ACTIVE SURVEILLANCE OR WATCHFUL WAITING

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• Watchful waiting (WW)
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1 in 6 men will be diagnosed with prostate cancer during his lifetime.

2nd leading cause of cancer death in men. In developing countries it can be 1st cause.

93% of prostate cancers are discovered in the local or regional stage.

A new case is diagnosed every 2.3 minutes.
Estimated New Cases in 2017
161,360 (9.6%)

Estimated Deaths in 2017
26,730 (4.4%)

10-year relative survival 98%

Incidence of prostate cancer has increased dramatically.

- PSA
- digital rectal examination

Overdetection
Overtreatment

PROSTATE CANCER IS HETEROGENEOUS

INDOLENT
Asymptomatic and pathological features

LETHAL
Symptom, metastases, & deaths

Harms
Unnecessary biopsies
Overdiagnosis
Overtreatment

Benefits
Metastases
Mortality

INDOLENT PROSTATE CANCER

Autopsy studies

Men may live their entire natural life without having any symptoms from prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>Detection rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>US</td>
<td>249</td>
<td>24</td>
</tr>
<tr>
<td>2005</td>
<td>Hungary</td>
<td>139</td>
<td>38</td>
</tr>
<tr>
<td>2013</td>
<td>Russia</td>
<td>320</td>
<td>37</td>
</tr>
<tr>
<td>2007</td>
<td>US</td>
<td>164</td>
<td>42</td>
</tr>
<tr>
<td>2003</td>
<td>Spain</td>
<td>167</td>
<td>18</td>
</tr>
<tr>
<td>2006</td>
<td>Greece</td>
<td>212</td>
<td>18</td>
</tr>
</tbody>
</table>

GLEASON 6 DISEASE HAS A LOW RISK OF DEATH

N= 9557

- Prostate cancer specific mortality
- Mortality from competing causes

- 15-year prostate cancer–specific mortality: 0.2%.
- Only **1 patient** died of prostate cancer (Gleason: 4+3=7)

Eggener et al, J Urol. 2011;185(3):869
TRENDS IN THE MANAGEMENT OF PROSTATE CANCER

[Diagram showing trends in management of low-risk, intermediate-risk, and high-risk prostate cancer over different time periods, with AS/WW, RP, RT, and PADT categories.

LOCALIZED PROSTATE CANCER

- Very low risk
  - Active surveillance
  - Watchful waiting
- Low risk
- Intermediate risk
  - Surgery
  - Radiation

Management

AVOID TREATEMENT

ACTIVE SURVEILLANCE

Avoidance or postponement of immediate therapy combined with careful surveillance; definitive treatment is then offered if there is evidence that the patient is at increased risk for disease progression.

WATCHFUL WAITING (observation)

Decision is made at the outset to forego definitive treatment (comorbidities & life expectancy) and to provide systemic or local treatment to palliate symptoms if disease progresses locally or at distant metastatic sites.

CONTRASTING AA vs WW

<table>
<thead>
<tr>
<th></th>
<th>AS</th>
<th>WW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment intent</strong></td>
<td>Curative</td>
<td>Palliative</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Predefined</td>
<td>Patient specific</td>
</tr>
<tr>
<td><strong>Assessment</strong></td>
<td>DRE, PSA, biopsy, MRI*</td>
<td>Not predefined</td>
</tr>
<tr>
<td><strong>Life expectancy</strong></td>
<td>&gt; 10 yr</td>
<td>&lt; 5-10 yr</td>
</tr>
<tr>
<td><strong>Aim</strong></td>
<td>Minimize toxicity without compromising survival</td>
<td>Minimize treatment-related toxicity</td>
</tr>
</tbody>
</table>

WHERE ARE WE?

• Prostate cancer is a **common disease**.

• **NOT** all cancer need to be treated.

• To strategies to **avoid treatment toxicity**.

Trials evaluating outcomes...
TRIALS EVALUATING AS and WW

SPCG-4 (Sweden)
N = 695, 1989-1999
12% PSA-detected (T1c)

PIVOT (USA)
N = 731, 1994-2002
50% PSA-detected (T1c)

PROTECT (UK)
N = 1643, 1999-2008
100% PSA-detected

WW vs. Surgery

AS vs. Surgery/Radiation

WATCHFUL WAITING
SPCG-4 MORTALITY WITH WW

End point | RR with RP vs WW | P value
--- | --- | ---
Death for prostate cancer | 0.56 | 0.001
  - Low risk | 0.54 | 0.17
  - Intermediate risk | 0.38 | <0.001
  - High risk | 0.87 | 0.84

No planned protocol

PIVOT: radical prostatectomy or observation

**All-cause mortality** was NOT significantly lower with surgery than with observation

13 yr vs 12.4 yr

\[ P = 0.06 \]

The **cumulative incidence of death** due to prostate cancer or treatment was 7.4% with surgery and 11.4% with observation

\[ P = 0.06 \]

No planned protocol

ACTIVE SURVEILLANCE
RECOMMENDATIONS FOR ACTIVE SURVEILLANCE

- For most patients with **low-risk (Gleason score ≤6)** localized prostate cancer, **AS is the recommended** disease management strategy.

- For patients with **limited life expectancy (< 5 years)** and low risk cancer, **watchful waiting** may be more appropriate than AS.

- **Active treatment (RP or RT)** is recommended for most patients with **intermediate-risk (Gleason score 7)** localized prostate cancer.
  - Selected patients with low volume, **intermediate-risk** (Gleason 3 +4=7) localized prostate cancer, **AS** may be offered.

## RISK STRATIFICATION for localized prostate cancer

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td>PSA &lt;10 ng/ml AND Gleason score ≤6 AND clinical stage T1-T2a</td>
</tr>
<tr>
<td><strong>Intermediate risk</strong></td>
<td>PSA 10-&lt;20 ng/ml OR Gleason score 7 OR clinical stage T2b-c</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>PSA ≥20 ng/ml OR Gleason score ≥8 OR clinical stage ≥T3.</td>
</tr>
</tbody>
</table>

RISK OF PROGRESSION WITH VERY-LOW RISK CANCER

Metastatic progression rate of <1% at 15 years.

<table>
<thead>
<tr>
<th>Event / 100 persons-year</th>
<th>Overall</th>
<th>Very-low risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Prostate cancer</td>
<td>0.03</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>• All causes</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Grade reclassification</td>
<td>3.8</td>
<td>3.4</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Caution: high-risk groups may harbor aggressive disease

- PSA density
- African-American
- Younger age

# PATIENT ELIGIBILITY FOR AS

<table>
<thead>
<tr>
<th>PROGRAMS</th>
<th>Clinical stage</th>
<th>Serum PSA level (ng/ml)</th>
<th>Gleason score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns Hopkins</td>
<td>T1c</td>
<td>N/A</td>
<td>≤6</td>
</tr>
<tr>
<td></td>
<td>≤T2a</td>
<td>≤10</td>
<td>≤6</td>
</tr>
<tr>
<td>Sunnybrook (Klotz)</td>
<td>NA</td>
<td>≤10</td>
<td>≤6</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>10-20</td>
<td></td>
</tr>
<tr>
<td>Göteborg</td>
<td>≤T2a</td>
<td>≤10</td>
<td>≤6</td>
</tr>
<tr>
<td>UCSF</td>
<td>&lt;T2</td>
<td>≤10</td>
<td>≤6</td>
</tr>
<tr>
<td>Royal Marsden</td>
<td>&lt;T2</td>
<td>N/A</td>
<td>≤6</td>
</tr>
<tr>
<td></td>
<td>&lt;15</td>
<td>≤3+4</td>
<td></td>
</tr>
<tr>
<td>Australian</td>
<td>≤T2a</td>
<td>&lt;10</td>
<td>≤6</td>
</tr>
<tr>
<td>PRIAS</td>
<td>≤T2</td>
<td>≤10</td>
<td>≤6</td>
</tr>
<tr>
<td>University of Copenhagen</td>
<td>≤T2a</td>
<td>≤10</td>
<td>≤6</td>
</tr>
<tr>
<td>University of Miami</td>
<td>≤T2</td>
<td>≤10</td>
<td>≤6</td>
</tr>
</tbody>
</table>

Eligibility criteria vary significantly across different programs

SURVEILLANCE PROTOCOL

Initial

Diagnosis

3-6 months

PSA

Confirmatory prostate biopsy 6-12m

12 months

DRE

Prostate biopsies Every 2-5yr

OBSERVATIONAL COHORTS

During the first 2 yr of AS: there is a shift from an expectant stance toward definitive therapy in **20–30% of patients.**

<table>
<thead>
<tr>
<th>Program</th>
<th>N</th>
<th>Follow up</th>
<th>Treatment free</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>U. Toronto</td>
<td>993</td>
<td>6.4 yr</td>
<td>55% at 15yr</td>
<td>65%*</td>
</tr>
<tr>
<td>PRIAS</td>
<td>5302</td>
<td>NA</td>
<td>27% at 10yr</td>
<td>92%</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>1298</td>
<td>5 yr</td>
<td>43% at 10yr</td>
<td>94%</td>
</tr>
<tr>
<td>Canary</td>
<td>905</td>
<td>2.4 yr</td>
<td>81%</td>
<td>99%</td>
</tr>
</tbody>
</table>

* Included intermediate-risk

PROTECT TRIAL: AS vs RP or RDT

Planned protocol for curative radical intervention on disease progression

AS n=545
291 received radical treatment (54.8%)

- 49% RP
- 33% RT
- 8% BT

PROTECT TRIAL: AS vs RP or RDT

17 prostate-cancer–specific deaths
- AS = 8
- RP = 5
- RDT = 4  \( P = 0.4 \)

Metastases development/disease progression
- AS = 33 / 112
- RP = 13 / 46
- RDT = 16 / 46  \( P = 0.004 \)

Radical prostatectomy group experienced the greatest negative effect on sexual function and urinary continence. Radiotherapy group the bowel function was worst. No significant differences in measures of anxiety, depression, or general health-related or cancer-related quality of life.

### CRITERIA FOR INTERVENTION

<table>
<thead>
<tr>
<th>Program</th>
<th>Gleason Score</th>
<th>+ Cores</th>
<th>Maximum % cores +</th>
<th>PSAV</th>
<th>PSADT (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns Hopkins²</td>
<td>&gt;6</td>
<td>&gt;2</td>
<td>&gt;50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sunnybrook</td>
<td>Upgrade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;3&lt;sup&gt;$\text{§}$&lt;/sup&gt;</td>
</tr>
<tr>
<td>UCSF</td>
<td>&gt;6</td>
<td>&gt;33%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Royal Marsden</td>
<td>≥4+3</td>
<td>&gt;50%</td>
<td>-</td>
<td>&gt;1</td>
<td>-</td>
</tr>
<tr>
<td>St. Vincent’s</td>
<td>&gt;6</td>
<td>&gt;20%</td>
<td>&gt;8 mm</td>
<td>&gt;0.75</td>
<td>&lt;3</td>
</tr>
<tr>
<td>PRIAS</td>
<td>&gt;6</td>
<td>&gt;2</td>
<td>-</td>
<td>-</td>
<td>&lt;3</td>
</tr>
<tr>
<td>University of Copenhagen</td>
<td>≥4+3</td>
<td>&gt;3</td>
<td>-</td>
<td>-</td>
<td>&lt;3</td>
</tr>
<tr>
<td>University of Miami</td>
<td>&gt;6</td>
<td>&gt;2</td>
<td>Increase</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CRITERIA FOR SWITCHING TO DEFINITIVE THERAPY

Rising PSA
- PSA velocity >0.75ng/mL/yr
- PSADT < 3 yr

Imaging, biopsy and/or treatment

Biopsy reclassification
- Increase grade
- Extent of disease

Recommended treatment

Changes in MRI or other markers

***

ANCILLARY TESTS
mpMRI ASSESSMENT IN AS

59 yo – PSA 4.6ng/mL –

**mpMRI**: lesion in the left mid-peripheral zone

**Biopsy**: Gleason 6 (3+3)

The patient elected active surveillance

1 yr FU → lesion is stable in size

Control biopsy: Gleason 3 + 3

77 yo – PSA 7.7ng/mL – Gleason 6 (3+3)

Plan → AS

**mpMRI**: large left-sided anterior transition zone lesion

Subsequent targeted biopsy confirmed Gleason 4 + 4 disease in 80–90% of cores

Barret T, et al. AJR 2017; 208:131–139
mpMRI ASSESSMENT IN AS

105 patients with low-risk, low-grade localized prostate cancer who were candidates for AS

Multiparametric MRI

For intermediate- and high-risk prostate cancers
- Sensitivity = 92%
- Specificity = 76%
- PPV = 81%
- NPV = 90.5%

mpMRI ASSESSMENT IN AS

1. Accurately identify those in active surveillance who have occult coexistent higher–Gleason score cancer
   • Direct biopsies to a specific target or lesion

2. It is recommended that when a patient’s clinical findings are discordant with the pathologic findings.
   • When: at initiation of AS or during follow-up

3. Problem: **High cost**

FUTURE PERSPECTIVE
POTENTIAL BIOMARKERS

Whom to biopsy
- PSA
- PHI
- PCA3

When to re-biopsy
- ConfirmMDX
- PCA3
- PCMT
- TMPRSS2-ERG
- PTEN

Whom to treat or whom NOT to treat
- Oncotype DX
- Prolapal
- Declipher
- CTCs
- TMPRSS2-ERG
- PTEN

POTENTIAL BIOMARKERS

- Decipher: Genomic Classifier
- IHQ PTEN
- Oncontype DX: Genomic prostate score
- ProMark
- Prolaris: Cell cycle progression

22 gene assay in tissue

- RNA expression
- Predicts metastasis at 10 years post radical prostatectomy
ONCONTYPE DX

- 17-gene panel (oncogenesis).
- 20-point increase is associated with increased risk of high-grade and biochemical recurrence.

N=35 very low risk
N=71 low risk
N=52 low-intermediate risk

PROLARIS

- qRT PCR
- 31 cell cycle-related & 15 housekeeping genes
- **10-year risk of PCSM**

![Diagram showing pre-test and post-test changes in intended treatment categories](image)

<table>
<thead>
<tr>
<th>AUA Risk Category</th>
<th>Change in Intended Treatment from Pre-test to Post-test (n = 305)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Intervention to Non-Intervention</td>
</tr>
<tr>
<td>Low (n = 135)</td>
<td>75 (55.6%)</td>
</tr>
<tr>
<td>Intermediate (n = 131)</td>
<td>29 (22.1%)</td>
</tr>
<tr>
<td>High (n = 39)</td>
<td>4 (10.3%)</td>
</tr>
</tbody>
</table>

SHARED DECISION MAKING
SHARED DECISION MAKING

• Collaborative process between patients and their clinicians.
  o Encourage the conversation with different specialists (urology, radiation oncology and medical oncology).
## RECOMMENDATION: LEVEL OF EVIDENCE

<table>
<thead>
<tr>
<th>Level</th>
<th>Very low risk</th>
<th>Low risk</th>
<th>Favorable ½ risk</th>
<th>Unfavorable ½ risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Strong</td>
<td><strong>AS</strong></td>
<td>-</td>
<td>RP or RT</td>
<td>RP or RT</td>
<td>RP or RT</td>
</tr>
<tr>
<td>B/Moderate</td>
<td>-</td>
<td><strong>AS</strong></td>
<td>RT wo H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B/Conditional</td>
<td>-</td>
<td>RP or RT</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C/Conditional</td>
<td>-</td>
<td>Cryo</td>
<td><strong>AS or Cryo</strong></td>
<td>Cryo</td>
<td>-</td>
</tr>
<tr>
<td>Expert opinion</td>
<td>-</td>
<td>Focal</td>
<td>Focal</td>
<td>Focal</td>
<td>-</td>
</tr>
</tbody>
</table>

TAKE HOME MESSAGES

1. Prostate cancer in a **global health problem**.

2. The majority of men will present with **localized disease**.

   - Balance risks & benefits.

4. The AS and WW strategies emerged to **avoid unnecessary morbidity**.
TAKE HOME MESSAGES

1. **AS is a safe option** to minimize overtreatment in men with favorable-risk prostate cancer
   - Does **NOT** affect QoL

2. **AS is a collaborative and changing** process with long term monitoring

3. **Our current challenge is patient selection**
   - Identify aggressive occult cancers

4. **The future perspectives:** mMRI, genomic biomarkers
FIGHT
BELIEVE
HOPE
Prostate Cancer Awareness