PROSTATE CANCER

STATE OF THE ART IN
SCREENING, DIAGNOSTICS AND TREATMENTS

Harm van Melick, Urologist
Amsterdam 11-11-2021
ABOUT ME
Harm van Melick

• Oncologic urologist St. Antonius Nieuwegein-Utrecht
• Train residents
• Researcher oncologic urology
• Chair scientific committee Dutch Urologic Association
• Medical advisor Netherlands Comprehensive Cancer Organization (IKNL)
WHAT IS THIS TALK ABOUT?
Screening, diagnostics and treatments

• About the prostate and PSA
• Facts and numbers of prostate cancer
• Imaging and prostate biopsies
• Treatments
• Screening
Who votes for screening for prostate cancer in the Netherlands?
PROSTATE
Anatomy & functioning

• PRO STATE gland (voorstander klier)
• Reproductive system
• Seminal fluid
• Fully encloses urethra
PSA HISTORY

- Glycoprotein that liquefies seminal fluid
- Discovered by Richard Ablin 1970
- Papsidero 1980 blood test
- Clinically available about 1990

- Specific for prostate, not cancer
PROSTATE CANCER INCIDENCE
World wide
PROSTATE CANCER INCIDENCE

Incidence western world

PSA test 90’s
PROSTATE CANCER INCIDENCE
Netherlands
PROSTATE CANCER INCIDENCE

Netherlands
MORTALITY

TIEN MEEST VOORKOMENDE KANKERSOORTEN

percentage van alle nieuwe kankerdiagnoses (incidentie) in 2019 en percentage van de kankersterfte in 2018

incidentie (bron NKR/IKNL)
- huid: 19,3%
- borst: 12,7%
- long: 11,7%
- prostaat: 11,5%
- darm: 10,6%
- hemato: 8,1%
- hoofdhals: 2,4%
- nier: 2,2%
- alveesklier: 2,2%
- slokdarm: 2,2%

sterfte (bron CBS)
- huid: 2,0%
- borst: 6,8%
- long: 22,8%
- prostaat: 6,4%
- darm: 11,0%
- hemato: 8,6%
- hoofdhals: 2,1%
- nier: 1,9%
- alveesklier: 6,4%
- slokdarm: 4,3%

* exclusief basaalcellkarciom, ** hematologische maligniteiten

Nederlandse Kankerregistratie (NKR), beheerd door Integraal Kankercentrum Nederland (IKNL)

3000 patients die from PCa per year
RISK CLASSIFICATION

- Lokaal beperkt (T1-T2):
  - Laag risico: 19%
  - Matig risico: 20%
  - Hoog risico: 20%

- T3-T4 en/of N+:
  - Lokaal uitgebreid: 21%
  - Uitgezaaid: 16%
  - onbekend: 5%

60% 40%
CONCLUSIONS STATISTICS

• Nr 1 male cancer (1 out of 8 men)
• Incidence increasing; about 13,000/yr NL
• Mortality of 3,000/yr NL (equal to breast cancer)
• Large variability in mortality (stage dependant)

Willet Whitmore 80’s quote ‘more men die with prostate cancer than from prostate cancer’
Diagnosis for Prostate Cancer

- Digital rectal examination
- Transrectal ultrasound (TRUS)
- MRI Fusion biopsy
- PCA3 (Prostate CAncer gene 3)
- Prostate-specific antigen blood test (PSA)
DIAGNOSTICS
When a man goes to his GP

- ‘I have urinary problems. Do I have prostate cancer?’
- ‘My friend told me I should test my PSA’
When a man goes to his GP

Ideally, GP tells his patient about the pro’s and cons of PSA testing; **decision aid available**
PRACTICE VARIATION

- Patient variation
  - Socio-economic status
  - Educational level
- GP variation ?!
Major changes last 5-10 years
Old school: ultrasound random biopsies
DIAGNOSTICS: REVOLUTION

MRI prostate

Since 2019 in EAU guidelines:
MRI before biopsy
RANDOM VERSUS TARGET BIOPSY
TARGET BIOPSY TECHNIQUES

In-bore MRI

MRI-US *fusion*

Cognitive *fusion*

**Pro**
- precision

**Contra**
- expensive
- availability
- time consuming

**Pro**
- office based (possible)
- urologist
- learning curve?
- expensive

**Contra**
- precise?

**Pro**
- office based
- cheap
- urologist
**DIAGNOSTICS**

**MRI prostate and target biopsy**

Advantages MR guided target biopsy

<table>
<thead>
<tr>
<th></th>
<th>MR TBx</th>
<th>Standard</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>No biopsies performed</td>
<td>31%</td>
<td>6%</td>
<td>Less biopsies needed</td>
</tr>
<tr>
<td>Significant PCa</td>
<td>38%</td>
<td>26%</td>
<td>More significant cancers</td>
</tr>
<tr>
<td>Gleason 6 PCa</td>
<td>9%</td>
<td>22%</td>
<td>Less overdiagnosis</td>
</tr>
<tr>
<td>Overall PCa</td>
<td>47%</td>
<td>48%</td>
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</tr>
</tbody>
</table>
BIOPSY ROUTE

Transrectal versus transperineal

• Transrectal, classic
  - PRO: fast
  - CON: more infections

• Transperineal route, new
  - PRO: less infections
  - CON: time consuming; local anesthetics
CONCLUSIONS DIAGNOSIS

- Major improvement due to MRI (image) guided biopsy
- Less men need biopsies
- More accurate
- Less low-risk cancers (less overdiagnosis)
- More finding of the cancers that are relevant
- Change to perineal biopsy route
PROSTATE CANCER POSSIBLE TREATMENT OPTIONS*

*Some of the most chosen options for treating prostate cancer depending on its stage

- Active surveillance
- Surgery of the prostate
- Hormonal treatments
- Radiotherapy
- Chemotherapy
- Immunotherapy
TREATMENTS
Many options, many choices

*Geen actieve therapie omvat zowel actief volgen als een afwachtend beleid
TREATMENTS

low risk disease: do we treat?

Majority low-risk
TREATMENTS
Active surveillance

• First choice for low-risk disease
• Important: Good Selection & Good Follow-up

• 2 PhD’s last week
• Innovative studies: PASPORT trial 1/2
TREATMENTS

Intermediate and high risk prostate cancer
TREATMENTS
Surgery and radiotherapy outcomes

Oncological outcomes

Functional outcomes
- Urinary problems
- Bowel problems
- Incontinence
- Erectile dysfunction
TREATMENTS
Developments surgery

1. Injection of multimodal tracer and pre-operative SPECT-PET/CT imaging
2. Audio-guided tumor detection with gamma probe
3. Tumor visualization and delineation with NIR camera
4. Ex vivo measurement (quantification)
TREATMENTS

Metastatic disease

- 16% M1 at diagnosis
- Progression to M1 disease
INNOVATIVE THERAPY

PSMA-Lutetium

\[^{177}\text{Lu}-\text{PSMA}-617\] binds to PSMA on the cell membrane with high affinity.

β particle emission

Endocytosis

Prostate cancer cell

DNA damage

*Reduction binding in the liver, salivary glands, lachmer, GI glands, and bone marrow.
TREATMENTS
Evaluating new modalities

• Start 2020 UMCU and St. Antonius
• All patients with local Pca included
• All data in prospective database including imaging and PROMS (!)
• All treatments identical data collection to make meaningful comparison possible
UPC
Inclusion

- 600+ patients included
CONCLUSION TREATMENTS

- Good staging very important
- NOT treating in low-risk disease: active surveillance
- Different options in intermediate-high risk disease
  - RT innovation: MR-Linac
  - Surgical innovation: image guided surgery
- Combination (systemic) treatments in metastatic disease
  - Innovative: Lu-PSMA
SCREENING

- Males complain: females have nation wide screening for breast cancer en cervical cancer
- In 2019 died 2954 men from prostate cancer and 3050 women from breast cancer
- So why is there no screening program for men?
# RESULTS SCREENING STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>PSA screening</th>
<th>Control</th>
<th>Incidence rate ratio (95% CI)</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labrie (Quebec)</td>
<td>153/281 182*</td>
<td>75/148 852*</td>
<td>1.08 (0.82 to 1.42)</td>
<td></td>
</tr>
<tr>
<td>Lundgren (Stock)</td>
<td>86/2400†</td>
<td>771/25 081†</td>
<td>1.05 (0.83 to 1.27)</td>
<td></td>
</tr>
<tr>
<td>PLCO 2017</td>
<td>255/533 014*</td>
<td>244/529 860*</td>
<td>1.04 (0.87 to 1.24)</td>
<td></td>
</tr>
<tr>
<td>ERSPC (core) 2014</td>
<td>355/825 018*</td>
<td>545/1 011 192*</td>
<td>0.79 (0.69 to 0.91)</td>
<td></td>
</tr>
<tr>
<td>CAP 2018</td>
<td>549/1 853 167*</td>
<td>647/2 095 405*</td>
<td>0.96 (0.85 to 1.08)</td>
<td></td>
</tr>
</tbody>
</table>

Random effect: $P=0.05$ for heterogeneity, $I^2=58%$

* Rate by total number of person years
† Rate by total number of patients
ERSPC
Lancet 2014

n >270,000
8 countries
Median FU 13 yrs
Reduction risk death = 21%
NNI = 781
NND = 27
Health council (Gezondheidsraad) refused license for pilot screening study

Reasons, advantages do not counterbalance disadvantages:
- High number of **overdiagnosis**
- High percentage of **overtreatment** (of low risk disease)
- Psychological burden and stress for patients
FINETUNING ERSPC

1. Screening the right way
2. Correction population data
3. Secondary endpoints
4. Improvements since ERSPC
FINETUNING ERSPC

1. Screening the right way

Gothenburg

- N = 20,000
- Reduction risk death = 35% (vs 21%)
- NNI = 231 (vs 781)
- NND = 10 (vs 27)

Differences from ERSPC:
- Age: 50–64
- Screening every 2 years
- Long follow-up
- (High participation)
- (Low contamination)
## FINETUNING ERSPC
Comparing to other types of screening

<table>
<thead>
<tr>
<th></th>
<th>Breast</th>
<th>Cervix</th>
<th>Colorectal</th>
<th>ERSPC</th>
<th>Gothenburg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction risk death</td>
<td>15-20%</td>
<td>20-60%</td>
<td>15%</td>
<td>27%</td>
<td>35%</td>
</tr>
<tr>
<td>NNI</td>
<td>100-2000</td>
<td>1140 (10 yrs)</td>
<td>600-1200 (17 yrs)</td>
<td>781</td>
<td>231</td>
</tr>
<tr>
<td>NND</td>
<td>10</td>
<td>?</td>
<td>?</td>
<td>27</td>
<td>10</td>
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</tbody>
</table>
FINETUNING ERSPC
Correction of population data

ERSPC overall:
• Non-participation: Mortality reduced 21% > 27%

Simulation:
• Non-participation: 20% > 27%
• Additional contamination: 27% > 29-31%
FINETUNING ERSPC
Secondary endpoint

Metastases
• 30% risk reduction
• Less hormones / palliative treatment

Quality of life
• Quality adjusted life years (QALYs) gained per 1000 men being screened (every year screening): 56
FINETUNING ERSPC
Improvements since ERSPC

ERSPC started in the 90s; it’s history!

ERSPC = no MRI, no target biopsies, few active surveillance

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<th>Post-ERSPC era</th>
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<tr>
<td>Less biopsies needed</td>
</tr>
<tr>
<td>More significant cancers</td>
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<td>Less overdiagnosis</td>
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<td>More Active Surveillance</td>
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SCREENING IN MODERN TIMES

Awareness

‘Intelligente opsporing’ van prostaatkanker
Een alternatief voor bevolkingsonderzoek

Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and Commission

Hendrik Van Poppel\textsuperscript{a,b,*}, Renée Hogenhout\textsuperscript{b}, Peter Albers\textsuperscript{c,d}, Roderick C.N. Jelle O. Barentsz\textsuperscript{c,e}, Monique J. Roobol\textsuperscript{a,b}
CONCLUSIONS
State of the art in screening, diagnostics and treatments

- Rising incidence and mortality; variations in NL
- Diagnostic revolution: MRI selection and MRI target biopsy
- Innovative therapy
  - Image guided radiotherapy
  - Image guided surgery
  - New (combinations) systemic therapy
- Screening discussion completely different from 1990 ERSPC
Who votes for screening for prostate cancer in the Netherlands?