ESMO ADVANCED COURSE

PSA screening: Is it still relevant?

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DISCLOSURES

• Speaker Bureau: Pfizer, J&J, Sanofi, Novartis, MSD

• Advisory Board/ Consultant: GSK, Novartis, Bayer, J&J, Mundipharma, Astellas, MSD, BMS, Amgen

• Research support: Sanofi, J&J, Astellas
The value of PSA screening

- 2 large RCTS
  - ERSPC
  - PLCO

- Smaller screening studies
  - Goteborg
  - Stockholm
  - Noorkoping
ERSPC

- PSA screening on PCa mortality
- 7 EU countries, n=182,000 men
- PSA testing every 4 years
- Age 50-74 years
- Latest update – 13 years F/U

- Screening variation
  - Sweden screen 2 years, Belgium 7 years
  - On average, men screened 2.3 times

Lancet. 2014 December 6; 384(9959): 2027–2035
Men included
All ages
182,160

Men randomised
Core age group
(aged 55-69)
162,388

145 died before randomisation date
(62 intervention arm - 83 control arm)

Intervention arm
N = 72,891

Prostate cancer cases
Years 1-11 6797
Years 1-13 7408 (10.2%)

Distribution of risk groups:
<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>570</td>
</tr>
<tr>
<td>Low</td>
<td>4441</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1625</td>
</tr>
<tr>
<td>High</td>
<td>518</td>
</tr>
<tr>
<td>M1 and/or PSA &gt; 100</td>
<td>254</td>
</tr>
</tbody>
</table>

Deaths all causes
15369

Prostate cancer deaths
Years 1-11 265
Years 1-13 355 (0.49%)

Control arm
N = 89,352

Prostate cancer cases
Years 1-11 5262
Years 1-13 6107 (6.8%)

Distribution of risk groups:
<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>600</td>
</tr>
<tr>
<td>Low</td>
<td>2543</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1711</td>
</tr>
<tr>
<td>High</td>
<td>667</td>
</tr>
<tr>
<td>M1 and/or PSA &gt; 100</td>
<td>586</td>
</tr>
</tbody>
</table>

Deaths all causes
19108

Prostate cancer deaths
Years 1-11 415
Years 1-13 545 (0.61%)

* Low risk = T1,T2 with Gleason score (GS) <= 6; Intermediate risk = T1,T2 with GS 7 and T3 with GS <=7; High risk = T1,T2,T3 with GS 8-10 and T4 with any GS; M1 or PSA > 100 may occur any T stage or GS; “Missing” = missing T stage or GS, not M1 or PSA>100
ERSPC

- PCa mortality
  - HR 0.79 (95% CI 0.69-0.91, p=0.001)

- Relative RR 21%

- Absolute RR 1.28 per 1000 men randomised
Figure 3

PC Mortality rate in each arm by 4 year period
ERSPC

- 75% of those who underwent biopsy for elevated PSA – no cancer diagnosis in 1 year

- Average 20% PSA screen contamination
  - 8.6% Spain to 36% Italy

- 41% of the 4235 cancers > screening arm were detected outside protocol
  - ? Frequency of PSA testing every 4 years
Summary

Table 5.1: Follow-up data from the ERSPC study [99]

<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>Number needed to screen</th>
<th>Number needed to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1,410</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>979</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>781</td>
<td>27</td>
</tr>
</tbody>
</table>
PLCO

- PCa mortality by PSA screening
- N=76 685 men, 55-74 years
- PSA year, DRE every 2 years
- PSA >4, abnormal DRE -> trigger 'usual care'

- Opportunistic screen if requested by patient

**Figure 3.** Cumulative deaths from prostate cancer in the intervention and control arms from year 1 to year 13. C = control arm; I = intervention arm; PY = person-years.
<table>
<thead>
<tr>
<th>Data</th>
<th>PLCO</th>
<th>ERSPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (yr)</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>PSA screening interval</td>
<td>Annually for 6 yr</td>
<td>Every 2 to 4 yr</td>
</tr>
<tr>
<td>Nonattendance (%)</td>
<td>15.0</td>
<td>17.4</td>
</tr>
<tr>
<td>Contamination (%) †</td>
<td>85</td>
<td>24</td>
</tr>
<tr>
<td>Difference in rate of PSA testing between study groups (%) ‡</td>
<td>0</td>
<td>58.6</td>
</tr>
<tr>
<td>Prerandomization PSA testing (%)</td>
<td>44</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rate ratio for death from prostate cancer in men undergoing randomization to screening vs. usual care (95% CI)</td>
<td>1.09 (0.87–1.36)</td>
<td>0.79 (0.65–0.98)</td>
</tr>
</tbody>
</table>

* Data are from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial or the European Randomized Study of Screening for Prostate Cancer (ERSPC) unless noted otherwise. CI denotes confidence interval, and PSA prostate-specific antigen.

† Data on contamination are from Pinsky et al.² for the PLCO screening trial and from Kerkhof et al.³ for the ERSPC.

‡ The difference in the rate of PSA testing between study groups refers to the difference in the rate of testing between those who underwent randomization to usual care and those who underwent randomization to screening.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Characteristics</th>
<th>Weaknesses</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERSPC</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• RCT (N = 182,160)</td>
<td>• Heterogeneity of Protocols</td>
<td>• 21% reduction in PC mortality in screening group</td>
</tr>
<tr>
<td></td>
<td>• PSA at 4-year intervals</td>
<td>• Treatment bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA cut-off: ≥ 3 ng/mL (mainly)</td>
<td>• Findings significant only in core group (55–69-year-old men)</td>
<td></td>
</tr>
<tr>
<td><strong>Prostate, Lung, Colorectal, and Ovarian</strong></td>
<td>• RCT (N = 76,693)</td>
<td>• Highly pre-screened population</td>
<td>• No difference in PC mortality between groups</td>
</tr>
<tr>
<td>Cancer screening trial (PLCO)**&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• PSA/DRE annually</td>
<td>• Contamination of control arm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA cut-off: &gt; 4 ng/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Goteborg

- PSA screening on PCa mortality
- Randomised, population-based prostate screening

- N=20,000, age 56-64
- Median f/u 14 years
- PSA testing every 2 years
- PSA threshold 3.0 (ERSPC level)

- Above threshold -> DRE, sextant TRUS biopsy

- Diagnosis of cancer tracked via West-Swedish Regional Cancer Registry

*Lancet Oncol.* 2010 August; 11(8): 725–732
Total male population in Göteborg on December 31, 1994, aged 50-64 yrs, n = 32,298

Randomized in a 1:1 ratio, n = 20,000

Excluded: (n = 48)
- Deceased or emigrated before randomization date: (n = 19)
- Men with prevalent prostate cancer: (n = 29)

Screening group (invited biennially for PSA testing 1995-2008), n = 9,952

- Attendees, n = 7,578
  - PC, n = 1,046
  - Death from PC, n = 27

- Non-attendees, n = 2,374
  - PC, n = 92
  - Death from PC, n = 17

Control group, not invited, n = 9,952

- Excluded:
  - Deceased or emigrated before randomization date: (n = 21)
  - Men with prevalent prostate cancer: (n = 27)

- PC, n = 718
- Death from PC, n = 78

Figure 1.
CONSORT diagram of the study
Goteborg

- Incidence PCa – 12.7% vs 8.2%
- (HR 1.64, 95% CI 1.5-1.8, p<0.0001)

- NNS – 239
- NNT – 12
Figure 3.
Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates
A summary of evidence so far…

- PSA screening general population
  - 50 years onwards
  - PSA > 3
  - 2 to 4 yearly

- Reduction in PCa mortality ~ 20%

- Numbers
  - 1:239 to 1: 781 NNS (same as mammogram data!)
  - 1:12 to 1: 27 NNT
2012 US Preventive Services Task Force (USPTF)
Grade D recommendation
Recommend against routine PSA testing
All ages

However this has changed since 2017:
- For patients 55-69 years, its Grade C recommendation
- They should be informed of the benefits and harms of PSA screening and its association with a small survival benefit
ESMO Guidelines

**recommendations**

- Population-based PSA screening for prostate cancer reduces prostate cancer mortality at the expense of over diagnosis and overtreatment and is not recommended [I, C].
- Testing for prostate cancer in asymptomatic men should not be done in men over the age of 70 years [I, B].
### Guidelines for screening and early detection

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LE</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.</td>
<td>3</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status (PS) and a life-expectancy of at least ten to fifteen years.</td>
<td>3</td>
<td>Strong</td>
</tr>
</tbody>
</table>
| Offer early PSA testing in well-informed men at elevated risk of having PCa:  
- men > 50 years of age;  
- men > 45 years of age and a family history of PCa;  
- African-Americans > 45 years of age. | 2b | Strong |
| Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk:  
- men with a PSA level of > 1 ng/mL at 40 years of age;  
- men with a PSA level of > 2 ng/mL at 60 years of age;  
Postpone follow-up to eight years in those not at risk. | 3 | Weak |
| Stop early diagnosis of PCa based on life expectancy and PS; men who have a life-expectancy of < fifteen years are unlikely to benefit. | 3 | Strong |
Baseline PSA

- Copenhagen City Heart Study
- 4383 men - 20-94 yr
- Danish general population
- PSA measured from samples obtained 1981-1983
- Median follow-up - 18 yr

Eur Urol. 2012 May;61(5):865-74
Baseline PSA Midlife

- 40-59 years old US physicians
- N= 22,071
- Physician’s Health Study
- Aspirin vs B-carotene trial
- 234 PCa, 711 age-matched controls

Journal of Clinical Oncology 2016 34:23, 2705-2711
• Median PSA (controls)
  • 40-49 years (0.68 ng/ml)
  • 50-54 years (0.88)
  • 55-59 years (0.98)

• Risk of lethal PCa if PSA >90th percentile per age group
  • OR 8.7 (1.0 to 78.2) - 40 to 49 years
  • OR 12.6 (1.4 to 110.4) 50 to 54 years
  • OR 6.9 (2.5 to 19.1) 55 to 59 years
A population-based stratified approach…

- PSA screening general population
  - not offer routinely
  - coupled with physical examination
  - Higher risk individuals
  - 50 years onwards ≥40
  - baseline PSA
  - 2 to 4 yearly depending on baseline PSA
  - those with less than 10 years life expectancy
To your next patient...

- A discussion of pros and cons is mandatory
- Benefits
  - PCa mortality
  - Earlier stage
- Cons
  - Over diagnosis
  - PSA cripple
Take Home Messages

- PSA screening reduces PCa mortality/ M1 disease

- Screening strategies include:
  - Personalised, no ideal one as of now
  - Use baseline PSA at middle age to decide, 40-50 years??
  - Family history, race

- Screening relevance
  - Contextual to patient
  - Optimal biopsy technique
  - Stratification of risk
THANK YOU
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