ACTIVE SURVEILLANCE

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DISCLOSURE OF INTEREST

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Astellas - research funding
Ipsen – research funding
Janssen – advisory board
Amgen – advisory board
Sanofi – support
AstraZeneca - support
MALIGNANT TRANSFORMATION OCCURS FREQUENTLY

<table>
<thead>
<tr>
<th>PIN</th>
<th>Localized</th>
</tr>
</thead>
</table>

Malignant transformation

**Autopsy studies**

<table>
<thead>
<tr>
<th></th>
<th>Sanchez-Chapado</th>
<th>Holund</th>
<th>Kabalin</th>
<th>Ward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36-94</td>
<td>20-80</td>
<td>31-82</td>
<td>44-92</td>
</tr>
<tr>
<td>PSA range</td>
<td></td>
<td></td>
<td>0-2 ng/ml</td>
<td></td>
</tr>
<tr>
<td>PCa Prevalence (%)</td>
<td>22</td>
<td>18.5</td>
<td>38</td>
<td>23</td>
</tr>
</tbody>
</table>

Sanchez-Chapado, Prostate 2003, 54, 238-247
Kabalin, J.Urol 1989, 141, 1091-4
Ward, Urol. Oncol., 2004, 22; 40-7
TRANSFORMATION INTO LETHAL PHENOTYPE

Localized

Locally advanced

Metastatic

Death

- Does not occur systematically
- Might take a very long time
- Is, to some extent, predictable
TRANSFORMATION INTO LETHAL PHENOTYPE

Albertsen PC et al,
20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer

- 767 patients with clinically localized PCa followed up for a median of 24 Years, 71 % being diagnose by BPH surgery.
- 222 deaths from PCa
- 470 deaths from other causes
MORTALITY OCCURS MOSTLY IN HIGH GRADE PCA?

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Nº of person-years</th>
<th>% of patient</th>
<th>Mortality rate death/1000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 4</td>
<td>1784.9</td>
<td>24%</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>1413.7</td>
<td>20%</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>2803.2</td>
<td>37%</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>976.3</td>
<td>13%</td>
<td>65</td>
</tr>
<tr>
<td>8 – 10</td>
<td>451.2</td>
<td>6%</td>
<td>121</td>
</tr>
<tr>
<td>Overall</td>
<td>7429.3</td>
<td></td>
<td>31</td>
</tr>
</tbody>
</table>

- Gleason score correlates with mortality rates
- Mortality significantly increases for Gleason 7 and higher
- But, Gleason 7 and higher represent only 30% of the tumours

IS TRANSFORMATION INTO LETHAL PHENOTYPE PREDICTABLE?

C. Parker et al.
A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival
Follow-up of Prostatectomy versus Observation for Early Prostate Cancer


CONCLUSIONS

After nearly 20 years of follow-up among men with localized prostate cancer, surgery was not associated with significantly lower all-cause or prostate-cancer mortality than observation. Surgery was associated with a higher frequency of adverse events than observation but a lower frequency of treatment for disease progression, mostly for asymptomatic, local, or biochemical progression. (Funded by the Department of Veterans Affairs and others; PIVOT ClinicalTrials.gov number, NCT00007644.)
A Randomized Trial Comparing Radical Prostatectomy with Watchful Waiting in Early Prostate Cancer

Scandinavian Prostatic Cancer Group Study NEJM (2002)

- Distress from urinary leakage
- Protective aids against leakage
- Distress re sexual dysfunction
- Erectile dysfunction

% patients

- Watchful Waiting
- Radical Prostatectomy
THE PROBLEM

Normal / BPH

Prostate cancer

Potentially Lethal prostate cancer

IDEAL SCREENING TEST
“ACTIVE SURVEILLANCE”

• Is not a “treatment option”
• Consists of *deferring* treatment in patients with low risk cancers that are candidate for *immediate* radical treatment
• Implies revisiting periodically the status of the patient and treating upon progression.

≠ from Watchful Waiting that implies delaying treatment until symptoms occurs in patients that are not candidate or refuse radical treatment
ACTIVE SURVEILLANCE

Criteria
- Gleason
- PSA
- Clinical stage
- Number of positive biopsy cores number
- Amount of cancer per core
<table>
<thead>
<tr>
<th>Author</th>
<th>cT</th>
<th>PSA (ng/ml)</th>
<th>Gleason</th>
<th>PSA density</th>
<th>Pos. cores</th>
<th>Max % per core</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein, 1994</td>
<td>T1c</td>
<td></td>
<td>Gr. &lt; 3</td>
<td>&lt; 0.15</td>
<td>&lt;3</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Dall’Era, 2008</td>
<td>≤T2a</td>
<td>≤10</td>
<td>Gr. &lt; 3</td>
<td>&lt; 0.15</td>
<td>&lt;33%</td>
<td></td>
</tr>
<tr>
<td>Soloway, 2008</td>
<td>≤T2</td>
<td>&lt;15</td>
<td>Gr. &lt; 3</td>
<td>&lt;0.20</td>
<td>&lt;3</td>
<td></td>
</tr>
<tr>
<td>PRIAS, 2007</td>
<td>≤T2b</td>
<td>&lt;10</td>
<td>Gr. &lt; 3</td>
<td></td>
<td>&lt;3</td>
<td></td>
</tr>
<tr>
<td>Van Ass, 2008</td>
<td>≤T2a</td>
<td>&lt;15</td>
<td>Sc &lt; 7(3+4)</td>
<td>&lt;50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klotz, 2010</td>
<td>≤T2a</td>
<td>&lt;10</td>
<td>Sc &lt; 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stattin, 2010</td>
<td>≤T2b</td>
<td>&lt;20</td>
<td>Sc ≤ 3+4</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
ACTIVE SURVEILLANCE

• Gleason ≤ 6 (grade < 4)
• PSA <11-15 ng/mL
• T1c – T2a
• 1 or 2 biopsies; max 30-50% cancer
• PSA density < 0.20 ng/mL

Does it identify precisely indolent PCa?
ACTIVE SURVEILLANCE

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Does it identify precisely indolent PCa?

With current accepted criteria, there is a:
- 25 to 50% upgrading to Gleason 7
- < 10% upgrading to Gleason ≥ 8
- 10-25% upstaging to extra-capsular disease
- < 3% positive lymph nodes

But, this is extremely dependent on the biopsy regimen
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How to define progression?
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- T1c – T2a
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How to define progression?

A biopsy is required to define progression
ACTIVE SURVEILLANCE

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What are the results?
Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer

Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer

CONCLUSIONS

At a median of 10 years of follow-up, 10-year outcomes were similar among all groups, irrespective of the treatment assigned, with nearly all patients remaining disease-free and alive. Patients in the watchful waiting and radiotherapy arms were more likely than those in the active monitoring and protected trial arms to have a disease recurrence or develop metastases than was observed in the current study (ProtecT Current Study, Clinical Trials Register No. NCT02044172.)
450 men, Gleason ≤ 6, PSA ≤ 10 ng/mL (patients > 70 y.O. PSA ≤ 15 ng/mL or Gleason ≤ 3 + 4)  
Progression PSA doubling time (DT) of less than 3 y.; histologic upgrade; clinical progression  
Biopsy: 6 to 12 months and then every 3 to 4 years until 80 years old  

30% of patients have been reclassified as higher risk and have been offered definitive therapy.
ACTIVE SURVEILLANCE

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- T1c –T2a
- 1 or 2 biopsies; max 30-50% cancer
- PSA density < 0.20 ng/mL

Is there a “loss of chance” for curative treatment?
Can active surveillance really reduce the harms of overdiagnosing prostate cancer? A reflection of real life clinical practice in the PRIAS study

Drost et al Transl Androl Urol 7:98-105, 2018
ACTIVE SURVEILLANCE

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- T1c–T2a
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Can we improve the identification of non-indolent disease?

- PSA velocity
- PSA density

Amsterdam UMC
**ACTIVE SURVEILLANCE**

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- PSA < 11-15 ng/mL
- T1c – T2a
- 1 or 2 biopsies; max 30-50% cancer
- PSA density < 0.20 ng/mL

---

What is the role of new biomarkers?
## Active surveillance (AS)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer AS to patients suitable for curative treatment but with low-risk PCa.</td>
<td>Strong</td>
</tr>
<tr>
<td>Perform multiparametric magnetic resonance imaging before a confirmatory biopsy.</td>
<td>Strong</td>
</tr>
<tr>
<td>During confirmatory biopsy include systematic and targeted biopsies.</td>
<td>Strong</td>
</tr>
<tr>
<td>Base follow up on digital rectal examination, prostate-specific antigen and repeated biopsies.</td>
<td>Strong</td>
</tr>
<tr>
<td>Counsel patients about the possibility of needing further treatment in the future.</td>
<td>Strong</td>
</tr>
</tbody>
</table>
Active Surveillance in Low Risk Disease: Who Doesn’t Need Treatment?

- Rationale for active surveillance
- Results of active surveillance
RATIONALE FOR ACTIVE SURVEILLANCE

- **Some** men with prostate cancer benefit from radical treatment

- Treatment is toxic, and should be given only to those who stand to benefit

- **Most** men with screen detected prostate cancer do not benefit from attempted curative treatment
A Randomized Trial Comparing Radical Prostatectomy with Watchful Waiting in Early Prostate Cancer
Scandinavian Prostatic Cancer Group Study NEJM (2005)/(2014)

56% vs 69% mortality HR .71 p<0.001

70% vs 72% p.52
A Randomized Trial Comparing Radical Prostatectomy with Watchful Waiting in Early Prostate Cancer
Scandinavian Prostatic Cancer Group Study NEJM (2005)/(2014)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cumulative Incidence</th>
<th>Absolute Risk Reduction with Radical Prostatectomy</th>
<th>Relative Risk with Radical Prostatectomy (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no. of events (N = 347)</td>
<td>% (95% CI)</td>
<td>no. of events (N = 348)</td>
</tr>
<tr>
<td>Death from prostate cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>63</td>
<td>17.7 (14.0 to 22.4)</td>
<td>99</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td></td>
<td>31</td>
<td>18.3 (13.1 to 25.7)</td>
<td>58</td>
</tr>
<tr>
<td>≥65 yr</td>
<td></td>
<td>32</td>
<td>17.3 (12.5 to 24.0)</td>
<td>41</td>
</tr>
<tr>
<td>Tumor risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>11</td>
<td>10.2 (5.8 to 18.0)</td>
<td>20</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>24</td>
<td>15.1 (10.2 to 22.2)</td>
<td>50</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>28</td>
<td>33.1 (24.0 to 45.7)</td>
<td>29</td>
</tr>
</tbody>
</table>
Prostate cancer is not what it used to be!

US PROSTATE CANCER INCIDENCE
Conclusions: Overall RP did NOT reduce all-cause or prostate-cancer-mortality

PIVOT Trial
Wilt et al NEJM July 2012 367; 203-13

731 man 1994-2002
T1-T2 M0, PSA<50, age<75
Randomised to prostatectomy or observation.
Median FU 10 years.

No difference in primary endpoint of overall survival

Cause-specific mortality 5.8% vs 8.4% p=0.09

For high risk tumours cause specific mortality 9.1% vs 17.5% P=0.02. No significant benefit for intermediate or low risk.
ACTIVE SURVEILLANCE AS A TREATMENT OPTION

- **Aim**
  - To select patients that will benefit from treatment.

- **Who?**
  - Suitable for radical treatment
  - Low volume cancer
  - Low grade (usually Gleason score $\leq 3+3$)

- **How?**
  - Regular PSA/clinical assessment
  - Repeat biopsy
  - MRIs
RESULTS OF ACTIVE SURVEILLANCE OF LOCALISED PROSTATE CANCER
• Klotz et al 2014
• 993 men median FU 6.4 years
• treat if DT<3 years or Clinical ↑ or Gleason↑
• Median FU 6.4 years
• 2.8% developed metastases
• 1.5% died of prostate cancer (CSS at 10 yrs 98%)
Active Surveillance for Prostate Cancer

Royal Marsden Series (Dr Chris Parker):

PSA and DRE q 3 monthly year 1, q4 monthly year 2 then 6 monthly
Re-biopsy every 2 years.

Results: 471 patients 2002- 2011 median FU 5 years
93% Gleason 3+3
median PSA 6.4

5 yr biopsy progression 22%
Treatment-free at
5 years 70% (95% CI 86-92%)

Selvadurai et al 2013 Eur Urol
**RMH prospective study of active surveillance of early prostate cancer**

**Indications for treatment**

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy progression</td>
<td>18</td>
<td>13%</td>
</tr>
<tr>
<td>PSA v &gt;1ng/ml</td>
<td>56</td>
<td>41%</td>
</tr>
<tr>
<td>Both</td>
<td>23</td>
<td>17%</td>
</tr>
<tr>
<td>Patient decision</td>
<td>40</td>
<td>29%</td>
</tr>
</tbody>
</table>
### RMH prospective study of active surveillance of early prostate cancer

#### Multivariate analysis of time to treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%free PSA</td>
<td>&lt;0.001</td>
<td>0.93 (0.89-0.97)</td>
</tr>
<tr>
<td>PSAV &gt;1</td>
<td>&lt;0.001</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>T stage</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>PSAD</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Gleason 3+4</td>
<td>0.005</td>
<td>3.4 (1.4-8.0)</td>
</tr>
</tbody>
</table>
AS TRIALS

- PRIAS- International database with 4000 registered men on AS recruited between 2006-2013

- ProtecT—UK prospective RC phase 3 trial. Men from 337 primary care centres in 9 cities.
  230,000 men invited for PSA and counseled.
  100,000 attended and 82k had PSA.
  11% (8.5k) had PSA >3.0 of whom 87% had Bx.
  39% of Bx positive (mainly Gleason 6 T1C).
  2664 eligible for 3 arm trial of which 62% consented:
    Radical Px versus RT vs Active Surveillance.
Management of local/loco-regional disease

- In men with low-risk disease, no benefit for active treatment has been demonstrated in overall survival. Observation should be discussed and should be an option for these patients.
- Options for patients with intermediate-risk prostate cancer include radical prostatectomy, external beam RT plus androgen deprivation therapy (ADT) or high-dose rate brachytherapy.
- Watchful waiting with delayed hormone therapy is an option for men who are not suitable for radical treatment [I, A].

National Institute for Health and Clinical Excellence (NICE) guidelines

3. Men with low-risk localised prostate cancer who are considered suitable for radical treatment should first be offered active surveillance.