
<td>117/232</td>
<td>0.84 (0.65–1.08)</td>
<td>0.81</td>
</tr>
<tr>
<td>Black</td>
<td>53/121</td>
<td>46/111</td>
<td>0.93 (0.62–1.38)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11/26</td>
<td>8/21</td>
<td>0.85 (0.34–2.11)</td>
<td></td>
</tr>
<tr>
<td>Charlson score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>86/220</td>
<td>82/224</td>
<td>0.90 (0.66–1.21)</td>
<td>0.79</td>
</tr>
<tr>
<td>≥1</td>
<td>97/147</td>
<td>89/140</td>
<td>0.84 (0.63–1.13)</td>
<td></td>
</tr>
<tr>
<td>Performance score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>146/310</td>
<td>139/312</td>
<td>0.89 (0.71–1.13)</td>
<td>0.66</td>
</tr>
<tr>
<td>1–4</td>
<td>37/57</td>
<td>32/52</td>
<td>0.82 (0.51–1.31)</td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>101/241</td>
<td>110/238</td>
<td>1.03 (0.79–1.35)</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt;10</td>
<td>77/125</td>
<td>61/126</td>
<td>0.67 (0.48–0.94)</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>54/148</td>
<td>62/148</td>
<td>1.15 (0.80–1.66)</td>
<td>0.07</td>
</tr>
<tr>
<td>Intermediate</td>
<td>70/120</td>
<td>59/129</td>
<td>0.69 (0.49–0.98)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>49/80</td>
<td>42/77</td>
<td>0.74 (0.49–1.13)</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>125/261</td>
<td>113/254</td>
<td>0.86 (0.67–1.12)</td>
<td>0.87</td>
</tr>
<tr>
<td>≥7</td>
<td>47/86</td>
<td>50/98</td>
<td>0.84 (0.56–1.25)</td>
<td></td>
</tr>
</tbody>
</table>
### SPCG-4
- Pre-PSA era
- Higher risk cancer
- 23 year follow-up
- Surgery superior to WaWa
- Especially if <65y age or intermediate risk cancer

### PIVOT
- PSA era
- Lower risk cancer
- 10 year follow-up
- No diff. between surgery and Wawa
- But surgery may be superior for higher risk cancer
RADIATION

• Reasonable choice for treatment
• Never been compared with watchful waiting or with surgery in a RCT
• Traditionally surgery and XRT thought to be equal for cancer control
• Several high quality but retrospective studies show that Surgery is superior to radiation, especially for higher risk cancer
OUTLINE

• PSA screening controversy
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Long-Term Functional Outcomes after Treatment for Localized Prostate Cancer
Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries

![Graph showing relative risk (RR) and 95% confidence intervals (CI) for second solid cancers by site of first cancer, comparing radiotherapy versus no radiotherapy. The graph highlights the prostate site with a relative risk of 1.26 (95% CI: 1.21-1.30), with 5548 cases in the radiotherapy group and 8023 in the no radiotherapy group.]

**Figure 1**: Relative risk of second solid cancer for radiotherapy versus no radiotherapy by site of first cancer.
Risk of secondary malignancies after XRT is greater for younger men

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Diagnosed age &lt;45 years</th>
<th>Diagnosed age 45-59 years</th>
<th>Diagnosed age 60-74 years</th>
<th>Diagnosed age ≥75 years</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/pharynx</td>
<td>0.70 (0.49 to 0.99)</td>
<td>1.18 (1.03 to 1.35)</td>
<td>1.14 (0.99 to 1.33)</td>
<td>1.27 (0.63 to 2.58)</td>
<td>0.10</td>
</tr>
<tr>
<td>Rectum*</td>
<td>1.09 (0.48 to 2.27)</td>
<td>1.00 (0.78 to 1.27)</td>
<td>1.19 (1.00 to 1.42)</td>
<td>1.61 (0.91 to 2.72)</td>
<td>0.14</td>
</tr>
<tr>
<td>Larynx†</td>
<td>1.04 (0.46 to 2.57)</td>
<td>1.52 (1.07 to 2.21)</td>
<td>1.17 (0.76 to 1.83)</td>
<td>—</td>
<td>0.73</td>
</tr>
<tr>
<td>Lung (non-small cell)</td>
<td>1.42 (0.93 to 2.12)</td>
<td>1.29 (1.11 to 1.50)</td>
<td>1.20 (1.03 to 1.38)</td>
<td>1.14 (0.58 to 2.11)</td>
<td>0.33</td>
</tr>
<tr>
<td>Female breast</td>
<td>1.83 (1.46 to 2.29)</td>
<td>1.45 (1.29 to 1.62)</td>
<td>1.15 (1.03 to 1.28)</td>
<td>1.03 (0.63 to 1.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cervix (external beam)*†</td>
<td>3.25 (2.21 to 4.79)</td>
<td>1.48 (1.06 to 2.08)</td>
<td>1.15 (0.76 to 1.75)</td>
<td>—</td>
<td>0.00068</td>
</tr>
<tr>
<td>Endometrium (external beam)*</td>
<td>3.25 (2.08 to 5.04)</td>
<td>1.65 (1.37 to 1.98)</td>
<td>1.72 (1.47 to 2.01)</td>
<td>0.92 (0.46 to 1.74)</td>
<td>0.036</td>
</tr>
<tr>
<td>Prostate (external beam)†‡</td>
<td>—</td>
<td>1.85 (1.53 to 2.22)</td>
<td>1.48 (1.38 to 1.58)</td>
<td>1.16 (0.96 to 1.14)</td>
<td>0.00070</td>
</tr>
<tr>
<td>Thyroid* †</td>
<td>1.34 (0.69 to 2.52)</td>
<td>1.08 (0.58 to 1.93)</td>
<td>0.78 (0.39 to 1.47)</td>
<td>—</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Data are relative risk (RR; 95% CI) unless otherwise stated. RR adjusted for sex, attained age, and attained year through the use of external rates and additionally adjusted for stage, age at diagnosis, and year of diagnosis through stratification. For endometrial and prostate cancer the group treated with external beam radiotherapy includes patients treated with external beam and brachytherapy. *Second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate). †Highest age group of 60 years or older used because of small numbers. ‡No second cancers recorded in the youngest age group.
TAKE HOME MESSAGES

• USPSTF does not recommend PSA screening
  – Concern about over-diagnosis and over-treatment

• AUA recommends shared decision making

• ERSPC trial showed 21% reduction in mortality with PSA screening
  – Number of cancer that need to be detected: 37
TAKE HOME MESSAGES

• Several strategies to use PSA more effectively and reduce over-diagnosis
  – Do not screen elderly or with limited life expectancy
  – Re-check PSA in several weeks
  – Baseline PSA at an early age predicts long term risk of cancer metastases and mortality
TAKE HOME MESSAGES

• Low risk cancer:
  – Active surveillance (reduce overtreatment)

• Intermediate or High risk cancer
  – Surgery or XRT
  – Surgery may be superior to XRT

• Both surgery and XRT have long term adverse effects
  – Surgery: urinary and sexual effects
  – XRT: also bowel function and risk of secondary malignancies
Questions ?